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5-Hydroxytryptamine Inhibits Glutamatergic Synaptic Transmission in Rat Corticostriatal Brain Slice

Hyeong Seok Cho, Se Joon Choi, Ki-Jung Kim, Hyun Ho Lee, Seong Yun Kim, Young Jin Cho, and Ki-Wug Sung

Department of Pharmacology, MRC for Cell Death Disease Research Center, College of Medicine, The Catholic University of Korea, Seoul 137–701, Korea

Striatum is involved in the control of movement and habitual memory. It receives glutamatergic input from wide area of the cerebral cortex as well as an extensive serotonergic (5-hydroxytryptamine, 5-HT) input from the raphe nuclei. In our study, the effects of 5-HT on synaptic transmission were studied in the rat corticostriatal brain slice using *in vitro* whole-cell recording technique. 5-HT inhibited the amplitude as well as frequency of spontaneous excitatory postsynaptic currents (sEPSC) significantly, and neither γ-aminobutyric acid $(GABA)_A$ receptor antagonist bicuculline (BIC), nor N-methyl-D-aspartate (NMDA) receptor antagonist, DL-2-amino-5-phosphonovaleric acid (AP-V) could block the effect of 5-HT. In the presence non-NMDA receptor antagonist, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenxo[f] quinoxaline-7-sulfonamide (NBQX), the inhibitory effect of 5-HT was blocked. We also figured out that 5-HT change the channel kinetics of the sEPSC. There was a significant increase in the rise time during the 5-HT application. Our results suggest that 5-HT has an effect on both pre- and postsynaptic site with decreasing neurotransmitter release probability of glutamate and decreasing the sensitivity to glutamate by increasing the rise time of non-NMDA receptor mediated synaptic transmission in the corticostriatal synapses.

Key Words: Striatum, 5-Hydoxytrptamine, Spontaneous EPSC, Synaptic transmission

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is one of the major bioactive substances and widely distributed in the body, and a large number of physiological functions and pathological responses are mediated by 5-HT receptors (Hu et al, 2004). It has been reported that 5-HT receptors can be classified into seven types and further distinguished into at least 14 subtypes. Almost all known 5-HT receptors including $5\text{-HT}_{1,2,4\text{-}7}$ receptors belong to the super family of G-protein coupled receptors, whereas 5-HT_3 receptor is unique and referred to as a ligand-gated ion channel. Histochemical studies have shown that the mammalian cerebral cortex receives an extensive 5-HT input originating from midbrain raphe nuclei 5-HT neurons (Zhou & Hablitz, 1999). It has been also suggested that multiple 5-HT receptor subtypes, including $5\text{-HT}_{1\text{-}6}$, are expressed in the striatum (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).

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) 82-2-590-1204, (Fax) 82-2-536-2485, (E-mail) sungkw@catholic.ac.kr

The striatum regulates motor output, and it is thought that changes in the synaptic efficacy of inputs to the striatum contribute to motor learning and habit formation. The striatum receive convergent glutamatergic inputs from the cortex and thalamus and dopaminergic inputs from the substantia nigra *pars compacta* (Ronesi & Lovinger, 2005) and 5-HT inputs from the raphe nuclei (Yakel et al, 1988). The glutamatergic synaptic transmission at the corticostriatal synapses is mediated by α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors with a very little involvement of N-methyl-D-aspartate (NMDA) receptors (Herrling, 1985; Cherubini et al, 1988; Lovinger et al, 1993).

Recent studies showed that 5-HT exerts multiple electrophysiological effects on neurons of the central nervous system (Muramatsu et al, 1998; Rainnie, 1999; Zhou & Hablitz, 1999; Laurent et al, 2002; Bouryi & Lewis, 2003; Zhong & Yan, 2004). However, it is still unclear how 5-HT modulates corticostriatal synaptic transmission in the striatum. Therefore, using *in vitro* whole-cell recording technique in corticostriatal slice, we studied the modulatory mechanism of 5-HT on corticostriatal glutamatergic synaptic transmission.

ABBREVIATIONS: 5-HT, 5-hydroxytryptamine, serotonin; sEPSC, spontaneous excitatory postsynaptic current; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; NMDA, N-methyl-D-aspartate; AP-V, DL-2-amino-5-phosphonovaleric acid; NBQX, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenxo[f]quinoxaline-7-sulfonamide; BIC, bicuculline.

METHODS

Slice preparation

Brain slices were prepared from 14- to 20-day-old Sprague-Dawley rats using previously described techniques (Sung et al, 2001). Rats were killed by decapitation, and the brains were removed and placed in ice-cold, modified artificial cerebrospinal fluid (aCSF) containing (in mM) 194 sucrose, 30 NaCl, 4.5 KCl, 1 $MgCl_2$, 26 $NaHCO_3$, 1.2 NaH_2PO_4, and 10 D-glucose adjusted to pH 7.4 by bubbling with 95% O_2/5% CO_2. Coronal slices (300 μm thick) were cut

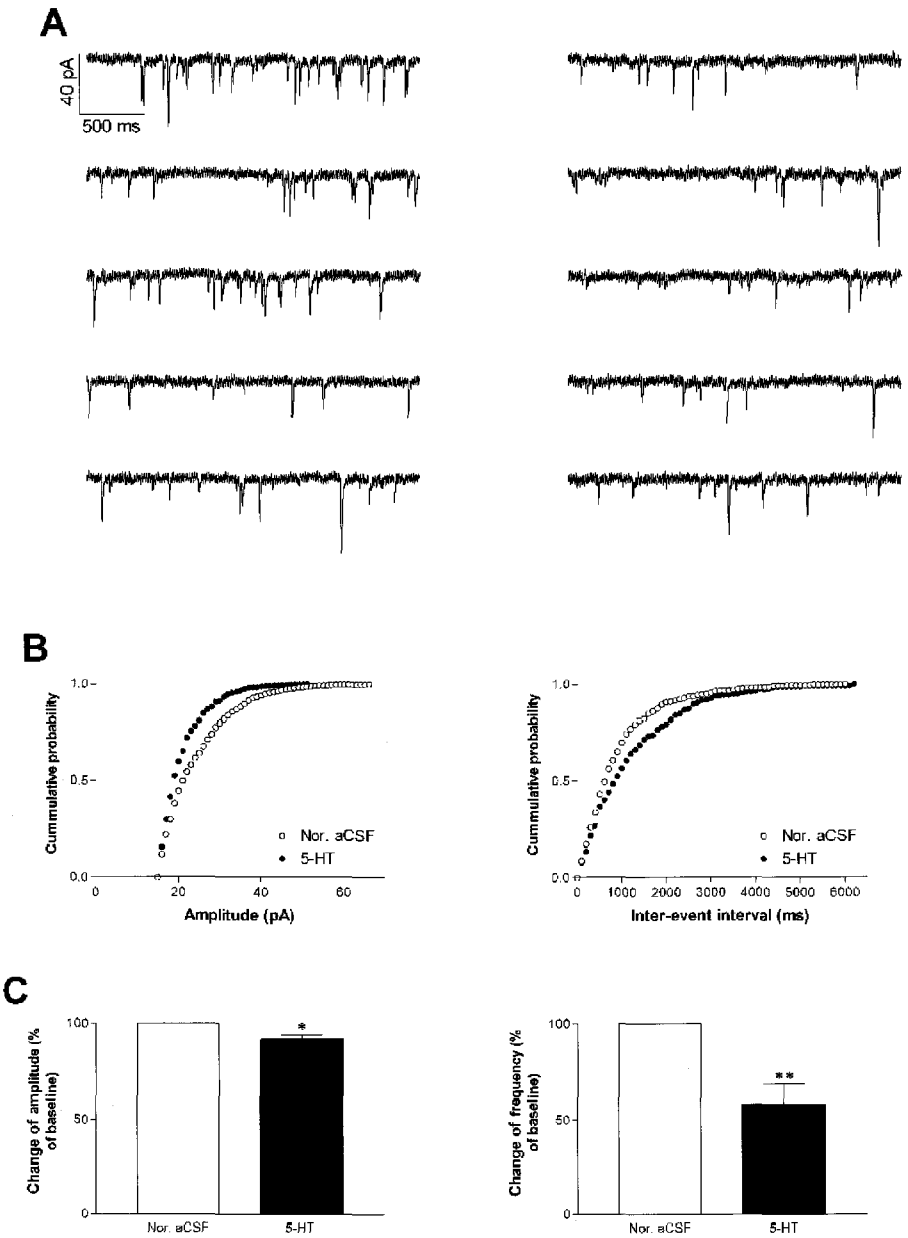

Fig. 1. 5-Hydroxytryptamine (5-HT) decreases corticostriatal spontaneous excitatory postsynaptic currents (sEPSC) amplitude and frequency. (A) Representative traces of sEPSC are showing in the presence of normal artificial cerebrospinal fluid (aCSF; left column) and 50 μM of 5-HT (right column). (B) Representative cumulative amplitude and inter-event interval were calculated. The plot of the cumulative amplitude showed a left shift by 5-HT treatment, which supports the decrease of amplitude and a right shift in inter-event interval which means the inter-event interval has been increased with 5-HT treatment. The increase of the inter-event interval represents decrease of sEPSC events and as a result, it shows reduce of frequency. (C) Bar graphs showing the averaged changes of normalized amplitude and frequency by the treatment of 5-HT on the corticostriatal slices. Note the significant decrease on both amplitude and frequency by 5-HT treatment. $^*P<0.05$, $^{**}P<0.01$, compared with before 5-HT treatment.

using a manual vibrotome (Campden Instruments, 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, and 10 D-glucose adjusted to pH 7.4 by bubbling with 95% O_2/5% CO_2 at room temperature. Slices were used for electrophysiological experiments beginning 1 hour after the end of slice preparation. A hemislice containing the cortex and striatum was completely submerged in a recording chamber and continuously superfused (at a flow rate of 2~3 ml/min) with aCSF that was constantly bubbled with 95% O_2/5% CO_2. The temperature of the bath solution was kept at 30~32°C.

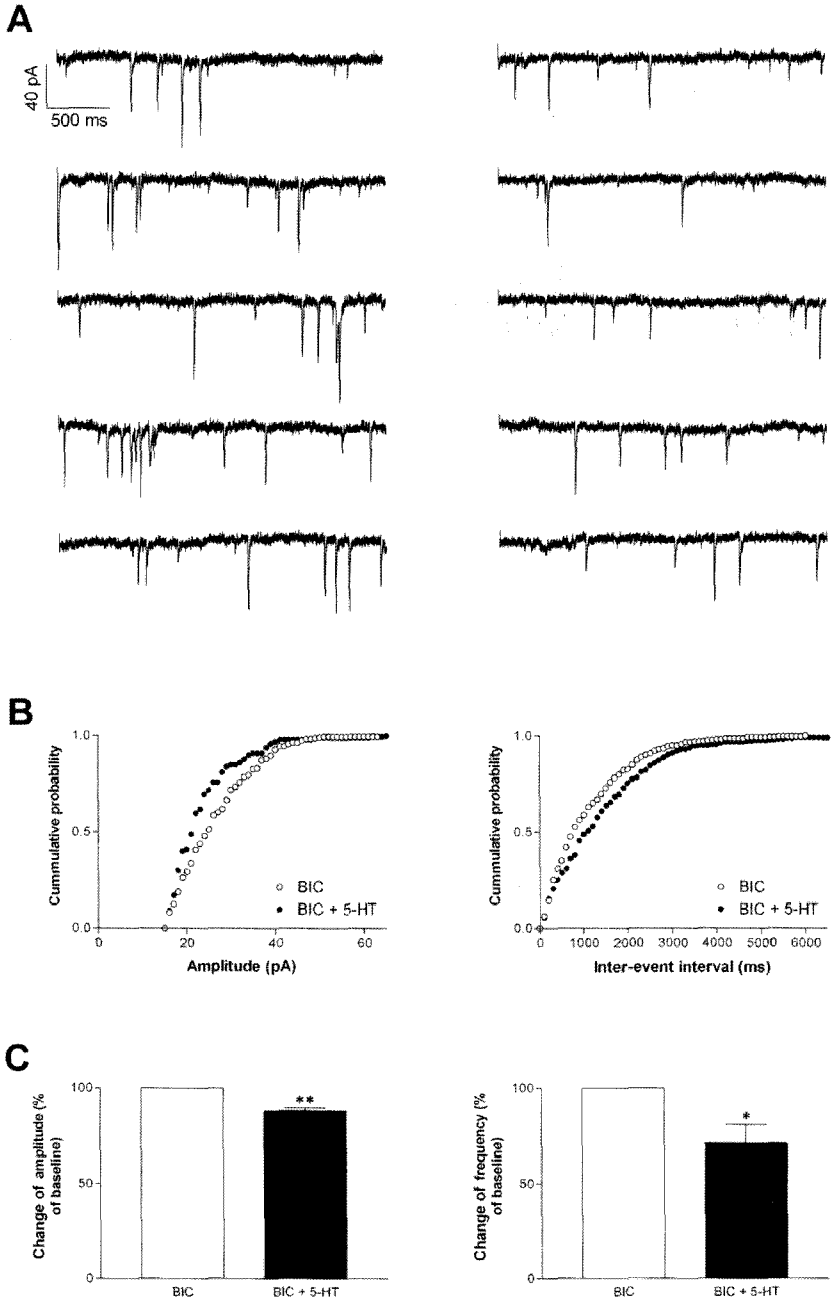

Fig. 2. In the presence of BIC, a $GABA_A$ receptor antagonist, 5-HT still decreases corticostriatal sEPSC amplitude and frequency. (A) Representative trace is showing the prior to drug in the presence of 10 μM BIC (left column) and flowing 5-HT treatment (right column). (B) Cumulative amplitude and inter-event interval distribution displays the same trend compared with only 5-HT treatment in Fig. 1. (C) Bar graphs showing the average of normalized amplitude and frequency are both decreased within 5-HT treatment. It means that there was no significant involvement of GABA receptors in the inhibitory effects of 5-T on the corticostriatal synaptic transmission. $^*P<0.05$, $^{**}P<0.01$, compared with BIC only.

Whole-cell recording

Whole-cell voltage-clamp recordings were performed to record the spontaneous excitatory postsynaptic currents (sEPSC) at striatal synapses. Slices were placed in the recording chamber and superfused with aCSF as described previously. Tight-seal whole-cell recordings were obtained using pipettes made from borosilicate glass capillaries pulled on a P-97 micropipette puller (Sutter Instruments, Novato, CA). Pipette resistance ranged from 4.5 to 7.5 MΩ, filled with internal solution containing (in mM) 120 CsMeSO$_3$, 5 NaCl, 10 tetraethylammonium chloride, 10 HEPES, 5 lidocaine N-ethyl bromide (QX-314) (Br^2 salt), 1.1 EGTA, 4 ATP (Mg^{2+} salt), 0.3 GTP (Na^+ salt), pH adjusted to 7.2 with CsOH, osmolarity adjusted to 290~300 mOsm with sucrose. Medium-sized neurons within two or three layers below the surface of the slice were identified using an Olympus BX50WI (Tokyo, Japan) differential interference

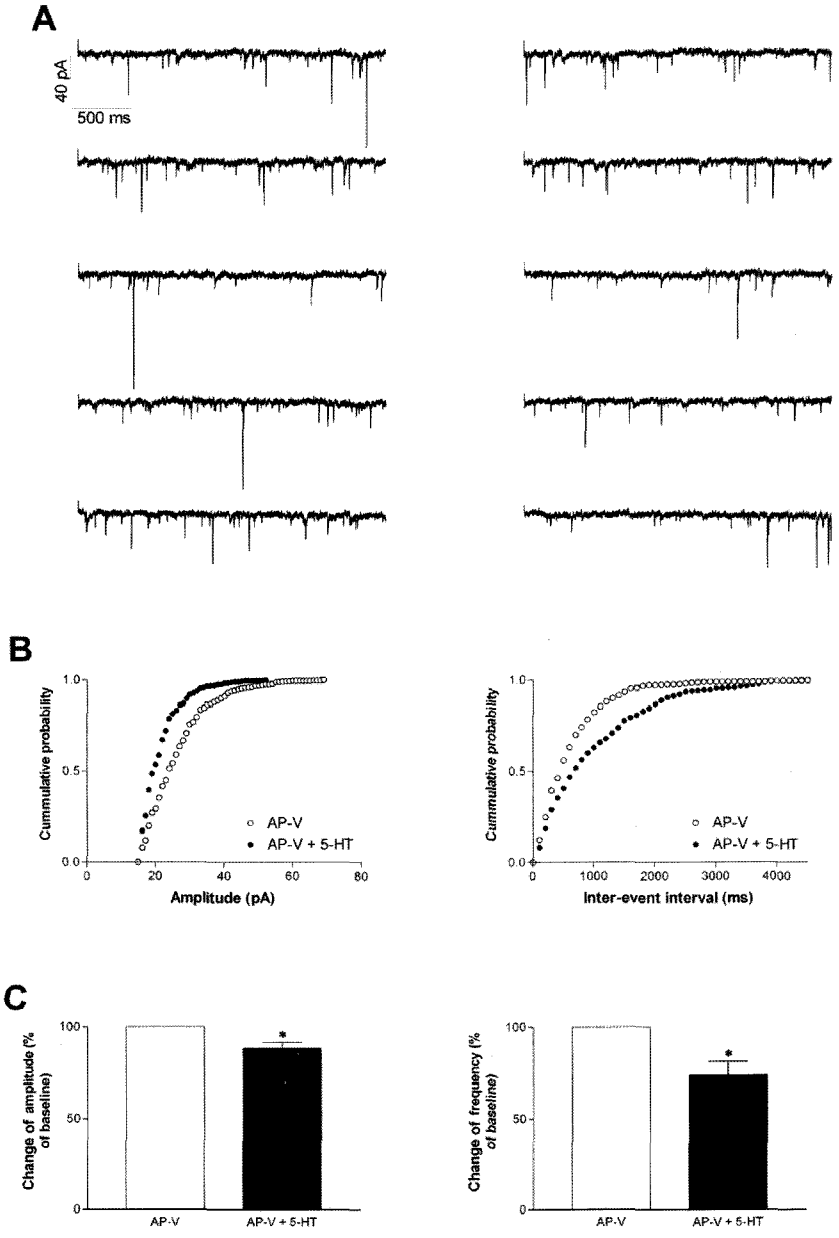

Fig. 3. Non-NMDA receptor mediated sEPSC amplitude and frequency, isolated by AP-V, affected by 5-HT. (A) Representative trace is showing the sEPSC in the presence of 100 μM AP-V (left column) and flowing 5-HT treatment (right column). (B) Cumulative amplitude and inter-event interval distribution were still changed even in the presence of AP-V by the treatment of 5-HT. (C) Bar graphs showing the change of normalized amplitude and frequency. It represents that the effect of 5-HT was not affected by AP-V, showing that AMPA receptor mediated synaptic transmission may possibly be the target of 5-HT. *$P<0.05$, compared with AP-V only.

contrast (DIC) microscope. Neurons were voltage-clamped at −70 mV, sEPSC recorded with an Axopatch 1D patch-clamp amplifier (Axon Instruments, Foster City, CA) were filtered at 5 kHz, digitized at 20 kHz using a Digidata 1322A (Axon Instruments) and stored on a personal computer using pClamp 9.2 software (Axon Instruments).

Spontaneous synaptic events were analyzed off-line using the Mini Analysis Program (Synaptosoft, Decatur, GA). The threshold amplitude for the detection of an event was adjusted generally to the baseline noise level (typically 15 pA). Events were visually inspected following automated analysis to prevent false positive identification and false negative rejection. This software was used to calculate sEPSC amplitude, frequency, rise time and decay time for each event. Frequencies were expressed a number of events per second (in Hz).

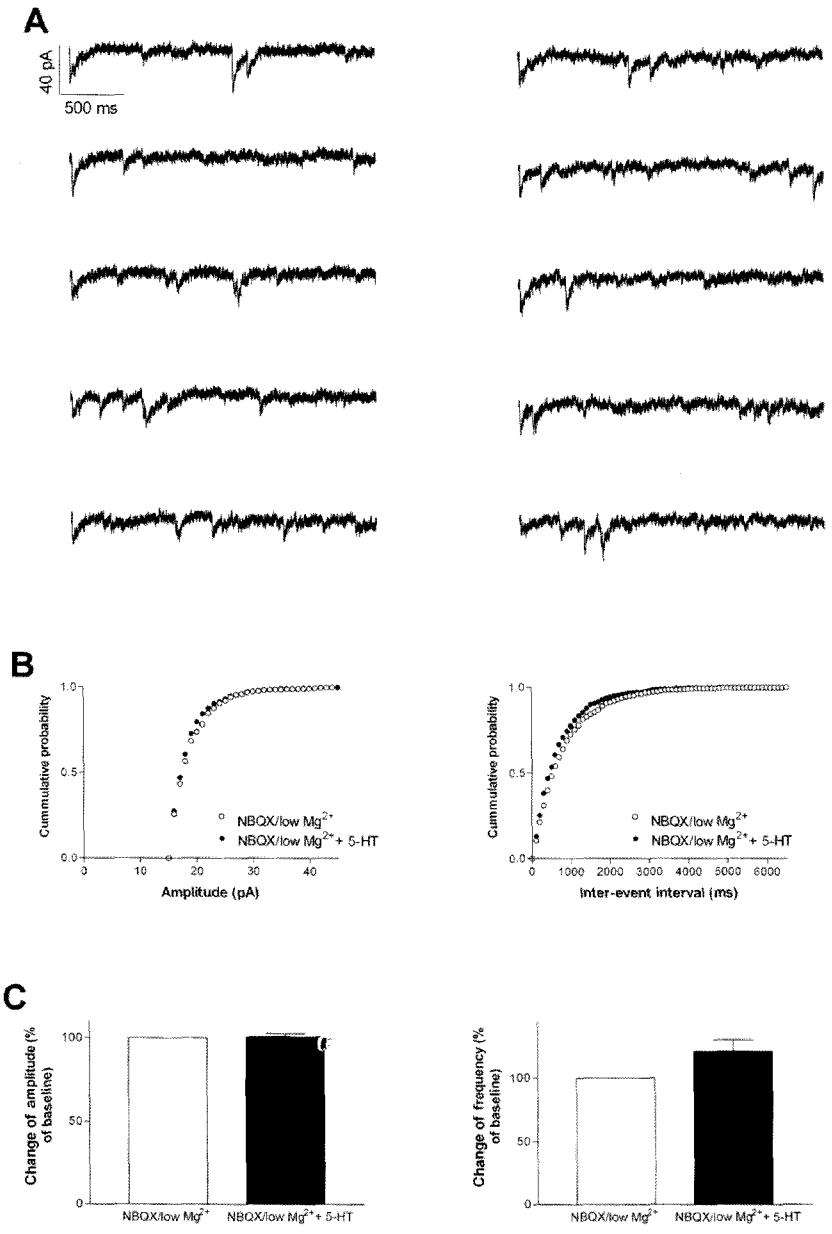

Fig. 4. NMDA receptor mediated sEPSC amplitude and frequency isolated by NBQX and low Mg^{2+} (0.2 mM) was not affected by 5-HT. (A) Representative trace is showing the prior to drug in the presence of 10 μM NBQX and 0.2 mM low Mg^{2+} aCSF (left column) and flowing 5-HT treatment (right column). (B) Cumulative amplitude and inter-event interval distribution shows there is no difference with each other. (C) Bar graphs showing normalized amplitude and frequency. There is no significant effect by 5-HT within NMDA receptor mediated synaptic transmission in corticostriatal brain slices. This supports the possibility of the inhibitory effect of 5-HT may limited on the AMPA receptor mediated synaptic transmission. $^*P<0.05$, compared with NBQX+low Mg^{2+} only.

Data analysis

All averaged data were presented as means±SE. Statistical significance was determined by the Student's t-test. The criterion for significance was $P<0.05$.

Drugs and chemicals

Bicuculline (BIC), DL-2-amino-5-phosphonovaleric acid (AP-V), and 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenxo[f]quinoxaline-7-sulfonamide (NBQX) were purchased from Tocris Cookson (Avonmouth, UK). All other chemicals were purchased from Sigma (St. Louis, MO).

RESULTS

Effect of 5-HT on glutamatergic synaptic transmission

In our study, as presented in Fig. 1, 50 μM of 5-HT significantly inhibited corticostriatal sEPSC amplitude as well as its frequency. Compared with control, 5-HT decreased the amplitude to 91.8±5.6% (n=6, $P<0.05$) of the baseline and frequency to 58.2±25.3% (n=6, $P<0.01$) of the baseline. To clarify whether the synaptic inhibition by 5-HT was glutamatergic synaptic transmission, we studied the effect of 5-HT on sEPSC in the presence of BIC (10 μM), a γ-aminobutyric acid $(GABA)_A$ receptor antagonist (Fig. 2). The amplitude was decreased to 88.2±3.3% (n=5, $P<0.01$) and the frequency was decreased to 71.0±22.2% (n=5, $P<0.05$) of the baseline, and there was no significant difference of 5-HT responses between the group with or without BIC treatment. As based on the quantal hypothesis, changes of amplitude means there is a postsynaptic change of sensitivity to glutamate and changes of frequency there is a presynaptic change involving glutamate release (Muramatsu et al, 1998; Bennett & Kearns, 2000). Our data is showing that 5-HT has an effect on both pre- and postsynaptic sites of glutamatergic synaptic transmission.

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

We previously demonstrated that 5-HT inhibits glutamatergic synaptic transmission in the rat corticostriatal region (Choi et al, 2003). The glutamatergic synaptic transmission at the corticostriatal synapses is mediated by AMPA receptors with a very little involvement of NMDA receptors (Herrling, 1985; Cherubini et al, 1988; Lovinger et al, 1993). Therefore, it was highly possible that 5-HT could also modulate these two classes of ionotrophic glutamate receptors differentially. First, we isolated the AMPA receptors mediated sEPSC pharmacologically by bath application of NMDA receptor antagonist, AP-V (50 μM). In the presence of AP-V, 5-HT could still inhibit the amplitude to 88.3±7.6% (n=6, $P<0.05$) and frequency to 73.7±18.2% (n=6, $P<0.05$) of the baseline sEPSC (Fig. 3). These results suggest that AP-V did not significantly change the effect of 5-HT on the corticostriatal sEPSC.

Next, we examined whether that 5-HT affected NMDA receptor mediated synaptic transmission. We used NBQX, (10 μM), a non-NMDA receptor antagonist to isolate NMDA receptor mediated synaptic transmission, and the Mg^{2+} in the aCSF was decreased to 0.2 mM to activate the NMDA receptor. In these conditions, the effect of 5-HT was blocked. The amplitude was 100.8±4.1% (n=5, $P>0.05$) and frequency was 121.4±20.5% (n=5, $P>0.05$) of the baseline (Fig. 4). These results suggest that 5-HT had no effect on NMDA receptor mediated synaptic transmission.

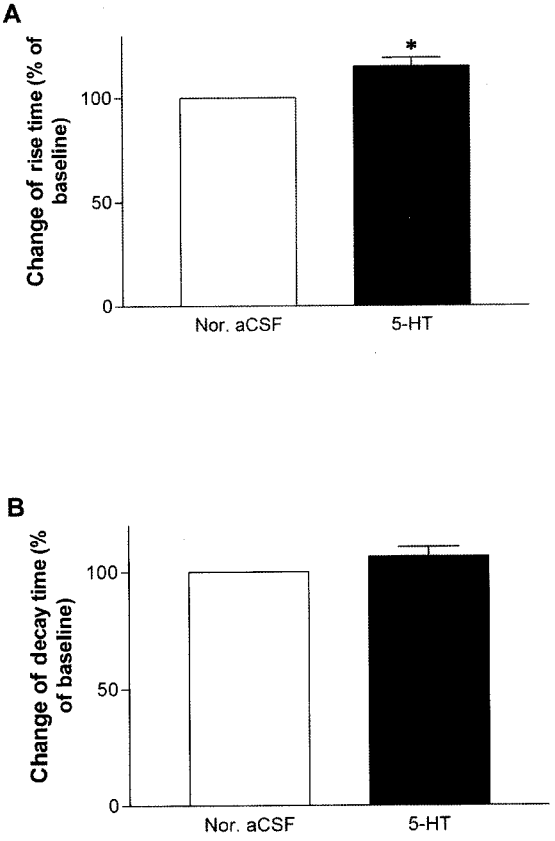

Fig. 5. Change of channel kinetics by 5-HT treatment. Only rise time was affect by 5-HT treatment. (A) Bar graph shows a significant increase of normalized rise time by 5-HT treatment. B. 5-HT had no significant effect on the normalized decay time through the experiment. It shows that the decrease of the sEPSC amplitude is because of the increase of rise time of the postsynaptic receptors. *$P<0.05$, compared with before 5-HT treatment.

Effect of 5-HT on channel kinetics

Fig. 5 shows that the 5-HT has an effect on the channel kinetics of the corticostriatal sEPSC. The rise time increased to 115.0±10.0% (n=6, $P<0.05$) of the baseline and the decay time was 106.5±10.4% (n=6, $P>0.05$) of the baseline. 5-HT had significantly increased the rise time, but not the decay time of the corticostriatal sEPSC. This result indicates that 5-HT decreases the amplitude by increasing the rise time of the sEPSC.

DISCUSSION

The results of this study demonstrate that 5-HT has an inhibitory effect on corticostriatal synaptic transmission. The inhibition of glutamatergic transmission by 5-HT observed here could be mediated by a presynaptic mechanism

involving decreased glutamate release or a postsynaptic decrease of sensitivity to glutamate. Analysis of sEPSC might help to discriminate between these two alternatives. As based on the quantal hypothesis, changes of amplitude means there is a postsynaptic change of sensitivity to glutamate and changes of frequency there is a presynaptic change involving glutamate release (Muramatsu et al, 1998; Bennett & Kearns, 2000). Because our result shows that 5-HT decreased the amplitude as well as the frequency, a postsynaptic decrease of sensitivity to glutamate and a presynaptic decrease of neurotransmitter release both seem to be involved in the action. We used BIC to block $GABA_A$ receptors to rule out the possibility of GABAergic synaptic transmission that might be involved in our experiments, and there was no contribution of GABA receptors in the inhibitory effects of 5-HT on the corticostriatal synaptic transmission in our study. Furthermore, we tested this inhibitory modulation of excitatory synaptic transmission by 5-HT with pharmacologically blocking the two different subtypes of ionotrophic glutamate receptors, NMDA and non-NMDA receptors. The modulation of corticostriatal synaptic transmission by 5-HT was found to be dependent on non-NMDA receptors, but not NMDA receptors, because inhibitory effects of 5-HT were blocked by pretreatment of NBQX, but not by AP-V. The data from analysis of the channel kinetics of sEPSC shows that the inhibition of the amplitude is through the increased of the rise time of sEPSC. These results suggest that 5-HT inhibits corticostriatal synaptic transmission through presynaptic reduce of neurotransmitter release and postsynaptic decrease of sensitivity to glutamate by increasing the rise time of non-NMDA glutamate receptor.

Various subtypes of 5-HT receptors ($5\text{-}HT_{1B}$, $5\text{-}HT_{1D}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_3$, $5\text{-}HT_4$, $5\text{-}HT_{5A}$, and $5\text{-}HT_6$) exist in the striatum (Barnes & Sharp, 1999), and studies about the presynaptic inhibition by 5-HT on other brain regions, including globus pallidus, nucleus accumbens, and suprachiasmatic nucleus, has been reported (Muramatsu et al, 1998; Jiang et al, 2000; Querejeta et al, 2005). Also, immunohistochemical studies discovered that $5\text{-}HT_{2A}$ 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 $5\text{-}HT_3$ receptor is also co-localized on striatal nerve fiber (Nayak et al, 2000). These facts might explain the possibility that 5-HT inhibits the release of neurotransmitter through the activation of the 5-HT receptors located on the presynaptic nerve terminals in the striatum.

The synaptic transmission in the corticostriatal synapses has been reported to be mediated by both non-NMDA and NMDA receptors. However, the main synaptic transmission is predominantly mediated by non-NMDA receptors. The sEPSC we recorded in our experiments also had both of these components, and as described above our results indicate that the decrease of the amplitude of sEPSC by 5-HT is mediated via the increase of non-NMDA receptor rise time. In different regions of the brain, such as the neocortex, transitional cortex, prefrontal cortex, suprachiasmatic nucleus, and basolateral amygdala, 5-HT had an effect within synaptic transmission by postsynaptic, or pre- and postsynaptic both (Aghajanian & Marek, 1997; Rainnie, 1999; Jiang et al, 2000; Cai et al, 2002). Cai et al. (2002) reported that activation of $5\text{-}HT_{1A}$ receptors decrease AMPA receptor mediated synaptic transmission in prefrontal cortex pyramidal neurons by inhibiting Ca^{2+}/calmodulin-dependent kinase II, which is achieved by the inhibition of protein kinase A (PKA) and ensuing activation of protein phosphatase-1 (PP1). This might be a clue to explain the inhibitory effect of 5-HT on non-NMDA receptors in our study, because PKA and PP1 also has an important role in NMDA and non-NMDA receptor channel phosphorylation in the striatum through dopamine- and cAMP-regulated phosphoprotein, M_r 32 kDa (DARPP-32) as well as activation of $5\text{-}HT_4$ and $5\text{-}HT_6$ receptors also plays a role in phosphorylating DARPP-32 in the striatum (Svenningsson et al, 2004). Therefore, to achieve more straight evidence for the modulation of 5-HT in corticostriatal synaptic transmission, further study is needed by using selective 5-HT receptor subtype agonist or antagonist to discover which 5-HT receptor subtype is activated during our examination and for identifying the exact mechanism of it.

Taken together, this study provides evidence showing that serotonin can suppress corticostriatal glutamatergic synaptic transmission via both pre- and postsynaptic mechanisms by decreasing the release of glutamate and inhibiting the non-NMDA receptors.

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