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SHORT COMMUNICATION

Response contingency directs long-term cocaine-induced neuroplasticity in prefrontal and striatal dopamine terminals

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Abstract
Exposure to addictive substances such as cocaine is well-known to alter brain organisation. Cocaine-induced neuroadaptations depend on several factors, including drug administration paradigm. To date, studies addressing the consequences of cocaine exposure on dopamine transmission have either not been designed to investigate the role of response contingency or focused only on short-term neuroplasticity. We demonstrate a key role of response contingency in directing long-term cocaine-induced neuroplasticity throughout projection areas of the mesocorticolimbic dopamine system. We found enhanced electrically-evoked [^{3}H]dopamine release from superfused brain slices of nucleus accumbens shell and core, dorsal striatum and medial prefrontal cortex three weeks after cessation of cocaine self-administration. In yoked cocaine rats receiving the same amount of cocaine passively, sensitised dopamine terminal reactivity was only observed in the nucleus accumbens core. Control sucrose self-administration experiments demonstrated that the observed neuroadaptations were not the result of instrumental learning per se. Thus, long-term withdrawal from cocaine self-administration is associated with widespread sensitisation of dopamine terminals throughout frontostriatal circuitries.

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1. Introduction

It has been proposed that repeated, intermittent cocaine exposure causes dopaminergic axon terminals within projection areas of the mesocorticolimbic system to become hyperresponsive (Robinson and Berridge, 1993; Vanderschuren and Kalivas, 2000; Vezina and Leyton, 2009). This persistent chemical sensitisation, which most frequently has been observed in the nucleus accumbens (NAc), may render the brain hypersensitive to cocaine and cocaine-associated stimuli. In most preclinical studies supporting the dopamine sensitisation theory, drugs were administered by the experimenter. However, it is now generally accepted that paradigms in which drug administration is contingent on an instrumental response (self-administration) are a better model for human addiction (Jacobs et al., 2003). Although some cocaine self-administration studies have reported increases in dopamine releasability (e.g. Calipari et al., 2013; Hooks et al., 1994), the majority have not (e.g. Homberg et al., 2003; Siciliano et al., 2015).

Multiple factors could underlie the discrepancies between forced administration and self-administration studies. First, there is ample evidence that the cognitive aspects of active self-administration behaviour critically affect the nature and direction of drug-induced neuroplasticity (Jacobs et al., 2003). Secondly, cocaine self-administration studies have almost exclusively focused on dopamine signalling within the NAc, despite the potential importance of changes in dopamine release in other brain regions, such as the dorsal striatum (DS) and medial prefrontal cortex (mPFC). Finally, self-administration studies have mostly focused on short-term changes in dopamine releasability (during self-administration and early withdrawal), when tolerance effects may mask sensitisation (Vanderschuren and Pierce, 2010). In the present study we used a yoked control paradigm (Jacobs et al., 2003) to analyse the long-term consequences of active and passive cocaine administration on *ex vivo* dopamine release in four brain areas: NAc core, NAc shell, DS, and mPFC.

2. Experimental procedures

Methods will be described briefly below as they have been reported in detail previously (De Vries et al., 2002; Homberg et al., 2003).

2.1. Animals and surgery

All experiments were approved by the Animal Care Committee of the VU University Amsterdam. 88 Male Wistar rats (Harlan, Horst, The Netherlands) weighing 280–300 g (age: 7 weeks) at arrival were pair-housed in Macrolon cages in a temperature- and humidity-controlled room on a reversed 12 h light-dark cycle (lights off 7 am) with food (Hope Farms, Woerden, The Netherlands) and water available *ad libitum* for the entire duration of the study. Intravenous catheters were surgically implanted under isoflurane anaesthesia one week after arrival (De Vries et al., 2002). Rats used for the sucrose experiment were sham-operated, i.e. incised and fitted with a connector pedestal on the head. After surgery, all rats were single-housed.

2.2. Self-administration

Cocaine self-administration sessions commenced 5–7 days after surgery and were performed five days/week between 9 am and 3 pm using custom-made operant chambers (De Vries et al., 2002). Sessions lasted for 2 h or until 20 (sessions 1–2) or 40 (sessions 3–10) rewards were received. 24 Rats were simultaneously run in "master-yoked control" pairs. In each pair, the "master" rat was allowed to self-administer cocaine (500 μg/kg/infusion) by responding in the active nosepoke hole (FR1 schedule of reinforcement). Nosepokes of the "yoked control" rat had no consequences. Instead, it received a cocaine infusion every time the master rat did. To reduce unpredictability and stress in yoked controls, drug infusions for both rats were cued by turning off the houselight 1 s earlier. An additional 10 rats were allowed to self-administer saline instead of cocaine.

Sucrose self-administration was conducted on 54 rats under the same experimental conditions as described above, with the exception that a pellet receptacle was placed between the nosepoke holes to deliver 45 mg sucrose pellets (Bio-Serv, Frenchtown, USA) to sucrose self-administering rats and their yoked controls. "No sucrose control" rats were placed in the cage daily, but never received sucrose pellets. Training sessions lasted for 1 h or until 100 rewards were received.

2.3. *Ex vivo* neurotransmitter release

Dopamine release measurements were conducted over 5 (cocaine experiment) or 6 (sucrose experiment) days ('replicate experiments'), 3–4 weeks following the last self-administration session. For each replicate experiment, 2–3 rats from each of the three experimental groups were decapitated and the NAc core, NAc shell, DS and mPFC were rapidly dissected out and pooled within each experimental group. Tissue slices ($0.3 \times 0.3 \times 2$ mm) were prepared using a McIlwain tissue chopper. Subsequently, spontaneous and electrically-evoked efflux of [^{3}H]dopamine was measured in superfused slices (Homberg et al., 2003). In each replicate experiment, electrically-evoked [^{3}H]dopamine release from brain slices of the three experimental groups was studied simultaneously in 48 parallel superfusion chambers, yielding 4 observations/group/brain region.

2.4. Statistics

For each replicate superfusion experiment, electrically-evoked [^{3}H]dopamine release in each superfusion chamber was calculated as the percentage of the average release measured in the 4 chambers containing brain slices of the relevant control (saline self-administering or no sucrose control rats, respectively). Then, data of the different replicate experiments were combined and analysed using nonparametric Kruskal–Wallis H tests followed by Dunn's post-hoc testing, because some data failed the Shapiro–Wilk normality test and/or Levene's homoscedasticity test. Multiple comparisons were controlled with Bonferroni correction.

3. Results

Most cocaine self-administering (cocaine SA) rats acquired cocaine self-administration within the first session, clearly distinguishing between the active and inactive nosepoke hole, and reached the maximum number of rewards throughout most of the experiment (Figure 1a). In the sucrose self-administering (sucrose SA) group, active responding gradually increased and reached stable levels from session 6 onward (Figure 1b). In contrast, the yoked cocaine and sucrose rats virtually stopped responding in