Abstract: The α1-adrenoceptor agonist phenylephrine and the β-adrenoceptor agonist isoproterenol have opposite effects on evoked EPSPs (eEPSPs) in the cerebral cortex. The suppressive effects of phenylephrine on eEPSPs are mediated by modulation of postsynaptic glutamate receptors, whereas enhancement of eEPSPs by isoproterenol is due to facilitation of glutamate release from presynaptic terminals. The present study used whole-cell patch-clamp recordings from layer V pyramidal neurons in visuocortical slice preparations to assess the effects of phenylephrine and isoproterenol on the release probability of γ-aminobutyric acid (GABA). The present study recorded evoked inhibitory postsynaptic potentials (eIPSCs) by repetitive electrical stimulation (duration, 100 μs; 10 stimuli at 33 Hz) and miniature IPSCs (mIPSCs). The effects of phenylephrine (100 μM) depended on the amplitude of eIPSCs: phenylephrine decreased the paired-pulse ratios (PPRs) of eIPSCs with smaller amplitudes (<~600 pA) but increased PPRs of eIPSCs with larger amplitude. Phenylephrine also exhibited amplitude-dependent modulation of mIPSCs, i.e., an increase in the frequency of smaller mIPSC events (<~20 pA) and a decrease in the frequency of larger events. These findings suggest that α1-adrenoceptor activation facilitates GABA release from a subpopulation of GABAergic terminals that induce smaller-amplitude IPSCs in postsynaptic neurons. In contrast, isoproterenol (100 μM) consistently decreased the PPR of eIPSCs and increased the frequency of mIPSCs, suggesting that presynaptic β-adrenoceptors increase release probability from most GABAergic terminals. The complexity of adrenoceptor modulations in GABAergic synaptic transmission by α1-adrenoceptor and β-adrenoceptor activation may be due to the presence of pleiotropic subtypes of GABAergic interneurons in the cerebral cortex. (J Oral Sci 56, 49-57, 2014)

Keywords: neocortex; presynaptic; postsynaptic; whole-cell patch-clamp; visual cortex; interneuron.

Introduction

Noradrenaline contributes to physiological functions of the inhibitory system in the cerebral cortex. Komatsu and Yoshimura (1) demonstrated that noradrenaline controls the maintenance of long-term potentiation (LTP) of inhibitory postsynaptic potentials (IPSPs) in the visual cortex, which may have a role in experience-dependent refinement of visual responsiveness. In the entorhinal cortex, noradrenaline reduces epileptiform discharges induced by bicuculline, a GABA_A receptor antagonist (2). In the cerebral cortex, 10-20% of neurons are non-spiny smooth neurons, which are thought to be GABAergic (3). Anatomical studies have identified at least 19 types of smooth neurons in the cerebral cortex (4,5). Recent electrophysiological studies have revealed that GABAergic interneurons can be divided into more than four classes according to their firing properties (6). These findings indicate that GABAergic interneurons have multiple subtypes that may exhibit different electrophysiological and pharmacological responses to noradrenaline.

Activation of α1-adrenoceptors suppresses glutamate-
ergic synaptic transmission through a postsynaptic mechanism (7). Less information is available on the mechanisms of adrenergic modulation on GABAergic synaptic transmission. Regarding α-adrenergic receptor-mediated effects on IPSCs, it has been reported that epinephrine increases GABA_\_ receptor-mediated spontaneous IPSC (sIPSC) frequency through α-adrenergic receptors in rat sensorimotor cortex (8,9) and that these facilitatory effects on sIPSCs were mediated by depolarization of the resting membrane potential of several types of GABAergic interneurons via α_1-adrenoceptor activation (9). Although several studies have shown an increase in miniature IPSC (mIPSC) frequency by noradrenaline through α_1-adrenoceptors (9,10), Bennett et al. (8) reported that adrenaline has heterogeneous effects on the amplitude of evoked IPSCs (eIPSCs), i.e. an enhancement of eIPSCs in ~33% of pyramidal neurons and a decrease in ~40% of neurons, suggesting pleiotropic modulation of inhibitory synaptic transmission by α_1-adrenoceptors agonists. The reason for these seemingly conflicting findings remains to be identified.

β-Adrenergic receptor agonists presynaptically facilitate glutamate release in the neocortex (11-14), and activation of β-adrenoceptors induces depolarization of the resting membrane potential or blockade of spike accommodation, with an increase in firing frequency (7,15-17). However, little is known of the effects of β-adrenoceptor activation on inhibitory synaptic transmission in the cerebral cortex.

To elucidate the presynaptic mechanism of IPSC modulation via β-adrenoceptors, the present study used whole-cell patch-clamp recordings from layer V pyramidal neurons in rat visuocortical slice preparations to examine eIPSCs and mIPSCs and found that phenylephrine and isoproterenol, α_1- and β-adrenoceptor agonists, respectively, had differing effects on the properties of eIPSCs and mIPSCs.

**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 the Institutional Animal Care and Use Committee of the Nihon University School of Dentistry (AP10-D004-1). All efforts were made to minimize the number and suffering of animals used.

**Slice preparations**

Male and female Sprague-Dawley rats (age, 14-35 postnatal days) were used for whole-cell patch-clamp recording. Sodium pentobarbital (75 mg/kg, i.p.) was applied to anesthetize the animals. After decapitation, tissue blocks including the visual cortex 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_4, 1.25 NaHPO_4, 26 NaHCO_3, 2.5 CaCl_2, and 10 D-glucose. Coronal slices (thickness, 350 μm) were cut using a microslicer (Linearslicer Pro 7, Dosaka EM, Kyoto, Japan) and 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_4, 1.25 NaHPO_4, 26 NaHCO_3, 2.0 CaCl_2, 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_2 / 5% CO_2. Slices were thereafter maintained at room temperature until used for recording.

**Whole-cell patch clamp recording**

After more than 1-h incubation in a submersion-type holding chamber, the slices were transferred to a recording chamber that was continuously perfused with normal ACSF (humidified with 95% O_2 / 5% CO_2) at a rate of 1-1.5 mL/min. Whole-cell patch-clamp recordings were obtained from pyramidal cells identified in layer V with Nomarski optics (~40, Olympus BX51, Tokyo, Japan) and an infrared-sensitive video camera (Hamamatsu Photonics, Hamamatsu, Japan). Electrical signals were recorded by an amplifier (Axoclamp 200B, Axon Instruments, Foster City, CA, USA), digitized (Digidata 1322A, Axon Instruments), observed online, and stored on a computer hard disk using Clampex 9 software (Axon Instruments). The composition of the pipette solution for voltage-clamp recordings was (in mM) 120 cesium gluconate, 20 bicucullin, 10 N-(2-hydroxyethyl)piperazine-N’-2-ethanesulfonic acid (HEPES), 8 NaCl, 5 N-(2,6-dimethylphenyl carbamoylmethyl)triethylammonium bromide (OX-314), 2 magnesium adenosine triphosphate (ATP), 0.3 sodium guanosine triphosphate (GTP), and 0.1 1,2-bis(2-aminophenoxy)ethane-N,N,N’,N’-tetraacetic acid (BAPTA). Pipette solutions had a pH of 7.3 and an osmolarity of 300 mOsm. The liquid junction potential for voltage-clamp recordings was 10 mV, and all voltages were corrected accordingly. Thin-wall borosilicate patch electrodes (2-4 MΩ; diameter, 1.5 mm; Harvard Apparatus, Holliston, MA, USA) were pulled on a Flaming-Brown micropipette puller (P-97, Sutter Instruments, Novato, CA, USA).

Recordings were obtained from layer V pyramidal cells at 30-31°C. Seal resistance was >5 GΩ, and only data obtained from electrodes with access resistance of 8-20
MΩ and <20% change during recordings were included in this study. Series resistance was 70% compensated.

eIPSCs were recorded at a holding potential of −70 mV under application of 6,7-dinitroquinoxaline-2,3-dione (DNQX, 30 μM) and D(-)-2-amino-5-phosphonopentanoic acid (D-APV, 50 μM). For induction of eIPSCs, a train of 10 rectangle pulses (100 μs) was applied at 33.3 Hz through a unipolar tungsten electrode placed at the border of layers IV/V. Stimulation intensity was set at 1.2-1.5 times the threshold (4-20 μA). mIPSCs were recorded at 0 mV under application of 1 μM tetrodotoxin (Wako, Tokyo, Japan), 30 mM DNQX, and 50 μM D-APV.

The following drugs were directly added to the perfusate: bicuculline methiodide (10-20 μM, Tocris Cookson, Bristol, UK), isoproterenol (100 μM, Research Biochemicals International, Natick, MA), and phenylephrine (100 μM, Sigma-Aldrich, St. Louis, MO, USA).

Histology
To visualize biocytin-labeled neurons after whole-cell patch-clamp recording, slices were fixed, cryoprotected, and sectioned (60 μm). Sections were then processed using the ABC method (Vector Laboratories, Burlingame, CA, USA) and nickel-intensified diaminobenzidine as the chromogen. The slices were examined with a microscope to verify their morphology and location. All chemicals were purchased from Sigma-Aldrich, unless otherwise specified.

Data analysis
Membrane currents and potentials were low-pass filtered at 1-2 kHz and digitized at 4-8 kHz. eIPSCs and GABA-induced currents were analyzed with Clampfit (pClamp 9, Axon Instruments). mIPSCs were automatically detected by custom software (kindly provided by Dr. J. Huguenard), using the second derivative of the current traces as the trigger (18). Threshold values were set at three times the standard deviation of baseline noise amplitude. For every recording, we visually checked at least 10% of the file, to determine whether the software accurately detected events. Over 95% of the visually identified events were detected by the software, and false-positives accounted for <1% of the events detected by the software. Threshold values for mIPSCs recorded in normal ACSF were 6.8 ± 0.3 pA (n = 26). mIPSC frequency was measured from continuous recordings that were at least 2 min in duration.

Data are presented as mean ± standard error of the mean (SEM). eIPSCs between control and drug application were compared by using the paired t-test. The inter-event interval and amplitude of mIPSCs were analyzed by nonparametric statistical analysis (Kolmogorov-Smirnoff [K-S] test), to assess the significance of shifts in cumulative probability distributions of the control and drug applied condition. The paired t-test was also used to compare average mIPSCs amplitude, inter-event interval, and 10-90% rise time. A P value <0.05 was considered to indicate statistical significance on the paired t-test, and a P value <0.01 was considered to indicate significance on the K-S test.

Results

Properties of eIPSCs
The present study first examined the effects of α₁- and β-adrenoceptor agonists on GABAergic synaptic transmission by recording eIPSCs in the presence of 40 μM DNQX, a non-NMDA receptor antagonist, and 50 μM
D-APV, an NMDA receptor antagonist (holding potential = 0 mV). Repetitive electrical stimulation (duration, 100 μs; 10 stimuli at 33 Hz) was applied through a unipolar tungsten electrode 50-100 μm toward the pial surface from the recorded cell in layer V. eIPSCs were abolished by bath application of 10 μM bicuculline methiodide, indicating that they were mediated by GABA A receptors (n = 3, Fig. 1A). In 16 of 31 cells (51.6%), eIPSCs exhibited paired-pulse depression (PPD); the other cells (15/31 cells, 48.4%) showed paired-pulse facilitation (PPF). There was no significant correlation between the amplitude of first eIPSCs and the PPR of the second eIPSC amplitude to first eIPSC amplitude, as shown in Fig. 1B (R = −0.17, P > 0.3). The effects of phenylephrine and isoproterenol on PPR had little correlation with short-term plasticity, i.e., PPD or PPF. Therefore, both groups of cells were included in the subsequent analyses.

**Multiple effects of phenylephrine on eIPSCs**

Bath application of 100 μM phenylephrine induced inconsistent effects on the amplitude of the first eIPSC (a) and larger amplitude of the first eIPSC (b), under application of 40 μM DNQX and 50 μM D-APV. Ten traces were averaged. Phenylephrine decreased the amplitude of most second to 10th eIPSCs in a, and increased the amplitude of second to 10th eIPSCs in b. The right panels of a and b show time-expanded traces of first and second eIPSCs. Black and red lines indicate traces obtained from control and phenylephrine conditions, respectively. B. Normalized amplitude of first eIPSC amplitude under 100 μM phenylephrine application was plotted against the first eIPSC amplitude in control. No correlation was seen (n = 12). C. Ratio of PPRs of the first and second eIPSCs during phenylephrine application divided by PPRs in control was plotted against the first eIPSC amplitude in control (n = 12). There is a significant positive correlation (r = 0.72, P < 0.01).
amplitude of the first eIPSCs (93.9 ± 6.4% of control, n = 12). There was little correlation between the amplitude of first eIPSCs and the effects of phenylephrine on them (Fig. 2B). The PPR of synaptic responses is associated with presynaptic manipulations of transmitter release but remains unaltered after postsynaptic manipulation of synaptic transmission (19,20). In the present study, phenylephrine had variable effects on PPR (second eIPSC amplitude / first eIPSC amplitude), similar to its effect on the first eIPSC amplitude, and the overall PPR was 0.80 ± 0.12 in control and 0.80 ± 0.13 (n = 12) during phenylephrine application. There was a significant correlation between the first eIPSC amplitude and phenylephrine-induced change in PPR (Fig. 2C): i.e., phenylephrine tended to decrease the PPR of eIPSCs with smaller amplitudes (Fig. 2Aa) and increase PPR at larger amplitudes (Fig. 2Ab).

Isoproterenol suppresses the PPR of eIPSCs

Similar to phenylephrine, isoproterenol (100 μM) had inconsistent effects on the first eIPSC amplitude. The first eIPSC amplitude was significantly increased in 3 of 19 neurons (15.8%; 21.8% increase in amplitude), decreased in 2 of 19 neurons (10.5%; 21.5% decrease in amplitude), and unchanged in the remaining 14 of 19 neurons (73.7%). Overall, isoproterenol had little effect on the average amplitude of the first eIPSCs (102.2 ± 5.0% of control, n = 19). There was little correlation between the first eIPSC amplitude and the effects of isoproterenol on them (Fig. 3B). In contrast, isoproterenol significantly suppressed PPR, from 1.14 ± 0.14 in control to 1.02 ± 0.12 (n = 18, P < 0.02, paired t-test). There was no significant correlation between first eIPSC amplitude and isoproterenol-induced change in PPR (Fig. 3C).

Both phenylephrine and isoproterenol increased mIPSC frequency and decreased mIPSC amplitude

To examine the effects of phenylephrine and isoproterenol on inhibitory synaptic transmission, the present study examined mIPSCs from layer V pyramidal neurons under application of 1 μM tetrodotoxin, 40 μM DNQX, and 50 μM D-APV (holding potential = 0 mV). Bath application of bicuculline methiodide (10 μM) diminished mIPSCs,
which suggests that mIPSCs were generated by activation of GABA\textsubscript{A} receptors (data not shown).

Figures 4A and B show a representative example of the effects of phenylephrine on mIPSCs. Cumulative amplitude and inter-event interval distribution were obtained by pooling 150 events from each of nine pyramidal neurons (number of total events, 1350) before and during phenylephrine application. Bath application of 100 μM phenylephrine significantly decreased the inter-event interval of mIPSCs (P < 0.001, K-S test). The mean inter-event interval of mIPSCs was 0.70 ± 0.19 s in control and was decreased to 0.50 ± 0.12 s by phenylephrine application (n = 9, P < 0.05, paired t-test; Fig. 4D). Phenylephrine suppressed mIPSC amplitude (n = 9, P < 0.001, K-S test). The mean amplitude of mIPSCs was significantly decreased by phenylephrine (15.4 ± 1.3 pA in control and 13.6 ± 1.0 pA under phenylephrine application, n = 9, P < 0.01, paired t-test; Fig. 4D). The effect of phenylephrine on 10-90% rise time was not significant (1.27 ± 0.11 to 1.29 ± 0.11 ms, n = 9, Fig. 4F). The half-duration of mIPSCs was also unaffected by phenylephrine (15.3 ± 1.2 to 15.1 ± 1.4 μs, n = 9). These results suggest that phenylephrine increases GABA release from inhibitory presynaptic terminals while slightly decreasing GABA\textsubscript{A} receptor-mediated synaptic currents by activating \alpha\textsubscript{1}-adrenoceptor receptors on the postsynaptic membrane.

Representative examples of isoproterenol are shown in Figs. 5A and B. Cumulative amplitude and inter-event interval distribution were obtained by pooling 150 events from each of eight pyramidal neurons (number of total events, 1,200) before and during isoproterenol application. Isoproterenol significantly decreased the inter-event interval of mIPSCs (P < 0.05, K-S test). The mean inter-event interval of mIPSCs in control (0.45 ± 0.16 s) was significantly decreased by isoproterenol (0.34 ± 0.11 s, n = 8, P < 0.05, paired t-test; Fig. 5D), and isoproterenol decreased the amplitude of mIPSCs (P < 0.01, K-S test). The mean amplitude of mIPSCs in control was 17.9 ± 2.0 pA and was significantly decreased by isoproterenol, to 16.3 ± 1.4 pA (n = 8, P < 0.05, paired t-test; Fig. 5D). Isoproterenol had little effect on 10-90% rise time (1.18 ± 0.03 to 1.16 ± 0.30 μs, n = 8; Fig. 5D) and half-duration (15.5 ± 1.2 to 15.5 ± 1.4 μs, n = 8). These findings suggest that isoproterenol facilitates GABA release from presynaptic terminals but decreases GABA\textsubscript{A} receptor-mediated synaptic currents.

**Differential modulation of mIPSC frequency between phenylephrine and isoproterenol**

Both phenylephrine and isoproterenol increased mIPSC frequency, as shown in Figs. 4 and 5. However, the profiles of changes in frequency by phenylephrine and isoproterenol differed in their details. Population histograms of mIPSC amplitude were obtained from pooling events used to plot the cumulative probability curves shown in Figs. 4C and 5C. As shown in Fig. 6A, phenylephrine increased mIPSC events with smaller amplitudes (6-18 pA) and decreased larger mIPSC events (22-50 pA). Similar to the effects of phenylephrine, isoproterenol increased smaller mIPSC events (6-14 pA; Fig. 6B). However, it had only marginal effects on larger events.
The principal findings of this study are that: 1) phenylephrine decreased the PPR of eIPSCs with smaller amplitude but decreased PPR at larger amplitude, 2) isoproterenol consistently decreased the PPR of eIPSCs, 3) both phenylephrine and isoproterenol decreased mIPSC amplitude, and 4) phenylephrine increased the frequency of smaller mIPSC events, with a decrease in larger events, while isoproterenol increased the frequency of mIPSCs with smaller amplitudes and had little effect on larger events. These findings suggest that the modulatory mechanisms of phenylephrine on glutamatergic and GABAergic synaptic transmission differ in several ways, as discussed below.

α1-Adrenoceptors in presynaptic terminals
Regarding α-adrenergic receptor-mediated effects on IPSCs, it has been reported that adrenaline increases the frequency of GABA_A receptor-mediated spontaneous IPSCs (sIPSCs) through presynaptic α-adrenergic
receptors in rat sensorimotor cortex (8). Kawaguchi and Shindou (9) reported an increase in sIPSC frequency by $\alpha_1$-adrenoceptor activation in rat frontal cortex and extended this finding by demonstrating that the $\alpha_1$-adrenoceptor agonist 6-fluoronoephrine depolarizes the resting membrane potential of several types of GABAergic interneurons, a phenomenon that is frequently accompanied by spike discharges. These findings indicate that noradrenaline-induced increase of sIPSCs is mediated by its excitatory effect on interneurons.

Although several studies reported that the presynaptic $\alpha_1$-adrenoceptors are the $\alpha_1$ type (21), the present study showed an increase in mIPSC frequency by phenylephrine, suggesting that $\alpha_1$-adrenoceptors are present in GABAergic presynaptic terminals. Some studies showed an increase of mIPSC frequency by noradrenaline via $\alpha_1$-adrenoceptors in the frontal (9) and entorhinal cortices (10). A recent immunoelectron microscopic study supports the hypothesis that $\alpha_1$-adrenoceptors are present in the presynaptic terminals: a small number of immuno-reaction products of $\alpha_1$-adrenoceptors were detected in axons and presynaptic sites, in addition to postsynaptic regions such as the soma and dendrites, in rat visual cortex. Taken together these findings indicate that it is likely that $\alpha_1$-adrenoceptors exist not only in the postsynaptic sites, but also in presynaptic terminals, and that these receptors have a facilitatory role in GABA release.

The above view of presynaptic $\alpha_1$-adrenoceptors suggests a question: is the effect of activating presynaptic $\alpha_1$-adrenoceptors homologous regardless of the multiple types of GABAergic neurons? GABAergic interneurons in the cerebral cortex can be divided into at least three main categories by their electrophysiological firing properties, namely, fast-spiking (FS) cells, late-spiking (LS) cells, and low-threshold-spiking (LTS) cells (6,22). FS cells, which display abrupt firing discharge with little adaptation, induced larger unitary IPSCs (uIPSCs) in amplitude (22), and their axons mainly project to the soma or proximal dendrites (22). However, LTS cells, which are characterized by low-threshold spikes or rebound spikes after hyperpolarizing current pulse injections, induced smaller uIPSCs, and their axons innervate to distal dendrites (22,23). The present eIPSC recordings showed that phenylephrine decreased the PPR of eIPSCs at smaller amplitudes but increased the PPR at larger amplitudes (Fig. 2). The PPR of synaptic responses is associated with presynaptic manipulations of transmitter release but remains unaltered after postsynaptic manipulation of synaptic transmission (19,20). Therefore, it is likely that phenylephrine increases the release probability of GABAergic terminals in sites distal from a recording electrode and decreases the release probability of terminals in proximal dendrites or soma. This hypothesis is supported by the present findings of mIPSC recordings, which showed that phenylephrine increases the frequency of smaller mIPSC events, with a decrease of larger events (Fig. 6), and may explain the heterogeneous effects of adrenaline on eIPSC amplitude (Fig. 2) (8). Phenylephrine may decrease the amplitude of eIPSCs that are mainly composed of GABAergic fibers terminating at proximal dendrites or somata, while eIPSCs evoked by stimulation of fibers projecting to distal dendrites may be less affected or increased by phenylephrine.

**Presynaptic facilitation of GABA release by $\beta$-adrenoceptor agonist**

A previous whole-cell patch-clamp study found that activation of presynaptic $\beta$-adrenoceptors facilitates glutamate release from presynaptic terminals in rat prefrontal cortex (13), which was confirmed in a study of the rat visual cortex (7). These results agree with anatomical evidence of presynaptic localization of $\beta$-adrenoceptors (24) and with studies that show glutamate release by $\beta$-adrenoceptor activation in preparations of cerebrocortical synaptosomes (11,12). However, little information is available on $\beta$-adrenoceptor–mediated GABA release in the cerebral cortex. The present results on PPR reduction and the increase in mIPSC frequency by isoproterenol suggest that GABA release is facilitated by activation of $\beta$-adrenoceptors. In contrast to the effects of phenylephrine, isoproterenol tended to decrease PPR across a broader range of eIPSC amplitude (Fig. 3C). In consideration of the decrease in mIPSC amplitude, the decreased effect of isoproterenol on large-amplitude mIPSCs (>20 pA) may be due to increased release probability of the terminals on proximal dendrites and somata.

**Functional implications**

The present study suggests that both $\alpha_1$- and $\beta$-adrenoceptors in presynaptic terminals contribute to facilitate GABA release from, at least, a subpopulation of GABAergic interneuron terminals. However, activation of $\alpha_1$-adrenoceptors had little effect on glutamate release, although $\beta$-adrenoceptor activation facilitated glutamate release. These findings suggest the presence of varying mechanisms for modulating neurotransmitter release in the cerebral cortex. Indeed, several important proteins involved in neurotransmitter release machinery, such as synapsin, synaptophysin, and synaptosomal-associated protein (SNAP)-25, are differentially expressed in gluta-
matergic and GABAergic axon terminals in rat cerebral cortex (25). It may be that α₁- and β-adrenoceptors have different mechanisms for phosphorylating these proteins.

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