Serotonin Activates Presynaptic and Postsynaptic Receptors in Rat Globus Pallidus

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Hashimoto K, Kita H. Serotonin activates presynaptic and postsynaptic receptors in rat globus pallidus. J Neurophysiol 99: 1723–1732, 2008. First published January 30, 2008; doi:10.1152/jn.01143.2007. Although recent histological, behavioral, and clinical studies suggest that serotonin (5-HT) plays significant roles in the control of pallidal activity, only little is known about the physiological action of 5-HT in the pallidum. Our recent unit recording study in monkeys suggested that 5-HT provides both presynaptic and postsynaptic modulations of pallidal neurons. The present study using rat brain slice preparations further explored these presynaptic and postsynaptic actions of 5-HT. Bath application of 5-HT or the 5-HT1A/1B/1D/5/7 receptor (R) agonist 5-carboxamidotryptamine maleate (5-CT) depolarized some and hyperpolarized other pallidal neurons. Pretreatments of slices with blockers of the hyperpolarization–cyclic nucleotide-activated current or with the 5-HT3R–selective antagonist mesulergine occluded 5-CT–induced depolarization. The 5-HT1AR–selective blocker N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate occluded the 5-CT–induced hyperpolarization. These results suggested involvement of 5-HT3R and 5-HT1AR in the postsynaptic depolarization and hyperpolarization, respectively. 5-CT presynaptically suppressed both internal capsule stimulation–induced excitatory postsynaptic currents (EPSCs) and striatal stimulation–induced inhibitory postsynaptic currents (IPSCs). The potencies of 5-CT on the presynaptic effects were 20- to 25-fold higher than on postsynaptic effects, suggesting that 5-HT mainly modulates presynaptic sites in the globus pallidus. Experiments with several antagonists suggested involvement of 5-HT1BR in the presynaptic suppression of EPSCs. However, the receptor type involved in the presynaptic suppression of IPSCs was inconclusive. The present results provided evidence that 5-HT exerts significant control over the synaptic inputs and the autonomous activity of pallidal neurons.

INTRODUCTION

The rodent globus pallidus (GPe, the homologue of the external pallid segment in the primate) receives major afferents from two major basal ganglia–input nuclei, the striatum (Str) and the subthalamic nucleus (STN), and sends its output to many basal ganglia nuclei. The level and the pattern of GPe firing activity change with the development of basal ganglia diseases, and abnormal activity patterns in GPe neurons are thought to have far-reaching consequences for basal ganglia function (Boraud et al. 2001; Nini et al. 1995; Wichmann and Soares 2006).


However, physiological studies of 5-HT on GPe are scarce. Querejeta et al. (2005) found that local application of 5-HT or a 5-HT1R agonist excites most of the GPe neurons in anesthetized rats. Our recent study in monkeys suggested that 5-HT provides both presynaptic and postsynaptic modulations of GPe neurons (Kita et al. 2007). The aim of this study was to explore the presynaptic and postsynaptic actions of 5-HT, which were suggested from the earlier monkey study, using rat brain slice preparations.

METHODS

Slice preparation

This study was performed in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Sprague–Dawley juvenile rats (16–21 days old) were anesthetized with an intraperitoneal injection of a mixture of ketamine (85 mg/kg) and xylazine (15 mg/kg) and were perfused through the heart with cold oxygenated artificial cerebrospinal fluid (ACSF) containing (in mM): 126 NaCl, 3 KCl, 1.24 NaH2PO4, 26 NaHCO3, 6 MgSO4, and 10 glucose. After decapitation, the brain was removed quickly and a block containing the GPe was obtained. Oblique sagittal or horizontal slices (350 μm thick) were cut from the blocks on a vibrating blade microtome (Leica VT1000S; Leica Microsystems, Nussloch, Germany) after preincubation in ice-cold oxygenated ACSF containing (in mM): 126 choline chloride, 3 KCl, 1.24 NaH2PO4, 26 NaHCO3, 0.5 CaCl2, 6.3 MgSO4, 0.2 thiourea, 0.2 ascorbic acid, and 20 D-glucose (pH 7.4). The slices were then incubated in a standard ACSF containing (in mM): 126 NaCl, 3 KCl, 1.24 NaH2PO4, 26
Electrophysiological recordings

The slices were transferred to a recording chamber with oxygenated ACSF continuously superfused at a flow rate of 1–2 ml/min. The temperature of the recording chamber was kept at 34 ± 1°C. Whole cell patch-clamp recording pipettes with a tip diameter of about 1.5 μm were pulled from 1.5-mm, thin-wall, borosilicate glass capillaries on a horizontal electrode puller (P-97; Sutter Instrument, Novato, CA). The whole cell recording pipettes contained (in mM): 135 K-glucuronate, 5 KCl, 10 HEPES, 2 Mg-ATP, and 0.2 Na-GTP (pH 7.2, 280 mOsm). For recording inhibitory postsynaptic currents (IPSCs), we used high-Cl electrodes containing 90 K-glucuronate, 5 KCl, 10 HEPES, 2 Mg-ATP, and 0.2 Na-GTP (pH 7.2, 270 mOsm, EC\textsubscript{Cl} = −26 mV). The pipette resistance was 4 to 8 MΩ. The liquid junction potential was about 8 mV and was not corrected for. Neurons and recording pipettes were visualized using an infrared-differential interference contrast microscope (BX50WI; Olympus, Tokyo, Japan) with a ×40 water-immersion objective and a CCD camera (4990 series; Cohu Electronics, San Diego, CA). Data were collected using an Axopatch 200B amplifier and AxoGraph 4.6 (Axon Instruments, Foster City, CA). Signals were filtered at 2 kHz, digitized at 5 kHz with a computer interface ITC-18 (InstruTECH, Port Washington, NY), and stored on the hard disc drive of a Macintosh G4 computer. For later off-line analysis, signals were also digitized and stored on a data recorder (CDAT4; Cygnus Technology, Delaware Water Gap, PA).

To activate striato-GPe or subthalamo-GPe fibers, electrical stimulation (±300 μA, 200 μs duration) was applied through a bipolar stimulating electrode with a tip distance of 0.2–0.3 mm placed on the Str or on the internal capsule (IC). To isolate GABAergic IPSCs, we used computer interface ITC-18 (InstruTECH, Port Washington, NY), and stored on the hard disc drive of a Macintosh G4 computer. For later off-line analysis, signals were also digitized and stored on a data recorder (CDAT4; Cygnus Technology, Delaware Water Gap, PA).

Iontophoretic application of GABA and glutamate

Two-barreled pipettes, one barrel containing monosodium L-glutamate (0.1 M, pH 7.0) or GABA (0.1 M, pH 4.8) and the other saline, were placed approximately 30 μm from the neuron recording. Electric current pulses with an intensity of 10–50 nA and duration of 30–100 ms were applied between the drug- and the saline-containing barrels using a constant-current pump Neuro Phore BH-2 (Medical Systems, Greensville, NY).

Chemicals

3-[3-(dimethylamino)propyl]-4-hydroxy-N-[4-(4-pyridyl)phenyl] benzamide dihydrochloride (GR55562), 2-[5-[3-[4-(methylsulfonyl)amino] benzyl]-1,2,4-oxadiazol-5-yl]-1H-indol-3-yl] ethanamine (L694247), 8b(S)-9,10-didehydro-N-[1-(hydroxymethyl)propyl]-1,6 dimethylerythrol-8-carboxamide maleate (mexiletine), 5-carboxamidodtopramine maleate (5-CT), and 4-ethylphenylamino-1,2-dimethyl-6-methylaminopyrimidinum chloride (ZD7288) were obtained from Tocris Cookson (Ellisville, MO). 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), gabazine (SR-95531), N\textsuperscript{-}[8-(4-pyridyl)-1,6-dimethylergolvin-8-yl]-N,N-dimethylsulfamido hydrochloride (mesulergine), NBQX, 5-HT, TTX, and N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate (WAY100635) were obtained from Sigma–Aldrich RBI (St. Louis, MO).

RESULTS

Type of neurons recorded

The neurons included in this report had spontaneous firing of <20 Hz and spike amplitudes >60 mV under control conditions. On depolarizing current injection, the neurons generated repetitive firings without prominent spike accommodation, and hyperpolarizing currents induced either prominent or moderate sags due to inwardly rectifying hyperpolarization–cyclic nucleotide-activated (HCN) current. These neurons included both type A and type B of Cooper and Stanford (2000) or the type I and type II neurons of Poisik et al. (2003).

Postsynaptic responses

Bath application of 5-HT (50 μM) for 3–5 min induced various changes in GPe neurons, 5-HT reversibly depolarized the somatic membrane >3 mV and increased spontaneous firing rates in 5 of 12 neurons tested. The depolarization value was estimated from the membrane potential between spikes (i.e., at spike afterhyperpolarizations; Fig. 1, A and C). The 3 mV is an arbitrarily cut line based on the observations that the membrane potential of established recording neurons seldom shift >3 mV. In 4 neurons, 5-HT hyperpolarized >3 mV (Fig. 1D). The membrane potential of 3 other neurons was not altered >3 mV by 5-HT. These results suggested that 5-HT activates multiple types of receptors in GPe.

To narrow down receptor types, we examined effects of the 5-HT\textsubscript{1A/1B/1D/5/7R} agonist 5-CT. All the recorded neurons were current-clamped at −65 mV before application of 5-CT. ACSF contained gabazine (10 μM), NBQX (5 μM), and CPP (30 μM) to block GABAergic and glutamatergic synaptic inputs. Of 17 neurons tested, bath application of 5-CT (1 μM) for 5–10 min depolarized the somatic membrane >3 mV in 8, hyperpolarized >3 mV in 3, and caused <3-mV change in 6 neurons. Of the 8 depolarized neurons, 5 had prominent and 3 less prominent sags in response to strong hyperpolarizing current pulses. Of the 3 hyperpolarized neurons, 2 had prominent sags. When the 5-HT\textsubscript{1A,1B,1D,5,7}–R–selective blocker WAY100635 (5 μM) was bath applied 5 min prior to 5-CT, 5-CT (1 μM) depolarized all 7 of the neurons tested (Fig. 2B). The current–voltage (I–V) relationship curves were obtained by injecting intracellular current pulses into neurons that were current-clamped at −65 mV (Fig. 2, C and D). Comparison of the I–V relationships of 7 neurons obtained before and during 5-CT application revealed significant decreases in the input resistance (Fig. 2E). Of the 7 neurons, 5 had prominent and 2 less prominent sags in response to strong hyperpolarizing current pulses. To obtain the 5-CT dose–membrane depolarization relationship, 5-CT was applied to neurons current-clamped at −65 mV and pretreated with WAY100635 (5 μM) and with TTX (1 μM) to block the action potential and spontaneous synaptic inputs. The depolarizations were measured by averaging the membrane potentials for 1 min immediately after 5-CT (0.1 to 100 μM) application (Fig. 2F). The IC\textsubscript{50} of 5-CT...
was about 1 μM (Fig. 2F). A survey of the literature suggested that one receptor that could be activated by 5-CT and could induce postsynaptic depolarization in other brain areas is 5-HT7R and that activation of 5-HT7R increases HCN current (Bengtson et al. 2004; Bobker and Williams 1990; Chapin and Andrade 2001). To test the possible involvement of HCN current, 5-CT (3 μM) was applied to neurons pretreated with TTX (1 μM), WAY100635 (5 μM), and ZD7288 (50 μM) or CsCl (2 mM). 5-CT failed to depolarize any of these neurons (Fig. 2G). In 10 neurons pretreated with the 5-HT2/7R–selective antagonist mesulergine (10 μM), 5-CT (1 μM) induced small but significant hyperpolarizations (Fig. 3, A and B, P < 0.001, n = 10) without accompanying large conductance changes (Fig. 3, C–E). Because 5-CT–induced hyperpolarizations were small and were not accompanied by changes in the input resistance, we did not perform further investigations.

Suppression of glutamatergic inputs

To evoke glutamatergic EPSCs, electrical stimulation (≤300 μA, 200 μs duration) was applied through a bipolar electrode (0.3 to 0.5 mm tip distance) placed on the internal capsule (IC) immediately caudal to GPe. EPSCs were isolated using gaba-

![FIG. 1. Bath application of serotonin [5-hydroxytryptamine (5-HT)] either depolarized or hyperpolarized external globus pallidus (GPe) neurons. A–C: 5-HT reversibly depolarized and increased the firing rate of a neuron. A: a slow trace shows an approximately 5-mV depolarization, estimated at levels of spike afterhyperpolarizations, at the end of 5-HT application. Action potentials were truncated. B: the depolarization was accompanied by an increase in the firing rate. Each point in the plots represents the average frequencies for 2 s. C: fast trace recordings, at the times marked in A. D: in another GPe neuron without spontaneous firing, 5-HT hyperpolarized about 4 mV.](http://jn.physiology.org/)

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selective agonist L694247 (10 μM) also suppressed the EPSCs by 26.8 ± 8.0% (Fig. 5E, n = 5) without changing the holding currents of neurons. Application of 1 μM L694247 had no significant effect (P > 0.05, n = 5).

To examine possible involvement of postsynaptic receptors, effects of 5-CT on the responses to iontophoretically applied glutamate were examined. 5-CT (1 and 10 μM) failed to decrease the exogenous glutamate responses in all five tested neurons (Fig. 6A). To further verify the presynaptic suppression, we examined the effects of 5-CT on TTX-insensitive mEPSCs. mEPSCs were recorded in the presence of gabazine (10 μM) and TTX (1 μM). Because

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some neurons did not show frequent mEPSCs, only neurons exhibiting mEPSCs with the amplitude >5 pA and frequency >1 Hz were selected for this experiment. NBQX (10 μM) application blocked the mEPSCs (data not shown). 5-CT (0.1 μM) significantly and reversibly reduced the frequency without altering the mean amplitude or the amplitude distribution of the mEPSCs (Fig. 6, B–E).

Suppression of GABAergic inputs

To evoke GABAergic IPSCs, electrical stimulation (200 μs duration, ±200 μA) was applied through a bipolar electrode (0.3 to 0.5 mm tip distance) placed on the Str. IPSCs were recorded with high Cl-containing pipettes in the presence of the AMPA/kainate receptor antagonist NBQX (5 μM) and N-methyl-D-aspartate antagonist CPP (30 μM). To minimize contamination of IPSCs mediated by local GPe axon–collateral synapses, the IPSCs with latencies >5 ms were evoked by adjusting stimulus current intensities (Kita 2007; Ogura and Kita 2000).

Bath application of 5-HT or 5-CT reversibly reduced Str stimulation–induced IPSCs in GPe neurons (Fig. 7A). The reduction was dose dependent and was accompanied by an increase in the paired-pulse ratio (Fig. 7B–D). The IC50 of the 5-CT reduction of IPSCs was about 0.05 μM and was nearly 20 times lower than the effect of 5-CT on the postsynaptic depolarization described earlier. The pretreatment of preparations with methysergide (10 μM) for 10 min blocked the effects of 5-CT (Fig. 7E). However, 5-CT (0.1 μM) exerted similar degrees of reduction of IPSCs to control (56.8 ± 14.5%, P < 0.005, n = 5) in preparations pretreated with ZD7288 (ZD, 50 μM) or CsCl (Cs, 2 mM).
WAY100635 (10 μM, 48.2% IPSC reduction, \( P < 0.01, n = 4 \)), GR55562 (10 μM, 44.6% IPSC reduction, \( P < 0.001, n = 6 \)), and mesulergine (30 μM, 52.2% EPSC reduction, \( P < 0.005, n = 4 \)). L694247 (10 μM) also suppressed Str stimulation–induced IPSCs by 32.2 ± 18.4% (Fig. 7F, \( n = 5 \)), whereas the effects were not antagonized by GR55562 (10 μM, 25.4 ± 17.5%, \( P > 0.05, n = 4 \)).

To examine possible involvement of postsynaptic receptors, effects of 5-CT on the responses to iontophoretically applied GABA were tested. The exogenous GABA-induced responses were sensitive to gabazine (10 μM; data not shown). 5-CT (1 and 10 μM) failed to decrease the responses to exogenous GABA in all five tested neurons (Fig. 8A). We also examined the effects of 5-CT on TTX-insensitive mIPSCs. mIPSCs were recorded in the presence of NBQX (10 μM), CPP (30 μM), and TTX (1 μM) using high Cl-containing pipettes. Only mIPSCs with amplitudes >5 pA were analyzed, and neurons exhibiting mIPSCs with frequency >1 Hz were selected for this experiment. Gabazine (10 μM) application blocked the mIPSCs, confirming that they were mediated via GABA A receptors (data not shown). 5-CT (0.1 μM) significantly and reversibly reduced the frequency without altering the mean amplitude or the amplitude distribution of the mIPSCs (Fig. 8, B–E).

**DISCUSSION**

**Postsynaptic responses**

The present results suggest that 5-HT activates multiple receptors and can depolarize or hyperpolarize GPe neurons. In the slices pretreated with WAY100635, 5-CT depolarized neurons by increasing the ZD7288 and cesium-sensitive HCN currents. The GPe neurons capable of generating repetitive firings without prominent spike accommodation express both

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**FIG. 4.** 5-HT and 5-CT reduced the amplitude of internal capsule (IC) stimulation-induced excitatory postsynaptic currents (EPSCs) in a dose-dependent manner. A: paired-pulse, 20 ms interval, stimulation-induced EPSCs recorded in control, during 5-HT application, and after 10 min wash. ACSF contained gabazine (10 μM) and the neuron was voltage-clamped at −70 mV. B: 5-HT dose-dependently reduced amplitudes of EPSCs and the reductions were associated with an increase in paired-pulse ratios. C: 5-CT also dose-dependently reduced EPSCs and increased paired-pulse ratios. 5-CT was more potent than 5-HT. In B and C, each plot represents an average of 10 trials (mean ± SD).

**FIG. 5.** A summary of 5-CT and L694247 effects on EPSCs. A: 5-CT dose–EPSC reduction curve. The IC_{50} of the 5-CT effect was about 0.04 μM. B and C: 5-CT (0.1 μM) significantly reduced amplitude of EPSCs and increased paired-pulse ratios. D: the 5-CT failed to reduce EPSCs in preparations pretreated with the 5-HT_{1B/DR}–selective antagonist GR55562 (GR, 10 μM). E: the 5-HT_{1B/DR}–selective agonist L694247 (10 μM) also suppressed the EPSCs.
amplitudes of mEPSCs in 4 neurons. These results suggested all GPe neurons have 5-HT1AR. The involvements of HT7R and activation of HCN current are selective to these agonists and the antagonist is 5-HT7R.

The present results revealed that 5-HT and 5-CT presynaptically reduce glutamate release in GPe. The IC50 of the 5-CT effect on EPSCs was about 0.04 μM and was comparable to that of the suppression of IPSCs. The IC50 of the 5-CT effect on the suppression of EPSCs was about 25 times lower than that of the postsynaptic effect, suggesting that 5-HT mainly modulates presynaptic sites in GPe. The higher IC50 for postsynaptic effects also suggests the reduction of synaptic responses by 0.1 μM 5-CT did not involve significant changes in postsynaptic membrane conductance. The antagonistic effect of GR55562 suggested an involvement of 5-HT1B/1DR. L694247, a selective 5-HT1B/1DR agonist, had an agonistic effect but the effective concentration was much higher than that of 5-CT, suggesting activation of receptors other than 5-HT1B/1DR. The involvement of 5-HT1BR in presynaptic suppressions of glutamatergic responses was reported in a number of other brain areas (Chen and Regehr 2003; Li and Bayliss 1998; Minar et al. 2003; Muramatsu et al. 1998; Pickard et al. 1999; Singer et al. 1996; Smith et al. 2001). Another possible receptor involved in the suppression of glutamatergic excitations is 5-HT1AR (Bouryi and Lewis 2003; Schmitz et al. 1998). We have also suggested an involvement of 5-HT1AR in the suppression of glutamatergic excitations in monkey pallidum because local application of WAY100635 blocked the effect of subsequent applications of 5-CT in suppressing cortical stimulation–induced excitations (Kita et al. 2007). In the present study using rat brain slices, WAY100635 was ineffective.

Suppression of GABAergic inputs

The present results suggested that activation of presynaptic 5-HT1R on the Str–GPe afferent fibers reduces GABA release from their synaptic boutons. The receptor appears to be a more efficient receptor than 5-HT7R. However, our study in monkey GPe also suggested 5-HT1AR–mediated the inhibitory effect of 5-HT (Kita et al. 2007). However, we did not perform further investigations because the hyperpolarizing response of rat GPe neurons to 5-HT and 5-CT was small and was not accompanied with clear conductance changes.

Suppression of glutamatergic inputs

The stimulation of the IC nonselectively activates afferent fibers to GPe, including those from the subthalamic nucleus, the intralaminar thalamic nuclei, the cerebral cortex, and the pedunculopontine tegmentum. Among those, the subthalamic boutons are most numerous in GPe (Okoyama et al. 1987). The present results revealed that 5-HT and 5-CT presynaptically reduce glutamate release in GPe. The IC50 of the 5-CT effect on EPSCs was about 0.04 μM and was comparable to that of the stimulation of the IC nonselectively activates afferent fibers to GPe, including those from the subthalamic nucleus, the intralaminar thalamic nuclei, the cerebral cortex, and the pedunculopontine tegmentum. Among those, the subthalamic boutons are most numerous in GPe (Okoyama et al. 1987). The present results revealed that 5-HT and 5-CT presynaptically reduce glutamate release in GPe. The IC50 of the 5-CT effect on EPSCs was about 0.04 μM and was comparable to that of the postsynaptic effect, suggesting that 5-HT mainly modulates presynaptic sites in GPe. The higher IC50 for postsynaptic effects also suggests the reduction of synaptic responses by 0.1 μM 5-CT did not involve significant changes in postsynaptic membrane conductance. The antagonistic effect of GR55562 suggested an involvement of 5-HT1B/1DR. L694247, a selective 5-HT1B/1DR agonist, had an agonistic effect but the effective concentration was much higher than that of 5-CT, suggesting activation of receptors other than 5-HT1B/1DR. The involvement of 5-HT1BR in presynaptic suppressions of glutamatergic responses was reported in a number of other brain areas (Chen and Regehr 2003; Li and Bayliss 1998; Minar et al. 2003; Muramatsu et al. 1998; Pickard et al. 1999; Singer et al. 1996; Smith et al. 2001). Another possible receptor involved in the suppression of glutamatergic excitations is 5-HT1AR (Bouryi and Lewis 2003; Schmitz et al. 1998). We have also suggested an involvement of 5-HT1AR in the suppression of glutamatergic excitations in monkey pallidum because local application of WAY100635 blocked the effect of subsequent applications of 5-CT in suppressing cortical stimulation–induced excitations (Kita et al. 2007). In the present study using rat brain slices, WAY100635 was ineffective.

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FIG. 6. A: 5-CT (1 and 10 μM) failed to reduce responses of a GPe neuron to iontophoretically applied glutamate. The neuron was voltage-clamped at −70 mV and glutamate was applied through a pipette containing 0.1 M monosodium glutamate (pH 7) placed about 30 μm from the recording neuron with ionophoretic current pulses of −26 nA and 50 ms duration. B–E: 5-CT reduced the frequency but not the amplitude of miniature (m)EPSCs. mEPSCs were recorded from 4 GPe neurons in the presence of TTX (1 μM) and gabazine (10 μM). The neurons were voltage-clamped at −70 mV. B: examples of mEPSCs in normal ACSF. C: 5-CT (0.1 μM) reversibly and significantly reduced the frequency of mEPSCs. D: relative cumulative probabilities of mEPSCs show that 5-CT did not alter the amplitude distribution [Kolmogorov–Smirnov (K–S) test, P > 0.5]. E: 5-CT also did not change mean amplitudes of mEPSCs in 4 neurons.

HCN1 and HCN2 channels that play crucial roles in controlling autonomous firing of GPe neurons (Chan et al. 2004). Which HCN channel was activated by 5-CT could not be determined because 5-CT depolarized both neurons with a prominent sag in response to strong hyperpolarizing current pulses, an indication of strong HCN2 current, and those without prominent sags. The effects of 5-CT were about 30-fold more potent than those of 5-HT and were blocked by mesulergine. The receptor that is selective to these agonists and the antagonist is 5-HT1-R.

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release from rat GPe slices (Chadha et al. 2000). These previous studies suggested the involvement of 5-HT1BR. A recent study reported local application of the 5-HT1BR agonist N-[4-[[5-[3-(2-aminoethyl)-1H-indol-5-yl]-1,2,4-oxadiazol-3-yl]-methyl]phenyl]-methanesulfonamide excites most GPeneurons, which can be due to presynaptic suppression of GABAergic inhibitions, in anesthetized rats (Querejeta et al. 2005). The 5-HT1B/1DR–selective agonist L694247 mimicked the effects of 5-CT. However, the effective concentration of L694247 was much higher than 5-CT and the 5-HT1B/DR–selective antagonist GR55562 failed to block 5-CT effects. The effects of 5-CT were blocked by preapplication of the 5-HT1A/2A/5/6/7R antagonist methysergide (methy, 10 μM). F: the 5-HT1B/1DR–selective agonist L694247 (10 μM) also suppressed the IPSCs.

Identification of 5-HTRs

The differences in the actions of 5-HT agonists and antagonists between the present and previous studies summarized earlier are difficult to understand. It is conceivable that different receptors exert similar effects in different brain areas or in different animal species. This speculation is based on the fact that 5-HTRs can be grouped based on similarity of signaling pathways and that previous studies suggest that the post- and presynaptic effects of 5-HT reported in different brain areas do not share a single receptor. It is also possible that activation of combinations of 5-HTRs or combinations of 5-HTRs and dopaminergic or noradrenergic receptors exerted synergistic effects (e.g., Bishop and Walker 2003; Carta et al. 2007) and blockade of any one of the synergistic receptors exerted similar effects. We also think that most of the agonists and antagonists used are selective but are not specific enough to identify receptors involved, especially when used in relatively high concentrations in both in vivo and in vitro physiological experiments.

Functional implication

The present results provided evidence that 5-HT exerts significant control over the synaptic inputs and the autonomous activity of GPe neurons. Presynaptically, 5-HT can suppress the synaptic release of glutamate and GABA, which means 5-HT can dampen Str and STN inputs and increase or decrease the spontaneous activity of in vivo GPe neurons (Galvan et al. 2005; Kita et al. 2004, 2007). 5-HT can also postsynaptically increase or decrease firing. More detailed studies on the receptors involved and on their localizations are required to understand the roles of these two opposing effects. It has been postulated that parkinsonisms are associated with...
increased activity of striato-pallidal and subthalamo-pallidal projections, which increase synchronized burst activity in GPe (Bergman et al. 1998; Boraud et al. 1998; Magill et al. 2001; Nini et al. 1995; Wichmann and Soares 2006; Wichmann et al. 1990). The potent effects of 5-HT agonists on the modulation of GPe activity suggest a great potential for therapeutic applications of 5-HT–related drugs. For instance, administration of 5-HT1A agonist may decrease burst activity and suppress some parkinsonisms, as was shown in a rodent model of Parkinson’s disease (Chadha et al. 2000). However, more studies are required for understanding the diverse effects of 5-HT involving multiple receptor types and the plastic changes in the receptor distributions and expressions that might occur in advanced stages of Parkinson’s disease with decreased numbers of 5-HT neurons and 5-HT uptake sites in the basal ganglia (Chinaglia et al. 1993; Halliday et al. 1990; Jellinger 1990; Kish 2003).

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