Regulation of Extracellular Concentrations of 5-Hydroxytryptamine (5-HT) in Mouse Striatum by 5-HT1A and 5-HT1B Receptors1

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Accepted for publication December 8, 1999  This paper is available online at http://www.jpet.org

ABSTRACT

The ability of selective serotonin (5-HT) receptor agonists to reduce the extracellular concentration of 5-HT was examined in the striatum of awake, unrestrained mice by in vivo microdialysis. Systemic administration of either 8-OH-PIPAT (R-(+)-trans-8-hydroxy-2-[N-n-propyl-N-(3’-iodo-2’-propenyl)] aminotetralin), a novel 5-HT1A receptor agonist, or CP 94,253, a selective 5-HT1B receptor agonist, resulted in significant dose-related reductions of striatal 5-HT. The effect of 8-OH-PIPAT (1.0 mg/kg) was blocked by pretreatment with WAY 100635 (0.1 mg/kg), a selective 5-HT1A receptor antagonist, but it was not blocked by pretreatment with GR 127935 (0.056 mg/kg), a selective 5-HT1B/1D receptor antagonist. The effect of CP 94,253 (1.0 mg/kg) was blocked by pretreatment with GR 127935 (0.056 mg/kg) but was not blocked by pretreatment with WAY 100635 (0.1 mg/kg). Neither WAY 100635 nor GR 127935 altered extracellular 5-HT levels at the doses that were able to completely block the effects of either 8-OH-PIPAT or CP 94,253. The present findings suggest that, on systemic administration, both 8-OH-PIPAT and CP 94,253 are potent and selective agonists at the somatodendritic 5-HT1A autoreceptor and terminal 5-HT1B/1D autoreceptor, respectively, and are each able to cause decreases in extracellular levels of 5-HT in the mouse striatum by activating a distinct set of receptors.

Drugs that are effective in treating a number of psychiatric disorders appear to produce their effects by altering serotonin (5-HT) neurotransmission. For example, selective serotonin reuptake inhibitors, the most commonly prescribed antidepressants, exert their effects by blocking the reuptake of 5-HT, thereby increasing extracellular levels of 5-HT (for reviews, see Preskorn, 1994; Wong et al., 1995) and fenfluramine, an effective antiobesity drug, increases the release of 5-HT (Samadin and Garattini, 1993). The release of 5-HT is known to be regulated by different populations of autoreceptors: both the somatodendritic 5-HT1A and terminal 5-HT1B/1D autoreceptors (for review, see Hen, 1992). The 5-HT1A autoreceptors are located on serotonergic cell bodies and reduce both the rate of discharge of 5-HT neurons and the synthesis of 5-HT, resulting in a corresponding decrease of the release of 5-HT from nerve terminals (Blier et al., 1987; Kennett et al., 1987; Sprouse and Aghajanian, 1988). In contrast, the 5-HT1B autoreceptor is predominantly located on axon terminals, according to studies that have localized the 5-HT1B receptor in the projection zones of neurons expressing 5-HT1B receptor mRNA (Boschert et al., 1994). Activation of 5-HT1B receptors results in the inhibition of 5-HT release evoked from rat cortical slices, consistent with the role of terminal presynaptic autoreceptors (Engel et al., 1986; Maura et al., 1986). A better understanding of the differing roles of the somatodendritic and terminal autoreceptors has been limited by a lack of potent, selective agonists at each autoreceptor and by drugs that can be administered systemically.

In vivo microdialysis studies have played an important role in characterizing the regulation of 5-HT release in a number of mammalian species. In rats, systemic administration of selective 5-HT1A receptor agonists, such as 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), has been shown to cause a reduction of extracellular 5-HT in the striatum, hippocampus, and other terminal brain regions (Hjorth and Sharp, 1991; Kreiss and Lucki, 1994). These effects were shown to be caused by activation of presynaptic 5-HT1A receptors because similar effects were produced by the local infusion of 8-OH-DPAT within the raphe nuclei, and administration of 5-HT1A receptor antagonists into the raphe nuclei prevented the effects of 8-OH-DPAT when given systemically (Kreiss and Lucki, 1994). Systemic administration of selective 5-HT1A receptor antagonists prevents the effects of 8-OH-DPAT.

ABBREVIATIONS: 5-HT, serotonin; 8-OH-DPAT, 8-hydroxy-2-dipropylaminotetralin; 8-OH-PIPAT, R-(+)-trans-8-hydroxy-2-[N-n-propyl-N-(3’-iodo-2’-propenyl)] aminotetralin; AUC, area under the curve; TFMPP, N-(3-trifluoromethyl)phenyl)piperazine.

Received for publication December 8, 1999.

1 This research was supported by U.S. Public Health Service Grant MH 48125 and predoctoral National Research Service Award Grant MH 12147 (to D.A.K.).
without changing extracellular 5-HT levels when given alone (Assie and Koek, 1996; Allen et al., 1997).

Studies of the activity of the terminal 5-HT 1B receptor have been limited by the lack of a selective 5-HT 1B receptor agonist that can activate the 5-HT 1B Receptor on systemic administration. Perfusion of selective 5-HT 1B or 5-HT 1B/1D receptor agonists, such as CP 93,129, RU 24969, or sumatriptan, through the microdialysis probe has been shown to reduce extracellular 5-HT levels in a variety of terminal regions in rats or guinea pigs, including the cortex, ventral hippocampus, and diencephalon (Hjorth and Tao, 1991; Chopin et al., 1994; Roberts et al., 1997). Systemic administration to rats of RU 24969 reduced extracellular levels of 5-HT and N-(3-trifluoromethylphenyl)piperazine (TFMPP) increased extracellular levels of 5-HT (Auerbach et al., 1991). Although both of these drugs have high affinity for 5-HT 1B receptors, they also interact with other receptors and their effects were not characterized with selective antagonists.

Recently, investigators have adapted in vivo microdialysis techniques to mice to measure extracellular levels of a variety of neurotransmitters (Boschi et al., 1995), including 5-HT (Trillat et al., 1997). The study of neurotransmitter release in mice has become especially compelling because rapid advances in the techniques of molecular genetics have made possible the development of mice with specific genetic deletions. The aim of the present study was to determine the roles of 5-HT 1A and 5-HT 1B receptors in regulating extracellular 5-HT in mice with the technique of in vivo microdialysis. These studies also involved pharmacological characterization of the effects of two novel 5-HT receptor agonists, the selective 5-HT 1A receptor agonist 8-OH-PIPAT (R-4-[trans-8-hydroxy-2-[N-n-propyl-N-(3'-iodo-2'-propenyl)] aminotetrinal; Zhuang et al., 1995) and the selective 5-HT 1B/1D receptor agonist CP 94,253 (Koe et al., 1992). Systemic administration of the 5-HT 1B receptor agonists, either 8-OH-PIPAT or CP 94,253, reduced extracellular 5-HT in the mouse striatum. Moreover, these effects were demonstrated to be regulated differentially by either 5-HT 1A or 5-HT 1B/1D receptors by studies with selective 5-HT receptor antagonists.

Materials and Methods

Subjects. Male 129 SVEM/+ test mice purchased from Jackson Laboratories (Bar Harbor, ME) 6 to 8 weeks in age were used in these studies. Mice were housed four per cage, given free access to standard rodent chow and water, and maintained on a 12-h light/dark schedule with lights on at 7:00 AM in a temperature-controlled (22°C) colony room. All studies were carried out in accordance with the Guide for the Care and Use of Laboratory Animals by the U.S. National Institutes of Health and were reviewed by the Institutional Animal Care and Use Committee.

Surgery. Mice were anesthetized with sodium pentobarbital (40 mg/kg i.p.) and positioned in a mouse stereotaxic instrument (Kopf Instruments, Tujunga, CA). Mice were implanted with a probe at the following coordinates (in millimeters) taken from bregma, in the striatum, +0.6 AP, +1.7 ML, and −4.5 DV, according to the atlas of Franklin and Paxinos (1997). A drop of cyanoacrylate was spread thinly over the exposed skull and the probe was then cemented in place. After surgery, the mice were placed into a clear polycarbonate cylindrical in vivo microdialysis apparatus (21.5 cm in height × 17.5 cm in diameter) with a counterbalance arm holding a liquid swivel (Instech Laboratories, Plymouth Meeting, PA) and allowed to recover overnight. At the completion of the experiment, brains were removed and frozen at −80°C. The brains were then sectioned with a refrigerated cryostat, stained with Neutral Red, and the tissue examined for the location of the dialysis probe. Only data from animals with probes in the striatum were used.

Dialysis Procedure. Microdialysis procedures were performed as previously described (Kirby et al., 1997) with several adaptations for mice. Concentric dialysis probes were made of hollow cuprammonium rayon fibers with a 224-μm o.d. and 35,000 mol. wt. cutoff (C series; Terumo Corp., Somerset, NJ). The dialysis fiber was inserted into a 10-mm piece of 25-gauge thin-wall stainless steel tubing (Small Parts, Inc., Miami, FL) and secured with cyanoacrylate gel so that 2.5 mm of surface area was exposed. The open end of the dialysis fiber was sealed with a 0.5-mm epoxy plug. Infow and outflow tubes were 19 and 32 mm in length, respectively, and made of polyimide-coated fused silica tubing (Polymeric Technologies, Phoenix, AZ). Infow and outflow tubes were inserted into the open end of the stainless steel tube and secured with cyanoacrylate. Polyethylene tubing (Clay Adams, Parsippany, NJ) was tightly fitted to the probe body and extended to cover most of the exposed infow and outflow tubes. Polyethylene 20 tubing was glued to the inflow tubing to connect it to the liquid swivel of the in vivo microdialysis apparatus (Instech Laboratories). The probes were tested for in vitro recovery of 5-HT the day before use. The probe recovery values ranged from 10 to 41% and the average was 21.2 ± 0.6% (n = 110).

The probes were continuously perfused with filtered artificial cerebrospinal fluid (147 mM NaCl, 1.7 mM CaCl2, 0.9 mM MgCl2, and 4 mM KCl, pH 6.3–6.5) at a rate of 0.8 μl/min using a Harvard Apparatus syringe pump. Dialysate samples were collected into polypropylene microcentrifuge vials 17 to 20 h after surgery at 20-min intervals for 2 h before injections or infusions. Samples were stored immediately after collection at −80°C until analysis.

Analysis of Dialysate. Samples were automatically injected into a Bioanalytical Systems 460 high-pressure liquid chromatograph by a BAS (West Lafayette, IN) sample sentinel microsampler set to a 12-μl injection volume. The HPLC mobile phase ([2.42 mM citric acid, 39.85 mM NaPO4 (monobasic), 0.25 mM EDTA, 0.737 mM 1-decanesulfonic acid, 10.0 mM NaCl, 0.2% triethylamine, 15–19% MeOH, pH 4.3] was pumped through a reversed phase 1 × 100 mm ODS 3-μm microbore column (C18; BAS) at a flow rate of 90 μl/min (Kreiss et al., 1993). The 5-HT from chromatograms of dialysate samples was identified by comparing their elution times with those of reference standards. The amount of 5-HT in each dialysate sample was quantified from their respective peak heights by a linear regression analysis of the peak heights obtained from a series of reference standards. The detection limit, defined as the sample amount producing a peak height twice the height of background noise, was 0.5 fmol. This sensitivity was sufficient to measure baseline levels of 5-HT, and reductions produced by 5-HT autoreceptor agonists, without the addition of a 5-HT reuptake inhibitor to the perfusion medium.

Data Analysis. The first four samples were averaged to derive the baseline value against which the remaining sample values were compared. Baseline values were expressed as femtomoles/10-μl sample corrected for individual probe recoveries. The overall effect of treatments on extracellular 5-HT levels was determined by two-factor ANOVAs with repeated measures over time. Individual time periods that differed from baseline were determined by a priori Dunnett’s test, two-tailed. Area under the curve (AUC) values were used to measure the summed effects of treatment over the course of an experiment. Comparisons between experimental and control groups were made with ANOVA followed by Dunnett’s test.

Drugs. Fluoxetine hydrochloride (Eli Lilly, Indianapolis, IN), GR 127505 (Glaxo Wellcome, Hertfordshire, UK), and WAY 106835 (Wyeth-Ayerst, Philadelphia, PA) were all dissolved in deionized water and administered in a volume of 8 ml/kg i.p. R-8-OH-PIPAT (custom synthesized by Dr. Hank Kung, University of Pennsylvania,
The effects of acute administration of the 5-HT$_{1A}$ receptor agonist 8-OH-PIPAT on extracellular 5-HT in the mouse striatum are shown in Fig. 2. An overall ANOVA revealed significant effects for treatment ($F_{4,120} = 11.46, P < .001$), time ($F_{9,120} = 2.72, P < .01$), and for the interaction between treatment and time ($F_{27,120} = 3.08, P < .001$). 8-OH-PIPAT decreased striatal 5-HT levels to a maximum of 53% below the baseline value at 40 min postinjection with 1 mg/kg, and to a maximum of 66% below baseline at 20 min postinjection with 10 mg/kg. AUC values for the 5-HT$_{1A}$ receptor agonist were significantly different between doses ($F_{4,36} = 16.42, P < .001$) (Fig. 2, inset). The AUC values for the two highest doses of 8-OH-PIPAT (1.0 and 10 mg/kg) were significantly different from the AUC value for saline administration.

The effects of acute administration of the 5-HT$_{1B}$ receptor agonist CP 94,253 on extracellular 5-HT in the mouse striatum are shown in Fig. 3. An overall ANOVA revealed significant effects of treatment ($F_{2,22} = 6.19, P < .01$) and time ($F_{9,198} = 4.557, P < .001$), but no significant interaction between treatment and time ($F_{18,198} = 1.29, P = .19$). CP 94,253 decreased striatal 5-HT levels to a maximum of 27%
increased AUC values, whereas AUC values for the GR
127935 + CP 94.253 did not differ significantly from saline.

The effects of acute administration of the 5-HT1A receptor
antagonist WAY 100635 are shown in Fig. 6A. An overall
ANOVA revealed significant effects for treatment ($F_{2,11} =
6.44, P = .01$), time ($F_{9.99} = 1.95, P < .05$), and the interac-
tion between treatment and time ($F_{18.99} = 1.80, P < .05$).
WAY 100635 (0.3 mg/kg) significantly reduced striatal 5-HT
levels 80 to 180 min after injection to a minimum of 40%
below basal values at 180 min postinjection. WAY 100635
(0.1 mg/kg) did not significantly reduce striatal 5-HT levels
at any time point in comparison to baseline. In comparison
with saline administration, the 0.3 mg/kg dose of WAY
100635 significantly increased AUC values (data not shown).

The effects of acute administration of the 5-HT1B/1D antag-
onist GR 127935 are shown in Fig. 6B. An overall ANOVA
revealed a significant effect of treatment ($F_{3,15} = 4.82, P <
.05$) but no significant effect of time ($F_{9.135} = 1.59, P = .12$)
or interaction between treatment and time ($F_{27,135} = 1.13, P =
.32$). GR 127935 (0.3 mg/kg) significantly reduced striatal
5-HT levels at 40, 60, and 120-180 min after injection to a
minimum of 47% below basal values at 160 min postinjection.
GR 127935 did not significantly reduce striatal 5-HT levels at
any time point at either the 0.1 mg/kg or 0.056 mg/kg dose as
compared with baseline. Analysis of AUC values for GR
127935 (data not shown) confirmed that the 0.3 mg/kg dose
of GR 127935 significantly reduced extracellular 5-HT levels in
comparison with saline administration.
Discussion

The technique of in vivo microdialysis has been used most frequently with larger species to measure extracellular levels of neurotransmitters but only recently has been adapted to mice because this species is being used to elucidate the genetic regulation of elements involved in neurotransmission. The baseline values for extracellular 5-HT measured in the mouse striatum were similar to those we have previously reported in the rat (Kung et al., 1995; Zhuang et al., 1995). 8-OH-PIPAT was efficacious, as was 5-HT, in stimulating [3H]guanosine-5'-O-(3-thio)triphosphate binding in membranes from S9 cells coexpressing the 5-HT1A receptor with either G_{i2} or G_{o} and in Chinese hamster ovary cells stably expressing the 5-HT1A receptor (D. Manning and R. Windh, personal communication). Recently, we have found that administration of 1.0 mg/kg R-8-OH-DPAT produced a peak reduction of extracellular 5-HT in the striatum to 60% in mice from a 129 substrain bred at the University of Pennsylvania (D.A.K. and I.L., unpublished data), an effect similar to that obtained with R-8-OH-DPAT in the present study. However, it is likely that enantiomeric differences can produce critical differences in potency and efficacy between agonists because administration of 10 mg/kg (+)-8-OH-DPAT produced only a 35% reduction of extracellular 5-HT in mouse striatum (data not shown). The effects of 5-HT1A receptor agonists on extracellular levels of 5-HT in the mouse are similar to previous studies in other species (Sharp et al., 1989; Kreiss and Lucki, 1994; Portas et al., 1996; Rex et al., 1997).

To ensure that the reduction of striatal extracellular 5-HT by 8-OH-PIPAT was due to selective activation of the 5-HT1A receptor, we attempted to block this effect by pretreatment with either the selective 5-HT1A receptor antagonist WAY 100635 (Fletcher et al., 1996) or the selective 5-HT1B/1D receptor antagonist GR 127935 (Skingle et al., 1996). As expected, WAY 100635 completely antagonized the effects on extracellular 5-HT produced by 8-OH-PIPAT. In contrast, GR

![Fig. 5. The effects of systemic administration of CP 94,253 (1.0 mg/kg) on extracellular 5-HT in the mouse striatum either when given alone (A, n = 6; baseline = 10.67 ± 1.22 fmol/10 μl (2.06 ± 0.27 fmol uncorrected); same as Fig. 3) or after pretreatment with either 0.056 mg/kg GR 127935 (B, n = 6; baseline = 6.83 ± 0.54 fmol/10 μl (1.29 ± 0.13 fmol uncorrected)) or 0.1 mg/kg WAY 100635 (C, n = 6; baseline = 7.17 ± 1.14 fmol/10 μl (1.44 ± 0.25 fmol uncorrected)). Controls were given saline pretreatment followed by saline administration (D, n = 6; baseline = 7.8 ± 1.1 fmol/10 μl (2.04 ± 0.19 fmol uncorrected; same as Fig. 4)). Values represent mean changes in 5-HT content, expressed as a percentage of baseline values. Vertical bars indicate 1 S.E. Asterisks indicate values that differ significantly from AUC values after administration of saline following saline pretreatment according to Dunnett’s test (⁎P < .05; **P < .01).](https://jpet.aspetjournals.org/content/1115/F5)

![Fig. 6. The effects of systemic administration of selective 5-HT receptor antagonists given alone on extracellular levels of 5-HT. Values represent mean changes in 5-HT content, expressed as a percentage of baseline values. Vertical bars indicate 1 S.E. A, effects of systemic administration of either saline (C, n = 6; baseline = 7.8 ± 1.1 fmol/10 μl (2.34 ± 0.53 fmol uncorrected); same as Fig. 4) or the 5-HT1A receptor antagonist WAY 100635 at 0.1 mg/kg (D, n = 4; baseline = 6.25 ± 0.74 fmol/10 μl (1.59 ± 0.30 fmol uncorrected)) or 0.3 mg/kg (E, n = 5; baseline = 10.40 ± 0.68 fmol/10 μl (1.87 fmol uncorrected)). B, effects of systemic administration of either saline (C, n = 6; baseline = 7.8 ± 1.1 fmol/10 μl (2.34 ± 0.53 fmol uncorrected); same as Fig. 4) or the 5-HT1B/1D receptor antagonist GR 127935 at 0.056 mg/kg (F, n = 4; baseline = 9.50 ± 0.96 fmol/10 μl (2.17 ± 0.17 fmol uncorrected)); 0.1 mg/kg (G, n = 4; baseline = 10.25 ± 1.53 fmol/10 μl (1.95 ± 0.27 fmol uncorrected)); or 0.3 mg/kg (H, n = 4; baseline = 10.25 ± 2.25 fmol/10 μl (2.31 ± 0.23 fmol uncorrected)).](https://jpet.aspetjournals.org/content/1115/F6)
127935 did not alter the effects of 8-OH-PIPAT. Thus, as measured by in vivo microdialysis in the mouse, 8-OH-PIPAT appears to reduce extracellular 5-HT by specifically activating the 5-HT\textsubscript{1A} receptor.

The demonstration that systemic administration of the 5-HT\textsubscript{1B/1D} receptor agonist CP 94,253 elicited a dose-dependent decrease in extracellular 5-HT in the striatum of mice is the first reported instance of a selective 5-HT\textsubscript{1B/1D} receptor agonist that is capable of reducing extracellular 5-HT levels when administered systemically. CP 94,253 has been found to have at least a 40-fold greater selectivity for the 5-HT\textsubscript{1B} receptor over the 5-HT\textsubscript{1A} receptor (5-HT\textsubscript{1A} receptor, \(K_i = 89 \pm 15 \text{nM}\); 5-HT\textsubscript{1B} receptor, \(K_i = 2 \pm 0.4 \text{nM}\); Koe et al., 1992). The specificity of the effects of CP 94,253 were demonstrated by showing that pretreatment with GR 127935 completely blocked the effects of CP 94,253, whereas pretreatment with a dose of WAY 100635 that was effective at preventing the effects of 8-OH-PIPAT could not diminish the effect of CP 94,253. Although the effects of other less selective 5-HT\textsubscript{1B} receptor agonists such as RU 24969 and TFMPP have been examined on extracellular 5-HT in rats, only RU 24969 reduced extracellular 5-HT (Auerbach et al., 1991) and it is not clear whether this effect was mediated by 5-HT\textsubscript{1B} or 5-HT\textsubscript{1A} receptors. These findings also support the idea that systemic administration of CP 94,253 produces behavioral effects by selectively activating central 5-HT\textsubscript{1B} receptors (Lee and Simansky, 1997; Boutrel et al., 1999), although presynaptic and postsynaptic components could not be distinguished.

Although radioligand-binding studies have shown that CP 94,253 is at least 20-fold more selective for the 5-HT\textsubscript{1B} receptor over the 5-HT\textsubscript{1D} receptor (5-HT\textsubscript{1D} receptor, \(K_i = 2.0 \pm 0.4 \text{nM}\); 5-HT\textsubscript{1D} receptor, \(K_i = 49 \pm 3 \text{nM}\); Koe et al., 1992), there still could be a 5-HT\textsubscript{1D} receptor component to the activity of CP 94,253 in vivo. This possibility is minimized, however, by evidence that indicates low levels of 5-HT\textsubscript{1D} receptor mRNA in rodent brain and very high levels of 5-HT\textsubscript{1B} receptor mRNA, particularly in the striatum (Bruinvels et al., 1994). Additionally, autoradiographic studies in the mouse brain have shown an extremely low intensity of 5-HT\textsubscript{1D} receptor mRNA in glomerular pallidus, substantia nigra, entopeduncular nucleus, and internal capsule (Boschert et al., 1994). The feasibility of a 5-HT\textsubscript{1D} receptor component of the in vivo effects of CP 94,253 remains but elucidation of this component is further confounded by the lack of pharmacological agents that could satisfactorily discriminate the effects at 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors. GR 127935 has been found to be a mixed 5-HT\textsubscript{1B/1D} receptor antagonist (Skingle et al., 1996). Ketanserin, a mixed 5-HT\textsubscript{1A/1D/2A/2C} receptor antagonist, was considered for this purpose. However, ketanserin produced an intrinsic reduction of striatal 5-HT when given alone at both the 1- and 3-mg/kg doses (data not shown) and therefore could not be used as an antagonist in these experiments. Several compounds have recently been discovered that are selective for 5-HT\textsubscript{1B} (e.g., SB 224289) or 5-HT\textsubscript{1D} receptors (e.g., BRL-15572) and may be suitable for this purpose (Price et al., 1997; Selkirk et al., 1998). Recently, we have found that CP 94,253 was ineffective at reducing extracellular 5-HT in 5-HT\textsubscript{1B} receptor knockout mice (D.A.K. and L.L., unpublished observations), suggesting that the decrease in extracellular 5-HT by this compound was mediated by 5-HT\textsubscript{1B} receptors.

To confirm that the doses of both the 5-HT\textsubscript{1A} receptor antagonist WAY 100635 and the 5-HT\textsubscript{1B/1D} receptor antagonist GR 127935 had no intrinsic activity on extracellular 5-HT, the effects of each of these drugs were examined at various doses when given alone. At the doses of WAY 100635 and GR 127935 that were able to completely block the corresponding agonist effects of 8-OH-PIPAT and CP 94,253, no intrinsic effects were measured. At higher doses, however, both WAY 100635 and GR 127935 showed intrinsic effects; both caused a significant decrease in extracellular 5-HT in the striatum of the mouse. Both WAY 100635 itself and its metabolite WAY 100634 have high affinity for \(\alpha\)-1 adrenoceptors, in addition to 5-HT\textsubscript{1A} receptors (Osman et al., 1998), so that it is possible that either WAY 100635 or its metabolite could account for these effects on extracellular 5-HT in the mouse through antagonism of 5-HT\textsubscript{1A} receptors (Osman et al., 1998; Assie and Koek, 1996). Previous work by Roberts et al. (1997, 1998) showed that GR 127935 caused an increase in extracellular 5-HT in terminal regions of the guinea pig brain when it was infused through the microdialysis probe, whereas a decrease in extracellular 5-HT was elicited in terminal regions of the guinea pig brain when GR 127935 was given systemically. They speculated that GR 127935 binds to 5-HT\textsubscript{1B/1D} receptors on nerve terminals that innervate the dorsal raphe nuclei and causes a local increase in extracellular 5-HT in the dorsal raphe. The increased 5-HT then can activate somatodendritic 5-HT\textsubscript{1A} autoreceptors that elicit a decrease in extracellular 5-HT in terminal regions innervated by the dorsal raphe, such as the striatum. Whether similar physiological regulation of extracellular 5-HT occurs in the mouse remains to be determined.

In conclusion, the present study showed that in vivo microdialysis is a viable technique in mice and that microdialysis studies in mice are capable of measuring changes in extracellular 5-HT in a similar manner to studies performed in a variety of other species. Furthermore, these studies have illustrated the putative ability of 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} autoreceptors to differentially regulate the release of 5-HT in the mouse striatum, and highlighted the ability of two novel compounds, 8-OH-PIPAT and CP 94,253, to selectively activate 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} receptors, respectively. A greater understanding of the activities of these two serotoninergic autoreceptors could contribute to a greater understanding to the pathogenesis of diseases such as depression and anxiety.

References


