

**Original**

# Isoproterenol facilitates GABAergic autapses in fast-spiking cells of rat insular cortex

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**Abstract:** In the cerebral cortex, fast-spiking (FS) cells are the principal GABAergic interneurons and potently suppress neural activity in targeting neurons. Some FS neurons make synaptic contacts with themselves. Such synapses are called autapses and contribute to self-inhibition of FS neural activity.  $\beta$ -Adrenoceptors have a crucial role in regulating GABAergic synaptic inputs from FS cells to pyramidal (Pyr) cells; however, the  $\beta$ -adrenergic functions on FS autapses are unknown. To determine how the  $\beta$ -adrenoceptor agonist isoproterenol modulates inhibitory synaptic transmission in the autapses of FS cells, paired whole-cell patch-clamp recordings were obtained from FS and Pyr cells in layer V of rat insular cortex. Previous studies found that isoproterenol (100  $\mu$ M) had pleiotropic effects on unitary inhibitory postsynaptic currents (uIPSCs) in FS $\rightarrow$ Pyr connections, whereas autapses in FS cells were always facilitated by isoproterenol. Facilitation of autapses by isoproterenol was accompanied by decreases in the paired-pulse ratio of second to first uIPSC amplitudes and the coefficient of variation of the uIPSC amplitude, which suggests that  $\beta$ -adrenergic facilitation is likely mediated by presynaptic mechanisms. The discrepancy between isoproterenol-induced modulation of uIPSCs in FS autapses and in FS $\rightarrow$ Pyr connections may reflect the presence of different presynaptic mechanisms of GABA release in each synapse. (*J Oral Sci* 56, 41-47, 2014)

**Keywords:**  $\beta$ -adrenoceptor; autapse; fast-spiking cell; whole-cell patch-clamp; interneuron.

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## Introduction

In the cerebral cortex, GABAergic neurons make up 10-20% of cortical neurons (1) and regulate neural activity by inducing inhibitory postsynaptic Cl<sup>-</sup> currents. Electrophysiologically, GABAergic interneurons are divided into more than 4 classes, according to their firing properties (2). Among GABAergic neurons, fast-spiking (FS) cells are believed to be essential in suppressing postsynaptic neurons. FS cells are characterized by their unique afterhyperpolarization, i.e., a large amplitude with rapid repolarization, shorter duration of action potential, and extreme high-frequency repetitive firing in response to a long depolarizing current pulse injection, without spike adaptation (2-5). Interestingly, many FS cells have autapses, self-synapses formed by the axon of a neuron on its own somata or dendrites (6). FS autapses suppress FS neural firing by self-inhibition. However, the physiological and pharmacological properties of FS autapses in the cerebral cortex are poorly understood.

Activation of  $\beta$ -adrenoceptors in glutamatergic synaptic transmission has been well studied:  $\beta$ -adrenoceptor agonists increase glutamate release from presynaptic terminals (7-10). In contrast, the effects of isoproterenol are pleiotropic. Application of isoproterenol reduces unitary inhibitory postsynaptic current (uIPSC) amplitude in non-FS cell to pyramidal cell (non-FS $\rightarrow$ Pyr) connections but facilitates uIPSCs age-dependently in FS $\rightarrow$ Pyr connections, i.e., older animals ( $\geq$ postnatal day 24) are more likely to show isoproterenol-induced facilitation of uIPSCs than are younger animals (5). These findings indicate that the functional roles of  $\beta$ -adrenoceptors in synaptic transmission are differently regulated in gluta-

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matergic and GABAergic synapses.

The effects of isoproterenol on uIPSCs recorded from FS autapses were examined by obtaining paired whole-cell patch-clamp recordings from FS and Pyr cells in layer V of the insular cortex (IC) and comparing isoproterenol-induced modulation of uIPSCs between FS autapses and FS→Pyr connections.

## Materials and Methods

All experiments were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by Institutional Animal Care and Use Committee in the Nihon University (AP10-D004-1). All efforts were made to minimize the number and suffering of the animals used.

### Slice preparations

Male and female vesicular GABA transporters (VGAT)-Venus line A transgenic rats (postnatal day 17-46), in which the yellow fluorescent protein Venus (11) is expressed in almost all cortical GABAergic cells (12), were deeply anesthetized with sodium pentobarbital (75 mg/kg, i.p.) and decapitated. Tissue blocks including the IC around the intersection of the middle cerebral artery and rhinal fissure were rapidly removed and stored for 3 min in modified ice-cold artificial cerebrospinal fluid (M-ACSF) containing (in mM) 230 sucrose, 2.5 KCl, 10 MgSO<sub>4</sub>, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 26 NaHCO<sub>3</sub>, 2.5 CaCl<sub>2</sub>, and 10 D-glucose. Coronal slices (thickness, 350 μm) were cut using a microslicer (Linearslicer Pro 7, Dosaka EM, Kyoto, Japan). Slices were incubated at 32°C for 40 min in a submersion-type holding chamber that contained 50% M-ACSF and 50% normal ACSF (pH 7.35-7.40). Normal ACSF contained (in mM) 126 NaCl, 3 KCl, 2 MgSO<sub>4</sub>, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 26 NaHCO<sub>3</sub>, 2.0 CaCl<sub>2</sub>, and 10 D-glucose. Slices were then placed in normal ACSF at 32°C for 1 h. Normal ACSF was continuously aerated with a mixture of 95% O<sub>2</sub> / 5% CO<sub>2</sub>. Slices were thereafter maintained at room temperature until used for recording.

### Cell identification and paired whole-cell patch-clamp recording

The slices were transferred to a recording chamber that was continuously perfused with normal ACSF (humidified with 95% O<sub>2</sub> / 5% CO<sub>2</sub>) at a rate of 1.0-1.5 mL/min. Paired whole-cell patch-clamp recordings were obtained from fluorescent neurons and Pyr cells identified in layer V by a fluorescence microscope equipped with Nomarski optics (×40, Olympus BX51, Tokyo, Japan) and an infrared-sensitive video camera (Hamamatsu Photonics, Hamamatsu, Japan). The distance between Venus-

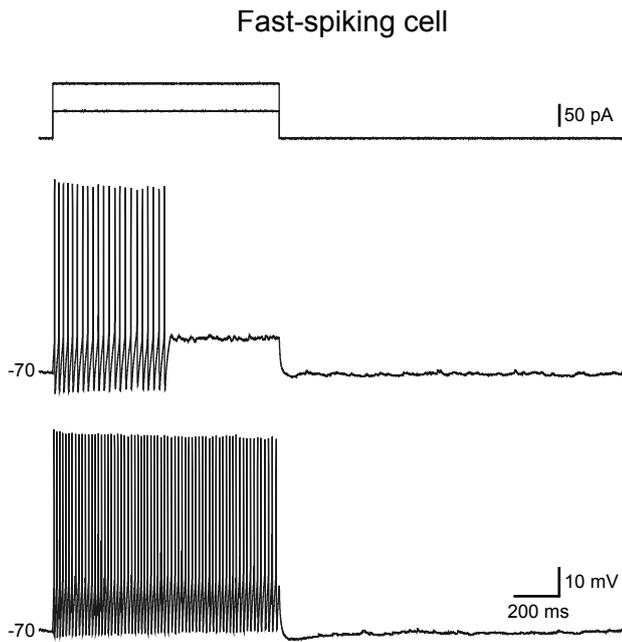
positive and Pyr cells was <50 μm. Electrical signals were recorded by an amplifier (Axoclamp 700B, Axon Instruments, Foster City, CA, USA), digitized (Digidata 1322A, Axon Instruments), observed online, and stored on a computer hard disk using software (Clampex 9, Axon Instruments).

The composition of the pipette solution used for FS cell recordings was (in mM) 70 potassium gluconate, 70 KCl, 10 *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid (HEPES), 15 biocytin, 0.5 EGTA, 2 MgCl<sub>2</sub>, 2 magnesium adenosine triphosphate (ATP), and 0.3 sodium guanosine triphosphate (GTP). Pyr cells were recorded using the following pipette solution (in mM): 120 cesium gluconate, 20 biocytin, 10 HEPES, 8 NaCl, 5 *N*-(2,6-dimethylphenylcarbamoylmethyl) triethylammonium bromide (QX-314), 2 magnesium ATP, 0.3 sodium GTP, and 0.1 1,2-bis(2-aminophenoxy) ethane-*N,N,N',N'*-tetraacetic acid (BAPTA). The presence of QX-314 and cesium in the pipette solution precluded recording GABA<sub>B</sub>-receptor-mediated IPSCs. Both pipette solutions had a pH of 7.3 and an osmolarity of 300 mOsm. The liquid junction potentials for current-clamp and voltage-clamp recordings were -9 and -12 mV, respectively, and voltage was corrected accordingly. Thin-wall borosilicate patch electrodes (2-5 MΩ) were pulled on a Flaming-Brown micropipette puller (P-97, Sutter Instruments, Novato, CA, USA).

Recordings were obtained at 30-31°C. Seal resistance was >5 GΩ, and only data obtained from electrodes with an access resistance of 6-17 MΩ and <20% change during recordings were included in this study. Series resistance was 70% compensated. Repetitive firing in response to long (1 s) depolarizing current pulses was recorded to classify GABAergic interneuron subtypes. uIPSCs were recorded from Pyr cells by applying depolarizing step voltage pulses (+80 mV, 2 ms, 0.05 Hz) to presynaptic Venus-positive cells. Pyr cells were voltage-clamped at -70 mV during uIPSCs recordings. To block GABA<sub>A</sub> receptors, 10 μM bicuculline methiodide (Tocris Cookson, Bristol, UK) was bath-applied. Isoproterenol (100 μM, Research Biochemicals International, Natick, MA, USA) was added directly to the perfusate. Membrane currents and potentials were low-pass filtered at 5-10 kHz and digitized at 20 kHz. All chemicals, unless otherwise specified, were purchased from Sigma-Aldrich (St. Louis, MO, USA).

### Data analysis

uIPSCs were analyzed with pClamp 9 suite program Clampfit (Axon Instruments). Amplitudes of uIPSCs were measured as the difference between peak postsyn-



**Fig. 1** An example of repetitive spike firing in a Venus-positive FS cell. Repetitive firing is induced by a depolarizing current pulse injection (1 s). The resting membrane potential was  $-70$  mV. The FS cell exhibited large and fast afterhyperpolarization and high-frequency spike firing without spike adaptation.

aptic currents and baseline currents taken from a 2-ms time window close to the onset of the uIPSCs. Average amplitude, paired-pulse ratio (PPR), and coefficient of variation (CV) of uIPSCs were calculated from 10-20 consecutive sweeps.

Data are presented as mean  $\pm$  standard error of the mean (SEM). uIPSC amplitude and PPR between control and isoproterenol application were compared using the paired *t*-test. CVs for the control and isoproterenol application were compared using the Wilcoxon test. A *P* value of  $<0.05$  was considered to indicate statistical significance.

## Results

### Cell classification

Dual whole-cell patch-clamp recordings were obtained from Venus-positive GABAergic and Venus-negative Pyr cells in layer V of the IC. As previously reported, Venus-positive cells were classified as FS and non-FS cells (5,13,14). Among these GABAergic cells, FS cells are the major cell subtype that has autapses (5,15); therefore, the present study focused on FS cells rather than on non-FS cells.

FS cells were identified by their characteristic repetitive spike firing: i.e., a higher frequency of spike firing ( $>100$  Hz) than in other cell subtypes (including Pyr

cells), large and short afterhyperpolarizations, and less spike adaptation (5,13,14; Fig. 1).

### Identification of autapses

Figure 2 shows an example of a dual whole-cell recording from FS and Pyr cells. In this example, FS and Pyr cells were recorded under current- and voltage-clamp modes (holding potential,  $+10$  mV), respectively. Intracellular depolarizing current pulse injection into the FS cell induced action potentials followed by depolarizing potentials (Fig. 2B, arrowheads). In response to the action potentials in the FS cell, outward synaptic currents were observed in the Pyr cell, which were recorded using the Cs-based low  $\text{Cl}^-$  internal solution (see Materials and Methods), thereby identifying synaptic contacts from the FS to the Pyr cells.

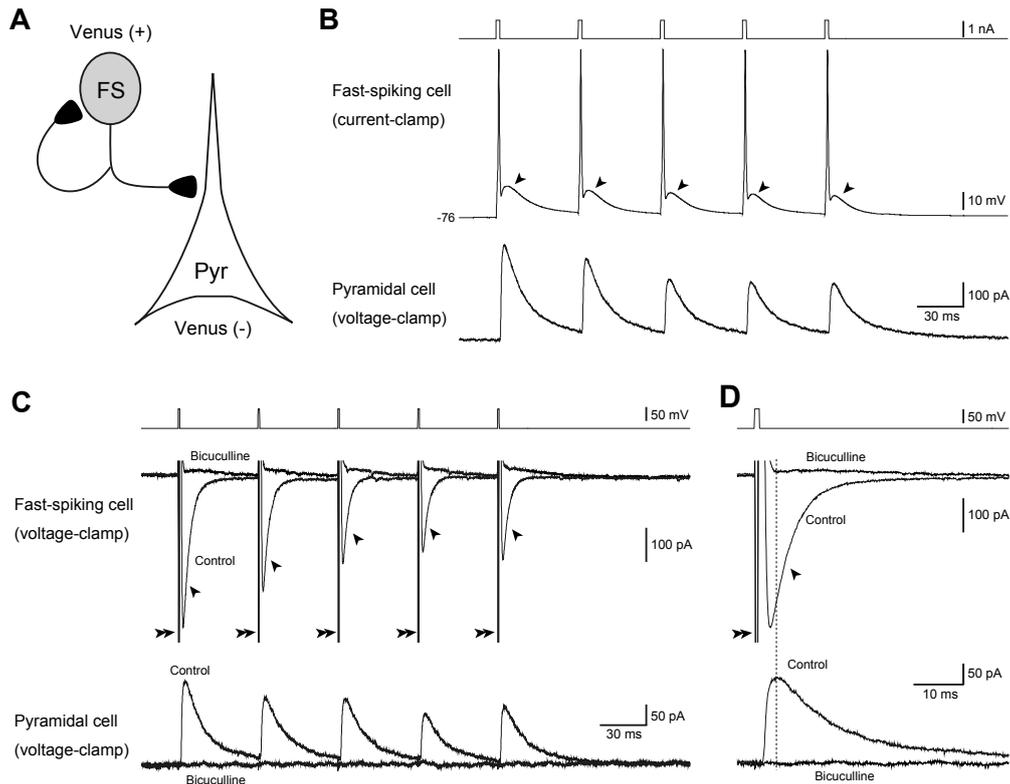
The varied amplitude of these depolarizing potentials indicated that they were mediated by synaptic transmission. The FS cell was recorded using a high concentration of  $\text{Cl}^-$ , which induced depolarizing synaptic potentials via autapses. Thus, these depolarizing potentials were likely to be mediated by autapses.

To confirm this possibility, both cells were recorded in voltage-clamp mode, and I examined whether uIPSCs in FS and Pyr cells were blocked by the  $\text{GABA}_A$  receptor antagonist bicuculline (Fig. 2C). In the FS cell, the holding potential was set at  $-70$  mV, and action currents (double arrowheads, Fig. 2D) followed by inward currents (Fig. 2CD, arrowheads) were observed in response to a depolarizing voltage pulse injection (Fig. 2C, top trace). The action currents induced uIPSCs in the Pyr cell (Fig. 2C, bottom trace). Application of  $10 \mu\text{M}$  bicuculline abolished uIPSCs in both FS and Pyr cells, indicating that these currents were mediated by  $\text{GABA}_A$  receptors.

### Effects of isoproterenol on inhibitory synaptic transmission

To examine the effects of a  $\beta$ -adrenoceptor agonist on uIPSCs obtained from FS autapses,  $100 \mu\text{M}$  isoproterenol was bath-applied. Dual recordings were obtained from FS and Pyr cells that exhibited FS autapses and FS $\rightarrow$ Pyr connections, and profiles of isoproterenol-dependent modulation of autaptic uIPSCs were compared with those from FS $\rightarrow$ Pyr connections.

Figures 3A and B show an example of isoproterenol-induced synaptic facilitation in an FS autapse, accompanied by a decrease in uIPSC amplitude of the FS $\rightarrow$ Pyr connection. The increase in the amplitude of autaptic uIPSCs was prominent in the first event, and the third to fifth autaptic uIPSCs were less affected by isoproterenol, suggesting that isoproterenol-induced



**Fig. 2** uIPSC recording from an FS and Pyr cell pair. **A:** Scheme for dual recording from an FS and Pyr cell pair. **B:** uIPSCs recorded from a postsynaptic Pyr cell (bottom) in response to presynaptic action potentials (middle) evoked by depolarizing current pulse injection (top) to FS cells in **A**. Five pulses were applied to the presynaptic cell at 20 Hz. Note the depolarizing humps (arrowheads) mediated by autapses. The presynaptic FS cell and postsynaptic Pyr cell were recorded under current- and voltage-clamp conditions, respectively. The holding potential of the postsynaptic cell was 0 mV. **C:** Bath-application of bicuculline (10  $\mu$ M) completely blocked uIPSCs in the FS autapses (arrowheads) and the FS $\rightarrow$ Pyr connection. The presynaptic FS cell and postsynaptic Pyr cell were recorded under voltage-clamp conditions. **D:** Time-expanded traces of the first uIPSCs, shown in **C**. The FS cell induced action current (double arrowheads) followed by an autaptic uIPSC (arrowhead). In the Pyr cell, uIPSC was elicited by presynaptic action current. The latency of the uIPSC peak in FS was shorter than that in the Pyr cell.

facilitation of the autapse is likely mediated by presynaptic mechanisms.

Figures 3C and D show another example of simultaneous recording of FS autapse and FS $\rightarrow$ Pyr connection. This pair shows isoproterenol-induced synaptic facilitation in the FS autapse, without change in the first uIPSC amplitude of the FS $\rightarrow$ Pyr connection. Similar to the pair shown in Figs. 3A and B, the amplitude increase in the autaptic uIPSCs was prominent in the first event.

### Isoproterenol-induced facilitation of autapses accompanies increases in PPR and CV

As previously reported (5), FS $\rightarrow$ Pyr connections showed pleiotropic modulation of uIPSC amplitude: facilitation in 4 of 9 pairs, suppression in 4 of 9 pairs, and no effect in 1 of 9 pairs (Fig. 4A). In contrast, FS autapses showed relatively consistent facilitation by isoproterenol ( $129.1 \pm 10.6\%$ ;  $n = 9$ ;  $P < 0.05$ , paired *t*-test). Isoproterenol-induced facilitation of autaptic uIPSCs was partially

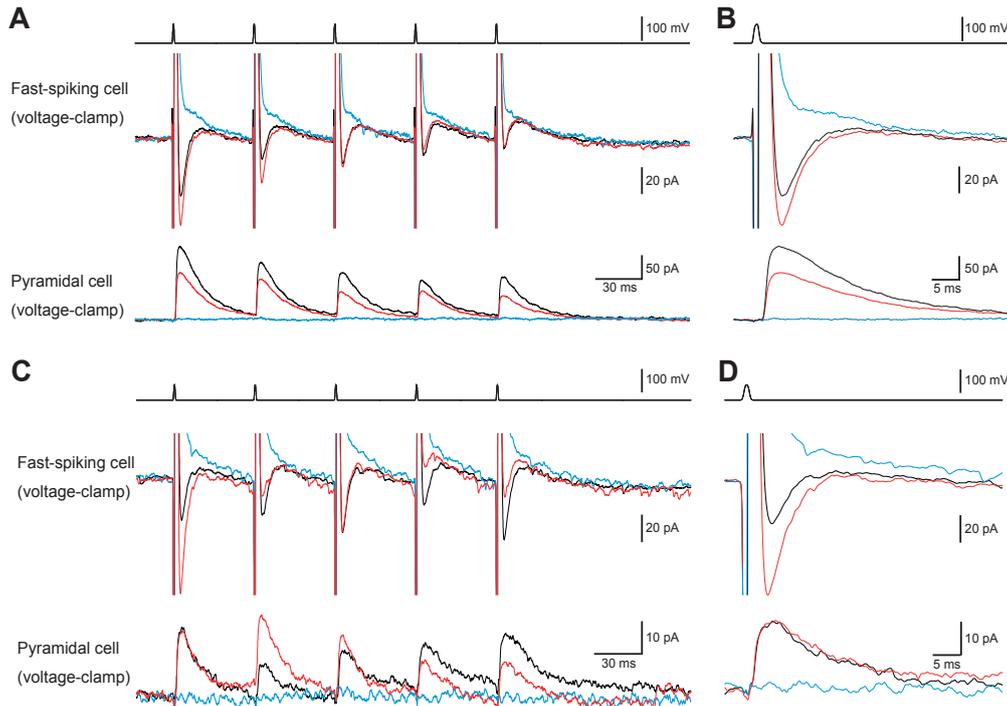
recovered by a 10-min washout (Fig. 4B).

The facilitation of autaptic uIPSCs by isoproterenol was accompanied by decreases in PPR ( $0.73 \pm 0.04$  to  $0.62 \pm 0.04$ ;  $n = 9$ ;  $P < 0.01$ , paired *t*-test) and CV ( $0.35 \pm 0.10$  to  $0.16 \pm 0.03$ ,  $n = 9$ ;  $P < 0.01$ , Wilcoxon test), which suggests that presynaptic mechanisms are involved in isoproterenol-induced facilitation of autapses.

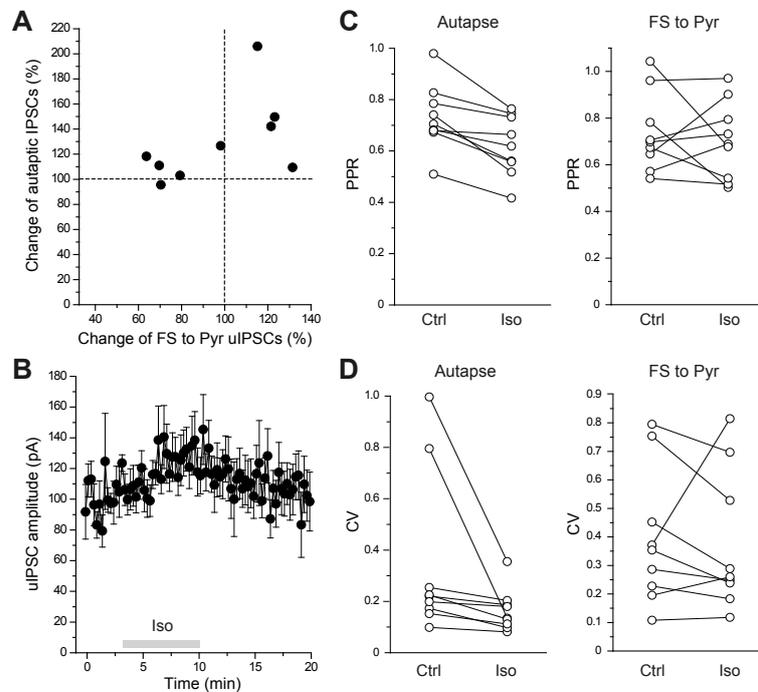
## Discussion

The principal findings of this study are that 1) isoproterenol consistently increased the amplitude of uIPSCs obtained from FS autapses, 2) this facilitation was accompanied by decreases in PPR and CV, and 3) the simultaneously recorded FS $\rightarrow$ Pyr connections showed pleiotropic modulation of uIPSC amplitude by isoproterenol. In sum, these findings suggest that FS autapses have intrinsic mechanisms of GABA release that differ from those of FS $\rightarrow$ Pyr connections.

Isoproterenol-induced facilitation of uIPSCs in FS



**Fig. 3** Facilitative effects of isoproterenol on autaptic uIPSCs obtained from FS cells. **A:** An example of the effects of 100  $\mu$ M isoproterenol on five consecutive autaptic (middle) and FS $\rightarrow$ Pyr uIPSCs (bottom). The averages of 10 traces in control (black) and during application of isoproterenol (red) and 10  $\mu$ M bicuculline (blue) are shown. Note facilitation of autaptic uIPSC amplitude by isoproterenol, in contrast to suppression of uIPSCs in the FS $\rightarrow$ Pyr connection. **B:** Time-expanded traces of the first uIPSCs in **A**. **C:** Another example of the effects of 100  $\mu$ M isoproterenol on autaptic (middle) and FS $\rightarrow$ Pyr uIPSCs (bottom). Note facilitation of autaptic uIPSC amplitude by isoproterenol without effect on uIPSCs in the FS $\rightarrow$ Pyr connection. **D:** Time-expanded traces of the first uIPSCs in **C**.



**Fig. 4** Profiles of isoproterenol-induced facilitation of autaptic uIPSCs. **A:** Changes in autaptic uIPSC amplitude by isoproterenol, normalized with control values, are plotted against changes in uIPSC amplitude in FS $\rightarrow$ Pyr connections. **B:** Time course of the amplitude of autaptic uIPSCs before, during, and after 100  $\mu$ M isoproterenol application ( $n = 9$ ). **C:** PPR in control and during isoproterenol application in autapses and FS $\rightarrow$ Pyr connections. **D:** CV in control and during isoproterenol application in autapses and FS $\rightarrow$ Pyr connections.

autapses was accompanied by decreases in CV and PPR, suggesting modulation of presynaptic GABA release mechanisms.  $\beta$ -Adrenoceptors are coupled to Gs proteins, which activate cAMP-dependent protein kinase (PKA) and its downstream signaling pathways, including p42/p44 mitogen-activated protein kinase (MAPK). These kinases facilitate glutamate release from presynaptic terminals in the cerebral cortex (9), and similar mechanisms may therefore be involved in FS autapses.

It is worth noting that isoproterenol often had contradictory effects on uIPSCs in the same FS cell, as shown in Figs. 3A and B. This suggests that presynaptic terminals are not homogeneously regulated by  $\beta$ -adrenoceptors. A possible explanation for the different profiles for isoproterenol-induced uIPSC modulation is variability in  $\text{Ca}^{2+}$  channel subtypes. At present, however, controversy remains regarding the types of voltage-gated calcium channels (VGCCs) that exist in FS interneuronal synaptic terminals. It is reported that cortical FS GABAergic terminals exhibit only P/Q-type  $\text{Ca}^{2+}$  channels (16), similar to those in the hippocampus (17). In contrast, Ali and Nelson (18) reported that N-type  $\text{Ca}^{2+}$  channels play a critical role in releasing GABA in FS cells in the cerebral cortex. Further study of  $\text{Ca}^{2+}$  channel distribution in FS cells including FS autapses will help elucidate the mechanisms of divergence of GABAergic synaptic responses.

Autapses in FS cells regulate their own neural activities: they suppress spike firing by hyperpolarizing the membrane potential (6). Enhancement of autaptic uIPSCs by isoproterenol may contribute to further suppression of FS neuronal activities. In addition, autapses have a critical role in regulating the precision of spike-timing in FS and Pyr cells (19). This autaptic mechanism of spike firing is essential for well-timed spike firing in the presence of synaptic noise. The present results suggest that noradrenaline controls spike-timing via  $\beta$ -adrenoceptors, which may increase output from layer V Pyr cells.

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