

Ethanol reverses the direction of long-term synaptic plasticity in the dorsomedial striatum

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Abstract

The striatum is a critical structure for the control of voluntary behaviour, and striatal synaptic plasticity has been implicated in instrumental learning. As ethanol consumption can cause impairments in cognition, learning, and action selection, it is important to understand the effects of this drug on striatal function. In this study we examined the effects of ethanol on long-term synaptic plasticity in the dorsomedial striatum (DMS), a striatal subregion that plays a central role in the acquisition and selection of goal-directed actions. Ethanol was found to impair *N*-methyl-D-aspartic acid receptor (NMDAR)-dependent long-term potentiation (LTP) dose-dependently in the DMS, and to promote long-term depression (LTD) at the highest concentration (50 mM) used. These results suggest that ethanol, at a concentration usually associated with mild intoxication, could significantly change experience-dependent modification of corticostriatal circuits underlying the learning of goal-directed instrumental actions.

Introduction

Ethanol is a widely used and abused drug with many effects on learning and behaviour. Compared to other addictive substances such as cocaine and nicotine, the effects of ethanol are more diffuse, with diverse documented effects on various ligand-gated and voltage-gated channels (Celentano *et al.*, 1988; Lovinger, 1997; Kobayashi *et al.*, 1999; Woodward, 2000). Consequently, the mechanisms underlying ethanol's actions on the central nervous system are difficult to pin down. Although many effects of direct, acute ethanol application on synaptic transmission and plasticity have been reported, they are typically found at high concentrations (Morrisett & Swartzwelder, 1993; Schummers *et al.*, 1997; Izumi *et al.*, 2005a; Izumi *et al.*, 2005b). No clear evidence exists to link these laboratory observations to the operations of neural systems mediating alcohol seeking and taking.

Reward-guided behaviours are often attributed to the cortico-basal ganglia networks coursing through the neostriatum (Packard & McGaugh, 1996; White, 1997; Hikosaka *et al.*, 2000). Because traditional measures of reward-guided behaviour often confound learning with performance, they are incapable of accurately assessing what animals actually learn on behavioural tasks and thus which neural substrates are necessary for learning (Smith-Roe & Kelley, 2000; Bailey & Mair, 2006; Atallah *et al.*, 2007). The introduction of contemporary behavioural assays from the instrumental learning paradigm has made it possible to probe, for the first time, the type of representations animals acquire to control their instrumental performance (Colwill & Rescorla, 1986; Dickinson & Balleine, 1993). These assays include post-training manipulations of the value of the outcome or reward (e.g. outcome devaluation by sensory-specific

satiety or by taste aversion induction) and of the contingency between action and outcome (e.g. instrumental contingency degradation). Such assays can establish whether the behaviour in question (e.g. lever pressing) is goal-directed or habitual (Dickinson, 1994; Yin & Knowlton, 2006). In particular, recent studies have shown that, not only is the neostriatum (dorsal striatum) critical in the control of voluntary behaviour, specific regions within it appear to play distinct roles in the acquisition of goal-directed actions and stimulus-driven habits. The dorsomedial striatum (DMS), in particular, was shown to be critical for the learning of goal-directed actions, the performance of which is sensitive to outcome devaluation and to instrumental contingency degradation (Yin & Knowlton, 2004; Yin *et al.*, 2005a; Yin *et al.*, 2005b). On the other hand, the dorsolateral striatum appears to be involved in the formation of habits (Yin *et al.*, 2004, 2006).

In parallel with such findings from behavioural studies, studies of striatal synaptic plasticity in brain slices found that long-term potentiation (LTP) is preferentially expressed in the DMS, and requires the activation of *N*-methyl-D-aspartic acid receptors (NMDARs; Partridge *et al.*, 2000; Dang *et al.*, 2006). This form of LTP has been linked to instrumental learning, as it is significantly correlated with initial acquisition of lever pressing (Reynolds *et al.*, 2001), and NMDAR blockade in the DMS impairs instrumental learning (Yin *et al.*, 2005a).

In this study we examined the effects of ethanol on long-term synaptic plasticity in the DMS. As one of the most well-established effects of ethanol is inhibition of NMDAR-mediated glutamatergic transmission (Lovinger *et al.*, 1989), we hypothesized that ethanol can impair LTP in this region by inhibiting NMDARs. As the behavioural research mentioned above has shown that blockade of NMDARs in the DMS can prevent action-outcome learning and promote habit formation, any disruption of NMDAR-dependent LTP by EtOH exposure is expected to produce a similar effect.

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Materials and methods

Brain slice preparation

Brain slices containing both striatum and cortex were prepared, as described previously (Gerdeman *et al.*, 2002), from postnatal day (P) 14–19 Sprague–Dawley rats. Animals were anaesthetized with halothane and transcardially perfused with ice-cold modified artificial cerebrospinal fluid (aCSF) containing (in mM) 194 sucrose, 30 NaCl, 4.5 KCl, 1 MgCl₂, 26 NaHCO₃, 1.2 NaH₂PO₄, and 10 D-glucose. They were then decapitated, and their brains transferred rapidly to the modified aCSF, which was brought to pH 7.4 by aeration with 95% O₂ and 5% CO₂. Coronal sections (350- μ m thick) were cut in ice-cold modified aCSF using a Vibrotome 1000 slicer (St Louis, MO). Slices were transferred immediately to a nylon net submerged in normal aCSF containing (in mM) 124 NaCl, 4.5 KCl, 2 CaCl₂, 1 MgCl₂, 26 NaHCO₃, 1.2 NaH₂PO₄, and 10 D-glucose. Normal aCSF was maintained at pH 7.4 by bubbling with 95% O₂ and 5% CO₂ at room temperature (19–22 °C). Following at least 1 h of incubation at room temperature, hemislices were transferred to a recording chamber and submerged in normal aCSF. For all experiments, the temperature of the bath was maintained at 28–31 °C stable within ± 1 °C during any given experiment.

Whole-cell voltage-clamp recording of NMDAR-mediated currents

Whole-cell recordings from medium spiny neurons (MSNs) were performed as described previously (Gerdeman *et al.*, 2002). Pipettes were pulled from borosilicate glass capillaries on a Flaming–Brown micropipette puller (Sutter Instruments, Novato, CA). Test stimuli were delivered via a Master-8 stimulator (A.M.P.I., Jerusalem, Israel) at a frequency of 0.05 Hz through a bipolar twisted tungsten wire placed in the DMS. Pipette resistance ranged from 2.5 to 4 M Ω , when filled with an internal solution containing (in mM) 120 caesium methane sulphate, 5 NaCl, 10 tetraethylammonium chloride, 10 HEPES, 4 lidocaine *N*-ethyl bromide, 1.1 EGTA, 4 Mg-ATP, and 0.3 Na-GTP, pH adjusted to 7.2 with CsOH, and osmolarity set to 298 mOsm with sucrose. The osmolarity of the external solution (normal aCSF) was adjusted to 315 mOsm with sucrose. Recordings were made from MSNs (soma diameter 10–15 μ m) identified with the aid of differential interference contrast (DIC)-enhanced visual guidance. Cells were voltage-clamped at 30–40 mV throughout the experiments, and the stimulus intensity was set to the level at which EPSC amplitude was 200–600 pA. To isolate NMDAR-mediated currents, 50 μ M picrotoxin was added to the solution to block GABA_A receptor-mediated currents, and 10 μ M NBQX was added to block AMPAR-mediated currents. We analysed only recordings with series resistance <20 M Ω (usually ranging from 11 to 16 M Ω). The series resistance was not compensated, and if it changed by more than 20% during the course of an experiment, the cell was discarded.

Synaptic currents were recorded with an Axopatch 1D amplifier (Axon Instruments, Foster City, CA), filtered at 5 kHz, digitized at 10 kHz, and stored on a Dell microcomputer (Round Rock, TX). EPSC amplitudes were examined using peak detection software in pCLAMP8 (Union City, CA).

Field potential recording

Extracellular field recordings were obtained with micropipettes (2–4 M Ω) filled with 1 M NaCl solution. Regular aCSF was used as the external solution. Test stimuli were delivered via a S45

stimulator (Grass Instruments, West Warwick, RI) at a frequency of 0.05 Hz through a bipolar twisted tungsten wire placed in the DMS.

In striatal field potential recordings we can only estimate relative synaptic efficacy by measuring the amplitude of the population spike (PS, also known as N2), rather than field EPSP amplitude or slope. For the dendrites of striatal MSNs are not uniformly orientated and dendritic arbors are not subregionally separated as they are for example in the hippocampus; and as a result, the dipole produced by synaptic current flow is not sufficient to induce a measurable field EPSP. Nevertheless, current flow into large numbers of adjacent MSN cell bodies due to synchronous synaptically driven postsynaptic action potentials generates a PS with an amplitude that consistently reflects the efficacy of excitatory synaptic input (Misgeld *et al.*, 1979).

In our recordings of striatal field PSs, stimulus intensity was set to yield an evoked PS amplitude approximately half the size of the maximal evoked response. The half-maximal responses ranged from 0.4 to 1.5 mV, and were evoked with stimuli 0.2–0.9 mA in intensity and 0.01–0.04 ms in duration. For experiments with EtOH application, EtOH at the stated concentration is present in the bath continuously (flow rate, approximately 2 mL/min) unless specified otherwise.

The high frequency stimulation (HFS) protocol used to induce LTP in the DMS consisted of four 1 s, 100 Hz trains delivered every 10 s. Data were filtered (highpass, 0.1 Hz; lowpass 3 kHz) and then amplified and digitized using an Axoclamp 1D amplifier and Digidata 1322 interface (Axon Instruments/Molecular Devices, Sunnyvale, CA).

Results

Ethanol dose-dependently impairs LTP in the DMS

Field potential recordings were carried out to examine the effect of ethanol on synaptic plasticity in striatum. Planned comparisons were made for each group between baseline PS amplitude and PS amplitude recorded 20–30 min after HFS. Ethanol altered the direction of striatal synaptic plasticity in a concentration-dependent manner (Fig. 1A). The control slices showed significant LTP (138 \pm 11% of baseline, $P < 0.05$). With 2 mM EtOH treatment, a reduced but still statistically significant potentiation was observed (116 \pm 8% of baseline, $P < 0.05$). At 10 mM EtOH, LTP was completely abolished (98 \pm 8% of baseline, $P < 0.05$). At 50 mM EtOH, however, not only was the LTP abolished but a significant long-lasting depression was observed (79 \pm 7% of baseline, $P < 0.05$). In addition, EtOH did not have a significant effect on baseline PS amplitude (Fig. 1C; 103 \pm 7% of baseline, $P > 0.05$). We found no difference between the control group and the 2 mM EtOH group ($P > 0.05$), but the post-HFS increase in PS amplitude in all other groups was significantly lower than the control group ($P < 0.05$ for both the 10 mM and 50 mM EtOH groups).

We also examined the time course of the effects of EtOH on striatal LTP. As shown in Fig. 2, when 50 mM EtOH was washed out immediately after HFS, we did not observe any significant potentiation or depression (control group, 124 \pm 11% of baseline, $P < 0.05$; immediate washout group, 98 \pm 11% of baseline, $P > 0.05$). However, when EtOH was washed out 10 min after HFS, a significant long-term depression (LTD) was observed (66 \pm 9% of baseline, $P < 0.05$). These results show that while the induction of striatal LTP was blocked by EtOH exposure before HFS, EtOH must be present in the bath for a brief period post-HFS (10 min or less) to induce LTD.

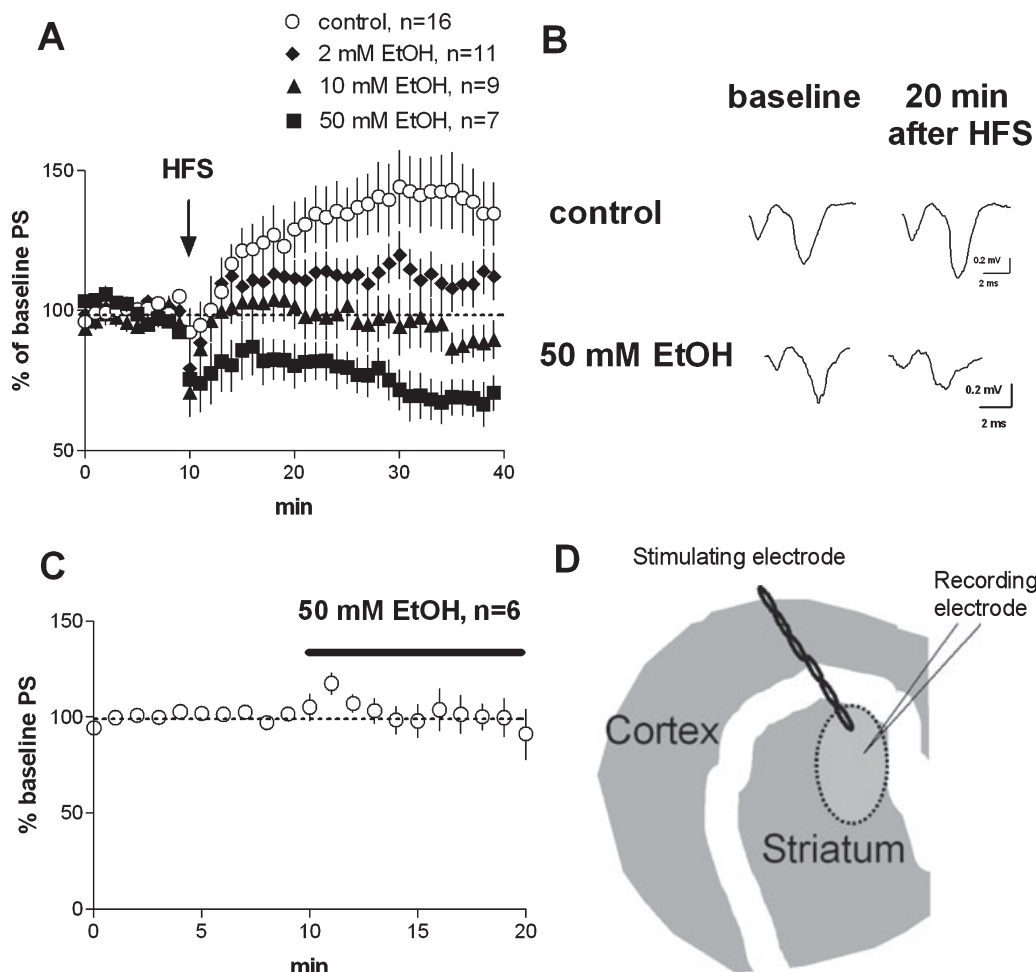


FIG. 1. EtOH dose-dependently reverses the direction of striatal synaptic plasticity. (A) The effects of EtOH on synaptic plasticity in the DMS. For groups with EtOH treatment, EtOH was present throughout the recording. (B) Representative traces. (C) EtOH did not alter baseline PS amplitude. (D) The area defined as DMS in this study. Stimulating and recording electrodes were placed in the region as illustrated here. We recorded from anterior as well as posterior regions of the DMS.

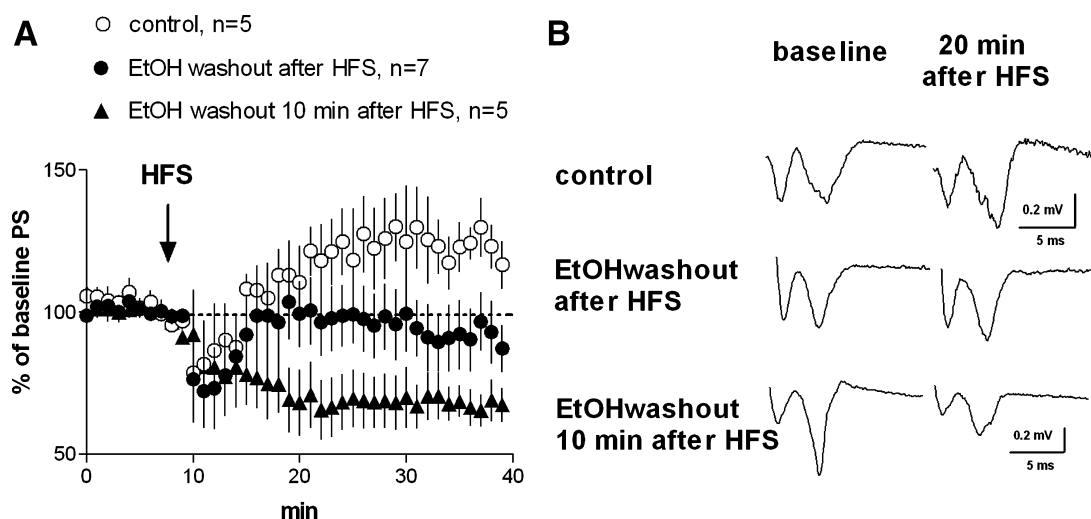


FIG. 2. Time course of the effects of EtOH on striatal synaptic plasticity. (A) 50 mM EtOH is present in the bath at the beginning of the experiment. When EtOH was washed out immediately after HFS, we did not observe any significant potentiation or depression, but when EtOH was washed out 10 min after HFS, a significant LTD was observed. These results show that while the induction of striatal LTP was blocked by EtOH exposure before the HFS, EtOH must be present in the bath for < 10 min in order to induce LTD. (B) representative traces.

The role of NMDARs in LTP and EtOH actions in the DMS

EtOH is known to inhibit NMDARs in the hippocampus (Lovinger *et al.*, 1989). We confirmed that ethanol can inhibit NMDARs in the DMS by measuring the effects of 50 mM EtOH applied to the bath on pharmacologically isolated NMDAR-mediated currents (Fig. 3D). We found that EtOH significantly and reversibly inhibits NMDAR-mediated currents (EPSC amplitude in EtOH = $78 \pm 7\%$ of baseline, $P < 0.05$).

Previous work has also shown that striatal LTP requires the activation of NMDARs and D1 receptors (Partridge *et al.*, 2000; Kerr & Wickens, 2001). We replicated these findings in the present study. As shown in Fig. 3B; LTP in the DMS was blocked by bath application of the NMDAR antagonist APV ($90 \pm 9\%$ of baseline, $P > 0.05$), but no significant LTD was observed. When APV was combined with 50 mM EtOH, HFS resulted in LTD (Fig. 3B; $66 \pm 5\%$ of baseline, $P < 0.05$), suggesting that the mechanism underlying EtOH-promoted LTD is independent of its effects on NMDARs. LTP was also blocked by bath application of the D1 receptor antagonist SCH-23390 (Fig. 3C; control, $127 \pm 8\%$ of baseline, $P < 0.05$; SCH-23390, $82 \pm 9\%$ of baseline, $P > 0.05$).

Ethanol-mediated LTD requires activation of D2 and CB1 receptors

A particularly interesting observation from the aforementioned experiments is the complete reversal of the direction of synaptic plasticity – from LTP to LTD – observed after HFS with 50 mM EtOH in the bath. A well-established form of striatal LTD, mediated by retrograde endocannabinoid signalling (eCB-LTD), is usually found in the dorsolateral striatum, and requires the activation of D2-like dopamine receptors and of CB1 cannabinoid receptors (Calabresi *et al.*, 1992; Gerdeman *et al.*, 2002; Gerdeman *et al.*, 2003). To assess whether EtOH-enhanced LTD in DMS is similar to the endocannabinoid-dependent LTD previously observed, we tested whether blocking D2 receptors and CB1 receptors has any effect on EtOH-enhanced LTD. Whereas slices treated with 50 mM EtOH showed significant LTD ($69 \pm 7\%$ of baseline, $P < 0.05$), EtOH-mediated LTD was blocked by the D2 receptor antagonist sulpiride (Fig. 4A; $103 \pm 8\%$ of baseline, $P > 0.05$), and by the CB1 receptor antagonist AM251 (Fig. 4B; and $98 \pm 8\%$, $P > 0.05$).

Discussion

We identified a strong effect of EtOH on the overall direction of synaptic plasticity in a brain area critical for the learning and expression of explicitly goal-directed actions. Thus, at a dose that is comparable to intoxicating blood alcohol levels, the direction of synaptic plasticity could be reversed from LTP to LTD in the DMS. Surprisingly, LTP is abolished with a relatively low dose of 10 mM (Fig. 1A). Striatal LTP therefore appears to be more sensitive to acute ethanol treatment than other forms of NMDAR-dependent synaptic

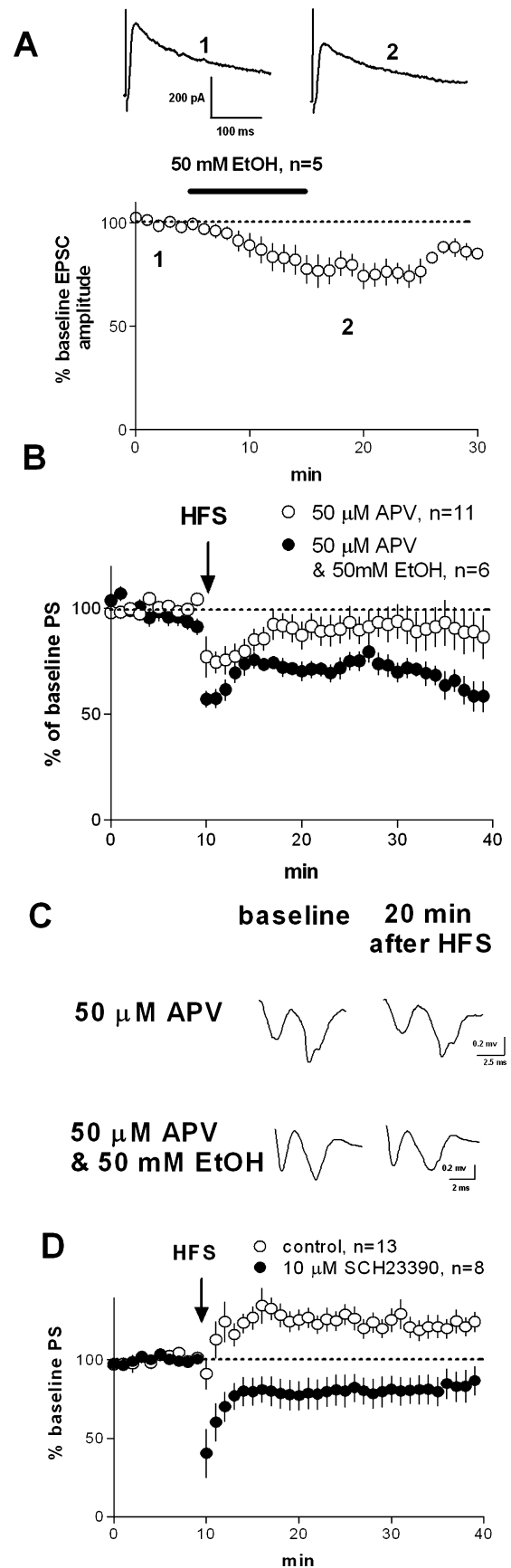


FIG. 3. Striatal LTP requires NMDAR and D1 receptor activation. (A) EtOH reduces NMDAR-mediated glutamatergic transmission in the DMS. (B) Striatal LTP is abolished in the presence of the NMDAR antagonist APV, but APV combined with 50 mM EtOH results in significant LTD, showing that the well-known inhibitory effects of EtOH on NMDAR-mediated currents cannot be the sole mechanism underlying the observed reversal of the direction of long-term synaptic plasticity. (C) Representative traces. (D) Striatal LTP is also abolished in the presence of the D1 receptor antagonist SCH-23390.

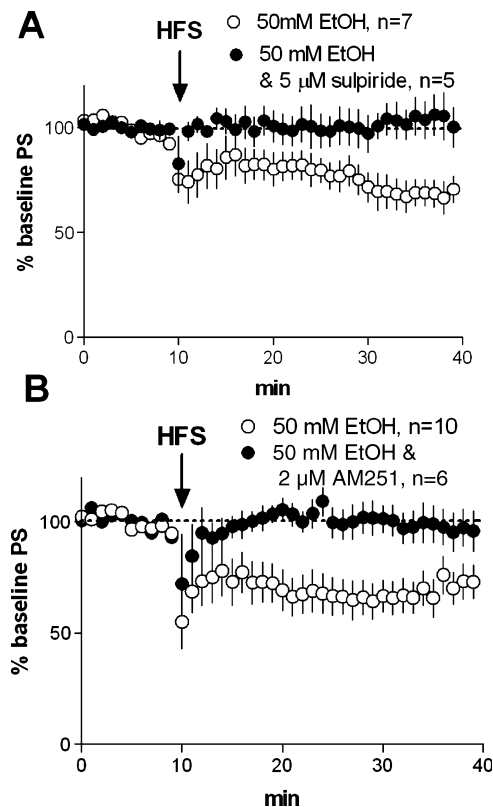


FIG. 4. EtOH-promoted LTD requires the activation of D2 receptors and CB1 receptors. (A) EtOH-promoted LTD is blocked by the D2 receptor antagonist sulpiride. (B) EtOH-promoted LTD is blocked by the CB1 receptor antagonist AM251. EtOH is present in the bath throughout the experiment.

plasticity such as hippocampal LTP at the CA1 synapse (Morrisett & Swartzwelder, 1993; Schummers *et al.*, 1997; Izumi *et al.*, 2005a).

The loss of LTP in the presence of EtOH does not appear to be secondary to a decrease in fast AMPA receptor-mediated glutamatergic transmission. Application of EtOH did not alter the baseline population spike, indicating that it does not diminish excitatory synaptic drive. Furthermore, a recent study indicates that high concentrations of EtOH have only a weak effect on AMPAR-mediated synaptic current in striatum (Choi *et al.*, 2006).

Moreover, the observation that higher EtOH concentrations (e.g. 50 mM) not only abolished LTP but also enhanced LTD (Fig. 1A) cannot be explained by the inhibitory effects of ethanol on NMDARs. Blockade of NMDARs by APV, while sufficient to block LTP, did not produce LTD (Fig. 3B). Using whole-cell patch-clamp recording, we also found that 50 mM ethanol merely produced a modest and reversible inhibition of NMDAR-mediated currents (Fig. 3A).

If the observed effects of ethanol on striatal synaptic plasticity cannot adequately be explained by the inhibition of NMDARs alone, there may be additional targets of ethanol responsible for promoting LTD. Some possibilities are suggested by previous research on the mechanisms underlying striatal plasticity. In particular, striatal LTP requires the activation of D1 receptors – the D1 receptor antagonist SCH-23390 can impair LTP, as illustrated in Fig. 3D. Thus it is possible that EtOH can inhibit D1 receptor function. Little is known about the cellular and molecular mechanisms for EtOH–dopamine receptor interactions, partly because results from the relevant previous studies were inconclusive (Barbaccia *et al.*, 1980; Reggiani *et al.*, 1980; Rabin & Molinoff, 1981). There is, however, recent evidence

that D1, but not D2, receptors in the hippocampus are required for the learning of a passive avoidance task, while pretraining administration of EtOH dose-dependently impaired performance on this task (Rezayof *et al.*, 2007). Nevertheless, while the combined effects of NMDAR and D1 receptor inhibition could explain the ability of EtOH to block striatal LTP, it is not clear whether these mechanisms are sufficient to promote LTD induction.

On the other hand, in view of data from this study, EtOH could also potentiate D2 receptor function, which is directly implicated in LTD induction (Calabresi *et al.*, 1992; Gerdeman *et al.*, 2003). This hypothesis is in accord with the well-established finding that D2 receptors have important roles in ethanol sensitivity and self-administration (Phillips *et al.*, 1998; Cunningham *et al.*, 2000; Risinger *et al.*, 2000). Interestingly, we also observed that when EtOH (50 mM, a dose that resulted in LTD after HFS) was washed out immediately after HFS, neither LTP nor LTD was observed, a net result similar to that of the NMDAR antagonist APV. By contrast, when EtOH was washed out 10 min after HFS, LTD was observed. This pattern of results suggests that the mechanism by which EtOH prevents LTP induction is distinct from the mechanism by which it promotes LTD induction. As shown by previous work (Gerdeman *et al.*, 2002; Ronesi *et al.*, 2004), the blockade of CB1 receptors, which are necessary for LTD induction, is only effective in preventing LTD when applied to the bath during HFS or within 5–10 min after HFS, showing that retrograde endocannabinoid signalling within this short time window is critical for LTD induction. As EtOH can promote LTD so long as it remains in the striatum for 10 min after HFS, as observed here, it might simply do so by potentiating retrograde endocannabinoid signalling during this critical time window. There are of course multiple ways in which EtOH could affect endocannabinoid production and release – an intriguing topic for future research. But given the established role of striatal D2 activation in increasing anandamide levels in the striatum (Giuffrida *et al.*, 1999; Piomelli, 2003), the potentiation of D2-mediated signalling is clearly a candidate upstream mechanism for any effect EtOH might have on retrograde endocannabinoid signalling. These possibilities remain to be tested.

As already mentioned, identical HFS stimulation protocols can result in either LTD or LTP depending on the region of the dorsal striatum from which the recording is made. The regional variation in the type of long-term plasticity expressed is probably a direct consequence of gradients in the expression of key receptors (Gerdeman *et al.*, 2003). Under normal circumstances, after HFS LTP is more commonly found in the DMS, while LTD is more commonly found in the dorsolateral striatum (Partridge *et al.*, 2000; Gerdeman *et al.*, 2003). The present results suggest that this regional variation in the type of synaptic plasticity expressed is a matter of degree rather than of kind. When a high concentration of EtOH is in the bath, LTD is consistently observed even in the DMS.

Our results have significant implications for the study of striatal plasticity. The most straightforward explanation is that two parallel physiological processes can take place at the corticostriatal (or thalamostriatal) synapse, when a burst of high frequency synaptic activation occurs, and the net change in synaptic strength is the outcome of the combined action of these two processes. The first process by itself results in potentiation at the synapse. This form of LTP likely involves postsynaptic induction and expression mechanisms, given the similarities to NMDAR-mediated LTP in the hippocampus (Nicoll, 2003). The second process, by contrast, results in a net decrease in synaptic strength. This process is better understood in the striatum, and involves the activation of L-type calcium channels at the dendritic spines of the MSNs, the extrasynaptically located

group I mGluRs, and D2Rs, and the production and release of an endocannabinoid as a retrograde messenger to reduce glutamate release presynaptically (Gerdeman *et al.*, 2002; Ronesi *et al.*, 2004; Kreitzer & Malenka, 2005; Wang *et al.*, 2006). Because acute exposure to ethanol can completely reverse the direction of synaptic plasticity in the dorsal striatum, LTP and LTD appear to compete for expression in the same neurons, or at least among a population of neurons in a given striatal subregion.

Implications for the study of alcohol addiction

Our findings also have implications for understanding alcohol addiction. The latest model of instrumental learning posits two distinct systems mediating action–outcome and stimulus–response learning, respectively (Dickinson, 1985; Yin & Knowlton, 2006). As already mentioned in the introduction, whether a particular instrumental behaviour is goal-directed (controlled by the action–outcome contingency) or habitual (controlled by antecedent stimuli) can be assessed by behavioural assays that manipulate the value of the reward and of the causal relation between the action and the reward. Using such assays, studies have shown that the DMS is a critical structure in the acquisition of action–outcome contingencies, whereas the DLS appears to be involved in habit formation (Yin *et al.*, 2004; Yin *et al.*, 2005b). When NMDARs in the DMS are blocked, action–outcome learning is significantly impaired, and the alternative habit learning system assumes control over behaviour, which persists even when the outcome is no longer desirable, i.e. after outcome devaluation (Yin *et al.*, 2005a). If LTP in the DMS is necessary for action–outcome learning, then acute exposure to ethanol could impair this type of learning, at physiologically relevant doses. Alcohol could thus have a strong effect on the learning of all instrumental behaviours under its influence, even learning associated with other outcomes such as food rewards. This could explain, for example, why the effects of alcohol consumption are not limited to alcohol seeking behaviour alone, but could be extended to other behaviours during alcohol exposure. This hypothesis can be tested by local infusion of ethanol into the DMS during instrumental learning. Based on our results, such a manipulation is predicted to suppress action–outcome learning and promote habit formation, much like the effects of local NMDA receptor antagonism in the DMS (Yin *et al.*, 2005a).

To summarize, our results have shown for the first time that ethanol can reverse the direction of synaptic plasticity in a critical brain area implicated in the acquisition of action–outcome contingencies in instrumental learning. Because impaired action–outcome learning, a possible consequence of the observed alterations in striatal synaptic plasticity, is known to produce compensatory engagement of the alternative habit system and to promote habit formation, acute ethanol exposure could promote habit formation even at relatively low doses.

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Abbreviations

aCSF, artificial cerebrospinal fluid; DMS, dorsomedial striatum; HFS, high frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; MSNs, medium spiny neurons; NMDAR, *N*-methyl-D-aspartic acid receptor; PS, population spike.

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