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Dopaminergic Facilitation of GABAergic Transmission in Layer III of Rat Medial Entorhinal Cortex

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Abstract

The medial entorhinal cortex (MEC) receives a dense dopaminergic innervation and expresses dopamine receptors. However, little is known about the effect of dopamine on GABAergic transmission in this region of the brain. In this study, we recorded GABAA receptor-mediated spontaneous inhibitory postsynaptic currents (sIPSCs) and miniature inhibitory postsynaptic currents (mIPSCs) by using whole-cell patch-clamp technique. Application of dopamine at 10 μM and 100 μM significantly increased the frequency and amplitude of sIPSCs. This effect of dopamine is primarily mediated by acting at D1-like dopamine receptors, but not D2-like and α1 adrenergic receptors, since dopamine-induced increased in frequency and amplitude of the sIPSCs was completely blocked by D1-like, but not D2-like or α1 adrenergic, receptor antagonist. However, application of dopamine did not affect the frequency and amplitude of the mIPSCs, implying that the effect of dopamine on the GABAergic transmission is action potential-dependent. Together, these findings reveal an indirect mechanism by which activation of D1-like receptors could inhibit the excitability of layer III pyramidal neurons in the MEC.

Key Words: dopamine, GABAergic transmission, medial entorhinal cortex, mIPSCs, sIPSCs

Introduction

Dopaminergic neurons in the nervous system primarily arise from substantia nigra pars compacta, ventral tegmental area and hypothalamus, and project to many areas of the brain including the entorhinal cortex (EC) (9, 10). As a monoaminergic neurotransmitter in the central nervous system, dopamine plays important modulatory roles in motor activity, sleep and wakefulness, reward and punishment, and in higher cognitive functions, such as learning, working memory and attention (2, 3). Perturbations of dopaminergic systems are involved in many neuropsychiatric diseases, including Parkinson's disease, addiction and schizophrenia (13, 17, 18, 28).

The EC is widely regarded as the interface that links association cortices to the hippocampal formation, and has a crucial role in hippocampus-dependent learning and memory (26, 32). The EC has two subregions, the medial entorhinal cortex (MEC) and the lateral entorhinal cortex (LEC). The MEC consists of the functional neurons with spatial firing properties, and is a part of neuronal circuits that participate in spatial information processing (22, 31). The MEC layer III contains a high density of pyramidal neurons, which receive convergent sensory inputs and then relay the information to the CA1 and subiculum through the temporoammonic pathway (32). The excitatory inputs from MEC layer III pyramidal neurons to the hippocampus are crucial for temporal associa-

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tion memory since specific inhibition of synaptic transmission at the layer III to CA1/subiculum synapses caused impairments in spatial working memory in the T-maze tasks and in the trace fear-conditioning (27).

The physiological prosperities of MEC layer III pyramidal neurons and synaptic transmission are dynamically altered by a number neuromodulators including serotonin (6, 7), noradrenaline (15) and acetylcholine (34). Previous studies found that dopamine also directly inhibits the persistent network activity *via* D1-like dopamine receptors and causes membrane hyperpolarization of pyramidal neurons in MEC layer III (19). The activity of the MEC layer III pyramidal neurons is tightly controlled by the $GABA_A$ receptor-mediated fast spontaneous inhibitory postsynaptic currents (sIPSCs) and miniature inhibitory postsynaptic currents (mIPSCs) (23). sIPSCs and mIPSCs synchronize neural activities in the MEC and act as the precision clockwork for the gamma-theta oscillation coupling, which is thought to be crucially involved in learning and memory (24). Currently, the effect of dopamine on the GABAergic transmission in this brain region remains elusive. Work in this study used *in vitro* whole-cell clamp recording from the identified layer III pyramidal neurons of the rat MEC to explore the role of dopamine in modulating the GABAergic transmission.

Materials and Methods

Slice Preparation

All procedures involving animals were conducted in accordance with the National Institutes of Health Guide for the care and use of laboratory animals, and were approved by the Zhejiang Ocean University Committee on Ethics in the Care and Use of Laboratory Animals. Horizontal slices containing the EC were prepared from young Sprague Dawley rats (post natal day 15-21) as described previously (8). Briefly, after decapitation, brains were rapidly removed and slices (400 μm) were prepared with a vibratome in an ice-cold section solution, which contained (in mM): sucrose, 220; KCl, 2.5; NaH_2PO_4, 1.25; $NaHCO_3$, 26; $MgCl_2$, 6; $CaCl_2$, 1; glucose, 10, equilibrated with 95% O_2 and 5% CO_2. During recording sessions, the slices were transferred to a submerged chamber and continuously superfused with oxygenated (95% O_2-5% CO_2) artificial cerebrospinal fluid (ACSF, composition in mM: NaCl 124; KCl 3; $NaHCO_3$, 26; $MgCl_2$, 2; $CaCl_2$, 2; glucose 10) at room temperature.

Whole-Cell Clamp Recordings

Whole-cell clamp recordings using an EPC10 amplifier (HEKA Elektronik, Lambrecht/Pfalz, Germany) were performed on the principal neurons in layer III of the MEC visually identified with Leica differential interference contrast optics and an infrared video imaging camera. The recording glass pipettes (3-5 MΩ) were filled with the following solution (in mM): potassium gluconate 125; KCl, 20; Hepes, 10; EGTA, 1; $MgCl_2$, 2; ATP, 4; adjusted to pH 7.2-7.4 with 1 M KOH. For recordings of sIPSCs and mIPSCs, neurons were voltage-clamped at -60 mV and a Cs^+ pipette solution (composition in mM: CsCl, 145; HEPES, 10; $MgCl_2$, 2; EGTA, 1; ATP, 2; adjusted to pH 7.2-7.4 with 1 M CsOH) was used. Under these conditions, sIPSCs and mIPSCs were recorded as inward currents.

During recording sessions, series resistance was monitored by the delivery of a 5-mV (50 ms) hyperpolarizing voltage step. Cells were discarded if the series resistance changed by >10%. After stable recording of the baseline of sIPSCs and mIPSCs for 4 min, the dopamine was applied to the cells for about 8 min. Data were filtered at 2 kHz, digitized at 10 kHz, and stored for off-line analysis with Pulse/Pulsefit v.8.74 (HEKA Elektronik) and Igor Pro v.4.03 (WaveMatrics). The sIPSCs and mIPSCs recorded for 2 min before the application of dopamine and 2 min of the maximal effect of dopamine were analyzed manually by using Mini Analysis 6.0.1 (Synaptosoft, Decatur, GA, USA). Each detected event with fast onset and exponential decay kinetics was inspected visually to reject obvious artifacts.

Drugs

Dopamine, 6-cyano-7-nitroquinoxaline-2, 3-dione (CNQX), D-2-amino-5-phosphonovaleric acid (AP5), tetrodotoxin (TTX) and picrotoxin (PIC) were purchased from Sigma (St Louis, MO, USA). SCH23390, LE300, raclopride and corynanthine were obtained from Tocris Cookson (Ellisville, MO, USA).

Data Analysis

Data were presented as the means ± SEM. One-way ANOVA with repeated measures and Fisher's protected least significant difference (LSD) *post hoc* testing were used for statistical analysis; P values were reported throughout the text and significance was accepted when $P < 0.05$.

Results

Electroresponsiveness of Layer III Pyramidal Neurons

The principal neurons of the MEC layer III are pyramidal neurons, the axons of which project to the

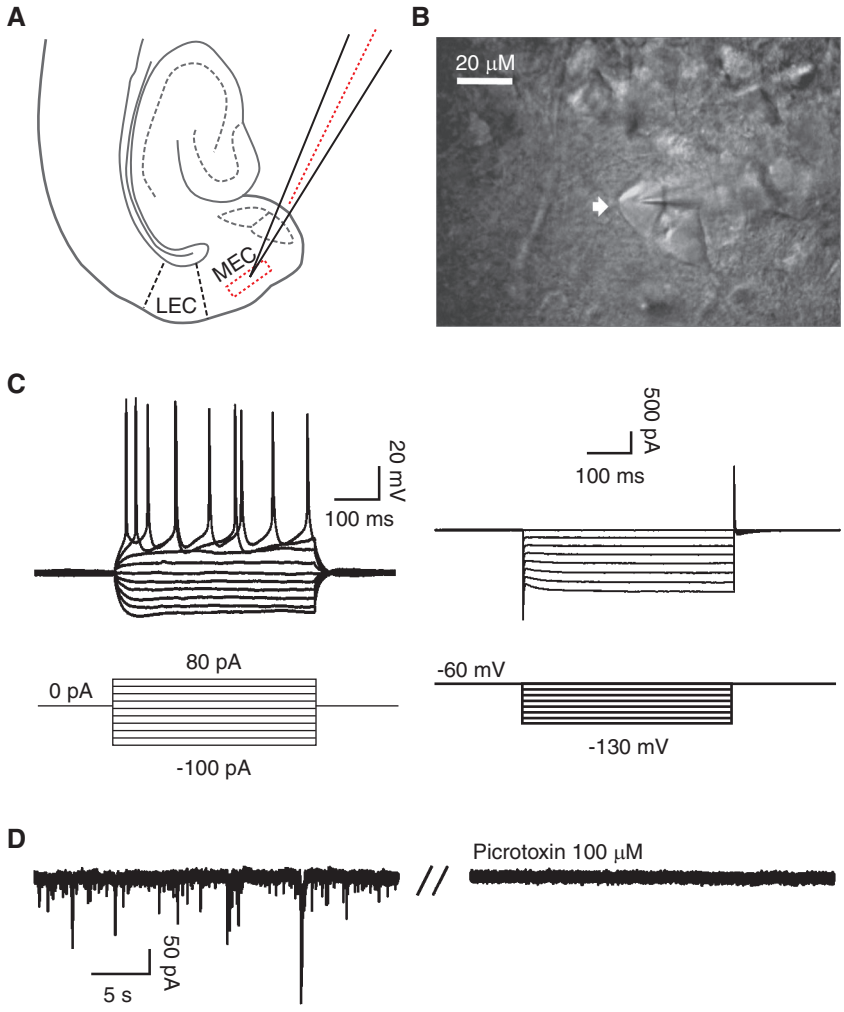

Fig. 1. Morphology and electroresponsive membrane properties of pyramidal neurons in the layer III of the medial entorhinal cortex (MEC). A. Schematic representation of the place of layer III of rat MEC. B. A plan microscopic image of a patched pyramidal neuron in the layer III of the MEC. C. Voltage responses generated by current injection (left) and whole-cell currents generated by hyperpolarizing voltage steps (right) of the layer III pyramidal neurons. D. The layer III pyramidal neurons showing a continuous level of fast spontaneous inhibitory postsynaptic currents (sIPSCs) in the presence of 10 μM CNQX and 50 μM APV, which were completely blocked by GABAA receptor antagonist picrotoxin at 100 μM.

CA1 and subiculum. We identified these neurons by a combination of observations including their morphology, localization and electrophysiological responses (Fig. 1, A and B). Pyramidal neurons have a triangular soma with one thick apical dendrite that runs to the surface of the cortex (Fig. 1B). The resting membrane potentials of these neurons were –59.79 ± 1.3 mV (n = 13) immediately after the formation of whole cell configuration and the input resistance were 125.08 ± 10.25 MΩ (n = 13). Pyramidal neurons had small depolarizing voltage sags in response to hyperpolarizing current pulses and small hyperpolarization (–60~ –130 mV, -10 mV, step) activated currents (Ih) in voltage-clamp recordings (Fig. 1C), likely reflecting a low expression level of hyperpolarization-activated, cation nonselective channels on the somata of these neurons.

Dopamine Increases the Frequency and Amplitude of sIPSCs

To study modulation of $GABA_A$ receptor-mediated sIPSCs, ionotropic glutamate receptors were blocked with 10 μM CNQX and 50 μM APV. After establishing the whole-cell configuration, a period of 10-15 min was allowed for the equilibration of intracellular and recording solutions. All layer III pyramidal neurons, like other cortical neurons, exhibited a continuous level of fast inhibitory activities which were completely blocked by 100 μM PIC, confirming that they were mediated by GABAA receptors (Fig. 1D). Application of dopamine reversibly increased the sIPSC activity (Fig. 2A). This effect was associated with a leftward shift of the interevent interval distribution

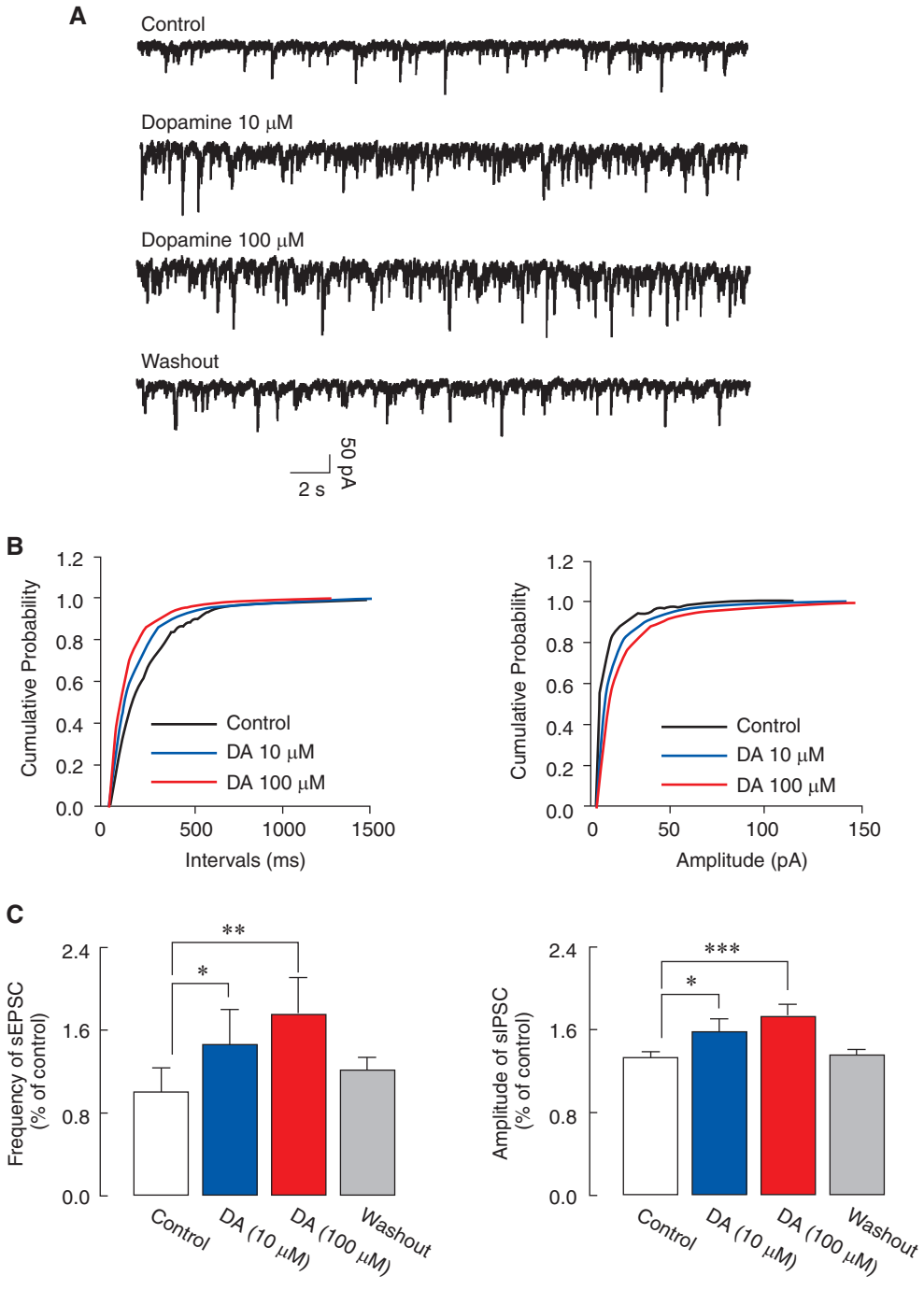

Fig. 2. Dopamine facilitates GABAergic transmission in layer III pyramidal neurons. A. Typical traces of sIPSCs observed before, during and after the application of dopamine. B. Cumulative probability curves of pooled data for interevent interval (left) and current amplitude (right) of sIPSCs. C. Pooled data from all recorded neurons (n = 5). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

and a rightward shift of the amplitude distribution (Fig. 2B). On average, dopamine at 10 μM and 100 μM significantly increased the frequency (10 μM: 147 ± 33% of control, n = 5, $P < 0.05$; 100 μM: 176 ± 35% of control, n = 5, $P < 0.01$; Fig. 2C) and amplitude (10 μM: 118 ± 10% of control, n = 5, $P < 0.05$; 100 μM: 130 ± 10% of control, n = 5, $P < 0.001$; Fig. 2C) of sIPSCs. Together, these results show that dopamine could facilitate the GABAergic transmission in the layer III of the MEC.

Dopaminergic Facilitation of sIPSCs Is Mediated by D1-Like Dopamine Receptors

The receptor mechanisms underlying the effect of dopamine on GABAergic transmission were deter-

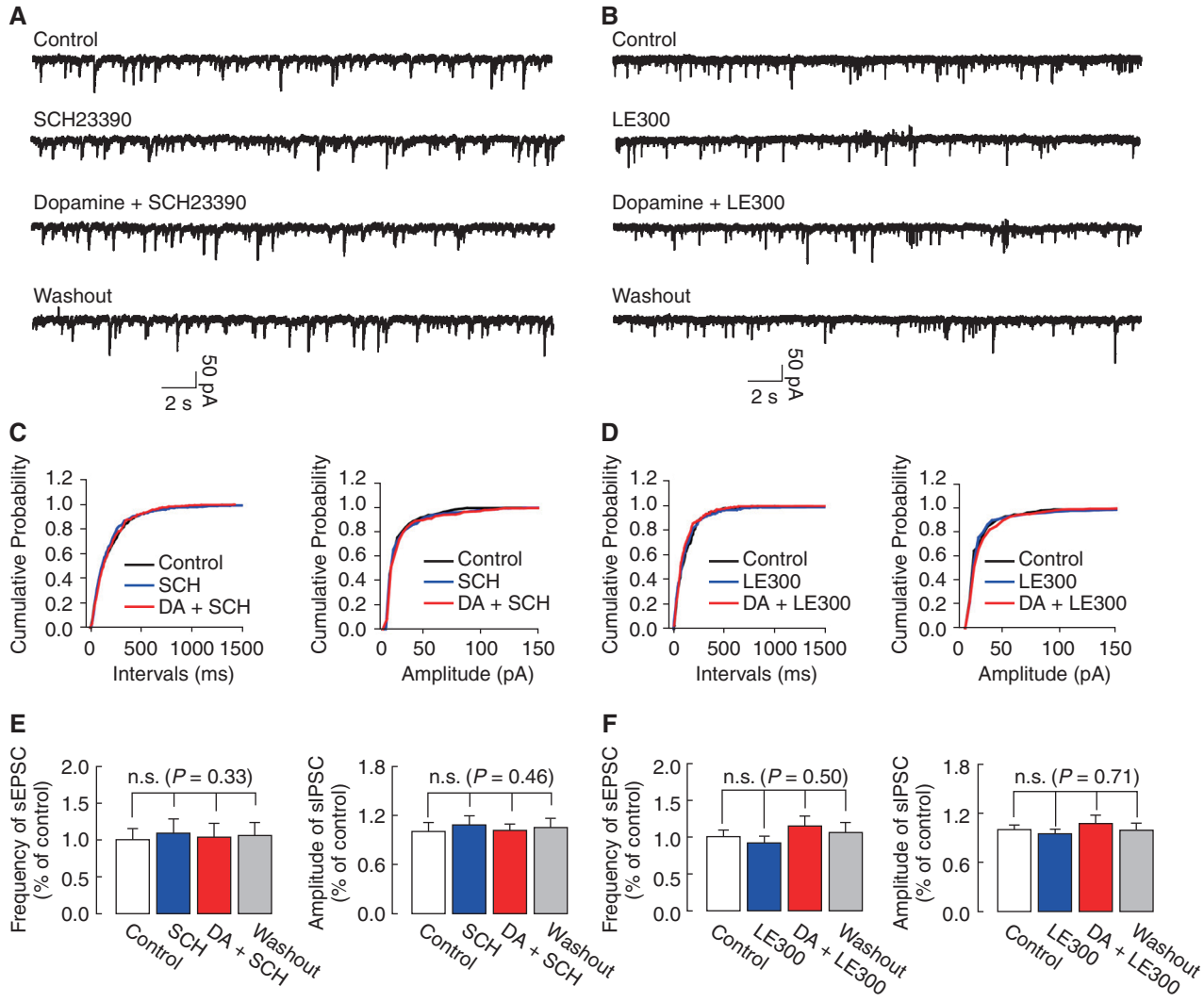

Fig. 3. Dopamine-induced facilitation of GABAergic transmission is mediated by D1-like receptors. Raw tracings showing sIPSCs recorded during control and application of 10 μM dopamine in either the presence of D1-like receptor antagonist SCH23390 at 10 μM (A) or LE300 at 100 nM (B). Cumulative probability curves of pooled data for interevent interval and current amplitude of sIPSCs during control and application of 10 μM dopamine in either the presence of SCH23390 (C) or LE300 (D). Bar histograms summarizing the effects of dopamine on the frequency and amplitude of sIPSCs in either presence of SCH23390 (n = 8) (E) or LE300 (n = 9) (F). n.s. indicates not significant.

mined by using the D1-like receptor antagonists SCH23390. Application of SCH23390 at 10 μM did not significantly alter sIPSC frequency (110 ± 19% of control, n = 8, $P = 0.18$, Fig. 3, A and C) and amplitude (108 ± 12% of control, n = 8, $P = 0.24$, Fig. 3, A and C) by itself, while it completely blocked dopamine (10 μM)-induced increase in sIPSC frequency (104 ± 18% of control, n = 8, $P = 0.32$, Fig. 3, A, C and E) and amplitude (102 ± 8% of control, n = 8, $P = 0.79$, Fig. 3, A, C and E). Considering the previous finding that SCH23390 affected the inward rectifying K^+ channels (14), we further tested the effects of another D1-like receptor antagonist LE300, which has a different structure and higher potency compared to the SCH23390. Application of LE300 at 100 nM did not affect the frequency (92 ± 9% of control, n = 9, $P = 0.46$, Fig. 3, B, D and F) and amplitude (95 ± 15% of control, n = 9, $P = 0.29$, Fig. 3, B, D and F) of the sIPSCs. However, similar to the SCH23390, LE300 completely blocked dopamine (10 μM)-induced increase in sIPSC frequency (114 ± 14% of control, n = 9, $P = 0.42$, Fig. 3, B, D and F) and amplitude (108 ± 10% of control, n = 9, $P = 0.61$, Fig. 3, B, D and F). In the presence of LE300, dopamine failed to alter the cumulative probability of sIPSC frequency and amplitude (Fig. 3D). Together, these results suggest that dopamine-induced augment of sIPSCs is mediated by the activation of D1-like receptors.

To further confirm the receptor mechanism underlying the dopamine-induced enhancement of sIPSCs, we tested the D2-like receptor antagonist raclopride.

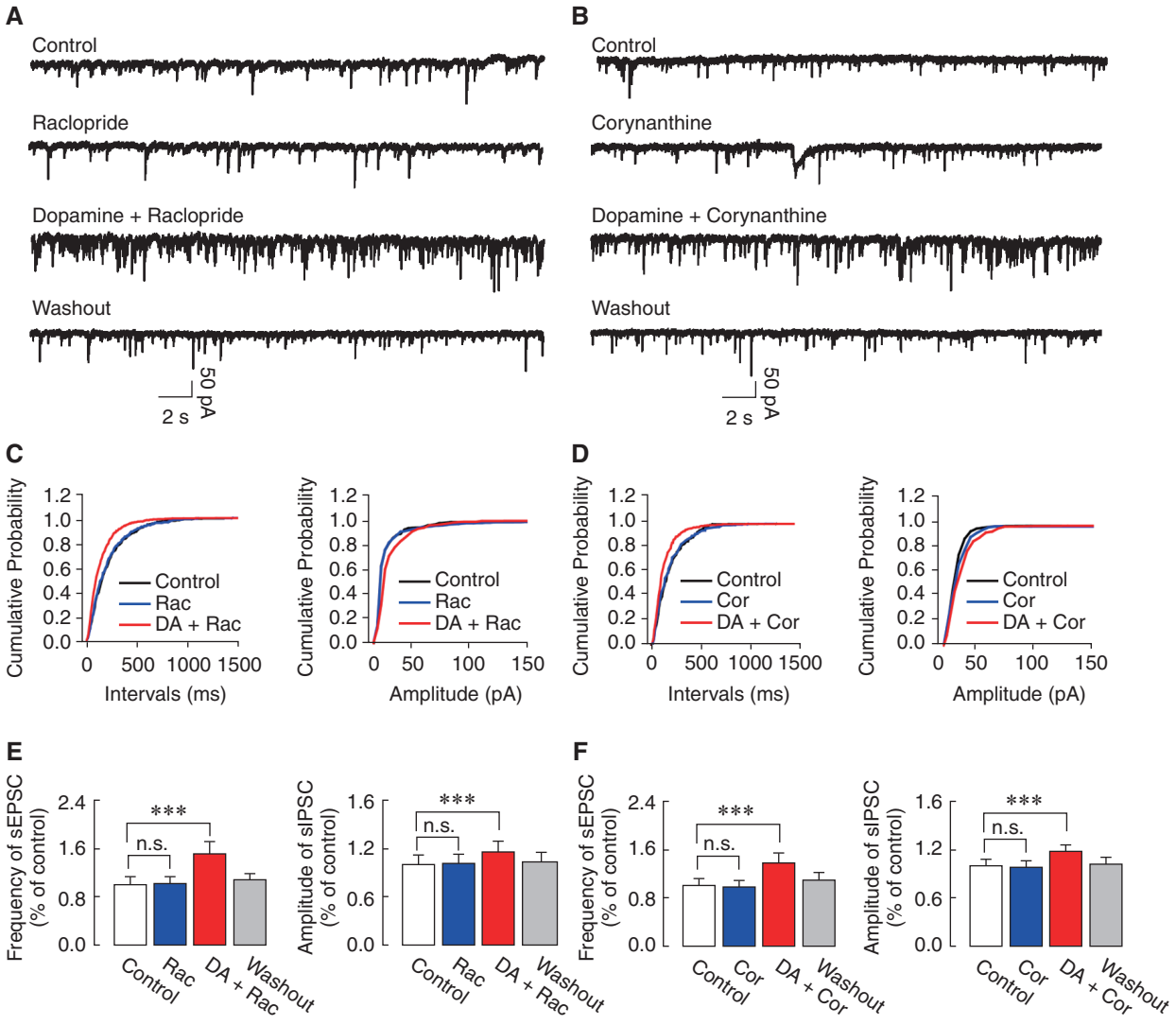

Fig. 4. Dopamine-induced enhancement of sIPSCs is independent of D2-like and α1 adrenergic receptors. Raw tracings showing sIPSCs during control and application of 10 μM dopamine in either the presence of D2-like receptor antagonist raclopride at 200 nM (A) or α1 adrenergic receptor antagonist corynanthine at 100 μM (B). Cumulative probability curves of pooled data for interevent interval and current amplitude of sIPSCs during control and application of 10 μM dopamine in either presence of raclopride (C) or corynanthine (D). Bar histograms summarized the effect of dopamine on the frequency and amplitude of sIPSCs in either presence of raclopride (n = 6) (E) or corynanthine (n = 10) (F). n.s. indicates nonsignificant and ***$P < 0.001$.

Unlike the D1-like receptor antagonists, bath application of raclopride at 200 nM failed to prevent the subsequent enhancement of sIPSCs after the application of dopamine, which significantly increased the frequency (151 ± 20% of control, n = 6, $P < 0.001$, Fig. 4, A, C and E) and amplitude (116 ± 13% of control, n = 6, $P < 0.001$, Fig. 4, A, C and E) of sIPSCs. We observed significant effect of raclopride (200 nM) on sIPSC frequency (101 ± 12% of control, n = 6, $P = 0.77$, Fig. 4, A, C and E) and amplitude (100 ± 12% of control, n = 6, $P = 0.70$, Fig. 4, A, C and E). Several lines of evidence indicate that DA can act *via* the α1 adrenergic receptors, the activation of which could facilitate GABAergic transmission in the EC (5, 15). Moreover, it has been demonstrated that in the layer II of the EC, dopamine increased the frequency, but not the amplitude, of sIPSCs *via* activation of α1 adrenergic receptors. To rule out the possibility that the enhancement of sIPSCs was due to the dopaminergic effects on α1 adrenergic receptors, we investigated the effect of α1 adrenergic receptor antagonist corynanthine. Application of the corynanthine at 100 μM did not affect the frequency (98 ± 10% of control, n = 10, $P = 0.73$, Fig. 4, B, D and F) and amplitude (98 ± 8% of control, n = 10, $P = 0.44$, Fig. 4, B, D and F) of the sIPSCs. In the presence corynanthine, dopamine still increased the frequency (138 ± 17% of control, n = 10, $P < 0.001$, Fig. 4, B, D and F) and amplitude (117 ± 8%

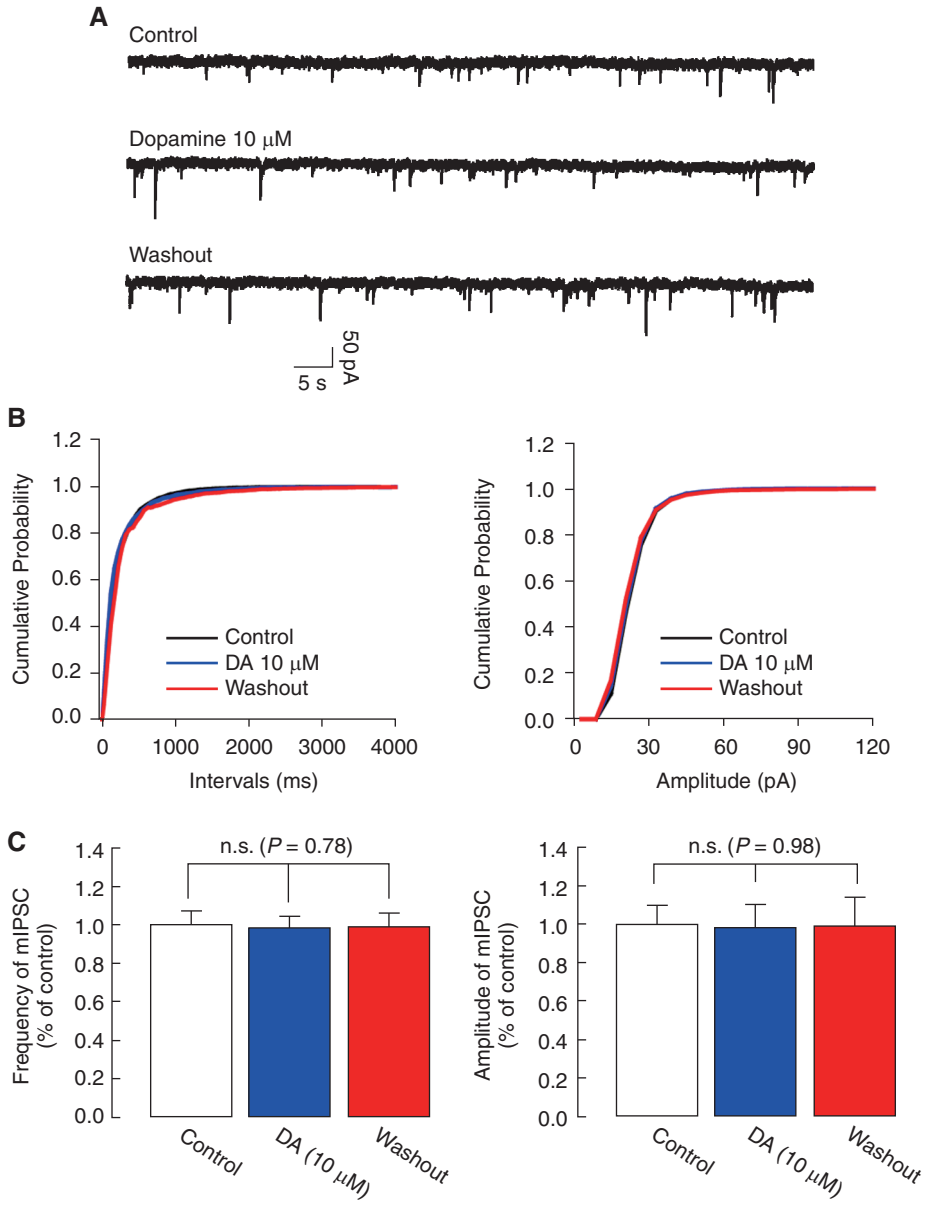

Fig. 5. Dopamine does not influence the frequency and amplitude of the miniature postsynaptic inhibitory currents (mIPSCs). A. Typical tracings showing mIPSCs before and after application of 10 μM dopamine. B. Cumulative distribution curves for interevent interval (left) and current amplitude (right) of mIPSCs in the presence and absence of 10 μM dopamine. C. Bar histograms summarizing the effect of dopamine on the frequency (left) and amplitude (right) of mIPSCs (n = 8). n.s. indicates not significant.

of control, n = 10, $P < 0.001$, Fig. 4, B, D and F) of sIPSCs. Together, these results strongly suggest that dopamine increases sIPSCs by the activation of D1-like receptors, but not the D2-like and α1 adrenergic receptors.

Dopamine Does Not Affect the Frequency and Amplitude of mIPSCs

To clarify the mechanism underlying the action of dopamine on the sIPSCs, we next examined the effects of dopamine on mIPSCs recorded in the presence of 1 μM TTX to block the voltage-gated Na^+ channels. After a stable recording of mIPSCs, application of 10 μM dopamine did not affect the cumulative distribution curves for mIPSC interevent interval (Fig. 5B, left) and amplitude (Fig. 5B, right). On average, dopamine failed to alter the either the frequency (98 ± 6% of control, n = 8, $P = 0.78$, Fig. 5C, left) or the amplitude (98 ± 12% of control, n = 8, $P = 0.98$, Fig. 5C, right) of mIPSCs, indicating that dopamine facilitates GABAergic transmission is ac-

tion potential-dependent.

Discussion

The present work for the first time shows that dopamine effectively increases the frequency and amplitude of sIPSCs in the layer III of the MEC. This action of dopamine was primarily mediated by acting on D1-like receptors since dopamine-induced facilitation of GABAergic transmission was blocked by the potent and selective D1-like receptor antagonists SCH23390 and LE300, but not by D2-like receptor antagonist raclopride or the α1 adrenergic receptor antagonist corynanthine. The ability of D1-like receptor stimulation to enhance GABAergic transmission has been reported for several other brain regions. In prefrontal cortex slices, application of dopamine increased inhibitory over excitatory currents and inhibited the spread of local activity *via* D1-like dopamine receptor activation (1, 25). In the substantia nigra pars reticulate and globus pallidus, activation of D1-like receptors has been shown to increase extracellular levels of GABA (11, 30).

In this study, we also recorded the mIPSCs in the presence of TTX to block the voltage-gated Na^+ channels. A change in the amplitude of mIPSCs reflects a postsynaptic mechanism, while an alteration in the frequency of these currents indicates a change in the presynaptic release (15, 16). Application of dopamine did not affect the amplitude and frequency of the mIPSCs. These results imply that the facilitation of D1-like receptor activation on sIPSCs is not due to its direct interaction with the presynaptic release machinery or influence on the postsynaptic $GABA_A$ receptors. As the sIPSCs are action potential-dependent whereas mIPSCs are not, these results also suggest that dopamine in the MEC facilitates GABAergic transmission in an action potential-dependent manner. D1-like receptors are coupled to Gs protein, the stimulation of which could increase the cellular concentrations of cAMP (21). A previous study has been shown that D1-like receptors depolarized neocortical fast-spiking interneurons (29). Thus, it is reasonable to speculate that the facilitation of GABAergic transmission observed here might have resulted from the dopamine-induced increase in the excitability of GABAergic interneurons. However, additional studies are needed to determine the direct effect of dopamine on the excitability of GABAergic interneurons in the MEC.

Similar to the pyramidal neurons in the layer III, previous studies found that dopamine facilitated the GABA release on the stellate neurons in the layer II of the MEC. Interestingly, the effect of dopamine in the in the layer II was mediated by α1 adrenoreceptors, but not by dopamine receptors. Moreover, it has been shown that dopamine depolarizes and increases the firing frequency of interneurons *via* the α1 adrenoreceptor-induced inhibition of inward rectifying potassium channels (5). Multiple subtypes of GABAergic neurons including parvalbumin-, cholecystokinin- and somatostatin-positive basket cells have been identified in the superficial layers of the MEC, and cholecystokinin-positive basket cells have been shown to cell type–specifically target the principal projection neurons (20, 33). The distinct cellular mechanisms underlying the effect of dopamine in the layer II stellate neurons and the layer III pyramidal neurons suggest that the activities of stellate neurons and pyramidal neurons are targeted by different subtypes of GABAergic interneurons.

The MEC layer III consists of a high density of spiny and nonspiny pyramidal cells. Due to the caveat of our approach, in the present study we cannot distinguish between these two subtypes of principal neurons (4, 12). Spiny and nonspiny pyramidal cells have different dendritic projection patterns, which might hint at different functions of the dopaminergic modulation in these cell types. The present study primarily focused on the pyramidal neurons in layer III because the axons of these neurons synapse on the distal dendrites of pyramidal neurons in the CA1 and subiculum and exert a tight control over the excitability of CA1 pyramidal neurons (32). Moreover, a recent study has found that the excitatory inputs from pyramidal neurons in layer III to hippocampus is required for the temporal association learning (27). In the present study, we found dopamine acting at D1-like receptors exerts inhibition in the MEC through indirect mechanisms. The dopamine-induced inhibition, thus, might constrain the inflow of excitatory inputs to the hippocampus so that only strong and synchronous sensory information to the MEC may be sufficient to activate EC projection neurons, and thus participate in the cognitive functions.

In summary, we found that dopamine significantly increases the frequency and amplitude of sIPSCs. This effect of dopamine was action potential-dependent and primarily mediated by acting at D1-like but not D2-like dopamine receptors. These findings suggested that dopamine stimulating at D1-like receptors inhibit the excitability of layer III pyramidal neurons in the MEC through an indirect mechanism.

Acknowledgments

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