Korean J Physiol Pharmacol
Vol 7: 295–301, December, 2003

Inhibitory Modulation of 5-Hydroxytryptamine on Corticostriatal Synaptic Transmission in Rat Brain Slice

Se Joon Choi[1], Won Soon Chung[1], Ki-Jung Kim[1], and Ki-Wug Sung[1,2]

Departments of [1]Pharmacology, [2]MRC for Cell Death Disease Research Center, College of Medicine, The Catholic University of Korea, Seoul 137–701, Korea

Striatum plays a crucial role in the movement control and habitual learning. It receives an information from wide area of cerebral cortex as well as an extensive serotonergic (5-hydroxytryptamine, 5-HT) input from raphe nuclei. In the present study, the effects of 5-HT to modulate synaptic transmission were studied in the rat corticostriatal brain slice using *in vitro* extracellular recording technique. Synaptic responses were evoked by stimulation of cortical glutamatergic inputs on the corpus callosum and recorded in the dorsal striatum. 5-HT reversibly inhibited coticostriatal glutamatergic synaptic transmission in a dose-dependent fashion (5, 10, 50, and 100 μM), maximally reducing in the corticostriatal population spike (PS) amplitude to 40.1±5.0% at a concentration of 50 μM 5-HT. PSs mediated by non-NMDA glutamate receptors, which were isolated by bath application of the NMDA receptor antagonist, *d,l*-2-amino-5-phospohonovaleric acid (AP-V), were decreased by application of 50 μM 5-HT. However, PSs mediated by NMDA receptors, that were activated by application of zero Mg^{2+} aCSF, were not significantly affected by 50 μM 5-HT. To test whether the corticostriatal synaptic inhibitions by 5-HT might involve a change in the probability of neurotransmitter release from presynaptic nerve terminals, we measured the paired-pulse ratio (PPR) evoked by 2 identical pulses (50 ms interpulse interval), and found that PPR was increased (33.4±5.2%) by 5-HT, reflecting decreased neurotransmitter releasing probability. These results suggest that 5-HT may decrease neurotransmitter release probability of glutamatergic corticostriatal synapse and may be able to selectively decrease non-NMDA glutamate receptor-mediated synaptic transmission.

Key Words: Striatum, 5-Hydroxytryptamine, Population spike, Synaptic transmission, Depression

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter or neuromodulator in the central nervous system (CNS) and in the peripheral nervous system. Within the brain, 5-HT neurons originate primarily in the raphe nuclei of the brainstem, and they send projections to most parts of the brain (Azmitia & Whitaker-Azmitia, 1991). 5-HT has been shown to have numerous different physiological actions in the brain, and this is not surprising, because of the nature of the 5-HT neuronal system and the variety of different 5-HT receptors (Barnes & Sharp, 1999). Many studies have shown an important role of 5-HT played in the function of both the peripheral and central nervous systems, including sensory and motor regulation, cortical function, and emotional and mental illness, such as depression, schizophrenia, generalized anxiety disorder, and obsessive compulsive disorder (Jones & Blackburn, 2002). 5-HT is known to interact with other neurotransmitter systems through intracellular mechanisms or receptor interaction, and the literature is particularly rich with publications on the interactions of 5-HT systems with dopaminergic systems (Lieberman et al, 1998). 5-HT receptors comprise a complex family. On the basis of their pharmacology, signal transduction mechanisms and molecular structure, more than a dozen types of 5-HT receptors have been identified. With the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel, 5-HT receptors belong to the G-protein coupled receptor (GPCR) superfamily, and they together with at least 14 distinct members represent one of the most complex families of neurotransmitter receptor. Multiple 5-HT receptor subtypes are expressed in the striatum, and histochemical studies have shown that 5-HT_1, 5-HT_2 and 5-HT_3, 5-HT_6 receptors are abundant in the striatum (Barnes & Sharp, 1999).

The neostriatum (caudate and putamen) is involved in the control of movement (Groves, 1983; Graybiel et al, 1994; Mink, 1996), and it appears that certain forms of learning and memory involve changes in neostriatal function (Jog et al, 1999). The major excitatory input to the neostriatum arises from neurons in the neocortex that uses glutamate as a neurotransmitter (Graybiel, 1990; Parent, 1990). Synaptic transmission at corticostriatal synapses is mediated by

Corresponding to: Ki-Wug Sung, Department of Pharmacology, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Seocho-gu, Seoul 137-701, Korea. (Tel) 02-590-1204, (Fax) 02-536-2485, (E-mail) sungkw@cmc.cuk.ac.kr

ABBREVIATIONS: aCSF, artificial cerebrospinal fluid; AP-V, *d,l*-2-amino-5-phosphnovaleric acid; CNS, central nervous system; 5-HT, 5-hydroxytryptamine; NBQX, 2,3-dioxo-6-nitro1,2,3,4-tetrahydrobenxo[f]quinoxaline-7-sulfonamide; NMDA, N-methyl-D-aspartate; PPR, paired-pulse ratio; PS, population spike.

AMPA receptors with very little involvement of NMDA receptors (Herrling, 1985; Cherubini et al, 1988; Lovinger et al, 1993).

Electrophysiological studies showed that 5-HT modulates synaptic transmission in various brain regions (Singer et al, 1996; Roerig et al, 1997; Zhou & Hablitz, 1999; Mlinar et al, 2001; Rammes et al, 2001). Singer et al. (1999) reported that 5-HT modulates glutamatergic synaptic transmission via presynaptic mechanism in motoneurons, and Roerig et al. (1997) suggested that fast postsynaptic transmission mediated by nicotinic acetylcholine receptors and 5-HT_3 receptors might be important during development in visual cortex. However, it is still unclear how 5-HT modulates corticostriatal synaptic transmission in striatum. Therefore, using *in vitro* extracellular recording technique in corticostriatal slice, we studied modulatory mechanism of 5-HT on corticostriatal glutamatergic synaptic transmission.

METHODS

Slice preparation

Brain slices were prepared from 15- to 25-day-old Sprague Dawley rats using previously described technique (Sung et al, 2001). Rats were killed by decapitation, and brains were quickly removed and placed in ice-cold, modified artificial CSF (aCSF) containing (in mM) 194 sucrose, 30 NaCl, 4.5 KCl, 1 $MgCl_2$, 26 $NaHCO_3$, 1.2 NaH_2PO_4, 10 D-glucose and pH adjusted to 7.4 by bubbling with 95% O_2/5% CO_2. The brain which contains the cerebral cortex and striatum was sectioned coronally (400 μm thick) with manual vibratome (Campden Instrument, Loughborough, UK). Brain slices were transferred to aCSF containing (in mM) 124 NaCl, 4.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 26 $NaHCO_3$, 1.2 NaH_2PO_4, 10 D-glucose and pH adjusted to 7.4 by bubbling with 95% O_2/5% CO_2, and allowed to equilibrate for at least 1 hour at room temperature. One hemislice containing the cortex and striatum was then transferred to a recording chamber. The slices were submerged and constantly superfused (at a flow rate of 2~3 ml/min) with aCSF constantly bubbled with 95% O_2/5% CO_2 through a peristaltic pump (Miniplus 2, Gilson, France). The temperature of the bath solution was kept at 31±1°C.

Extracellular field potential recording

All recordings were performed in the dorsolateral striatum to record population spikes (PSs) evoked by stimulation of excitatory afferents from cerebral cortex. Electrical stimuli were delivered through a bipolar, Teflon-coated tungsten electrode placed in the white matter dorsal to the striatum. Synaptically driven PSs were recorded with a glass micropipette (<1 MΩ tip resistance) filled with 0.9% saline, which was placed at a striatum 1~2 mm ventral to the stimulating electrode. The position of the recording electrode was optimized by recording responses to low frequency stimulation (0.02~0.2 ms, 0.5~1.5 mA at 0.1 Hz), and the electrode was set at the depth where the maximal PS amplitude was observed. Stimulus intensity was then adjusted to evoke a PS with amplitude approximately half of the maximum by stimulus isolator (A360, WPI, Sarasota, USA). Once a PS of half-maximal amplitude triggered by 0.05 Hz stimuli was stably maintained for 10 to 15 min, drugs were started to deliver. Field potentials were amplified 1000× using a differential AC amplifier (Model1700, A-M systems, Seattle, WA), and low-pass filtered at 5 kHz. Amplified signals were digitized using a CIO-DAS08/JR-AO interface (Measurement Computing Corporation, Middleboro, MA, USA) and stored on a computer using LTP230d program (Anderson & Collingridge, 2001). Paired-pulse responses were evoked by paired identical 2 stimuli with an inter-stimulus interval of 50 ms. Paired-pulse ratio (PPR) was calculated as the ration of the amplitude of the second PS to that of the first PS.

Drugs from stock solutions were dissolved in aCSF to their final concentrations and delivered to the recording chamber. Drug-containing solutions were allowed to equilibrate in the recording chamber for at least 3~4 min.

Data analysis

All averaged data were presented as means±SE. Amplitudes of the first 30 PSs before application of drug were averaged and defined as baseline responses, and drug responses were compared with this value. The statistical significance of changes in synaptic responses relative to baseline response amplitude was determined using a Student's paired *t*-test. The statistical criterion for significance was $P<0.05$.

RESULTS

Characterization of striatal population spike

A typical field potential is shown in Fig. 1. The characteristic field potential evoked by stimulation of corpus callosum consisted of two negative spikes. The amplitude of first spike (N1) was not changed when the stimulation intensity was increased, however, the amplitudes of second spikes (N2) were proportional to the intensity of electrical stimulation. Therefore, N1 is a presynaptic fiber volley and

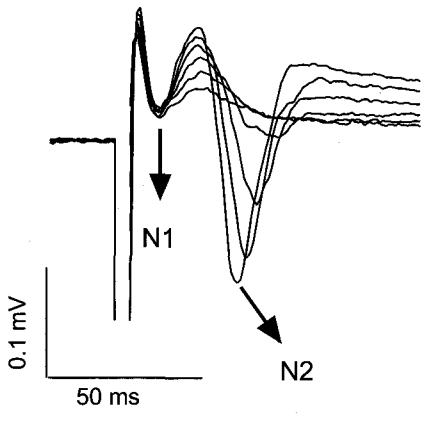

Fig. 1. Example of striatal population spike (PS) evoked by different stimulus intensity. Electrical stimulation delivered through a bipolar tungsten electrode located in corpus callosum provokes two negative-going field potential changes labeled as N1 and N2. The N1 component reflects a fiber potential and direct activation of medium spiny neurons, and N2 is a synaptically induced population spike mediated by glutamatergic synaptic transmission.

is though to correlate with the presynaptic axon stimulation or direct activation of medium spiny neurons. The second (N2) is a synaptically induced population spike. Therefore, we used N2 amplitudes to analyze population spikes that were synaptically induced by the activation of corticostriatal afferents.

Effect of 5-HT on corticostriatal synaptic transmission

As shown in Fig. 2, superfusion of 5-HT containing aCSF into the recording chamber reversibly decreased the amplitude of PS in dose dependent manner (5, 10, 50, 100 μM). At the concentration of 5 μM, the average amplitude of PS was decreased to 7.6±1.6% (n=7, $P<0.05$) of the baseline, and the average PS amplitude was decrease to 16.1±5.7% (n=6, $P<0.05$) of the baseline at 10 μM 5-HT. Further-

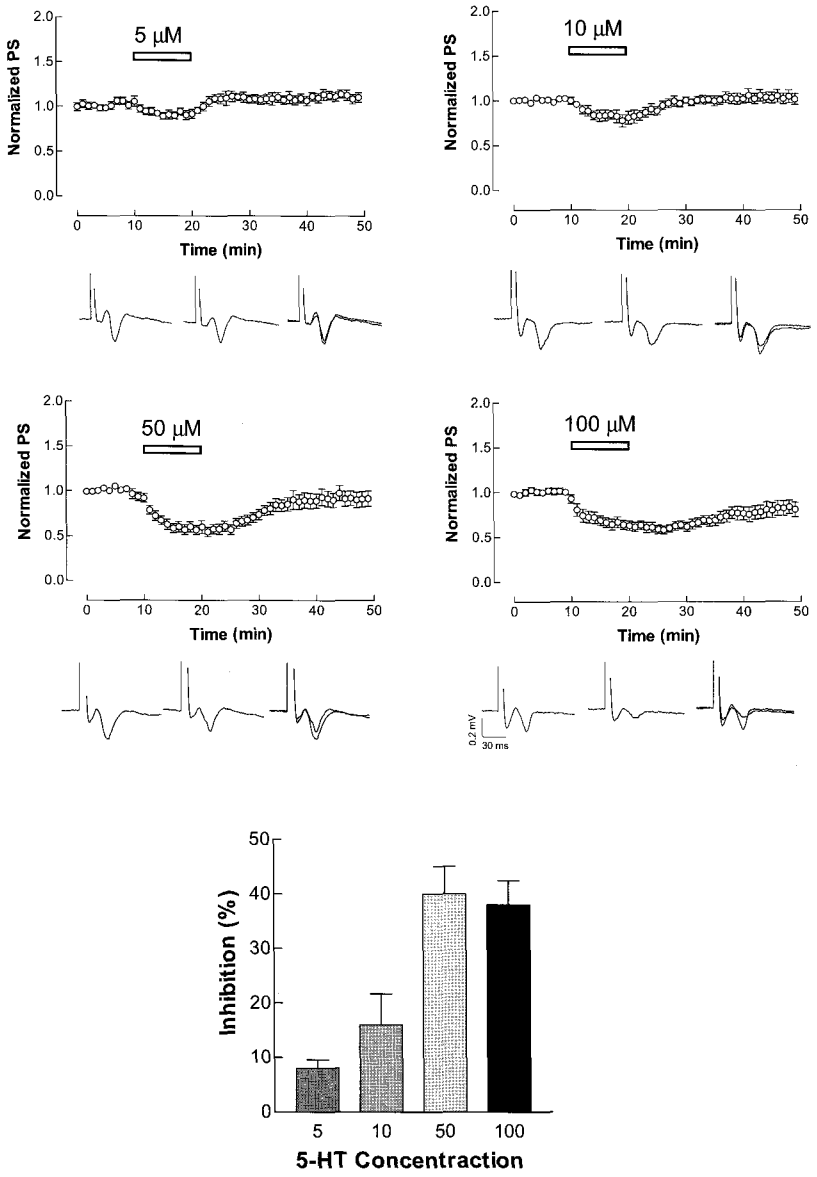

Fig. 2. 5-HT depresses corticostriatal population spikes (PSs) in a dose-dependent manner. After stable baseline was recorded under normal aCSF for 10 min, 5-HT was added for 10 min. A, B, C, D. Plotted averaged PS graph showing that increasing concentration of 5-HT (5, 10, 50, and 100 μM) increased the inhibition of corticostriatal PS amplitude in dose-dependent manner. The bars show the period of 5-HT application. E. The dose-response curve showing inhibition of PSs by each concentration of 5-HT. The inhibition induced by 5-HT treatment reached the maximum level at 50 μM, and the calculated EC_{50} was 10.5 μM. Representative superimposed PS traces for each experiment are presented below the plotted graph.

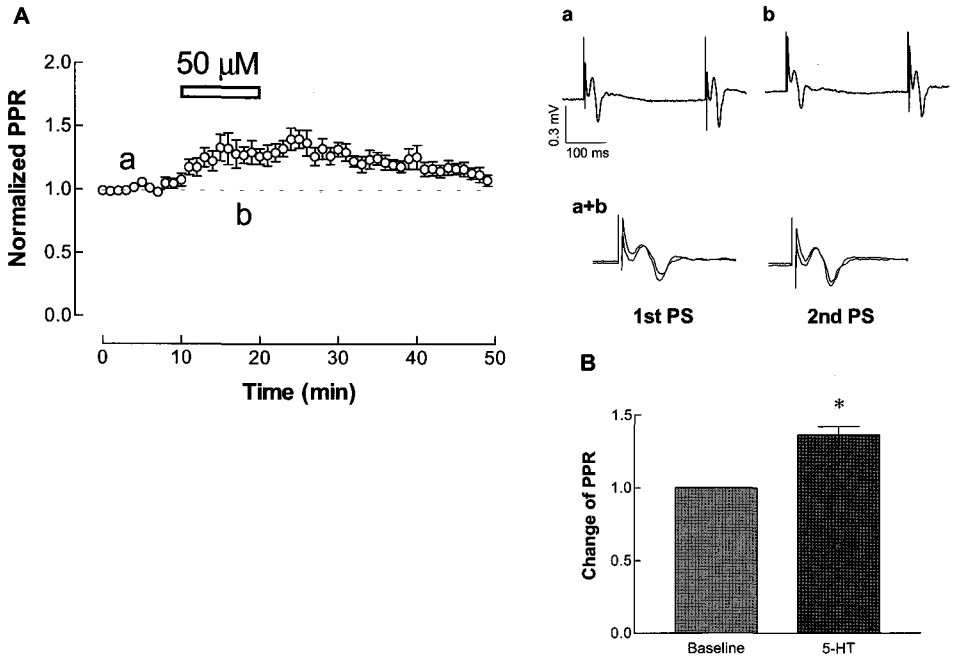

Fig. 3. Paired-pulse ratio (PPR) was increased by 5-HT application. A. Plotted graph showing time-dependent change of normalized PPR after treatment of 5-HT. The 5-HT (50 μM) increased PPR (40$\pm$6.7%, n=9). a. Representative trace of PS to show baseline PPR under normal aCSF. b. Representative trace of PS to show PPR under 5-HT treatment. B. Bar graph showing averaged PPR data. The baseline is PSs which was recorded for 10 min under normal aCSF. *$P<0.001$, compared with baseline.

more, average PS amplitude was 40.1$\pm$5.0% (n=11, $P<$ 0.001) of the baseline at 50 μM 5-HT, and was 38.7$\pm$4.4 (n=9, $P<0.001$) of the baseline at 100 μM 5-HT. Maximal decrease of PS amplitude by 5-HT was shown at 50 μM. We used 50 μM 5-HT as a testing concentration in the next experiments.

Paired-pulse ratio change by 5-HT

It has been well established that glutamate is the major excitatory neurotransmitter in the striatum (Cherubini et al, 1988; Jiang & North, 1991; Lovinger et al, 1993). There exists a possibility that the inhibition of synaptic transmission may be mediated by change in the amount of neurotransmitter which is released from presynaptic nerve terminal, and it has been suggested that the changes of neurotransmitter release could most likely be electrophysiologically estimated by analysis of PPR (Zucker & Regehr, 2002). Therefore, to determine whether 5-HT could probably change neurotransmitter release, we measured PPR with paired-pulse protocol. As shown in Fig. 3, PPR was increased 40$\pm$6.7%, (n=9, $P<0.001$) of the baseline at 50 μM 5-HT. These results indicate that 5-HT increased glutamate release in the corticostriatal presynaptic nerve terminal.

Effect of 5-HT on non-NMDA or NMDA glutamate receptor-mediated synaptic transmission

It has been demonstrated that striatal excitatory postsynaptic potentials evoked by cortical afferents stimulation have both non-NMDA and an NMDA component, although the non-NMDA component predominates under normal experimental condition (Jiang & North, 1991; Lovinger et al, 1993). Therefore, it was highly possible that 5-HT could also modulate these two classes of ionotrophic glutamate receptors differentially. Accordingly, non-NMDA glutamate receptors were pharmacologically isolated by bath application of NMDA receptor antagonist, DL-2-amino-5-phosphonovaleric acid (AP-V, 100 μM). In the presence of AP-V, the amplitude of PS was decreased to 44.6$\pm$2.9% (n=8, $P<$ 0.05) of the baseline by the application of 50 μM 5-HT (Fig. 4). AP-V alone did not significantly change PS amplitude.

Next, we examined whether that 5-HT affected NMDA glutamate receptor-mediated PS. As seen in Fig. 5, the removal of Mg^{2+} ion from normal aCSF led to 47.6$\pm$1.9% increase of the baseline. When non-NMDA glutamate receptor antagonist, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenxo[f] quinoxaline-7-sulfonamide (NBQX, 10 μM), was used to isolate NMDA receptor-mediated synaptic responses, PS was completely blocked, and the drug effect could not be analyzed. Thus, we could not use NBQX in this experiment. 5-HT decreased 4.7$\pm$5.1 (n=7, $P>0.05$) of PS amplitude under zero Mg^{2+} condition, but these responses were not statistically significant.

DISCUSSION

In the present study, we demonstrated for the first time the inhibitory action of 5-HT on striatal excitatory synaptic transmission, which is mediated by glutamate. These

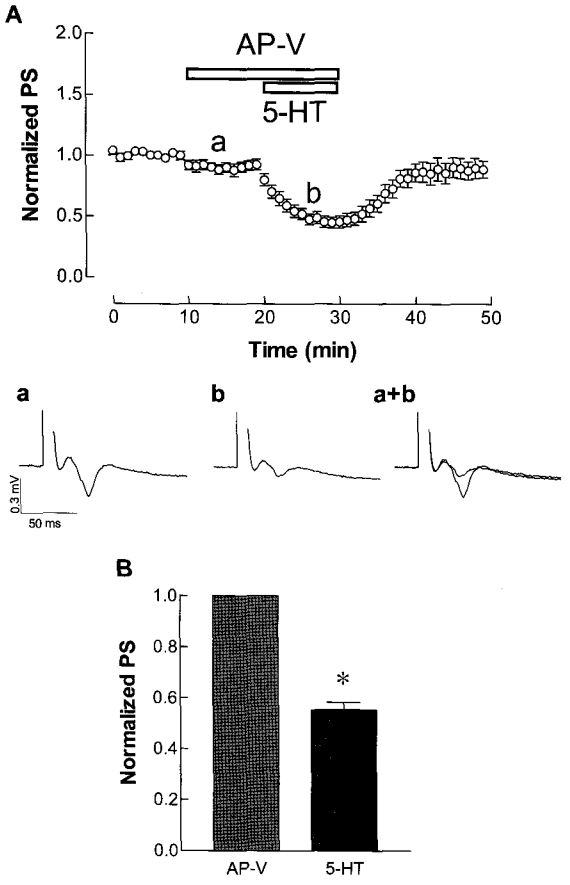

Fig. 4. 5-HT depressed the PSs mediated by nonNMDA glutamate receptors that were pharmacologically isolated by AP-V (100 μM), a NMDA glutamate receptor antagonist. A. Plotted PS data showing that PSs were depressed (44$\pm$4.9%, n=8) by co-application of 50 μM 5-HT with 100 μM AP-V. B. Bar graph shows averaged PSs data. *$P<0.001$, compared with AP-V only.

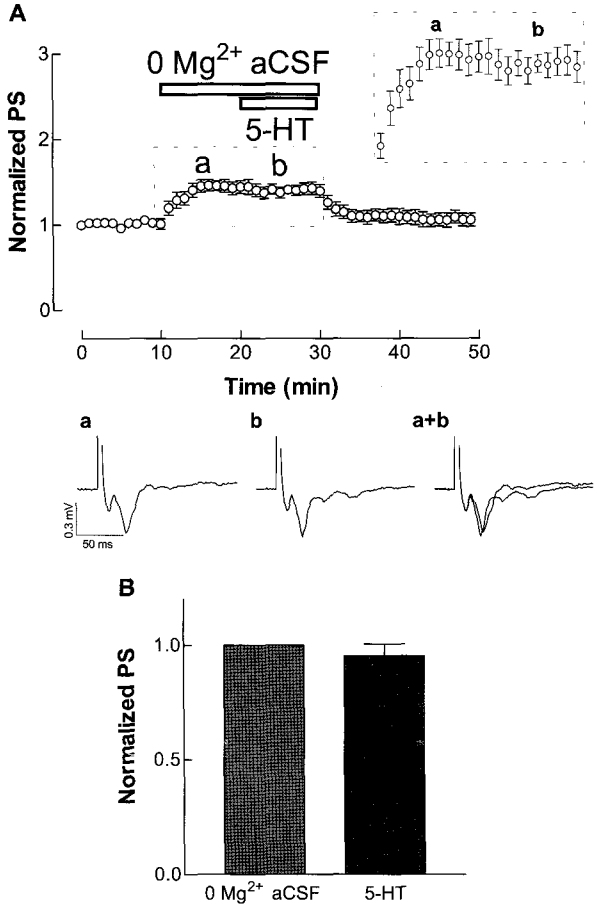

Fig. 5. 5-HT did not affect the PS mediated by NMDA glutamate receptors. To induce NMDA receptor-mediated PS, Mg^{2+} was omitted from normal aCSF. A. Plotted data showing PSs under Mg^{2+} free aCSF were not changed by 5-HT treatment. The inset shows the magnification of dotted box. B. Bar graph shows averaged data. PS was depressed by 50 μM 5-HT treatment (5.7$\pm$2.3%, n=7) under the Mg^{2+} free aCSF. The difference was not statistically significant.

results indicate that 5-HT may act as an important modulator of striatal synaptic transmission, and further suggest that 5-HT inhibits glutamatergic synaptic transmission in the corticostriatal synapses. There exist a few mechanisms which may possibly explain this inhibitory effect of 5-HT in the corticostriatal synaptic transmission. First, 5-HT decreases the release of neurotransmitters from the presynaptic nerve terminals. Second, 5-HT decreases the postsynaptic neuronal responses without a change of neurotransmitter release. In the present study, 5-HT inhibited PS that was induced by synaptic activation, and this inhibition was accompanied by the PPR increase. Because PPR analysis is one way to study possible changes of the neurotransmitter release from the presynaptic nerve terminals, the increase of PPR by 5-HT suggests that this inhibitory effect was mediated by the reduction of neurotransmitter release probability from presynaptic nerve terminals. Furthermore, we tested this inhibitory modulation of excitatory synaptic transmission by 5-HT pharmacologically blocking two different subtypes of ionotrophic glutamate receptor. To isolate non-NMDA glutamate receptor-mediated synaptic transmission, corticostriatal slice was superfused by AP-V, a NMDA receptor antagonist. However, we superfused zero Mg^{2+} aCSF in the slice to activate NMDA component of corticostriatal synaptic transmission, instead of using non-NMDA receptor blockade, NBQX, because NBQX completely blocked PS amplitude, so that we could not analyze PS changes by 5-HT in the presence of this antagonist. Under these conditions, we could test the effects of 5-HT on the 2 different kinds of excitatory glutamate receptors separately; e.g. NMDA receptor and non-NMDA receptor. The modulation of striatal synaptic transmission by 5-HT was found to be more selective to non-NMDA glutamate receptor than NMDA glutamate receptor. Also, these results suggest that 5-HT inhibits corticostriatal synaptic transmission through both presynaptic and postsynaptic mechanisms.

Early studies indicate that various neurotransmitters have an inhibitory effect on glutamate release from the presynaptic nerve terminals in the corticostriatal synapse (Malenka & Kocsis, 1988; Calabresi et al, 1991; Lovinger, 1991; Jiang & North, 1992; Lovinger & Choi, 1995; Singer et al, 1996). Most of these neurotransmitters are G-protein

coupled receptor and inhibit adenylate cyclase in the presynaptic nerve terminal. Although the exact role of adenylate cyclase inhibition played in the presynaptic nerve terminal is yet unclear, it has been generally accepted that it inhibits voltage-sensitive calcium channel or directly affects the vesicular secretion which modulates neurotransmitter release (Thompson et al, 1993).

Various 5-HT receptor subtypes (5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_3, and 5-HT_6) exist in the striatum (Barnes & Sharp, 1999), and immunohistochemical studies revealed that 5-HT_{2A} receptor subtype is abundant in the nerve terminal of the striatum, which originates from the cortex of rat (Bubser et al, 2001) and revealed that 5-HT_3 receptor, a ligand-gate ion channel, is co-localized on striatal nerve fiber (Nayak et al, 2000). These studies suggest the possibility that 5-HT modulates the release of neurotransmitter from nerve terminals through the activation of 5-HT receptors, which is located on the presynaptic nerve terminal.

The synaptic transmission in the corticostriatal synapses has been reported to be mediated by both non-NMDA and NMDA glutamate receptors, however, main synaptic transmission is predominantly mediated by non-NMDA receptors. The PSs, which were recorded in our experiment, also consisted of these 2 components. We, therefore, applied either selective antagonist of glutamate receptor subtypes or removed Mg^{2+} ion from aCSF to separate these 2 components, and then tested 5-HT on the corticostriatal synaptic transmission. We observed that 5-HT selectively decreased the non-NMDA receptor-mediated PS, but did not change the NMDA receptor-mediated PS amplitude. When we tested 5-HT on the brain slice without any treatments, we could also find the decrease of PS amplitude. These data could suggest two possibilities. First, the inhibitory effect of the non-NMDA receptor-mediated PS by 5-HT might be offset by the NMDA receptor-mediated PS. Second, if 5-HT increased NMDA glutamate receptor mediated PS, but decreased non-NMDA glutamate receptormediated PS, this could be masked by each other: we could not exclude the possibility of either that PS hanges by 5-HT were offset by alteration of non-NMDA glutamate receptor function following NMDA glutamate receptor activation, or that the effect on non-NMDA glutamate receptor and NMDA glutamate receptor was offset by each other. Moreover, we also do not exclude the limitation of PS recording technique, because *in vitro* extracellular recording technique measures electrical signal which is evoked in field where neuronal groups exists, but not single neuron. Since we could not apply 5-HT receptor subtype selective antagonist, we cannot be sure which subtype of 5-HT receptor activation, one of receptors existing on the striatal presynaptic nerve terminal, was responsible to decrease neurotransmitter directly from nerve terminal. Therefore, to obtain more direct evidence that 5-HT modulates neurotransmitter release from the striatal presynaptic nerve terminal, further study is needed by using intracellular recording in single neuron and by measuring miniature EPSP (excitatory postsynaptic potential) which detects the change of neurotransmitter release when electrical stimulation is not applied.

In conclusion, the decrease of neurotransmitter release from presynaptic nerve terminal by 5-HT may suppress the corticostriatal synaptic transmission, and these inhibitions could mainly be due to non-NMDA glutamate receptor subtype mediated synaptic transmission.

ACKNOWLEDGEMENT

This work was supported by the Korea Science & Engineering Foundation (KOSEF) through the Cell Death Disease Research Center at The Catholic University of Korea (R13-2002-005-01002-0).

REFERENCES

Anderson WW, Collingridge GL. The LTP Program: a data acquisition program for on-line analysis of long-term potentiation and other synaptic events. *J Neurosci Methods* 108: 71–83, 2001

Azmitia EC, Whitaker-Azmitia PM. Awakening the sleeping giant: anatomy and plasticity of the brain serotonergic system. *J Clin Psychiatry* 52 Suppl: 4–16, 1991

Barnes NM, Sharp T. A review of central 5-HT receptors and their function. *Neuropharmacology* 38: 1083–1152, 1999

Bubser M, Backstrom JR, Sanders-Bush E, Roth BL, Deutch AY. Distribution of serotonin 5-HT(2A) receptors in afferents of the rat striatum. *Synapse* 39: 297–304, 2001

Calabresi P, Mercuri NB, De Murtas M, Bernardi G. Involvement of GABA systems in feedback regulation of glutamate- and GABA-mediated synaptic potentials in rat neostriatum. *J Physiol* 440: 581–599, 1991

Cherubini E, Herrling PL, Lanfumey L, Stanzione P. Excitatory amino acids in synaptic excitation of rat striatal neurones in vitro. *J Physiol* 400: 677–690, 1988

Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci* 13: 244–254, 1990

Graybiel AM, Aosaki T, Flaherty AW, Kimura M. The basal ganglia and adaptive motor control. *Science* 265: 1826–1831, 1994

Groves PM. A theory of the functional organization of the neostriatum and the neostriatal control of voluntary movement. *Brain Res* 286: 109–132, 1983

Herrling PL. Pharmacology of the corticocaudate excitatory postsynaptic potential in the cat: evidence for its mediation by quisqualate- or kainate-receptors. *Neuroscience* 14: 417–426, 1985

Jiang ZG, North RA. Membrane properties and synaptic responses of rat striatal neurones in vitro. *J Physiol* 443: 533–553, 1991

Jiang ZG, North RA. Pre- and postsynaptic inhibition by opioids in rat striatum. *J Neurosci* 12: 356–361, 1992

Jog MS, Kubota Y, Connolly CI, Hillegaart V, Graybiel AM. Building neural representations of habits. *Science* 286: 1745–1749, 1999

Jones BJ, Blackburn TP. The medical benefit of 5-HT research. *Pharmacol Biochem Behav* 71: 555–568, 2002

Lieberman JA, Mailman RB, Duncan G, Sikich L, Chakos M, Nichols DE, Kraus JE. Serotonergic basis of antipsychotic drug effects in schizophrenia. *Biological Psychiatry* 44: 1099–1117, 1998

Lovinger DM. Trans-1-aminocyclopentane-1,3-dicarboxylic acid (t-ACPD) decreases synaptic excitation in rat striatal slices through a presynaptic action. *Neurosci Lett* 129: 17–21, 1991

Lovinger DM, Choi S. Activation of adenosine A1 receptors initiates short-term synaptic depression in rat striatum. *Neurosci Lett* 199: 9–12, 1995

Lovinger DM, Tyler EC, Merritt A. Short- and long-term synaptic depression in rat neostriatum. *J Neurophysiol* 70: 1937–1949, 1993

Malenka RC, Kocsis JD. Presynaptic actions of carbachol and adenosine on corticostriatal synaptic transmission studied in vitro. *J Neurosci* 8: 3750–3756, 1988

Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 50: 381–425, 1996

Mlinar B, Pugliese AM, Corradetti R. Selective inhibition of local excitatory synaptic transmission by serotonin through an unconventional receptor in the CA1 region of rat hippocampus.

J Physiol 534: 141–158, 2001

Parent A. Extrinsic connections of the basal ganglia. *Trends Neurosci* 13: 254–258, 1990

Rammes G, Eder M, Dodt HU, Kochs E, Zieglgansberger W. Long-term depression in the basolateral amygdala of the mouse involves the activation of interneurons. *Neuroscience* 107: 85–97, 2001

Roerig B, Nelson DA, Katz LC. Fast synaptic signaling by nicotinic acetylcholine and serotonin 5-HT3 receptors in developing visual cortex. *J Neurosci* 17: 8353–8362, 1997

Singer JH, Bellingham MC, Berger AJ. Presynaptic inhibition of glutamatergic synaptic transmission to rat motoneurons by serotonin. *J Neurophysiol* 76: 799–807, 1996

Sung KW, Choi S, Lovinger DM. Activation of group I mGluRs is necessary for induction of long-term depression at striatal synapses. *J Neurophysiol* 86: 2405–2412, 2001

Thompson SM, Capogna M, Scanziani M. Presynaptic inhibition in the hippocampus. *Trends Neurosci* 16: 222–227, 1993

Zhou FM, Hablitz JJ. Activation of serotonin receptors modulates synaptic transmission in rat cerebral cortex. *J Neurophysiol* 82: 2989–2999, 1999

Zucker RS, Regehr WG. Short-term synaptic plasticity. *Annu Rev Physiol* 64: 355–405, 2002