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Cocaine self-administration disrupts mesolimbic dopamine circuit function and attenuates dopaminergic responsiveness to cocaine

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Abstract

Dopaminergic projections from the ventral midbrain to the nucleus accumbens (NAc) have long been implicated in encoding associations between reward availability and environmental stimuli. As such, this circuit is instrumental in guiding behaviors towards obtaining maximal rewards based on previous experience. Cocaine acts on the dopamine system to exert its reinforcing effects and it is thought that cocaine-induced dysregulation of dopamine neurotransmission contributes to the difficulty that cocaine addicts exhibit in selecting environmentally appropriate behaviors. Here we used cocaine self-administration combined with *in vivo* fast scan cyclic voltammetry in anesthetised rats to examine the function of the ventral tegmental area to NAc projection neurons. Over 5 days of cocaine self-administration (fixed-ratio 1; 1.5 mg/kg/injection; 40 injections/day), animals increased their rate of intake. Following cocaine self-administration, there was a marked reduction in ventral tegmental area-stimulated NAc dopamine release. Additionally, there was a decreased augmentation of stimulated dopamine overflow in response to a cocaine challenge. These findings demonstrate that cocaine induces a hypodopaminergic state, which may contribute to the inflexible drug-taking and drug-seeking behaviors observed in cocaine abusers. Additionally, tolerance to the ability of cocaine to elevate dopamine may lead to increased cocaine intake in order to overcome decreased effects, another hallmark of cocaine abuse.

Introduction

The nucleus accumbens (NAc) is situated at the confluence of a wide array of afferents relaying information concerning emotional salience, predicted outcomes and the contextual relevance of environmental inputs (Mogenson *et al.*, 1980). This includes a dense innervation of dopaminergic afferents projecting from the ventral tegmental area (VTA) (Doucet *et al.*, 1986), which respond in accordance with previously learned environmental contingences in order to guide goal-directed motor outputs (Waelti *et al.*, 2001; Tobler *et al.*, 2005). Proper function of this circuit is critical for the selection and performance of environmentally appropriate behaviors. Disruption of dopamine neurotransmission diminishes responding for natural (Woolverton & Virus, 1989; Thanos *et al.*, 2008) and psychostimulant (Roberts *et al.*, 1980; Ritz *et al.*, 1987; Woolverton & Virus, 1989; Thanos *et al.*, 2008) reinforcers and prevents learning of associations between rewards and the discrete and contextual cues that predict their availability (Taylor & Robbins, 1986; Ranaldi & Beninger, 1993) . As such, drug-induced alterations in dopaminergic neurotransmission are hypothesised to, at least in part, mediate the maladaptive and inelastic behaviors characteristic of drug addiction. For example, reductions in the functioning of this system following repeated drug administration may result in an inability to dynamically modulate behaviors in an environmentally appropriate manner, and thus may contribute to a cycle of repeated relapses in response to cue exposure in drug abusers despite negative physical, social and financial outcomes (Graybiel, 1995, 2008).

One phenomenon that has been observed in examinations of cocaine-dependent humans is a marked decrease in the ability of cocaine to elevate NAc dopamine levels (Volkow *et al.*, 1996, 1997, 2006). Previous work from our laboratory has effectively modeled the cocaine tolerance observed in humans by demonstrating a decreased ability of cocaine to inhibit the dopamine transporter (DAT) following cocaine self-administration in rats (Ferris *et al.*, 2011, 2012; Calipari *et al.*, 2013; Siciliano *et al.*, 2015). Demonstrations of tolerance have been limited to *ex-vivo* slice preparations, which assessed cocaine effects at the dopamine terminal in isolation. Further, dopamine signaling in response to cocaine-associated cues has been shown to decrease over the course of cocaine self-administration (Willuhn *et al.*, 2014); however, it remains to be determined whether these alterations are occurring directly in VTA dopamine neurons or are a result of deficits to afferent inputs onto dopamine neurons. Here we used fast scan cyclic voltammetry to examine the effects of cocaine self-administration on dopamine system function and cocaine potency.

We found that, following cocaine self-administration, electrically-stimulated dopamine release from the VTA to NAc core projection

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was severely blunted. Additionally, we found that the ability of cocaine to increase electrically-stimulated dopamine release was attenuated in cocaine self-administration animals. Together, these data demonstrate that cocaine induces profound hypofunction of the mesolimbic dopamine circuit that is not ameliorated by cocaine and may underlie anhedonia during withdrawal and contribute to the blunted self-reported effects of cocaine observed in cocaine addicts.

Materials and methods

Animals

Adult male Sprague-Dawley rats (325–375 g; $n = 5$ control, $n = 4$ self-administration) were housed in pairs on a 12/12 h light/dark cycle with food and water available *ad libitum*. All protocols, animal care and euthanasia procedures were approved by the Institutional Animal Care and Use Committee at Wake Forest School of Medicine.

Self-administration

Rats were anesthetised with ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and implanted with chronic indwelling jugular catheters as previously described (Calipari *et al.*, 2014c). Animals were singly housed, and each 6 h session took place in the home cage during the active/dark cycle (09:00–15:00 h). Without any prior operant training, animals were given access on a fixed-ratio 1 schedule to a cocaine-paired lever, which, upon responding, initiated an intravenous injection of cocaine (1.5 mg/kg, infused over ~4 s, depending on animal weight). After each response/infusion, the lever was retracted and a stimulus light was illuminated for a 20-s timeout period. Sessions lasted for 6 h or until 40 injections were taken. Under these conditions, all animals acquired a stable pattern of intake within 1–5 days. Acquisition (Day 1) was counted when the animal reached 35 or more responses with a stable and consistent interinjection interval. Following acquisition, the animals were given access to 40 injections per day for a period of five consecutive days before voltammetry experiments. Control animals were naive rats housed under the same reversed light/dark cycle for at least 1 week prior to the voltammetry experiments.

In vivo *voltammetry*

Rats were anesthetised with urethane (1.5 g/kg, i.p.) and placed in a stereotaxic apparatus. A stimulating electrode was lowered into the VTA (from bregma: −5.2 anterior/posterior, +1.1 medial/lateral, −7.0 dorsal/ventral), and a carbon fiber electrode was initially lowered into the caudate putamen (from bregma: +1.3 anterior/posterior, +1.3 medial/lateral, −4.5 dorsal/ventral), until a 1 s stimulation train elicited dopamine (60 pulses; 60 Hz; monophasic; 2 ms pulse width; 7.5 μA). These stimulation parameters were chosen because preliminary studies revealed that detection of dopamine using a smaller number of pulses was prohibitively difficult (if not impossible) in cocaine self-administering rats, which relates to the hypofunctioning dopamine system in these animals. Extracellular dopamine was recorded by applying a triangular waveform (−0.4 to +1.2 to −0.4 V vs. Ag/AgCl, 400 V/s) scanning every 100 ms. Once the stimulator and carbon fiber electrode locations achieved adequate levels of release in the caudate putamen, the carbon fiber electrode was lowered 2 mm further into the NAc core. The NAc core was selected because of its instrumental role in guiding the selection and execution of motivated behaviors based on previously learned environmental contingencies (Humphries & Prescott, 2010). Once the peak height of the extracellular dopamine response was stable (<10% variation across three consecutive stimulations spaced 5 min apart), animals were given an injection of cocaine (10 mg/kg, i.p.).

Data analysis

DEMON VOLTAMMETRY AND ANALYSIS software was used (Yorgason *et al.*, 2011) for all analyses of fast scan cyclic voltammetry data. Recording electrodes were calibrated by recording responses (in electrical current; nA) to a known concentration of dopamine (3 μM) using a flow-injection system. This was used to convert electrical current to dopamine concentration.

Statistics

GRAPHPAD PRISM (version 6, GraphPad, La Jolla, CA, USA) was used to statistically analyse data sets and create graphs. Baseline dopamine release data were subject to a Student's *t*-test. Cocaine challenge data were subject to a repeated-measures two-way ANOVA with treatment group as the between-subject factor and time as the within-subject factor. When main effects were obtained, differences between groups were tested using a Bonferroni post-hoc test. *P*-values of < 0.05 were considered to be statistically significant.

Results

Rate of cocaine intake escalates over days

Animals completed five consecutive days of cocaine self-administration (1.5 mg/kg/injection), with a maximum of 40 injections per day. The number of injections per day was held constant to avoid potential differences in neurochemical effects due to differential cocaine intake. Consistent with previous results with this procedure, animals completed the maximum of 40 injections in less time each day (Fig. 1A). A one-way ANOVA revealed a main effect of session on the rate of cocaine intake (Fig. 1B; $F_{4,15} = 3.55$, $P = 0.0314$). Bonferroni post-hoc analysis revealed that the number of infusions per hour was higher on Day 5 compared with Day 1 ($P < 0.05$), indicating that animals increased their rate of intake over days.

Cocaine self-administration results in attenuated stimulated dopamine

At approximately 18 h following cessation of the final cocaine self-administration session (i.e. the following morning), animals were anesthetised with urethane (1.5 g/kg, i.p.) and a recording electrode and stimulating electrode were lowered into the NAc core and VTA. We found that cocaine self-administration resulted in a robust hypodopaminergic state (Fig. 2A). Indeed, the dopamine release magnitude was greatly attenuated in cocaine self-administration animals as compared with controls (Fig. 2B; $t_7 = 1.92$, $P = 0.048$). Additionally, we found that the area under the stimulated dopamine transient curve was reduced in cocaine self-administration animals, further indicating hypofunction of the VTA to NAc projection neurons (Fig. 2C; $t_7 = 2.18$, $P = 0.033$).

Cocaine self-administration results in tolerance to the dopamine-elevating effects of cocaine

We then determined the effects of cocaine self-administration on the dopaminergic responsiveness to cocaine by administering a cocaine challenge (10 mg/kg, i.p.). Cocaine was injected immediately

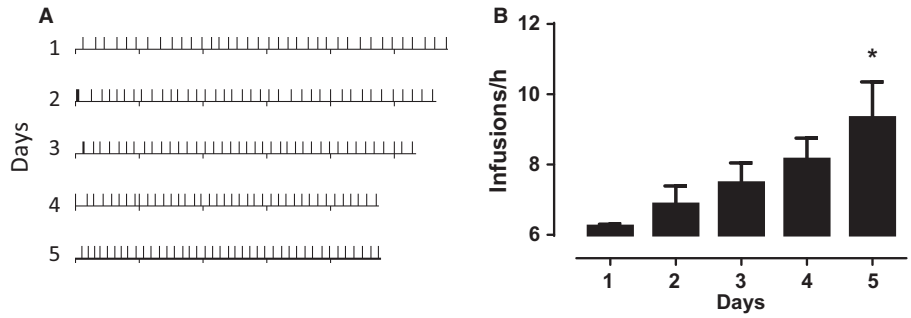

FIG. 1. Rate of cocaine intake escalates over 5 days of self-administration. (A) Event records of 5 days of cocaine self-administration from a representative animal. Downward tics denote hours, whereas upward tics denote infusions. Over the course of 5 days, 40 injection sessions are completed in a shorter amount of time. (B) Group data indicating that animals increased rate of cocaine intake over days. *$P < 0.05$ vs. day 1.

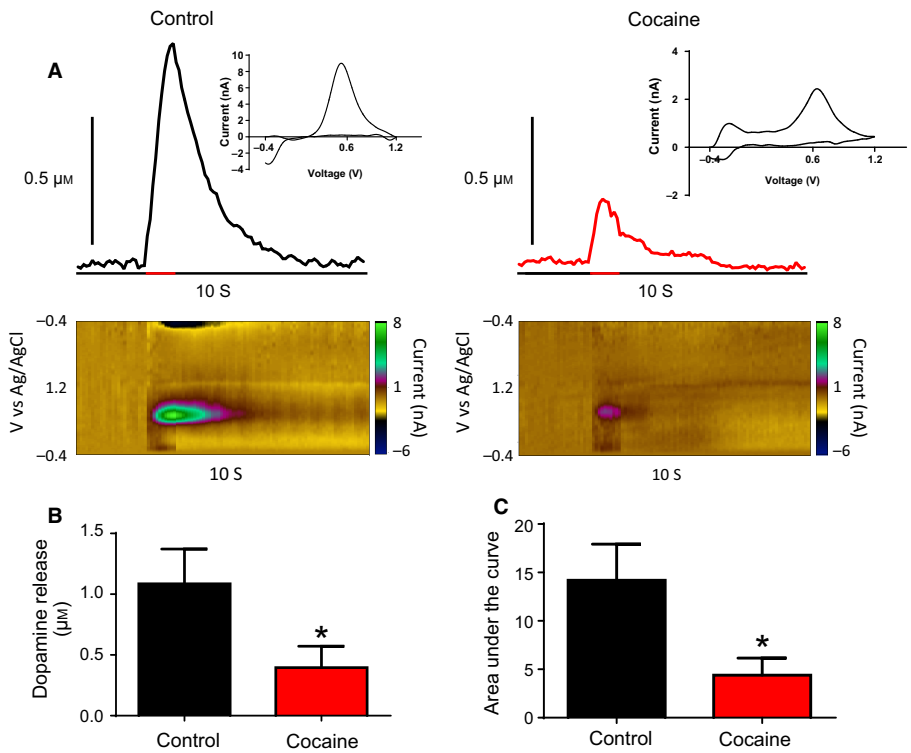

FIG. 2. Cocaine self-administration results in reduced dopamine release in the NAc following VTA stimulation. (A) Representative traces and pseudo-color plots from control (left) and cocaine self-administration (right) animals demonstrating decreased stimulated (60 pulses, 60 Hz, denoted by red bar on *x*-axis) dopamine release following cocaine self-administration. Inset: cyclic voltammogram from peak of representative trace. (B) Amplitude of dopamine release is decreased in cocaine self-administration animals. (C) Area under the curve is decreased in cocaine self-administration animals. *$P < 0.05$ vs. control.

following the final baseline collection. We found that cocaine-induced increases in stimulated dopamine were blunted in cocaine self-administering animals (Fig. 3A). Following a cocaine challenge, a two-way repeated-measures ANOVA revealed a main effect of time (Fig. 3B; $F_{12,84} = 5.83$, $P < 0.0001$) on dopamine release, as well as a group × time interaction ($F_{12,84} = 2.132$, $P = 0.0229$). Bonferroni post-hoc analysis revealed that, in control animals, dopamine release was elevated compared with baseline at 15 ($P < 0.01$), 20 ($P < 0.001$), 25 ($P < 0.001$), 30 ($P < 0.001$), 35 ($P < 0.01$), 40 ($P < 0.001$), 45 ($P < 0.01$) and 50 ($P < 0.001$) min post-cocaine injection. In contrast, cocaine did not elevate stimulated dopamine release at any time point in cocaine self-administration animals, as compared with their own baseline.

Similarly, with regard to the area under the curve, which accounts for changes in both stimulated dopamine release and uptake, a two-way repeated-measures ANOVA revealed a significant effect of time (Fig. 3C; $F_{12,84} = 5.004$, $P < 0.0001$) and a time × group interaction ($F_{12,84} = 3.378$, $P = 0.0005$). Bonferroni post-hoc analysis revealed that, in control animals, the area under the curve was elevated compared with baseline at 15 ($P < 0.001$), 20 ($P < 0.0001$), 25 ($P < 0.001$), 30 ($P < 0.001$), 35 ($P < 0.001$), 40 ($P < 0.001$), 45 ($P < 0.001$) and 50 ($P < 0.0001$) min post-cocaine injection, whereas there was no effect in cocaine self-administration animals. These results indicate that cocaine self-administration animals were less responsive to cocaine effects on dopamine neurotransmission.

To further assess the effects of a history of cocaine self-administration on the effects of acute cocaine, we calculated the effects on cocaine on stimulated dopamine release and the area under the curve as a percent of the pre-cocaine baseline for each group. A two-way repeated-measures ANOVA revealed a main effect of time on stimulated

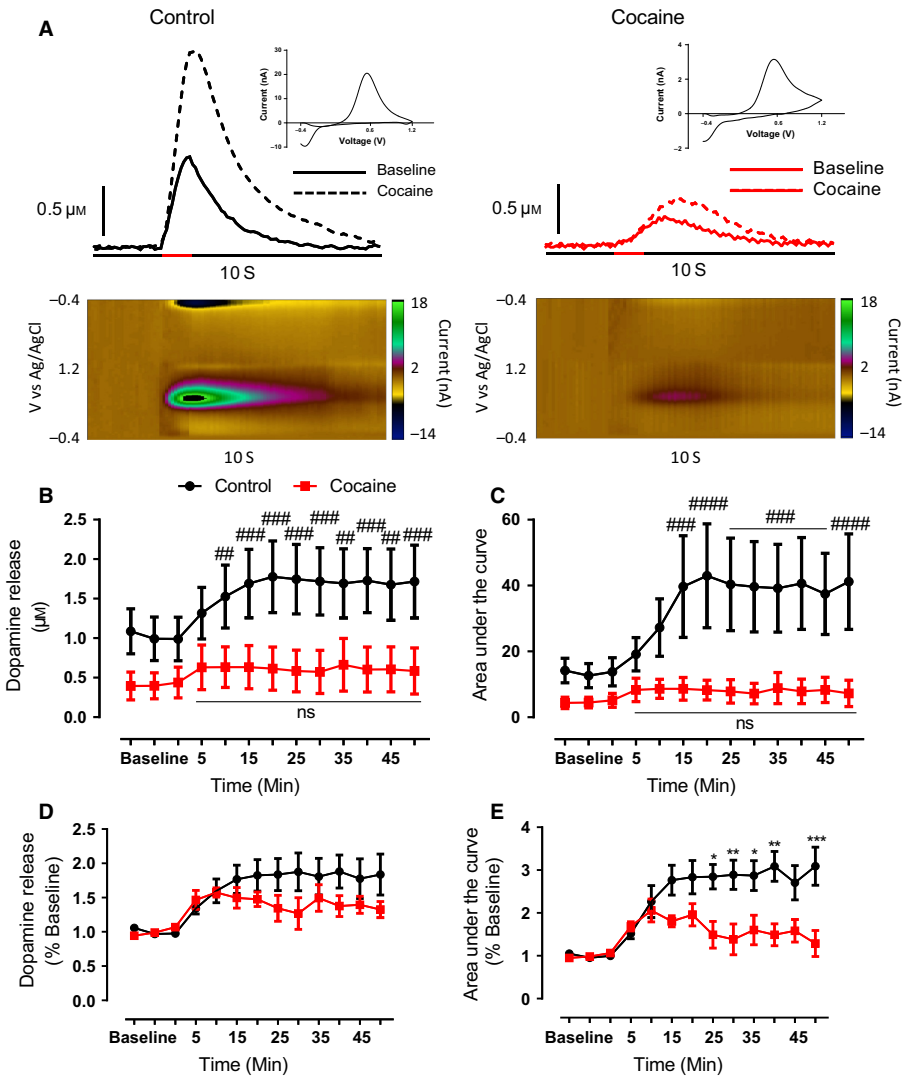

FIG. 3. Cocaine self-administration results in tolerance to the ability of cocaine to increase dopamine. (A) Representative traces and pseudo-color plots from control (left) and cocaine self-administration (right) animals demonstrating decreased stimulated (60 pulses, 60 Hz, denoted by red bar on *x*-axis) dopamine transmission following a cocaine challenge (10 mg/kg, i.p.). Cocaine was injected immediately following the final baseline collection, and representative traces were taken at 15 min (three collections) following injection. Inset: cyclic voltammogram from peak of post-injection representative trace. (B) Group data representing severely blunted dopamine release at baseline and following a cocaine challenge in cocaine self-administration animals as compared with controls. (C) Area under the curve is attenuated at baseline and following a cocaine challenge in cocaine animals. (D) When represented as a percent of baseline, the effect of a cocaine challenge on dopamine release is attenuated by a history of cocaine self-administration. Although an ANOVA revealed a main effect of time, and a time × group interaction, Bonferroni post-hoc analysis did not reveal a significant difference at any of the time points. (E) When represented as a percent of baseline the effect of a cocaine challenge on area under the curve is blunted in cocaine animals. $^{\#\#}P < 0.01$ vs. baseline; $^{\#\#\#}P < 0.001$ vs. baseline; $^{\#\#\#\#}P < 0.0001$ vs. baseline, $^{*}P < 0.05$ vs. cocaine; $^{**}P < 0.01$ vs. cocaine; $^{***}P < 0.001$ vs. cocaine.

dopamine release (Fig. 3D; $F_{12,84} = 9.768$, $P < 0.0001$), as well as a time × group interaction ($F_{12,84} = 2.177$, $P = 0.0200$); however, we found no post-hoc significance. With regard to cocaine-induced increases in the area under the curve, we found a main effect of time (Fig. 3E; $F_{12,84} = 11.20$, $P < 0.0001$) and group ($F_{1,7} = 9.385$, $P = 0.0182$), as well as an interaction ($F_{12,84} = 4.795$; $P < 0.0001$). Bonferroni post-hoc analysis revealed that the area under the curve was attenuated in cocaine self-administration animals as compared with controls at 25 ($P < 0.05$), 30 ($P < 0.01$), 35 ($P < 0.05$), 40 ($P < 0.01$) and 50 ($P < 0.001$) min post-injection.

Discussion

Here we demonstrate *in vivo* that cocaine self-administration induces hypofunction of the mesolimbic dopamine pathway. We found that the amplitude of stimulated dopamine was attenuated, as was the area under the curve of the evoked dopamine curve. Additionally, we found that the dopaminergic response to an injection of cocaine was greatly reduced in cocaine self-administration animals. These data, together with mounting evidence in both pre-clinical and human investigations, suggest that hypofunction of the dopamine system is a neurochemical consequence of cocaine abuse.

Given the integral involvement of the mesolimbic dopamine pathway in guiding the selection and execution of goal-directed behaviors and the maladaptive behaviors of cocaine addicts (Volkow *et al.*, 2012; Siciliano *et al.*, 2015), it is of critical importance to determine the way in which cocaine exposure alters its function. Here we show that the responsiveness of this projection is greatly reduced by cocaine self-administration, which has implications for the affective state of the animal as well as the ability of the animal

to modulate behavioral outputs. Indeed, decreased basal dopamine has been linked to increases in intracranial self-stimulation thresholds, indicating that animals are less sensitive to reward (Kokkinidis & McCarter, 1990), a state that is thought to model anhedonia in psychostimulant addicts during abstinence (Dackis & Gold, 1985; Markou & Koob, 1991). Anhedonia induced by cocaine use may contribute to the decreased reward experienced by detoxified cocaine addicts in response to non-drug stimuli (Siegel, 1982; Gawin *et al.*, 1986).

With regard to the role of dopamine in selecting goal-directed behaviors, the decreased stimulated dopamine release observed here is a critical determinant in the progression from cocaine use to addiction. It was recently demonstrated that extended-access cocaine self-administration results in decreased phasic dopamine neurotransmission in the NAc and this was highly correlated with the escalation of cocaine intake (Willuhn *et al.*, 2014). Previous investigations have focused on cue-elicited dopamine release, without investigating whether these changes are due to cocaine-induced alterations to VTA neurons *per se* or changes in non-dopaminergic afferent projections to the VTA or NAc. Additionally, changes in cue-elicited dopamine transient amplitude could be attributable to either reduced releasable dopamine or changes in dopamine cell firing. Determining if these changes are occurring specifically at the VTA to NAc projection is particularly important as cocaine self-administration has been shown to alter the strength of synaptic inputs to the VTA (Chen *et al.*, 2008). Here we demonstrate that cocaine self-administration results in disruption of dopamine neurotransmission within the VTA to NAc projection, regardless of possible differences in cell firing, and that this depression of dopamine neurotransmission persists for at least 18 h following cessation of cocaine use.

In addition to reductions in stimulated dopamine neurotransmission, cocaine self-administration resulted in tolerance to the ability of cocaine to augment dopamine. We were unable to use kinetic modeling of the current data to isolate the contribution of release and uptake due to insufficient concentrations of dopamine release in the cocaine self-administration animals. However, as indicated by our previous *ex-vivo* studies, the decreased effect of cocaine on dopamine neurotransmission is due to a decreased ability of cocaine to produce uptake inhibition (Ferris *et al.*, 2011, 2012; Calipari *et al.*, 2013). Although the mechanism for decreased cocaine-induced uptake inhibition following cocaine self-administration has not been clearly defined, it is likely that extensive cocaine blockade of the DAT produces an allosteric alteration to the cocaine-binding site, or to the conformational state of the DAT, which has been shown to alter cocaine effects (Kohut *et al.*, 2014). The self-administration paradigm used in the current investigation has been shown to reduce both membrane-associated and total DAT expression (Calipari *et al.*, 2014a,b,c; Ferris *et al.*, 2015). However, genetically increasing DAT levels and thereby the dopamine uptake rate has been shown to have no effect on cocaine potency (Salahpour *et al.*, 2008; Calipari *et al.*, 2013). Finally, tolerance to cocaine effects at the DAT has been shown to generalise to other DAT blockers, whereas the potency of DAT substrates is unaffected (Ferris *et al.*, 2011, 2012). Thus, it is unlikely that decreases in cocaine potency are due to an orthosteric alteration to DAT function or to DAT expression.

One point of interest is that differences in cocaine effects between the two groups appear to only be present at $\geq$ 15 min post-injection, whereas early time points are not affected by the cocaine self-administration history. This suggests that the decreased effect of cocaine may be due to a shift in efficacy rather than potency, whereby the maximal effect of cocaine on dopamine uptake is shifted downwards by a history of cocaine self-administration. Regardless of mechanism, given that cocaine's actions at the DAT have been shown to mediate the discriminative stimulus effects of the drug (Cunningham & Callahan, 1991; Melia & Spealman, 1991), it is likely that tolerance of the DAT to cocaine results in the reduced subjective effects of the compound. Indeed, in human studies, DAT occupancy by cocaine predicts the self-reported euphoric effects of cocaine and this effect is blunted in cocaine addicts (Volkow *et al.*, 1996, 1997, 2006). Given that animals titrate their cocaine intake based on its subjective effects, it is possible that the increase in the rate of cocaine intake over days observed in these animals occurs in compensation for the decreased effects of cocaine as tolerance develops.

Together, these data give further support to the phenomenon of hypodopaminergia induced by cocaine self-administration, and demonstrate that cocaine-induced dysregulation of the mesolimbic dopamine system occurs within the mesolimbic dopamine pathway. Additionally, we have demonstrated that, as in the human cocaine addict, cocaine self-administration results in marked tolerance to the ability of cocaine to augment dopamine neurotransmission. The decreased function of the mesolimbic dopamine pathway is likely to lead to an inability of the system to respond appropriately to environmental stimuli, resulting in the inflexible and maladaptive behaviors of psychostimulant addicts, including relapse and uncontrolled cocaine use.

Conflict of interest

The authors have no conflicts to report.

Acknowledgements

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Abbreviations

DAT, dopamine transporter; NAc, nucleus accumbens; VTA, ventral tegmental area.

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