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Differential Effects of 5-Hydroxytryptamine$_{1A}$ Selective Drugs on the 5-HT Behavioral Syndrome

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SMITH, L. M. AND S. J. PEROUTKA. *Differential effects of 5-hydroxytryptamine$_{1A}$ selective drugs on the 5-HT behavioral syndrome.* PHARMACOL BIOCHEM BEHAV 24(6) 1513–1519, 1986.—The effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), 5-methoxy-N,N-dimethyltryptamine (5-MeODMT), buspirone and isapirone were examined at 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) binding sites and on the 5-HT behavioral syndrome in the rat. 8-OH-DPAT, 5-MeODMT, buspirone and isapirone are all potent inhibitors of ^{3}H-8-OH-DPAT binding to rat brain membranes (K_i values=1.9–13 nM). However, these drugs have differential effects on the 5-HT behavioral syndrome. 8-OH-DPAT, 5-MeODMT and buspirone induce hindlimb abduction, flattened body posture and Straub tail. Isapirone induces only a slight flattening of body posture. By contrast, 8-OH-DPAT and 5-MeODMT, but not buspirone and isapirone, also induce forepaw treading, head-weaving and tremor. However, both buspirone and isapirone antagonize the induction of these three behaviors by 8-OH-DPAT or 5-MeODMT. These data show that 8-OH-DPAT and 5-MeODMT are "full agonists" in relation to six components of the 5-HT behavioral syndrome. Buspirone and isapirone, on the other hand, act as "antagonists" in relation to forepaw treading, head-weaving and tremor. Therefore, these data suggest that specific components of the 5-HT behavioral syndrome are mediated by 5-HT$_{1A}$ receptors.

5-HT$_{1A}$ receptor 5-HT syndrome 8-OH-DPAT 5-MeODMT Buspirone Isapirone TVX Q 7821

INCREASES in central serotonergic activity in the rat result in a specific behavioral syndrome which consists of reciprocal forepaw treading, side to side head-weaving, tremor (primarily of the head and forelimbs), hindlimb abduction, and Straub tail. In addition, flattened body posture, head-twitches, hypertonicity, hyperactivity and hyper-reactivity are often considered to be part of this syndrome [6–8, 13, 16, 35]. These behavioral responses are induced by 5-HT agonists or drugs which significantly increase synaptic 5-HT levels. Presumably, the behaviors are mediated by specific 5-HT receptors in the central nervous system.

Radioligand binding studies have been used to differentiate two distinct classes of central 5-HT receptors: 5-HT$_1$ and 5-HT$_2$ sites [26]. More recently, 5-HT$_1$ binding sites have been shown to be heterogenous [21,28], and 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1C}$ binding site subtypes have been identified and characterized in brain membranes [19, 20, 22, 30]. Of these three 5-HT$_1$ binding sites, the 5-HT$_{1A}$ subtype is the only site which can be selectively labeled in rat brain membranes [2, 5, 10] as compared to the 5-HT$_{1B}$ and 5-HT$_{1C}$ sites which are labeled by radioligands that also bind to other receptor sites [19,20]. The 5-HT$_{1A}$ binding site has high affinity for 8-OH-DPAT, 5-MeODMT, buspirone, and isapirone (formerly called TVX Q 7821) [2, 5, 10, 22].

Both 5-MeODMT and 8-OH-DPAT produce the full 5-HT behavioral syndrome [1, 7, 12, 36, 37]. By contrast, initial studies of buspirone and isapirone found that these drugs produce only certain signs of the 5-HT behavioral syndrome [11,31]. In the present study, the effects of 8-OH-DPAT, 5-MeODMT, buspirone and isapirone were analyzed at 5-HT$_{1A}$ binding sites labeled by ^{3}H-8-OH-DPAT in brain membranes and on the 5-HT behavioral syndrome in the rat.

METHOD

Animals

For radioligand studies, adult rat brains were obtained either immediately following decapitation or purchased from Pel-Freeze Inc. (Rogers, AK) and stored at −20°C until needed. For behavioral studies, male albino Sprague-Dawley rats were obtained form Simonsen Laboratories, Inc. (Gilroy, CA). Rats were housed with free access to food and water and maintained on a 12 hour (8 a.m.–8p.m.) on/off cycle at constant temperature (22°C). All experiments were

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performed during the light phase of the cycle. Rats weighed 250–350 g at the time of the behavioral studies.

Radioligand Studies

Receptor binding assays were performed as previously described [22,24]. Briefly, on the day of study, the brains were defrosted and the frontal cortex was dissected. Tissues were homogenized in 20 volume of 50 mM Tris-HCl (pH 7.7 at 25°C) using a Brinkmann Polytron and then centrifuged in an IEC B20A centrifuge at 49,000 × g for 10 minutes. The supernatant was discarded and the pellet was resuspended in the same volume of Tris-HCl buffer and incubated at 37°C for 10 minutes prior to a second centrifugation at 49,000 × g for 10 minutes. The final pellet was resuspended in 80 volume of Tris-HCl buffer containing 10 μM pargyline, 4 mM calcium chloride and 0.1% ascorbic acid. The suspensions were immediately used in the binding assay.

Binding assays consisted of 1.0 ml ^{3}H-8-OH-DPAT (final concentration=0.2–0.3 nM), 0.1 ml buffer or displacing drug and 0.8 ml tissue suspension. Following incubation at 25°C for 30 minutes, the assays were rapidly filtered under vacuum through Whatman GF/B filters with two 5 ml washes using 50 mM Tris-HCl buffer. Radioactivity was measured by liquid scintillation spectroscopy in 7 ml of Aquasol (New England Nuclear; Boston, MA) at 54% efficiency. Specific binding was defined using 10 μM 5-HT in all experiments. Generally, 75–80% of total binding was specific for ^{3}H-8-OH-DPAT. IC_{50} values were determined by log-logit analysis and converted to apparent K_i values using the equation $K_i = IC_{50}/(1 + [I]/K_D)$. The K_D for ^{3}H-8-OH-DPAT binding was 0.75 nM as previously determined in rat frontal cortex [24].

Behavioral Measurements

Five to ten minutes before intraperitoneal (IP) injection, rats were placed in individual clear Plexiglas cages with a layer of sawdust covering the bottom. Five minutes after injection, observation periods of 45 seconds per rat were initiated. Observations were repeated every 5 minutes for a period of one hour for time course studies and a period of 30 minutes for blocking studies. The following signs were rated in individual rats: (1) forepaw treading, (2) head-weaving, (3) tremor, (4) hindlimb abduction, (5) flattened body posture, (6) Straub tail. A 4-point ranked intensity scale was used (0=absent, 1=equivocal, 2=definite, 3=intense) [36].

Drugs

For radioligand studies, drugs were dissolved and diluted in 50 mM Tris-HCl buffer. For behavioral studies, 8-OH-DPAT, buspirone and isapirone were dissolved directly in 0.9% NaCl solution. 5-MeODMT was dissolved in 0.2 ml of glacial acetic acid before being diluted in normal saline. Drugs were administered by IP injection of 1 ml volume. Drugs were obtained from the following sources: ^{3}H-8-OH-DPAT (116 Ci/mmole; Research Products International Corp.; Mount Prospect, IL), 8-OH-DPAT, 5-MeODMT (Research Biochemicals, Inc.; Waltham, MA), buspirone (Bristol-Myers; Evansville, IN), isapirone (Troponwerke, Cologne); 5-HT (Sigma Chemical Co.; St. Louis, MO).

RESULTS

Radioligand Binding Studies

Drug competition studies versus ^{3}H-8-OH-DPAT binding were performed in rat frontal cortex. In each study, drug concentrations ranged from 10^{-11} M through 10^{-4} M and were analyzed at half-log unit intervals. As shown in Fig. 1, 8-OH-DPAT, 5-MeODMT, buspirone and isapirone are all potent inhibitors of specific ^{3}H-8-OH-DPAT binding. Each of the drugs produces monophasic inhibition of ^{3}H-8-OH-DPAT binding with Hill slopes of approximately unity. Furthermore, each drug produces total displacement of ^{3}H-8-OH-DPAT binding as difined by 10^{-5} M 5-HT. 8-OH-DPAT is the most potent agent with a K_i value of 1.9±0.4 nM. 5-MeODMT and isapirone are slightly less potent agents with K_i values of 3.4±0.7 nM and 6.2±2 nM, respectively. Buspirone is the weakest agent analyzed at the 5-HT_{1A} site labeled by ^{3}H-8-OH-DPAT, with a K_i value of 13±2 nM.

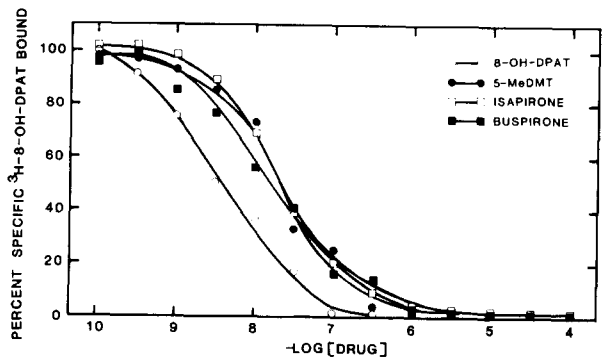

FIG. 1. Drug inhibition of ^{3}H-8-OH-DPAT binding to 5-HT_{1A} binding sites in rat frontal cortex. ^{3}H-8-OH-DPAT binding was performed as described in the Method section. Data shown are the means of a single experiment performed in triplicate. Each experiment was repeated 4 times. Drugs studied are 8-OH-DPAT (○), 5-MeDMT (●), isapirone (□) and buspirone (■).

Time Course of Behavioral Response to 5-HT_{1A} Selective Agents

The six previously listed behavioral signs were rated at 5 minute intervals for one hour following IP injection of 8-OH-DPAT, 5-MeODMT, buspirone or isapirone. Sedative effects were not observed with any drug dose analyzed. Using the 0–3 rating scale, a maximal total behavioral score of 18 was possible during a single observation period. As shown in Fig. 2A, only a minimal drug effect was observed following injection of 0.1 mg/kg 8-OH-DPAT. At 0.3 mg/kg 8-OH-DPAT, most components of the 5-HT behavioral syndrome were weakly present between 5 and 25 minutes after injection, with peak behavioral scores ranging from 5.3–5.7. At 1 and 3 mg/kg 8-OH-DPAT, a rapid onset of action was noted, with peak behavioral scores (8.3 and 10.3, respectively) recorded 5 minutes after injection. The behavioral scores slowly decreased over the next 30–40 minutes. A dose of 10 mg/kg 8-OH-DPAT resulted in the rapid onset of the entire 5-HT behavioral syndrome. A peak behavioral score of 14.7 was observed within 5 minutes of injection. The behavioral score decreased over the next 55 minutes, but remained elevated for an hour after injection (behavioral score=5.3).

A similar pattern was observed with 5-MeODMT (Fig. 2B). A dose of 0.1 mg/kg 5-MeODMT had essentially no

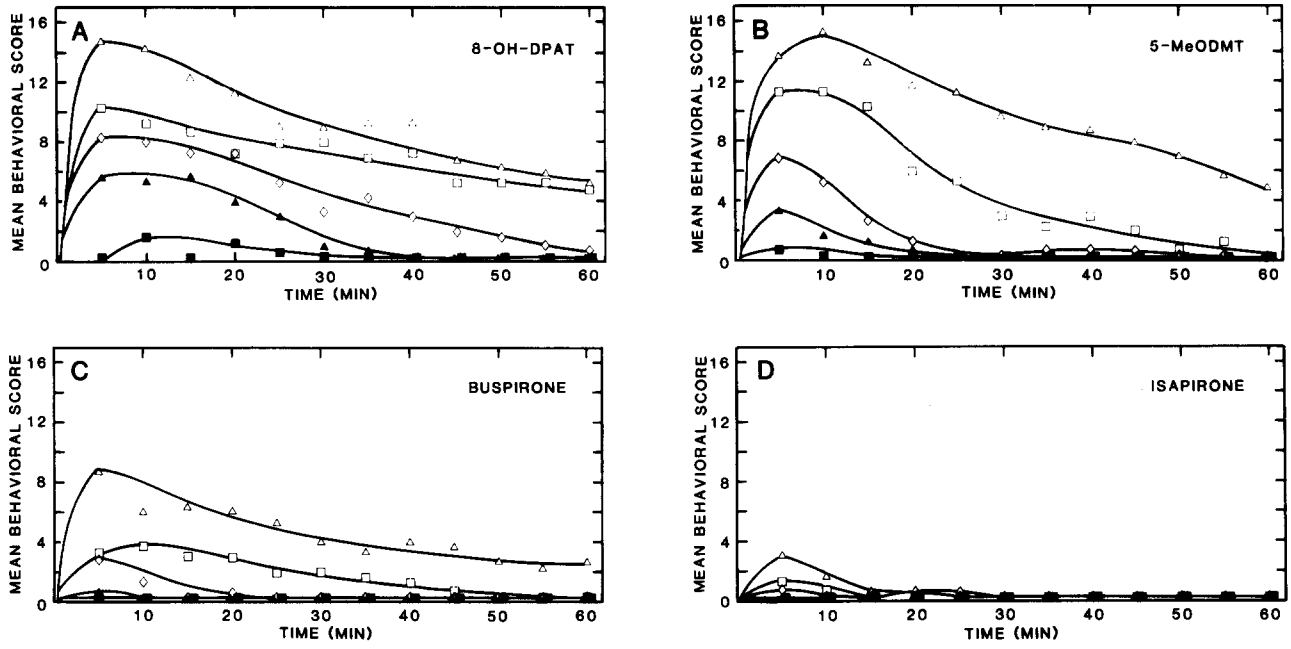

FIG. 2. Time course of 8-OH-DPAT, 5-MeODMT, buspirone and isapirone effects on the 5-HT behavioral syndrome. The behavioral response was quantified using the ranked intensity scale as described in the Method section. Scores for forepaw treading, head-weaving, tremor, hindlimb abduction, flattened body posture and Straub tail were recorded at 5 minute intervals between 5 and 60 minutes after doses of 0.1 (■), 0.3 (▲), 1 (◇), 3 (□) and 10 (△) mg/kg of each drug. Data shown are the mean scores for 3 animals in each condition. Drugs studied were (A) 8-OH-DPAT, (B) 5-MeODMT, (C) buspirone, and (D) isapirone.

TABLE 1

MEAN BEHAVIORAL SCORES FOR INDIVIDUAL 5-HT SYNDROME COMPONENTS INDUCED BY 8-OH-DPAT, 5-MeODMT, BUSPIRONE, ISAPIRONE OR SALINE

	Behavioral Score				
Sign	8-OH-DPAT	5-MeODMT	Buspirone	Isapirone	Saline
Forepaw treading	23 ± 2	24 ± 5	0 ± 0	0 ± 0	0 ± 0
Head-weaving	22 ± 2	22 ± 5	0 ± 0	0 ± 0	0 ± 0
Tremor	13 ± 2	16 ± 3	0 ± 0	0 ± 0	0 ± 0
Hindlimb abduction	22 ± 2	23 ± 4	26 ± 0.5	1.0 ± 0.5	0 ± 0
Flattened posture	24 ± 2	28 ± 5	24 ± 1	5.0 ± 0.8	0 ± 0
Straub tail	8.7 ± 2	3.7 ± 1	4.7 ± 1	1.7 ± 1	2.0 ± 0.8
Total	110 ± 9	120 ± 20	55 ± 3	7.7 ± 1	2.0 ± 0.8

The intensity of forepaw treading, head-weaving, tremor, hindlimb abduction, flattened body posture and Straub tail was scored at 5 minute intervals on a ranked intensity scale (0–3). Twelve measurements were made from 5–60 minutes after IP injection of 10 mg/kg drug. Interval scores for each sign were summed over the 1 hour period. Values given are the mean summed scores ± standard error of 3 rats per condition.

TABLE 2

BUSPIRONE AND ISAPIRONE ANTAGONISM OF 8-OH-DPAT- OR 5-MeODMT-INDUCED FOREPAW TREADING, HEAD-WEAVING AND TREMOR

Agonist	Dose (mg/kg)	Behavioral Score: Buspirone	Behavioral Score: Isapirone
8-OH-DPAT (3 mg/kg)	Saline	25 ± 2	25 ± 2
	0.1	24 ± 2	20 ± 0.5
	0.3	24 ± 2	19 ± 2
	1	14 ± 2	19 ± 0.6
	3	2.7 ± 1	12 ± 0
	10	0.67 ± 0.3	0.67 ± 0.3
5-MeODMT (3 mg/kg)	Saline	21 ± 3	21 ± 3
	0.1	20 ± 0.3	18 ± 1
	0.3	12 ± 2	17 ± 2
	1	9.0 ± 2	20 ± 2
	3	4.3 ± 2	12 ± 1
	10	2.7 ± 1	4.7 ± 1

Intensity scores (0–3) for forepaw treading, head-weaving and tremor were recorded following IP injections of 3 mg/kg of 8-OH-DPAT or 5-MeODMT. Experiments were performed in the absence or presence of various doses of buspirone or isapirone (injected IP 1 minute before 8-OH-DPAT or 5-MeODMT). The intensity of each sign was rated every 5 minutes from 5–30 minutes after injection and the results summed after 6 observation periods. Values given are mean summed scores ± standard error of 3 rats per condition.

TABLE 3

BUSPIRONE AND ISAPIRONE INTERACTIONS WITH 8-OH-DPAT- OR 5-MeODMT-INDUCED HINDLIMB ABDUCTION, FLATTENED POSTURE AND STRAUB TAIL

Agonist	Dose (mg/kg)	Behavioral Score: Buspirone	Behavioral Score: Isapirone
8-OH-DPAT (3 mg/kg)	Saline	24 ± 2	24 ± 2
	0.1	34 ± 2	23 ± 3
	0.3	29 ± 3	25 ± 4
	1	26 ± 3	22 ± 0
	3	23 ± 3	19 ± 0.6
	10	29 ± 0.3	24 ± 0.3
5-MeODMT (3 mg/kg)	Saline	31 ± 5	31 ± 5
	0.1	26 ± 3	27 ± 5
	0.3	26 ± 3	26 ± 3
	1	34 ± 2	25 ± 0.5
	3	28 ± 2	24 ± 3
	10	31 ± 0.3	29 ± 1

Intensity scores (0–3) for hindlimb abduction, flattened posture and Straub tail were recorded following IP injections of 3 mg/kg of 8-OH-DPAT or 5-MeODMT. Experiments were performed in the absence or presence of various doses of buspirone or isapirone (injected IP 1 minute before 8-OH-DPAT or 5-MeODMT). The intensity of each sign was rated every 5 minutes from 5–30 minutes after injection and the results summed after 6 observation periods. Values given are mean summed scores ± standard error of 3 rats per condition.

effect on rat behavior. A slight behavioral effect was observed at 0.3 mg/kg, while definitive signs of the 5-HT behavioral syndrome were first noted at a dose of 1 mg/kg 5-MeODMT. As also observed with 8-OH-DPAT, a dose of either 3 or 10 mg/kg 5-MeODMT resulted in the rapid onset of all components of the 5-HT behavioral syndrome, with peak behavioral scores of 11.3 and 15.3, respectively, observed within the first 5–10 minutes.

A markedly different pattern was observed with buspirone (Fig. 2C). No behavioral effect was noted following a dose of either 0.1 or 0.3 mg/kg buspirone. At both 1 and 3 mg/kg buspirone, certain of the behavioral components of the 5-HT behavioral syndrome were noted. At a dose of 10 mg/kg buspirone, the 5-HT behavioral score was elevated within 5 minutes to 8.7. This submaximal score is somewhat misleading in that it represents the intense appearance of certain components of the entire syndrome, with other components completely absent (see section below).

A third behavioral pattern was observed with isapirone (Fig. 2D). Essentially no behavioral effect was observed at doses of 0.1–3 mg/kg isapirone. The behavioral score was only slightly increased to 3.0 at 5 minutes following a dose of 10 mg/kg isapirone. The behavior following this dose was marked by mild flattened body posture.

Effect of 10 mg/kg Drug on Individual Components of 5-HT Behavioral Syndrome

The effects of 10 mg/kg of each of the four 5-HT_{1A} agents on individual components of the 5-HT behavioral syndrome were examined. Again, behavioral signs were rated at 5 minute intervals following IP drug injection and interval scores were summed over an hour. Mean summed scores for individual signs are shown in Table 1. Both 8-OH-DPAT and 5-MeODMT significantly increased the behavioral scores for forepaw treading, head-weaving and tremor. In marked contrast, neither buspirone nor isapirone elicited any of these three components of the 5-HT behavioral syndrome. 8-OH-DPAT, 5-MeODMT and buspirone strongly elicited hindlimb abduction and flattened body posture at a dose of 10 mg/kg. The mean summed behavioral scores observed for these two signs were essentailly identical following IP injections of 10 mg/kg 8-OH-DPAT, 5-MeODMT or buspirone (range=22–28). By contrast, isapirone did not elicit hindlimb abduction and produced only mild flattened body posture. At 10 mg/kg, 8-OH-DPAT, 5-MeODMT and buspirone also produced intermittent intense Straub tails. Following injection of 10 mg/kg isapirone, however, there were no definite signs of Straub tail and the rating of this behavioral sign could not be distinguished from that following injection of normal saline.

Interactions of Buspirone and Isapirone with 8-OH-DPAT-or 5-MeODMT-Induced Behaviors

Behavioral signs were rated at 5 minute intervals for 30 minutes following IP injection of 3 mg/kg 8-OH-DPAT or 5-MeODMT to rats previously injected (1 minute earlier) with various doses of buspirone or isapirone. Interval scores were summed for two distinct groups of behavioral components: forepaw treading, head-weaving and tremor (Table 2), and hindlimb abduction, flattened body posture and Straub tail (Table 3).

At a dose of 0.1 mg/kg, buspirone had no significant effect

on 3 mg/kg 8-OH-DPAT- or 5-MeODMT-induced forepaw treading, head-weaving or tremor (Table 2). However, at higher doses, an inhibitory effect of buspirone was observed on these induced behaviors. At 10 mg/kg buspirone, the induction of forepaw treading, head-weaving and tremor by 3 mg/kg 8-OH-DPAT or 5-MeODMT was almost completely blocked. A similar pattern of drug effects was observed when isapirone was given 1 minute before 3 mg/kg 8-OH-DPAT or 5-MeODMT. Isapirone at a dose of 0.1 mg/kg had little effect on the appearance of 8-OH-DPAT- or 5-MeODMT-induced forepaw treading, head-weaving or tremor. With higher doses of isapirone, an inhibitory effect on these drug-induced behaviors was observed. The higher dose of isapirone needed to inhibit the appearance of these three behavioral components suggests that isapirone is slightly less potent than buspirone in this regard.

In contrast, a dose-dependent effect of buspirone or isapirone on 8-OH-DPAT- or 5-MeODMT-induced hindlimb abduction, flattened body posture and Straub tail was not observed (Table 3). As noted above, buspirone induced these behavioral signs independently. The induction of these three signs by 3 mg/kg 8-OH-DPAT or 5-MeODMT was not affected by any dose of buspirone administered 1 minute previously. Similarly, treatment with various doses of isapirone had no effect on the induction of hindlimb abduction, flattened body posture and Straub tail by 3 mg/kg 8-OH-DPAT or 5-MeODMT.

DISCUSSION

The major finding of the present study is that four potent 5-HT$_{1A}$ agents have differential effects on the 5-HT behavioral syndrome in the rat. 8-OH-DPAT and 5-MeODMT may be considered full agonists since they elicit all six components of the 5-HT behavioral syndrome. Buspirone acts as an agonist since it elicits three components of the 5-HT syndrome (hindlimb abduction, flattened body posture and Straub tail). Isapirone, on the other hand, only minimally induces these behaviors and does not inhibit their appearance following induction by 8-OH-DPAT or 5-MeODMT. In marked contrast, both buspirone and isapirone display antagonist properties in that they block three other components of the 5-HT behavioral syndrome induced by 8-OH-DPAT and 5-MeODMT (forepaw treading, head-weaving, tremor). Therefore, the results of the present study demonstrate that both buspirone and isapirone may be considered "mixed agonists/antagonists" of the 5-HT behavioral syndrome.

The ability of 8-OH-DPAT and 5-MeODMT to produce the full 5-HT behavioral syndrome has been well documented. When administerd to rats, 8-OH-DPAT induces a complex of behaviors characteristic of the 5-HT syndrome [1, 12, 35, 36]. Even after reserpine pretreatment, at least two signs of the syndrome, forepaw treading and flattened body posture, are induced by 8-OH-DPAT [35,36]. This finding suggests that indirect catecholamine mechanisms are not involved in the production of these two signs. Since 8-OH-DPAT is an extremely potent and selective 5-HT$_{1A}$ agonist [12, 17, 22], it was concluded that forepaw treading and flattened posture occur as a result of 5-HT$_{1A}$ receptor activiation [35,36]. A similar behavioral response occurs following administration of 5-MeODMT [4, 7, 35, 37].

Extensive behavioral analysis of buspirone and isapirone has not been reported previously. These agents are structurally similar and share a high affinity for the 5-HT$_{1A}$ binding sites [23]. As shown in the present study, buspirone clearly induces hindlimb abduction, flattened body posture and Straub tail. These findings are in agreement with the results of Hjorth and Carlsson [11]. These authors also reported forepaw extension and treading following 10 mg/kg buspirone injections. In the present study, forepaw treading was either absent or only weakly present within the first 5–10 minutes after injection of 10 mg/kg buspirone. This study demonstrates that, in addition to its direct behavioral effects, buspirone antagonizes 8-OH-DPAT- or 5-MeODMT-induction of three components of the 5-HT syndrome.

Despite their similar structures and receptor profiles, the behavioral effects of buspirone and isapirone are quite distinct. In the present study, the only direct behavioral effect of 10 mg/kg isapirone observed was a slight flattening of body posture. Similarly, Spencer *et al.* [31] reported mild flattening of body posture and absence of forepaw treading after a dose of 5 mg/kg isapirone. Even at doses as high as 80 mg/kg, only minimal evidence for the presence of the full 5-HT syndrome was observed [31]. The ability of isapirone to act as an antagonist of direct acting 5-HT$_{1A}$ selective agonists such as 8-OH-DPAT and 5-MeODMT has not been reported previously.

The 5-HT behavioral syndrome has been used extensively as a model for the activation of central 5-HT receptors. The majority of studies have focused on the role of 5-HT$_2$ receptors in the mediation of "head-twitches" or "head shakes" [4, 14, 16, 25, 38]. More recently, it has been suggested that other components of the 5-HT behavioral syndrome may be mediated by 5-HT$_1$ receptors [4, 16, 35]. Following chronic administration of monoamine oxidase inhibitors, the 5-HT behavorial syndrome was inhibited, and a concurrent decrease occurred in ^{3}H-5-HT binding to 5-HT$_1$ sites in brainstem and spinal cord [15]. Non-selective 5-HT antagonists blocked or inhibited six components of the behavioral syndrome, while 5-HT$_2$ receptor selective antagonists had no blocking effect [16]. These findings were considered to further evidence for 5-HT$_1$ receptor mediation of the 5-HT behavioral syndrome. By contrast, other laboratories have reported that non-selective 5-HT antagonists such as metergoline do not block the behavioral syndrome produced by 8-OH-DPAT [12] or lisuride [29]. In agreement with these reports are studies showing that 5-HT$_2$ antagonists may block or inhibit the appearance of certain signs of the 5-HT behavioral syndrome besides the head-twitch [4, 9, 18, 35, 36].

Some of these apparent discrepancies in the literature are likely to be due to the different methods used to rate the syndrome, the choice of the specific behavioral signs to be rated and the drugs used to induce the syndrome. However, the recent development and characterization of 5-HT$_{1A}$ selective agents may clarify the role of 5-HT receptor subtypes in the mediation of specific behaviors. The results of behavioral studies with 8-OH-DPAT and 5-MeODMT indicate that forepaw treading and flattened body posture may be regarded as behavioral models of 5-HT$_{1A}$ receptor activation [35–37]. The results of the present study with 8-OH-DPAT and three other 5-HT$_{1A}$ selective agents indicate that other components of the 5-HT syndrome are also likely to be indicative of 5-HT$_{1A}$ receptor activation. In particular, all 5-HT$_{1A}$ selective agents are able to modulate the appearance of forepaw treading, head-weaving and tremor, either inducing or inhibiting the behaviors. However, the effects of 5-HT$_{1A}$ selective agents on hindlimb abduction, flattened body posture and Straub tail may not be mediated solely by

the 5-HT_{1A} site, as evidenced by the failure of isapirone to induce or inhibit these behaviors.

8-OH-DPAT, buspirone and isapirone are also similar in that they all display anxiolytic activity in animal models [3, 27, 33, 34]. Moreover, buspirone has been shown to be clinically effective for the relief of anxiety in human trials and, unlike benzodiazepines, does not produce sedation, motor incoordination or memory disturbances [32,33]. Therefore, a greater understanding of the behavioral effects of these novel agents and their underlying receptor mechanisms may yield important information concerning the pathophysiology of anxiety.

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