Dopamine Inhibits High-Frequency Stimulation-Induced Long-Term Potentiation of Intrinsic Excitability in CA1 Hippocampal Pyramidal Neurons

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Key Words

Dopamine • Intrinsic plasticity • Hippocampus

Abstract

The efficiency of neural circuits is modified by changes not only in synaptic strength, but also in intrinsic excitability of neurons. In CA1 hippocampal pyramidal neurons, bidirectional changes in the intrinsic excitability are often presented after induction of synaptic long-term potentiation or depression. This plasticity of intrinsic excitability has been identified as a cellular correlate of learning. Besides, behavioral learning often involves action of reinforcement or rewarding mediated by dopamine (DA). Here, we examined how DA influences the intrinsic plasticity of CA1 hippocampal pyramidal neurons when high-frequency stimulation (HFS) was applied to Schaffer collaterals. The results showed that DA inhibits the decrease in rheobase and increase in mean firing rate of pyramidal neurons induced by HFS, and that this inhibition was abolished by the D₁-like receptor antagonist SCH23390 but not by the D₂-like receptor antagonist sulpiride. The results suggest that DA inhibits the potentiation of excitability induced by presynaptic HFS, and that this inhibition depends on the activation of D₁-like receptors.

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Introduction

Although synaptic plasticity has been considered the best candidate mechanism for the formation and storage of memories, more and more attention has been given to activity-dependent changes in the intrinsic excitability of neurons [1–13]. Since its original description, the induction of synaptic long-term potentiation (LTP) has been known to be accompanied by a lasting increase in the intrinsic excitability of hippocampal neurons [14]. This activity-dependent intrinsic plasticity has been suggested to be the other side of the engram for learning and memory [5, 10, 13, 15–18].

Behavioral learning often involves reward processes. In such learning, the activity of dopamine (DA) neurons has been shown to encode prediction error and uncertainty [19]. Animal experiments have shown that blockade of DA receptors impairs learning and memory, and DA receptor agonists can improve learning and memory [20, 21]. The hippocampus, a brain region that receives extensive dopaminergic projections from mesolimbic structures such as the ventral tegmental area and substantia nigra [22, 23], has a key role in learning and memory [24, 25]. The effects of DA in the hippocampus are multiple: the transmitter inhibits the excitability of pyra-

midal neurons [26–31] while it facilitates LTP [32–34] in the hippocampus. The effects of DA on long-term depression in the hippocampus have been less clear. The activation of D₁-like DA receptors was found to facilitate long-term depression in some experiments [32, 35] but to reverse it in others [34, 36].

Although the effects of DA on excitability and synaptic plasticity have been extensively investigated in the hippocampus, little is known about whether the DA system interacts with the activity-dependent intrinsic plasticity. Here we use whole-cell patch clamp recording to study whether the intrinsic plasticity induced by high-frequency stimulation (HFS) is modified by bath application of DA. The results showed that DA application inhibits the potentiation of excitability in CA1 pyramidal neurons induced by HFS on Schaffer collaterals, and that this inhibition depends on the activation of D₁-like receptors.

Materials and Methods

Animal Treatment

All procedures were performed in accordance with the institutional guidelines for the care and use of laboratory animals as approved by the Animal Care Committee of Shaanxi Normal University.

Electrophysiology

Slice Preparation. Brain slices were prepared as reported previously [8]. Briefly, 10- to 17-day-old Sprague-Dawley rats were anesthetized with pentobarbitone sodium (55 mg/kg) and decapitated. Brains were removed rapidly and glued with the anterior surface down. Transverse brain slices of 300 μ m were cut with a vibratome (1,000 plus; Vibratome Company, USA). Slices containing the hippocampus were incubated in the slice solution gassed with 5% CO₂ and 95% O₂ for 1–3 h and then transferred to a recording chamber (1.5 ml) that was perfused with the slice solution gassed with 5% CO₂ and 95% O₂ at room temperature (23–25°C) for recording. The standard slice solution contained (in mM): 126 NaCl, 2.5 KCl, 1.25 NaH₂PO₄, 2 MgCl₂, 2 CaCl₂, 10 glucose, 26 NaHCO₃, pH 7.4, when gassed with 5% CO₂ and 95% O₂.

Whole-Cell Patch Clamp Recording. Cells were visualized with a $\times 40$ water immersion lens on a Leica DM LFSA upright microscope (Leica, Germany) equipped with differential interference contrast optics. Patch electrodes with a resistance of 4–7 M Ω for somatic recordings were pulled from glass capillaries using a P-97 electrode puller (Sutter Instruments, Novato, Calif., USA) and polished by an MF-830 microforge (Narishige, Japan). Cells with the seal resistance <1.2 G Ω and a resting membrane potential more positive than –63 mV were rejected. Pyramidal neurons were patched in either the voltage clamp or the current clamp configuration. The pipette solution for whole-cell recordings contained (in mM): 120 K-gluconate, 20 KCl, 2 MgCl₂, 10 HEPES, 0.2 EGTA, 4 Na₂ATP, 0.3 Na₃GTP, and 7 phosphocreatine, pH adjusted to 7.2 with KOH. A Multiclamp 700B amplifier (Axon Instruments, USA) was used to perform whole-cell recordings.

Conditional Stimulus. To evoke presynaptic glutamate release, a concentric bipolar stimulating electrode (CBARC75, FHC) was placed in the stratum 100–200 μ m from the soma of recorded pyramidal neurons to deliver extracellular stimulation to the Schaffer collateral pathway. Stimuli were delivered by a Grass S88X stimulator via a Grass SIU isolation unit (Grass Instruments, Quincy, Mass., USA). The intensity of HFS was set as the minimal test stimulus intensity that could induce the maximal amplitude of the Schaffer collateral-CA1 synaptic response. The duration of each pulse was 0.1 ms. Three trains of 100 pulses at 100 Hz were delivered with an intertrain interval of 20 s.

Data Analysis

Recorded signals were sampled at 10 kHz by pClamp 10.2 software (Axon Instruments, USA). Analyzed data were further processed with Origin 8.0 (Microcal Software, USA) and SPSS 15.0 (IBM SPSS, USA). Statistical data are presented as means $\pm$ SEM. Repeated measures analysis of variance (ANOVA) and Student's *t* test were used to examine statistical significance. *p* values less than 0.05 were considered to be significant.

Results

HFS Induced an Increase in Excitability

Whole-cell patch clamp recordings were performed in CA1 pyramidal neurons from acutely isolated hippocampal slices. The conditional stimulus used in this study was an HFS which consisted of 3 trains of 100 pulses at 100 Hz with an intertrain interval of 20 s. To study intrinsic excitability, step current injections were applied to the soma of hippocampal CA1 pyramidal neurons before and after HFS application. The membrane potential of pyramidal neuron soma was recorded, and rheobase and mean firing rate were analyzed to measure intrinsic excitability (fig. 1).

Under the control conditions, the resting membrane potential of CA1 pyramidal neurons was -68.3 ± 0.57 mV. After HFS, the resting potential did not change (*p* = 0.2485, 0.5518, 0.7193, 0.4172 for 15, 30, 45, 60 min vs. control; paired *t* test, *n* = 16 cells; fig. 1b).

Intrinsic excitability of a neuron can be assessed with rheobase, which is defined as the minimal current injection needed to evoke a spike. Under the control conditions, the rheobase of hippocampal pyramidal neurons was 76.3 ± 4.6 pA. HFS induced a persistent decrease in the rheobase of pyramidal neurons (65.0 ± 5.0 pA at 15 min after HFS). The decrease became significant at 15 min after application of HFS (fig. 1b; *p* = 0.0028, 0.0005, 0.0002, 0.0000 for 15, 30, 45, 60 min vs. control; paired *t* test, *n* = 16 cells).

The total membrane conductance, called input resistance, measures the asymptotic sensitivity of the mem-

Fig. 1. HFS-induced increase in excitability. **a** Whole-cell current clamp recordings from a representative pyramidal neuron showing HFS-induced decrease in rheobase and increase in mean firing rate. Bottom lines show injected currents (in picoamperes). **b** Statistics of rheobase, firing rate, input resistance (R_{input}) and resting membrane potential. The rheobase decreased 15 min after application of HFS. The mean firing rate evoked by 100 pA current injection increased 15 min after HFS induction. The input resistance increased 15 min after HFS. The resting membrane potential remained unchanged. * $p < 0.05$, ** $p < 0.01$; paired t test, compared to control, $n = 16$. **c** Whole-cell voltage clamp recordings

from a representative pyramidal neuron showing whole current before (left) and 45 min after (right) HFS induction. Bottom lines show holding potentials (in millivolts). **d** Statistics of 16 neurons showing the steady-state whole current I-V relation measured before and 45 min after HFS induction. * $p < 0.05$, repeated measures ANOVA, $n = 16$. **Inset** Whole-cell voltage clamp recordings of the steady-state whole current. **e** In the absence of HFS induction, rheobase, mean firing rate and input resistance remained stable within 60 min and the resting membrane potential was slightly depolarized after 30 min of patching. * $p < 0.05$, ** $p < 0.01$; paired t test, $n = 10$.

brane potential to injected or intrinsic currents, and is reciprocally related to the rheobase. Under the control conditions, the input resistance of hippocampal pyramidal neurons was $207.2 \pm 8.7 \text{ M}\Omega$. HFS induced a persistent increase in the input resistance ($226.6 \pm 11.7 \text{ M}\Omega$ at 15 min after HFS). The increase became significant at 15 min after application of HFS (fig. 1b; $p = 0.0252, 0.0047, 0.0120, 0.0085$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 16$ cells).

When 100 pA current injection, which was sufficient to evoke spikes in all neurons we recorded, was applied to the neuron soma, the mean firing rate was $6.8 \pm 1.2 \text{ Hz}$. HFS induced a persistent increase in the mean firing rate ($9.3 \pm 1.6 \text{ Hz}$ at 15 min after HFS). The increase became significant at 15 min after application of HFS ($p = 0.0135, 0.0046, 0.0010, 0.0015$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 16$ cells; fig. 1b). Both decrease in rheobase and increase in mean firing rate suggest an increase in intrinsic excitability after HFS, which is consistent with previous works.

In the absence of HFS induction, there was no significant change in rheobase and mean firing rate (fig. 1e; rheobase: $p = 0.0800, 0.5983, 0.1705, 0.1036$ for 15, 30, 45, 60 min vs. control; mean firing rate: $p = 0.1879, 0.2530, 0.1205, 0.1551$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 10$ cells). Consistent with the rheobase, input resistance was not changed ($p = 0.9276, 0.1448, 0.7470, 0.9601$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 10$ cells). The resting membrane potential is slightly depolarized (control: $-66.63 \pm 0.59 \text{ mV}$, 15 min: $-65.13 \pm 0.94 \text{ mV}$, 30 min: $-64.18 \pm 0.99 \text{ mV}$, 45 min: $-64.33 \pm 0.93 \text{ mV}$, 60 min: $-64.21 \pm 0.27 \text{ mV}$), and the change is statistically significant ($p = 0.0654, 0.0061, 0.0174, 0.0269$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 10$ cells). Since the amplitude of depolarization is less than 3 mV, and the input resistance was not changed, we assume that the condition of neurons remained stable in 60 min of patching.

Neuronal excitability is determined by various types of transmembrane ionic current. To gain a sight of these ionic currents, whole-cell voltage clamping was performed to record the whole current and a steady-state I-V relation was measured after offline P/N subtraction (fig. 1c, d). This steady-state I-V relation measures the sum of the asymptotic value of all transmembrane currents, and it provides information about all persistent currents operating within a certain range of transmembrane potential. After HFS induction, the steady-state whole current was reduced significantly in the potential range of the above -10 mV (fig. 1d; $p = 0.031$; repeated measures ANOVA, $n = 16$ cells).

HFS-Induced Increase in Excitability Was Inhibited by DA Application

The aim of this study was to investigate how DA influences the activity-dependent intrinsic plasticity of CA1 hippocampal pyramidal neurons when HFS was applied to Schaffer collaterals. In our experiments, $20 \mu\text{M}$ DA was applied. This concentration is commonly used for in vitro studies and is comparable with the effective DA concentration in vivo [37].

To study the effect DA might exert on the plasticity of excitability induced by HFS, $20 \mu\text{M}$ DA was applied 2 min before HFS and then washed out 2 min after the end of HFS. In the presence of DA, both rheobase and mean firing rate (fig. 2b) showed no significant change after HFS (rheobase: $p = 0.7533, 1, 0.1199, 0.2156$ for 15, 30, 45, 60 min vs. control; mean firing rate: $p = 0.6380, 0.6583, 0.3662, 0.4097$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 13$ cells). Input resistance and resting membrane potential were not changed either (input resistance: $p = 0.8532, 0.9352, 0.7980, 0.8767$ for 15, 30, 45, 60 min vs. control; resting membrane potential: $p = 0.5471, 0.4114, 0.2646, 0.5996$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 13$ cells). In addition, the steady-state whole current remained unchanged after HFS induction (fig. 2c, d; $p = 0.762$; repeated measures ANOVA, $n = 13$ cells).

It is rational to assume that this DA effect may result from the decrease in excitability instead of the interaction with the HFS induction of intrinsic plasticity. We hypothesized that the DA application alone is not sufficient to cause a significant decrease in excitability, since the application of DA was limited in less than 7 min. To test this hypothesis, 11 neurons were recorded with 7-min DA bath application (which is similar to the experiment described above) but without HFS induction. Though the resting membrane potential was slightly depolarized after the short-term DA application ($p = 0.0111, 0.0103, 0.0896, 0.0804$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 11$ cells), no significant changes in rheobase, mean firing rate and input resistance after DA application were observed (fig. 2e; rheobase: $p = 0.6811, 0.6811, 0.2815, 0.1705$ for 15, 30, 45, 60 min vs. control; mean firing rate: $p = 0.5146, 0.4841, 0.1762, 0.2066$ for 15, 30, 45, 60 min vs. control; input resistance: $p = 0.1149, 0.4238, 0.7456, 0.9410$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 11$ cells). These data suggested that DA abolishes the HFS-induced increase in excitability via interaction with HFS induction rather than merely decreasing the excitability.

Fig. 2. DA-inhibited HFS-induced increase in excitability. **a** Recordings from a representative pyramidal neuron showing stable rheobase and mean firing rate after HFS induction when $20 \mu\text{M}$ DA was present. Bottom lines show injected currents (in picoamperes). **b** Statistics of 13 neurons showed that rheobase, firing rate, input resistance and resting membrane potential were not changed by HFS induction when DA was present. **c** Whole-cell voltage clamp recordings from a representative pyramidal neuron showing whole current before (left) and 45 min after (right) HFS induc-

tion when DA was present. Bottom lines show holding potentials (in millivolts). **d** Steady-state whole current did not change after HFS induction when $20 \mu\text{M}$ DA was coapplied with the HFS. **e** Eleven neurons were recorded with 7-min DA bath application but without HFS induction. There was no significant change in rheobase, mean firing rate and input resistance but a slight depolarization in resting membrane potential. * $p < 0.05$; paired t-test, $n = 11$.

Fig. 3. Blockade of D₁-like receptors abolishes the DA inhibition of HFS-induced intrinsic plasticity. **a** Recordings from a representative pyramidal neuron showing rescued decrease in rheobase and increase in mean firing rate after HFS induction when DA and SCH23390 were present. Bottom lines show injected currents (in picoamperes). **b** Statistics of 10 neurons showed that blockade of D₁-like receptors rescued the decrease in rheobase and increase in firing rate and input resistance. In the presence of DA and SCH23390, the rheobase decreased 45 min after HFS induction,

and the mean firing rate and input resistance increased significantly 15 min after HFS induction. * $p < 0.05$, ** $p < 0.01$, paired t test, versus control, $n = 10$. **c** Whole-cell voltage clamp recordings from a representative pyramidal neuron showing whole current before (left) and 45 min after (right) HFS induction when DA was present. Bottom lines show holding potentials (in millivolts). **d** Steady-state whole current decreased significantly 45 min after HFS in the presence of DA and SCH23390. * $p < 0.05$, repeated measures ANOVA, $n = 10$.

DA Inhibition of HFS-Induced Intrinsic Plasticity Required D₁-Like Receptor Activation

DA receptors are classified into 2 groups, D₁-like receptors (D₁/D₅ receptors), which activate adenylate cyclase, and D₂-like receptors (D₂/D₃/D₄ receptors), which inhibit adenylate cyclase [38]. The activation of D₁-like receptors has a central role in facilitating LTP induction and maintenance in many brain areas including the hippocampus [33]. To examine which subtype of DA receptor was responsible for DA inhibition of the HFS-induced intrinsic plasticity, a selective D₁-like or D₂-like antagonist was applied together with DA. When 10 μ M

SCH23390, a selective D₁/D₅ receptor antagonist, was added to the perfusion solution 1 min before DA treatment, the HFS-induced decrease in rheobase and increase in mean firing rate were rescued (fig. 3b). The rheobase decreased significantly 45 min after HFS induction ($p = 0.1690, 0.1038, 0.0232, 0.0028$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 10$ cells) and the mean firing rate increased significantly 15 min after application of HFS ($p = 0.0400, 0.0028, 0.0001, 0.0002$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 10$ cells). Input resistance also increased significantly ($p = 0.0027, 0.0140, 0.0223, 0.0104$ for 15, 30, 45, 60 min vs. control; paired t

Fig. 4. Sulpiride has no effect on the DA inhibition of HFS-induced intrinsic plasticity. **a** Recordings from a representative pyramidal neuron showing stable rheobase and mean firing rate after HFS induction when DA and sulpiride were present. Bottom lines show injected currents (in picoamperes). **b** Statistics of 14 neurons showed that rheobase, firing rate, input resistance and resting membrane potential were not changed by HFS induction

when DA and sulpiride were present. **c** Whole-cell voltage clamp recordings from a representative pyramidal neuron showing whole current before (left) and 45 min after (right) HFS induction when DA was present. Bottom lines show holding potentials (in millivolts). **d** Steady-state whole current did not change after HFS induction in the presence of DA and sulpiride.

test, $n = 10$ cells). The decrease in steady-state whole current was also rescued (fig. 3c, d; $p = 0.022$; repeated measures ANOVA, $n = 10$ cells). The resting membrane potential was not changed ($p = 0.0827, 0.0682, 0.2560, 0.1194$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 10$ cells).

To determine the role of D_2 -like receptors in DA inhibition of the HFS-induced intrinsic plasticity, we tested the effect of the D_2 -like receptor-selective antagonist sulpiride ($50 \mu\text{M}$) on DA inhibition of intrinsic excitability induced by HFS. No significant change was observed in rheobase, mean firing rate, input resistance and the resting membrane potential (fig. 4b; rheobase: $p = 1, 0.5470, 0.3356, 0.3019$ for 15, 30, 45, 60 min vs. control; mean fir-

ing rate: $p = 0.4997, 0.2192, 0.4953, 0.0872$ for 15, 30, 45, 60 min vs. control; input resistance: $p = 0.5833, 0.3449, 0.0968, 0.0849$ for 15, 30, 45, 60 min vs. control; resting membrane potential: $p = 0.9230, 0.5157, 0.3839, 0.4492$ for 15, 30, 45, 60 min vs. control; paired t test, $n = 14$ cells). In addition, the steady-state whole current remained unchanged after HFS induction (fig. 4c, d; $p = 0.694$; repeated measures ANOVA, $n = 14$ cells).

To further assess the difference between groups under different treatments, rheobase, mean firing rate and input resistance of 4 groups (HFS, HFS-DA, HFS-SCH23390-DA, HFS-sulpiride-DA) were normalized by their before-HFS value and were illustrated together in

Fig. 5. Comparison of normalized data from 4 groups. **a** Normalized rheobases of the HFS-DA group were significantly different from those of the HFS group ($p < 0.05$). **b** There were significant differences in the normalized mean firing rate between HFS-DA and HFS groups ($p < 0.05$) and between HFS-SCH-DA and HFS-DA groups ($p < 0.01$). **c** There were significant differences in the normalized input resistance between HFS-DA and HFS groups ($p < 0.05$) and between HFS-SCH-DA and HFS-DA groups ($p < 0.05$; repeated measures ANOVA, post-hoc least significant difference test).

Fig. 6. Comparison of normalized data from time control and DA control groups. There was no significant difference in either rheobase (**a**; $p = 0.329$), mean firing rate (**b**; $p = 0.839$) or input resistance (**c**; $p = 0.810$) between time control and DA control groups (repeated measures ANOVA).

figure 5. Repeated measures ANOVA was performed on the normalized data to compare these groups. There was a significant difference between these 4 groups in rheobase, mean firing rate and input resistance (rheobase: $p = 0.047$; mean firing rate: $p = 0.036$; input resistance: $p = 0.003$). Post-hoc comparisons using the least significant difference test revealed that the HFS-DA group was significantly different from the HFS group in rheobase ($p = 0.021$), mean firing rate ($p = 0.046$) and input resistance ($p = 0.036$). The HFS-SCH23390-DA group was significantly different from the HFS-DA group in mean firing rate ($p = 0.006$) and input resistance ($p = 0.024$) but not in rheobase ($p = 0.18$). [Note that SCH23390 only rescued the rheobase decrease at a later time point (fig. 3b), the post hoc test failed to reveal a significant difference be-

tween HFS-DA and HFS-SCH23390-DA groups in rheobase (fig. 5a).] There was no significant difference in rheobase ($p = 0.957$), mean firing rate ($p = 0.331$) or input resistance ($p = 0.474$) between the HFS-sulpiride-DA group and HFS-DA group. The results suggested that the HFS-induced intrinsic plasticity of pyramidal neurons is significantly changed by DA, and that this DA effect is D_1 -like receptor dependent.

To further determine the effect of short-term DA application on neurons in the absence of HFS induction, data observed from time control (fig. 1e) and DA control (fig. 2e) experiments were also normalized and compared (fig. 6) using repeated measures ANOVA. There was no significant difference in rheobase ($p = 0.329$), mean firing rate ($p = 0.839$) or input resistance ($p = 0.810$) between

these two groups, indicating that a 7-min bath of DA had no effect on the excitability of neurons when HFS induction was absent. This further confirmed that DA inhibited the HFS-induced increase in excitability through interaction with HFS induction rather than changed the excitability by itself.

Discussion

The hippocampus receives rich dopaminergic innervation from the mesocorticolimbic system. The effects of DA on synaptic plasticity as well as excitability of the hippocampus have been extensively investigated. However, little is known about whether the DA system interacts with the activity-dependent intrinsic plasticity of pyramidal neurons, which is considered a supplementary mechanism for learning and memory. Here we report that application of DA during presynaptic HFS induction inhibited the increased excitability induced by HFS alone. This result suggests that DA interacts with the activity-dependent intrinsic plasticity of pyramidal neurons. This effect implies a new mechanism that DA might employ to modulate the hippocampus.

How does D_1 -like receptor signaling influence the HFS-induced intrinsic plasticity? Experimental evidence has shown that in hippocampal CA1 pyramidal neurons, the induction of activity-dependent LTP of intrinsic excitability requires activation of N-methyl-D-aspartate (NMDA) receptors, subsequent Ca^{2+} increase in spines and local dendrites, activation of CaM kinase II, and protein synthesis activity [8]. This suggests that the induction mechanism for intrinsic plasticity shares the similar pathways with synaptic plasticity, which is the NMDA receptor/ Ca^{2+} /CaM kinase pathway. It has been found that DA partially inhibits NMDA receptor-mediated synaptic currents [34, 39, 40]. One would assume that this inhibition of NMDA receptor-mediated currents by DA would cause less calcium influx and, thus, attenuate activity-dependent intrinsic excitability.

Furthermore, the intrinsic plasticity should eventually result from changes in the kinetics, number and distribution of ion channels. Our results indicate that HFS-induced potentiation of intrinsic excitability was accompanied by a decrease in steady-state whole current over -10 mV, which is a net outward current. DA abolished this decrease in steady-state whole current, which was dependent on activation of D_1 -like receptors. The changes in input resistance, which measures the permeability of a membrane to charged ions, were consistent with the

changes in the steady-state whole currents. Although which channels and how these channels are modified by HFS induction and DA remains to be explored, it could be assumed that this decrease in outward whole current during membrane depolarization would contribute to the potentiation of excitability.

Both HFS-induced LTP of intrinsic excitability and the DA effect may involve multiple processes. Many channels may be modified and the processes of these modulations may function in different time scales. In our experiments, SCH23390 rescued the DA effect on firing rate and input resistance at early time points (15 min) but rescued the decline of rheobase at a later time point (45 min), indicating that a different mechanism underlies the changes in rheobase and other measures.

The higher cognitive function of the brain depends on its ability to integrate the information collected from the exterior environment. Information flow and processing in the neural network are primarily mediated by action potential propagation through neurons and the communication between neurons by synapses. Although it is widely accepted that the synapse is an important target, which is subject to activity-dependent persistent modulation and mediates learning and memory, the intrinsic property of neurons also undergoes activity-dependent plasticity to enhance the input-output functions of neurons, and thus plays an important role in learning and memory. The hippocampus, which has a key role in learning and memory, receives extensive dopaminergic projections. Our results suggest that the activity-dependent intrinsic excitability is also modulated by DA, which leads to a new insight into neural circuit functions underpinning rewarding and reinforcement of learning.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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