Explaining the Escalation of Drug Use in Substance Dependence: Models and Appropriate Animal Laboratory Tests

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Abstract

Escalation of drug use, a hallmark of drug dependence, has traditionally been interpreted as reflecting the development of tolerance to the drug's effects. However, on the basis of animal behavioral data, several groups have recently proposed alternative explanations, i.e. that such an escalation of drug use might not be based on (1) tolerance, but rather be indicative of (2) sensitization to the drug's reinforcing effect, (3) reward allostasis, (4) an increase in the incentive salience of drug-associated stimuli, (5) an increase in the reinforcing strength of the drug reinforcer relative to alternative reinforcers, or (6) habit formation. From the pharmacological perspective, models 1–3 allow predictions about the change in the shape of drug dose-effect curves that are based on mathematically defined models governing receptor-ligand interaction and signal transduction. These predictions are tested in the present review, which also describes the other currently championed models for drug use escalation and other components of apparent 'reinforcement' (in its original meaning, like 'tolerance' or 'sensitization', a purely descriptive term). It evaluates the animal experimental approaches employed to support or prove the existence of each of the models and reinforcement components, and recapitulates the clinical evidence, which strongly suggests that escalation of drug use is predominantly based on an increase in the frequency of intoxication events rather than an increase in the dose taken at each intoxication event. Two apparent discrepancies in animal experiments are that (a) sensitization to overall reinforcement has been found more

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often for psychostimulants than for opioids, and that (b) tolerance to the reinforcing and other effects has been observed more often for opioids than for cocaine. These discrepancies are resolved by the finding that cocaine levels seem to be more tightly regulated at submaximum reinforcing levels than opioid levels are. Consequently, animals self-administering opioids are more likely to expose themselves to higher above-threshold doses than animals self-administering psychostimulants, rendering the development of tolerance to opioids more likely than tolerance to psychostimulants. The review concludes by making suggestions on how to improve the current behavioral experimental approaches.

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Acb	Nucleus accumbens, region not specified [182]
AcbC	Nucleus accumbens core [182]
AcbSh	Nucleus accumbens shell [182]
CS	Conditioned stimulus
DA	Dopamine
DEC	Dose-effect curve
DSM-IV	Diagnostic and Statistical Manual, version 4, of the American Psychiatric Association
ED_{50}	Dose producing half-maximum effect
FR	Fixed ratio schedule of reinforcement
FR1	Fixed ratio 1 schedule, i.e., 1 operant response produces the reinforcer
ICD-10	International Classification of Diseases, version 10, of the World Health Organization
i.p.	Intraperitoneal
i.v.	Intravenous
LgA	Long access (6-hour self-administration sessions; [7])
MDMA	methylenedioxymethamphetamine
PIT	Pavlovian-to-instrumental transfer
PR	Progressive ratio schedule of reinforcement
S^D	Discriminative stimulus
ShA	Short access (1-hour self-administration sessions; [7])
S^P	Pavlovian stimulus
S^R	Secondary reinforcer
S^{R-}	Secondary negative reinforcer
s.c.	Subcutaneous
TO	Time-out (e.g. TO5s is a 5-second time-out)
VTA	Ventral tegmental area

Abbreviations for defined brain regions follow the nomenclature in Paxinos and Watson's rat brain atlas [182].

Introduction

Escalation of drug use is a hallmark of drug dependence [14, 254]. Escalation of drug use has traditionally been interpreted as reflecting the development of tolerance to the drug's effects, defined '*by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect* [or] *(b) markedly diminished effect with continued use of the same amount of the substance*' [14]. However, on the basis of behavioral data in laboratory animals, several groups have recently proposed alternative and sometimes mutually exclusive explanations, i.e. that such an escalation of drug use might not be based on (1) tolerance but rather be indicative of (2) sensitization to the drug's reinforcing effect [64], (3) reward allostasis [7, 131], (4) sensitization to the incentive salience of the drug-associated stimuli (i.e. sensitization to drug 'wanting') [27, 196], (5) an increase in the reinforcing strength of the drug reinforcer

relative to alternative reinforcers [4, 6, 98, 110] or (6) habit formation [80].

From the pharmacological perspective, models 1–3 (i.e. tolerance, sensitization and reward allostasis) allow predictions about the change in the shape of drug dose-effect curves (DECs) that are based on mathematically defined models governing receptor-ligand interaction and signal transduction [32, 104, 122, 123, 260, 262, 266]. These predictions will be tested below.

For the pharmacologist, the development of sensitization in drug dependence seems the most counterintuitive model, as it runs against the well-known and extensively documented fact that upon repeated administration, most in vitro, ex vivo and in vivo systems show tolerance to the effects of the tested compounds, in particular to the effects of μ-opioid agonists such as morphine or heroin [57, 58, 211, 212]. The development of tolerance is not restricted to opioids, with e.g. cocaine or nicotine producing less dopamine transporter inhibition after repeated administration [113]. Significant tolerance to opioid effects can even develop after only a single administration of a high dose, and 100-fold rightward shifts in opioid dose-effect curves (DECs) can be obtained under certain experimental conditions [58, p. 210].

That escalation of drug use by substance-dependent patients may be due to the development of sensitization to the drugs' effects is also hard to understand for the physician who, for example, is confronted with a methadone-substituted intravenous opioid user who still co-abuses opioids and marijuana and tries to convince the physician to prescribe enough flunitrazepam so that he can maintain his daily flunitrazepam dose at 10–30 mg, with the recommended hypnotic dose being 1 mg [Norbert Kriechbaum, pers. commun.]. Anecdotally, such methadone-substituted i.v. opioid users have often increased their daily consumption of the benzodiazepine flunitrazepam so much that they do not describe their benzodiazepine use in terms of individual tablets any more but in terms of bulk units, i.e. 'strips' containing 10 tablets each [Norbert Kriechbaum, pers. commun.]. To summarize, what the clinician often sees is a drug-taking pattern that seems much more indicative of the development of massive tolerance than of sensitization to the drug effects desired by the dependent user.

This review will describe the currently championed models used to explain the escalation of drug use in substance dependence. To enable a better understanding of these models, we shall first draw attention to the various components that constitute what the experimenter observes and calls 'reinforcement' – in its original meaning,

like 'tolerance' or 'sensitization', a purely descriptive term. We then intend to evaluate the nonhuman animal experimental approaches employed to support each of the currently championed models, evaluate the underlying changes in 'apparent reinforcement' components, and recapitulate the clinical evidence, which strongly suggests that escalation of drug use is predominantly based on an increase in the frequency of intoxication events rather than on an increase in the dose taken at each intoxication event. This review will conclude by making suggestions on how to improve the current behavioral experimental approaches. In the preparation of this review, it has become apparent that many of the central terms used in drug dependence research have acquired sometimes alarmingly different meanings for different subgroups or laboratories. Therefore, great care will be taken to present the original meaning of each of these central terms and to describe how their use has changed over time.

Several reviews are available which have discussed possible mechanisms underlying the observed changes in drug intake following chronic drug exposure or chronic drug self-administration [160, 231, 253]. The contribution of the present review lies in (a) evaluating the experimental evidence from the pharmacological perspective, in paying close attention to (b) the applicability of pharmacological principles to the behavioral experimental data and to (c) the shortcomings of the experimental approaches, and in (d) trying to integrate animal experimental with human behavioral and clinical data from a psychotherapeutic perspective. The two main conclusions of the present review are that (1) the clinical evidence strongly suggests that escalation of drug use is predominantly based on an increase in the frequency of intoxication events rather than on an increase in the dose taken at each intoxication event, and that (2) cocaine levels seem to be more tightly regulated at submaximum reinforcing levels than opioid levels are. Therefore, self-administering animals are more likely to expose themselves to higher above-threshold doses of opioids than of psychostimulants, rendering the development of tolerance to opioids more likely than tolerance to psychostimulants.

In order to help the reader evaluate the experimental evidence presented below, a number of definitions are in order. To begin, the term 'unit dose' (as opposed to a 'dose' in general) refers to a particular dose per drug administration event in an experiment during which different doses are tested (e.g. responding to an injection of a unit dose of cocaine of 0.01 vs. 0.032 mg/kg i.v.) or refers to the single dose administered per intoxication event.

Sometimes, the impact of the reinforcing effect of a drug on the organism's behavior is referred to as 'reinforcing efficacy'. This is a term that a pharmacologist would avoid, because in pharmacology, 'efficacy', or 'signal transduction efficacy' [264], is a numerically defined term (abbreviated 'e') that describes how small a fraction of the total receptor population an agonist ligand-receptor system needs to obtain its half-maximum effect. For example, an efficacy of 5 indicates that the receptor system under investigation needs only $1/5 = 0.2 = 20\%$ of the receptor population to obtain its half-maximum effect [91, 262]. The higher the efficacy, the higher the 'receptor reserve' or number of 'spare receptors' is said to be. Of note, μ-opioid agonists have a much greater efficacy in tests of drug reinforcement than in analgesia (e.g. alfentanil, 36-fold; nalbuphine, 208-fold [263]), indicating that (1) in order to inhibit a μ-opioid's reinforcing effect, one needs to block a much larger fraction of μ-opioid receptors than to inhibit its antinociceptive effect, and suggesting that (2) opioid reinforcement is mediated by more potent or more numerous amplifying system(s) than opioid analgesia. For example, alfentanil in rhesus monkeys has an efficacy of 391 in drug reinforcement, i.e. only 0.3% of the μ-opioid receptor population is needed for the half-maximum effect, versus 11 in a test of antinociception (50°C warm-water tail-withdrawal assay, i.e. 9% of the receptor population is needed [263]). Thus, there is numerical pharmacological proof that reinforcement mediated via μ-opioid receptors is vastly amplified through its own signal transduction cascade and/or other receptor systems downstream of the μ-opioid receptor system.

Finally, when describing evidence obtained from different experimental subjects, we should not forget that humans, like primates or rodents, are animals too (as in 'human primate' vs. 'nonhuman primate'). For the sake of brevity, however, we shall use the terms 'human' and 'animal' in the following.

Definitions of Tolerance and Sensitization, Dependence and Withdrawal

For the pharmacologist, 'tolerance' describes the experimental observation that upon repeated drug administration, the investigated system (be it an intact organism or an in vitro preparation) shows a decreased response to a constant dose of the drug. Thus, 'tolerance' is a purely descriptive term. This definition of tolerance has not changed over the years, in particular not over the last decade, as the comparison of the 1996 and 2006 editions

of arguably the most influential pharmacology textbook, *Goodman's & Gilman's Pharmaceutical Basis of Therapeutics*, reveals [38, 104]. In his chapter on drug abuse, Charles O'Brien [171, 172] differentiates innate (genetically determined) tolerance (i.e. decreased sensitivity to even the first dose of a drug – which for us would not be an accurate definition of tolerance, the development of which is based on repeated drug administration) from acquired tolerance [38, table 23-3]. Acquired tolerance can be divided into three types, based on the underlying mechanism: pharmacokinetic, pharmacodynamic and learned tolerance. According to O'Brien, pharmacodynamic tolerance refers to within-system changes, i.e. downregulation of receptor density and/or signal transduction efficacy resulting in a decreased overall efficacy of the drug [211], whereas learned tolerance refers to apparent tolerance that is due to a stimulation of compensatory systems acquired by past experience (one of us, G.Z., would suggest the term 'counterregulation-based apparent tolerance' as a better descriptor; see section on reward allostasis below). O'Brien [172] further divides learned tolerance into behavioral tolerance (i.e. the ability to compensate for the intoxicating effects of a drug, e.g. walking a straight line while under the influence of alcohol) and conditioned tolerance (i.e. pavlovian conditioning of compensatory physiological responses to drug-paired stimuli (cues) such as sights, smells or situations). Finally, O'Brien lists acute tolerance, i.e. tolerance developing rapidly with repeated use on a single occasion such as in a 'binge' (see also below). Acute tolerance is sometimes called 'tachyphylaxis'. O'Brien then proceeds to define 'sensitization' as 'reverse tolerance', i.e. as *an increase in response with repetition of the same dose of the drug'* [172, p. 611]. As examples of sensitization, O'Brien mentions laboratory animal findings on (1) cocaine-induced increase in motor activity and (2) cocaine-induced increase in nucleus accumbens dopamine release. Any mentioning of sensitization to the reinforcing effects of drugs of abuse is notably absent, even in the 2006 version of O'Brien's chapter [172]. 'Physical dependence' is defined as *a state that develops as a result of the adaptation (tolerance) produced by a resetting of homeostatic mechanisms in response to repeated drug use'* [172, p. 611]. He continues: 'Drugs can affect numerous systems that previously were in equilibrium; these systems find a new balance in the presence of inhibition of stimulation by a specific drug.' This definition of a 'new balance' is useful when considering reward allostasis (see below).

Traditionally, 'physical' dependence has been differentiated from 'psychological dependence', a separation that has not remained uncontested. To quote Eric Nestler: *'The traditional distinction between physical and psychological dependence is artificial, because both are mediated by the brain, possibly even by similar neural mechanisms'* [170, p. 995].

The degree of dependence can be observed and quantified in withdrawal. Withdrawal occurs after (a) discontinuation of the drug administration or (b) precipitation of withdrawal by antagonist treatment (e.g. naltrexone administered to chronic heroin users). A number of neurochemical, electrophysiological, molecular-biological and histological adaptations to chronic drug administration [6, 58, 132, 153, 170, 198, 217] can plausibly explain the multitude of withdrawal symptoms that, furthermore, are drug class specific [14, 254].

One of us (S.S.N.), however, argues that there is at present no a priori way to determine which (if any) withdrawal signs associated with a particular drug might influence the reinforcing effects of that drug. Accordingly, if one is interested in the impact of withdrawal on drug reinforcement, one should study the effects of withdrawal directly on drug-maintained responding.

To summarize, in the strictest pharmacological sense (i.e. pharmacodynamic tolerance or pharmacodynamic sensitization), 'tolerance' and 'sensitization' refer to drug effects (e.g. guanosine triphosphate-γ-S binding) that can only be measured after the drug has been administered (be that self-administered or passively received by the individual) and that are based on within-system changes in receptor density and/or signal transduction. However, in the animal behavioral experimental literature on drugs of abuse, the terms 'tolerance' and 'sensitization' have also been used to describe phenomena that require associative learning and that immediately precede (and/or accompany) drug administration (e.g. activation of physiological system to counteract the drug's sedative effect), or describe phenomena that may more remotely precede the actual drug self-administration (e.g. operant behavior that the animal emits in order to obtain the drug). To complicate matters, the phenomenon we call 'drug reinforcement' or 'drug reward' (terms originally used only to describe the fact that drugs of abuse produce an increase in operant responding) has now been demonstrated to consist of a considerable number of clearly distinguishable components (fig. 1). Thus, when evaluating any claim of an experimental proof of 'sensitization' or 'tolerance' to the 'reinforcing effect' of a drug or 'drug reward', one has to look closely which component of 'reward' or 'reinforcement' has actually been studied (fig. 1).

No Pharmacokinetic Tolerance for Psychostimulants or Opioids

Repeated drug administration may affect the pharmacokinetics of the drug itself. Thus, observed changes in behavior upon repeated administration of a certain drug dose may simply be due to changes in the effective drug concentration at the drug's site of action which are brought about by changes in the drug's absorption and/or distribution and/or elimination. The development of such a pharmacokinetic tolerance, also called 'dispositional' tolerance [184], would be the most parsimonious explanation for the escalation of drug consumption by human drug users. To illustrate, the same drug concentration would still produce the same effect at its site of action (e.g. the extracellular space surrounding the μ-opioid receptors in the cell membranes of neurons in the ventral tegmental area), it just happens that in the pharmacokinetically tolerant opioid user, less drug is present at this site (e.g. because of faster elimination from the brain). The proof of the development of substantial pharmacokinetic tolerance would thus save us the need to devise models and experiments that are based on a changed responsiveness of the individual upon repeated administration of the same dose, leading to the same drug concentration at its site(s) of action. Pharmacokinetic sensitization would mean that the drug concentration at its site(s) of action in the chronic drug user becomes consecutively higher upon repeated administration, producing a larger effect upon repeated administration of the same dose or causing the user to need less and less of the drug to produce the same effect. The evidence reviewed below, however, suggests that pharmacokinetic tolerance does not develop in chronic opioid or psychostimulant users, whereas some degree of pharmacokinetic sensitization may develop in chronic psychostimulant users.

Human volunteers receiving up to a final dose of 5 × 400 mg/day (i.e. 2,000 mg/day) of oral cocaine at the end of up to 16 daily sessions showed decreases in urinary elimination of cocaine (suggesting that elimination was slowed down and that higher cocaine concentrations remained in the body), resulting in pharmacokinetic sensitization [116] (see also animal data below). The same researchers also found cocaine elimination to be decreased in plasma and saliva of chronic street users compared to occasional users [157]. To complicate matters, it has been suggested that cocaine abuse may increase elimination of methadone in substituted patients [223].

Under controlled laboratory conditions, human volunteers who received up to 5 doses of 0.3 mg/kg oral amphetamine failed to show any changes in amphetamine pharmacokinetics [34], while reporting an increase in the subjective effects of amphetamine over the same 5 amphetamine administrations, i.e. these subjects did not show pharmacokinetic tolerance or sensitization while displaying sensitization to the subjective effects of amphetamine (see section on subjective effects below).

Because opioids are also used to treat chronic pain, accurate pharmacokinetic data are available for this drug class that have been obtained under conditions where the administered dose was precisely known, i.e. in pain patients under close clinical observation (as opposed to street users whose consumed drug dose can only be estimated). Chronic treatment with subcutaneous infusions of morphine (60–3,000 mg/day for 8–160 days) in terminally ill cancer patients [230] resulted in considerable intra- and interindividual variation of morphine pharmacokinetics with, however, no systematic changes occurring under this chronic morphine regimen. Large interindividual variation in pharmacokinetics is a well-known phenomenon of other psychotropic drugs as well. For example, the same dose of the antidepressant citalopram (i.e. a 20-mg tablet given once daily) resulted in citalopram plasma levels that varied 24-fold [139]. In another clinical study, long-term treatment of cancer patients over a period of 6–8 months, during which daily morphine doses had to be increased 10- to 20-fold, did not change the pharmacokinetics of oral morphine [202]. Similarly, the clearance of codeine, norcodeine or morphine was not changed after chronic codeine treatment [49].

To summarize the above human evidence, chronic (intermittent or continuous) opioid or psychostimulant administration does not seem to lead to any systematic changes in the pharmacokinetics of opioids. Interestingly, one group [116] reported that cocaine elimination was decreased in chronic users (i.e. pharmacokinetic sensitization might have developed), which would be expected to produce systematically increasing cocaine levels upon repeated administration of the same cocaine dose, thus falsely suggesting sensitization to cocaine's effects. However, it should be emphasized that the above opioid data were all obtained under conditions when the administered dose was known accurately, whereas only some of the psychostimulant data were obtained under such conditions. In contrast to psychostimulants and opioids, pharmacokinetic tolerance to other classes of drugs of abuse may occur. For example, enhanced elimination has been demonstrated in chronic nicotine users [184].

In a series of very thorough rat studies, Jay Justice and coworkers [186] noncontingently administered subcutaneous cocaine once daily for up to 30 days (10 mg/kg on days 1–5 and 20 mg/kg on days 6–10 or 6–30) and determined cocaine levels by microdialysis in the nucleus accumbens (Acb) and in the blood flowing through the right external jugular vein (with the aid of a microdialysis probe inserted into this blood vessel) after an intraperitoneal cocaine challenge. Peak cocaine levels in the Acb were increased by 86% after 10 days and by 56% after 30 days. Venous blood cocaine levels were increased by 60% after 10 days and by 180% after 30 days [186]. Cocaine concentrations in adipose tissue taken from the testes of these animals (epididymal fat pads) were not changed after 10 days of noncontingent subcutaneous cocaine [174]. Notably, pharmacokinetic parameters after an intravenous cocaine challenge (7.5 mg/kg i.v.) did not differ between cocaine-naïve rats and rats that had received cocaine once daily for 10 days [174]. The only pharmacokinetic parameter that significantly changed – an increase of only 50% – was the rate of absorption after an intraperitoneal injection of cocaine [174]. Justice and coworkers concluded: *'Enhanced cocaine concentrations in brain and blood observed after an intraperitoneal challenge dose in rats exposed to cocaine for 10 days by subcutaneous administration are traced to a change in the absorption process from the site of an intraperitoneal injection to general circulation'* [174, abstract]. This would constitute a form of pharmacokinetic sensitization that is, however, hardly relevant for intravenous cocaine users, because the modest (i.e. 1.5-fold) increases in cocaine elimination that were observed by Justice and coworkers in the rat model are insufficient to explain the considerable (i.e. up to 20-fold) escalation of daily cocaine use that can be observed in humans (see section on human drug abuse patterns). Similar to the data by Justice and his group [174] on the effects of chronic noncontingent cocaine on pharmacokinetics, cocaine pharmacokinetics in the Acb during self-administration sessions remained unchanged [10] in rats that had escalated their daily self-administered amount of cocaine 1.9-fold (i.e. rats that had had 6-hour self-administration sessions vs. control rats that had had only 1-hour sessions and, consequently, escalated their self-administered cocaine amount only 1.05-fold).

Thus, after reviewing the experimental evidence given above, we concur with Brian Cox's summary: *'Careful studies of the rates of metabolism and elimination of opiate drugs after chronic treatment with morphine have failed to find evidence of changes in the rates of drug absorption, metabolism or excretion of sufficient magnitude to account for the degree of tolerance developed'* [58, p. 210].

To summarize the animal experimental evidence discussed above, substantial pharmacokinetic tolerance or sensitization does not seem to develop during chronic psychostimulant or opioid exposure, following either contingent or noncontingent administration. Therefore, models that try to explain why drug-dependent humans escalate their drug intake – and try to prove their predictions in an animal laboratory setting – have to base these predictions on changes in drug responsiveness in general, and on changes in apparent drug reinforcement in particular.

Definitions of Reinforcer, Reinforcement, Reward and Punishment

'Reinforcement' and 'reward', like 'tolerance' or 'sensitization', are purely descriptive terms. The phenomena they endeavor to describe are based on a number of components that, if tested appropriately, tell us more about the underlying neural processes.

Although the terms 'reinforcer' and 'reinforcement' were originally coined by Ivan Petrovich Pavlov [181] to describe laboratory procedures used to reinvigorate the conditioned (originally, 'conditional') responses that had been weakened upon repeated presentation of the conditioned stimulus (CS) alone, it was Burrhus Frederic Skinner [215] who used the term 'positive reinforcer' to describe a stimulus (e.g. food) that 'increased or strengthened' the behavior that led to its presentation [for a recent review on the etymology of operant conditioning terms, see 73]. In contrast to a positive reinforcer, a 'negative reinforcer' is a stimulus that increases the probability of behavior that prevents its delivery (avoidance behavior) or terminates its delivery (e.g. terminates the delivery of a painful electric stimulus; escape behavior).

'Reinforcement' either denotes the operation (i.e. the delivery of consequences when a response occurs) or the process: 'the increase in responding that results from the reinforcement operation' [47, p. 71ff]. Although a reinforcer can thus be positive or negative, in the drug abuse research field, the term 'reinforcer' usually denotes a positive reinforcer unless stated otherwise. Of note, withdrawal symptoms can serve as negative reinforcers which increase the probability of behavior, i.e. taking the drug again, that avoids or terminates their occurrence (one of us, D.M., points out that the drug in this situation is the 'negative reinforcer', not the withdrawal symptoms).

Maintenance programs (also called 'substitution programs') for opioid-dependent patients [74, 133] are based on this premise.

Negative reinforcement must be distinguished from punishment, and punishers can be divided into two categories, positive or negative [252, citing 46, 47]. A positive punisher is a stimulus that, when presented, decreases the probability of the response that preceded it. In contrast to positive punishment, a decrease in the probability of a response as a consequence of the removal of a stimulus is termed negative punishment. Thus the difference between a negative reinforcer and a positive punisher (usually simply called 'punisher') is that a negative reinforcer increases the probability of behavior that leads to its termination or avoidance (see above), whereas a (positive) punisher decreases the behavior that leads to its presentation.

When applying these definitions to drug consumption, one of us (S.S.N.) would argue that drug injections technically function as positive reinforcers in typical drug self-administration studies, because responding produces them. One can hypothesize that the drug terminates an aversive subjective state in withdrawn dependent subjects, and that drug-induced termination of this hypothetical aversive state serves as a negative reinforcer. However, this hypothesis is not substantively different from the more general hypothesis that drug abuse evolves from efforts at 'self-medication' (e.g. to alleviate aversive states of 'anxiety' or 'depression'). While superficially appealing, the 'self-medication' approach to drug abuse research has not been especially fruitful, perhaps because the alleged aversive states have been so poorly defined. The concept of negative reinforcement may well be more useful in drug addiction research when the stimulus being terminated is more precisely defined. One of us (D.M.) concurs with S.S.N.'s argument only in that every reinforcer, including drugs of abuse, has both positive and negative reinforcing effects at the same time, and that these positive and negative reinforcing effects are not mutually exclusive, and are hard to differentiate and easily confused.

As put succinctly by Charles Catania [47], 'reinforcement' has occurred only if at least 3 requirements are met: (1) the response must have consequences; (2) the response must increase in probability, and (3) the increase must occur because the response has the consequences the researcher has identified and not for some other reason. When investigating drugs as reinforcers, the fulfillment of the third requirement is proved less often than one would like to think (e.g. the discussion on lever response stereotypy below, or, as D.M. points out, the scarcity of studies examining the effects of noncontingent administration of drugs in self-administering animals).

The term 'reward' does not have the strict operational definition that 'reinforcement' has, although it is often used to denote the same phenomenon. To quote Catania [45, p. 344], responses are reinforced, while 'organisms may be said to be rewarded'. In contrast to 'reinforcer', 'reward' always carries a positive connotation (i.e. there is no 'negative reward') and often refers to a stimulus that is considered 'good' by the experimenter, its positive valence being thought to produce positive reinforcement in operant conditioning paradigms. Sometimes, however, 'reward' is also used to denote the positive reinforcement process.

Since the pioneering studies of Jim Weeks [239], the drug abuse research field has avidly adopted operant conditioning approaches to assess the abuse liability of drugs: a laboratory animal is trained to associate an operant response, usually a lever press, with the delivery of a drug (usually by the intravenous route through an automated system). Because delivery of the drug under these circumstances is made contingent upon the response (e.g. lever presses) of the animal, this manner of drug administration is called 'contingent' administration or 'self-administration', as opposed to 'noncontingent' drug administration during which the animal receives the drug passively by the experimenter without having to emit a response (i.e. without having to 'work for the drug'). For practical purposes, the rates of responding maintained for the drug in these self-administration experiments are equated with the 'rate of responding' measure associated with the older (i.e. non-drug) operant literature and interpreted according to operant principles. Experimental schedules were generated that allowed the fast determination of complete unit dose-response (rate) relationships [244], because complete DECs are a prerequisite for the proper pharmacological analysis of underlying behavior. An important field of behavioral pharmacology was thus created.

The combination of operant conditioning and pharmacology, so important for the advancement of the drug abuse research field, has, on the other hand, created a number of interpretative problems. Among the 2 most common are (1) the tendency to rely on just one discipline while ignoring the other and, even more deleterious, (2) the inclination to usurp 1 of the 2 contributing disciplines without paying proper attention to its principles when interpreting the experimental data [266 and the ensuing debate]. For example, and as Richardson and Roberts

[191] point out in their review of progressive ratio schedules of reinforcement (see also below), the overall rate of drug self-administration usually shown in the self-administration literature has little to do with the 'rate of responding' measure in the original (i.e. non-drug-related) operant literature, which distinguishes a number of 'response rates' according to their temporal relationship with the reinforcer. As Richardson and Roberts state [191]: *'The most important* [of these various "response rates"] *is "running rate" which is the "sustained constant rate" prior to reinforcement.'* From the pharmacological perspective, the time span between the measured responses and the previous drug injection is of extreme importance, because the drug could, through its acute effects on systems other than those involved in mediated drug reinforcement (often called 'direct pharmacological' effects in the literature), impair the operant output (e.g. an animal sedated by the previous opioid injection will respond less vigorously to the next opioid injection). However, with the exception of a few articles dedicated to special aspects of drug reinforcement, most groups unswervingly continue to publish response rate data (1) that are averaged across the whole interreinforcement interval, and (2) apply this whole interreinforcement interval averaging to all unit doses tested, although, on pharmacokinetic principles, high drug concentrations that most likely produce acute drug effects which, in turn, confound the measurement of apparent reinforcement, are maintained for a longer period of time at a higher unit dose. Thus, simple experimental schedules that were originally introduced to generate a lot of data quickly are most likely flawed at a very basic level, both from the operant and the pharmacological perspective.

Components of Apparent Drug Reinforcement

Let us return to the phenomenon of 'drug reinforcement', that is, in the drug abuse field, most often implicitly equated with an overall increased rate of response to a certain unit dose of the drug: what the experimenter usually calls 'drug reinforcement' or 'drug reward' must be considered, as recently argued by Everitt and Robbins [80], Cardinal et al. [43] or Kent Berridge and Terry Robinson [26, 195], the composite function of a number of contributory factors.

In a 2002 review, Cardinal et al. [43] identified 6 components that constitute 'apparent reinforcement': (1) knowledge about the stimulus-response and action-outcome contingencies; (2) the incentive value (goal status) of the reinforcer; (3) the hedonic value of the reinforcer as it is experienced directly; (4) the effects of any conditioned stimuli associated with the reinforcer to promote responding via a process variously called 'pavlovian-to-instrumental transfer (PIT)' or the 'incentive salience of conditioned stimuli'; (5) stimulus-response habits, and (6) the effects of discriminative stimuli which can signal the instrumental contingency currently in force.

As an example of how careful one must be when using psychological constructs: Some of us (R.W.F., D.M.) emphasize that 'knowledge' cannot be directly assessed in the laboratory animal, and that 'experience' can be measured, 'knowledge' only inferred, while one of us (R.N.C.) disagrees, arguing that 'experience', too, can also only be inferred, and that 'knowledge' is clearly demonstrable, and suggests 'representation of information about' as a more generic term.

Kent Berridge and Terry Robinson parse 'reward' a little differently, i.e. into 3 major components [27, fig. 1]: motivation, learning and emotion/affect. Motivation consists in turn of two components: (a) cognitive incentives, i.e. wanting, which is conscious and can thus be put into words by humans (subjective ratings of desire), and (b) incentive salience, i.e. 'wanting' – note the quotation marks which indicate that it is unconscious. According to Berridge and Robinson, incentive salience can be measured by conditioned approach, autoshaping, PIT and cue-triggered relapse. Learning can also be dissociated into two components: (a) a cognitive one, i.e. reward expectancy and an understanding of the act-outcome causation (expressed by rational inference and verbal explanation), and (b) associative ones, i.e. conditioned stimulus-unconditioned stimulus associations, stimulus-response associations, and response-reinforcement associations; these associations can be measured by pavlovian conditioned responses and instrumental response reinforcement. Finally, Berridge and Robinson posit that reward-related emotion or affect also consists of two components: (a) conscious pleasure, i.e. liking (note the absence of quotation marks), which can be put into words and can thus be measured via subjective ratings of pleasure, and (b) a core hedonic impact, i.e. 'liking' – note the quotation mark which denotes its unconscious nature [27] – that can be measured by investigating facial affective expressions and human conscious 'liking' [27, fig. 1]. One of Berridge's and Robinson's contributions to the drug dependence research field consists in hypothesizing and providing supportive evidence for their assertion that the hedonic value of a reinforcer ('liking') and the incentive salience attributed to the conditioned stimuli

associated with this reinforcer ('wanting') are, in contrast to older psychological models of motivation [reviewed in 195], mediated by two different neural systems [195, fig. 2 for a schematic representation of the various psychological models]. Excessive incentive salience is experienced as 'craving' [195]. According to the evidence reviewed by Berridge and Robinson [24, 27, 195], 'wanting' seems to be proportional to the activation of mesolimbic dopaminergic systems, whereas 'liking' is not (see section on sensitization to the incentive salience of drug-associated stimuli below).

It should be noted that the incentive value of the reinforcer may be positive or negative. A positive incentive value makes a reinforcer 'attractive', i.e. its expectation elicits preparatory responses, also called appetitive responses (e.g. approach), with the animal eventually working for and approaching the positive reinforcer. A reinforcer with negative incentive value makes it 'aversive', i.e. produces avoidance responses if the organism expects the reinforcer or – if a negative reinforcer is presented – produces responses (e.g. retreat behavior or lever presses) that lead to its termination [80]. A drug may be attractive and aversive at the same time, as demonstrated in the literal sense for cocaine in the runway operant conditioning paradigm by Aaron Ettenberg and coworkers [96] who showed that rats displayed both appetitive (i.e. approach) and aversive (i.e. retreat) behavior for a cocaine reinforcer, with the benzodiazepine diazepam selectively decreasing retreat behavior, resulting in a net increase in 'overall approach' behavior. The co-occurrence of approach and avoidance (retreat) behavior for a cocaine reinforcer in the rat runway procedure has been confirmed and extended to opioids by some of us [235].

We also have to consider that the incentive value of the reinforcer is not only dependent on the reinforcer itself, but also on (a) withdrawal symptoms that the organism suffers from and that the consumption of the drug can relieve (see section on withdrawal, below); (b) the social consequences of drug taking (e.g. more attacks by cagemates due to drug-induced sedation), and (c) alternative reinforcers (see [100] for an example drawn from a vast literature, the discussion of which is beyond the scope of this review).

Using the same dichotomy as in the case of the incentive value of a reinforcer, a reinforcing stimulus with positive hedonic value is said to be 'liked', whereas a stimulus with negative hedonic value is 'disliked' [27]. This distinction is important when it is considered that drugs of abuse cause positive and negative subjective effects

that may be subject to the development of tolerance at different rates and to different degrees. For example [185], ex-smokers and non-smokers suffer almost equally from the 'unpleasantness' of smoking a cigarette (with current smokers displaying considerable tolerance to these unpleasant effects), whereas tolerance to the subjective effect 'headrush' is much more pronounced in ex-smokers (who resemble current smokers in that respect) than in non-smokers, with all three groups remaining equally sensitive to the 'feel drug' effect over a large range of nicotine plasma levels. It should also be kept in mind that the hedonic value of the drug can change instantaneously, whereas changes in the incentive salience of drug-associated stimuli and the incentive value of the drug need time and repeated drug exposures in order to change [43], although some of us (D.M., R.N.C.) would disagree with this assertion. R.N.C. emphasizes that the mechanism by which incentive learning occurs to 'update' instrumental incentive value with current hedonic value can be rapid.

To summarize the above discussion, observed changes in operant response to drugs, i.e. 'apparent drug reinforcement' – and its changes upon chronic drug use – are at least dependent on the following factors (fig. 1) that impact in a major way on the measurement of apparent drug reinforcement under controlled laboratory conditions. To emphasize, it is very hard to imagine that a single laboratory study could account for all these contributing factors. Thus, any study designed to test 1 or a few factors will, by necessity, have to control for the other factors. In order to allow the reader to better orient him/herself among this plethora of factors, one of us (G.Z.) has chosen to number them, while others (R.N.C., P.S.) object to doing so. Of note, some factors are a composite of others. Finally, as pointed out by R.N.C., the reader should be warned against believing that these 17 different factors correspond to 17 different processes. The factors are:

(1) Knowledge about the Action-Outcome Contingency
This is a prerequisite for operant behavior (although one of us, D.M., disagrees). One of us (G.Z.) would like to remind the reader that this 'knowledge' does not have to be conscious at all. One of us (D.M.) posits that operant conditioning certainly takes place whether or not an organism 'knows' it is happening and that, therefore, 'knowledge' is not important, or at least critical. Note also the discussion of the terms 'knowledge' versus 'experience' above. The contents of this knowledge will change during the course of chronic drug consumption as ac-

tion-outcome contingencies change. An example: someone finds out – either consciously or unconsciously – that consumption of a glass of prosecco has made it easier for her to talk to other people at social gatherings (knowledge about action-outcome contingency). She drinks at social gatherings as a result.

(2) Discriminative Stimulus Effects of the Drug

An example: experienced intravenous cocaine users know that the intensity of somatic symptoms (e.g. massive tingling and hot flashes crawling up the spine, high-pitched sound) that occur immediately (i.e. within 1–2 s) after the initial partial emptying of the syringe predicts the intensity of the desired central-nervous-system (CNS) effects ('high', 'kick'). They adjust the self-dosing of the rest of the cocaine that has remained in the syringe accordingly [261].

(3) Positive Hedonic Value ('Liking') of the Drug

An example: a newborn child, a monkey or a rat displays characteristic facial expressions and behaviors after presentation of a food considered highly palatable by most humans, indicating that it 'likes' the presented food [27]. These responses are correlated with the amount consumed, and disappear if an aversion to the food is later learned.

(4) Negative Hedonic Value ('Disliking') of the Drug

An example: when challenged with a quinine solution which tastes bitter and is aversive for most nonadapted humans, newborn humans, monkeys or rats show a characteristic pattern of facial expressions and behavior that is aimed at eliminating that liquid from the oral cavity [27].

(5) Withdrawal Symptoms as Negative Reinforcers and Discriminative Stimuli

Examples: The 'mid-week blues' (as negative reinforcer) renders the Ecstasy user more likely to consume methylenedioxymethamphetamine (MDMA) not only at weekend raves, but also in the middle of the week. Awareness of late-Sunday-morning headache (a caffeine withdrawal symptom often occurring in heavy workday coffee drinkers) reminds the individual that 'it might be time for a cup of coffee' (i.e. also sets the occasion for drug-seeking behavior, i.e. acts as a discriminative stimulus).

(6) Positive (Social) Consequences of Drug Consumption: Drug Consumption as an Operant Response Necessary to Obtain the Reinforcer 'Social Contact/Status', to Facilitate Social Contact or, in General, to Succeed in an Operant Task That Follows Drug Consumption

An example: most likely, every reader has experienced considerable peer pressure to consume alcoholic beverages at certain social events. In this context, alcohol cannot be regarded as the positive reinforcer, but alcohol consumption must be considered the operant response ('price') for obtaining the reinforcer 'social contact'. For an introduction to this important aspect of drug taking, the reader is referred elsewhere [11]. In a similar vein, Chris-Ellyn Johanson and coworkers [107] found that subjects with social anxiety showed a greater preference for 10 mg diazepam over placebo (single-blinded condition) than controls (82 vs. 36%) before a public speech talk but not before a computer task requiring vigilance.

(7) Negative (Social) Consequences of Drug Consumption

An example: animals that are sedated at the end of an opioid self-administration session are more vulnerable to cagemate attack upon being returned to the group cage. Knowledge of this contingency may well lower the positive incentive value of the drug. We are not aware of any experiments that tested this directly. At a more general level, Roland Griffiths and coworkers [210] provided evidence in the human behavioral laboratory showing that drug reinforcement can be modulated by the behavioral requirements following drug self-administration. In their experiments, human subjects were first given the opportunity to self-administer psychostimulant D-amphetamine or the benzodiazepine triazolam and were then subjected to a vigilance task or a relaxation task. The psychostimulant was selectively self-administered (i.e. preferentially chosen) if followed by the vigilance task, whereas the depressant was always chosen if followed by the relaxation task. By extrapolation, when an animal is put back into the group cage after the self-administration session (a situation requiring the animal's vigilance), the positive reinforcing of a sedative drug of abuse may be very differently affected than the positive reinforcing effect of a psychostimulant drug.

(8) Alternative Reinforcers

Example: the prospect of spending the evening, alert and not intoxicated, with an engaging date may well keep someone from intoxicating himself.

An impressive amount of research effort has been directed over the last two decades towards quantifying the effect that the availability of alternative reinforcers has on the apparent incentive value of a drug reinforcer.

The following two factors are actually a composite of factors 3–8 listed above. However, as they can be found as specific terms in the literature, they are listed as separate entities.

(9) Positive Incentive Value of the Drug (Positive Instrumental Incentive Value, Positive Skinnerian Incentive Value, Positive Goal Status)

Individuals will work for and approach a drug with positive incentive value. The positive instrumental incentive value of a drug corresponds most closely to what the field may call the drug's 'true' (as opposed to 'apparent') positive reinforcing effect. Please note that, for the sake of term symmetry, one of us (G.Z.) suggests that 'positive incentive value' may also be termed 'skinnerian incentive value' in order to better distinguish it from 'pavlovian incentive value' (factors 14 and 15) following the convention in the literature to differentiate 'pavlovian', i.e. respondent conditioning, from instrumental conditioning – which, by analogy, would be 'skinnerian' conditioning [93, 199]. To repeat, instrumental = skinnerian versus respondent = pavlovian. However, R.N.C. emphasizes that nobody refers to 'instrumental conditioning' as 'skinnerian conditioning', historical anachronism though that may be, and an additional term ('skinnerian incentive value') is not needed in what are to most people very muddy waters.

(10) Negative Incentive Value of the Drug (Negative Instrumental Incentive Value, Negative Skinnerian Incentive Value, Negative Goal Status)

As first demonstrated by Wise et al. [248], the same drug dose can possess both positive and negative incentive value, i.e. can be both attractive and aversive. An example: alcohol can induce considerable nausea at doses that are nevertheless consumed avidly.

The following items again describe individual (i.e. 'not further divisible') factors contributing to apparent drug reinforcement.

(11) Pavlovian Stimuli = Conditioned Stimuli Associated with the Drug

Previously neutral stimuli, after being paired with the drug reinforcer, elicit preparatory and consummatory responses as well as an affect [43]. An example: a smoker who is used to consuming a cigarette with his coffee pass-es by a café. He notices the smell of coffee wafting out of the café's door. He becomes more lively and approaches the door (preparatory responses), and lights a cigarette (consummatory response), eagerly anticipating the effects of the first draw (affect).

(12) Discriminative Stimuli = Conditioned Stimuli Associated with the Drug

A discriminative stimulus, while not being sought out in itself, indicates to the individual that a response will, in all likelihood, lead to the delivery of the drug reinforcer. An example: a smoker flying into the USA might 'not even think' of having that long-overdue cigarette when passing through US Customs & Immigration but may, while chasing a connecting flight, find 'time for one smoke after all' when going past a dedicated smoking area.

(13) Secondary Reinforcers = Conditioned Stimuli Associated with the Drug

In contrast to a discriminative stimulus, a secondary reinforcer is sought out in itself. An example: an ex-drinker may discover that he spends an increasing amount of time and effort, i.e. taking a more circuitous route on his way home, to again pass by the pub at which he used to have his after-work drink before he became abstinent.

The following two factors are a composite of factors 11–13. Again, as they are commonly used as specific terms in the literature, they are listed as individual entities.

(14) Positive Incentive Salience of Drug-Associated Stimuli ('Wanting', Positive Respondent Incentive Value, Positive Pavlovian Incentive Value) Attributed to the Conditioned Stimuli Associated with the Drug

'Wanting' (in quotes) refers to unconscious responses underlying the conscious wanting that a drug user can put in words. Example: you might find yourself wandering by the new coffee machine in the office corridor more and more often, although, if asked, you may not be able to give a reason for doing that. Some of us (R.N.C., G.Z.) would argue that 'wanting' essentially corresponds to the pavlovian stimuli associated with the drug (factor 11 above). However, as the terms 'incentive salience' and 'wanting' have been so vigorously introduced as a separate entity into the drug abuse literature by Kent Berridge and Terry Robinson [27, 195] and have been taken up so avidly by the field, 'incentive salience' is listed here as a separate term.
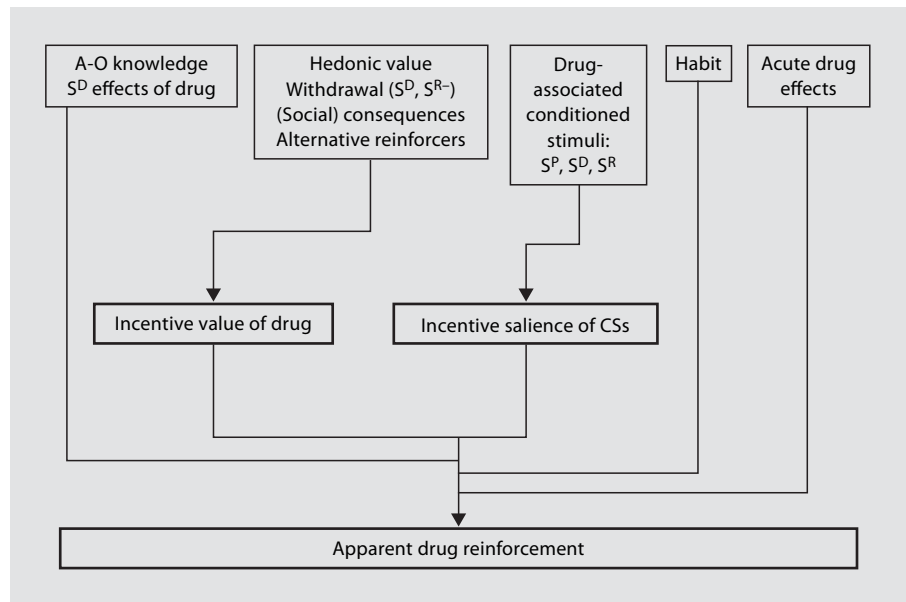
Fig. 1. Schematic diagram of factors contributing to apparent drug reinforcement. See text for details. A-O = Action-outcome contingency; CS = conditioned stimuli; S^D = discriminative stimulus; S^P = pavlovian stimulus; S^R = secondary reinforcer; S^{R-} = secondary negative reinforcer.

(15) Negative Incentive Salience of Drug-Associated Stimuli ('Avoiding', Negative Respondent Incentive Value, Negative Pavlovian Incentive Value) Attributed to the Conditioned Stimuli Associated with the Drug

Drugs may also produce effects that are aversive. An example: after having intoxicated yourself with a lime-scented alcoholic beverage to the point of vomiting, the taste of lime in a different, nonalcoholic beverage can make you avoid drinking this beverage.

(16) Habit/Compulsion Formation (Stimulus-Response Learning)

Habit formation is demonstrated experimentally by the persistence of operant responding upon drug reinforcer devaluation. A reinforcer is devalued by (self-)administering it to satiety before the test session. Example: a smoker finds himself reaching for his pack of cigarettes again and again, although he has smoked his usual daily number of cigarettes already, to the point of feeling sated with nicotine. Compulsive drug taking is defined by persistence in the face of adverse consequences. An example: a smoker, well aware that further smoking will worsen his bronchitis, still does not refrain from doing so. It is not currently clear whether compulsive drug use is qualitatively different, e.g. mediated by different neural systems, from drug habit formation. Therefore, both are subsumed under the same heading.

(17) Acute ('Pharmacological') Drug Effects

Example: an intoxicated drinker finds it difficult to get up and obtain his next beer from the bar, although he clearly desires another one.

Figure 1 (this review) shows a hierarchical order of some of these constituting factors, with independent variables at the top, dependent variables in the middle, and the composite 'apparent drug reinforcement' at the bottom of the schematic diagram.

Definitions of Saturation and Satiety

For the pharmacologist [123, 259, 260], 'saturation' means that essentially all receptors of the system under investigation are occupied by the drug under investigation (e.g. all μ-opioid receptors in a brain membrane preparation are occupied by the μ-opioid receptor agonist remifentanil). 'Saturation' should not be confounded with 'satiety', a word that has increasingly been used as a technical term in the drug abuse research field [80, 173, 226]. For example, Vladimir Tsibulsky and Andrew Norman [226] define the 'satiety threshold' for cocaine as 'the maximal level of cocaine at which the probability of self-administration approximates 1 and above which the probability of self-administration is low'. Any mentioning of 'saturation' or 'saturable' is notably absent in their seminal contribution [226].

The web site www.yourdictionary.com defines 'satiety' as *'the condition of being full to or beyond satisfaction'*. Its thesaurus lists 'engorgement, repletion, satiation, surfeit' as synonyms. The original Latin noun, 'satietas', with 'saturitas' as synonym, can be translated as *'sufficiency, abundance'* but also as *'the state of being glutted or sated; a loathing, a disgust, satiety'*. The Latin adjective 'satis' means *'enough, sufficient, satisfactory'*. Thus, 'satiety' originally described a state in which the consumption of a substance produces both positive and negative subjective effects. Extrapolating this definition to the drug abuse research field, 'satiety' can be defined as a state in which positive reinforcing effects (increasing behavior aimed at obtaining more drug), (positive) punishing effects (decreasing behavior aimed at obtaining more drug), and negative reinforcing effects (increasing drug aversion in a literal sense) are in balance – which is a state that may be far removed from the state at which consumption of a substance produces saturation of the receptor system(s) that this substance interacts with. This is exactly what seems to be the case in rat cocaine fixed-ratio 1 (FR1) self-administration experiments (see section on continuous vs. intermittent schedules of reinforcement below), during which cocaine is tightly kept at a level that seems to be much lower than that necessary to saturate the system(s) mediating apparent positive reinforcement (fig. 11, synthesis section). The tightly self-titrated cocaine levels [7, 238], most likely reflecting the tight balance between positive reinforcing, punishing and negative reinforcing effects, can be shifted towards higher self-titrated cocaine levels by chronic cocaine self-administration [7].

However, one of us (S.H.A.) considers that the proposition that cocaine is titrated at a level much lower than the saturation level is highly speculative. There is currently no empirical evidence that inspires such a speculation. Also, there is apparently no logical or functional link between the precision of drug titration and the concept of drug saturation.

Clinical Evidence

After eliminating pharmacokinetic tolerance as a major determinant of drug use escalation, at least in chronic psychostimulant or opioid users (see the section on definitions of tolerance and sensitization, above), we have to consider models which explain escalation of drug use by changes in drug responsiveness.

To evaluate better the strengths and weaknesses of each of the models detailed below in (a) explaining the escalation of drug use by human drug users and (b) predicting animal behavior under laboratory conditions, a recapitulation of the human situation seems worthwhile, the more so as it has recently been shown that self-reports of intravenous drug users about such basic aspects of drug consumption as the time course of subjective drug effects after an intravenous injection do in some aspects dramatically differ from the perception of drug abuse experts, researchers and therapists alike [261].

Human Drug Abuse Patterns

Interestingly, the two most influential clinical diagnostic standards, the International Classification of Diseases (ICD-10) [254] of the World Health Organization (WHO) and the Diagnostic and Statistical Manual (DSM-IV) [14] of the American Psychiatric Association (APA), emphasize that drug use by substance-dependent patients escalates at the expense of other, personally and societally beneficial activities (i.e. drug-unrelated occupational, social and recreational activities). These definitions suggest that dependent drug use is characterized better by a shift in time spent in drug-related versus non-drug-related behavior than in an escalation of drug use during a single intoxication event (which may consist of a single injection or a bout of closely spaced single injections called a 'binge', see also below). Such a shift from time spent in non-drug-related activities to time spent in drug-related activities can also be demonstrated in the rat behavioral laboratory (feeding vs. drug seeking during 23-hour lever-press/nose-poke sessions [48]; resting and scanning vs. drug seeking in the runway [235]). Accordingly, the DSM-IV explicitly requests the diagnosing physician/psychotherapist/clinical psychologist to specify whether the diagnosis of 'substance dependence' is associated 'with physiological dependence' or occurs 'without physiological dependence'. Thus, the DSM-IV acknowledges that full-blown substance dependence can be present without any clinical sign of tolerance or withdrawal. This is borne out by clinical evidence: In Wikler's classic study [242] *'of a patient during experimental self-regulated re-addiction to morphine'*, the subject was given unlimited access to intravenous injections of morphine (administered by the inpatient ward staff at the patient's request). Over the course of less than 4 months, he increased his daily dose of intravenous morphine 46-fold, from 30 to 1,780 mg/day (this review, fig. 2). Although the subject

Fig. 2. Forty-six-fold escalation of daily intravenous morphine consumption over less than 4 months under controlled clinical conditions. In Wikler's classic study [242], a previously opioid-dependent and then detoxified inpatient was given the opportunity to ask for intravenous injections of morphine at a dose of his choosing whenever he wanted. From October 17, 1947, to February 1, 1948, he increased his total daily morphine consumption (solid bars) 46-fold, i.e. from 30 mg (small circles) once daily to 115 mg (large circles) 12 times daily, totaling 1,780 mg/day (left-hand ordinate scale). The change in the temporal pattern of his morphine use is reflected by the changing distribution of individual doses along the ordinate (00.00–24.00 h, right-hand ordinate scale, top to bottom). After February 1, 1948, he was started on methadone maintenance (outlined bars = daily methadone dose). Reproduced from Wikler [242] with permission.
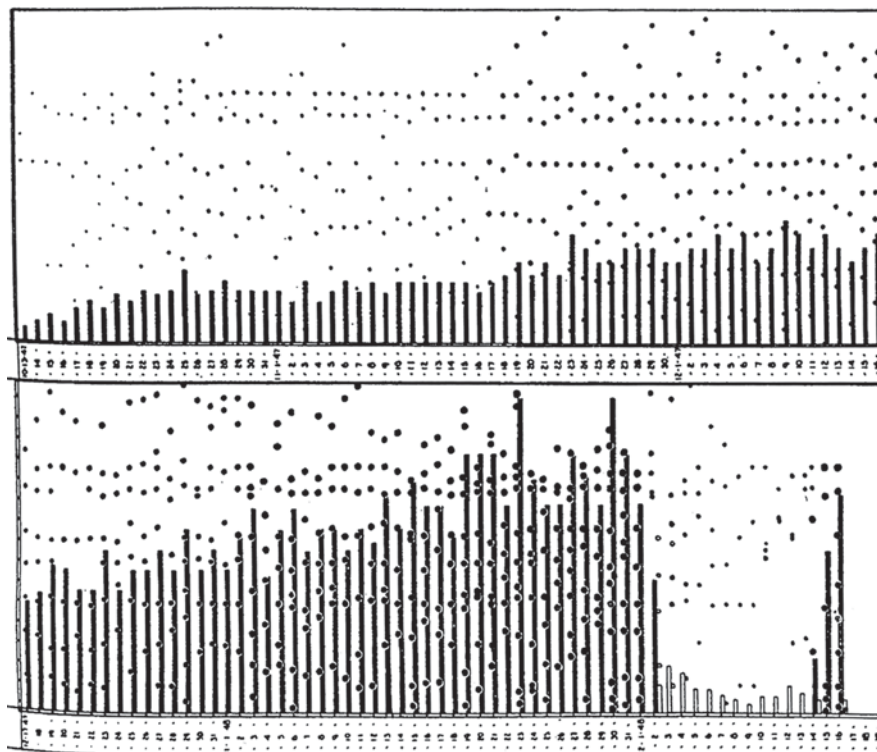
could choose both the unit dose (i.e. amount per intoxication event) and the dosing interval, he increased his unit doses only 3.8-fold, whereas his daily self-dosing frequency increased 12-fold [242]. Forty-nine years later, a study on oral MDMA abuse patterns of 40 users [90, 179] differentiated 'low' versus 'medium' versus 'high' MDMA use on the basis of at least 10-fold differences in lifetime use frequency (1–99 occasions vs. 100–499 occasions vs. ≥500, no mean or median numbers given), whereas the 'usual' number of tablets taken per occasion (2 vs. 2 vs. 4) or the maximum number of tablets taken per occasion (4 vs. 5 vs. 11) differed only about 2-fold between low and high MDMA users. Similarly, 9 intravenous cocaine users undergoing detoxification reported that their daily cocaine during the initial stage of their dependence ranged from 0.5 to 2 g/day, corresponding to 1–4 injections of 0.5 g cocaine/injection (purity unknown), whereas their daily cocaine doses before admission ranged from 10 to 20 g/day, corresponding to 10–20 injections of 1 g (purity unknown) each, taken in a binge-like pattern with interinjection intervals of 10–30 min [Ekkehard Madlung, unpubl. observation]. This corresponds to a ≤2-fold increase in cocaine dose per intoxication event, to a ≤10-fold increase in intoxication events per day, and

to a ≤20-fold increase in the daily cocaine dose. In another series of clinical interviews [261], drug users dependent on opioids and/or psychostimulants and/or MDMA and/or marijuana typically reported that they initially consumed the drug or drugs (opioid, cocaine or MDMA, or a mixture thereof, typically cocaine followed by heroin or morphine, or MDMA followed by an opioid or a benzodiazepine) only on weekends, then also in the middle of the week, with their drug consumption eventually spreading to a pattern of daily or almost daily use, whereas doses per intoxication event increased less (i.e. about 2- to 3-fold).

To summarize the above evidence, escalation of human drug use – both under controlled experimental and naturalistic conditions – seems to be based much more on an increase in the frequency and duration of intoxication events per 24-hour period than on an increase in the dose used per intoxication event. Thus, the development of pharmacological tolerance seems to contribute much less to the escalation of human drug use than to an increase in time spent in procuring the drug, consuming the drug and being intoxicated. In accordance with this finding, intravenous drug abusers who repeatedly presented for detoxification at the same inpatient ward over

the course of up to 7 years required only a 20% increase in the initial methadone dose required to treat their opioid withdrawal symptoms [145]. If one accepts that this initial methadone dose is an indirect measure of the amount of opioid abused per intoxication event, this patient population showed only a modest development of additional tolerance over the course of up to 7 years of intravenous heroin and morphine use, in sharp contrast to the 46-fold increase in daily morphine use by the subject in the classic Wikler study [242]. One might argue that the patients of the Madlung study [145] had already developed massive tolerance to opioids before their first detoxification and would thus develop no additional tolerance that could be assessed at subsequent detoxifications. However, the mean initial methadone dose at the first detoxification of these patients was 66 mg/day for men and 60 mg/day for women [145]. In comparison, drug-naïve humans would just survive an acute dose of 40 mg methadone, while usual methadone maintenance doses for dependent opioid users are in the range of 80–120 mg/day, and, anecdotally, a dose of 800 mg methadone was survived by a methadone maintenance patient [Ekkehard Madlung, unpubl. observation]. This corresponds roughly to a 20-fold increase in survivable methadone doses due to opioid tolerance, with the required methadone dose of the subjects in the Madlung study [145] being actually below that of many patients in methadone maintenance programs. Taken together, these data indicate that the degree of tolerance that the subjects of the Madlung study had developed before their first detoxification was not pronounced, and that they had in no way exhausted their potential to develop further opioid tolerance. Interestingly, the interadmission interval of the intravenous drug abusers remained at a remarkably stable interval of 17 months, i.e. the rate of the modest tolerance development did not increase over time [145].

Subjective Effects Indicative of Abuse Liability

Some of the models proposed to explain drug escalation by drug-dependent humans (see below) make predictions about the occurrence and/or direction of changes in baseline subjective states ('mood') and changes in drug-induced subjective effects. Again, it is worthwhile to review the human situation.

To repeat the evidence on human drug abuse patterns given above, the escalation of drug use by individuals seems to be based much more on an increase in the time spent in drug-related behavior than on an escalation of the unit drug dose consumed. Analysis of the intoxication event per se, however, suggests that tolerance or reward allostasis (see below) but not sensitization (see below) to the drug's subjective effects has developed. For example, Wikler's subject '... *maintained he had to increase his* [intravenous morphine] *dose because he wasn't getting the "hold" long enough, or intensely enough ...'* [242], a description of tolerance found in the most recent diagnostic standards, the DSM-IV [14] and the ICD-10 [254]. Most interestingly, however, the development of tolerance to the subjective effects of morphine seemed to depend on the type of subjective effect experienced by Wikler's subject: *'On the other hand, he continued to get 6 or 7 "thrills" per day (compared to orgasms) since he developed tolerance ...'* [242]. A similar dissociation, i.e. the development of pronounced tolerance to some subjective effects but not others, has also been demonstrated for nicotine [185].

Importantly, dependent drug use seems also to be associated with the development of tolerance to the negative drug-induced subjective effects [185]. This tolerance development may involve learning to appreciate the mood change associated with a drug (e.g. reporting caffeine-induced arousal more as 'energetic' rather than 'nervous') and may also reflect learning to ignore negative aspects of drug use such as being jittery after taking caffeine [Richard W. Foltin, unpubl. observation]. In a similar vein, current smokers report smoking a cigarette to be less 'unpleasant' than ex-smokers or nonsmokers, whereas all three groups report the same 'feel drug' effect [185]. On the other hand, there is evidence that sensitization develops to some negative effects such as psychostimulant-induced psychosis (see below).

There are a number of studies that report the development of between-session tolerance to the positive subjective effects in humans (e.g. methylphenidate effects in cocaine users [233] or methamphetamine in previously methamphetamine-naïve volunteers [55]).

Finally, within-session tolerance, also called 'acute tolerance', to the subjective effects of drugs has been amply demonstrated, whereas there is no experimental evidence for acute sensitization. Human use of intravenous or smoked cocaine typically occurs in 'binges', i.e. in bouts of repeated self-administration that might last from a few hours to several days [94]. It has been repeatedly shown that the subjective or cardiovascular effects of a single dose of intravenous or smoked cocaine decrease more rapidly than would be expected from cocaine's elimination half-life [51, 56]. Thus, the development of acute tolerance is a plausible reason why a binge use pattern is
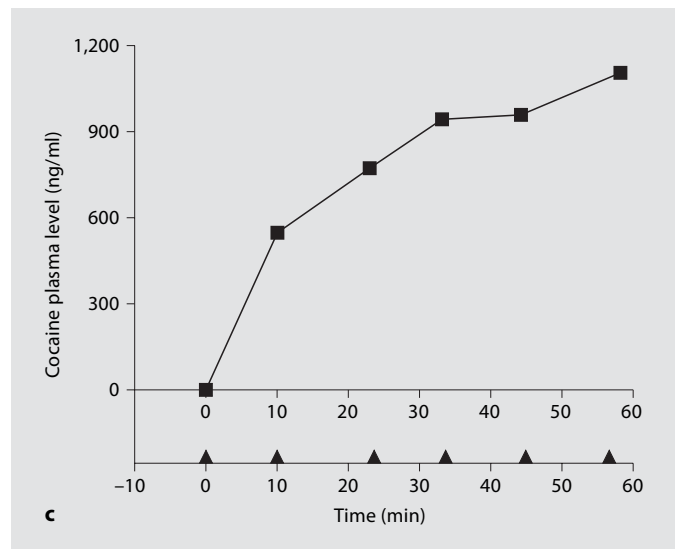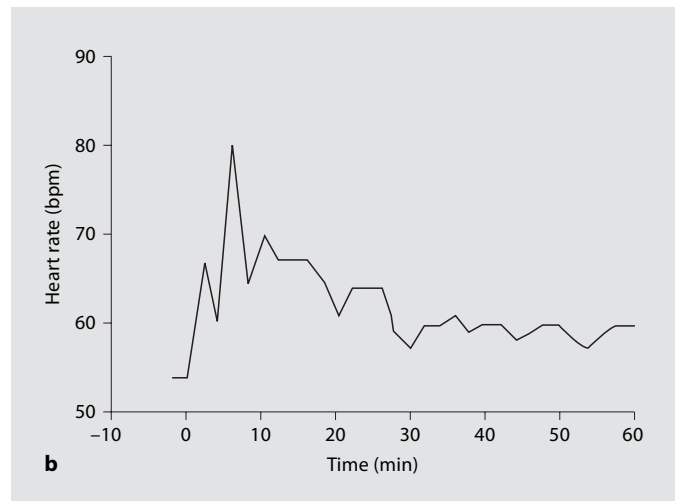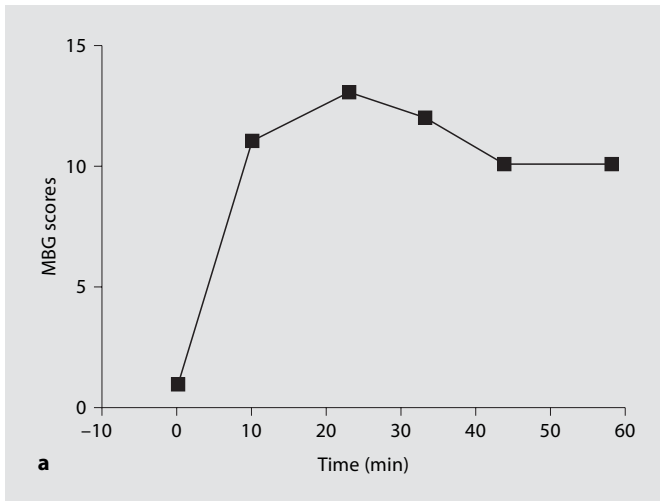
Fig. 3. Acute within-session tolerance to the subjective effects of cocaine. A human subject was given the choice between saline and 32 mg i.v. cocaine, and subjective effects as well as plasma levels of cocaine were determined. **a** MBG scores, i.e. subjective effects listed in the morphine-benzedrine group of the Addiction Research Center Inventory [146]; see also [35]. **b** Heart rate. **c** Cocaine plasma levels in nanograms per milliliter. Figure 4 from Fischman [85], reprinted with permission.

established. Cocaine users typically report that they are unable to achieve the initial euphoric feeling (often referred to as a 'rush' or 'kick') that accompanied the first cocaine dose with the subsequent doses, although they desperately 'chase' that first-dose euphoria [37, 225]. In laboratory settings, cocaine users show the greatest subjective and cardiovascular effects after the first or second cocaine dose, with subsequent doses maintaining, but not incrementing the initial effect (this review, fig. 3) [78, 89, 105].

In the first laboratory study on acute tolerance to cocaine, Fischman et al. [86] demonstrated that the effects of a single intravenous dose of cocaine, when administered 1 h after participants had received a single large dose (1.4 mg/kg) of intranasal cocaine, were significantly weak-er than when these had received a tiny dose (0.06 mg/kg) of intranasal cocaine. An elegant demonstration of acute tolerance was presented by Ambre et al. [13], who administered a single bolus dose of intravenous cocaine followed by a continuous cocaine infusion that maintained a stable cocaine venous plasma level: the subjective and cardiovascular effects of cocaine declined throughout the session [134]. Both Evans et al. [77] and Foltin and Fischman [88] examined the response to a range of intravenous and smoked cocaine doses given twice within a laboratory session. The cardiovascular and behavioral effects of intravenous and smoked cocaine were significantly greater on the ascending limb of the cocaine venous plasma concentration curve than on the descending limb, clearly demonstrating the development of acute tolerance [117].

Whenever sensitization to subjective drug effects was found, it was during the initial phase of drug consumption, i.e. when the drug consumer was learning to appreciate the drug's subjective effects. For example, novelty-seeking healthy volunteers who received up to 5 doses of 0.3 mg/kg oral amphetamine showed continuously increasing scores on self-reports of 'energetic', 'agreeable', 'confident', 'clearheaded' and 'alert' [34]. Interestingly, these subjects did not report any significant changes in amphetamine-induced euphoria, anxiousness and, to emphasize, drug wanting [34, 220, but see 234].

A notable exception to the absence of long-term sensitization to drug-induced subjective effects is methamphetamine-induced psychosis, which has also been shown to develop in long-term methamphetamine abusers who had consumed methamphetamine daily for an average of 6.6 years [201]. A similar phenomenon has been demonstrated for cocaine [21, 200]. However, as some of us (R.N.C., G.Z.) point out, psychotic symptoms may be more an indicator of cumulative neural damage than of sensitization (which would require intact neurons capable of increased responsiveness).

To summarize the evidence on changes of drug-induced subjective effects in humans upon repeated drug administration, any sensitization to the positive subjective effects of a drug of abuse seems to occur only in the initial phase, when the drug user learns to associate drug taking with positive effects and/or learns that peripheral effects, some of them intensely aversive (e.g. opioid itching), are predictive of the drug's centrally mediated subjective effects [261]. Once this initial learning phase is over, the majority of studies find only tolerance to the drug's positive and negative subjective effects. It is reasonable to expect that the development of tolerance to both the negative and positive subjective drug effects would lead to an escalation of drug consumption. Thus, to quote Richard Foltin: 'Initial sensitization studies may tell us more about learning than about drug effects' [unpubl. observation].

Incentive Salience of Drug-Associated Stimuli

A number of human behavioral experiments suggest that drug-associated stimuli become more salient to regular drug users [83]. Of note, these drug-associated stimuli may be not only external stimuli such as sights, sounds, smells, tastes or tactile stimuli associated with drug taking (e.g. a certain song playing on the radio, the sight of drug paraphernalia), but also internal stimuli such as affective states (e.g. dysphoria, anxiety or boredom). To quote Barry Everitt and Trevor Robbins: '*Drug cues, especially those associated with stimulants, have powerful motivational effects in human drug abusers, eliciting craving and engendering drug-seeking behavior*' [79, p. 20, original references cited therein].

Clinical Evidence: Summary

To summarize and extend the above clinical and human behavioral experimental evidence given above, the escalation of drug use by substance-dependent patients, which is predominantly based on an increase in the frequency of intoxication and, to a smaller degree, on an increase in the drug dose consumed per intoxication event, can be explained by at least the following factors (some of which have not been discussed previously): (a) an increase in withdrawal symptoms, serving both as discriminative stimuli and to increase the overall incentive value of the drug; (b) a decrease in the incentive value of alternative reinforcers; (c) a decrease in the positive hedonic value ('liking') of the previously consumed drug dose; (d) a decrease in the negative hedonic value ('disliking') of the drug; (e) an increase in the positive incentive value of the drug; (f) a decrease in the negative incentive value of the drug; (g) an increase in the positive incentive salience ('wanting') attributed to the conditioned stimuli associated with the drug; (h) a decrease in the negative incentive salience ('avoiding') attributed to the conditioned stimuli associated with the drug; (i) a decrease in the acute reinforcement-unrelated ('pharmacological') drug effects (e.g. sedation).

Limitations of Currently Used Animal Behavioral Experimental Approaches

Before proceeding to describe those models used to explain escalation of drug use that go beyond the descriptive level of 'tolerance' or 'sensitization' to 'apparent drug reinforcement' or 'apparent drug reward', we have to consider the limitations of the animal experimental models currently used to demonstrate them.

As stated above, drug 'reinforcement' or drug 'reward' is a behavioral composite of a considerable number of components that can be operationally defined. Thus, any experimental approach that (a) does not exclusively test one of these components or (b) does not provide a clear

differentiation of the individual 'apparent reinforcement' components – and none of the experiments reviewed below did – most likely yields inconclusive or, in the worst case, misleading data, especially when trying to model escalation of drug use in human substance dependence in the animal behavioral laboratory.

The most commonly used animal experimental approach to model dependent drug consumption uses operant conditioning experiments in which the animal is given the opportunity to emit a response (most commonly, a lever press or a nose poke) to obtain an intravenous infusion of the drug under investigation, with the rate of responding being the primary measure of the drug's reinforcing effect and, hence, its abuse liability. Most often, rats are used as experimental animals. For a variety of reasons, mostly economic ones, monkeys (rhesus monkeys, baboons, squirrel monkeys, etc.) are employed less often as experimental subjects than rats. Researchers who have experience with both rats and monkeys often assert that high rates of response to the same drug of abuse are much harder to obtain from rats than from monkeys. In order to increase the overall signal size of the dependent variable 'response rate', most researchers have resorted to (1) giving the animals only limited access to the drug (mostly only 1–3 h/day, as opposed to the 24 h/day availability under which Wikler [242] was able to demonstrate the massive escalation of morphine consumption in a human); (2) increasing the number of responses required for drug delivery (which brings operant response more under the control of the schedule of reinforcement rather than the acute effects of the drug and which, importantly, starts to measure drug 'seeking' more than titration of drug levels by the animal), and (3) preferentially investigating psychostimulant drugs of abuse which engender the highest rates of response. However, psychostimulants seem to have additional effects on motor systems that amplify goal-directed behavior, e.g. 'lever response stereotypy', which most likely contributes to the effects of stimulants, at least in rodents [reviewed in 191]. The possible impact of lever response stereotypy as a confounding variable – a reason why experiments on drug-induced reinstatement of responding will not be covered in this review – will be discussed in the sections describing the various models of drug use escalation (see below).

However, some of us (S.H.A., D.M.) disagree with the statement that cocaine-induced focused stereotypies are a serious concern in the interpretation of self-administration data in rats. Though it is true that most rats show behavioral stereotypies during stimulant self-administration, these are generally produced away from the operant lever [Serge Ahmed, unpubl. observations]. When a rat happens to press on the lever in a stereotyped manner, it is generally during the first days of acquisition but not during the maintenance of drug self-administration. Finally, stereotyped responding is associated with a very high level of time-out responses, a phenomenon that is seldom observed after acquisition.

Biphasic Dose-Effect Curves

In addition, the overwhelming majority of the experiments reviewed here did not test drug reinforcement in a drug-free state. In multiple-injection-based self-administration procedures, the drug administered during the initial phase of the experimental session may directly influence subsequent measures of 'reinforcement', especially if they are based on frequency of operant behavior (such as response rate). A direct pharmacological effect to decrease response rates may be the most parsimonious explanation for the fact that multiple-injection-based self-administration procedures typically produce dose-response relationships that are biphasic, i.e. are, according to the commonly used description of the field, shaped like an 'inverted U' [154, 266] – although 'inverted-V (Λ)-shaped' might be a better description. Especially for cocaine DECs, and especially at the level of the individual animal, typical self-administration DECs (fig. 4 and 6) show an ascending and a descending part, with response rates increasing with drug dose at low to intermediate unit doses, and decreasing again at intermediate to high unit doses. For the benefit of those readers who are less versed in the pharmacological principles governing behavioral pharmacological experiments, an overview of the possible shapes of DECs is given in figure 4.

DECs that look like an inverted V (Λ) at the individual animal level become more rounded when averaged across several animals in order to obtain group means [267]. Some [9, 226] argue that the descending part of the biphasic DEC is mainly due to the fact that the experimental animals aim for 'satiety' or a 'saturating' (see definitions above) drug level, i.e. argue that the individual titrates the level of drug in its blood or brain or other pharmacokinetic compartment, and that such a 'saturating' drug level is obtained at increasingly lower rates of response as the unit dose of the drug increases. Most importantly, such self-titration can be observed if cocaine is used as an experimental drug [9, 226, 238], but is not found with the μ-opioid agonist remifentanil, a compound that shares a number of pharmacokinetic features
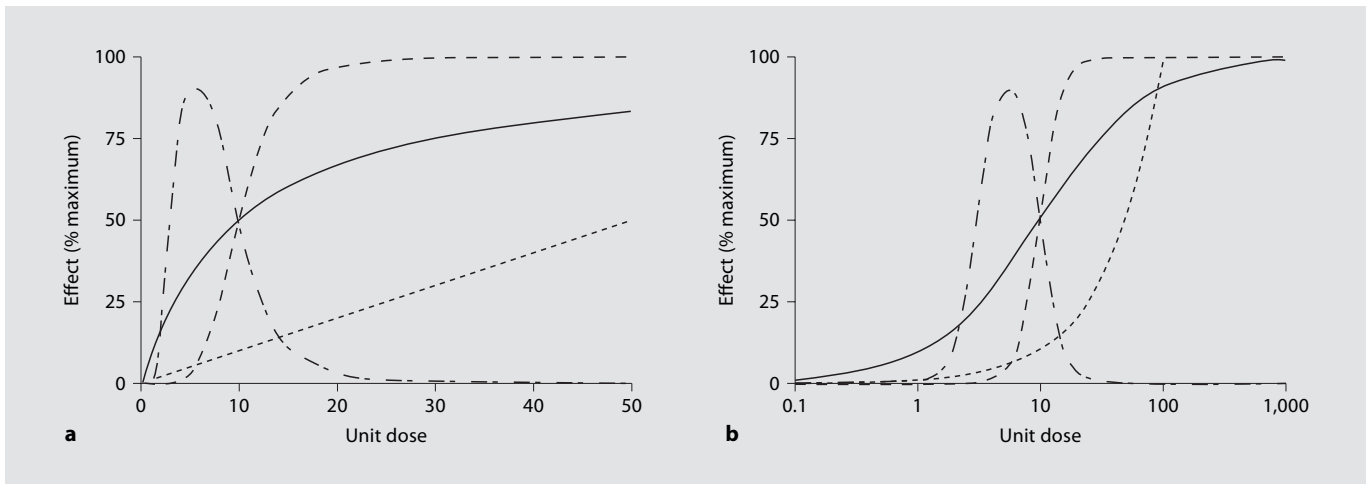
Fig. 4. Linear, monophasic sigmoid and biphasic DECs, plotted on a linear-linear scale, i.e. in a linear plot (**a**), or on a logarithmic-linear scale, i.e. in a semilogarithmic or 'semilog' plot (**b**). The semilog plot is typically used to describe dose-effect relationships in pharmacology, because it covers a wider range of unit doses than a linear plot could. The following dose-effect relationships were plotted: dotted line = the effect is linearly proportional to the unit dose (i.e. a linear DEC); solid line = the effect is a logistic function of the unit dose with the slope of the logistic function being unity, i.e. effect = (maximum effect · unit dose^{slope})/[(dose producing half-maximum effect)^{slope} + unit dose^{slope}] or y = $(E_{max} \cdot x^1)/(ED_{50}^1 + x^1)$. This equation describes a situation in which the observable effect is the result of the drug interacting with only one saturable receptor system. A receptor system is defined as a group of structurally identical binding sites which are linked to a homogeneous signal transduction system; if an agonist interacts with (i.e. binds to) these binding sites, the signal transduction system is activated, resulting in a cellular response; if an antagonist interacts with these binding sites, the signal transduc-tion system remains silent, and no cellular response results. Values used for generating this curve: E_{max} = 100, ED_{50} = 10, slope = 1. Dashed line = The effect is a logistic function of the unit dose, but the observed effect is the result of the drug interacting with 5 closely interacting saturable receptor systems. Consequently, the slope in the logistic equation is not 1 but 5. The DECs for a number of behavioral measures are as steep as this. Values used for generating this curve: E_{max} = 100, ED_{50} = 10, slope = 5. Dotted-dashed line = The observed effect is the function of the drug interacting with two systems, one increasing the effect (e.g. a response-rate-increasing effect), the other decreasing the effect again (e.g. a response-rate-decreasing effect). The resulting curve is biphasic and inverted-V- (Λ) shaped. Such curves are typically seen in self-administration experiments, especially in cocaine self-administration experiments using an FR1 schedule of reinforcement. Values used for generating this curve: E_{max}, ascending = 100, E_{max}, descending = 100; ED_{50}, ascending = 3, ED_{50}, descending = 10, slopes for the ascending and descending part of the DEC = 5.

with cocaine (this review, fig. 12; see synthesis section). In the case of remifentanil, careful analysis of the changes in drug concentrations during an FR1 schedule of reinforcement revealed that titration of the drug concentration (a) within the Acb as a deep brain region, (b) in total brain (including intracerebral vascular space and cerebral fluid) or (c) in blood does not determine within-session response [59, 60, 175]. This discrepancy (discussed in detail in the synthesis section) impacts in a major way on the fact that sensitization has been found much more often for psychostimulants than for opioids (see synthesis section).

In 2004, some of us (G.Z., E.M., C.H., A.S.) attempted to describe the biphasic shape by a simple 2-component pharmacological system, with the ascending phase determined by a sigmoidal (logistic) function relating the unit dose to its reinforcing effect, and the descending part based on a sigmoidal function relating unit dose to (un-specified) rate-decreasing effects of the drug [266]. This simple 2-component pharmacological model allowed predictions about the change in shape and direction of shifts of the biphasic DEC under various conditions, i.e. tolerance or sensitization to the reinforcing or the rate-decreasing effect of the drug. Applying this model to published self-administration data of chronically self-administering animals or animals self-administering drugs of abuse under agonist treatment, it was shown that a vertical upward shift of the dose-response curve accompanied by a parallel rightward shift of the descending part of the biphasic dose-response relationship could be explained more parsimoniously by tolerance to the rate-decreasing effect of the drug than by sensitization to its ap-

parent reinforcing effect [266]. The ensuing debate was lively and productive [8, 121, 168, 187, 197].

What did some of us (G.Z., E.M., C.H., A.S.) learn from the debate and the subsequent mathematical refinement of some of the opposing models [9]? First of all, we became convinced that the apparent reinforcing effect of a drug as determined in these types of experiments is actually a composite of a considerable number of different, operationally defined, components of which 'incentive salience' (i.e. drug 'wanting') is but one (see above and fig. 1). This makes multiple-injection self-administration experiments a rather blunt behavioral pharmacological tool that limits the investigation of the determinants of drug consumption to a superficial descriptive level. Kent Berridge and Terry Robinson went so far as to state that 'behaviorist reinforcement should not be mistaken to be an explanation of either drug-taking or drug addiction in either a physiological or psychological sense' [197, p. 352] in direct quotation of their earlier work. They continued: '... *we do not believe an upward shift (or a shift in any direction) in a cocaine dose-effect curve necessarily indicates sensitization to anything. If anyone else has said so, we think they might misunderstand incentive-sensitization theory.*' Although this is a radical position, it is a sentiment that will resurface at various points in this review. The behavioral pharmacological investigation of substance dependence is an immense task that must combine extremely diverse research fields (theoretical psychology, experimental psychology, pharmacology, neurochemistry, to name only a few) and, as drugs are pharmacological agents, must observe the principles and mathematical models used in pharmacology. It will be demonstrated later that, indeed, many experimental approaches have been too negligent with respect to pharmacokinetic factors and to the relative contribution of the various components of 'apparent reinforcement' to yield data that are amenable to meaningful interpretation from both extremes, i.e. the pharmacological as well as the psychological perspective.

As a point in case, the original assertion of some of us (G.Z., E.M., C.H., A.S.) [266] that the ascending part of the dose-response rate curve or dose-intake/time curve simply reflected the reinforcing effect of a drug was too simplistic: a host of factors influences its shape [8, 121], notably the response requirement if one chooses to employ intermittent schedules of reinforcement, e.g. fixed-ratio schedules with a response requirement of 5 or higher (i.e. FR5) or progressive ratio (PR) schedules. Under experimental conditions aimed at giving acute drug effects more weight as determinants of the observed apparent reinforcing effect, i.e. FR1 or FR2 schedules (see be-

low), mounting evidence suggests that rats, at least, either respond or do not respond to obtain the drug. Below a certain threshold unit dose, responding drops essentially to zero [9, 75], a feature explicitly expressed in the mathematical formulation developed by Glen Sizemore and Jeff Martin [214], or by the mathematical model developed by Serge Ahmed and George Koob [9] to quantify reward allostasis. This discontinuity of response for perithreshold unit doses in lever-press-based operant paradigms is confirmed by microanalysis of behavior in the rat runway, another operant conditioning procedure [235]: rats either commit or do not commit to running through an alley to obtain a reinforcer. Whenever they are committed, their running speed does not change. To our knowledge, the only evidence for a gradual increase in response rates on the ascending limb of the biphasic cocaine DEC under an FR1 schedule was obtained by Graham Florey and Jim Woods in rhesus monkeys [87]. The reasons for this discrepancy are currently unknown. However, even in rats, the inverted-V-shaped DEC obtained under an FR1 schedule of reinforcement (fig. 5b, reproduced from fig. 1 of [161], which shows only the descending part of the inverted V-shaped DEC; for a DEC showing the full inverted V, see fig. 6) can be transformed into a gradual increase over the same unit dose range if intermittent schedules of reinforcement, especially PR schedules, are used (this review, fig. 5a, reproduced from fig. 1 of [161]). Similar biphasic-to-monophasic DEC conversions have been demonstrated by other laboratories for cocaine [183, fig. 3], amphetamine [20, fig. 3], and heroin [237, fig. 3].

We posit that such a conversion from the inverted-V shape of the DEC, obtained under FR1 schedules of reinforcement, to a sigmoid monophasic shape, obtained under intermittent schedules of reinforcement, occurs because (1) at the construct validity level, PR schedules are more a measure of the apparent reinforcing effect of the drug than FR1 (or low FR) schedules, which are more a measure of within-session titration of drug levels than PR schedules, and because (2) drug-associated stimuli that have acquired discriminative stimulus effects or secondary reinforcer effects in intermittent schedules of reinforcement may maintain a response to drug unit doses that do not engender response under a simple FR1 schedule [see the articles in *Pharmacol Rev* 1975;27(3, 4)].

The simple pharmacological analysis provided previously by some of us [266] of DECs obtained in the multiple-injection self-administration paradigm was also jeopardized by the fact that it did not take pharmacokinetics into account but, in the simple form applied, was based on receptor-ligand interactions at equilibrium. It

Fig. 5. The shape of drug reinforcement DECs depends on the schedule of reinforcement used. Cocaine DECs were obtained before (squares; baseline condition) and after (diamonds) 10 days of a discrete trial procedure (DT4; four 15-min FR1 trials/h for 24 h/day) followed by 7 days of forced abstinence. **a** DEC under a progressive ratio schedule (ratio value progression: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, etc.). **b** DEC under an FR1 TO20s schedule (maximum of 40 obtainable reinforcers). Asterisks represent statistically significant increases from baseline condition. Figure 1 from Morgan et al. [161], reprinted with permission.
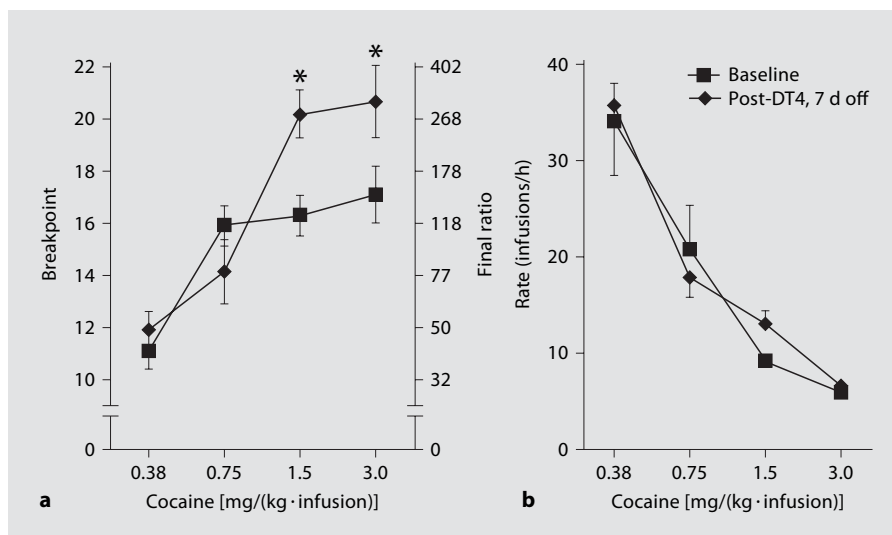
now seems that the mathematical model of reward allostasis [9], published 1 year after our incendiary letter [266], may explain the observed shape of the shifts in cocaine dose-response functions obtained under an FR1 schedule of reinforcement (in essence a drug self-titration procedure; see below) better than tolerance to the rate-decreasing effects of the drug. It certainly explains it better than sensitization to the apparent reinforcing effects of cocaine (fig. 6; but see the detailed discussion below), in particular because the model by Ahmed and Koob [9] (similar to the model by Tsibulsky and Norman [226] and in contrast to the model by Sizemore and Martin [214]) takes pharmacokinetics into account (i.e. the continuous within-session and response-dependent change of drug concentration during a self-administration session) whereas classic pharmacological models relating dose to effect are static with respect to the single experimental session [123], although they are suited to describe between-session changes in responsiveness [260, 262].

Most of us are still not convinced that sensitization to the 'true' reinforcing effect of the drug (i.e. its incentive value) was the mechanism underlying the observed changes in the cocaine dose-response functions detailed in our 2004 letter [266]. There are, however, researchers who persist in explaining upward shifts of DECs as obtained in the above-mentioned multiple-lever-press-based operant conditioning experiments as *'sensitization to the reinforcing effects of drugs of abuse'* [187], an assertion which we think is not supported by careful analysis of the relevant experimental evidence.

The Quest for the Sigmoid Dose-Effect Curve

To summarize the above discussion, the biphasic nature and inverted-V-like shape of DECs obtained in most operant conditioning experiments assessing the reinforcing effects of drugs of abuse is the bane of this experimental approach, inviting over- and misinterpretations and inciting infertile debates. From the pharmacological perspective, a biphasic DEC indicates that at least 2 opposing processes contribute to the variable chosen for measure [266], which complicates further quantitative analysis and interpretation (see the above discussion). On pharmacological principles, only a monophasic saturating DEC that (1) shows the typical sigmoid shape in semilogarithmic plots (with the logarithm of the unit dose given on the x-axis and the dependent variable plotted in a linear fashion on the y-axis; fig. 4) and that (2) can be fitted to a logistic equation with a slope factor ('Hill slope') of 1, i.e. if the dose range producing between 10 and 90% maximum effect is 81 [e.g. 2 responses/min for 0.01 mg/(kg·injection) cocaine, 18 responses/min for 0.81 mg/(kg·injection) cocaine, with the maximum response rate being 20 responses/min] can be thought to reflect the situation that the measured variable is dependent on the activation of only a single receptor system (although, theoretically, it could be many systems with low cooperativities adding up to 1, e.g. μ-opioid receptors and cannabinoid CB1 receptors with a cooperativity of 0.5 each) [for details of the practical application of pharmacological models, see e.g. 123, 260, 262]. A monophasic sigmoid DEC with a slope of 1 makes further pharmacological
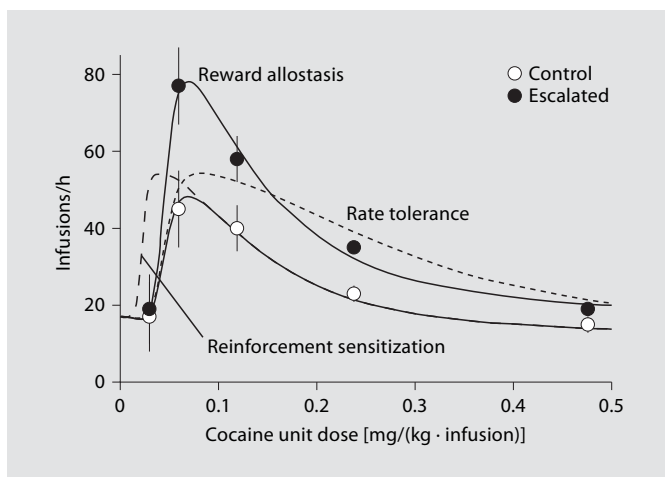
Fig. 6. Escalation of cocaine intake in chronically self-administering rats is more likely to be based on reward allostasis than on tolerance to the rate-decreasing effects of cocaine or sensitization to overall cocaine reinforcement when assessed in a cocaine self-titration procedure. Data obtained under an FR1 TO20s schedule of reinforcement by Serge Ahmed and George Koob [7, fig. 2C] was redrawn and fitted by hand to a two-system pharmacological model, i.e. a rate-increasing (roughly corresponding to 'apparent reinforcement', but consider the host of other factors impacting on rate of response) and a rate-decreasing system. Both systems were described mathematically by the general logistic function [33] that is thought to underlie dose-effect relationships. The following parameters gave the best fit for the control rats (open circles): baseline, 17 infusions/h; maximum effect of the rate-increasing system ($E_{max\ inc}$), 40 infusions/h; slope of the rate-increasing system ($Hill_{inc}$), 7; the cocaine dose at which the rate-increasing system was half-maximally activated by cocaine ($ED_{50\ inc}$), 0.046 mg/(kg·infusion); E_{max} of the rate-decreasing system ($E_{max\ dec}$), 45 infusions/h; slope of the rate-decreasing system ($Hill_{dec}$), 2.5; and ED_{50} of the rate-decreasing system ($ED_{50\ dec}$) 0.14 mg/(kg·infusion). Rats that had had 6-hour access to self-administered cocaine for 22 days (escalated, closed circles) showed a biphasic DEC that could best be fitted to the following parameters: baseline, 17; $E_{max\ inc}$, 80; $Hill_{inc}$, 7; $ED_{50\ inc}$, 0.046; $E_{max\ dec}$, 80; $Hill_{dec}$, 2.4, and $ED_{50\ dec}$, 0.13 (units see above). Thus, the only parameters that had to significantly change (i.e. double) to fit the dose-effect curve of the escalated rats were the maximum effects of the rate-increasing and -decreasing systems, i.e. the number of infusions/h. This fit corresponds well to the overall 1.3- to 2-fold increase in cocaine intake observed by Ahmed and Koob [7, fig. 2D] (see also fig. 12) across all cocaine unit doses. The reward allostasis model predicts such an upward shift in the DEC's maximum [9, fig. 7A]. In contrast, doubling the apparent reinforcing potency of cocaine [i.e. decreasing $ED_{50\ inc}$ from 0.046 to 0.023 mg/(kg·infusion); dashed line] – which would correspond to sensitization to cocaine's apparent reinforcing effect – or halving the potency of cocaine's rate-decreasing effect [i.e. increasing $ED_{50\ dec}$ from 0.14 to 0.28 mg/(kg·infusion), dotted line] – which would correspond to tolerance to cocaine's rate-decreasing effects – was far less successful in fitting the experimental data. However, it should be kept in mind that an FR1 schedule of reinforcement is essentially a drug self-titration procedure (see text).

analysis (e.g. antagonist experiments followed by proper Schild analysis [16] to unequivocally determine the underlying receptor system) easier to evaluate, although the Schild analysis can be properly applied also to those dose-response relationships that are not simple monophasic functions described by a logistic equation with a slope factor of 1 [28, 123, 251]. Limited-access and multiple-injection-based self-administration procedures are certainly not the correct experimental approach to obtain such a monophasic DEC. Griffiths and coworkers [101] were able to obtain monophasic benzodiazepine DECs in baboons by enforcing a 3-hour time-out (TO) after each injection, thus allowing the benzodiazepine to be eliminated to a substantial degree before remeasuring operant response. Similarly, Olmstead et al. [173] have demonstrated that responses to higher doses of cocaine (i.e. 0.78 and 1.5 mg/kg i.v.) were monotonically increased by increasing the TO from 0 to 4 to 12 min (80% of brain cocaine eliminated with a half-life of 1.6 min; see synthesis section). In order to obtain a reasonable number of data points, however, they had to extend the experimental session to close to 24 h. It seems that if one intends to keep to continuous or intermittent schedules of response (see below) for the investigation of drug reinforcement, such an unlimited-access approach [158–160, 193] in which the intertrial interval allows for extensive elimination of the drug between infusions (ideally, >4 elimination half-lives) seems the most promising to obtain monophasic DECs. Accordingly, Everitt and coworkers [15] restricted the analysis of their second-order schedule data to the first, drug-free interval precisely in order to avoid any confounding direct pharmacological drug effect (see section on second-order schedules).

However, a simple monophasic DEC does not rule out that 2 opposing systems, for which the investigated drug has equal affinity (i.e. binds to both receptor systems at the same half-maximum concentration or dose), were summed up to produce the apparent monophasicity. When considering rate-dependent measures of reinforcement, with the 'reinforcement' system increasing response rates and an opposing rate-decreasing system lowering them, the resulting maximum response rate would depend on the relative contribution of each of the 2 opposing systems. In such a system, tolerance to the rate-decreasing effect would show up as an increase in the maximum effect and a steeper DEC, with changes in response that are small in the low-unit-dose range and large in the high-unit-dose range (not shown).

When evaluating data obtained by progressive ratio schedules of reinforcement – which at a superficial glance

do most often yield monophasic DECs (but may also show a downturn at high unit doses, i.e. a decrease in breaking points when high to very high unit doses are compared [176]) – one should look closely at the y-axis: often, the number of injections rather than the completed number of responses ('breaking points' or 'breakpoints', see below) are plotted on the y-axis (this review, fig. 10). However, in a PR schedule the number of responses to be completed for each injection is very often programmed to increase exponentially [191] from injection to injection. Thus, plots like figure 10 should be considered logarithmic-exponential plots rather than logarithmic-linear (i.e. semilogarithmic) plots. After transformation of these logarithmic-exponential to logarithmic-linear plots, it often becomes obvious that the dependent variable (i.e. the breaking point) either linearly or exponentially increases with unit dose until the breakpoint-unit dose relationship reaches a ceiling (fig. 3 and 9). Obviously, PR schedule dose-effect relationships cannot be described by the logistic equation that would be required for proper pharmacological analysis of the underlying receptor/signal transduction systems.

Some of us (S.S.N., G.Z.) point out that choice procedures uniformly generate monophasic DECs [163, 164].

Conditioned place preference paradigms also seem to come close to producing monophasic DECs for many compounds, with the notable exception of cocaine [19]. Similarly, in the operant conditioning paradigm of the rat runway (which simply consists of a start area, a straight alley, and a goal area, in which the rat receives the reinforcer once it has traversed the alley [61, 95, 235]), overall runtime shows monophasic DECs for many compounds, again with the notable exception of cocaine [235]. However, straightforward interpretation of runway data is complicated by the fact that overall runtime is determined by (1) the latency to leave the runway, indicative of the positive incentive value of the drug and the incentive salience attributed to the drug-associated conditioned stimuli if any are presented, (2) retreats, indicative of the drug's negative incentive value, and (3) the time span needed to traverse the runway alley, indicative of the drug's positive incentive value and the incentive salience attributed to the drug-associated conditioned stimuli, and motor performance.

The rat runway example illustrates that even if the overall measure of the drug's reinforcing effect yields a monophasic DEC, this does not necessarily mean that the activation of a single receptor system underlies the observed behavior. One also has to look at the slope of the monophasic DEC: if the dose range producing 10–90%

maximum effect extends over less than a unit dose range of 81 (e.g. from 0.01 to 0.81 or from 0.1 to 8.1 mg/kg cocaine, a positive interaction of at least two receptor systems must be expected. The ascending parts of cocaine DECs, for example (fig. 5, 6, 10, and 12), usually extend over much less than a unit dose range of 81.

Continuous versus Intermittent Schedules of Reinforcement

The response requirement for the delivery of the drug can also be varied. At one extreme, each response is followed by drug delivery, in an FR1, i.e. a continuous reinforcement (CRF) schedule. The FR1 schedule gives much more weight to the contribution of acute (i.e. 'direct pharmacological') drug effects as opposed to drug 'reinforcement', which per definition requires multiple exposures and associative learning (D.M., however, would argue that FR1 schedules, by requiring the experimental subject to give an all-or-none answer, are very good for determining whether a drug is reinforcing or not). Consequently, FR1 schedules are preferred by those researchers who investigate whether within-session titration of drug levels occurs [9, 59, 60, 175, 226, 227] but are much less useful – exactly because of confounding acute drug effects on responding – when trying to assess the 'true' reinforcing effects of a drug, i.e. the incentive value of the drug and the incentive salience of drug-associated stimuli (fig. 1). To quote Dave Roberts: *'In this case* [i.e. an FR1 schedule], *rate of responding largely reflects rate of consumption. Although such rates can be sensitive to changes in motivational state, it would be a mistake to estimate reinforcer magnitude based on rates of consumption'* [191, p. 7].

In intermittent schedules of reinforcement, the individual has to emit several responses to obtain a reinforcer. Whenever FR schedules of reinforcement are used, rats are commonly trained to emit a maximum of only 5 responses to each reinforcer (FR5), whereas monkeys are able to fulfill response requirements of up to 30–100 (FR30–FR100) or even higher. Unit dose/response rate relationships obtained under these schedules of reinforcement are usually biphasic. Some of us (R.N.C., D.M.) point out that the above interspecies comparison is misleading, because rats are well capable of fulfilling response requirements of at least FR40, provided that the experimental design and training are adequate.

Progressive Ratio Schedules

A special form of an intermittent schedule of reinforcement is the PR schedule (see Richardson and Roberts [191] for a methodologically insightful review). In this schedule, the individual has to emit increasingly more responses to each subsequent drug delivery (i.e. 1 response to the first cocaine injection, 2 responses to the second cocaine injection, 4 to the third, 6 to the fourth, 9 to the fifth, … 32 to the tenth, … 268 to the twentieth injection, etc.). Many current PR schedules use exponentially increasing response requirements. At some point, the individual stops responding to the drug stimulus. The 'breaking point' or 'breakpoint' is sometimes defined as the response requirement at which responding fails; sometimes those terms refer to the last completed response requirement [191], or sometimes to the number of reinforcers obtained in a session (D.M.).

PR schedules seem much less vulnerable than FR schedules – in particular, the FR1 schedule – to acute rate-decreasing effects of the drug, be that a rate-decreasing effect due to impairment of motor output or a reflection of a self-titration process [9, 226]. As an example, in rats self-administering essentially the same cocaine unit doses, i.e. 0.18–1.5 mg/(kg·injection) under a PR schedule versus 0.37–3 mg/(kg·injection) under an FR1 schedule, an ascending DEC was obtained with the PR schedule, whereas a descending dose-effect function was seen under the FR1 schedule [194]. Another example of this DEC shape conversion [at cocaine unit doses ranging from 0.38 to 3.0 mg/(kg·inj.)] was shown by Morgan et al. ([161, fig. 1], reprinted here in this review as fig. 5; see also section on biphasic DECs in multiple-injection-based self-administration paradigms, above).

For many drug abuse researchers, the PR schedule has very good face validity with respect to the instrumental incentive value of the drug, but may, like the multiple-injection FR schedules, be seriously jeopardized by confounding acute pharmacological effects. In addition, because of the continuously increasing interinfusion intervals (inherent in the schedule) at any constant unit dose, the drug brain concentration at which the response requirement is (or should be) fulfilled is continuously changing, whereas, in principle, it can remain the same in an FR or fixed-interval (FI) schedule once the drug's steady state is reached. Now, some drugs of abuse, notably opioids at higher doses, produce sedation, thus impairing motor output – which is especially important in PR schedules that depend on the ability of animals to sustain responses for increasingly longer durations – while others,

notably psychostimulants, stimulate motor output, which may even incorporate lever responding that is not drug reinforced [232]. This effect has been termed 'lever response stereotypy' [191; for a different view on the increase in non-drug-reinforced responding in animals previously exposed to noncontingent amphetamine, see Vezina, 231]. It is easily conceivable that sedation by the opioid doses introduced in quick succession during the first infusions (when response requirements are still low) may depress subsequent operant responding (as demonstrated), while psychostimulants are able to stimulate operant responding until response requirements become so high and, consequently, interinfusion intervals become so long that the psychostimulant levels fall below a critical level, ending acute motor stimulation of the operant response, and causing responding to stop. This is a plausible explanation for the well-known fact that the PR schedule strongly favors psychostimulants over opioids. Indeed, as Richardson and Roberts emphasized in their methodologically very thorough review [191, p. 8f], his group was unable to generate meaningful opioid data in a single PR session with PR schedules successfully used for cocaine: *'Clearly, the PR series developed for cocaine self-administration (beginning with one and escalating exponentially with each subsequent drug injection) was ineffective for evaluating the initial motivation to seek opiates.'* Interestingly, Panlilio and Schindler [176] were able to obtain DECs in single-session PR experiments for both heroin and remifentanil, a μ-opioid agonist with an extremely short elimination half-life, i.e. 0.3 min in rat blood and 10 min in rat Acb [60]. Although there have been efforts to investigate and discount these confounding variables [191], one of us (G.Z.) is still not convinced that pharmacokinetics and likely differential effects of psychostimulants versus opioids on lever response stereotypy have been excluded as confounding variables to a satisfactory degree. We would therefore suggest that, in future PR experiments, the acute drug effects on motor output should be minimized by imposing TOs that equal ≥4 elimination half-lives of the drug, which can be accomplished without an unreasonable extension of the session length by employing drugs of abuse with short elimination half-lives, e.g. cocaine or remifentanil, which are eliminated from brain structures such as the Acb with elimination half-lives around 10 min [59, 61, 108]. However, one of us (D.M.) warns that if TOs were kept that long (i.e. 40+ min), cocaine would not maintain breakpoints above ratios of 10 or more.

Richardson and Roberts [191] also emphasized that in order to get the animal 'started' to respond to a psycho-

stimulant on a PR schedule, very often a 'priming' infusion (i.e. a noncontingent administration of the drug at the beginning of the experiment) is necessary. One of us (D.M.) points out that Dave Roberts no longer uses priming injections, but that many researchers still do. Keeping in mind that psychostimulant-induced lever response stereotypy (see above) may represent a significant confounding variable, the necessity – and common experimental practice – of administering a priming dose seriously jeopardizes the face validity of the PR schedule for explaining human drug use escalation. For the therapy of human substance dependence, the situation in which a user craves the drug in a drug-free state (i.e. before a relapse which sometimes occurs after long periods of abstinence) is of more interest and possible therapeutic benefit than the situation in which the user has begun a binge and is unable to stop it.

Finally, some of us would argue (D.M., R.W.F., G.Z.) that PR schedules model fairly well the hallmark of human substance dependence, i.e. an increased percentage of time spent in drug-related activities. In PR schedules, increasing the response requirement usually leads to longer periods of responding and not to an increase in reinforcement frequency, i.e. the experimental animal has to allocate an increasing fraction of its time to obtaining the drug. In contrast, some (R.N.C.) would argue that in this respect, PR schedules are not intrinsically superior to other intermittent schedules of reinforcement.

Second-Order Schedules and Tandem Schedules

Another special form of intermittent schedules of reinforcement are second-order schedules of reinforcement [for a recent review, see 79]. In this schedule, the individual, human [135] or animal, responds ('works') to the presentation of a drug-associated stimulus (i.e. a secondary reinforcer). The drug itself (i.e. the primary reinforcer) is made available only after several of these drug-associated secondary reinforcers have been obtained. For example, the term 'FI10 min (FR30:S)' describes a second-order schedule in which the animal has to emit 30 responses to obtain the drug-associated stimulus (often, the illumination of a cue light). If at least 1 such 'component schedule' or 'unit schedule' is completed after the 10-min time period of the fixed interval has elapsed, the animal receives the drug itself [15, p. 333]. Arroyo et al. [15] have successfully used an FI15 min (FR10:S) second-order schedule to obtain an almost linear monophasic cocaine DEC ranging from 0.24 to 1.5 mg/(kg·infusion)

cocaine [15, fig. 3A]. However, to our knowledge, data on overall drug reinforcement under second-order schedules before and after chronic drug self-administration are still lacking.

Barry Everitt, Tony Dickinson and coworkers used another schedule of reinforcement, a tandem schedule, to (a) obtain monophasic DECs for cocaine and (b) separate cocaine 'seeking' from cocaine 'taking': using a multiple [chain (tandem FR1 random interval 30 s) FR] TO schedule, in which rats had to press a 'seeking' lever to gain access to a 'taking' lever which had to be pressed in turn for drug delivery, Olmstead et al. [173] found that responses monotonically increased for the cocaine doses of 0.25, 0.78 and 1.5 mg/kg i.v., whereas, interestingly, the latency to start emitting these responses also increased monotonically. If, however, the TOs between each of the trials were increased, this latency to respond decreased for the two higher cocaine doses, which was taken by Olmstead et al. as an indication that between-trial elimination of cocaine significantly influenced overall response: *'More likely, the TO period allowed the short-term satiety effect produced by the preceding infusion to dissipate before the animal had the opportunity to re-engage in drug seeking'* [173, p. 129].

Continuous versus Intermittent and Contingent versus Noncontingent Drug Administration

The modes of drug administration used to mimic chronic drug abuse, i.e. chronic versus intermittent and contingent (i.e. self-administered, voluntary) versus noncontingent (administered to the animal by the experimenter), also influence measures of drug reinforcement in animals. Kleven and Woolverton [128] were able to show tolerance to the apparent reinforcing effect of cocaine in rhesus monkeys (as evidenced by a parallel rightward shift of the descending part of the cocaine DEC in a food and cocaine component FR schedule with response requirements for cocaine ranging between FR50 and FR100 for the individual monkey) only when the animals received cocaine continuously [4 mg/(kg·day)] but not if they received the same daily dose in 4 daily injections. Proof of the development of tolerance to the reinforcing effect of drugs of cocaine [76] and opioids [246] has, however, been obtained by other groups even under intermittent schedules of noncontingent drug administration. Some would argue that, with respect to face validity, intermittent drug administration models human drug abuse patterns much better than continuous drug ad-

ministration. A detailed discussion of the differences between contingent versus noncontingent drug administration is beyond the scope of this review; suffice it to say that some researchers using animal models of chronic drug abuse do take great care to prove that the results they have obtained under noncontingent conditions [211] can be replicated under contingent (i.e. self-administration) conditions [212].

Alternative Reinforcers: Enriched Environment and Choice Procedures

With respect to the availability of alternative reinforcers, the paucity of the usual animal experimental environment, in itself the result of a sensible methodological decision with respect to limiting and controlling experimental variables, certainly falls short of modeling the human situation in which a number of other reinforcers are available [5, 9]. Field convention calls all these other, nondrug reinforcers 'alternative' reinforcers. In its strictest experimental form, and true to its Latin roots *'alter'* (the other of two) and *'nativus'* (born; i.e. born as the other of two), the drug reinforcer is compared with only one nondrug reinforcer (see choice procedures below). In its most extreme experimental form, a large number of nondrug reinforcers is introduced into the experimental environment: this is called 'environmental enrichment'. Mike Bardo and coworkers [100] demonstrated a clear downward shift in the ascending part of amphetamine self-administration DECs both under FR1 and PR schedules in rats when exposed to such an 'enriched' (as opposed to the usual stimulus-poor) experimental environment, strongly indicating that the availability of nondrug reinforcers decreased the apparent reinforcing effect of the drug of abuse. One of us (G.Z.) concedes, however, that introducing a multitude of alternative reinforcers in the form of an 'enriched environment' as an additional variable presents a formidable experimental and interpretational challenge, while one of us (R.N.C.) points out that the experiments by Bardo and coworkers show that the associated problems can be managed.

A choice procedure represents a rate-independent experimental approach to quantify the reinforcing strength of a drug stimulus relative to one alternative reinforcer (or, theoretically, several other reinforcers), and has been used successfully in models of chronic opioid or cocaine self-administration ([163, 164]; see below for a detailed discussion). It should be kept in mind, however, that choice procedures cannot tell us whether the increase in

the relative reinforcing strength of the drug reinforcer is (a) only due to an increase in the reinforcing strength of the drug reinforcer, (b) only due to a decrease in the reinforcing strength of the alternative reinforcer, or (c) due to both. Some of us (S.S.N., D.M.), while agreeing with the above argument, suggest that single-operant procedures also measure 'relative' reinforcement; however, in these procedures, behavior maintained by other stimuli is not measured.

Minimum Experimental Design Criteria

To summarize the above discussion of the limitations of currently used behavioral experimental models, and in order to yield data that are amenable to interpretation of reasonable certainty, the following minimum experimental design criteria should be observed when a drug, i.e. a pharmacological agent, is examined for its 'true' reinforcing effect, as opposed to its 'acute pharmacological effects' (fig. 1). However, one of us (D.M.) argues that experimental requirements should be determined only by the hypothesis being tested.

(1) Operant responding should be tested in an essentially drug-free state, i.e. after a TO of at least 4 elimination half-lives of the drug in the extracellular space of the brain. For cocaine and remifentanil, a short-acting μ-opioid agonist, this time span would be at least 4×10 min = 40 min [61], for morphine, an intermediate-acting μ-opioid agonist, the time span would be at least 4×40 min = 160 min [Crespo and Zernig, unpubl. observation]. One of us (D.M.) warns that imposing such a requirement would make it nearly impossible to do most experiments.

(2) Whenever the incentive value of the drug or the incentive salience of drug-associated stimuli is compared either across unit doses of this same drug or compared with an alternative reinforcer, care should be taken to render the unit dose-operant response relationship monophasic and proportional (i.e. an increase in the unit dose of the drug should produce an increase in operant responding, the degree of increase depending on the location of this unit dose on the DEC, i.e. on the linear or the asymptotic part of the DEC).

(3) The component(s) underlying the measured overall 'apparent drug reinforcement' (this review, fig. 1) in the chosen experimental approach should be clearly identified and, if possible, differentiated experimentally. In any case, they must be controlled for.

(4) The effect should be proven both for a psychostimulant – most often this will be cocaine – and an opioid drug of abuse. Cocaine is in many ways a unique drug, and the incorrect generalization from cocaine to all drugs of abuse is, unfortunately, made implicitly and automatically in the drug abuse research field. The opposite is not true: some of us (G.Z., J.C., P.S., A.S.) preferentially study opioids, and have been consistently and correctly asked by a number of reviewers from various journals to extend our experiments to cocaine. On the other hand, some of us (D.M., R.N.C.) point out that in many instances, researchers do not want to test hypotheses that need to be extended to drugs of abuse in general.

(5) Care should be taken that the animal does not suffer negative social consequences (i.e. impaired defensive behavior against cagemate attacks) because of acute drug effects. If the experimental drug may plausibly produce such acute effects, or has actually been demonstrated to do so, animals should be housed singly for ≥4 elimination half-lives of a drug before being put in a group cage.

(6) If one accepts one of the major assertions of this review, i.e. that the escalation of human drug use is predominantly due to a shift in time spent in drug-related versus non-drug-related activities (see also criteria 5 and 6 of the DSM-IV [14] and criterion 5 of the ICD-10 [254] diagnostic standards), any self-administration experiment assessing this shift should cover a long enough portion of the diurnal cycle, preferably ≥21 h/day.

As the above discussion has shown, the overwhelming majority of experimental work (including our own; G.Z., A.S., J.C., P.S.) investigating the reinforcing effects of drugs of abuse – and their changes due to chronic drug use – has not fulfilled these minimum criteria. In particular, none of the experiments assessing the escalation of drug use in substance dependence has. Most likely, this is the reason why the debate about the mechanisms underlying the escalation of drug use in substance dependence has remained so controversial. Drug abuse research has produced an impressive amount of data, and it is very hard for us to draw conclusions from it that are beyond reasonable doubt. For the same reason, most interpretations of the experimental work that are voiced in this review must also be regarded as tentative.

Models Used to Explain the Escalation of Drug Use

A number of groups have investigated changes in drug intake and/or changes in operant response to drugs after chronic contingent or noncontingent drug administration but, for a variety of reasons, decided to test only one drug dose. Because these single-dose studies (as opposed to studies covering significant parts of the drug's DEC) are extremely hard, if not impossible, to interpret with respect to the models evaluated below, they will not be considered further in this review, unless they contain additional experiments that specifically addressed the hypotheses evaluated below.

Tolerance of Apparent Drug Reinforcement

Before proceeding to review the experimental evidence, we should remind ourselves that experimentally determined drug apparent reinforcement is a composite of a considerable number of contributing factors (see fig. 1 and the section on components of apparent drug reinforcement). Therefore, the explanatory power of the following experimental evidence remains low as regards the underlying reasons for changes in drug consumption upon chronic exposure.

In two seminal studies, Emmett-Oglesby and Lane [75] and Emmett-Oglesby et al. [76] provided evidence that they interpreted as development of tolerance to the reinforcing effects of cocaine. Transformation of figure 3 of Emmett-Oglesby et al. [76], in which the less common measure of inter-response interval had been given, to the more commonly used measure of response rate (fig. 7) reveals that noncontingent administration of 5 mg/kg i.v. cocaine every 8 h over 7 days raised the descending part of the cocaine unit-dose-response-rate curve (obtained in an FR2 self-administration procedure performed 24 h after the end of the chronic cocaine treatment), with the most pronounced rise occurring at the lowest cocaine unit dose tested (i.e. 0.5 mg/kg per injection). On pharmacological principles, such an upward shift of the DEC can also be explained by the development of tolerance to the acute rate-decreasing effect of cocaine [266] – an explanation that Emmett-Oglesby and coworkers discuss but dismiss as improbable [76, p. 253], because the chronically treated animals failed to respond for the lowest cocaine doses that had previously maintained responding, i.e. 0.125 and 0.25 mg/(kg·injection). Most likely, (1) tolerance to both the discriminative stimulus effects and the reinforcing effects at these threshold doses and (2) tolerance to the rate-de-
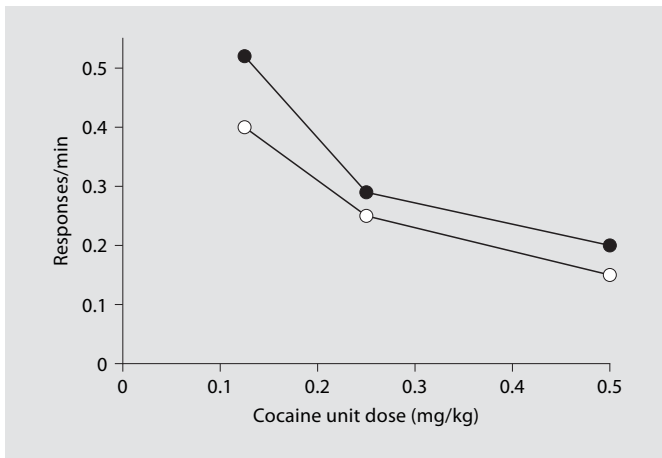
Fig. 7. Rightward shift of the cocaine self-administration DEC after chronic noncontingent cocaine administration. Shown are response rates under an FR2 TO20s schedule of reinforcement before (open circles, thin line) and after (filled circles, thick line) 10 days of 60 mg/day of noncontingent intravenous cocaine injections (administered by the experimenter in bins of 10 injections of 0.25 mg each every 8 h to rats weighing 250 g). Redrawn from figure 3 from Emmett-Oglesby [76].

creasing effects of the higher doses caused the observed shift in dose-effect functions. If one regards the experiment as a cocaine self-titration procedure, as Ahmed and Koob [9] did, reward allostasis (see below) had occurred.

Gail Winger and Jim Woods [246] determined the self-administration of various opioids and cocaine under an FR30 schedule of reinforcement in rhesus monkeys before, during and after noncontingent administration of 3.2 mg/(kg·day) s.c. morphine for 27–99 days. This chronic noncontingent morphine administration produced a 3-fold parallel rightward shift of the ascending part of the self-administration DECs of morphine and heroin, and even a 10-fold rightward shift of nalbuphine's DEC, but essentially did not shift the DEC for cocaine [246, fig. 1]. Figure 8 shows that in the case of nalbuphine, the strict parallel rightward shift of the biphasic DEC after chronic morphine treatment even produced a crossover point at a unit dose of 0.032 mg/(kg·infusion), i.e. response rates for this dose of nalbuphine were higher after chronic noncontingent morphine treatment – a beautiful example of how an increase in response rates might actually reflect the development of tolerance to both the reinforcing and the rate-decreasing effects of chronic drug exposure. The parallel rightward shifts were completely reversed within 7–95 days. Thus, clear and reversible tolerance to the apparent reinforcing effects of the μ-opioid

agonists (which was inversely proportional to the opioid's efficacy [263]; see the definition of efficacy, above) developed during chronic noncontingent administration of the μ-opioid agonist morphine.

Sensitization to Apparent Drug Reinforcement

The most convincing evidence for sensitization to the composite we call 'apparent drug reinforcement' comes from experiments in which rats were given the opportunity to self-administer psychostimulants under a PR schedule of reinforcement (see above for the limitations of this experimental approach). Tony Phillips and co-workers [155] found that a total of 10 noncontingent administrations of 2 mg/kg i.p. amphetamine sulfate given every other day increased breakpoints for the single tested dose, i.e. 0.2 mg/kg i.v. amphetamine, 33 days after the noncontingent amphetamine treatment regimen. However, as only 1 unit dose was tested, further pharmacological evaluation of their data is impossible.

On pharmacological principles, an increase in the drug's reinforcing effect should become evident at low to intermediate unit doses (i.e. on the ascending part of the DEC), shifting the whole DEC to the left, an effect that, up to now, only Vezina et al. [232] have demonstrated, in a series of experiments that combined PR self-administration and in vivo microdialysis, for the dependent variable 'breaking point' in rats self-administering amphetamine under a PR schedule before and 15 days after 5 noncontingent intraperitoneal injections of 1.5 mg/kg amphetamine given every third day (see fig. 9, reprinted from [232, fig. 1B]). Vezina et al. went on to demonstrate that sensitization to cocaine reinforcement can be obtained by local administration of amphetamine into the ventral tegmental area (VTA) but not the nucleus accumbens core (AcbC) [232], thus confirming and extending previous findings on AcbC- but not VTA-mediated sensitization to the locomotor effects of amphetamine by Cador et al. [40]. Vezina and coworkers also demonstrated that the sensitization to amphetamine reinforcement was dependent on the activation of NMDA receptors, AMPA/kainate receptors [222], and D1 receptors [221], and that it could be prevented by activation of group II metabotropic glutamate receptors [126]. At the very same time when breakpoints for amphetamine were increased in the PR schedules, noncontingent administration of amphetamine produced an increase in AcbC dopamine (DA) release [144, 232].
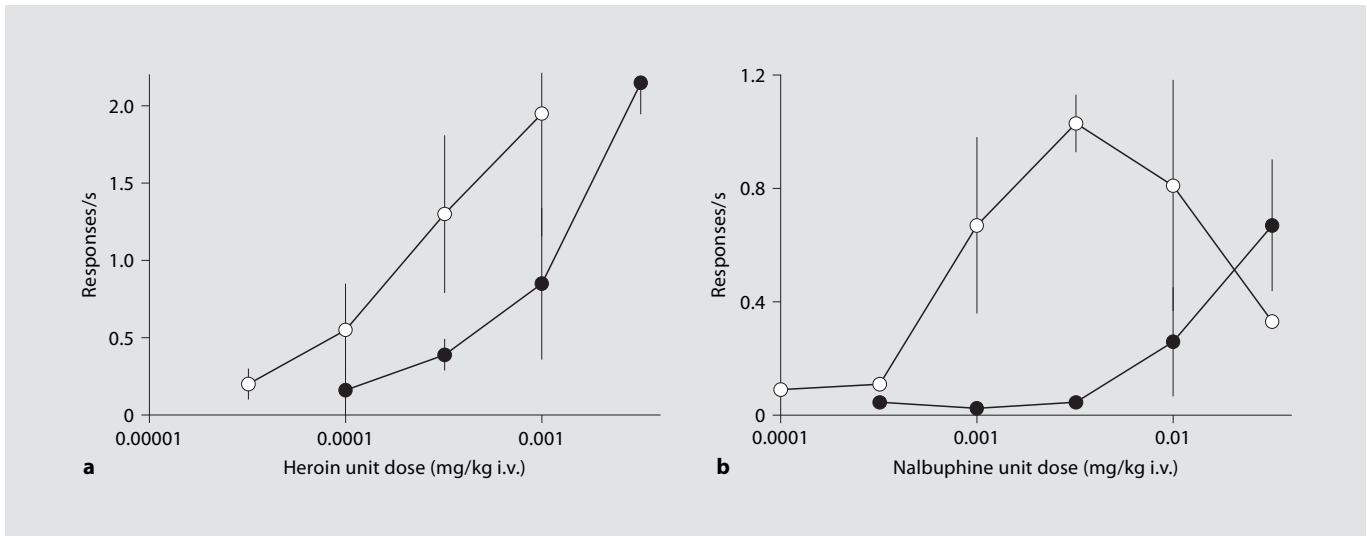
Fig. 8. Rightward shift of the heroin and nalbuphine self-administration DECs after chronic noncontingent morphine administration. Shown are FR30 TO45s dose-effect curves for heroin (**a**) and nalbuphine (**b**) before (open circles) and during (filled circles) 27–29 days of noncontingent administration of 3.2 mg/(kg·day) subcutaneous morphine. Redrawn from figure 1 from Winger and Woods [246].
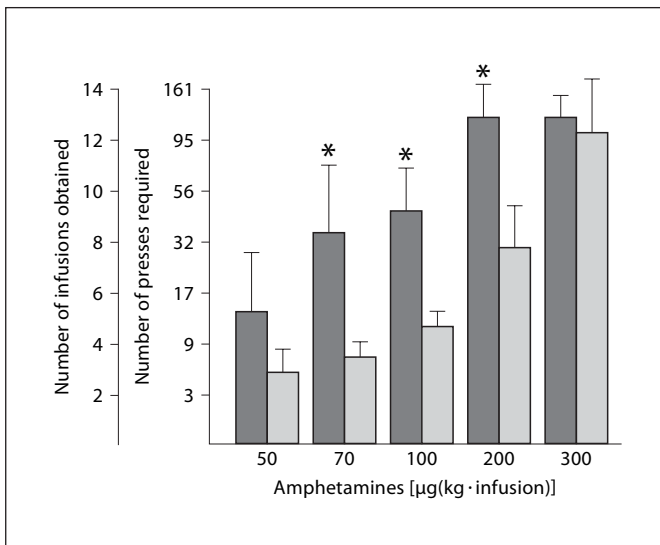

Fig. 9. Upward and leftward shift of the amphetamine self-administration DECs after chronic noncontingent amphetamine administration. Amphetamine DECs were obtained under a PR schedule (ratio value progression: 1, 3, 6, 9, 12, 17, 24, 32, 42, 56, 73, 95, 124, 161, 208, etc.) before (light grey bars) and after (dark grey bars) of 15 days of noncontingent amphetamine administration (5 × 1.5 = 7.5 mg/kg i.p. every 72 h). * p < 0.05. Figure 1B from Vezina et al. [232], reprinted with permission.

Model-oriented inspection of the PR DEC obtained by Vezina et al. (see fig. 1B of [232]; reprinted in fig. 10) reveals that in chronically treated rats, responding to the lowest amphetamine unit doses was increased the most, whereas when responding to high amphetamine unit doses, rats hit a 'ceiling' that was comparable to the highest response rate of control rats, a phenomenon well known for PR schedules [191]. Thus, with respect to the type of sensitization observed by Vezina et al., 'reverse reward allostasis', i.e. the activation of a second system that facilitated responding to amphetamine might have occurred, leading to a selective upward shift of the lower part of the ascending DEC. However, as Vezina points out, the above may be an overinterpretation, and simple 'sensitization' may be a more appropriate description of what he and his colleagues have demonstrated.

Interestingly, the rats ceased to respond to amphetamine when the additional DA increase produced by the self-administered amphetamine fell below an increase of 50% above baseline, regardless whether they had been treated with noncontingent amphetamine or not [232, figs. 2 and 3]. It seemed as if there had to be a noticeable difference in Acb DA levels for the animals to continue responding, and that 5 noncontingent administrations of amphetamine had increased the responsiveness of the VTA-Acb DA neurons to intravenous amphetamine to provide such a ≥50% increase even at higher absolute
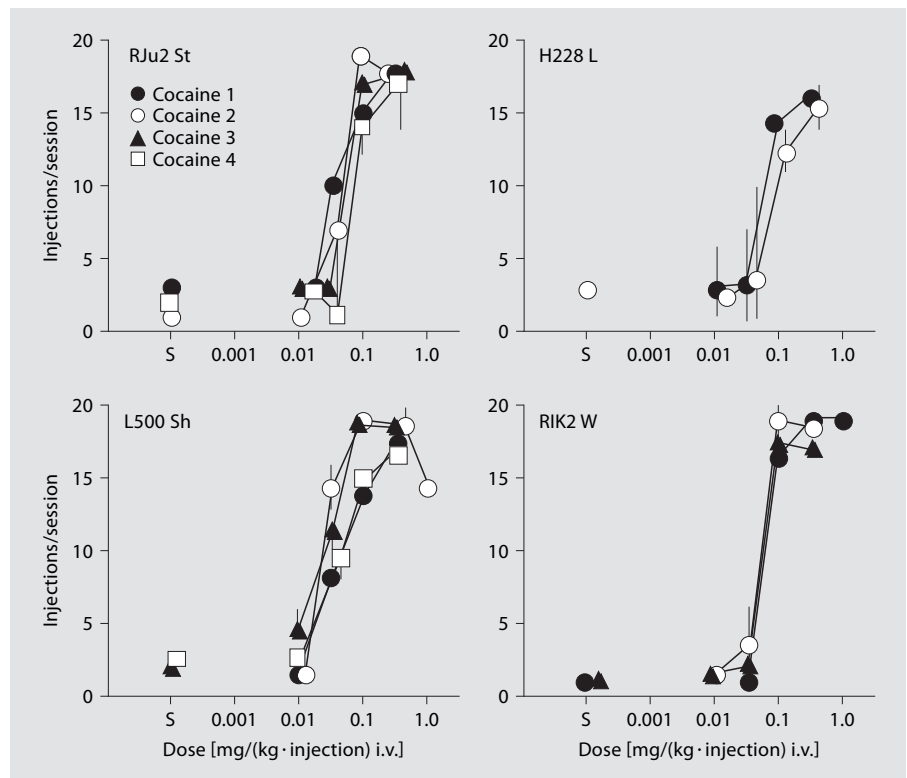
Fig. 10. Self-administration of cocaine by 4 rhesus monkeys remains stable over a period of up to 5 years. Dose-response functions for intravenous cocaine self-administration were obtained repeatedly in rhesus monkeys (labeled, in temporal order, cocaine 1 to cocaine 4). The schedule of reinforcement was a PR schedule with response requirement beginning at 100 and doubling after every 4 injections. A total of 20 injections were available, each followed by a TO of 30 min [243]. For monkey RJu2, cocaine 1 was obtained between January and February 1997, cocaine 2 between January and March 1998, cocaine 3 between August and November 2000, and cocaine 4 between September and November 2001. For the other monkeys, cocaine DECs were generated at the following dates: monkey H228, cocaine 1, September 2000–February 2001; cocaine 2, October–November 2001. Monkey L500, cocaine 1, January–April 1998; cocaine 2, September 2000–January 2001; cocaine 3, April–May 2001, and cocaine 4 October–November 2001. Monkey RIK2, cocaine 1, October 1997–February 1998; cocaine 2, October–November 2000, and cocaine 3 November 2001–February 2002. Daily sessions between dose-response determinations included baseline sessions of cocaine or saline self-administration and test sessions with varying doses of a number of drugs. S = Saline.

Acb DA levels. Clearly, the amphetamine exposure had produced a sensitization of the VTA-Acb DA neurons to intravenous amphetamine. On the other hand, this argues against sensitization to the positive incentive value effects of the drug (likely provided by the Acb DA release), as both pre- and posttreatment rats needed the ≥50% increase in Acb DA release to maintain response.

In contrast, in a series of studies in which various doses of self-administered drug were investigated, complete DECs were run, and the time courses of the self-administration-induced changes, including their reversal, were closely studied, Morgan et al. [161] found increases in breaking points for rats self-administering cocaine in a chronic binge-type pattern for 5 to 10 days only at high unit doses of cocaine ([161, fig. 1] not on the first day of withdrawal, but only on the seventh day [158]). Furthermore, these researchers showed that the self-administration history of the animals profoundly affected the increase in breaking points. In subsequent studies, rats were given the opportunity to self-administer cocaine over 5 consecutive days, but only those animals that self-administered only around 20 mg/(kg·day) cocaine showed a significant increase in breakpoints in the subsequent PR sessions performed over the next 14 days (thus fitting the definition of sensitization), whereas animals that self-administered around 60 or 100 mg/(kg·day) cocaine did not demonstrate any increase in breakpoints [159, fig. 2] In those animals that had self-administered an average of 95

mg/(kg·day) for 5 days, the PR DEC on the first day of withdrawal was actually shifted rightward (and, possibly, downward), with breakpoints of PR responding to the second-highest cocaine dose (1.5 mg/kg) being decreased by 17% [160], indicating the development of tolerance to the reinforcing effect of cocaine [159, fig. 2]. Breakpoints of PR responding to 1.5 mg/kg cocaine recovered to pre-binge levels within 3 days of withdrawal [160]. It thus seems that there is sensitization to the apparent reinforcing effect of psychostimulants in PR schedules of reinforcement and that the degree of this sensitization depends on the psychostimulant used (i.e. amphetamine vs. cocaine) and on the amount and pattern of pre-test drug exposure. When expressed, sensitization develops within the first 4–10 days of withdrawal and seems to persist for a considerable time, i.e. up to at least 14 days.

Using the long-access (LgA, i.e. 6 h) versus short-access (ShA, i.e. 1 h) FR1 session paradigm developed by Ahmed and Koob [7] and Lenoir and Ahmed [140], Athina Markou and coworkers [180, fig. 1] demonstrated an increase in cocaine breakpoints over the whole cocaine DEC [i.e. 0.095–0.77 mg/(kg·injection), assuming an average weight of 325 g/rat]. Most interestingly, in the hands of Markou and coworkers, the LgA rats had higher breakpoints also for saline. The increase in breakpoints for saline could be interpreted as the development of lever response stereotypy (see section on PR schedules). Together with the fact that breakpoint increases were most pronounced in the lower part of the ascending part of the cocaine DEC, a DEC shape-change-based pharmacological interpretation could also suggest reverse allostasis (see fig. 11, lower part). Please note also that Markou and coworkers had enforced a 2-day abstinence period before subjecting the rats to the PR schedule, and that they had subjected the rats to each cocaine dose for only 1 day. Finally, Klaus Miczek and coworkers [162], using a 16-hour binge-like self-administration paradigm, showed equivocal effects of cocaine bingeing on apparent cocaine reinforcement.

Most interestingly, sensitization to amphetamine's apparent reinforcing effect was paralleled by an increase in amphetamine-stimulated DA release in the AcbC and nucleus accumbens shell (AcbSh), both during the PR session itself and also upon noncontingent administration of amphetamine [232], whereas the sensitization to cocaine's reinforcing effect [after self-administration of daily doses of 73–78 mg/(kg·day) for 10 days] had developed in the face of tolerance to the Acb-DA-releasing effect of a noncontingent cocaine (1.5 mg/kg i.v.) administration [148]. The degree of tolerance to the AcbC-DA-releasing effect of cocaine was the same after 1 or 7 days

of withdrawal from the cocaine binge-type (73–78 mg/(kg·day) for 10 days) self-administration [148, fig. 2], while, as described above, the reinforcing effect of cocaine in the PR schedule was not different from pre-bingeing on day 1 of withdrawal but showed sensitization on day 7. Thus, 7 days after the end of the binge-type self-administration period, there was an apparent dissociation between tolerance to the DA-releasing effect of cocaine in the AcbC and AcbSh [induced by 10 days of 73–78 mg/(kg·day) cocaine self-administration] and sensitization to cocaine's reinforcing effect [induced by 10 days of 20-mg/(kg·day) cocaine self-administration]. This discrepancy can be most parsimoniously explained by the different self-administered cocaine doses, the low doses producing sensitization to the apparent reinforcing effect of cocaine and the high doses producing tolerance to cocaine-stimulated AcbC and AcbSh DA release. It remains to be seen how cocaine-induced accumbal DA release will change after 10 days of 20-mg/(kg·day) cocaine self-administration.

Vezina et al. [232] also provided evidence that amphetamine self-administration was also increased after noncontingent amphetamine administration when an FR (as opposed to a PR) schedule of reinforcement was employed [FR5; see fig. 3 of 232]. As, however, only 1 unit dose of amphetamine (0.2 mg/kg) was tested (instead of providing complete DECs for pharmacological analysis), interpretation of this data remains rather speculative.

Piervincenzo Piazza and colleagues [64] demonstrated a vertical upward shift of the descending part of the DEC in rats self-administering cocaine under a multiple-injection FR1 schedule of reinforcement and interpreted this as an increase in the incentive motivational effects of cocaine. On pharmacological principles, this can be better explained by the development of tolerance to the acute rate-decreasing effect of cocaine [266] or, when regarding the FR1 schedule used by Piazza and colleagues as a drug self-titration procedure, by reward allostasis [9].

In addition, sensitization to response under PR schedules has not been consistently observed. For example, rhesus monkeys that had been trained to self-administer intravenous cocaine under a PR schedule showed the same constant sensitivity to the drug over up to 5 years of repeated testing, showing neither tolerance nor sensitization to cocaine's reinforcing effect [Woolverton, previously unpubl. data shown in fig. 10; Foltin and Evans, unpubl. data]. Other groups [142, 143, 155, 159, 232] have demonstrated sensitization to the reinforcing effects of psychostimulants in rats under PR schedules but not under ShA FR schedules (see below for details).

Sensitization to the reinforcing effects of drugs of abuse has been demonstrated not only for psychostimulants but also for opioids. In the LgA versus ShA FR1 session paradigm developed by Ahmed and Koob [7] and Lenoir and Ahmed [140], responding to heroin [fig. 3 of 5] was also increased. Similarly, rats that had been implanted with subcutaneous morphine pellets showed increased breakpoints [44]. Please keep in mind that the increases in breakpoints can also be interpreted as reward allostasis [5, 7; see below].

One of us (D.M.), however, points out that these findings do not fit any definition of sensitization and that the effects of given doses of cocaine are functionally the same as a lower dose following escalation.

Reward Allostasis

In the context of O'Brien's definition of (physical) dependence, 'reward allostasis', i.e. *the chronic decrease in baseline reward sensitivity* [8], refers to a state in which one of the numerous components of 'apparent reinforcement' is affected by repeated drug administration. The model of reward allostasis was developed by George Koob and Michel Le Moal [129, 130] as a modification of Solomon's and Corbit's classic opponent-process theory of motivation [216] and was based on their findings on drug- and drug-withdrawal-induced changes in electrical intracranial self-stimulation thresholds in rodents [124, 125], but has been extended to predict changes in human behavior, however, without yet providing the required proof in human behavioral experiments. The reward allostasis model posits that the consumption of drugs of abuse leads to a state in which an individual is less responsive to 'natural' or 'physiological' reinforcers (rewards) due to counterregulatory mechanisms (in our words, shows counterregulation-based apparent tolerance). If one accepts that (1) baseline mood is dependent on the sum of all the 'natural' reinforcers experienced in the course of a day and that (2) drug users become less sensitive (i.e. tolerant) to nondrug reinforcers during the progression of their disease [2, 92, 147, 241], this would result in a decrease in their baseline mood compared to nondrug users. The drug user tries to correct this shift in baseline mood by the only apparent remaining means, i.e. by self-administering the drug of abuse. The self-administered drug produces an acute increase in reward sensitivity by amplifying the DA release induced by other, natural reinforcers. Upon withdrawal from the drug, however, a further activation of counterregulatory ('anti-

reward') systems occurs. This initiates a deleterious spiral towards increasingly negative baseline mood, only to be alleviated by increasingly higher doses of the drug. Thus, the reward allostasis model predicts that all drug users in the absence of the drug show more depressive symptoms than they had before the onset of their drug use, and that they are less able to experience pleasure from stimuli other than drugs of abuse, which limits their behavioral options.

The prediction that depressive symptoms are increased by substance use has been confirmed clinically. In retrospective semistructured diagnostic interviews of 2,945 US-American patients with a diagnosis of alcohol dependence [205], 15% suffered from independent major depression (defined as an episode that occurred either before the onset of alcohol dependence or during a period of 3 or more months of abstinence), whereas 26% suffered from substance-induced major depression (onset of regular drinking occurred at age 17 in both groups). Consequently, 23% of the alcohol-dependent patients with independent (primary) major depression had received 'major depression' as their first diagnosis by previous physicians during the progression of their disease, whereas none of the alcoholics with substance-induced major depression had. Most interestingly, among those alcohol-dependent patients suffering from independent major depression, 52% were women, whereas among those with substance-induced major depression only 30% were, confirming the known gender gaps for both primary major depression (higher prevalence for women) and primary alcohol dependence (higher prevalence for men) [265]. Of these 2,945 patients, 371 had tried to commit suicide: 39% of these severely depressed alcohol-dependent patients suffered from independent major depression, whereas 61% suffered from substance-induced major depression [189]. Similarly, a recent survey of 500 Iranian opioid users undergoing treatment showed that 55% developed depressive symptoms only after the onset of their opioid use, whereas only 7% had symptoms of major depression before the start of their drug use [3], a lifetime prevalence rate in good agreement with the general population [82, 190]. Another survey of 287 Norwegian alcohol-dependent patients yielded prevalence rates of 54% for primary major depression versus 22% for alcohol-induced depression [17].

Recently, the reward allostasis model was formulated by Serge Ahmed and George Koob [9] in a mathematical model that explains observed within-session patterns of response and is able to differentiate reward allostasis from reward sensitization based on the difference in the

changes in the shape and direction of the shifts of DEC functions obtained in laboratory animals (see also fig. 6).

Using this mathematical model, Ahmed and Koob showed that in rats that were given the opportunity to self-administer cocaine for extended periods of time (6 h/day) and that escalated their cocaine intake (even in the first hour of the 6-hour experimental period), reward allostasis and not sensitization to the reinforcing effect had occurred [9]. As a distinct advantage over simple steady-state pharmacological models [266], the model presented by Ahmed and Koob takes within-session drug pharmacokinetics into account [9]. The reward allostasis model also describes the change in the dose-effect curve (i.e. predominantly an increase in the maximum response rate, with a steep decrease to lower response rates at higher cocaine unit doses; [9, fig. 7A] and note that the drop in the dose-response function would be even steeper in the commonly used linear-logarithmic, i.e. 'semilogarithmic', plot) better than a model that assumes that only tolerance to the rate-decreasing effects has occurred in these animals (i.e. both an increase in the maximum response rates and a parallel shift of the descending part of the DEC; see this review, fig. 6) [266, fig. 2C] in cocaine intake-escalating rats, even though this has not yet been tested at a formal statistical level. Tolerance to the aversive [96, 235] effects of cocaine can be ruled out as the basis of the increased response to cocaine in rats that have escalated their cocaine intake in these experiments because the mean latency to obtain the first (high) dose of 0.75 mg/kg i.v. cocaine in cocaine-escalated rats (38 ± 16 s) did not differ significantly from that measured in non-escalated animals (41 ± 15 s; mean of the last 5 days of a 20-day period of escalation; Serge Ahmed, unpubl. data).

Ahmed and coworkers have also extended their investigations across pharmacological classes of drugs of abuse, i.e. from cocaine (see above) and amphetamine [127], i.e. psychostimulants, to heroin, a μ-opioid receptor agonist. In rats that have escalated their self-administration of heroin, an upward shift of the self-administration curve and a rightward parallel shift in the descending limb of the DEC can be found [Serge Ahmed, unpubl. observation]. In contrast, both an increase in the maximum response rates (predicted by reward allostasis) and a flattening or even an increase of the distinctly elevated high-dose part of the DEC can be seen (predicted by tolerance to the rate-increasing effects and an increase in the amplitude of the dose-reinforcement function) when these heroin-escalating rats are tested for heroin-induced reinstatement of response [140, fig. 3]. To one of us (G.Z.), the

pharmacologically oriented inspection of the DEC indicates that tolerance to the rate-decreasing effects of heroin impacts more in the heroin-induced reinstatement of the response procedure, which is in accordance with Lenoir's and Ahmed's findings that escalating heroin self-administration produces tolerance to heroin's motor impairment [140, fig. 5].

However, as pointed out by another of us (S.H.A.), in the reinstatement procedure, response was very low due to extinction and there was no evidence that heroin suppressed further this low level of response. ShA rats do not respond to heroin because they are not sensitive to its incentive effects. Finally, heroin did not produce 'motor impairment', as supposed by G.Z., but stimulated cage crossovers – an effect more pronounced in ShA rats than in LgA rats. This latter finding, according to S.H.A., actually contradicts what G.Z. is trying to say in the above paragraph.

One of the predictions of the reward allostasis model is that, over a large range of unit doses, preresponse brain levels of the self-administered drug should be the same regardless of unit dose, a prediction that is fulfilled for cocaine (see also Andrew Norman's and Vladimir Tsibulsky's experimental work testing their 'satiety threshold' model [226, 227]) but not for the μ-opioid agonist remifentanil [59]. Preresponse remifentanil levels, obtained 30 min after the start of the self-administration session, were found to be proportional to the remifentanil unit dose over the whole tested 128-fold range [0.00025–0.032 mg/(kg·injection)], the relationship between unit dose and mean levels being saturable (fig. 12) with a maximum level of 11 ng/ml for blood remifentanil and of 102 ng/ml for AcbC remifentanil [59].

Thus, in the case of remifentanil, it has been shown that the 'decision' to emit a response in ShA lever-press-based operant conditioning procedures is related to neither a certain tightly controlled 'threshold' nor 'ceiling' of brain levels or blood levels or changes thereof, with respect to either the self-administered drug or the drug-induced dopamine levels in the Acb [59, 60, 175 and fig. 5 of 247, but see 226 or the discussion of 247]. Thus, the reward allostasis model has been extremely useful for explaining the within-session determinants of cocaine self-administration in laboratory animals, while it seems far less successful in predicting the within-session regulation of opioid self-administration. With respect to the focus of the present review, it is extremely interesting that a dose-dependent development of acute within-session tolerance to opioids but not to psychostimulants presents a very plausible explanation for this psychostimulant-opioid discrepancy.

Finally, when attempting to test the predictions of the reward allostasis model within the long time window of a lifetime of drug use (and not during the limited time window of a self-administration session), one is faced with the extreme challenge of reliably quantifying changes in baseline mood levels – which were assumed to change in some studies, but were never actually measured – over a period of several years. Thus, at the clinical level, reward allostasis would appear simply as tolerance to the subjective effects of the drug. Furthermore, in clinical interviews, some of us (R.W.F., G.Z.) have found again and again that users take drugs (in particular, intravenous heroin, intravenous cocaine or marijuana) to experience subjective effects completely beyond the range of 'natural' reinforcers, consistently preferring the highest dose they think they can survive [261]. The consistent preference of the higher of 2 available drug doses can be demonstrated even at the animal experimental level [99, 152]. It would, at first sight, run counter to one of the most basic predictions of the reward allostasis model, because the within-session regulation model [9] that is used to test the shift in within-session drug level titration would predict that at very high unit doses, i.e. under conditions when the drug threshold can be obtained with a few self-administration events, within-session preference would shift to lower doses that are sufficient to maintain the titrated drug level. However, as pointed out by Serge Ahmed, in the behavioral-economic model of cocaine self-administration developed by Ahmed and Koob [9], the drug dose is an inverse equivalent of the price or response requirement necessary to maintain the titrated drug level: the lower the dose, the higher the price [30]. Thus, maintaining the titrated drug level with low doses is 'more expensive' than with high doses (i.e. you need to respond more for the same effect). Thus, as emphasized by Serge Ahmed, the set-point model predicts that facing a choice, animals would prefer high drug doses over low ones.

It should also be noted that all animal laboratory data reviewed above were obtained under limited behavioral options, whereas in the natural ecology humans have a much greater range of options.

Increase in the Incentive Salience of Drug-Associated Conditioned Stimuli

As detailed above, the apparent reinforcing effect of a drug is actually a composite of a considerable number of different, operationally defined, components (see the section on components of apparent drug reinforcement) of which 'incentive salience' or drug 'wanting' (the quotation marks denoting its unconscious nature) is but one (see fig. 1). Kent Berridge and Terry Robinson's major contribution [195] to the drug abuse field – and a refinement of previous seminal work by others [e.g. 31, 219] – was to draw attention to the possibility that the incentive salience of a drug-associated stimulus (i.e. drug 'wanting', to mention the easily remembered but hotly contested term) might be increased during continued drug use, whereas the drug's hedonic value (drug 'liking') might decrease. Berridge's and Robinson's proposition has been amply confirmed by experiments with food stimuli (and the modulation of food stimulus reward components by drugs) [23–25, 27] and, most recently, also for a drug of abuse, cocaine, using the approach latency and frequency of the approach of the rat to the drug-associated lever as measures of the incentive salience attributed to the drug-associated stimuli, i.e. the extended lever and a cue light [228].

When looking at the drug abuse pattern of dependent human users, an increase in incentive salience or, if you will, 'sensitization' to the incentive salience of the drug-associated stimuli (although a pharmacologist would like to keep the term 'sensitization' reserved for a drug stimulus), is well suited to describe the dramatic increase in the drug user's time spent in drug-related behavior (as opposed to the less impressive increase in the drug dose needed per intoxication event, indicating the development of tolerance; see section on human drug abuse patterns). Everitt and Robinson [80] have suggested that the subjective state of 'must do!' – likely a post-hoc rationalization of habitual behavior that is perceived as 'out-of-control' by the drug-taking individual [80, p. 1485] – might be better suited than 'wanting' to describe the compulsive nature of drug taking at a stage that is characterized by considerable control of drug-associated stimuli over the individual's behavior (see also the section on habit formation below).

However, to paraphrase Berridge and Robinson, the most commonly used multiple-injection self-administration procedures (during which acute drug effects confound the measure of reinforcement) are simply not able to test this hypothesis. Appropriate experimental approaches to investigate whether individuals have attributed incentive salience to drug-associated stimuli are PIT experiments [255]. Also, one might look at approach behavior in operant conditioning runway paradigms [61, 95, 235] in which the location of the conditioned stimulus is topographically separated from the goal area – or for

which response contingencies might be changed, i.e. by requiring the animal to run away from the conditioned stimulus to receive the drug.

Other powerful methods to quantify the impact of drug-associated stimuli on drug taking behavior are second-order schedules of reinforcement [79], the analysis of which should be restricted to the first, i.e. drug-free interval. Importantly, second-order schedules also assess the secondary reinforcing effects that the drug-associated stimulus has acquired, i.e. the animal has to emit responses ('work') to the presentation of this cue, whereas in experiments aimed at assessing only the incentive salience of a drug-associated stimulus, the stimulus has to be presented unexpectedly and relevant changes in response to the drug occur after this unexpected stimulus presentation [80].

Other approaches to quantify the changes in the incentive salience attributed to drug-associated stimuli induced by chronic self-administration of drugs are experiments on cue- or context-induced reinstatement of responding [67], a field of drug abuse research that has expanded considerably. In contrast to the experimental procedures described above, response to the drug is extinguished before it is reinstated by the presentation of a single stimulus (cue-induced) or a group of stimuli (context-induced). The detailed discussion of these types of experiments is, however, beyond the scope of the present review. The interested reader is referred to recent reviews [120, 151, 207].

Increase in the Relative Reinforcing Strength of Drug versus Alternative Reinforcers

Most of the above discussion was focused on the reinforcing strength of the drug when tested alone. In the human situation, however, a number of nondrug ('alternative') reinforcers compete with the drug to control an individual's drug-taking behavior (see also section on enriched environment and choice procedures above). A currently championed model, formulated by Gene Heyman [110], who adapted a general principle proposed by Richard Herrnstein [109] to drug dependence, posits that the escalation of drug use by substance-dependent individuals is due to an increase in the relative reinforcing strength of the drug compared to nondrug reinforcers. Please keep in mind that this can also mean that both drug reinforcers and nondrug reinforcers decrease in reinforcing strength, with nondrug reinforcers decreasing more than drug reinforcers [see the diagram in 4].

There is growing neurobiological experimental data supporting the relative-drug-reinforcement-increase hypothesis. For example, intracranial self-stimulation thresholds are elevated in rats that have escalated self-administered cocaine [6]. Also, neuroimaging studies seem to indicate that in chronic drug users, drug reinforcers are overvalued and nondrug reinforcers are undervalued [98]. It should be kept in mind that a relative increase in the reinforcing strength of the drug reinforcers compared with nondrug reinforcers is one of the major predictions of the reward allostasis model (see above).

At the behavioral experimental level, choice procedures (see above) seem best suited to test the hypothesis. Rhesus monkeys that were given the opportunity to self-administer heroin both during 2-hour food-versus-heroin choice sessions and 21-hour supplemental heroin self-administration sessions (FR10 TO15min) for at least 7 days, and which self-administered on average 3.9 mg/(kg·day) heroin during the supplemental sessions and 1.1 mg/(kg·day) during the food-versus-heroin choice sessions, totaling an average of 5 mg/(kg·day) self-administered heroin, the heroin-over-food choice did not increase during the supplemental self-administration period [half-maximum effect dose (ED_{50}) for heroin, 0.0091 mg/(kg·injection) before vs. 0.016 mg/(kg·injection) during the supplemental sessions] but increased by a factor of at least 3 [$ED_{50} < 0.0032$ mg/(kg·injection)] 24 h after termination of the supplemental heroin self-administration regimen [164]. Thus, under controlled animal laboratory conditions, there was no evidence for an increase in drug preference, at least during 7 days of massive heroin self-administration, a time period that may still be too short to model the human situation. However, withdrawal produced a striking increase in drug preference.

Habit/Compulsion Formation (Stimulus-Response Learning)

One of us (G.Z.) would opine that at first sight, the concept of 'habit formation' sounds less like a true explanation for drug dependence than like one of those self-excusatory rationalizations of drug-dependent patients that therapists are so familiar with [265]. However, habit formation is a psychological construct that has been amply confirmed, albeit predominantly for food reinforcers, in the animal behavioral laboratory: if a response persists in the face of a food reinforcer devalued by prefeeding the animal or by pairing the food with a nausea-inducing agent, habit formation is said to have occurred [18, 43, 80,

204]. One of us (S.H.A.) disagrees with the aim and feasibility of the procedure that is being proposed to probe the controlled versus automatic status of drug self-administration behavior in animals. Recent research strongly suggests that the dorsal striatum [80] may ultimately mediate such inflexible, habitual, 'compulsive', devaluation-resistant reinforcer-seeking behavior. With respect to the neuroanatomical basis of habit formation, Everitt and Robbins [80] have proposed that the 'transition from voluntary actions (governed mainly by their consequences) to more habitual modes of responding in drug seeking behavior represents a transition from prefrontal cortical to striatal control over responding, and from ventral to more dorsal striatal regions'.

While habit learning has been amply demonstrated for food reinforcers, experiments with drug reinforcers have remained scarce so far, because 'it is easy to devalue ingestive reinforcers, but it is much more difficult to devalue intravenously self-administered drugs such as cocaine' [80, p. 1484]. Accordingly, proof of habit formation for drug reinforcers has only been provided under conditions where an orally self-administered drug reinforcer (alcohol or cocaine) was devalued by gastric malaise [72, 156]. For one of us (G.Z.) this poses a considerable face validity problem, because gastric malaise is a subjective effect of a quality ('dimension') completely different from the positive subjective effects (including absence of fear, serenity or grandiosity) that cocaine or alcohol can provide (at least in humans), and that the addition of a subjective effect of such a different 'dimension' may not reflect devaluation (i.e. weakening of a subjective effect along the same 'dimension'). For others (R.N.C.), a key feature of instrumental incentive value is that it distils differences across many dimensions into a single value. Economic theory requires a utility function that assigns unidimensional values to real-world multidimensional events or outcomes such that the agent prefers outcomes with higher utility; psychologically and neurally, a similar process must also happen [208]. Incentive value may fulfill this requirement, and if so, then devaluation by gastric malaise is as valid as devaluation by any other mechanism for the purposes of demonstrating the existence of habit-bound response.

Finally, it has also been shown that amphetamine exposure enhances habit formation when a flavored sucrose or maltodextrin solution is used as a reinforcer [169].

A drug reinforcer devaluation procedure that would be acceptable from a pharmacological perspective would consist of pretreating the individual with a drug that acts as an agonist at the receptor system under investigation,

ideally by response-contingent (i.e. self-) administration of the agonist by the individual, before the test self-administration session itself. The overriding methodological concern regarding this type of experiment is that acute pharmacological drug effects (sedation, motor impairment) will, in most likelihood, severely confound a rate-dependent measure of drug reinforcement. Rate-independent measures of reinforcement, e.g. choice procedures (see above), may therefore be the best procedure to test habit formation in drug reinforcement.

How would the pretreatment with an agonist affect measures of reinforcement in a subsequent self-administration experiment? Psychological theory predicts that agonist pretreatment, by devaluing the drug reinforcers through satiety (see the section on definitions of saturation and satiety), would decrease the reinforcing effect of the self-administered drug. If, however, habit formation has occurred, the reinforcing effect of the subsequently self-administered drug would be resistant to such a devaluation. The pharmacological laws governing agonist-agonist interactions [123] would predict that, if apparent reinforcement were a monotonic function of receptor occupancy, pretreatment with a full agonist at a dose that produced a maximum reinforcing effect (determined in separate experiments) would produce a maximum reinforcing effect even of saline (or of a very low dose of a drug of the same chemical class) in the subsequent self-administration session (provided the agonist used for the pretreatment is eliminated slowly enough to be present at a substantial concentration during the subsequent self-administration session), whereas pretreatment with (1) a lower dose of the full agonist or (2) pretreatment with the maximal effective dose of a partial agonist would produce an intermediate reinforcing effect of the agonist at low doses (i.e. a higher reinforcing effect than if the agonist is given without partial agonist treatment). As the unit doses of the agonist made available in the test session are increased, its reinforcing effect would eventually reach the same maximum reinforcing effect, with the overall agonist DEC being shifted to the right to a degree that is dependent on the relative affinities of the partial agonist (given as pretreatment) and the full agonist (tested within-session). As one can imagine, the demonstration of such lawful relationships in rate-dependent measures of reinforcement is a formidable experimental challenge. Overall, however, the distinguishing power of the agonist pretreatment procedure is quite good, even in rate-dependent procedures: if agonist pretreatment leaves the subsequent response to the drug reinforcer unchanged, habit formation has occurred. If agonist pre-

treatment increases subsequent responding, apparent reinforcement is a monotonic function of receptor occupancy of the system under investigation. If agonist pretreatment decreases subsequent responding, acute confounding pharmacological effects (e.g. sedation, motor impairment) have overpowered the animal, or reinforcer devaluation has occurred.

There are to our knowledge only two groups who have demonstrated agonist pretreatment-induced increases in subsequent lever-press- and rate-based measures of reinforcement, i.e. an upward shift of the ascending part of the DEC. Caine et al. [41, 42] used an FR schedule of cocaine reinforcement in rats or rhesus monkeys pretreated with D2 agonists, and Roberts et al. [194] used a PR schedule of cocaine self-administration in rats pretreated with the long-lasting cocaine analog HD-23.

Interestingly, the HD-23-induced upward shift of the ascending part of the cocaine DEC obtained in rats self-administering 0.18–1.5 mg/(kg·injection) cocaine under the PR schedule [194, fig. 2] was paralleled by an downward shift of a descending DEC obtained in rats working for essentially the same cocaine unit doses, i.e. 0.37–3 mg/(kg·injection), under an FR1 schedule of reinforcement [194, fig. 1]. The upward shift of the ascending part of the cocaine DEC (PR schedule) indicates an HD-23-induced increase in the reinforcing effect of cocaine, whereas the downward shift of the descending cocaine DEC (FR schedule) indicates an HD-23-induced increase in the rate-suppressant acute pharmacological effects of cocaine [266] and/or a decrease in the self-titrated cocaine level [9]. Consistent with both findings, HD-23 pretreatment increased response to cocaine in a 24-hour/day access discrete trials FR1 schedule at periods when responding to cocaine was low under control conditions [194, fig. 3].

In most cases, however, pretreatment with partial agonists such as buprenorphine or nalbuphine or full agonists such as heroin only appears to suppress drug response in the subsequent full-agonist rate-dependent self-administration experiments, i.e. with alfentanil in the above examples [245]. Similarly, methadone pretreatment suppressed subsequent response rates for both heroin and food in a food-or-heroin choice procedure, whereas pretreatment with naloxone or buprenorphine increased them [164]. Accordingly, amphetamine pretreatment suppressed subsequent cocaine self-administration rates in second-order and PR schedules of reinforcement [165, 166].

Using a rate-independent choice procedure in rhesus monkeys; Steve Negus [164] and coworkers showed that during >7 days of supplemental 21-hour heroin self-administration sessions, during which the animals self-administered an average of 3.9 mg/(kg·day) heroin, heroin choice in the 2-hour test session remained unchanged, with an average heroin consumption of 1.1 mg/(kg·day). This, to one of us (G.Z.), is pharmacologically the most convincing experimental evidence so far that a drug habit has been formed, because in this rate-independent measure of reinforcement, devaluation of the drug reinforcer by massive presession drug self-administration did not change response (i.e. the response allocation in a choice procedure) to the drug in the subsequent test session.

Habit formation would also predict that within-session response would remain unchanged in the face of a within-session noncontingent administration of an agonist. There is, however, evidence from two independent laboratories [97, 226] that within-session noncontingent cocaine dose-dependently decreases rates of response. Finally, habit formation would predict that the shape of a DEC in self-administration experiments would flatten over time, i.e. that the actual reinforcing strength of the drug stimulus – as determined by its unit dose – would determine the rates of response less and less. As illustrated in figure 10, however, this is not the case, even in rhesus monkeys trained over 5 years under a PR of reinforcement.

R.N.C., however, emphasizes that ratio schedules are particularly ill-suited to demonstrate the development of habits. Actions trained on ratio schedules are less likely to become habitual than those trained on interval schedules [71], presumably because of the stronger response-reinforcer contingency that a ratio schedule involves [70]. It has been argued that a low level of experience of this contingency is the central factor governing habit development [69].

Recently, Panlilio et al. [177] provided evidence that squirrel monkeys self-administering cocaine over 100–300 sessions under an FR10 TO60s variable dose schedule eventually developed a tendency to self-administer the next cocaine injection before the most recent injection had been adequately distributed, suggesting that habit formation may have occurred in these animals.

Our understanding of the development of habit formation, i.e. the transition from goal-directed (action → outcome) to habitual (stimulus → response) behavior (i.e. behavior that is resistant to reinforcer devaluation) still needs deepening. For instance, it has been demonstrated that when the instrumental situation becomes complex (e.g. 2 different actions, 2 different reinforcers), behavior

remains sensitive to outcome devaluation, even after extended training [52–54, 63].

To summarize, there is limited experimental evidence of habit formation for drug reinforcers, in particular data provided by Negus [164], who used a rate-independent measure of reinforcement. Rate-dependent measures of reinforcement are prone to acute pharmacological effects on alertness and motor output and thus are of limited usefulness in modeling habit formation, which can clearly be observed clinically, especially with drugs of limited reinforcing efficacy, i.e. smoked nicotine. In the human situation, habit formation may play a role in the initiation of a bout of drug use, or in relapse, but seems of little importance once the drug has been self-administered and exerts its direct pharmacological effects.

Everitt and Robbins [80] emphasize that in drug-dependent individuals, the drug has progressed along a continuum from controlled to habitual to compulsive drug taking. They define 'compulsive' drug taking as persisting in the face of adverse consequence, in accordance with criterion 7 of the DSM-IV definition of substance dependence [14], and continue: *'This, too, has been modeled in rats, which continue to seek cocaine after a prolonged, but not brief, drug taking history in the face of conditioned or unconditioned aversive stimuli'* [64, 65, 80 (p. 1487), 229]. At the moment, it is not clear whether compulsive drug taking is subserved by other neural networks than habitual drug taking or whether both modes of drug abuse represent two stages on the same continuum of maladaptive behavior subserved by the same neural networks. It is well conceivable that habit differs from compulsion only in the relative intensities of the underlying positive and negative incentive salience components. We have therefore listed habit formation and compulsion formation under the same heading.

To summarize the previous 4 sections, there is experimental evidence, albeit at different quantitative degrees, for all 6 currently championed models of drug use escalation, i.e. for (1) the development of tolerance and (2) sensitization to apparent drug reinforcement, for (3) drug reward allostasis, for (4) an increase in the incentive salience of drug-associated stimuli, for (5) an increase in the reinforcing strength of the drug reinforcer relative to alternative reinforcers, and for (6) habit formation.

However, some of us (D.M., R.W.F., S.H.A.) point out that not all of these models are an attempt to explain the escalation of drug use. Some of us (G.Z., R.W.F.) would even argue that none of the experiments presented in this review could model, in a quantitatively convincing way, the clinical finding that the escalation of drug use is pre-dominantly based on an increase in the frequency of daily intoxication events rather than an increase in the amount of drug consumed per intoxication event. S.H.A. emphasizes that the LgA model does indeed represent a good model for the increase in the frequency of daily intoxication events, while G.Z. cautions that 6 h might not be long enough and would therefore like to see the data replicated in a ≥21-hour/day model before agreeing with S.H.A.

Having evaluated all of the currently championed models, we now proceed to evaluate other likely determinants of the escalation of drug consumption by chronic users. In doing so, we will follow the list presented in the section on components of apparent drug reinforcement (see above).

Tolerance of the Discriminative Stimulus Effects of the Drug

Chronic drug exposure has been shown to produce tolerance to the discriminative stimulus (S^D) effects of the drug, as demonstrated by numerous laboratories [178, 188, 236, 249, 250, 257]. In drug discrimination experiments in which food was used as the reinforcer and drugs of abuse (e.g. cocaine, morphine and fentanyl) as discriminative stimuli, noncontingent administration of drugs shifted the DEC to the right in a pharmacologically selective and dose-, efficacy-, and time-dependent manner. For example, noncontingent administration of 20 mg/kg i.p. cocaine every 8 h for 7 days shifted the cocaine dose-discrimination curve 2-fold to the right, indicating that tolerance to cocaine's S^D effect had developed [250]. This tolerance development to the S^D effects of the drug could also be shown for D-amphetamine (2.5 mg/kg i.p. every 8 h for 7 days) which produced a 4-fold rightward shift of the drug discrimination curve for both D-amphetamine itself and for cocaine, i.e. produced cross-tolerance to another psychostimulant [249]. This cross-tolerance was a drug-class-specific effect, because 7 days of escalating doses of morphine, i.e. up to 30 mg/kg i.p. every 8 h, which produced observable signs of opioid withdrawal, did not shift the discrimination curves of the psychostimulants [249]. Tolerance to the S^D effects of cocaine was fully reversed within 18 days [249, p. 123].

Withdrawal

Withdrawal symptoms can be powerful negative reinforcers, thus increasing the incentive value of a drug reinforcer. In addition, withdrawal symptoms can also

serve as discriminative stimuli, increasing the incentive salience of drug-associated stimuli. Accordingly, treatments that relieve withdrawal symptoms ('substitution' or 'maintenance' treatments) have so far proven most effective for the treatment of opioid dependence: methadone [12, 133, 145, 149], slow-release morphine [84] or buprenorphine [150]. Similarly, the currently most effective smoking cessation medication, varenicline [114], acts as a partial agonist at α4β-nicotinic acetylcholine receptors. Nicotine replacement treatments [115] are another case in point.

Please note that in all animal models of chronic drug self-administration, abstinence periods of various lengths, e.g. 18 h [5] to 2 days [180] were in effect between the chronic self-administration procedures themselves and other tests of reinforcement (e.g. PR schedules in the above-mentioned examples).

At the animal experimental level, considerable evidence obtained under rate-dependent tests of reinforcement, i.e. second-order schedule of reinforcement in monkeys [224], PR schedules in monkeys [256] and rate-independent choice procedures in monkeys [103, 164, 218], suggests that withdrawal increases the apparent reinforcing strength of opioid agonists. Most interestingly, the increase in the apparent reinforcing strength of the opioid agonist, e.g. heroin, critically depends on the animal's previous experience with this agonist in withdrawal, as shown in rats [111].

In the study by Steve Negus [164], 1 day after termination of noncontingent administration of 0.56 mg/(kg·day) methadone, given for 5 days, the intravenous heroin choice curve was shifted at least 3-fold to the left (from an ED_{50} of 0.01–0.013 mg/kg to an $ED_{50} < 0.0032$ mg/kg). In a second set of experiments [164], care was taken to quantify the severity of the opioid withdrawal symptoms induced by >7 days of self-administered heroin [average self-administered dose: 3.9 mg/(kg·day)] and compare the time course of their dissipation with the time course of choice for an intravenous heroin dose (i.e. 0.0032 mg/kg) that had not been chosen over food in nondependent monkeys. On the first day of heroin withdrawal, the monkeys showed a withdrawal score of over 4 (maximum obtainable score, 8) and chose the previously nonpreferred heroin dose in about 75% of occasions. Heroin choice dissipated with a time course similar to the withdrawal symptoms with, interestingly, observable withdrawal symptoms being completely gone (i.e. on day 5 of abstinence) 1 day before heroin choice completely reversed [164, fig. 7]. This finding strongly indicates that subtle withdrawal signs that escape observation still determine an individual's preference for a drug over an alternative food reinforcer.

In contrast to opioids, most data on cocaine suggest that withdrawal from exposure to extensive cocaine self-administration does not increase the reinforcing efficacy of cocaine under PR schedules in monkeys [62, 256] or rats [141, 160] or a choice procedure in monkeys [163].

In a series of PR studies in rats, Morgan et al. could see limited increases in the reinforcing strength of cocaine (i.e. increases in breakpoints only at high unit doses) only after the animals had self-administered a dose of 20 mg/(kg·day) cocaine [table 1; 158, 161]. However, no increase in breakpoints was observed in these parametric studies when the previously self-administered dose was increased again to 60–100 mg/(kg·day) cocaine (table 1), arguing against withdrawal symptoms as a major determinant of the observed increase in the reinforcing effect of cocaine, because withdrawal symptoms should increase monotonically with the self-administered daily drug dose. In contrast, Athina Markou and coworkers showed that after an abstinence period of 2 days, breakpoints for all tested cocaine doses (i.e. 0.095–0.77 mg/(kg·injection) as well as for saline itself were increased [180].

This apparent discrepancy between opioid and cocaine data can be resolved (see synthesis section) when one considers that cocaine levels in brain are much more tightly regulated by laboratory animals than opioid levels are, and that, in consequence, much higher relative doses of opioids are self-administered, rendering the emergence of withdrawal symptoms much more likely for opioids than for cocaine. This is paralleled in the human situation: clinically, withdrawal symptoms are known to be much more pronounced in human opioid users than in cocaine users, so much so that for a long time common knowledge affirmed that clinically relevant cocaine withdrawal symptoms in chronic cocaine users simply did not exist.

Increase in the Incentive Value or the Hedonic Value of the Drug

There is, to our knowledge, no experimental evidence in which changes of the hedonic value of a drug have been directly assessed (i.e. while taking care to eliminate the contribution of the other factors contributing to apparent drug reward; see fig. 1) before and after chronic drug consumption. In contrast to the hedonic value of a drug (so far an indivisible psychological entity), the incentive value of a drug is actually the consequence of several oth-

er factors (fig. 1 and section on definitions of reinforcement and reward). For example, withdrawal symptoms (see section on withdrawal) can increase the incentive value of a drug. Therefore, the reader is referred to the other sections of this review for a further discussion.

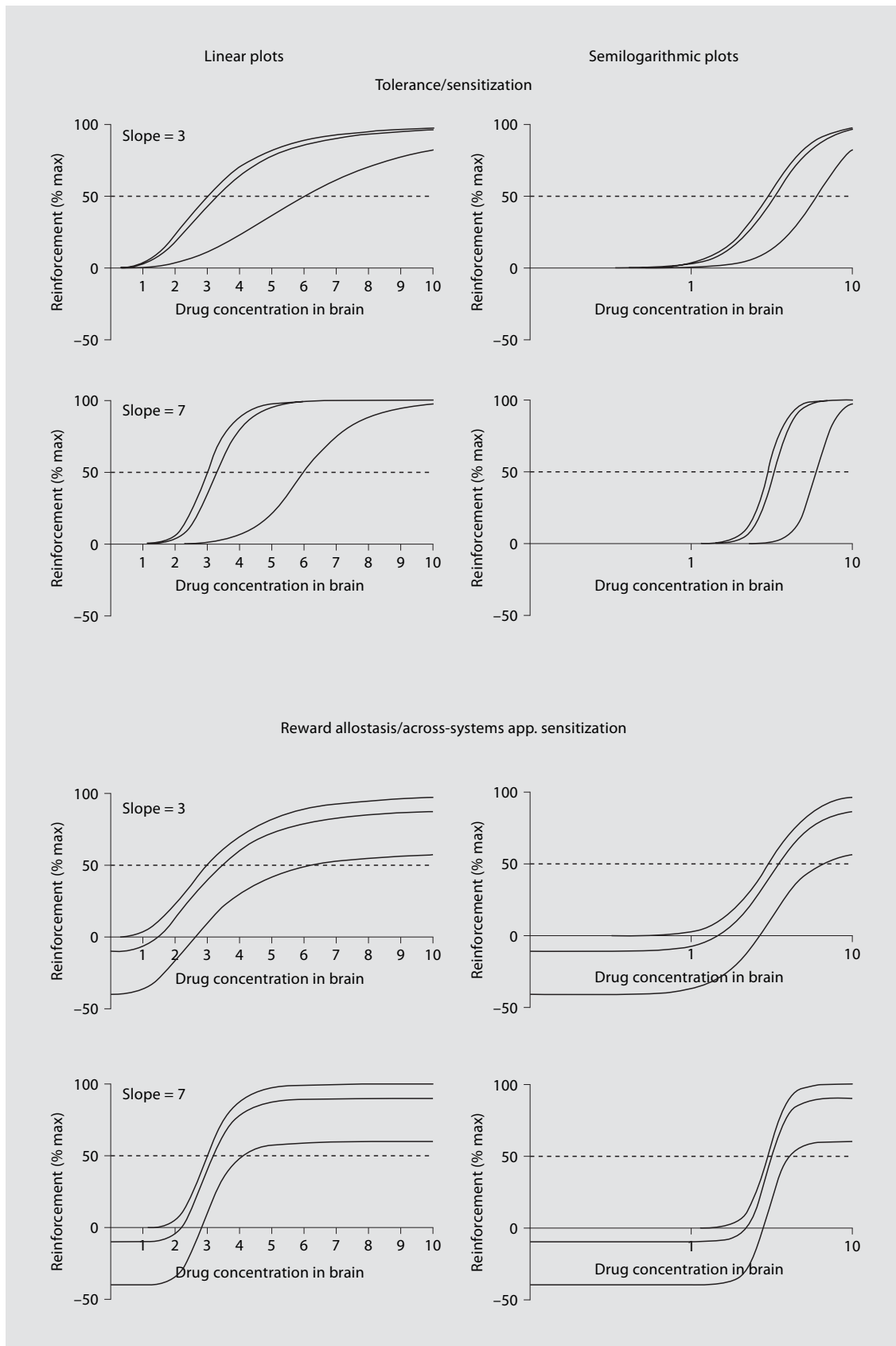*Predictions about Changes in Shapes and Shifts of Dose-Effect Curves*

Which changes in dose-reinforcement curves do the individual models predict, provided the experimental approaches yield monophasic DECs that are amenable to pharmacological analysis? Figure 11 summarizes the most distinctive features, both for linear and semilogarithmic dose-effect plots familiar to most researchers: if the change (tolerance or sensitization) occurs in one and the same system (or systems closely interacting and amplifying each other), DECs would be shifted in a parallel manner. In contrast, the reward allostasis (i.e. across-systems-based apparent tolerance) model or in 'reverse reward allostasis' (i.e. the activation of yet another system that increases apparent reinforcement), the lowermost and uppermost portions of the DEC (i.e. response to very low or very high drug unit doses) would be affected most. Thus, the following general rule emerges: if chronic drug consumption activates a system that had previously been silent (leading to either reward allostasis or 'reverse reward allostasis', i.e. across-system-based apparent sensitization), the lowermost and uppermost parts of the saturable monophasic DEC should be affected most, as has indeed been shown (shift in the lowermost portion of the DEC [232]; shift in the uppermost portion of the DEC [161]). If, however, the changes occur in the system(s) that had originally mediated the apparent reinforcing effect of the drug, parallel shifts of the whole DEC should occur [76, 246]. Please note that both the shape of the control DEC as well as the degree of the chronic drug administration-induced shift also strongly depend on the number of closely interacting/amplifying systems: the higher the number of closely interacting systems, the steeper the slope of the control DEC becomes (and steep slopes are a common feature of self-administration DECs; see, e.g., the figures in the present review). The larger the number of closely interacting systems that mediated apparent reinforcement under control conditions, the smaller the DEC shift induced by chronic drug intake becomes.

Animal Experimental Data: Changes in Nucleus Accumbens Dopamine Release upon Repeated Drug Exposure

Of all the possible changes in brain function and anatomy that could be or have been shown to be induced by chronic drug administration (contingent or noncontingent), this review will focus on the release of DA in the Acb, because Acb DA release is commonly agreed to be the central neurochemical correlate of (1) the acute, unconditioned and (2) the conditioned effects of drugs of abuse (see recent reviews on the role of Acb DA release in the apparent reinforcing effects of drugs [68, 81, 132, 240], but see Crespo et al. [61] for evidence necessitating modifications of the 'dopamine theory of reward').

Experimental evidence indicates that changes in behavior and DA transmission in the ventral striatum do not always progress jointly. The development of behavioral and neurochemical sensitization depends on the previous dosing and the time interval from last administration [1, 118, 119]. The development of tolerance (i.e. a decreased DA release upon contingent or noncontingent administration of drugs of abuse) with respect to overall Acb DA release was observed 1–3 days after the end of the chronic administration but tolerance dissipated by 4–7 days. Sensitization was not seen before 10–14 days after the end of chronic drug administration. A recent study on AcB DA release by DiChiara et al. [68] took both the accumbens shell/core- [106, 258] and the contingent/noncontingent dichotomies into account by using a master-yoked rat paradigm. Development of 'behavioral sensitization', i.e. increased locomotion and a simultaneous shift from nonstereotyped to stereotyped activities [39, 119, 136], increased during 3 weeks of chronic intermittent noncontingent cocaine administration (reflecting cocaine's unconditioned pharmacological effects) and were associated with a 1.6-fold (210%/130%) increase in peak AcbC DA release, whereas the AcbSh DA release remained the same (190%/190%). In discussing their work, DiChiara and coworkers draw attention to the fact that during the third week of noncontingent cocaine administration, i.e. at a time when cocaine-induced stereotypes and locomotion have become most pronounced, there is an actual reversal of the shell/core ratio from 190%/130% during week 1 to 210%/190% during week 3 [136, fig. 4].

In contrast to the unconditioned effects of cocaine, during contingent cocaine administration, i.e. when cocaine was self-administered by the rat (reflecting the conditioning of the cocaine stimulus and cocaine-associated nondrug stimuli by associative learning), both AcbSh

Linear plots

Semilogarithmic plots

Tolerance/sensitization

Reward allostasis/across-systems app. sensitization

Zernig et al.

and AcbC DA release were progressively increased, from 270 to 430% in the AcbSh (i.e. 1.6-fold) and from 170 to 250% (i.e. 1.5-fold) in the AcbC [136, fig. 4]. A similar increase in DA release in both the AcbSh and AcbC was seen for the cannabinoid (CB1) receptor agonist WIN 55,212–2 [137] and for nicotine [138]. It should be noted, however, that other laboratories have found either no change [10, 213] or decreases [148] in DA responsiveness to cocaine following extended histories of cocaine self-administration.

Some of us (G.Z., S.H.A.) would like to point out that the above section on Acb DA release must be considered largely incomplete, as it omits the work of many researchers in the field. It does, however, at least in the opinion of one of us (G.Z.), present a first glimpse to the novice in the field as to which challenges are to be faced when trying to combine behavioral and neurochemical evidence for the investigation of the phenomena known as 'tolerance' and 'sensitization'.

Synthesis

How can we reconcile the apparent discrepancies between the data discussed above? A direct comparison of the psychostimulant cocaine and the μ-opioid receptor agonist remifentanil, both short-acting drugs of abuse, is helpful here. Both prototypical drugs are pharmacoki-

Fig. 11. Shifts of monophasic DECs of overall drug reinforcement predicted by within-system or across-system changes possibly induced by chronic drug consumption. Shown are linear plots (left column) and semilogarithmic plots (right column) of DEC shifts predicted by tolerance or sensitization (upper 4 panels) versus reward allostasis or across-systems apparent sensitization ('reverse reward allostasis'; lower 4 panels). DECs were generated with the general logistic equation developed by Black and Leff [32] with the following common parameters: maximum effect, 100%; dose-producing half-maximum effect (ED_{50}), 3 drug brain concentration units; slopes were set at 3 and 7. In the case of development of tolerance, ED_{50} values were assumed to be changed from 3 to 3.3 to 6 concentration units (leftmost to rightmost curve), i.e. the apparent potency was assumed to be decreased by 10 or 50%. For sensitization, this family of curves can be read from the rightmost to the leftmost curve. In the case of development of reward allostasis (i.e. across-systems-based apparent tolerance), the baseline was assumed to be downshifted by 10 or 40% (leftmost to rightmost curve). For across-systems-based apparent sensitization, read the family of curves from the rightmost to the leftmost curve. Please note that for ≥3 closely interacting systems (i.e. a slope of 3), DECs are slightly sigmoid even in a linear plot. This effect is more pronounced for ≥7 closely interacting systems.
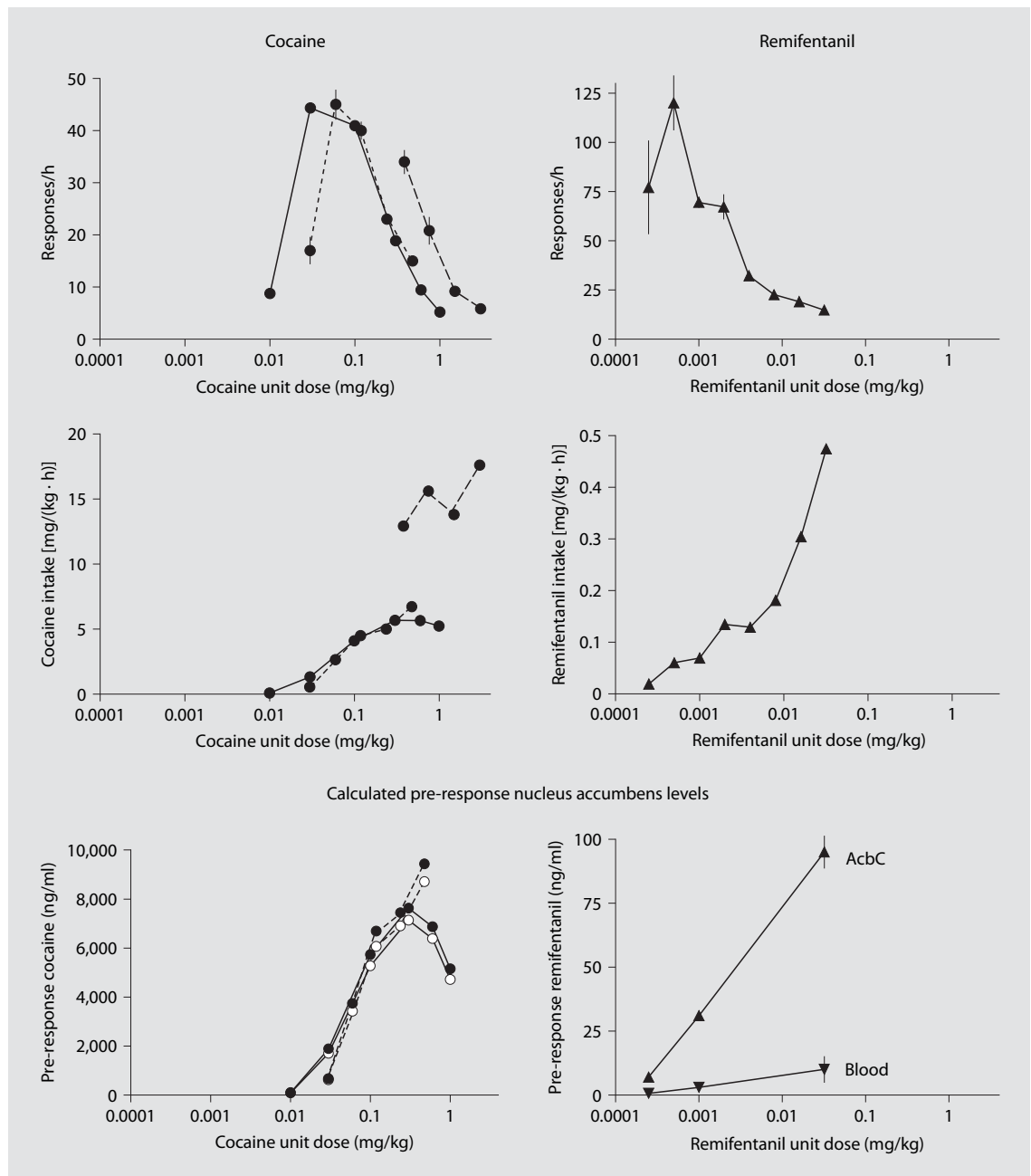
netically pure (i.e. are not metabolized to any significant degree to active metabolites with very different elimination half-lives, a bane of the pharmacological tool heroin, i.e. diacetylmorphine, which is metabolized to morphine). Both have similar pharmacokinetics: their elimination half-life in a deep brain structure, the AbcC, is essentially identical, at around 9–10 min [60, 61, 108, 174]. Their elimination from the blood is similar: the elimination half-life of remifentanil ranges from 0.3 to 0.7 min [60], while around 80% of cocaine is eliminated with a half-life of 1.6 min (the remaining 20% being eliminated with a half-life of 11 min), as close inspection [59] of the classic – and often misquoted – pharmacokinetic data of Pan et al. reveals [174, fig. 1, 4]. One of us (D.M.) points out that an approximately 3-fold difference in the speed of elimination from the blood between remifentanil and cocaine may be quite relevant, while another (G.Z.) would argue that despite this 3-fold difference, the elimination half-lives of cocaine and remifentanil in the blood can be regarded as quite similar, considering the vast overall differences in elimination half-lives of drugs of abuse used as experimental tools, e.g. 0.3–0.7 min for remifentanil or 1.6 min for cocaine versus 21 min for 90% of the available morphine as recalculated from Bhargava et al. [29] (these authors give a terminal half-life of 3.7 h for morphine) versus 68–75 min for amphetamine [192] versus 70 min for methamphetamine [50] (all data obtained in rats). G.Z. would also argue that despite the difference in the speed of elimination of cocaine and remifentanil from the blood, their elimination half-lives from the pharmacologically most relevant compartment, i.e. the extracellular space of a brain structure such as the Acb, is essentially identical (i.e. 9–10 min).

What does the comparison of the self-administration data of cocaine and remifentanil obtained under an FR1 schedule, which in essence is a drug self-titration procedure, tell us? First of all, figure 12 shows that the hourly intake and the brain level are more tightly regulated for the psychostimulant cocaine than for the μ-opioid receptor agonist remifentanil. This has already been proven by the elegant and numerically precise variability analysis of Panlilio et al. [175, fig. 5D]. We posit that cocaine levels in the brain and periphery are more tightly regulated because the ED_{50} for the aversive (e.g. cardiovascular or epileptogenic) effects of cocaine lies closer to its ED_{50} for apparent reinforcement than the respective ED_{50}s of remifentanil. Accordingly, cocaine has been shown to exert both positively reinforcing and aversive effects at the very same self-administered unit dose (i.e. 5 intravenous cocaine injections of 0.75 mg/kg spaced 30 s apart) in the

Fig. 12. Brain cocaine levels are more tightly regulated than brain levels of the μ opioid agonist remifentanil. Self-administration data obtained under an FR1 schedule of reinforcement are shown for cocaine (left column) and remifentanil (right column). Data were obtained under an FR1 TO5s schedule by Panlilio et al. [175] (solid lines), under an FR1 TO20s schedule by Ahmed and Koob in ShA rats [7] (short-dashed lines), and under an FR1 TO20s schedule by Morgan et al. [161] (long-dashed lines). The top row shows unit dose versus response rate relationships; the middle row displays dose versus hourly intake relationships. The bottom row shows preresponse AcbC levels after 30 min (open circles) or 60 min (filled circles) of the FR1 self-administration experiment had elapsed. Brain concentrations of cocaine were calculated from the self-administration data by Panlilio et al. [175] (solid lines) or Ahmed and Koob [7] (dashed lines) using the following pharmacokinetic parameters from Pan et al. [174]: association half-life, 3 min; elimination half-life, 9 min; volume of distribution, 0.15 l/kg. For the calculation of prerepsonse AcbC remifentanil levels, raw self-administration data obtained by Panlilio et al. [175] were used to calculate the prerepsonse levels of remifentanil [59] in blood (inverted triangles) and AcbC (triangles) for 8 consecutive responses emitted after 30 min of the self-administration session had elapsed (i.e. under steady-state conditions), employing remifentanil pharmacokinetic parameters obtained by Crespo et al. [60]. Please note that the relationship between remifentanil unit dose and mean remifentanil levels is a saturable

rat runway procedure by Ettenberg and coworkers [96]. In the same vein, some of us [235], using the same operant conditioning paradigm, demonstrated that cocaine at intravenous unit doses between 0.0032 and 0.01 mg/kg (a 3-fold range) produced positive reinforcing effects [235, fig. 2, while becoming aversive at 0.1 mg/kg, i.e. at a 10-fold higher unit dose. In contrast, remifentanil [235, fig. 3] showed only positive reinforcing effects up to the highest dose tested, i.e. over a unit dose range of 0.0032–0.1 mg/kg (a 313-fold range). Although the rat runway experiments do not provide direct evidence for tight self-titration of psychostimulants, they show that overall pronounced positive reinforcement for cocaine occurs over only a small range of unit doses, and that positive reinforcing effects (observable as running towards the goal area in which the rat receives the drug) and negative reinforcing effects (observable as retreats) of cocaine can be observed at the very same unit dose tested.

As a result of the apparently tighter regulation of cocaine levels, DECs of drug response are narrower for cocaine than for remifentanil (fig. 12). This also holds true when cocaine and remifentanil are directly compared (both under an FR1 schedule) in the same laboratory [175, fig. 4A; redrawn in fig. 12].

The tighter regulation of cocaine levels compared to remifentanil levels by the experimental animal means that chronically self-administering animals, when tested over the whole dose range, are exposed to higher above-threshold doses of the opioid remifentanil than the psychostimulant cocaine (fig. 12). It should be emphasized here that 'above-threshold dose' does not refer to absolute dose [in mg/kg or mg/(kg·h)] which would be simply dependent on the affinity of the drug for the respective receptor system(s), but to dose [in mg/(kg·h)] with respect to the hourly intake at the threshold unit dose that engenders responding.

Figure 12 shows that for cocaine, hourly intake is held relatively constant from unit doses onwards that are at maximum only 10-fold higher than the threshold unit dose: 0.1 versus 0.01 mg/kg in the experiments by Panlilio et al. [175], 0.06 versus 0.03 mg/kg in those by Ahmed and

Koob [7, fig. 2D], and 0.38 mg/kg versus lower doses (not tested) in those by Morgan et al. [161]. Of note, the cocaine self-administration data by Morgan et al. [161] was obtained in rats with a history of escalating cocaine self-administration, plausibly explaining their higher overall intake compared to the rats studied by Panlilio et al. [175] and Ahmed and Koob [7].

In contrast to cocaine, hourly intake of remifentanil increases proportionally at least up to a unit dose that is 128-fold higher than the threshold unit dose (0.032 vs. 0.00025 mg/kg). Accordingly, calculated prerespone remifentanil levels in the AcbC also rise continuously over a large range of self-administered remifentanil unit doses, i.e. from 0.00025 to 0.032 mg/kg (fig. 12) [59]. Again, this also holds true when cocaine and remifentanil are compared directly (both under an FR1 schedule) in the same laboratory [175, fig. 4B; redrawn in fig. 12].

It should be emphasized that the tight titration of cocaine levels described above does not mean that this occurs at cocaine levels that are close to saturating the reinforcement-mediating system(s). On the contrary, we posit that cocaine is self-titrated by rats to levels that are well below levels that would saturate (i.e. fully use the potential) of reinforcement-mediating system(s). So far, this is very hard to prove at the quantitative pharmacological level, because even for very simple behavioral measures, such as cocaine-stimulated motor activity, the correlation between in vivo DA transporter binding (occupancy) by cocaine and behavioral effect of cocaine (motor activity) is poor. Desai et al. [66, fig. 4] determined a correlation coefficient of only 0.61 between DA transporter occupancy and locomotor stimulation in mice. An r of 0.61 corresponds to an r^2 of only 0.37, which means that only 37% of the variation in the motor stimulation of cocaine could be explained by DAT occupancy, although numerically, ED_{50} values for in vivo binding and motor stimulation were essentially identical (0.038 vs. 0.048 mg/kg i.p. with widely overlapping 95% confidence intervals) [66, table 2]. This indicates that even a simple behavioral effect of cocaine such as motor stimulation is most likely mediated by more than cocaine binding to only the DAT. Desai et al. state this in their discussion: '*Collectively, these findings suggest ... that factors in addition to levels of DA transporter occupancy are involved in the behavioral effects of DA uptake inhibitors.*' [66, p. 403]. One can easily imagine that the situation might be even more complicated for apparent reinforcement, a much more complex behavioral measure. In other words, we simply do not know at a quantitatively satisfactory level which systems in addition to the DAT substantially contribute to

one (a linear relationship would yield an upwardly concave curve on a semilogarithmic plot, see fig. 4b), suggesting that brain remifentanil saturation by self-titration (and, likely, saturation/satiation of the μ-opioid receptor system subserving apparent reinforcement) was approached only at the highest remifentanil unit dose, i.e. 0.032 mg/(kg·infusion). Blood remifentanil levels were calculated as described by Crespo et al. [59].

cocaine's apparent positive or negative reinforcing effects or punishing effects.

A methodological note regarding the analysis presented in figure 12: actual brain concentrations of the drug under investigation would, of course, be the best measure to assess receptor events mediating apparent reinforcement. Performing the in vivo microdialysis or in vivo voltammetry experiments that would be required for this measure during a multiple-injection lever-press-based self-administration experiment is, however, a formidable experimental challenge few laboratories have faced. Therefore, we chose to take pharmacokinetic data obtained by in vivo microdialysis under less demanding experimental conditions, i.e. the runway operant conditioning paradigm [59–61], and used this data to calculate the drug levels in a deep brain structure, the AcbC (see bottom row of fig. 12). If, furthermore, the brain distribution and brain elimination half-lives of the drug are much shorter than 1 h (which is the case with cocaine or remifentanil, see above), then the hourly intake (see right column of fig. 12) is also a fair approximation of the steady-state brain levels reached during the experimental session, the differences between minimum and maximum brain levels being proportional to the unit dose.

Importantly, the dose of the chronically administered drug (again, regardless of whether the drug was administered contingently or noncontingently; table 1) is critical for the development of tolerance or sensitization: low doses of chronically administered drug, e.g. 20 mg/(kg·day) intravenous contingent cocaine, favored the development of sensitization [158, 161], whereas high doses, e.g. 73–78 mg/(kg·day) intravenous contingent cocaine, were more likely to induce tolerance [160]. Similarly, tolerance to the rate-decreasing effects of cocaine in an FR2 schedule of reinforcement was seen after noncontingent administration of 20 mg/kg every 8 h, i.e. 60 mg/(kg·day), for 10 days [76].

Taken together, the fact that (1) cocaine but not opioid levels are so tightly regulated in self-titration procedures (i.e. FR5- or FR1 self-administration), and the conclusion that (2) animals self-administering opioids but not cocaine will be exposed to drug doses that are much higher than the threshold dose that is just sufficient to elicit a response, make the development of tolerance much more likely for opioids [246] than for cocaine [7, 161]. Whenever the development of tolerance to the effects of cocaine was observed, animals had been exposed to at least 60 mg/(kg·day) intravenous cocaine for several days (table 1), which must be considered a massive dose. This fits with the clinical observation that at commonly abused doses, cocaine produces only a very moderate withdrawal syndrome [14], in contrast to the much more pronounced withdrawal syndromes of opioids, benzodiazepines, barbiturates and alcohol.

Furthermore, the time point at which tolerance or sensitization was found depended critically on the temporal relationship between the actual experiment and the chronic drug treatment (contingent or noncontingent; table 1): tolerance to apparent reinforcement [246] or rate-decreasing effects [76] was seen during treatment or 1 day after cessation of treatment, whereas sensitization to the apparent reinforcing effect was found not earlier than 7 days after cessation of the chronic drug treatment.

It is very well conceivable that reward allostasis (i.e. the apparent tolerance to the reinforcing effect of 'natural' rewards that is based on the activation of previously 'silent' systems that counter the 'natural' reward-induced changes in brain activity) contributes to the increase in drug-taking frequency in rats that had self-administered cocaine for an extended period of time [7]. More importantly, the reward allostasis model predicts that relatively modest (i.e. 1.3- to 2-fold) increases in self-titrated cocaine intake that have been observed in the animal laboratory [7] – and which presumably occur at below 50% of maximum possible reinforcement – translate to a pronounced (i.e. 40%) decrease in maximum possible reinforcement (see fig. 11), i.e. at a range of the DEC most likely relevant for human drug users who strive for profound drug-induced changes in the their subjective state.

At the construct validity level, we should be aware that FR1 or FR schedules of reinforcement with response requirements of 5 or less (one of us, R.N.C., warns against giving an exact cutoff in what is actually a continuum) are not suited to assess the incentive value of the drug or the incentive salience of drug-associated stimuli but should be regarded as drug self-titration procedures. Intermittent schedules of reinforcement, especially progressive ratio schedules or second-order schedules, seem much better suited to quantify apparent reinforcement [79, fig. 1], provided that responding occurs in an essentially drug-free state (i.e. ≥4 brain elimination half-lives after the last drug infusion or, as strongly emphasized by Everitt and Robbins [79], during the first drug-free interval of a second-order schedule). For the same reason, priming the animals with a noncontingent dose of the drug at the beginning of the self-administration session should be avoided at all cost. Again, one of us (D.M.) points out that if priming does not affect the hypothesis being tested it may well be used.

Table 1. Time course of the development of tolerance or sensitization and its reversal

Possible mechanism	Change in experimental measure	Chronic drug treatment	Onset of change (days after end of treatment)	Reversal of change (days after end of treatment)	Reference
Tolerance to the apparent reinforcing effect of opioids	Parallel rightward shift of ascending part of FR30 DEC in rhesus monkeys	Noncontingent: 3.2 mg/(kg·day) s.c. morphine	27–29 days within treatment	7–95 days	[246]
Tolerance to rate-decreasing effect of cocaine Reward allostasis	Upward shift of descending part of FR2 DEC in rats	Noncontingent: 20 mg/kg i.v. cocaine every 8 h = 60 mg/(kg·day) i.v. for 10 days	1 day	6 days	[76]
Tolerance to apparent reinforcing effect of cocaine	Decrease in breakpoints for high cocaine unit dose in PR DEC in rats	Contingent: 20 mg/(kg·day) i.v. cocaine for 10 days in FR1 discrete trials procedure	1 day	3 days	[160]
Tolerance to the discriminative stimulus effects of cocaine	Parallel rightward shift of drug discrimination DEC in rats	Noncontingent: 20 mg/kg i.p. cocaine every 8 h = 60 mg/(kg·day) i.p.	1 day	18 days	[249]
Tolerance to cocaine-induced DA release in AcbC and ACbSh	Decreased cocaine-induced DA release in rats	Contingent: 73–78 mg/(kg·day) over 10 days cocaine in FR1 discrete trials procedure	1 day	7 days still full tolerance	[148]
Sensitization to apparent reinforcement of amphetamine Reverse reward allostasis	Leftward shift of PR DEC in rats	Noncontingent: 5 × 1.5 = 7.5 mg/kg i.p. amphetamine every 72 h	15 days	?	[232]
Sensitization to apparent reinforcement of cocaine	Increases in breakpoint in PR only at high cocaine unit doses, i.e. 1.5–3 mg/(kg·injection)	Contingent: approx. 60 mg/(kg·day) cocaine in a 24-hour/day access FR1 discrete trials procedure for 10 days	7 days (no effect on day 1)	28 days? (still full effect at 21 days)	[161]
Sensitization to apparent reinforcement of cocaine	Upward shift in DEC	Contingent: 20 mg/(kg·day) cocaine in FR1 trials for 5 days. No effect when cocaine was increased to 60–100 mg/(kg·day)	Develops over 7–14 days	28 days? (still full effect at 21 days)	[159]
Sensitization to apparent reinforcement of cocaine Reverse reward allostasis	Increases in breakpoint in PR for saline and all tested cocaine doses, i.e. 0.095–0.77 mg/(kg·injection) in LgA rats	Contingent 14 + 5 days LgA (6 h): 89 mg/(kg·day) vs. ShA (1 h): 13 mg/(kg·day)	2 days	?	[180]

At the theoretical level, the best approach is to view 'sensitization' in drug dependence as a learning process, a change in priorities, that leads human drug users to spend an increasingly larger fraction of their daily time in drug-related activities, a process that is accelerated by the increase in the apparent reinforcing effects of the drug which is based on a number of factors detailed above. Accordingly, long-access (≥21 h/day) self-administration paradigms in which response to the drug under intermittent schedules is determined in an essentially drug-free state (≥4 elimination half-lives after the last drug administration) may be the best way to model human substance dependence. Progressive ratio schedules, second-order schedules or chain (tandem) schedules might be best suited to quantify such an increase in the percentage of daily time spent in drug-seeking activity. Thus, these intermittent schedules of reinforcement start

to get at the complexity of the human situation in which allocation of effort in drug seeking is the hallmark of substance dependence. However, FR1 schedules in sessions extending ≥21 h/day have also been able to model the fact that the escalation of human drug use is based much more on frequency than unit dose [158–160, 193]. Rate-free choice procedures [164, 167, 209] may be another experimental approach to assess the mechanisms underlying escalating drug use, again provided that the allocation of responses has consequences with respect to relative time spans spent in drug- versus non-drug-related behaviors, and that these relative times are observed over long (≥21 h/day) experimental sessions. However, some of us (D.M., S.H.A.) point out that 6-hour sessions are long enough to detect and statistically validate the escalation of drug consumption and the change in time spent in drug-related versus non-drug-related activities.

At the clinical level, the observation that the escalation of drug use by substance-dependent humans is predominantly due to an increase in time spent in drug-related activities rather than an increase in the drug dose consumed per intoxication event (see above) might indicate that increases in the incentive salience of a drug stimulus, and especially drug-associated stimuli [43, 80, 112], seem to be more important than the development of tolerance to the subjective (apparent reinforcement-relevant) effects of the abused drugs. Investigating these changes in the incentive salience of drugs might be best accomplished by PIT procedures [255] or second-order schedules (see 79 for a recent review). Alternatively, operant conditioning procedures that allow the quantification of pavlovian approach behavior, such as the runway procedure [61, 95, 235], may also be suited to assess the changes in incentive salience.

Future Directions

As has been true for a lot of scientific debates, most likely we shall find out that all of the above systems and effects – and likely many more – are substantially involved and contribute in a predominantly parallel mode to such a pervasive mental disorder as drug dependence.

At the quantitative level, the above review of the available experimental evidence suggests that none of the explanations provided so far is of an impact great enough to explain the massive escalation of drug consumption observed in human drug users (i.e. up to 20-fold for intravenous cocaine and up to 46-fold for intravenous morphine), most importantly because the expected increase in the percentage of daily time spent in drug-seeking activities has not been quantified yet at the animal experimental level.

Also, our laboratory models emphasize conditions that lead to excessive drug use by employing simple approaches and limiting alternative behaviors and/or enrichment. The fact that so few drug-exposed humans actually become drug dependent (in the case of alcohol, ≥95% have been exposed by the age of 18, yet only 5% of the adult population in most industrialized countries actually are alcohol dependent [265]; the incidence rates should be much lower for illicit intravenous drugs) argues that the current animal models provide little data about which factors are responsible for the fact that most people do not become substance dependent [5].

One of these factors that has not been covered in this review, but is the subject of intensive research efforts [22, 204], is the chronic drug-use-mediated impairment in systems conferring impulse control (prefrontal and anterior cingulate cortical systems with 'superego' functions, to use an apt psychoanalytical term). In a similar vein, various psychotherapeutic and psychoanalytical theories have often asserted that substance dependence in humans is only a symptom of profound narcissistic deficits, i.e. deficits in satisfying representations of oneself and of role models. It would, in the opinion of some of us (P.G., C.H., E.M., G.Z.), be very worthwhile to investigate the neuroanatomical and neurochemical basis of such assertions, while one of us (D.M.) cannot imagine that this is possible.

Finally, we should not forget that most drugs of abuse have provided dependent individuals with subjective effects of an intensity and quality that were far beyond the levels attainable by their nondrug activities. In the psychotherapeutic setting, one can often make the baffling observation that renouncing the drug produces the most intense feeling of loss and mourning the drug users have known in their lives. A number of neuroimaging studies of the neuroanatomical basis of these overwhelming drug-induced subjective effects are available [36, 203, 206]; expanding this type of research to laboratory animals would be worthwhile. Hopefully, the recent and very rigorous behavioral study on psilocybin-induced spiritual experiences by Griffiths et al. [102] will have opened the way for the proper scientific investigation of the neurological basis underlying such intense drug-induced subjective effects and their pharmacotherapeutic and psychotherapeutic targeting.

Acknowledgments

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