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Individual differences in dopamine cell neuroadaptations following cocaine self-administration

James E. McCutcheon, Francis J. White[†], and Michela Marinelli

Department of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine, and Science, The Chicago Medical School, 3333 Green Bay Rd, North Chicago, IL 60064

Abstract

Background—Addictive drugs produce neuroadaptations in dopamine neurons of the ventral tegmental area (VTA). It is unknown if individual differences in these neuroadaptive responses can account for naturally-occurring differences in drug addiction liability.

Methods—To study this question, we took advantage of high- and low-responder (HR and LR) rats, a population that exhibits spontaneous differences in several models of addiction. HR and LR rats were allowed to self-administer saline or a high dose of cocaine (500 µg/kg/infusion) over a brief period, to normalize drug intake across individuals. Drug-induced changes in the baseline activity of VTA dopamine neurons were recorded after various periods of withdrawal.

Results—All rats developed self-administration behavior and showed similar levels of drug intake. Withdrawal from cocaine self-administration increased dopamine cell firing and bursting in all animals. However these changes in firing rates and patterns were more persistent in HR than in LR rats.

Conclusions—These results demonstrate individual differences in the duration of drug-induced neuroadaptations in dopamine neurons of the VTA. More persistent elevation of dopamine cell activity and reduced capacity to return to baseline levels may be an important factor contributing to the development of addiction in “at risk” individuals.

Keywords

cocaine; self-administration; dopamine; VTA; individual differences; addiction

Introduction

Neuroadaptations resulting from drug exposure and withdrawal are critical determinants of drug addiction. Dopamine neurons of the ventral tegmental area (VTA) are a key site for such neuroadaptations. For example, exposure and withdrawal from psychostimulant drugs transiently increases the impulse activity of VTA dopamine neurons (for review see ¹). Because of its transient nature, this response does not influence the *expression* of addictive behaviors (which persist long after dopamine cell activity has recovered). However, it appears to be

Corresponding author: Michela Marinelli, Department of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, The Chicago Medical School, 3333 Green Bay Rd, North Chicago, IL 60064, Phone: 847-578-8673, Fax: 847-5783268, micky.marinelli@rosalindfranklin.edu.

[†]In memory

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critical for their *development* (^{2, 3}). This short-lived increase in dopamine cell activity is believed to serve as a “driving force” for transferring information to the forebrain, which exhibits more persistent drug-induced neuroadaptations (^{4, 5}). Thus, when this transient increase in VTA dopamine cell firing is prevented by pharmacological manipulations, psychostimulant drugs no longer produce enduring neuroadaptations in the forebrain or increased drug reactivity (³).

Recently, it has been proposed that not only the presence but also the *duration* of dopamine cell neuroadaptations is an important determinant of addiction (⁶). As such, prolonging VTA dopamine cell plasticity extends the duration of the neuroadaptations observed in the nucleus accumbens (⁷). However, it is unknown if differences in the duration of drug-induced neuroadaptations contribute to increased addiction liability in “at-risk” populations. To address this question, we chose to study dopamine cell neuroadaptations after drug exposure in a model of spontaneous addiction liability: high- and low-responder (HR and LR) rats. HR and LR rats are identified according to their high or low locomotor reactivity to a novel environment. Relative to LR rats, HR rats show enhanced addiction liability in several models: acquisition of psychostimulant self-administration (^{8, 9}), escalation of drug intake (¹⁰), sensitization (¹¹), and impulsivity (¹², but see ¹³).

Rats identified as HRs or LR rats were allowed to self-administer cocaine or saline and the activity of the VTA dopamine cells was recorded at various withdrawal time-points. We found that, even after controlling for drug intake, HR rats showed a more persistent elevation in dopamine cell activity than LR rats.

Methods and Materials

Procedures (Figure 1A) were conducted as reported previously (^{8, 14}) and as described in more detail in the Supplementary Methods. Briefly, the HR-LR phenotype was determined in adult male Sprague-Dawley rats, by measuring locomotion in a novel environment for 2 h. Rats with locomotor scores above the sample median were defined as HRs, whereas those below were designated LR rats (¹⁵) (Figure 1). One-two days later, rats underwent surgery to implant an intravenous catheter. After 7–10 days of recovery, rats were allowed to self-administer saline or cocaine (500 µg/kg/infusion) for seven consecutive daily sessions, using nose pokes as the operant response. After self-administration, rats were left in their home cages, and dopamine cell activity was recorded on different withdrawal days (WDs). Recordings were performed under chloral hydrate anesthesia, and dopamine cells were identified and recorded as described in the Supplementary Methods. Data were analyzed with analysis of variance (ANOVA), as detailed in the Supplementary Methods.

Results

Self-administration

All rats learned to self-administer cocaine (Hole effect $F_{1,36}=37.43$, $P<0.001$) and saline (Hole effect $F_{1,20}=39.93$, $P<0.001$). As expected, rats self-administering cocaine showed better discrimination of the active vs. inactive hole (Drug $\times$ Hole interaction $F_{1,56}=15.39$, $p<0.001$) and took more self-infusions compared with rats self-administering saline (Figure 1B, Drug effect $F_{1,56}=75.73$, $p<0.001$).

Consistent with the literature (¹⁶), HR and LR rats did not differ for cocaine self-administration behavior at the high dose of cocaine used in these experiments (Figure 1B); thus, HR and LR rats took a similar amount of cocaine both overall (Group effect $F_{1,35}=0.03$, $P=0.855$) and across all seven self-administration days (Group $\times$ Days interaction $F_{6,210}=0.73$, $P=0.629$).

VTA Dopamine Cell Firing After Self-administration

Dopamine cell activity was recorded at different withdrawal time-points from self-administration, in groups counterbalanced for similar cocaine intake (WD effect $F_{3,36}=0.31$, $P=0.817$). Dopamine cell activity in animals that had self-administered saline was similar at all withdrawal times (WD effect $F_{3,48}=0.12$, $P=0.946$) and, therefore, these data were pooled. Firing rates among these animals ranged from 0.8 to 8.6 Hz, with a mean of 4.24 ± 0.29 Hz, which is similar to that observed in naïve animals (¹). In addition, as expected from studies of naïve rats (⁸), dopamine cells fired faster in HR vs. LR rats (Figure 2, $F_{1,50}=5.74$, $P=0.020$). Together, these results indicate that operant responding did not modify either baseline dopamine cell activity or the HR- LR phenotype.

As figure 2 shows, dopamine cell activity in HR and LR rats was differentially modified by cocaine self-administration and withdrawal (Group $\times$ Drug $\times$ WD interaction $F_{3,156}=3.06$, $P=0.030$). In LR rats, cocaine self-administration and withdrawal increased dopamine cell firing rates ($F_{4,76}=7.22$, $P<0.001$). However, this effect was observed only on WD1 ($P<0.001$), and firing rates returned to baseline by WD3 ($P=0.619$). In HR rats the firing rate was also increased ($F_{4,86}=4.12$, $P=0.004$) but remained at a high level for a longer time period, that included WD1 ($P=0.047$) and WD3 ($P=0.044$), before returning to baseline by WD10 ($P=0.965$) (Figure 2 and Supplementary Figure).

Analysis of burst data in a subset of rats revealed similar group differences. Thus, the percentage of time spent bursting was modified by self-administration and withdrawal (LR: $F_{3,63}=9.42$, $P<0.001$; HR $F_{3,65}=3.62$, $P<0.01$). In LR rats, the percentage of time spent bursting after saline self-administration was 6.3%; this was increased to 24.7% on WD1 from cocaine self-administration ($P<0.001$) but it returned to baseline levels by WD3 (5.4%, $P=0.999$) and remained low thereafter (6.7% on WD10, $P=0.999$, and 2.4% on WD30, $P=0.816$). In contrast, in HRs, the percentage of time spent bursting was still elevated at WD3 (23.7% vs. 10.8% in the saline group, $P=0.023$) and it did not return to baseline levels until WD10 (16.9%, $P=0.685$) and WD30 (8.5%, $P=0.951$). Firing patterns from individual rats showing higher levels of bursting activity during withdrawal from cocaine self-administration are reported in the Supplementary Figure.

Discussion

In this study we show that animals with higher addiction liability exhibit more persistent VTA neuroadaptations after drug exposure than their counterparts with lower addiction liability. Specifically, withdrawal from cocaine self-administration produced an increase in firing and bursting of VTA dopamine cells in all animals, but this increase was longer lasting in HR rats compared with LR rats.

Relative to LR rats, HRs exhibit higher drug responding in a number of models including acquisition of low dose of cocaine self-administration, escalation of drug intake, and behavioral sensitization (¹⁵). Here we designed the self-administration paradigms to minimize differences in drug intake. Thus, we used a high drug dose, a low workload to obtain the drug, and short training. Under these conditions, HRs and LR rats are known to exhibit similar acquisition of self-administration behavior (^{10, 15, 16}), which ensured that all animals acquired the operant response at a similar rate and took a similar amount of cocaine (¹⁶). Despite similar drug intake, HR rats showed a more persistent elevation in dopamine cell firing during withdrawal than LR rats. Thus, this difference is independent of learning of operant responding and of amount of drug consumed. Such prolonged drug-induced plasticity in HR rats may be viewed as a reduced ability of dopamine cells to return to baseline. In contrast, LR rats have greater elasticity and ability to return to baseline.

Recent evidence suggests that the duration of drug-induced neuroadaptations of VTA dopamine cells is critical for determining long-lasting addiction ⁽⁶⁾. Mameli *et al.* ⁽⁷⁾ demonstrated that manipulations that prolong neuroadaptations in excitatory synaptic drive onto VTA dopamine neurons also lead to a more persistent form of plasticity being transferred to the nucleus accumbens. Using a paradigm similar to ours, Chen *et al.* ⁽¹⁷⁾ showed that VTA neuroadaptations are longer-lasting if associated with self-administration of cocaine rather than yoked or experimenter-delivered drugs. These authors observed persistent changes in VTA excitatory synaptic strength that lasted nearly three months. Interestingly, in measurements of cell firing, baseline levels were re-established within one week of drug withdrawal (present study, and 14, 18). This indicates that an increase in the strength of excitatory synapses onto dopamine neurons does not translate into the integrated output of these cells as measured by firing activity. Thus, increases in firing rate observed during drug withdrawal may primarily depend on other mechanisms, such as changes in the function of dopamine D2 autoreceptors ⁽¹⁴⁾ or metabotropic glutamate receptors ⁽⁷⁾. The longer-lasting increases in excitatory synaptic strength observed by Chen *et al.* ⁽¹⁸⁾ would, instead, be important by enabling dopamine cells to fire more readily in response to salient stimuli such as drug cues ⁽¹⁴⁾.

This is the first study, to our knowledge, that examines VTA neuroadaptations in a naturally occurring population of individuals with differential reactivity to drugs of abuse. Studies that use pharmacological or genetic manipulations have shown that changing dopamine cell excitability can modify addiction-related behaviors ⁽¹⁾. However, such studies are not designed to detect mechanisms that confer addiction risk in the natural population. Our finding that rats with elevated addiction liability show prolonged neuroadaptations of dopamine cell activity suggests that such plasticity contributes to addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A) Timeline showing screening for high-responder (HR) and low-responder (LR) phenotype, self-administration training, and withdrawal days (WDs) on which electrophysiology was performed to record dopamine neuron activity: WD1, WD3, WD10 (WDs 10–12), and WD30 (WDs 28–34). (B) Locomotor scores of HR and LR rats ($n=27$ LR, $n=31$ HR). (C) Self-administration of saline (left panel) and cocaine (right panel) in HR and LR rats. Self-administration of cocaine was higher than self-administration of saline; HR and LR rats showed similar self-administration behavior. Data are mean $\pm$ SEM ($n=10$ LR Saline, $n=11$ HR Saline, $n=17$ LR Cocaine, $n=20$ HR Cocaine). See results section for statistics.

Figure 2.

Ventral tegmental area (VTA) dopamine cell firing at different withdrawal days (WDs) from self-administration. High-responder (HR) rats exhibited higher basal firing rate than low-responder (LR) rats after saline self-administration (left panel). After cocaine self-administration, LR rats (middle panel) showed a more transient elevation of dopamine cell activity than HR rats (right panel) whose dopamine cell activity remained elevated through WD3. Data for saline animals are pooled across withdrawal days. Data are means $\pm$ SEM. (for saline: $n=26$ /group; For cocaine: LRs $n=17, 17, 9, 12$; HRs $n=17, 11, 17, 20$ for WD1, 3, 10, 30, respectively). See results section for statistics.