Emergence of phasic dopamine signaling in the dorsolateral striatum during cocaine self-administration mediates discriminated drug-taking behavior

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Introduction

Drug addiction is a neuropsychiatric disorder that marks the end stage of a progression that begins with recreational drug taking but culminates in habitual and compulsive drug use [1]. This progression is considered to reflect transitions among multiple neural loci [2]. Dopamine neurotransmission in the ventromedial striatum (VMS) is pivotal in the control of drug use [3], but emerging evidence indicates that once drug use is well-established, its control is dominated by the dorsolateral striatum (DLS) [4]. In the current work, we conducted longitudinal neurochemical recordings to establish the spatiotemporal profile of striatal dopamine release and investigate how it changes during the period from initial to established drug use. Furthermore, we blocked dopamine signaling in the dorsolateral striatum to investigate its specific role in the control of drug taking.

Methods

Multiple electrodes for fast-scan cyclic voltammetry or guide cannulas for microinfusion were chronically implanted in the striatum of rats bearing indwelling intravenous catheters for cocaine self-administration. Animals had access to cocaine for one hour per day for 20 days. During a self-administration session, a nose poke into the active hole elicited a cocaine infusion (FR1, 0.5 mg/kg/infusion) that was accompanied by a 20-second presentation of an audiovisual stimulus (drug cue). Additional responses during this time-out period or nose pokes into the inactive hole (control) were without consequences. The effects of the dopamine receptor antagonist flupenthixol (5 µg dissolved in 0.5 µl vehicle into each side; 0.5 µl/min) or vehicle on drug-taking behavior were examined in single sessions during the first or third weeks of self-administration. One group of rats received flupenthixol or vehicle in the first week of cocaine self-administration, counterbalanced on two days, and a separate group received counterbalanced infusions in the third week.

Results and Discussion

Animals self-administered cocaine with stable intake across three weeks (Fig. 1A). However, the rate of non-reinforced responding (responses during time out or in inactive port) deceased over this period (Fig. 1B). Consequently, the efficiency of responding (successful / total nose pokes) increased (Fig. 1C). Throughout this self-administration training, we observed phasic dopamine release in the VMS. In contrast, response-contingent dopamine signals in the DLS developed only during later stages of training. Bilateral blockade of
dopamine receptors in the DLS with alpha-flupenthixol increased drug intake (Fig. 1D) both early on in training (before DLS dopamine signals were detected) and in later stages of training (when DLS dopamine signals were present). However, non-reinforced responding was only affected by DLS dopamine receptor blockade at the late time point (Fig. 1E), conferring a decrease in the response efficiency (Fig. 1F). This effect of antagonist essentially reversed the gain in efficiency acquired over training, implicating the emergent phasic dopamine signal in the DLS in the establishment of discriminated drug taking.

Figure 1. Blockade of dopamine receptors in DLS disrupts discriminated drug-taking behavior. The rate of reinforced nose pokes remained stable across weeks (A), but the rate of non-reinforced nose pokes decreased (B) and response efficiency increased (C) during the second and third weeks compared to the first week. Infusion of flupenthixol into DLS produced an increase in reinforced nose pokes (D) in both the first (n = 16) and the third weeks (n = 16). The average number of non-reinforced responses was only increased after flupenthixol during the third, but not the first week (E). Response efficiency was decreased after flupenthixol at the late, but not the early time point (F). *P<0.05, **P<0.01, ***P<0.001.

Our results demonstrate that phasic dopamine release in DLS emerges progressively during drug taking over the course of weeks. This recruitment of phasic dopamine signaling in DLS mediated discriminated behavior to obtain drug but did not promote escalated use. Thus, our data demonstrate that the engagement of DLS dopamine, which is thought to be closely linked to stimulus-response processing [5], is not sufficient to account for the loss of control over drug intake characteristic of addiction, underlining the important dissociation between habitual and compulsive stages of drug taking and their neural substrates [6]. Instead, our data identify the spatiotemporal pattern of phasic dopamine release in the striatum that promotes a switch from exploratory drug seeking to exploitation of the drug environment.
References