

## Full-length article

# *l*-Stepholidine increases the frequency of sEPSC via the activation of D<sub>1</sub> dopamine signaling pathway in rat prelimbic cortical neurons<sup>1</sup>

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**Key words**

*l*-stepholidine; prelimbic cortex; whole-cell patch clamp; spontaneous excitatory postsynaptic currents; dopamine receptor

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**Abstract**

**Aim:** To investigate the effect of *l*-stepholidine (SPD) on the frequency of spontaneous excitatory postsynaptic currents (sEPSC) in the pyramidal cells between layers V and VI in the prelimbic cortex (PL). **Methods:** A whole-cell patch clamp in rat brain slices was used. **Results:** SPD significantly increased the frequency of sEPSC in a concentration-dependent manner. A selective D<sub>1</sub> dopamine receptor antagonist SCH23390 blocked SPD-mediated effects, whereas the D<sub>1</sub> agonist SKF38393, but not the D<sub>2/3</sub> antagonist sulpiride, mimicked SPD-mediated increase in the frequency of sEPSC. Moreover, both protein kinase A (PKA) inhibitor *N*-(2-[*p*-bromocinnamylamino]-ethyl)-5-isoquinolinesulfonamide hydrochloride and protein kinase C (PKC) inhibitor chelerythrine attenuated the effect of SPD on sEPSC. **Conclusion:** SPD elicits its effect on the frequency of sEPSC on the PL pyramidal cells via presynaptic D<sub>1</sub> receptors, and is dependent on PKA and PKC signaling pathways.

**Introduction**

*l*-Stepholidine (SPD), isolated from the Chinese herb *Stephania*, is a tetrahydroprotoberberine alkaloid. Previous studies in neuropharmacology, neurochemistry, electrophysiology, and behavioral experiments have demonstrated that SPD not only acts as a partial D<sub>1</sub> agonist<sup>[1–5]</sup>, but also as a full D<sub>2</sub> antagonist<sup>[2,5,6]</sup>. SPD is the first known drug to possess the dual properties toward the dopamine (DA) receptor. Clinical trials have implicated that SPD is effective in the treatment of both positive and negative syndromes in schizophrenia<sup>[7]</sup>. Furthermore, SPD was also found to enhance the antipsychiatry effectiveness of other drugs and reduce tardive dyskinesia<sup>[8]</sup>. However, the mechanism of SPD's anti-schizophrenia has not been explored.

The prelimbic cortex (PL) is well known as a critical structure in cognitive function. It is also believed that functional abnormalities in PL are associated with many neuropsychiatric disorders and symptoms including negative symptoms and cognitive impairment in schizophrenia<sup>[9–12]</sup>. The functional activity of the PL is mainly mediated by the intrinsic neurons and their interactions with other brain regions. The

dopaminergic project from the ventral tegmental area (VTA) to the PL pyramidal cells located in layers V–VI is of particular importance for modulating PL function<sup>[13–19]</sup>. Particularly layers V contains a high density of D<sub>1</sub> receptors<sup>[20]</sup>. Furthermore, many studies documented the importance of PL DA transmission via D<sub>1</sub> receptors for optimal PL function<sup>[21,22]</sup>. D<sub>1</sub> receptor stimulation is generally believed to promote *N*-methyl-*D*-aspartate (NMDA) receptor function on the excitable neurons via the medium spiny neuronal transmission, further supporting the hypothesis that DA transmission at D<sub>1</sub> receptors in the PL is involved in the cognitive impairment and the negative symptoms of schizophrenia<sup>[12,19,23,24]</sup>.

Anatomical studies have shown that the dendritic and somatic regions of PL pyramidal neurons receive synaptic inputs from both glutamatergic terminals arising from cortical and subcortical sources and dopaminergic afferents from VTA<sup>[25–29]</sup>. Furthermore, ultrastructural studies demonstrate that dopaminergic and glutamatergic axon terminals are in direct apposition to each other on the same postsynaptic pyramidal neuron in the PL which forms so-called “synaptic triads”, suggesting that both presynaptic and postsynaptic

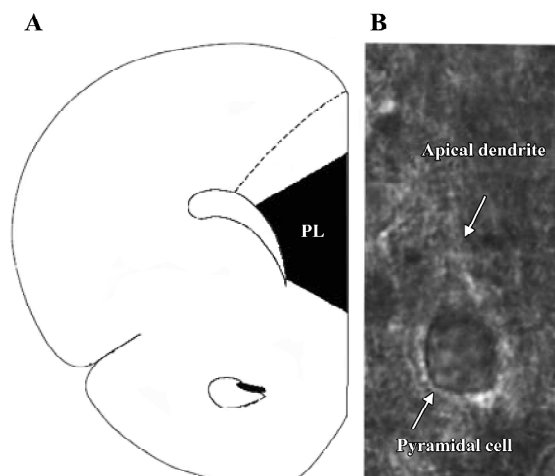
inputs participate in the modulation of synaptic transmission<sup>[30–32]</sup>. SPD is found to potently enhance the amplitude of NMDA-mediated currents in PL pyramidal neurons in brain slices via a postsynaptic mechanism<sup>[12]</sup>. However, the potential role of presynaptic regulation in mediating the effect of SPD is unknown and of interest since it has reported that DA can act on presynaptic D<sub>1</sub> receptors and increase the frequency of sEPSC in PL pyramidal neurons in brain slices<sup>[33]</sup>.

The present work was designed to study the effect and signaling mechanism for the SPD-modulated frequency of sEPSC in PL pyramidal neurons. The results indicate that presynaptic mechanism plays a critical role in the SPD-elicited effect on the frequency of sEPSC in PL pyramidal cells via D<sub>1</sub> receptors.

## Materials and methods

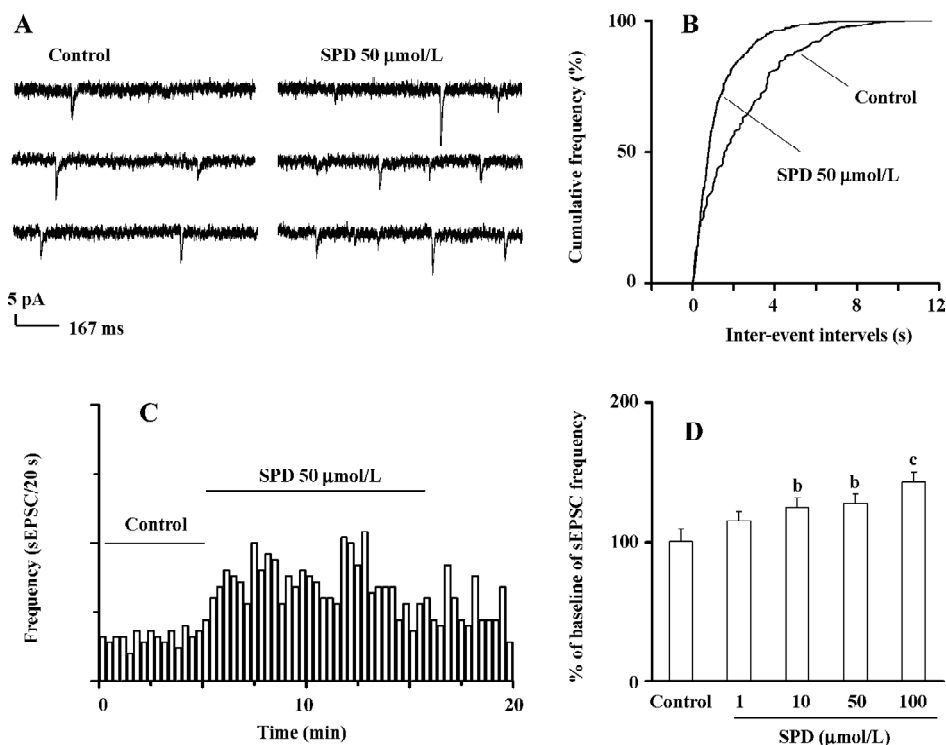
**Preparation of prelimbic cortical slices** Sprague-Dawley rats (Shanghai Experimental Animal Center, Chinese Academy of Sciences, Shanghai, China), weighing 30–50 g, were housed under standard laboratory conditions with constant temperature (22–23 °C) and humidity (50%–60%). All animal experiments were conducted in compliance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). Prelimbic cortical slices were prepared according to procedures described previously<sup>[33]</sup>. The rats were anesthetized with chloral hydrate (400 mg/kg, ip). Following decapitation, the brain was quickly removed and submerged in ice-cold perfusive medium containing 130 mmol/L NaCl, 5 mmol/L KCl, 2 mmol/L CaCl<sub>2</sub>, 2 mmol/L MgSO<sub>4</sub>, 1.25 mmol/L NaH<sub>2</sub>PO<sub>4</sub>, 26 mmol/L NaHCO<sub>3</sub>, 10 mmol/L glucose, 10 mmol/L sucrose, and saturated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The PL was removed and placed on a layer of moistened filter paper glued to the cutting stage of automatic oscillating tissue slicer (OTS-4000, Electron Microscopy Sciences, Fort Washington, PA, USA). Serial coronal slices (380 μm) were cut and transferred to an incubating chamber (28–30 °C) for at least 1 h before recording.

**Visualization of pyramidal cells** To visualize the cell, the slice was placed in a recording chamber and viewed with a fixed stage, upright microscope (BX51 WI, Olympus, Tokyo, Japan). To increase the clarity of the cell, infrared light was used to illuminate the slice. The resultant infrared differential interference contrast (DIC) images were visualized on a black–white TV monitor through the use of a light sensitive charge coupled device (CCD) camera. Recordings were made from pyramidal cells located in layers V–VI. They were identified by their pyramidal shape, large soma, and presence of apical dendrites (Figure 1).



**Figure 1.** Location and morphology of the pyramidal neurons in this study. (A) area of the PL; (B) infrared DIC image of a live neuron in a PL brain slice. Neuron was identified as a pyramidal neuron based on its pyramidal shape, large soma, and the presence of an apical dendrite. Scale bar=10 μm.

**Whole-cell recording** The slice was continuously perfused with the above perfusive medium and saturated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. Electrodes (4–6 MΩ), pulled from glass capillaries with a Sutter micropipette puller (P-97, Novato, CA, USA), were filled with a solution (pH 7.25) containing 140 mmol/L K-gluconate, 0.1 mmol/L CaCl<sub>2</sub>, 2 mmol/L MgCl<sub>2</sub>, 1 mmol/L ethylene glycol tetraacetic acid (EGTA), 2 mmol/L ATP·K<sub>2</sub>, 0.1 mmol/L GTP·Na<sub>3</sub>, and 10 mmol/L N-(2-hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid) (HEPES). Voltage and current signals were recorded with an Axon patch 700A amplifier (Union City, CA, USA) connected to a Digidata 1322A interface (Union City, CA, USA). The data were digitized and stored on disks using Clampfit (version 8.2.0.228, Axon, USA). Resting membrane potential and action potential were recorded under the current clamp mode. The recording pyramidal cell had a resting membrane potential less than -50 mV, an action potential amplitude greater than 80 mV, and no spontaneous action potentials. sEPSC, which had variable amplitude with a fast rising phase and a slower decay, were recorded at a holding potential of -70 mV (Figure 2A). These currents were blocked by an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainite glutamate receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX, 10 μmol/L). The series resistance was monitored by measuring the instantaneous current in response to a 5 mV voltage step command. Series resistance compensation was not used, and cells whose series resistance changed more than 15%



**Figure 2.** Effect of SPD on sEPSC frequency in the PL pyramidal cells. (A) typical whole-cell patch clamp recordings of sEPSC in control conditions and the bath application of SPD (50 μmol/L); (B) cumulative distributions of the inter-event intervals of sEPSC in control and bath application of SPD; (C) time-course of SPD on sEPSC frequency; (D) concentration-response curve for SPD-modulated sEPSC frequency. *n*=5. Mean±SEM. <sup>b</sup>*P*<0.05, <sup>c</sup>*P*<0.01 compared to control, respectively.

were discarded.

**Offline data analysis** Offline data analysis was performed using the Mini Analysis Program 5.0 (Synaptosoft, Fort Lee, NJ, USA) and Origin 7.0 (OriginLab Corporation, Northampton, MA, USA). The record of the sEPSC was shown with high resolution, and events that did not show a typical sEPSC waveform were rejected. The frequency and the inter-event intervals of sEPSC were measured. The effects of drugs were compared before and after drug injection with ANCOVA. The covariate was the baseline value prior to the drug injection. Statistical significance of distribution was made with the Kolmogorov-Smirnov (K-S) test. All numerical data were expressed as mean±SEM. In all cases, *n* refers to the number of cells studied.

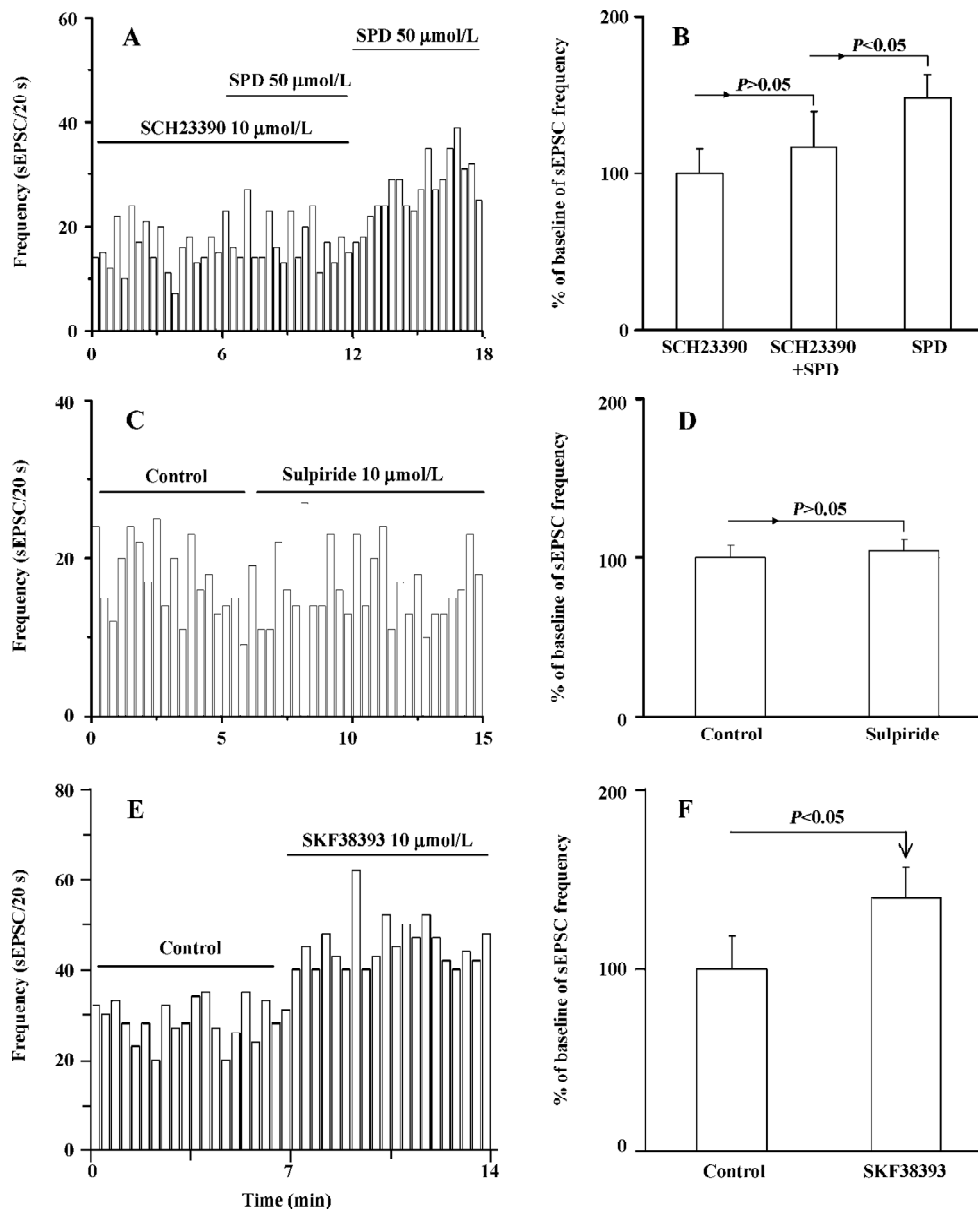
**Drugs** SPD (Shanghai Institute of Materia Medica, Chinese Academy of Sciences, China) was dissolved in 0.1 mmol/L H<sub>2</sub>SO<sub>4</sub>, then diluted and neutralized with 0.1 mmol/L NaOH (pH 5.0). NBQX, K-gluconate, ATP-K<sub>2</sub>, GTP-Na<sub>3</sub>, SCH23390, *N*-(2-[*p*-bromocinnamylamino]-ethyl)-5-isoquinolinesulfonamide hydrochloride (H-89), SKF38393, sulpiride, and chelerythrine were purchased from Sigma (St Louis, MO, USA). All drugs were applied through bath perfusion.

## Results

### SPD increases frequency of sEPSC

In PL pyramidal cells, bath application of SPD (50 μmol/L) resulted in an apparent increase in sEPSC frequency. A typical current trace is shown at Figure 2A. A plotting cumulative distribution of sEPSC intervals with the K-S statistical analysis indicated that SPD induced a clear shift towards shorter intervals in the cumulative curve (Figure 2B). On average, sEPSC frequency significantly increased after SPD (*P*<0.05, *n*=13 cells, Figure 2C). A SPD-elicited increase in sEPSC frequency was concentration dependent (*n*=5 cells, Figure 2D). A significant increase in the sEPSC (125.2%±6.8%, *P*<0.05) at 10 μmol/L was already observed; it reached its maximum at 100 μmol/L (*P*<0.01).

**SPD-induced increase in sEPSC frequency is mediated by the D<sub>1</sub> receptor** The above results showed that SPD produced an increase of sEPSC frequency. We then determined the potential mechanism involved in the action of SPD. The application of the selective D<sub>1</sub> receptor antagonist SCH23390 (10 μmol/L) significantly blunted the SPD-induced increase in sEPSC frequency (Figure 3A, 3B). The stimulation on sEPSC frequency was recovered while SCH23390 was washed out. This was further supported by data that the D<sub>1</sub> partial agonist SKF38393 (10 μmol/L) mimicked the increase of SPD on the frequency of sEPSC (*P*<0.05, Figure 3E,F), while the D<sub>2/3</sub> receptor antagonist sulpiride (10 μmol/L) elicited no effects on sEPSC frequency (*n*=6 cells, Figure 3C,D). Thus, it is clear that the D<sub>1</sub> receptor, not the D<sub>2/3</sub>



**Figure 3.** Activation of  $D_1$  receptors mediates the enhancement on the sEPSC frequency by SPD. (A) SCH23390 (10  $\mu\text{mol/L}$ ) abolished SPD (50  $\mu\text{mol/L}$ ) induced increase in the frequency of sEPSC. But the stimulation by SPD was recovered when SCH23390 was washed out from the bath. (B) bar graph is the summary from 6 cells. (C)  $D_{2/3}$  receptor antagonist sulpiride (10  $\mu\text{mol/L}$ ) had no effect on SPD-induced increase on the frequency of sEPSC, and (D) Bar graph is the summary from 6 cells. (E) SKF38393 (10  $\mu\text{mol/L}$ ) increased the frequency of sEPSC. (F) bar graph is the summary from 6 cells. Mean  $\pm$  SEM. Activation of  $D_1$  receptors mediates the enhancement on the sEPSC frequency by SKF38393.

receptor, mediated the effect of SPD on sEPSC frequency.

#### Both PKA and PKC are involved in SPD-induced increase in the frequency of sEPSC

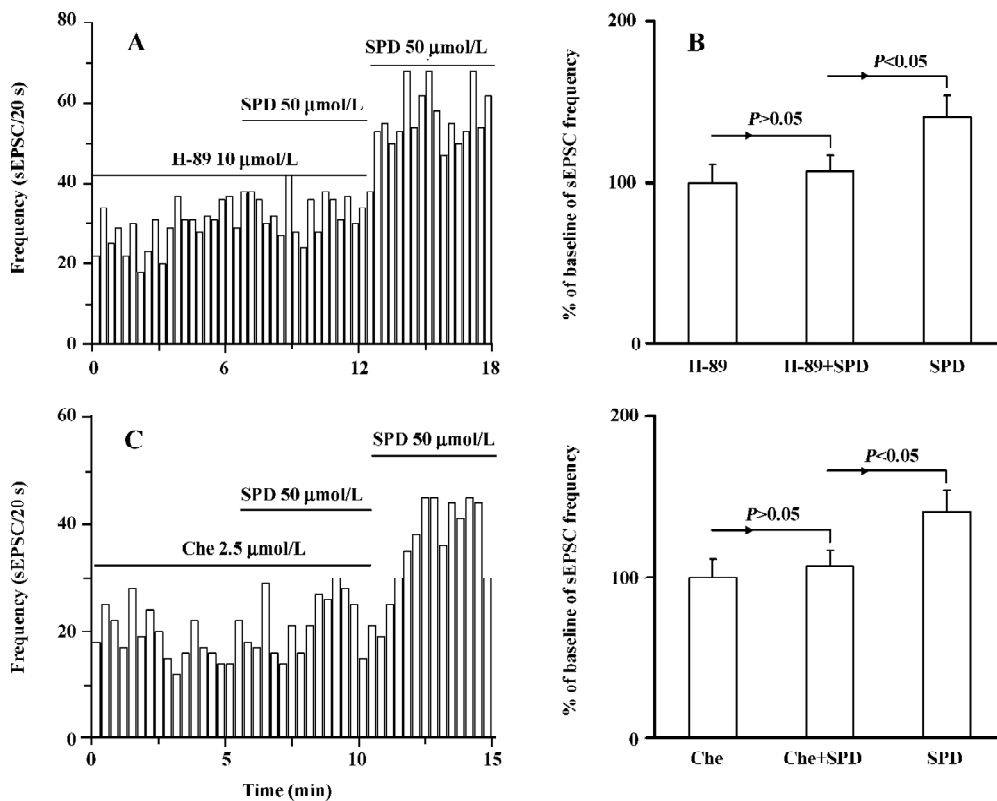
It is known that  $D_1$  receptor stimulation induces the activation of protein kinase A (PKA) and protein kinase C (PKC). We determined which intracellular pathway was involved in the SPD-altered frequency of sEPSC. As shown in Figure 4, when the specific PKA antagonist H-89 (10  $\mu\text{mol/L}$ ) was applied prior to or during SPD incubation, the SPD-elicited increase in the frequency of sEPSC was abolished. This was also true when the PKC inhibitor chelerythrine (2.5  $\mu\text{mol/L}$ ) was employed (Figure 4C, D). The results therefore implicated that both PKA and PKC were involved in the regulatory effect of SPD on sEPSC

frequency.

## Discussion

The present study demonstrated that SPD significantly increased the frequency of sEPSC in a concentration-dependent manner. Selective  $D_1$  receptor antagonist SCH23390 blocked SPD-mediated effects, whereas  $D_1$  agonist SKF38393, but not the  $D_{2/3}$  antagonist sulpiride mimicked a SPD-mediated increase in the frequency of sEPSC. Moreover, both PKA inhibitor H-89 and PKC inhibitor chelerythrine attenuated the effect of SPD on sEPSC.

Previous studies from our laboratory and others have



**Figure 4.** PKA and PKC are involved in SPD-modulated sEPSC frequency. (A) PKA antagonist H-89 (10 μmol/L) was added to the bath prior and during SPD (50 μmol/L) stimulation. The effect of SPD was recovered after the wash-out of H-89. (B) bar graph is the summary of the 6 cells. (C) selective PKC inhibitor chelerythrine (Che, 2.5 μmol/L) was added to the bath prior and during SPD (50 μmol/L) stimulation. The effect of SPD was recovered after the wash-out of the inhibitor. (D) bar graph is the summary of the 7 cells. Mean±SEM.

shown that SPD displays high affinity to both D<sub>1</sub>- and D<sub>2</sub>-like receptors. It is clear now that SPD possesses a dual property towards DA receptors. It acts as an agonist on the D<sub>1</sub> receptor and functions as an antagonist on the D<sub>2/3</sub> receptor<sup>[5,34-40]</sup>. Our data demonstrated that enhancement of sEPSC frequency in the PL pyramidal cells by SPD was mediated by the D<sub>1</sub> receptor, whereas D<sub>2/3</sub> receptors appeared not to associate with the action.

It is known that sEPSC are mainly resulted from the action potential-dependent glutamate release and thereby the increase in sEPSC frequency could be due to the activation of some neurotransmitter receptors, such as the D<sub>1</sub> receptor, that result in synaptic transmission from a presynaptic action<sup>[33,41-43]</sup>. In agreement with previous finding that D<sub>1</sub> receptors could modulate presynaptic glutamate release<sup>[44,45]</sup>, the present study showed that SPD increased sEPSC frequency via D<sub>1</sub> receptors. It therefore appeared that the underlying mechanism for the SPD-mediated increase in sEPSC frequency is associated with the drug-induced presynaptic release of glutamate, and subsequently, the modulation of the synaptic inputs to PL pyramidal cells.

Both PKA and PKC are known to be the important signaling molecules that transduce D<sub>1</sub>-like receptor signals<sup>[46,47]</sup>. A previous study demonstrated that DA stimulated the fre-

quency of sEPSC through PKA and PKC in rat PL pyramidal cells via the presynaptic D<sub>1</sub> receptor<sup>[33]</sup>. Present data also indicate that PKA and PKC play an important role in SPD-mediated modulation on sEPSC frequency. Therefore, it appears that both DA and SPD share common signaling pathways via the activation of the D<sub>1</sub> receptor in the modulation of sEPSC frequency.

More importantly, the present data provides novel evidence for the functional interaction between the D<sub>1</sub> and NMDA receptors in neurons. It is known that the interaction between the D<sub>1</sub> and NMDA receptors plays a critical functional role in the frontal cortex. It is interesting to note that the suggested alterations of the D<sub>1</sub>-NMDA receptor interaction in the PL are important pathological mechanisms underlying the neurochemical imbalance in schizophrenia<sup>[12,19]</sup>. Both the D<sub>1</sub> and NMDA receptors in the frontal cortex play a critical role in synaptic plasticity, memory, and cognition. Dysfunction of NMDA and D<sub>1</sub> receptor is believed to associate with the negative symptoms and cognitive impairment in schizophrenia<sup>[48-50]</sup>. Our results show that SPD increases the frequency of sEPSC via the activation of D<sub>1</sub> receptors located in the PL V-VI layers, presumably through enhancing the presynaptic glutamate release. Considering the advantageous benefits of SPD on negative

symptoms of schizophrenic patients<sup>[7]</sup>, the present study provides a potential molecular mechanism for the treatment of SPD on negative symptoms of schizophrenia. Furthermore, unique pharmacological properties of SPD (the D<sub>1</sub> agonist in the PL and the D<sub>2</sub>/D<sub>3</sub> antagonist in the subcortex) lead us to believe that SPD is a promising candidate as a novel antipsychotic agent.

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