Monoamines, Acetylcholine and Contingency of Reward Delivery in Instrumental Behaviour

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Introduction

There is much empirical support for the notion that acetylcholine (ACh) and the monoamine neurotransmitters noradrenaline (NA), dopamine (DA) and serotonin (5-HT) modulate cognitive processes (including attention, learning and memory, executive control and decision-making) in specific and distinct ways. The application of in-vivo brain microdialysis in closely controlled behavioural settings has greatly facilitated research in this area, particularly in defining with greater precision the different task contingencies that produce robust and specific changes in ACh, NA, DA and 5-HT release. In recent experiments we have adapted this technique in rats within the context of a 5-choice serial reaction time task (5-CSRTT)[1-5], which provides a sensitive behavioural assessment of visuo-spatial attention and impulsivity. The basic configuration of the task requires subjects to detect and respond to brief light stimuli presented randomly in one of five spatial locations over many trials in order to receive food reinforcement. The paradigm has a basic form that is analogous to the human continuous performance tests devised by Mirsky and Rosvold[6]; and still much used in clinical settings to quantify attentional deficits in AD/HD and schizophrenia. It is known that discrete lesions of different sub-divisions of the prefrontal cortex (PFC) affect different aspects of performance on the 5-CSRTT[7], especially lesions of the medial PFC (including anterior cingulate, prelimbic and infralimbic cortices). In this presentation we present data from several recent studies that combine behavioural testing on the 5-CSRTT with in-vivo microdialysis. Probes were implanted in the medial PFC and animals were tested under different behavioural contingencies in order to tease apart the unique involvement of ACh, NA, DA and 5-HT in instrumental (response-dependent) visual attentional performance.

Materials and Methods

Male Lister-Hooded rats (300-380g, Charles River, UK) were trained on the 5-CSRTT over a period of approximately 4-6 months. The apparatus consisted of eight nine-hole chambers (25x25cm), each placed in a ventilated sound-attenuating chamber and illuminated by a 3W bulb[7]. At the front of the box, a magazine connected with a food dispenser was present, with access monitored by an infrared beam. At the rear of the box were five apertures with infrared photocell

beams at the entrance to detect nosepoke responses. Rats were trained to report the occurrence of brief light stimuli presented randomly in one of the five spatial locations. Following training, a 2-mm concentric-design microdialysis probe was implanted in the medial PFC (AP +3.0 mm; L ±0.6 mm; V -4.0 mm; 12^{o} to the perpendicular) under ketamine/xylazine anaesthesia. Animals were tested on the 5-CSRTT after a 48-hour recovery period. HPLC-ECD was used to quantify NA, DA, 5-HT and ACh levels in the cortical dialysates. Three experimental manipulations were used. The first examined the impact of degrading the instrumental contingency of the task on NA and ACh release (i.e., the predictive relationship between behavioural actions and food reinforcement) using a yoked design procedure[1]. In this experiment half of the animals continued to perform the 5-CSRTT as before with response-dependent reinforcement ('contingent' group). The remaining animals ('non-contingent' group) received food rewards only when animals in the contingent group made a correct response. Animals in this group received the same visual stimuli as their contingent counterparts and were free to engage on the task, however, their actions had no programmed consequences. It was predicted that attentional demands would be less in this group and that this would be reflected by altered neurotransmitter release in the PFC, particularly ACh which has been strongly implicated in attentional processes. The second experiment evaluated the effects of increasing the load on inhibitory control mechanisms by delaying the onset of the target stimulus[2]. A failure to withhold responding before the onset of the target stimulus is a form of impulsive behaviour that, in other settings, has been linked to 5-HT dysfunction. The third experiment evaluated the effects of isolation-rearing on attentional performance[3]. Rats reared in social isolation from an early adolescent age are hyperactive and exhibit specific attentional impairments. Few studies, however, have assessed the impact of isolation-rearing on cortical monoamine function, particularly in conjunction with behavioural testing on the 5-CSRTT.

Results and Discussion

Prefrontal ACh release increased significantly during sustained performance on the 5-CSRTT. Subjects in the non-contingent group detected the change in instrumental contingency by the second 5-min block of trials, as revealed by fewer correct responses and more head entries in the food magazine. Cortical ACh release also increased in these subjects but this increase was significantly attenuated relative to the contingent group. By contrast, NA release, though not increased in contingent subjects, was increased in the non-contingent group, especially on the first day of testing. These data implicate ACh and NA in different cognitive functions; the former during sustained attentional performance, the latter in settings requiring new learning. The results of experiments 2 and 3 revealed a further dissociation in neurotransmitter function in the PFC with increases in DA, but not 5-HT release during established visual attentional performance. However, in the case of 5-HT, a significant positive relationship was

found between PFC efflux and impulsivity, implicating a specific component influence of this neurotransmitter in executive control processes. Support for this notion stems also from the results obtained in isolation-reared rats which were paradoxically less impulsive on the 5-CSRTT and showed reduced levels of 5-HT in the PFC following administration of the psychomotor stimulant d-amphetamine. These neurochemical findings are compatible with the view that NA, DA, ACh and 5-HT modulate different cognitive processes, presumably related to the adaptive imperative to optimize instrumental performance under different task demands. The challenge for future research will be to devise new behavioural strategies to dissociate further the different component processes modulated by the ascending cholinergic and monoaminergic systems.

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