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Short Communication

dcc haploinsufficiency results in blunted sensitivity to cocaine enhancement of reward seeking

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HIGHLIGHTS

- *dcc* haploinsufficient mice show comparable ICSS to wild-type littermates.
- Adult *dcc* haploinsufficient mice show blunted cocaine-induced potentiation of ICSS.
- *dcc* haploinsufficiency may confer resilience against drug abuse liability.

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ABSTRACT

Mesocortical dopamine connectivity continues to mature during adolescence. This protracted development confers increased vulnerability for environmental and genetic factors to disrupt mesocortical wiring and subsequently influence responses to drugs of abuse in adulthood. The netrin-1 receptor, DCC, orchestrates medial prefrontal cortex dopamine input during adolescence and dictates the functional organization of local circuitry. Haploinsufficiency of *dcc* results in increased dopamine innervation to the medial prefrontal cortex, which in turn leads to resilience against the behavioral activating effects of stimulant drugs. However, whether sensitivity to the rewarding effects of drugs of abuse is also altered in *dcc* haploinsufficiency remains to be resolved. Here, we used the curve-shift method to measure cocaine-induced facilitation of intracranial self-stimulation (ICSS) in adult *dcc* haploinsufficient mice and wild-type littermates. We found that *dcc* haploinsufficient mice acquire ICSS behavior at comparable stimulation parameters to wild-type controls. However, cocaine-induced potentiation of ICSS is significantly blunted in *dcc* haploinsufficient mice. These results are consistent with decreased sensitivity to the rewarding effects of cocaine and/or decreased proclivity to invest effort in the pursuit of reward in *dcc* haploinsufficient mice. Moreover, these findings suggest that DCC signaling determines adult susceptibility to drug abuse most likely by controlling prefrontal cortex development in adolescence.

1. Introduction

The mesocorticolimbic dopamine circuitry is a central substrate for the actions of drugs of abuse. Alterations in the function of this circuitry, especially within its mesocortical aspect, are thought to contribute significantly to the behavioral changes that define addiction [1]. The refinement of dopamine connectivity in the medial prefrontal cortex (mPFC) continues throughout adolescence and renders this region especially vulnerable to environmental intervention [2–5]. Genetic and environmental factors that influence mPFC dopamine maturation during adolescence may therefore be important determinants of individual patterns of drug taking and risk of becoming addicted.

Our group has identified *dcc* (deleted in colorectal cancer) as the first gene known to orchestrate the development of the prefrontal cortex in adolescence [3,4,6]. The *dcc* gene encodes a receptor for the bifunctional guidance cue netrin-1 and is expressed by mesocorticolimbic dopamine neurons from embryonic life to adulthood

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[6–8]. We have shown that DCC-mediated netrin-1 signaling within dopamine neurons controls the extent of their innervation to the mPFC during adolescence, most likely by preventing target recognition errors in striatal regions [3,4]. As such, even subtle variations in DCC receptor expression influence profoundly the structure and function of dopamine circuitry, altering vulnerability to the effects of drug abuse [3] and to developing addiction [7].

To investigate whether the effects of *dcc* on mPFC development produce changes in responses to drugs of abuse in adulthood we have utilized a mouse model of *dcc* haploinsufficiency. Adult *dcc* haploinsufficient mice have increased dopamine innervation and release in the mPFC; this increase results from ectopic ingrowth of DA fibers during adolescence [3,4,6,7]. Augmented mPFC dopamine function causes blunted amphetamine-induced dopamine release in the nucleus accumbens and resilience against behavioral effects of stimulant drugs. Specifically, adult *dcc* haploinsufficient mice show blunted locomotor response to amphetamine, methamphetamine, and cocaine, do not develop behavioral sensitization upon repeated drug exposure, and show resistance to amphetamine-induced deficits in sensorimotor gating function [6,7,9]. Furthermore, adult *dcc* haploinsufficient mice show reduced sensitivity to the Pavlovian conditioning effects of amphetamine or methamphetamine in a conditioned place preference (CPP) paradigm, suggesting reduced sensitivity to the rewarding effects of these drugs [6,9]. However, we found recently that *dcc* haploinsufficient mice self-administer methamphetamine at levels comparable to those of wild-type littermates [9]. In an attempt to reconcile these findings, here we investigated the reward-facilitating effects of cocaine in our mouse model of *dcc* haploinsufficiency using the intracranial self-stimulation (ICSS) paradigm.

ICSS is an operant behavior that can be used to evaluate the reward-facilitating or reward-attenuating properties of abused drugs by assessing whether drugs and the electrical stimulation activate common reward circuitries [10]. In the curve-shift variation of the ICSS paradigm, the frequency of the rewarding electrical brain stimulation is decreased logarithmically and the rate of behavioral responding is plotted as a function of the changes in pulse frequency [11,12]. The obtained "response rate-frequency" functions can then be viewed in a manner analogous to pharmacological dose-response curves. Changes in the location of these curves along the frequency axis can reflect alterations in the sensitivity or gain of brain-reward circuitry and/or in costs incurred in procuring rewards [13]. Drugs of abuse, particularly stimulants, facilitate ICSS behavior and shift the rate-frequency curve to the left [10,11,14]. Drug-induced left shifts of the curve can be quantified by assessing the stimulation frequency necessary to maintain responding at half of the maximal value (M_{50}) [12]. In this study we first determined if adult *dcc* haploinsufficient mice acquire ICSS behavior. Then, we assessed whether *dcc* haploinsufficiency leads to deficiencies in the ability of cocaine to potentiate ICSS and induce a left-shift in the rate-frequency curve.

2. Materials and methods

2.1. Animals

Adult male *dcc* haploinsufficient mice and wild-type littermates were used in all experiments [4]. Mice were kept on a 12-h light/dark cycle with *ad-libitum* access to food and water. All behavioral testing was conducted during the light phase of the cycle. Pups were weaned at postnatal day 21 and housed in cages with same-sex littermates. Experimental procedures began when mice were adults (PND 75 ± 15). All experiments were performed in accordance with the guidelines of the Canadian Council of Animal Care, and all animal procedures were approved by the McGill University/Douglas Hospital Animal Care Committee and by the Animal Research Ethics Committee (AREC) of Concordia University. A total of 6 *dcc* haploinsufficient and 7 wild-type mice were used in this study.

2.2. Drugs

Cocaine hydrochloride (Medisca Pharmaceutique Inc.) was dissolved in 0.9% saline. All injections were performed i.p. at a volume of 10 ml/kg. Doses were selected based on previous work showing that cocaine dose-dependently potentiates ICSS [15], and that *dcc* haploinsufficient mice have blunted locomotor activation to these doses of cocaine [7].

2.3. Surgery

Surgical procedures were performed as reported previously [14]. Monopolar electrodes (0.250-mm diameter; Plastics One, Roanoke, VA) were implanted in the right medial forebrain bundle (MFB) of the mice at the level of the lateral hypothalamus (-1.9 mm AP, ± 0.8 mm ML, -4.8 mm DV from bregma).

2.4. Intracranial self stimulation

Mice were trained to turn a 2 cm $\times$ 5 cm wheel manipulandum (Med Associates, St Albans, VT) to receive brain stimulation on a continuous-reinforcement schedule (CRF/FR1). Each quarter turn of the wheel earned a 0.5-s train of square-wave cathodal pulses (0.1 ms pulse duration) at a set frequency of 158 Hz. Stimulation current was adjusted to the lowest value that would sustain reliable responding for 3 consecutive days. Each mouse was then adapted to a descending series of stimulation frequencies, arranged so that the mouse responded maximally to the highest frequencies and not at all to the lowest frequencies. Each series (or rate–frequency 'curve') had a minimum of nine 1-min test trials at each frequency. Each trial had a 5-s 'priming' phase during which 5 trains of noncontingent stimulation were given, a 50-s test phase during which the number of responses was counted, and a 5-s time-out period during which no stimulation was available. The stimulation frequency was then lowered by 10% (0.05 log units), and the next trial was started. Each mouse generated six curves per day.

On each testing day, three rate–frequency curves were determined for each mouse immediately before drug treatment. The first curve served as a warm-up period; the second and third curves were averaged to obtain a response baseline. Each mouse then received one i.p. injection of either 10 mg/kg cocaine, 20 mg/kg cocaine, or saline vehicle per day, according to the experimental timeline (Fig. 1a). Immediately following this injection, three more rate–frequency curves were obtained to evaluate ICSS performance in response to drug or saline administration. Cocaine doses were given in ascending and then descending order, so that mice received every drug dose twice. Saline vehicle doses were interspersed between all drug treatment days. This drug regimen was designed to reduce the likelihood of any effects of sensitization or tolerance seen from repeated drug doses [15].

2.5. Data analysis

ICSS 'half-maximum' threshold (M_{50}, the pulse frequency at which the response rate is half maximal) was determined using MATLAB (MathWorks). On each testing day, the M_{50} from the three post-drug curves were averaged for analysis. Each mouse received each dose of cocaine twice (Fig. 1a). Because there were no significant differences in the M_{50} thresholds between the two administrations of the same dose in individual subjects, the M_{50} thresholds from these treatment days were collapsed into single

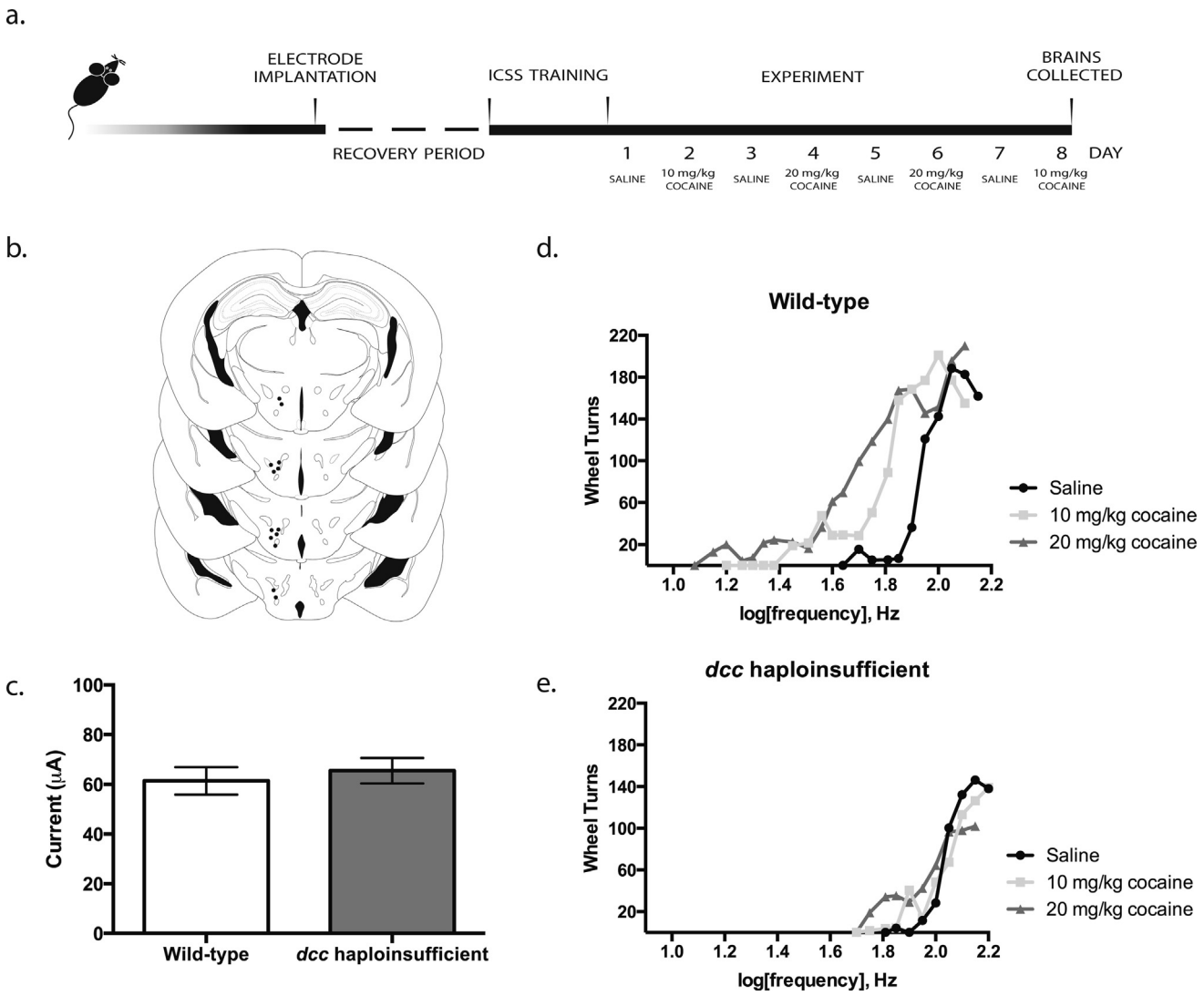

Fig. 1. (a) Experimental timeline. (b) Electrode placements. (c) Mean minimum stimulation current that sustained responding in wild-type or *dcc* haploinsufficient mice. (d) Rate-frequency curves from a representative wild-type mouse. (e) Rate-frequency curves from a representative *dcc* haploinsufficient mouse.

means for analysis. Difference scores were calculated by comparing the M_{50} of each mouse between vehicle and each cocaine dose. A two-way mixed design ANOVA was performed on the difference scores with genotype as a between-subjects variable and drug treatment as a within-subjects variable.

3. Results

3.1. Location of electrode tips

All stimulation sites lay within the lateral hypothalamus (Fig. 1b; coronal planes corresponding to Plates 48–51 of the Mouse Brain Altas [16]).

3.2. ICSS stimulation parameters do not differ between dcc haploinsufficient and wild-type mice

The minimum stimulation current that sustained behavioral responding did not differ between *dcc* haploinsufficient and wild-type mice (Fig. 1c).

3.3. Cocaine potentiation of ICSS is impaired in dcc haploinsufficiency

Cocaine shifts the rate-frequency curve to the left in wild-type mice (Fig. 1d). However, this effect is blunted in *dcc* haploinsufficient mice (Fig. 1e). Fig. 2 plots the differences between the ICSS M_{50} thresholds observed after the 10 mg/kg or the 20 mg/kg doses of cocaine in comparison to the M_{50} thresholds observed following saline administration. These difference scores between cocaine and saline injections indicate the magnitude of the shift induced by cocaine in the position of the rate-frequency curves along the frequency axis. Cocaine administration produced a dose-dependent left-shift in the ICSS M_{50} threshold in both *dcc* haploinsufficient mice and wild-type littermates. However, the left-shift in the M_{50} threshold was significantly smaller in the *dcc* haploinsufficient mice at both doses of cocaine. The 10 mg/kg dose of cocaine on average shifted the rate-frequency curve by $-0.12\log_{10}$ units (a 1.32 fold decrease) in wild-type mice, but only shifted the rate-frequency curve by $-0.06\log_{10}$ units (a 1.14 fold decrease) in *dcc* haploinsufficient mice. The 20 mg/kg dose of cocaine shifted the rate-frequency curve by $-0.18\log_{10}$ units (a 1.51 fold decrease) in wild-type mice, but shifted the rate-frequency curve by only

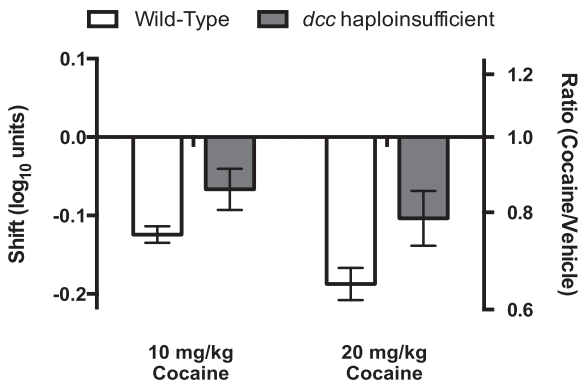

Fig. 2. Dose-dependent cocaine-induced potentiation of intracranial self-stimulation (ICSS) is blunted in adult *dcc* haploinsufficient mice. Difference scores (*left axis*: shift in $\log_{10}$ units; *right axis*: cocaine to saline ratios) are plotted for each cocaine dose and each genotype. Cocaine administration produced a dose-dependent left-shift in the ICSS M_{50} threshold in both *dcc* haploinsufficient mice and wild-type littermates. However, the left-shift in the M_{50} threshold was significantly smaller in the *dcc* haploinsufficient mice at both doses of cocaine. $N = 6$ and 7 per group, significant main effect of treatment, $p = 0.0018$; significant main effect of genotype, $p = 0.04$.

$-0.10\,\log_{10}$ units (a 1.25 fold decrease) in *dcc* haploinsufficient mice. (Fig. 2; main effect of treatment: $F_{(1,11)} = 16.66$, $p = 0.0018$; main effect of genotype: $F_{(1,11)} = 5.157$, $p = 0.04$; no significant treatment × genotype interaction, $F_{(1,11)} = 1.13$, $p = 0.31$.).

4. Discussion

Here we report that *dcc* haploinsufficient mice acquire ICSS behavior and that the parameters of the stimulation are comparable to those observed in wild-type littermates. The function of the circuitry subserving ICSS must therefore be intact in the mutant animals. Cocaine induces a dose-dependent left-shift in the rate frequency curve in both *dcc* haploinsufficient and wild-type mice. However, the potentiation of ICSS by both doses of cocaine is blunted in *dcc* haploinsufficiency. These results corroborate and extend our previous work showing that *dcc* haploinsufficiency protects against the behavioral effects of stimulant drugs of abuse. This new evidence supports our idea that the developmental reorganization of reward-related substrates by *dcc* haploinsufficiency produces resilience against the reward potentiating effects of drugs of abuse.

Because abused drugs are thought to have synergistic actions at circuitry that supports responding for brain stimulation reward, ICSS is often used as a primary screen to evaluate the abuse potential of substances [10]. Dopamine tone in the nucleus accumbens modulates ICSS [17,18], and the ability of drugs of abuse to increase dopamine release in the nucleus accumbens is highly correlated with their potentiating effects on this behavior [19]. We have previously shown that *dcc* haploinsufficiency leads to blunted dopamine release in the nucleus accumbens in response to stimulant drugs. We proposed that this reduction in dopamine tone confers resilience against the effects of stimulants on locomotion, conditioned place preference, and sensorimotor gating deficits [6,7]. The blunted cocaine-induced left-shifts in the rate-frequency curve that *dcc* haploinsufficient mice display may not only be a manifestation of reduced drug-induced dopamine release, but also a measure of dampened sensitivity to the abuse potential of drugs [10].

The altered effects of cocaine on ICSS may ultimately result from the increased dopamine innervation to the mPFC caused by impaired DCC signaling within dopamine neurons [3,4]. Increased dopamine function in the mPFC has been shown to exert a negative control over dopamine responsiveness in the nucleus accumbens to stimulant drugs [20,21]. Indeed, we have recently shown that mPFC dopamine depletion abolishes the resilient phenotype of *dcc* haploinsufficiency, most likely by releasing the mPFC 'brake' over dopaminergic neurotransmission in the nucleus accumbens [22].

Our current results suggest that reduced expression of *dcc* may dampen the abuse potential of cocaine. This conclusion seems to contrast with our recent report that *dcc* haploinsufficiency does not lead to altered methamphetamine self-administration [9]. In a short-access paradigm, both *dcc* haploinsufficient mice and their wild-type littermates self-administer methamphetamine and show a similar break point under a progressive ratio schedule. However, we cannot draw definitive conclusions regarding differential sensitivity to the rewarding effects of drugs of abuse based solely on this self-administration experiment. First, *dcc* haploinsufficient mice fail to titrate drug intake as a function of dose [9]. This is in contrast to evidence showing that following self-administration of high doses of a stimulant drug, there is typically a longer delay before the next infusion. That is, responding is inversely correlated with drug dose [23]. Because these titration patterns depend on dopamine released in the nucleus accumbens following each infusion, the differential consumption pattern of *dcc* haploinsufficient mice may in fact result from their blunted dopamine release in the nucleus accumbens in response to methamphetamine infusions [24]. Second, in the self-administration study we evaluated mice in a short-access paradigm only. Thus, we cannot predict how *dcc* haploinsufficient mice will behave under extended-access self-administration conditions. To shed light into this issue, it will be important to assess the effects of compromised DCC signaling on two aspects of drug taking behavior that are thought to have the strongest predictive validity for drug addiction: escalation of drug intake when exposed to long-access self-administration sessions and reinstatement of drug seeking following a period of extinction [25–27].

The blunted cocaine-induced potentiation of ICSS in *dcc* haploinsufficiency indicates that these mice have either decreased sensitivity to the rewarding effects of cocaine and/or decreased proclivity to invest effort in the pursuit of reward. Traditionally, cocaine potentiation of ICSS in the two-dimensional curve shift paradigm has been interpreted as a drug-induced increase in the sensitivity of reward circuitry [10,11]. However, by varying both the stimulation strength and opportunity cost, it is possible to distinguish between the effects of drugs on different stages of reward processing [13]. By evaluating the data in three dimensions (response strength, reward strength, and reward cost), it is possible to distinguish whether the drug influences the sensitivity of the reward substrate, or acts at later stages of processing by affecting the gain of the reward system or the subjective costs of performing the task. These two stages of processing represent orthogonal shifts in the three-dimensional structure, but are indistinguishable when flattened into a two-dimensional representation [13]. One limitation of our current design is that we cannot identify at which stage of neural processing *dcc* haploinsufficiency alters the cocaine-induced potentiation of ICSS. However, evidence from studies conducted in rats using this three-dimensional, 'reward-mountain' approach indicate that bi-directional alteration of nucleus accumbens dopamine tone acts at later stages of reward processing by altering either the gain of reward system function, the subjective opportunity costs, or both [13,28].

Our results extend our previous findings demonstrating that *dcc* haploinsufficiency generates a phenotype that is resilient or protective against the behavioral effects of drugs of abuse via the developmental reorganization of reward-related substrates. *DCC* haploinsufficiency has been identified in humans [29,30], indicating that our model has translational validity and raising the

possibility that *DCC* is a factor that influences susceptibility to the effects of abused drugs in patient populations.

Conflict of interest statement

The authors declare no conflict of interest.

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