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Short communication

Chronic ethanol self-administration in macaques shifts dopamine feedback inhibition to predominantly D2 receptors in nucleus accumbens core

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ABSTRACT

Background: Given the high level of homology between nonhuman primates and humans in regard to anatomy, physiology and ethanol drinking patterns, nonhuman primates represent an unparalleled preclinical model for examining the neurobiological basis of ethanol abuse.
Methods: Here we examined the neurochemical consequences of chronic daily ethanol use using fast-scan cyclic voltammetry in brain slices containing the nucleus accumbens core or dorsolateral caudate taken from male cynomolgus macaques following ethanol drinking.
Results: We found that in both regions the ability of ethanol to decrease dopamine release was unchanged, indicating that ethanol self-administration does not produce tolerance or sensitization to ethanol effects on dopamine release at the dopamine terminal at this time point. We also found that in the nucleus accumbens core, autoregulation of dopamine release was shifted from equal D2 and D3 receptor involvement in control animals to primarily D2 receptor-mediated in drinkers. Specifically, the effect quinpirole, a D2/D3 receptor agonist, on dopamine release was equal across groups; however, dopamine signals were reversed to a greater extent by the selective D3 receptor antagonist SB-277,011A in control animals, indicating a greater contribution of D2 receptors in quinpirole-induced inhibition following ethanol self-administration. In the dorsolateral caudate, the effects of quinpirole and reversal with SB-277,011A was not different between ethanol and control slices.
Conclusions: This work provides novel insight into the dopaminergic adaptations resulting from chronic ethanol use in nonhuman primates and indicates that alterations in D2/D3 dopamine autoreceptor signaling may be an important neurochemical adaptation to ethanol consumption during early use.

1. Introduction

Alcohol use disorders are a major public health concern and, as such, determining the neurobiological basis of alcoholism in search of pharmacotherapeutic targets has been an area of much research. Due to the physiological, genetic and behavioral similarities between nonhuman primates and humans, nonhuman primate models of human disease states are thought to possess high translational validity (Grant et al., 2014). Similarities between nonhuman primates and humans are particularly relevant in the study of voluntary ethanol drinking as nonhuman primates consume ethanol with similar daily intake to human alcoholics (Grant et al., 2008; Majchrowicz and Mendelson, 1970).

Alcohol abuse and addiction are thought to be mediated in part by ethanol-induced adaptations to dopaminergic signaling in the striatum (Koob, 2013). The striatum is composed of multiple distinct subregions that exert divergent control over behavioral outputs. Specifically, ventral regions of the striatum, such as the nucleus accumbens (NAc), encode associations between discrete cues, drug availability and previously learned contingencies. Conversely, dorsal regions, such as the putamen and dorsolateral caudate (DLC), mediate habitual and compulsive behaviors that emerge after repeated drug use (Porrino et al., 2004; Graybiel, 1995, 2008; Everitt and Robbins, 2013). The NAc and DLC both

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express D2 and D3 dopamine receptors, though distribution of these receptors is differential with the DLC preferentially expressing D2 and the NAc preferentially expressing D3 receptors (Murray et al., 1994). It is hypothesized that alterations to dopamine receptors contribute to pathological drinking behaviors, and in both rodents and humans, chronic ethanol exposure has been associated with decreased sensitivity of dopamine D2/D3 receptors in striatal regions (Volkow et al., 1996; Lucchi et al., 1988). However, the majority of these studies have not differentiated between post synaptic dopamine receptors located on striatal medium spiny neurons and presynaptic dopamine autoreceptors located on dopamine terminals originating from the ventral midbrain (Ford, 2014).

Here we sought to examine the effects of daily ethanol self-administration in male cynomolgus macaques on two important facets of dopamine terminal function: (1) the sensitivity of D2 and D3 autoreceptors and (2) the ability of ethanol to decrease dopamine release. These measures were assessed using fast scan cyclic voltammetry (FSCV), which allows for the isolated assessment of presynaptic dopamine autoreceptors, in brain slices containing the NAc core or the DLC.

2. Methods and materials

2.1. Subjects

All procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals and approved by the Oregon National Primate Research Center Institutional Animal Care and Use Committee. Eleven male cynomolgus monkeys (*Macaca fascicularis)* between the ages of 5.9–6.9 years were used for the current study (Daunais et al., 2014).

2.2. Drinking procedure

Monkeys (8 ethanol and 3 control) were trained to obtain fluids and their meals from an operant panel that replaced one of the walls of their home cage, as previously described (Vivian et al., 2001; Grant et al., 2008). Briefly, the panels had two spouts, one on each side of a 15″ video display screen. Near each spout the display showed a set of three stimulus lights (white, red, and green) that indicated an active session, food or fluid availability, respectively. A recessed dowel activated the fluid spouts and an infrared finger-poke detector activated the pellet dispenser (env-203-1000, Med Associates, St. Albans City, VT). Each spout was connected via Nalgene tubing to a 1-L fluid reservoir set on a digital scale (Ohaus Adventurer Pro Balances AV4101C, Ohaus Corporation, Pine Brook, NJ). Schedule-induced polydipsia was used to induce ethanol self-administration in daily 16-h sessions as previously described (Vivian et al., 2001; Grant et al., 2008). Following completion of ethanol drinking induction, animals began daily 22-h sessions during which water and ethanol were concurrently available. Animals were allowed ethanol access until the morning of necropsy, but sessions where the monkey was anesthetized for experimental (e.g., MRI imaging) or veterinary interventions (e.g., health check-ups) are not included in average ethanol intake calculations. The actual number of 22 h sessions used for intake measures exceeds 6 months and ranged between 201 and 205 days for controls and 204–214 days for ethanol drinking subjects. Intakes during the induction of ethanol self-administration are not included in the daily intake averages. Monkeys were anesthetized with ketamine (10 mg/kg), maintained on isoflurane, and perfused with ice-cold oxygenated monkey perfusion solution, as previously described (Daunais et al., 2010). Necropsy occured approximately 3.5–6.5 h after the last ethanol access period.

2.3. In vitro voltammetry

A vibrating tissue slicer was used to prepare 250 μm thick coronal brain sections containing either the DLC or NAc core, as previously described (Siciliano et al., 2014). The tissue was immersed in oxygenated artificial cerebrospinal fluid (aCSF) containing (in mM): NaCl (126), KCl (2.5), NaH_2PO_4 (1.2), $CaCl_2$ (2.4), $MgCl_2$ (1.2), $NaHCO_3$ (25), glucose (11), L-ascorbic acid (0.4) and pH was adjusted to 7.4. Once sliced, the tissue was transferred to testing chambers containing bath aCSF (32 °C), which flowed at 1 ml/min. A carbon fiber microelectrode (100–200 μM length, 7 μM diameter) and bipolar stimulating electrode were placed in close proximity on the tissue. Extracellular dopamine was recorded by applying a triangular waveform (−0.4 to +1.2 to −0.4 V vs Ag/AgCl, 400 V/s) to the recording electrode and scanning every 100 ms. Dopamine release was evoked by 1 pulse stimulations (350 μA, 4 msec, monophasic) applied to the tissue every 5 min until a stable baseline was established (3 collections within 10% variability), followed by bath application of ethanol (80 mM, 120 mM cumulatively), quinpirole (30 nM, 100 nM, cumulatively) or SB-277,011A (10 μM) to the slice (Austin et al., 2000; Rose et al., 2013). Signals were allowed to stabilize before subsequent concentrations were added to the bath. Quinpirole (100 nM) remained in the bath during SB-277,011A application. Demon Voltammetry and Analysis software was used for all analysis of FSCV data (Yorgason et al., 2011).

3. Results

3.1. Autoregulation of dopamine release shifts from D2/D3-mediated to primarily D2-mediated following ethanol exposure

Dopamine release and uptake kinetics as well as behavioral data from these animals were previously published in Siciliano et al. (2015a). The average amounts of ethanol consumed daily varied across individuals and ranged from 0.7 to 3.0 g/kg (Fig. 1A; group average: 1.79 ± 0.27 g/kg/day). Average BECs ranged from 6 to 144 mg/dl (Fig. 1B; group average: 62.38 ± 16.59). Ethanol self-administration increased dopamine release (control: 0.49 ± 0.16 μM, drinkers: 0.97 ± 0.11 μM) and uptake (control: 1.74 ± 0.16 μM/s, drinkers: 2.16 ± 0.08 μM/s) in the NAc core (depicted in Fig. 1C). Additionally, ethanol self-administration had the opposite effect in the DLC, where dopamine release (control: 0.85 ± 0.06 μM, drinkers: 0.41 ± 0.10 μM) and uptake (control: 2.09 ± 0.26 μM/s, drinkers: 1.31 ± 0.18 μM/s) were decreased in ethanol drinking animals (data not shown).

Given the implication of dopamine autoreceptors in regulating the rewarding properties of both natural and drug rewards (Bello et al., 2011), the effects of ethanol self-administration on D2/D3 autoreceptor sensitivity were examined. Quinpirole, a selective D2/D3 receptor agonist, was bath applied (30 and 100 nM) to slices containing the NAc core or DLC to determine differences in sensitivity between drinkers and control animals (Fig. 1C). Following application of quinpirole in the NAc core, a two-way repeated measures ANOVA revealed a main effect of concentration ($F_{1,7} = 11.91$, $p = 0.01$), but no effect of group ($F_{1,7} = 0.13$, $p = 0.73$) indicating that D2/D3 autoregulation of dopamine release was not changed by ethanol use (Fig. 1D). The selective D3 antagonist SB-277,011A was bath applied (10 μM) to the slice to determine the proportion of the quinpirole-induced decrease in dopamine release that was mediated through D3 receptors. A Student's t-test revealed that the quinpirole-induced decrease in dopamine release was restored by SB-277,011A to a greater extent in the control animals than in the ethanol exposed group (Fig. 1D) ($t_6 = 2.62$, $p = 0.02$), indicating that

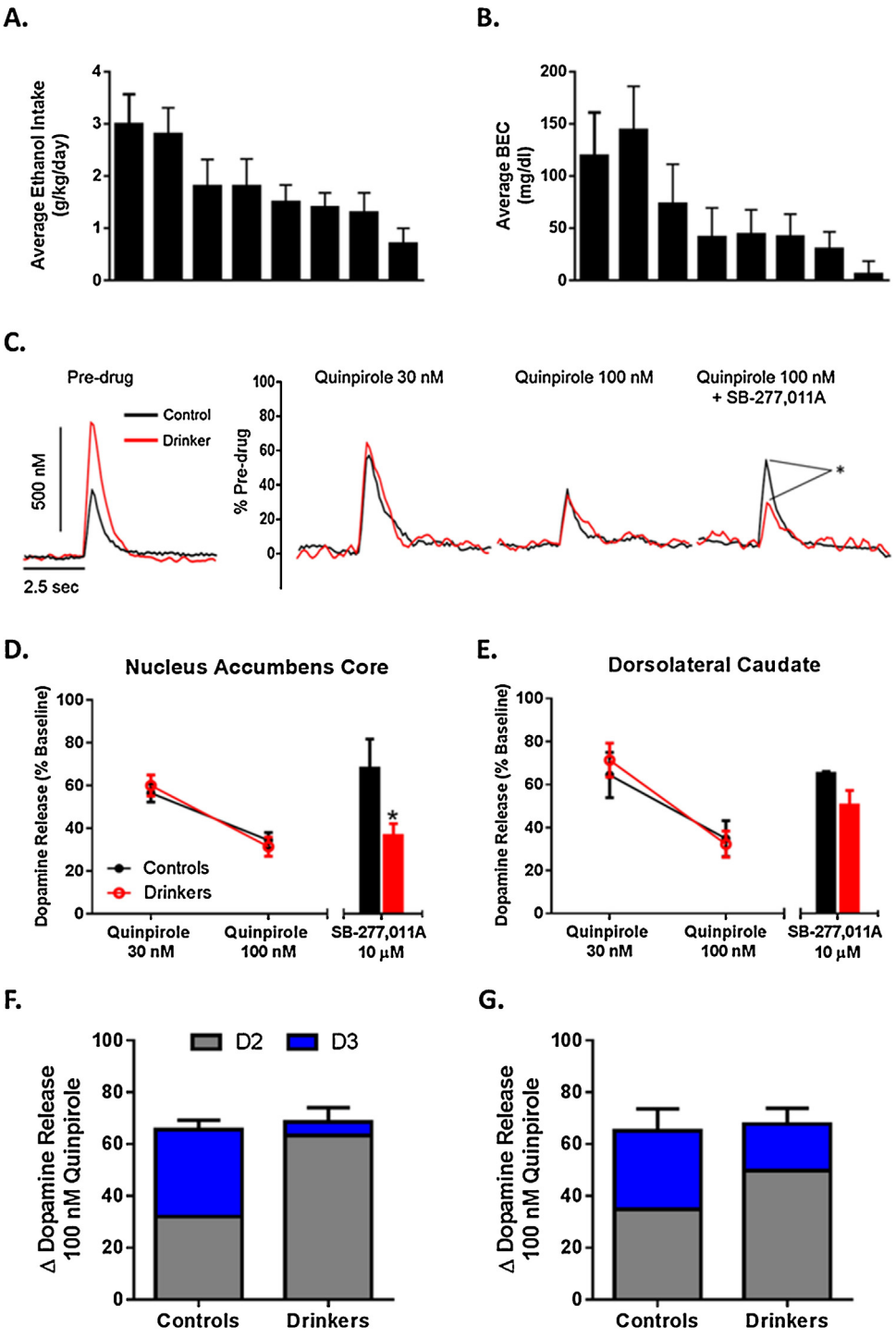

Fig. 1. *Ethanol self-administration shifts autoregulation of dopamine release from primarily D3-mediated to primarily D2-mediated.* (A) Average (±SD) daily ethanol intake for each animal. (B) Average (±SD) BEC taken every 5–7 days over the 6-month access period. Samples were collected 7 h after session onset. Animals are presented in the same order between graphs A and B. Data from graphs A and B were previously published by Siciliano et al. (2015a). (C) Representative traces demonstrating increased dopamine release and uptake in ethanol self-administration animals (left) and the effects of quinpirole and SB-277,011A on dopamine release between groups (right). (D) Group data ($n = 2$ for controls; $n = 6$ for drinkers) indicating no difference in sensitivity to D2/D3 agonist quinpirole between groups in the nucleus accumbens core. Application of the selective D3 antagonist SB-277,011A revealed a shift from a predominantly D3 mediated effect of quinpirole in controls to a predominantly D2 mediated effect in drinkers. (E) Group data ($n = 2$ for controls; $n = 6$ for drinkers) indicating no difference in sensitivity to D2/D3 agonist quinpirole between groups and a trend toward a more D2 mediated effect of quinpirole in the DLC of drinkers. (F) Total inhibition induced by quinpirole (whole bar) as well as the percent reversal induced by SB-277,011A (blue) in the NAc core. Inhibition present after application of SB-277,011A was presumed to be due to D2 receptor activation (gray). (G) Relative contribution of dopamine autoreceptor subtypes in the DLC. Total inhibition induced by quinpirole is depicted by the whole bar. Calculation of the contribution of D2 and D3 subtypes are represented in gray and blue, respectively. * $p < 0.05$ vs control. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

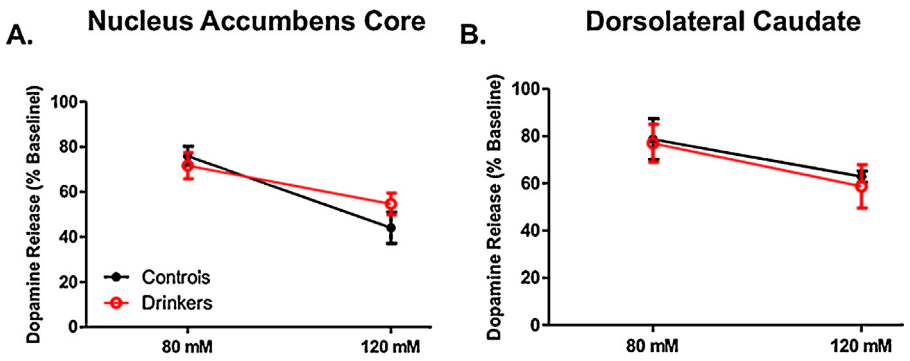

Fig. 2. *Ethanol sensitivity at the dopamine terminal is unchanged by ethanol self-administration.* Ethanol was bath applied to slice containing either the nucleus accumbens core (A) or dorsolateral caudate (B). (A) Group data ($n = 3$ for controls; $n = 7$ for drinkers) indicating no difference in ethanol sensitivity between groups in the nucleus accumbens core. (B) Group data ($n = 3$ for controls; $n = 7$ for drinkers) indicating no difference in ethanol sensitivity between groups in the dorsolateral caudate.

there is a reduced contribution of D3 receptors to autoregulation of dopamine release following ethanol use.

Following application of quinpirole in the DLC (Fig. 1E), a two-way repeated measures ANOVA revealed a main effect of concentration ($F_{1,7} = 70.58$, $p = 0.0001$), but no effect of group ($F_{1,7} = 0.04$, $p = 0.85$). In the DLC there was no difference in SB-277,011A-induced reversal of quinpirole effects between controls and drinkers (Figure 1E) ($t_6 = 1.15$, $p = 0.15$). Given the differential effect of SB-277,011A between drinkers and control animals, we calculated the relative contribution of D2 and D3 receptors to the total inhibition induced by quinpirole in the NAc core (Fig. 1F) and DLC (Fig. 1G). The percent change induced by SB-277,011A was plotted as D3 receptor contribution, while any remaining inhibition by quinpirole was assumed to be D2 receptor contribution.

3.2. Ethanol sensitivity at the dopamine terminal is unchanged following voluntary ethanol drinking

To determine if ethanol sensitivity at the dopamine terminal was altered by ethanol self-administration, 80 and 120 mM ethanol was bath applied to brain slices containing the DLC or NAc core. In the NAc core (Fig. 2A), a two-way repeated measures ANOVA revealed a main effect of concentration ($F_{1,8} = 33.34$, $p = 0.0004$), but no effect of ethanol self-admiration ($F_{1,8} = 0.15$, $p = 0.71$). In the DLC (Fig. 2B), a two-way repeated measures ANOVA revealed a main effect of concentration ($F_{1,8} = 21.23$, $p = 0.009$) whereby ethanol decreased dopamine release in a concentration-dependent manner. There was no effect of ethanol history on sensitivity to ethanol ($F_{1,8} = 0.04$, $p = 0.83$).

4. Discussion

We found that following free-access ethanol self-administration in male cynomolgus macaques there is a marked shift in the relative contribution of D2 versus D3 type autoreceptors in regulating dopamine release from presynaptic terminals in the nucleus accumbens core. Indeed, in control animals, autoregulation of dopamine release was roughly equally D2 and D3 receptor mediated, while in ethanol self-administration animals autoregulation was primarily D2 receptor mediated. Additionally, we found that the overall sensitivity of autoreceptors, when D2 and D3 receptors were measured together, was not different between control and ethanol slices. Finally, we found that following a history of chronic ethanol self-administration did not alter the ability of ethanol to decrease electrically stimulated dopamine release at this time point. These results give novel insights into specific, long-term dopaminergic adaptations induced by daily, voluntary ethanol drinking and suggest that ethanol-induced alterations in autoreceptor regulation of presynaptic dopamine release may be a consequence of chronic ethanol use.

Dopamine D2 and D3 autoreceptors regulate dopamine neurotransmission through inhibitory feedback that decreases dopamine release, nerve-terminal excitability and dopamine synthesis (Ford, 2014). Autoregulation of dopamine neurotransmission is important for modulating the rewarding and reinforcing aspects of natural rewards and drugs of abuse, and D2 autoreceptor knockout mice have greatly augmented cocaine reward and reinforcing efficacy of food (Bello et al., 2011). Here we show that the ability of the non-selective D2/D3 agonist quinpirole to decrease dopamine release is not different from controls in the NAc core and DLC following of monkeys given >200 consecutive days of ethanol drinking, which is a fairly short-term exposure in this monkey model (Grant et al., 2008). However, it is likely that as ethanol use persists, the sensitivity of autoreceptors is altered by ethanol, as previous work from our lab has demonstrated supersensitivity of autoreceptors in monkeys following 18 months of ethanol self-administration (Budygin et al., 2003). These findings are in contrast to reports of ethanol-induced decreases in D2/D3 receptor sensitivity, however this may be a result of measuring global dopamine receptor sensitivity (e.g. Volkow et al., 1996; Lucchi et al., 1988) as opposed to specifically measuring presynaptic autoreceptors (Budygin et al., 2003; current study). Further, the contingency of administration may be a critical factor in the development of ethanol-induced adaptations to dopamine receptors, and future work will aim to determine if these effects are a purely pharmacological consequence of ethanol exposure, or a product of voluntary consumption.

Additionally, we found that quinpirole-induced deceases in dopamine release were reversed with application of a selective D3 antagonist to a greater extent in controls animals. Further investigations are needed to (1) more fully characterize this effect by examining the effects of SB-277,011A across a concentration-response curve and (2) determine the behavioral relevance of ethanol-induced alterations to presynaptic dopamine receptor subtype regulation of dopamine neurotransmission. Another potential caveat of the current study is the low number of subjects, especially in the control group, thus limiting statistical power. However, these results indicate that ethanol self-administration decreased the contribution of D3 autoreceptors while maintaining the same overall effect of quinpirole, presumably by increasing the contribution of D2 receptors. One possibility is that increased D2 receptor regulation of dopamine release may produce long-lasting decreases in dopamine levels, due to reduced receptor desensitization as compared to D3 receptors (O'Hara et al., 1996), during withdrawal to produce hypofunction of the dopamine system. Moreover, the effects of ethanol self-administration on autoregulation of dopamine release were divergent across regions, which may be a function of greater D3 receptor availability in the NAc compared

to the DLC (Murray et al., 1994). It may be a promising avenue of future research to explore other striatal subregions. The NAc shell is of particular interest given its role in assigning motivational value to reinforcers, including abused drugs (Saddoris et al., 2013).

Many theories of addiction propose that following extensive use of a drug, the user adapts (becomes tolerant or sensitized) to the effects of the drug and that the neural basis of these adaptations is integral to the addiction process (Robinson and Berridge, 1993; MacRae et al., 1987; Koob, 2003; Siciliano et al., 2015b). We found that the inhibitory effects of ethanol on dopamine neurotransmission at the nerve terminal were unchanged by ethanol self-administration. However, it is important to note that the ability of ethanol to augment dopamine levels is dependent on interactions with the dopaminergic cell bodies projecting from the ventral midbrain to increase cell firing (Brodie et al., 1990; Mrejeru et al., 2015; Gessa et al., 1985). Thus, while we show that the inhibitory effects of ethanol at the dopamine terminal are unchanged, ethanol's excitatory effects on dopamine firing are unknown for primates. Together, the current findings give novel insight into the neurobiological basis of ethanol abuse and indicate that alterations in relative function of dopamine autoreceptor subtypes may contribute to aberrant drinking behaviors during early ethanol use.

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Nothing declared.

Conflict of interest statement

The authors have no conflicts to report.

Contributors

Cody Siciliano: designed and performed experiments, analyzed data, wrote manuscript.

Erin Calipari: designed and performed experiments, analyzed data.

Jordan Yorgason: provided equipment/reagents.

Yolanda Mateo: provided equipment/reagents.

Christa Helms: performed experiments.

David Lovinger: provided equipment/reagents.

Kathleen Grant: designed experiments, provided equipment/reagents.

Sara Jones: designed experiments, provided equipment/reagents, edited manuscript.

All authors have approved the final article.

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