5-Hydroxytryptamine_{1B} Receptors Block the GABA_B Synaptic Potential in Rat Dopamine Neurons

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Intracellular recordings were made from presumed dopamine-containing neurons in slices cut from the midbrain of the rat. Focal electrical stimulation produced a hyperpolarizing synaptic potential that was reduced by 75–95% by the GABA_B-receptor antagonist 2-hydroxysaclofen (300 μ M). 5-HT (3–100 μ M) reduced the amplitude of the GABA_B synaptic potential by 20–74%, with a 50% reduction at 10 μ M, but did not reduce the amplitude of synaptic potentials mediated by GABA_A receptors. 5-HT acted presynaptically because hyperpolarizations produced by exogenously administered GABA (1 mM) in picrotoxin (100 μ M) were not affected by 5-HT (30 μ M). ($\pm$)-Cyanopindolol (100 nM), a 5-HT_{1B} antagonist, blocked the effect of 5-HT (10 μ M); spiperone (1 μ M), which is an antagonist at 5-HT_{1A} and 5-HT₂ receptors, had no effect. The amplitude of the GABA_B synaptic potential was reduced by the 5-HT_{1B} receptor agonists 1-[3-(trifluoromethyl)-phenyl]-piperazine (300 nM) and 7-trifluoromethyl-4-(4-methyl-1-piperazinyl)-pyrrolo[1,2-a]quinoxaline (1 μ M), but not by the 5-HT_{1A} agonist *N,N*-dipropyl-5-carboxamido-tryptamine (1 μ M) or the 5-HT₂ agonist ($\pm$)-1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane (10 μ M). We conclude that 5-HT activates presynaptic 5-HT_{1B} receptors that inhibit the release of GABA onto GABA_B but not GABA_A receptors.

Dysfunction of dopamine output from neurons in the substantia nigra zona compacta (SNc) and the ventral tegmental area (VTA) has been implicated in the etiologies of a variety of neurological and psychiatric disorders. Loss of dopamine-containing cells in the SNc produces syndromes of akinesia and rigidity including Parkinson's disease, whereas excessive dopamine stimulation has been implicated in Tourette's syndrome, tardive dyskinesia, and chorea (Weiner and Lang, 1989). Schizophrenia (Tamminga et al., 1988) and drug abuse (Wise, 1988) have been linked to changes in dopamine output in the VTA and mesolimbic dopamine system. It seems reasonable to assume that some of these disorders might benefit from pharmacologic manipulation of synaptic inputs that control the activity of dopamine neurons.

Dopamine-rich areas of the midbrain have high concentrations of 5-HT (Saavedra et al., 1974; Steinbusch, 1981) and

receive substantial inputs from 5-HT-containing cells in the dorsal and medial raphe nuclei (Dray et al., 1978; Parent et al., 1981). The ventral midbrain also contains one of the highest concentrations of 5-HT receptors of any region in the brain (Pazos and Palacios, 1985). The vast majority of these receptors in rats and mice are 5-HT_{1B} receptors, whereas 5-HT_{1D} receptors are found in guinea pig, calf, and human midbrain (Waeber et al., 1989). Both receptors are negatively coupled to adenylyl cyclase (Bouhelal et al., 1988; Hoyer and Schoeffter, 1988); they have similar distributions in the brain (Waeber et al., 1989); they can inhibit release of 5-HT (Engel et al., 1986; Schlicker et al., 1989); and binding characteristics are similar with the exception that 5-HT_{1B} receptors have a higher affinity for β -adrenergic antagonists than do 5-HT_{1D} receptors (Peroutka, 1990). Thus, 5-HT_{1B} and 5-HT_{1D} receptors are thought to represent species differences of an anatomically and functionally identical receptor type (Hoyer and Middlemiss, 1989). Recently, it was reported that activation of 5-HT_{1B} receptors in the midbrain in rats (Guan and McBride, 1989) and of 5-HT_{1D} receptors in guinea pigs (Higgins et al., 1991) facilitates release of dopamine. These data suggest that 5-HT has an important role in the modulation of dopaminergic synaptic transmission, but this role has thus far not been elucidated at the cellular level.

Using microelectrodes to record membrane potentials in the *in vitro* rat midbrain, we have previously identified synaptic potentials in dopamine cells mediated by excitatory amino acids and GABA acting on GABA_A and GABA_B receptors (Johnson and North, 1992). We have also recently reported that 5-HT blocks the GABA_B synaptic potential but not the potential mediated by GABA_A receptors recorded in dopamine neurons (Sugita et al., 1992). The purpose of the present study was to identify the receptor type involved in the inhibition by 5-HT of the GABA_B-mediated synaptic input.

A preliminary report of this work has been published previously (Johnson et al., 1991).

Materials and Methods

Tissue preparation. Male Sprague–Dawley rats (180–300 gm) were anesthetized with halothane and killed by a blow to the chest. The scalp and skull were removed and the brain was excised. A block of tissue containing the midbrain was placed ventral surface up in a vibratome (Lancer), and serial horizontal slices (thickness, 300 μ m) were cut starting at the ventral surface. Slices were discarded until the floor of the interpeduncular fossa was reached; the next slice was placed on a nylon mesh in a recording chamber (volume, 500 μ l). The tissue was held in position with two electron microscopy grids that were weighed down by short (2–3 mm) pieces of 0.5-mm-diameter platinum wire. The slice was totally immersed in a solution continuously flowing at a rate of 2 ml/min at 36°C. The solution contained (in mM) NaCl, 126; KCl, 2.5;

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NaH₂PO₄, 1.2; MgCl₂, 1.2; CaCl₂, 2.4; glucose, 11; NaHCO₃, 18; saturated with 95% O₂ and 5% CO₂; pH 7.4.

Using a dissection microscope with illumination from below, the VTA and SNC were identified by their relationships to white matter tracts, which appeared darker than the adjacent nuclei. The SNC was identified as a crescent-shaped semiluent region rostral and caudal to the accessory optic tract, and the VTA could be identified medial to the accessory optic tract and lateral to the fasciculus retroflexus (Paxinos and Watson, 1986).

Intracellular recording. Intracellular recordings were made using glass microelectrodes filled with potassium chloride (2 M; resistance, 40–100 MΩ) or potassium acetate (2 M; 80–200 MΩ). Membrane potentials were amplified with an Axoclamp 2A amplifier and recorded on a Gould 2400 recorder. Representative action potentials and membrane responses to hyperpolarizing pulses were stored on a Tektronix 2230 digital storage oscilloscope and then plotted on an x-y plotter.

Synaptic potentials. Bipolar stimulation electrodes (tip separation, 300–500 μm) were made from electrolytically sharpened tungsten wire, and their tips were placed in the slice within 500 μm of the recording electrode. Single square-wave electrical pulses (100 μsec, 0.1 Hz) of constant voltage were used to evoke synaptic potentials. As described previously (Johnson and North, 1991), the late hyperpolarizing synaptic potential mediated by GABA_B receptors is preceded by a depolarizing synaptic potential mediated by excitatory amino acids and a hyperpolarizing synaptic potential mediated by GABA_A receptors. When studying the GABA_B synaptic potential, (–)-bicuculline methiodide (30 μM) or picrotoxin (100 μM) was used to block GABA_A receptors, and 2-amino-5-phosphonopentanoic acid (APV; 50 μM) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 10 μM) were used to block excitatory amino acid receptors. Trains of pulses (5–10 pulses in 100–200 msec), repeated at 0.017 Hz, were usually necessary to evoke the GABA_B synaptic potential. Studies on synaptic potentials mediated by excitatory amino acids were done in picrotoxin (100 μM). Synaptic potentials in figures are averages of four traces.

Drugs. All drugs were applied by superfusion. Solutions containing drugs entered the recording chamber within 30 sec of turning a tap, the delay being necessary for passage of the solution through a heat exchanger. Complete exchange of the bath solution occurred within 2 min. A stock solution of dopamine hydrochloride (Sigma) was made daily and kept on ice to retard oxidation. An oxygenated solution of dopamine for superfusion was used within 5 min of its preparation. Other drugs used were bicuculline (Sigma), picrotoxin (Sigma), APV (Research Biochemicals, Inc.), CNQX (Research Biochemicals), 5-hydroxytryptamine creatinine sulfate complex (serotonin, 5-HT; Sigma), 2-hydroxysaclofen (saclofen; Research Biochemicals), *N,N*-dipropyl-5-carboxamidotryptamine maleate (DP-5CT; Research Biochemicals), (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI; Research Biochemicals), 1-[3-(trifluoromethyl)phenyl]-piperazine hydrochloride (TFMPP; Research Biochemicals), 7-trifluoromethyl-4-(4-methyl-1-piperazinyl)-pyrrolo[1,2-*a*]quinoxaline 1:2 maleate salt (CGS 12066B; Research Biochemicals), 5-carboxamidotryptamine maleate (5-CT; Research Biochemicals), spiperone hydrochloride (Sigma), (±)-baclofen (Research Biochemicals), and γ -amino-*n*-butyric acid (GABA; Sigma). (±)-Cyanopindolol was a gift from Sandoz (East Hanover, NJ).

Statistics. Numerical data in the text and error bars in figures are expressed as the mean $\pm$ standard error of the mean.

Results

General description of dopamine cells

Intracellular recordings were made from 42 cells in the VTA and 42 cells in the SNC. All cells had the electrophysiologic characteristics illustrated in Figure 1. Action potentials were broad, measuring about 1 msec at 50% maximum height (Fig. 1A), and there was a time-dependent “sag” in membrane potential in response to hyperpolarizing pulses (Fig. 1B). Cells were typically spontaneously active (2–3 Hz) with a large postspike hyperpolarization (Fig. 1C). All cells were hyperpolarized by dopamine (30–100 μM; Fig. 1D). These characteristics are typical of cells that contain dopamine (Grace and Onn, 1989; Yung et al., 1991). Effects of 5-HT on GABA_B synaptic potentials were similar in the VTA ($n = 31$) and SNC ($n = 33$); therefore, results from both regions were pooled.

Figure 1. Electrophysiological and pharmacological characteristics of dopamine cells. *A*, Dopamine cells have relatively broad action potentials, measuring about 1 msec at 50% maximum height. *B*, Dopamine cells have a time-dependent “sag” in membrane potential in response to hyperpolarizing pulses. *C*, Dopamine cells are usually active spontaneously at 2–3 Hz, with a large postspike hyperpolarization. *D*, Dopamine cells are hyperpolarized by dopamine (30 μM).

GABA_B synaptic potentials

As described previously, the GABA_B-mediated hyperpolarization developed after a latency of 50 msec, reached its peak amplitude in 250 msec, and lasted 1–1.5 sec (Johnson and North, 1992). It was usually necessary to deliver a short train of stimuli to evoke this synaptic potential. Figure 2A shows that increasing the frequency of stimuli within a 200 msec train increased the amplitude of the GABA_B synaptic potential. Lengthening the duration of the train of stimuli also increased the amplitude of the response (Fig. 2B), but the 70 Hz stimulus was more effective than the 20 Hz stimulus. Figure 2C shows that saclofen, a GABA_B-receptor antagonist, blocked the hyperpolarization in a concentration-dependent manner but was more effective when the potential was produced by a single stimulus compared to those produced by trains of stimuli at 20 Hz or 70 Hz.

5-HT blocks the GABA_B synaptic potential

5-HT (1–100 μM) reduced the amplitude of the GABA_B synaptic potential in a concentration-dependent manner in 61 of 64 cells. Figure 3A shows that both 5-HT and saclofen reduced the GABA_B-mediated synaptic potential in the same neuron. As reported previously (Sugita et al., 1992), 5-HT produced a 50% reduction at about 10 μM (Fig. 3A,B). 5-HT had no effect on

Figure 2. Stimulus-response curves for evoking the GABA_B synaptic potential. All studies were done in APV (50 μ M), CNQX (10 μ M), and picrotoxin (100 μ M). *A*, The amplitude of the hyperpolarizing synaptic potential increases with increasing stimulus frequency (six or seven cells per data point). Stimuli were delivered at 10–90 Hz in a fixed time interval (200 msec). *B*, The amplitude of the hyperpolarization increases with increasing duration of the train of stimuli (four to seven cells per data point). The duration of the train was varied between 10 and 800 msec, and the frequency of stimuli within the train was fixed at either 70 Hz (open circles) or 20 Hz (solid circles). In both *A* and *B*, the numbers in parentheses represent the average number of stimuli delivered in each train of stimuli. *C*, Saclofen blocks the GABA_B synaptic potential in a concentration-dependent manner, but is significantly more effective when the synaptic potential is produced by a single stimulus (SS) compared to those produced by trains of stimuli at 20 Hz or 70 Hz (6–10 cells per data point). These differences were greatest at 300 μ M saclofen ($p < 0.01$, two-tailed paired t test).

the GABA_B potential in two cells, and the synaptic potential was increased by about 50% in one cell. During application of 5-HT, a small amount of hyperpolarizing current (20–50 pA) was needed to maintain the membrane potential at -60 mV in 12 cells, but no current was required in the other 52 cells. Synaptic potentials produced by single stimuli or trains of pulses (20 or 70 Hz) were blocked by 5-HT (30 μ M) equally well ($n = 8$ cells). Reduction in amplitude started 2–3 min after perfusion with 5-HT, but a maximum effect required 10 min. Recovery

from the effect of 5-HT frequently required 20–30 min. 5-HT appears to act presynaptically because 5-HT (10–30 μ M) did not affect hyperpolarizations produced by exogenously administered baclofen (1 μ M; $n = 4$) or GABA (1 mM; $n = 6$) (Fig. 3C). Increasing the stimulus intensity did not overcome the effect of 5-HT on the GABA_B synaptic potential ($n = 5$ cells). 5-HT (30 μ M) reduced the synaptic potential mediated by excitatory amino acids by only $16 \pm 9\%$ ($n = 6$). As we reported previously, 5-HT did not affect the synaptic potential mediated by GABA_A

Figure 3. 5-HT acts presynaptically in a concentration-dependent manner to reduce the amplitude of the GABA_B synaptic potential. *A*, Both saclofen (300 μ M) and 5-HT (10 μ M) reduce the GABA_B-mediated synaptic potential in the same neuron. *B*, 5-HT reduces the amplitude of the synaptic potential with a 50% reduction at about 10 μ M. In both *A* and *B*, trains of stimuli (70 Hz for 200 msec) were used to evoke synaptic potentials, and stimulus artifacts can be seen in the initial portions of each trace; recordings were in APV (50 μ M), CNQX (10 μ M), and bicuculline (30 μ M). *C*, 5-HT (10 μ M) fails to block the hyperpolarization produced by GABA (1 mM) administered exogenously. This experiment was done in picrotoxin (100 μ M).

Figure 4. Cyanopindolol, a 5-HT_{1B} receptor antagonist, completely blocks the ability of 5-HT to reduce the amplitude of the GABA_B synaptic potential. Recovery from the blockade occurred after 60 min of washout.

receptors (Sugita et al., 1992). This suggests that 5-HT acts presynaptically on a distinct population of GABA inputs to reduce the release of GABA acting at GABA_B receptors, whereas those inputs that release GABA onto GABA_A receptors are not affected.

5-HT acts at 5-HT_{1B} receptors

Cyanopindolol (100 nM), a 5-HT_{1B} antagonist (Engel et al., 1986; Offord et al., 1988), completely blocked the effect of 5-HT (10 μM) on the GABA_B synaptic potential ($n = 3$; Fig. 4); a partial antagonism was seen with 30 nM cyanopindolol ($n = 2$). TFMPP, a moderately selective 5-HT_{1B} agonist (Sills et al., 1984), reduced the synaptic potential by $35 \pm 20\%$ ($n = 3$) at 100 nM and reduced the amplitude by $51 \pm 3\%$ ($n = 3$) at 300 nM (Fig. 5A). CGS 12066B, a newer 5-HT_{1B} agonist (Neale et al., 1987), reduced the amplitude $31 \pm 17\%$ at 1 μM ($n = 3$), whereas the 5-HT₁ agonist 5-CT (30 nM) reduced the amplitude $34 \pm 14\%$ ($n = 6$). The GABA_B synaptic potential was unaffected by 1 μM DP-5CT ($n = 4$), a selective 5-HT_{1A} agonist, although higher concentrations produced some reduction in amplitude (Fig. 5B). The synaptic potential was also unaffected by DOI (10 μM; $n = 5$), a selective 5-HT₂ agonist (Fig. 5B). Spiperone (1 μM), which blocks 5-HT_{1A} and 5-HT₂ receptors but not 5-HT_{1B} receptors (Pazos et al., 1985; Lum and Piercey, 1988), did not block the effect of 5-HT ($n = 4$; Fig. 5C).

Discussion

5-HT and activity of dopamine neurons

The results of the present study suggest that 5-HT acts at presynaptic 5-HT_{1B} receptors to inhibit the release of GABA acting at GABA_B receptors on dopamine-containing cells. Because our experiments were done in antagonists of glutamate and GABA_A receptors, it is unlikely that the GABA_B-mediated synaptic po-

tential was polysynaptic. Therefore, the 5-HT_{1B} receptor is probably located on GABA-containing neurons or nerve terminals. *In vivo*, when GABA inputs are presumably active, 5-HT would be expected to facilitate the release of dopamine by reducing the inhibitory influence of GABA. This conclusion is supported by the findings that injection of 5-HT into the VTA increased dopamine turnover in nucleus accumbens (Guan and McBride, 1989) and induced contralateral circling behavior in rats (Redgrave and Horrell, 1976). In guinea pigs, which have high concentrations of 5-HT_{1D} receptors, injection of 5-HT_{1D} agonists into the substantia nigra induced contralateral circling behavior, which was blocked by haloperidol administered subcutaneously (Higgins et al., 1991). However, iontophoresis of 5-HT onto dopamine cells (Dray et al., 1976) and electrical stimulation of dorsal raphe nucleus (Dray et al., 1978; Kelland et al., 1990) produced a mixture of excitatory and inhibitory effects on dopamine neuronal activity recorded extracellularly. These mixed effects of 5-HT may be due to activation of receptors other than 5-HT_{1B} receptors. Systemic injection of 5-HT_{1B} agonists induced circling behavior in rats with unilateral 6-hydroxydopamine lesions, which is consistent with a dopamine-dependent mechanism (Gerber et al., 1988), although a mixture of excitatory and inhibitory effects on extracellularly recorded activity of dopamine cells has been observed (Sinton and Fallon, 1988; Kelland et al., 1990). Mixed results from systemically administered 5-HT_{1B} agonists may be due to effects on neurons other than dopamine neurons, or due to nonselective effects on other subtypes of 5-HT receptors.

Origin of GABA input

In humans, the density of 5-HT_{1D} receptors in the substantia nigra was significantly reduced in patients with Huntington's disease presumably due to degeneration of the GABA-contain-

Figure 5. Pharmacology of the 5-HT response. *A*, The 5-HT_{1B} agonist TFMPP (300 nM) reversibly reduced the amplitude of the GABA_A synaptic potential. Recovery was complete after 2 hr of washout. *B*, The action of 5-HT (100 μM) is not mimicked by DOI (10 μM), a 5-HT₂ receptor agonist. The 5-HT_{1A} agonist DP-5CT (3 μM) produces a small reduction in amplitude, but lower concentrations were ineffective. *C*, Spiperone (1 μM), after a 20 min perfusion, fails to block the effect of 5-HT (10 μM).

ing striatonigral pathway (Waeber and Palacios, 1989). In guinea pigs, a reduction of 5-HT_{1D} binding in substantia nigra was also reported following quinolinic acid-induced lesions of striatum (Waeber et al., 1990). In contrast, lesioning the midbrain with 6-hydroxydopamine failed to alter 5-HT₁ receptors (Waeber et al., 1989), indicating that 5-HT_{1D} receptors are not on dopamine cell bodies. In rats and mice, the 5-HT_{1B} receptor is thought to be functionally and anatomically identical to the 5-HT_{1D} receptor (Hoyer and Middlemiss, 1989). Therefore, we suggest that the 5-HT_{1B} receptor in rats is located on terminals of the striatonigral pathway, which is known to contain GABA (Kondo and Iwatsubo, 1978).

It should be noted that the highest density of 5-HT_{1B} receptors in the substantia nigra is in the zona reticulata (Pazos and Palacios, 1985), where there are few dopamine cells (Palkovits and Jacobowitz, 1974). However, dopamine neurons in the SNC have dendrites that may extend 100–200 μm into the reticulata (Juraska et al., 1977). It is possible that many of the 5-HT_{1B} receptors in the reticulata are on nerve terminals of the striatonigral pathway that synapse on dendrites of dopamine cells. Indeed, the ultrastructural study of Grofova and Rinvik (1970) showed that degenerating striatonigral nerve terminals following electrolytic lesions to caudate–putamen make synaptic contact with dendrites of compacta neurons that extend deep into the reticulata.

If 5-HT acts presynaptically to reduce GABA release, then one might expect ultrastructural evidence for axoaxonal synapses in the substantia nigra and VTA. However, electron microscopic studies of the VTA, SNC, and reticulata showed that axoaxonal synapses are not common (Rinvik and Grofova, 1970; Halliday and Tork, 1984). In fact, most 5-HT-containing terminals did not make classical synaptic junctions with postsynaptic membranes, although they may be in close apposition to axon terminals that do not contain 5-HT (Herve et al., 1987; Mori et al., 1987). It is possible that 5-HT is released extrasynap-

tically and may diffuse some distance before contacting GABA-containing terminals in the VTA and substantia nigra.

Our results are most consistent with the hypothesis that the striatonigral pathway releases GABA preferentially at GABA_B receptors on dopamine neurons. This is in conflict with a report by Precht and Yoshida (1971), who found that picrotoxin administered systemically blocked inhibitory field potentials recorded in SNC evoked by electrical stimulations of the caudate nucleus in the anesthetized cat. Also, Collingridge and Davies (1981) showed that bicuculline applied by microiontophoresis blocked the inhibition of spontaneous firing of dopamine cells produced by electrical stimulation of striatum in rats. It is possible that picrotoxin and bicuculline acted indirectly to inhibit the striatonigral pathway. Studies in our laboratory are in progress to test the hypothesis that the striatonigral pathway selectively activates GABA_B receptors.

Function of 5-HT_{1B} receptors in other CNS neurons

GABA_B synaptic potentials recorded in rat hippocampal CA1 cells (Segal, 1990) and septal neurons (Joels and Gallagher, 1988) were also blocked by 5-HT, leaving the synaptic potential mediated by GABA_A receptors unaffected or enhanced, but the receptor subtype was not identified. In rat locus ceruleus neurons, activation of 5-HT_{1B} receptors blocked synaptic potentials mediated by excitatory amino acids and GABA acting at GABA_A receptors (Bobker and Williams, 1989). In addition, the ability of 5-HT_{1B} (and 5-HT_{1D}) receptors to inhibit release of 5-HT has been well documented (Engel et al., 1986; Maura et al., 1986; Bobker and Williams, 1990).

Importance to neuropsychiatric diseases

Pharmacologic manipulation of GABA inputs to dopamine cells by drugs acting at presynaptic 5-HT receptors might be useful in the treatment of some neurologic and psychiatric diseases. Antagonists at the presynaptic 5-HT receptor would be expected

to increase the influence of GABA acting at GABA_B receptors. This increase in inhibitory tone should reduce firing of dopamine cells, and it is conceivable that this may be effective treatment for diseases such as Tourette's syndrome and tardive dyskinesia, which are thought to result from excessive dopamine stimulation (Weiner and Lang, 1989). It is also conceivable that this reduction in dopamine output from VTA cells might prove effective in the treatment of schizophrenia and drug abuse, both of which have been associated with increased activity in the mesocorticolimbic dopamine system. The clinical usefulness of drugs acting at presynaptic 5-HT receptors will most likely depend upon whether or not they are selective for those receptors that regulate the GABA system acting on dopamine neurons.

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