Behavioral/Systems/Cognitive

Dopamine D_1/D_5 Receptors Gate the Acquisition of Novel Information through Hippocampal Long-Term Potentiation and Long-Term Depression

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Hebbian learning models require that neurons are able to both strengthen and weaken their synaptic connections. Hippocampal synaptic plasticity, in the form of long-term potentiation (LTP) and long-term depression (LTD), has been implicated in both spatial memory formation as well as novelty acquisition. In addition, the ventral tegmental area–hippocampal loop has been proposed to control the entry of information into long-term memory, whereas the dopaminergic system is believed to play an important role in information acquisition and synaptic plasticity. D_1/D_5 dopamine receptors are positively coupled to adenylyl cyclase and have been to modulate certain forms of synaptic plasticity, particularly *in vitro*. We investigated how D_1/D_5 dopamine receptors modify long-lasting synaptic plasticity at CA1 synapses of adult freely moving rats and found that receptor activation lowered the threshold for the induction of both LTP and LTD. Specific types of learning are associated with specific types of hippocampal synaptic plasticity. We found that object-configuration learning, facilitation of late-phase LTD by object exploration, and late-phase LTP by exploration of empty space were all prevented by D_1/D_5 receptor antagonism. Furthermore, receptor antagonism prevented electrically induced late-LTP, whereas receptor activation facilitated induction of both LTP and LTD by patterned electrical stimulation. These findings suggest that the dopaminergic system, acting via D_1/D_5 receptors, gates long-term changes in synaptic strength and that these changes are a critical factor in the acquisition of novel information.

Key words: **long-term depression (LTD); long-term potentiation (LTP); novelty; CA1; hippocampus; dopamine**

Introduction

The hippocampal formation is intrinsically required for the formation of spatial and episodic memories (O'Keefe and Nadel, 1978; Eichenbaum, 1996). The detection of novelty is also believed to rely on the hippocampus (Jenkins et al., 2004). Novelty detection involves the comparison of an existing memory with new sensory information. The CA1 subregion of the hippocampus is in a unique position to perform this task. CA1 pyramidal cells receive both direct sensory information from the cortex as well as sequential phase-precession information from the dentate gyrus (DG)-CA3 recurrent network. CA1 pyramidal cells may thus detect mismatches between predictions from the DG–CA3 network relayed through the Schaffer collaterals (SCs) with actual sensory input from the cortex (Lisman and Otmakhova, 2001).

Neurons are believed to form memory engrams through the strengthening and weakening of their synaptic connections. Specifically, hippocampal long-term potentiation (LTP) and long-term depression (LTD) have been shown to encode different aspects of novelty acquisition: SC–CA1 late-LTP (L-LTP) is facilitated through the exploration of an empty novel environment, whereas late-LTD (L-LTD) is facilitated through the exploration of novel objects or familiar objects in novel spatial configurations (Manahan-Vaughan and Braunewell, 1999; Kemp and Manahan-Vaughan, 2004). Olfactory discrimination tasks also point to morphological changes in CA1 such as an increase in spine density along the apical dendrites of neurons (Knafo et al., 2004) as well as an increase in plasticity-related protein Fos expression (Roulett et al., 2005).

The dopaminergic system is a strong candidate for mediating novelty acquisition and synaptic plasticity in CA1. The major dopaminergic center in the brain is the ventral tegmental area (VTA). The VTA and hippocampus have been proposed to form a functional loop designed to detect novelty. This novelty signal would then gate behaviorally relevant information into long-term memory (Lisman and Grace, 2005). In support of this hypothesis, novel stimuli trigger burst firing of VTA cells (Steinfels et al., 1983; Ljungberg et al., 1992; Horvitz et al., 1997), which send projections to the hippocampus (Gasbarri et al., 1997). This dopaminergic novelty signal from the VTA is then detected by D_1/D_5 receptors that are expressed in hippocampal pyramidal cells (Ciliax et al., 2000; Khan et al., 2000). The heterosynaptic activation of CA1 pyramidal neurons through DA afferents has been proposed to trigger *de novo* protein synthesis in these neurons. The new plasticity-related proteins may then be sequestered

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to synaptic tags resulting in a focused facilitation or degradation in synaptic transmission (Frey and Morris, 1998; Morris et al., 2003). In the CA1 region, D_1/D_5 receptors have previously been reported to modify electrically induced SC–CA1 LTP and LTD (Frey et al., 1991; Huang and Kandel, 1995; Chen et al., 1996; Otmakhova and Lisman, 1996; Swanson-Park et al., 1999). The purpose of this study was to determine the effect that D_1/D_5 receptors may have on learning-relevant forms of synaptic plasticity at the SC–CA1 synapse.

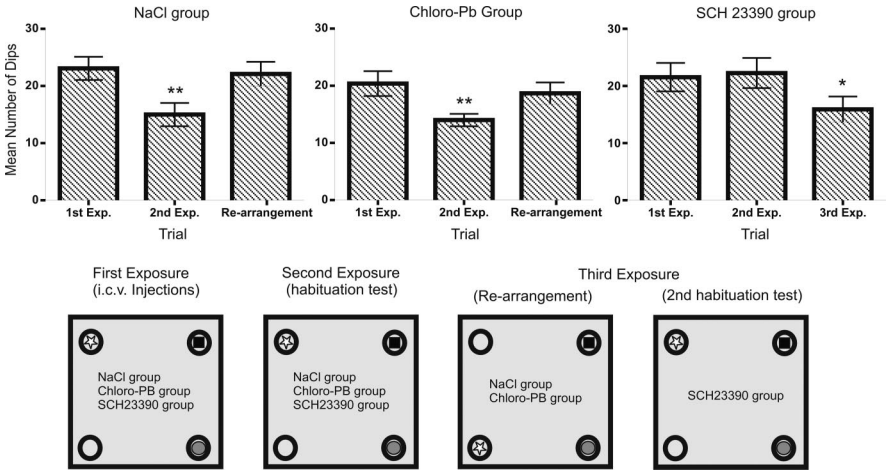

Figure 1. Learning object–place configurations in a large holeboard is dependent on D_1/D_5 receptor activation. Top, The mean number of dips displayed by animals, along with the SEs for each trial and condition are graphed. The number of dips in animals given injections of saline (control) was significantly reduced when the animals were re-exposed to the same object configuration (habituation) (**$p < 0.01$). Object rearrangement revealed behavior that was not significantly different from the first-time exposure (Exp.) and supports that the animal recognized the novelty of this configuration (new learning) with significant habituation on the second trial (**$p < 0.01$). The number of dips in the presence of the D_1/D_5 agonist chloro-PB (41.65 μg) was similar to that seen during saline treatment. However, dips in the presence of the D_1/D_5 antagonist SCH 23390 (29.7 μg) were unchanged after re-exposure to the same object configuration. Exposure to the same object configuration for the third time (after drug washout) revealed significantly fewer dips, consistent with a habituation effect. i.c.v., Intracerebroventricular ($p < 0.05$).

Materials and Methods

Electrophysiology. Male Wistar rats (Charles River, Sulzfeld, Germany), 7–8 weeks old at the time of surgery, underwent implantation of electrodes and a guide cannula under anesthesia (52 mg/kg pentobarbital), as described previously (Manahan-Vaughan, 1997). After surgery, the animals were housed in single cages and were allowed 7–10 d of recovery before the experiments began. Recordings were obtained in the CA1 stratum radiatum by stimulation of SCs. To determine the stimulus intensity that evoked field EPSPs (fEPSPs), which were 40% of the maximum, every experiment commenced with the recording of an input–output curve. Test fEPSPs were evoked at a frequency of 0.025 Hz. Each time point was the average of five consecutive stimulations. The first six data points recorded served as baseline, and all data were expressed as a mean percentage ± SEM of the average baseline value. To ensure that there was no drift in the response to stimulation, control experiments were conducted in which basal synaptic transmission was evoked by test pulses and followed for the same duration as plasticity experiments. Low-frequency stimulation (LFS), to elicit long-term synaptic depression, consisted of 900 pulses at 1 Hz. Alternatively, 600 pulses at 1 Hz were applied to elicit short-term synaptic depression (STD). During LFS, the stimulus strength was raised to 70% of the maximum. In this study, we defined LTD as a depression that endured for >4 h. Two high-frequency tetanus (HFT) protocols were used. To induce short-term potentiation (STP), two trains of 30 pulses at 100 Hz were given with an intertrain interval of 5 min (weak HFT). To induce LTP (>4 h), four trains of 30 pulses at 100 Hz, with an intertrain interval of 5 min, were given. Statistical evaluations were performed by using ANOVA with repeated measures, and *post hoc t* tests were used to assess differences among individual time points. The level of significance was set to $p < 0.05$.

Drugs. The D_1/D_5 receptor agonist chloro-PB (Sigma-Aldrich, St. Louis, MO) was dissolved in water to a concentration of 8.33 μg/μl. The D_1/D_5 receptor antagonist SCH 23390 (Tocris, Ellisville, MO) was dissolved in water to a concentration of 5.94 μg/μl. A volume of 5 μl was injected over a period of 5 min. In both the electrophysiological experiments and the behavioral experiment, injections were administered 30 min before holeboard exposure via a cannula implanted in the lateral cerebral ventricle.

Novelty exploration. To enable acclimatization, animals were always placed in the room where experiments were performed on the day before experimentation. The recording chamber measured 40 × 40 × 40 cm. It was constructed of gray Perspex, except for the removable front wall, which was made of clear Perspex. The boxes were open at the top. The implanted electrodes were connected by a flexible cable and swivel connector to the stimulation and recording equipment; thus, the animal could move around freely in the recording chamber. Each animal was assigned one recording chamber where all experiments were conducted. Plasticity experiments in the absence of a holeboard were always performed a minimum of 8 d before holeboard experiments. In subsequent experiments, a holeboard (39.8 × 39.8 cm, washable gray plastic) was inserted into the floor of the recording chamber. This was done just before application of LFS/HFT and after baseline recordings. The holeboard was removed immediately after LFS/HFT (or after 10 min, in experiments in which weak HFT was applied). Each corner of the holeboard corner contained a hole, 5.5 cm in diameter and 5 cm deep. Objects were placed in three of the four holes. The objects differed from each other in appearance and size and easily fitted within the holes. Each animal was always presented with the same three objects, except in the series in which no objects were present (empty holeboard; see Results).

Behavioral experiment. Thirty-nine animals were used. The holeboard used consisted of a gray Perspex box (80 × 80 × 80 cm). Each holeboard corner contained a hole (5.5 cm diameter and 4.5 cm deep). Three of the four holes contained objects. Three trials of 10 min duration were conducted at 24 h intervals. On the day before the first trial, the animals were placed in the experiment room and given an intracerebroventricular injection of 5 μl of saline (0.9% NaCl) to acclimatize them to the injection procedure. Thirty minutes before the first trial, 13 rats received 5 μl of chloro-PB (8.33 μg/μl), 13 rats received 5 μl of SCH 23390 (5.94 μg/μl), and the remaining rats were given saline. The experimenter recorded the occurrence of rearings and head dips in the holes. Locomotion was measured with the VideoMot 2 animal tracking system (TSE, Bad Homburg, Germany). No injections were given on subsequent exposures to the holeboard.

Results

Object–place configuration learning is dependent on D_1/D_5 receptor activation

To measure the animals' ability to learn spatial configurations of objects, behavioral experiments were conducted in an open-field holeboard (80 × 80 × 80 cm). The number of rears comprises a measure of exploratory activity of the holeboard environment, and the number of head-dippings into the holes is an expression of object exploration. If habituation occurs, it can be expected that re-exposure should lead to significantly fewer rears and head-dipping. Three groups of 13 rats were given injections of saline (Fig. 1), 41.65 μg of chloro-PB (D_1/D_5 agonist) (Fig. 1), or

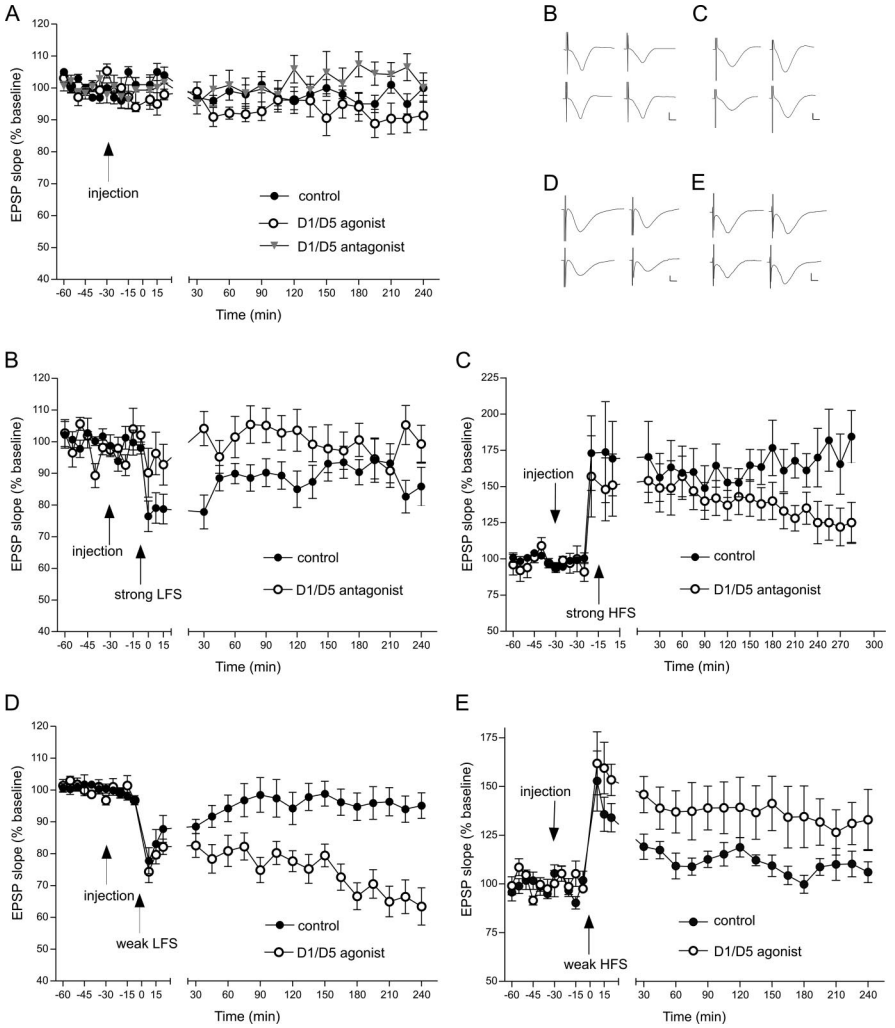

Figure 2. D_1/D_5 receptor modulates both LTD and LTP at the SC–CA1 synapse. The mean EPSP slope is graphed along with the corresponding SEs. ***A***, SC–CA1 synaptic transmission was stable in vehicle-injected animals throughout the recording period. Basal synaptic transmission was not significantly affected by intracerebroventricular injection of a selective D_1/D_5 agonist (41.65 μg of chloro-PB) or a selective D_1/D_5 antagonist (29.7 μg of SCH 23390). ***B–D***, Insets, Analog traces representing SC–CA1 field potentials before LFS and 4 h after LFS. Calibration: vertical bar, 1 mV; horizontal bar, 3 ms. ***B***, D_1/D_5 receptor activation is necessary for induction of LTD. Application of the antagonist SCH 23390 (29.7 μg) significantly impaired LTD maintenance. ***C***, D_1/D_5 receptors contribute to late stages of LTP. Application of the antagonist SCH 23390 (29.7 μg) prevents expression of LTP beyond ~3 h post-tetanus. ***D***, D_1/D_5 receptor activation facilitates STD into LTD. Application of the agonist chloro-PB (41.65 μg) before LFS (1 Hz, 600 pulses) results in robust LTD that endures for >4 h. ***E***, D_1/D_5 activation facilitates STP into LTP. Application of the agonist chloro-PB (41.65 μg) before tetanization results in robust LTP (2 trains of 30 pulses at 100 Hz) that endures for >4 h.

29.7 μg of SCH 2339010 (D_1/D_5 antagonist) 30 min before the first trial. Three trials, each lasting 10 min, occurred 24 h apart. Rearing between all groups and across all trials was not statistically significant. One rat from the control group and two rats from the D_1/D_5 antagonist group exhibited freezing behavior and were removed from the analysis. Total locomotion levels were not statistically different across groups or trials (t test, $p > 0.1$; within and between groups). This means that the general exploration level of the holeboard did not vary with repeated exposure and was not affected by D_1/D_5 receptor agonism or antagonism.

Differences were observed regarding levels of object exploration. The control group and D_1/D_5 agonist group conducted significantly less head-dipping when re-exposed to the holeboard compared with their performance in the first trial (t test, $p < 0.01$; within group) (Fig. 1). This suggests that the objects had become familiar to the animals and that learning had thus occurred, such that the control and agonist-treated animals were able to remember their environment 24 h after their first encounter with the holeboard. When objects were rearranged for the third trial, head-dipping significantly increased (t test, $p < 0.05$; within group) (Fig. 1). This suggests that the habituation that was evident 24 h after the first object exposure was attributable to a memory of the configuration of the objects, because when the now familiar objects were rearranged on the third trial, object exploration increased back to the levels seen during the first exposure.

Animals that were given injections of the D_1/D_5 antagonist before their first exposure to the holeboard explored the objects to an equal degree after re-exposure (Fig. 1). This suggests that the antagonist prevented habituation to the objects. During the second object exposure (no antagonist injection), learning did take place, however. This was demonstrated by the fact that when the animals were exposed to the same object configurations on the third trial, habituation of head-dipping was observed (t test, $p < 0.001$; both parameters, within group) (Fig. 1).

D_1/D_5 receptor modulates both LTD and LTP at the SC–CA1 synapse

SC–CA1 synaptic transmission was not significantly affected by intracerebral ventricular injection of vehicle ($n = 8$), a selective D_1/D_5 agonist [5 μl of chloro-PB (8.33 μg/μl); two-way ANOVA, $p = 0.2455$; $n = 8$], or a selective D_1/D_5 antagonist [5 μl off SCH 23390 (5.94 μg/μl); two-way ANOVA, $p = 0.4303$; $n = 10$] (Fig. 2*A*).

However, D_1/D_5 receptor antagonism blocks the induction of LTD as well as the L-LTP (Fig. 2*B*,*C*). Two groups of rats received an intracerebroventricular injection of 5 μl of SCH 23390 (5.94 μg/μl), a selective D_1/D_5 antagonist, 30 min before they were given LFS ($n = 9$) or high-frequency stimulation (HFS) ($n = 14$). Control experiments performed previously on both groups of rats received the same volume of vehicle (saline). The antagonism of D_1/D_5 receptors completely blocked the induction of LTD seen in the control experiment after LFS (900 pulses at 1 Hz) (Fig. 2*B*) (ANOVA; $F_{(1,24)} = 31.8$; $p < 0.001$) as well as the late stages of LTP seen in the control experiment after HFS (four groups of 30 pulses at 100 Hz, 5 min interval) (Fig. 2*C*) (ANOVA; $F_{(1,24)} = 27.0$; $p < 0001$).

In contrast to the antagonist study, agonist activation of D_1/D_5 receptors facilitates STD into LTD and STP into LTP (Fig. 2*D*,*E*). Here, two groups of rats received an intracerebral injection of 5 μl of chloro-PB (8.33 μg/μl), a selective D_1/D_5 agonist, 30 min before they were given a weak LFS (600 pulses at 1 Hz; $n = 10$) or a weak HFS (two groups of 30 pulses at 100 Hz, 5 min interval; $n = 7$). Control experiments performed previously on both groups of rats received the same amount of

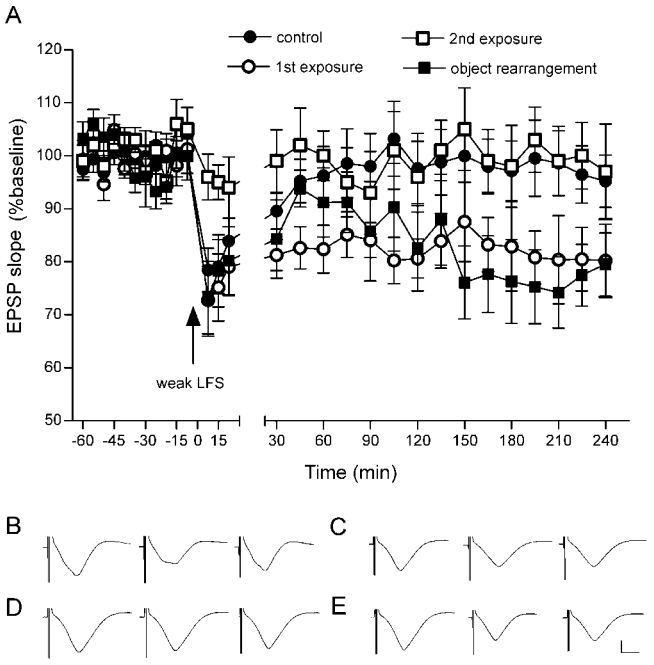

Figure 3. LTD is induced by animal exposure to novel spatial configurations of objects. The mean EPSP slope is graphed along with the corresponding SEs. ***A***, Application of LFS (arrow) induced short-term depression. LFS given simultaneously with holeboard exposure facilitated LTD after first-time exposure, or if the objects were repositioned (object rearrangement). No facilitation occurred after re-exposure to the holeboard containing the same object configuration as in the first exposure. ***B–E***, Analog traces representing SC–CA1 field potentials before LFS, 5 min after LFS, and 4 h after LFS (right to left) in controls (***B***), where novel holeboard exploration occurred (***C***), where holeboard re-exposure occurred (***D***), and where subsequent exposure to the holeboard with novel object configurations occurred (***E***). Calibration: vertical bar, 1 mV; horizontal bar, 3 ms.

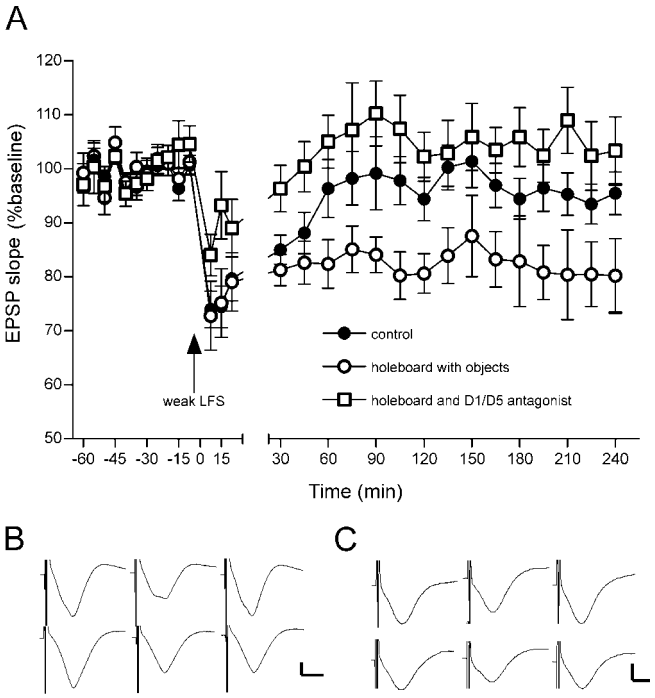

Figure 4. Antagonism of D_1/D_5 receptors inhibits exploration-induced LTD. The mean EPSP slope is graphed along with the corresponding SEs. ***A***, LFS applied under novel exploration induced LTD when animals were given injections of saline but not when given injections of 29.7 μg of the D_1/D_5 antagonist SCH 23390. ***B***, ***C***, Analog traces illustrate potentials evoked before LFS, 5 min after LFS, and 4 h after LFS (from left to right) under the following conditions: ***B***, control LFS stimulation (top) compared with LFS stimulation with novelty exploration (bottom); ***C***, control LFS stimulation compared with LFS with novelty exploration after D_1/D_5 antagonist administration. Calibration: vertical bar, 1 mV; horizontal bar, 5 ms.

saline. The activation of D_1/D_5 receptors facilitated the STD seen in the control experiment into LTD (Fig. 2*D*) (ANOVA; $F_{(1,24)} = 143.8$; $p < 0.0001$) as well as the STP seen in the other control experiment into LTP (Fig. 2*E*) (ANOVA; $F_{(1,24)} = 62.4$; $p < 0.0001$).

The facilitation of STD into L-LTD by animal exposure to a holeboard with objects is dependent on the novelty of the spatial configuration of the objects

An STD is observed at the SC–CA1 synapse in response to LFS (600 pulses at 1 Hz). This STD is facilitated into L-LTD when animals are concomitantly exposed to a holeboard containing objects during stimulation. This facilitation is dependent on the novelty of the spatial configuration of the objects (Fig. 3). All rats received a weak LFS (600 pulses at 1 Hz) that elicited STD. On the subsequent experiment, the rats received weak LFS in conjunction with exposure to a holeboard with novel objects. The result was LTD that endured for longer than 4 h. This facilitation of STD into L-LTD was not observed in the third experiment, 1 week later, when the rats were presented with the same holeboard containing the same objects in the same positions. In the final experiment, the objects were repositioned within the holeboard holes and presented to the rats during LFS. The result was again a robust LTD lasting over 4 h. The facilitation of the STD into L-LTD depended on the spatial novelty of the rats' environment. These results support previous findings by Kemp and Manahan-Vaughan (2004).

LTD requiring animal exposure to novel object–place configurations is dependent on D_1/D_5 receptor activation

LTD, facilitated through the exploration of objects in a holeboard, requires D_1/D_5 receptor activation. All rats received a weak LFS (600 pulses at 1 Hz) that elicited STD. The rats were then divided into two groups. Saline or SCH 23390 was administered intracerebroventricularly 30 min before LFS and holeboard introduction. A robust facilitation of STD into LTD was observed in the control group (Fig. 4) (ANOVA; $F_{(1,24)} = 32.48$; $p < 0.0001$). This effect was completely blocked in the group that received the D_1/D_5 antagonist.

L-LTP induced by novel environmental exposure without spatial cues is dependent on D_1/D_5 receptor activation

LTP facilitated through the exploration of an empty holeboard requires D_1/D_5 receptor activation. All rats received a weak HFS (2×30 pulses at 100 Hz) that elicited STP. The rats were then divided into two groups. Saline or SCH 23390 was administered intracerebroventricularly 30 min before HFS and holeboard introduction. A robust facilitation of STP into LTP was observed in the control group (Fig. 5) (ANOVA; $F_{(1,24)} = 22.4$; $p < 0.0001$). This effect was completely blocked in the group that received the D_1/D_5 antagonist.

Discussion

Substantial data support the importance of dopamine receptors for synaptic plasticity in the hippocampus (Frey et al., 1991; Ot-

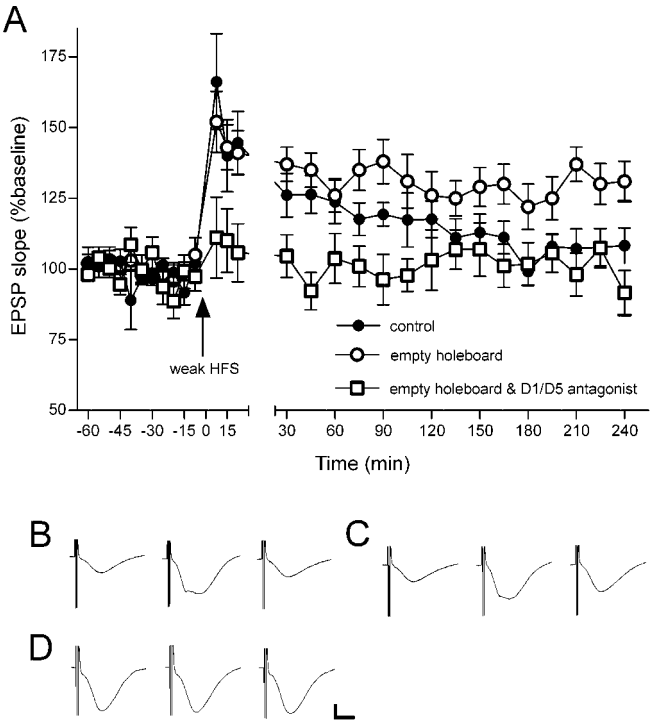

Figure 5. SCH 23390 inhibits exploration-induced LTP. The mean EPSP slope is graphed along with the corresponding SEs. ***A***, HFS applied under novel exploration induced LTP when animals were given injections of saline but not when given injections of 29.7 μg of the D_1/D_5 antagonist SCH 23390. Analog traces represent control HFS stimulation (***B***), HFS with novelty exploration (***C***), and HFS with novelty exploration and D_1/D_5 antagonist administration (***D***). They illustrate (from left to right) levels before LFS, 5 min after LFS, and 4 h after LFS. Calibration: vertical bar, 1 mV; horizontal bar, 4 ms.

makhova and Lisman, 1996; Sajikumar and Frey, 2004). Our results support a role for D_1/D_5 receptors in the bidirectional modulation of hippocampal SC–CA1 synaptic plasticity. Furthermore, a unique finding of our study is that D_1/D_5 receptors are involved in object configuration learning, LTD induced by object exploration, and LTP induced by exploration of empty space. These data are underpinned by our confirmation that synaptic plasticity that is induced by patterned electrical stimulation requires D_1/D_5 receptor activation. Here, we found, in agreement with *in vitro* findings (Chen et al., 1996), that a D_1/D_5 receptor antagonist blocks SC–CA1 LTD induction in freely moving rats and that D_1/D_5 receptor activation lowers the threshold for SC–CA1 LTD. We also confirmed that D_1/D_5 receptor activation is required for the maintenance of SC–CA1 L-LTP in freely moving rats and that D_1/D_5 activation lowers the threshold for LTP induction in agreement with reports *in vitro* (Frey et al., 1991; Swanson-Park et al., 1999). Our data offer an intriguing link between the role of D_1/D_5 receptors in synaptic plasticity and their role in hippocampus-based learning.

Previous studies have shown that hippocampal dopamine receptors play an essential role in spatial learning and the storage of unpredicted information/novelty detection (Besheer et al., 2001; Lisman and Otmakhova, 2001; Bevins et al., 2002; Li et al., 2003; Morris et al., 2003). Novelty exposure results in the phasic activation of dopaminergic VTA neurons, which project to the hippocampus. D_1/D_5 receptors can be selectively activated by phasic dopamine release at hippocampal–prefrontal cortex synapses (Goto and Grace, 2005). The result is a selective modulation of D_1/D_5 receptor-dependent transmission during novelty exploration, which may also be observed in SC–CA1 synapses. Resultant SC–CA1 synaptic plasticity may thus gate entry of novel information into long-term memory (Lisman and Grace, 2005). We show here that D_1/D_5 receptor activation has a bidirectional effect on synaptic plasticity at SC–CA1 synapses. This begs the question: How can D_1/D_5 receptor activation lower the threshold for both LTD and LTP?

Both L-LTP and L-LTD require protein synthesis and the activation of cAMP- dependent protein kinase A (Frey et al., 1993; Bear and Abraham, 1996; Kameyama et al., 1998; Manahan-Vaughan et al., 2000; Woo et al., 2002; Duffy and Nguyen, 2003; Sajikumar and Frey, 2004). It has been proposed that L-LTP and L-LTD may display similar functional properties at the cellular level such as "synaptic tagging" and "late associativity" that require the synthesis and targeting of these plasticity-related proteins (Frey and Morris, 1997, 1998). Recent work by Sajikumar and Frey (2004) provides evidence that dopamine receptor activation in area CA1 initiates processes directly related to the synthesis of plasticity-related proteins and that coincident dopaminergic and glutamatergic activity is involved in the setting and stabilizing of the synaptic tag. They propose that the ability of dopamine to induce either LTP or LTD could be attributable to a concentration-dependent effect on different phosphorylation processes.

Interestingly, our findings provide evidence for a differential role of dopamine in depotentiation of LTP in the DG and CA1 compared with LTD in area CA1. Pharmacological activation of D_1/D_5 receptors dose-dependently inhibits depotentiation in both the DG and CA1 (Otmakhova and Lisman, 1998; Kulla and Manahan-Vaughan, 2000). Our current findings, however, show that D_1/D_5 antagonism dose-dependently inhibits LTD in area CA1. This research argues for different mechanisms involved in the induction of depotentiation and LTD in the hippocampus.

Previous dose–response studies (Kulla and Manahan-Vaughan, 2000) and preliminary evaluations had established that the drug concentrations used in the present study were the minimum concentrations of chloro-PB and SCH 23390 needed to affect synaptic plasticity without affecting basal synaptic transmission. The effect of the agonist chloro-PB is very likely to have been mediated by D_1/D_5 receptor activation, because the K_I value of chloro-PB for D_1 receptors is 2.2 nM compared with >1000 nM for D_2 receptors (Andersen and Jansen, 1990). Furthermore, activation of D_2 receptors has been shown previously to inhibit basal synaptic transmission as well as negative forms of hippocampal synaptic plasticity while having no affect on LTP (Manahan-Vaughan and Kulla, 2003). The action of the antagonist SCH 23390 is also very likely to be mediated by D_1/D_5 receptors, because SCH 23390 has an affinity value (K_D) of 0.53 nM at D_1 receptors (Billard et al., 1984) and has no known activation on D_2 receptors (Beckstead et al., 1988; Hjorth and Carlsson, 1988). Previous studies showed that D_2 antagonists only affect weak forms of LTP and have no influence on negative forms of hippocampal synaptic plasticity (Manahan-Vaughan and Kulla, 2003). These data support that the concentrations of chloro-PB and SCH 23390 used in the present study selectively affect D_1/D_5 receptors and do not mediate their actions via additional activation of D_2 receptors.

According to the SOCRATIC model of Lisman and Otmakhova (2001), the dopaminergic input to the hippocampal cortex (HPC) during novelty exposure may selectively enhance CA3–CA1 transmission while blocking interfering sensory input from the entorhinal cortex, thus reinforcing the freshly acquired novel

information. This theory has been supported recently in clinical functional magnetic resonance imaging studies that showed that the rearrangement of learned configurations of objects lead to the concomitant activation of midbrain dopaminergic neurons and the HPC. Interestingly, increased HPC and midbrain activity predicted the ability of subjects to subsequently remember a novel stimuli (Reber et al., 2002; Schott et al. 2004). Our study has characterized the effect that the D_1/D_5 receptor has on bidirectional synaptic plasticity at the SC–CA1 synapse and how it affects the learning of object–place configurations. These data suggest that CA1 LTD encodes novel spatial configurations and that this learning and synaptic plasticity is D_1/D_5 receptor dependent. Our data support previous findings (Li et al., 2003) that showed that a brief exposure to a novel environment lowers the threshold for the induction of LTP and that this LTP facilitation is D_1/D_5 receptor dependent. However, for the first time, we have shown that both the learning of specific object–place configurations, as well as the concomitant lowering of the LTD induction threshold is dependent on D_1/D_5 receptor activation. We also found that the correlation between exploration of a new empty space and a reduced threshold for LTP induction also requires functional D_1/D_5 receptors. These data support an intrinsic role for dopamine D_1/D_5 receptors in the coupling of synaptic plasticity with information coding in the hippocampus.

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