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Differential Actions of Serotonin Antagonists on Two Behavioral Models of Serotonin Receptor Activation in the Rat[1]

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ABSTRACT

Ligand binding studies have identified certain serotonin (5-HT) antagonists with selective affinity for 5-HT_2 receptors and other serotonin antagonists with affinity for both 5-HT_1 and 5-HT_2 receptors. This study compared the actions of ketanserin and pipamperone, selective 5-HT_2 receptor antagonists, with metergoline and methysergide, nonselective 5-HT antagonists, on two behavioral responses in rats that are produced by the activation of 5-HT receptors: 1) the head shake response and 2) the 5-HT syndrome. Both the selective and the nonselective 5-HT antagonists blocked the head shake response produced by 5-hydroxy-L-tryptophan. The order of relative potency was: metergoline > ketanserin > pipamperone > methysergide. All four antagonists also blocked the head shake response produced by the 5-HT agonist quipazine. In contrast, the symptoms of the 5-HT syndrome produced by 5-methoxy-N,N-dimethyltryptamine were blocked by pretreatment with the nonselective 5-HT receptor antagonists but not by the 5-HT_2 receptor antagonists. The differential actions of 5-HT antagonists on these behavioral responses suggest that different 5-HT receptors are involved in the head shake response and the 5-HT syndrome. That the order of relative potency for these drugs to block the head shake response was the same as their reported affinity for the 5-HT_2 receptor suggests that the 5-HT_2 receptor is involved in the head shake response. In contrast, the ability of 5-HT antagonists with affinity for the 5-HT_1 receptor to block the 5-HT syndrome and the inability of 5-HT_2 receptor antagonists to block the syndrome suggests that this behavioral response probably involves the activation of 5-HT_1 receptors.

Early studies described a number of stereotyped behaviors and reflexes that were produced in rats by the administration of high doses of 5-HT precursors or MAOIs (Tedeschi *et al.*, 1959; Hess and Doepfner, 1961). Two of the described behavioral features, the head shake response and the symptoms of the 5-HT syndrome, have been studied extensively as behavioral models for the activation of CNS 5-HT receptors (Corne *et al.*, 1963; Grahame-Smith, 1971a,b; Jacobs, 1976; Bedard and Pycock, 1977).

The head shake response ("wet dog shakes," head and/or body twitches) can be produced in mice and rats by the administration of the 5-HT precursors tryptophan or 5-HTP, although the behavior does not occur if 5-HT synthesis is inhibited (Corne *et al.*, 1963; Bedard and Pycock, 1977; Matthews and Smith, 1980). Head shakes are also produced in rats by the administration of 5-HT agonists that directly activate 5-HT receptors such as 5-MeDMT, LSD or quipazine (Bedard and Pycock, 1977; Vetulani *et al.*, 1980), by drugs that release 5-HT like fenfluramine (Matthews and Smith, 1980) and by 5-HT when injected directly into the cerebral ventricles (Drust *et al.*, 1979; Lebrecht and Nowak, 1980). Furthermore, the destruction of central 5-HT neurons enhances the ability of direct-acting 5-HT agonists to produce the head shake response (Bednarczyk and Vetulani, 1978; Yamamoto and Ueki, 1981). A variety of 5-HT antagonists can prevent the head shake response caused by 5-HT agonists or precursors (Bedard and Pycock, 1977; Matthews and Smith, 1980). Although head shakes can also be produced by neuropeptides (Prange *et al.*, 1974; Wei *et al.*, 1977), they do not produce this behavior by activation of 5-HT receptors (Drust and Connor, 1983). Thus, the head shake response, when produced by 5-HT agonists, appears to be associated with the activation of CNS 5-HT receptors.

The 5-HT syndrome consists of a series of complex behavioral reflexes or symptoms that usually include repetitive treading of the forepaws, abduction of the hindlimbs, Straub's tail, hypertonicity, lateral weaving of the head and a resting tremor (Grahame-Smith, 1971a,b; Jacobs, 1976). The 5-HT syndrome can be produced by the administration of 5-HT precursors in combination with a MAOI, but not if 5-HT synthesis has been inhibited (Grahame-Smith, 1971a; Jacobs, 1974a; Deakin and Green, 1978), by systemic administration of 5-HT receptor

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ABBREVIATIONS: 5-HT, serotonin; MAOI, monoamine oxidase inhibitor; CNS, central nervous system; 5-HTP, 5-hydroxy-L-tryptophan; 5-MeDMT, 5-methoxy-N,N-dimethyltryptamine; LSD, *d*-lysergic acid diethylamide.

agonists such as 5-MeDMT (Grahame-Smith, 1971b) or LSD (Anden *et al.*, 1968; Trulson *et al.*, 1976b), by fenfluramine (Trulson and Jacobs, 1976) and by the central administration of 5-HT (Davis *et al.*, 1980). The destruction of 5-HT neurons enhances the action of direct-acting agonists in producing the 5-HT syndrome (Trulson *et al.*, 1976a; Deakin and Green, 1978). A variety of 5-HT antagonists prevent the appearance of the 5-HT syndrome (Jacobs, 1974a,b; Sloviter *et al.*, 1978; Deakin and Green, 1978), although not all 5-HT antagonists block the syndrome (Green *et al.*, 1981).

Recent evidence suggests that different types of 5-HT receptors exist in the CNS (see Aghajanian, 1981; Peroutka and Snyder, 1983). By using ligand binding studies, Peroutka and Snyder (1979) defined two types of 5-HT receptors: 1) 5-HT_1 receptors that were labeled by [^{3}H]-5-HT; and 2) 5-HT_2 receptors that were labeled by [^{3}H]spiperone. Some 5-HT antagonists like ketanserin and pipamperone are considered selective 5-HT_2 receptor antagonists because they potently displace [^{3}H]spiperone binding to the 5-HT_2 receptor at nanomolar concentrations, but do not displace [^{3}H]-5-HT binding at even micromolar concentrations (Leysen *et al.*, 1981). In contrast, metergoline and methysergide are examples of 5-HT antagonists that can be called nonselective because they displace both [^{3}H]spiperone and [^{3}H]-5-HT binding at nanomolar concentrations (Peroutka and Snyder, 1980; Leysen *et al.*, 1981). No 5-HT antagonists have been identified with a preferential affinity for the 5-HT_1 receptor site.

There has been some attempt to relate behaviors associated with 5-HT receptor activation with the two types of 5-HT receptors. On the basis of correlational studies between ligand binding and behavioral potency, the ability of drugs to block the head shake response has been associated with their potency to displace [^{3}H]LSD binding (Ögren *et al.*, 1979), [^{3}H]spiperone binding (Peroutka *et al.*, 1981) or [^{3}H]ketanserin binding (Leysen *et al.*, 1982) to rat frontal cortex. Although these studies agree that the head shake response is mediated by 5-HT_2 receptors, details of the behavioral testing procedures and comparisons of dose-effect curves were not provided by these reports. On the other hand, the 5-HT syndrome has been suggested to involve 5-HT_1 receptors because reducing the number of [^{3}H]-5-HT binding sites by chronic administration of MAOIs blocks the appearance of the syndrome (Lucki and Frazer, 1982a). However, Ortmann *et al.* (1982) reported that the ability of a variety of drugs to block the syndrome was correlated with their affinity for the 5-HT_2 receptor.

The present study was intended to provide more information concerning the relationship between behavioral responses produced by 5-HT receptor activation and the two types of central 5-HT receptors identified by Peroutka and Snyder (1979). Specifically, 5-HT_2 receptor antagonists (ketanserin and pipamperone) were compared with nonselective 5-HT antagonists (metergoline and methysergide) for the ability to block the appearance of the head shake response or the 5-HT syndrome. It was found that the two behavioral models of 5-HT receptor activation are associated with different types of 5-HT receptors. The head shake response is associated with 5-HT_2 receptors, whereas the 5-HT syndrome is related to 5-HT_1 receptors.

Materials and Methods

Animals. Male albino Sprague-Dawley rats (300–600 g; Ace Animals, Boyertown, PA) were housed in groups of four with free access to food and water. The animal colony was maintained on a 12 hr light cycle with lights on at 7:00 A.M.

Behavioral procedures. The animals were examined for head shake behavior or for signs of the 5-HT syndrome in individual clear Plexiglas cages (45 × 24 × 20 cm) with the floor covered with a layer of fresh sawdust. The observer of the behavior was always blind to the drug treatment condition of the animals.

Head shake behavior was studied in rats after injection of the peripheral aromatic acid decarboxylase inhibitor carbidopa (102 μmol/kg i.p.) followed 30 min later by the 5-HT precursor 5-HTP (681 μmol/kg s.c.), as described previously (Bedard and Pycock, 1977). A head shake response was defined as a rapid lateral twitch of the head similar to the pinna reflex. In experiments that examined a 180-min time course of the head shake response, rats were observed for six 5-min periods spaced 30 min apart starting 30 min after 5-HTP administration. The 5-HT receptor antagonists, 0.9% NaCl (saline) or Tween-80 were administered 30 min after the administration of 5-HTP. In experiments that examined the dose-effect relationship for 5-HT receptor antagonists on the head shake response, rats were observed for head shake behavior during a single 5-min period, starting at 90 min after the administration of 5-HTP. Rats were used more than once in different experiments but repeated observations with a rat always involved a different combination of drugs and were spaced at least 1 week apart. Using this procedure, control rats maintained a stable frequency of 5-HTP-induced head shake behavior throughout the duration of the experiments.

The head shake response was also observed for a 30-min period after the injection of rats with quipazine (12 μmol/kg i.p.). 5-HT receptor antagonists or saline were administered 1 hr before the start of the observation period.

The appearance of the 5-HT syndrome was examined for up to 30 min after the administration of 5-MeDMT (14 μmol/kg i.p.). Control rats usually displayed the syndrome within 5 min of the injection of 5-MeDMT. The following symptoms of the 5-HT syndrome were individually rated as having occurred at any time during the observation period: 1) repetitive dorsal-ventral treading of the forepaws; 2) abduction of the hindlimbs; 3) side-to-side movements of the head; 4) a resting tremor; 5) an outstretched, elongated posture with the abdomen resting close to the bottom of the cage; and 6) Straub tail. The occurrence of the individual symptoms of the 5-HT syndrome are expressed as the number of rats that showed a particular symptom, up to the maximum of six rats in each experimental group. In addition, at least four of the six symptoms had to appear in a single animal during the session for that animal to be rated as showing the 5-HT syndrome in an all-or-none fashion. This is similar to previously published methods for evaluating this behavioral syndrome (Jacobs, 1976; Lucki and Frazer, 1982a,b).

Drugs. Each drug solution was prepared before use and was administered by i.p. injection, except for 5-HTP which was dissolved in dilute hydrochloric acid and injected s.c. Carbidopa, metergoline and ketanserin were wet with Tween-80, diluted with deionized water and injected as a suspension. 5-MeDMT was dissolved using a few drops of glacial acetic acid. Other drugs were dissolved in deionized water.

The doses of all drugs are expressed as micromoles per kilogram. One micromole of the following compounds is equivalent to the associated value expressed in milligrams of base: metergoline, 0.40; ketanserin, 0.39; pipamperone, 0.38; methysergide, 0.35; 5-MeDMT, 0.22; quipazine, 0.21; 5-HTP, 0.22; and carbidopa, 0.24. Converting doses to milligrams per kilogram can be done by multiplying the dose in micromoles per kilogram by the corresponding conversion factor.

5-MeDMT and 5-HTP were purchased from Sigma Chemical Co. (St. Louis, MO) and quipazine maleate from Miles Scientific (Naperville, IL). Ketanserin, pipamperone hydrochloride (Janssen; Beerse, Belgium), metergoline (Farmitalia; Milan, Italy), methysergide bimaleate (Sandoz, East Hanover, NJ) and carbidopa (Merck Sharp & Dohme; West Point, PA) were generously donated by their suppliers.

Statistics. Regression lines were fit to the dose-effect curves for the 5-HT receptor antagonists using the method of least-squares. The

regression lines were analyzed for parallel slopes using t tests. ID_{50} values and confidence limits were calculated as described by Litchfield and Wilcoxon (1949). The effects of receptor antagonists on the 5-HT syndrome were analyzed using a χ^2 test.

Results

In rats pretreated with carbidopa, 5-HTP (681 μmol/kg) produced a high frequency of the head shake respone in rats, as shown in figure 1. The peak response to 5-HTP occurred between 90 to 120 min after the injection. By comparison, rats injected with saline showed a very low rate of head shake behavior, with the average response never exceeding one head shake in a 5-min period.

Pretreatment of rats with the 5-HT_2 receptor antagonists ketanserin or pipamperone reduced the number of head shakes produced by 5-HTP (fig. 1). The time course after ketanserin (2.6 μmol/kg) administration was similar to the normal time course for the effects of 5-HTP on the head shake response except that the response occurred at a reduced frequency. However, the time course with pipamperone (8.8 μmol/kg) suggests some loss of the ability of pipamperone to prevent the head shake response beyond 90 min after its injection. Because the peak head shake response occurred 90 to 120 min after the injection of 5-HTP and the 5-HT antagonists were effective 60 min after their injection, these time intervals were maintained to compare the relative effectiveness of a series of 5-HT antagonists on the head shake response.

The dose-effect curves of four 5-HT antagonists to block the 5-HTP-induced head shake response are presented in figure 2. The slopes of the dose-effect curves for the four antagonists

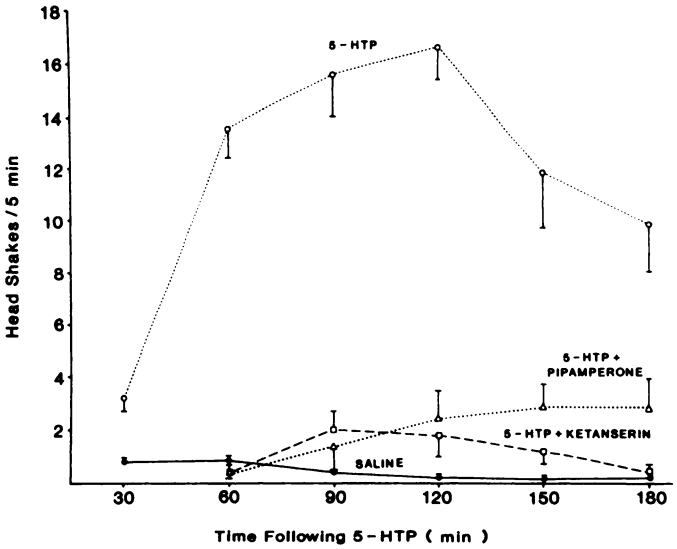

Fig. 1. Time course of the head shake response to 5-HTP and the effect of 5-HT_2 receptor antagonists. The head shake response was produced by injecting rats (N = 6) pretreated with carbidopa (102 μmol/kg 30 min earlier) with 5-HTP (681 μmol/kg). Rats were observed for head shake behavior for six 5-min periods starting 30 min after 5-HTP administration and continuing until 180 min after injection of the 5-HT precursor. Each value shown represents the mean total number of head shakes counted in 5 min with 1 S.E.M. shown as the vertical line. The base-line frequency of the head shake response was measured in other rats (saline, N = 6) that were pretreated with carbidopa and then injected with 0.9% NaCl. The 5-HT_2 receptor antagonists, ketanserin (2.6 μmol/kg) and pipamperone (8.8 μmol/kg) were administered 30 min after the injection of 5-HTP (N = 6/group). Both ketanserin and pipamperone reduced the frequency of head shakes produced by 5-HTP administration.

did not differ significantly ($P > .05$ for all comparisons), indicating that the 5-HT antagonists produced parallel reductions in the 5-HTP-induced head shake response. Metergoline was clearly the most potent of the 5-HT antagonists at blocking the head shake response and was followed in potency by ketanserin, pipamperone and methysergide.

The 5-HT agonist quipazine (12 μmol/kg) also produced the head shake response in rats, as shown in figure 3. Pretreatment with each of the 5-HT antagonists, metergoline, methysergide, ketanserin or pipamperone, reduced the frequency of head shakes caused by quipazine.

The four 5-HT antagonists were also examined for their ability to block the appearance of the 5-HT syndrome produced by 5-MeDMT (14 μmol/kg). As shown in table 1, this dose of 5-MeDMT produced the 5-HT syndrome in each of the six rats tested. Pretreatment of rats with metergoline (2.5 μmol/kg) or methysergide (19 μmol/kg) significantly prevented the appearance of the 5-HT syndrome. These antagonists prevented all of the symptoms of the syndrome except side-to-side head weaving, which appeared to be singularly resistant to blockade. In contrast, the selective 5-HT_2 receptor antagonists ketanserin and pipamperone were not effectve at blocking the appearance of any of the symptoms of the 5-HT syndrome at doses as high as 51.4 and 53.3 μmol/kg, respectively.

A comparison of the 5-HT antagonists on the two behaviors is summarized in table 2. ID_{50} values and confidence limits for blocking the 5-HTP-induced head shake response were calculated for each antagonist and are shown in table 2. The order of potency for these compounds to block the 5-HTP-induced head shake response is the same as their ability to displace [^{3}H]spiperone binding in rat frontal cortex (Leysen *et al.*, 1981). On the other hand, only metergoline and methysergide displace [^{3}H]-5-HT binding with high affinity and only these drugs were capable of blocking the 5-HT syndrome.

Discussion

The actions of four 5-HT antagonists were compared on two behavioral responses that have been associated with 5-HT receptor activation in rats, the head shake response and the 5-HT syndrome. Ketanserin and pipamperone were used as selective 5-HT_2 receptor antagonists because these compounds displace [^{3}H]spiperone binding at nanomolar concentrations but are not effective at displacing [^{3}H]-5-HT binding except at micromolar concentrations (Leysen *et al.*, 1981). In contrast, metergoline and methysergide were used as nonselective 5-HT receptor antagonists because they displace both [^{3}H]spiperone and [^{3}H]-5-HT binding at nanomolar concentrations (Leysen *et al.*, 1981).

The ability of all four 5-HT antagonists, but especially the 5-HT_2 receptor antagonists, to block the head shake response produced by either 5-HTP or quipazine suggests that this behavior involves the 5-HT_2 receptor. Comparison of the four 5-HT antagonists showed they produced parallel dose-effect curves, making comparison of their ID_{50} values meaningful. The order of potency for the 5-HT antagonists to block the head shake response (metergoline > ketanserin > pipamperone > methysergide) agrees with their reported affinity for the 5-HT_2 receptor based on *in vitro* binding studies (Leysen *et al.*, 1981). The 5-HT antagonists studied here also produce effects at other neurotransmitter receptors, but the order of potency reported for these effects at 5-HT_1, *alpha* or *beta* adrenergic,

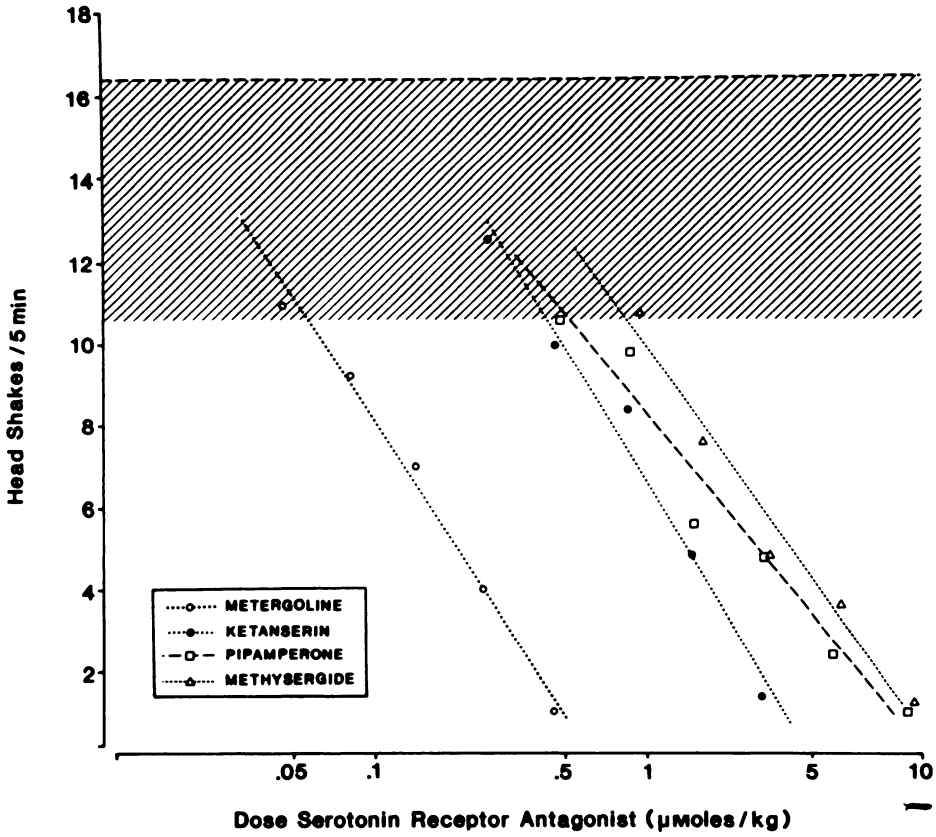

Fig. 2. Comparison of 5-HT antagonists at blocking the head shake response produced by 5-HTP. The 5-HT antagonists were injected 30 min after the administration of 5-HTP (to carbidopa-pretreated rats). Head shakes were then counted for 5 min, beginning 60 min later. All points shown represent the mean head shake response for separate groups of five rats. Regression lines were calculated according to the method of least-squares. The broken line and shaded area indicate the mean head shake response minus 1 S.D. for control rats ($N = 31$) that were injected with 0.9% NaCl instead of the 5-HT antagonists ($X = 16.4 \pm 5.8$ (S.D.) head shakes/5 min). Other rats ($N = 10$) injected with Tween-80 (used to prepare the solutions of metergoline and ketanserin) instead of saline showed a mean response of 14.6 ± 5.8 (S.D.) head shakes that was not significantly different than saline administration [$t(39) = 0.85$, $P > .05$].

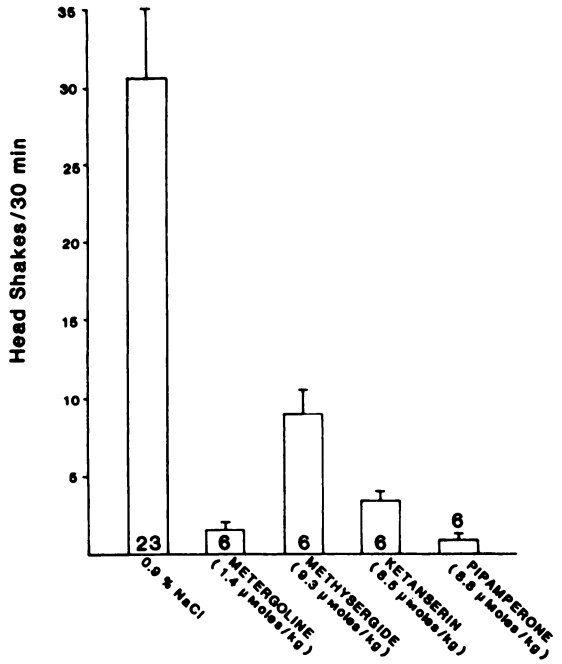

Fig. 3. Effect of 5-HT antagonists on the head shake response produced by the 5-HT agonist quipazine. The head shake response was measured by injecting rats with quipazine (12 μmol/kg) and counting the number of head shakes during the next 30 min. The 5-HT antagonists, or 0.9% NaCl, were administered 60 min before the injection of quipazine. The bars represent the mean total number of head shakes counted in 30 min with 1 S.E.M. indicated by the brackets. All of the antagonists reduced the frequency of the head shake response significantly ($P < .01$, Dunnett's test).

dopamine or histamine receptors (Leysen *et al.*, 1981) does not agree with the order of potency to block the head shake response.

The present findings agree with the previous suggestion of Peroutka *et al.* (1981) that the 5-HTP-induced head shake response may provide an *in vivo* model for studying the function of 5-HT_2 receptor sites in brain. Although Ögren *et al.* (1979) and Peroutka *et al.* (1981) correlated the ability of a variety of drugs to block 5-HTP-induced head shakes produced in mice with displacement of [^{3}H]LSD or [^{3}H]spiroperidol binding to rat frontal cortex, the present study shows that comparisons between this behavior and receptor binding can both be done in the rat. Leysen *et al.* (1982) has shown similarly that the ability of a variety of 5-HT antagonists to block mescaline-induced head shakes in rats was related to their affinity to displace [^{3}H]ketanserin binding *in vitro* to rat frontal cortex. In the present study, the selective 5-HT_2 receptor antagonists were shown to also block head shakes in rats produced either by 5-HTP or by the 5-HT agonist quipazine.

The 5-HT antagonists showed a different pattern of behavioral effects when studied with the symptoms of the 5-HT syndrome produced by 5-MeDMT. Metergoline and methysergide pretreatment blocked the appearance of the 5-HT syndrome. This agrees with previous demonstrations that these 5-HT antagonists block the occurrence of the 5-HT syndrome when produced by either 5-MeDMT or tryptophan-MAOI administration (Jacobs, 1974a; Sloviter *et al.*, 1978; Deakin and Green, 1978; Green *et al.*, 1981). Interestingly, the symptom of lateral head weaving was not prevented by the doses of metergoline or methysergide used in the present study. This may be significant because lateral head weaving is the only symptom of the syndrome that was blocked by striatal lesions, whereas

TABLE 1

Effect of 5-HT receptor antagonists on the 5-HT syndrome

The 5-HT syndrome was produced by the administration of 5-MeDMT (14 μmol/kg) to separate groups of six rats. Rats were observed for the appearance of any of the symptoms of the syndrome for 30 min. The 5-HT antagonists, or saline, were injected 60 min before the start of behavioral observations. The values shown represent the number of rats, out of a total of six, that showed a particular symptom of the syndrome.

Symptoms	Drug Dose (μmol/kg)						
	Saline	Metergoline		Methysergide		Ketanserin 51.4	Pipamperone 53.3
		0.7	2.5	9.4	19.0		
1) Forepaw treading	6	4	2*	6	3*	6	6
2) Head weaving	6	5	5	6	5	6	6
3) Tremor	6	2*	2*	4	3*	6	6
4) Hindlimb abduction	6	3*	1*	3*	3*	6	6
5) Extended posture	6	5	2*	5	3*	6	6
6) Straub's tail	5	1*	2*	1*	0*	6	6
Criteria for syndrome[a]	6	3*	0*	4	2*	6	6

[a] The criteria used for the appearance of the 5-HT syndrome was that four of the six symptoms appeared in the same animal during the period of observation (Jacobs, 1976).

* Value differs significantly from saline pretreatment according to the χ^2 test, $P < .05$.

TABLE 2

Comparison of the behavioral effects of 5-HT antagonists with their affinity for the different types of 5-HT receptors

	ID_{50} to Block 5-HTP-Induced Head Shakes[a]	K_i For [^{3}H]Spiperone[b]	Blocks the 5-HT Syndrome	K_i For [^{3}H]-5-HT[b]
	μmol/kg	nM		nM
1) Metergoline	0.09 (0.04–0.19)	0.9	Yes	20
2) Ketanserin	0.68 (0.33–1.37)	2.1	No	Inactive
3) Pipamperone	1.00 (0.40–2.46)	5.3	No	5000
4) Methysergide	1.51 (0.68–3.36)	12.0	Yes	99

[a] The values represent ID_{50} values and the values in parentheses represent confidence limits determined using the method of Litchfield and Wilcoxon (1949).

[b] From Leysen *et al.* (1981).

the other symptoms of the syndrome remained intact even when the spinal cord was severed (Jacobs and Klemfuss, 1975). However, higher doses of metergoline and methysergide (25 and 28 μmol/kg, respectively) have been reported to block head weaving produced by either 5-MeDMT or tryptophan-MAOI administration (Green *et al.*, 1981). Importantly, both 5-HT_2 receptor antagonists, ketanserin and pipamperone, were ineffective at blocking any symptoms of the 5-HT syndrome at doses up to 51 and 53 μmol/kg, respectively. These doses are 50- to 75-fold greater than their ID_{50} values for blocking the head shake response.

The differential efficacy of 5-HT antagonists that have good (metergoline and methysergide) *vs.* poor (ketanserin and pipamperone) ability to displace [^{3}H]-5-HT binding at preventing the 5-HT syndrome suggests that the syndrome is more closely associated with the activation of 5-HT_1 receptors than 5-HT_2 receptors. The failure to block the syndrome could not be due to the inability of the 5-HT_2 receptor antagonists to penetrate the CNS, as both drugs blocked the 5-HTP-induced head shake response at doses that are more than an order of magnitude less than the maximal doses used with the 5-HT syndrome and have been shown by *in vivo* binding studies to penetrate the CNS (Laduron *et al.*, 1982). Others have also shown that 5-HT antagonists with a high affinity for 5-HT_2 receptors, such as cyproheptadine, cinanserin, and mianserin (Peroutka and Snyder, 1979, 1980; Leysen *et al.*, 1981), did not prevent the 5-HT syndrome when produced by 5-MeDMT or tranylcypromine tryptophan administration (Green *et al.*, 1981). Spiperone itself has been shown to block the 5-HT syndrome (Jacobs, 1974b). However, even though spiperone has been used as a ligand for measuring 5-HT_2 receptors (Peroutka and Snyder, 1979), spiperone also potently displaces [^{3}H]-5-HT from a subpopulation of 5-HT_1 receptors, termed the 5-HT_{1A} site (Pedigo *et al.*, 1981; Monroe and Smith, 1983). Therefore, the blockade of the 5-HT syndrome by spiperone remains consistent with the suggestion that the syndrome involves 5-HT_1 receptors and further suggests association of the 5-HT_{1A} receptor with this behavior.

The 5-HT receptors responsible for producing the 5-HT syndrome are probably located in the spinal cord or lower brain stem because: 1) the ability to produce the syndrome remains intact after spinal transections at the thoracic level (Jacobs and Klemfuss, 1975); 2) selective depletion of serotonergic innervation to the spinal cord potentiates the ability of 5-HT agonists to produce the syndrome (Deakin and Green, 1978); and 3) the syndrome can be produced by administration of 5-HT into the intrathecal space of the spinal cord (Davis *et al.*, 1980). Because there is no evidence for the existence of 5-HT_2 receptors in the rat spinal cord (Leysen *et al.*, 1982; Monroe and Smith, 1983), but 5-HT_1 receptors are located there (Nelson *et al.*, 1978; Lucki and Frazer, 1982a; Monroe and Smith, 1983), it is likely that the type of 5-HT receptor that would be responsible for producing the syndrome would be classified as 5-HT_1 according to Peroutka and Snyder (1979). Furthermore, chronic administration of MAOIs to rats, which reduced the number of 5-HT_1 receptors in the brain stem and spinal cord, blocked the ability of 5-HT agonists to produce the 5-HT syndrome (Lucki and Frazer, 1982a).

The present study disagrees with the report of Ortmann *et al.* (1982) that the potency of a series of drugs to block the 5-HT syndrome correlated with their ability to displace [^{3}H] spiperone binding from rat frontal cortex. Although it is not clear how 5-HT_2 receptors located in rat frontal cortex could relate to the 5-HT syndrome if the behavior primarily involves receptors located in the spinal cord, several methodological differences with the present study, such as the use of different drugs to produce the syndrome, might contribute to the discrepancies between studies. A difference in the method used to measure the 5-HT syndrome deserves particular mention. Ortmann *et al.* (1982) attempted to quantitate the syndrome by assigning numerical scores for the intensity of symptoms and adding the scores together for repeated observations over a period of time. This method, however, allows the possibility

that the sedative effects of drugs, rather than their 5-HT antagonist properties, could reduce the scores obtained for the 5-HT syndrome by reducing the intensity of the symptoms without affecting the actual presence of the symptoms. This effect is especially important to consider when examining the behavioral effects of the neuroleptic drugs used by Ortmann *et al.* (1982) because they can produce debilitating motor deficits that influence measurement of the 5-HT syndrome (Sloviter *et al.*, 1978).

In the past, a number of investigators have referred to the 5-HT syndrome while in fact measuring head shake behavior. Although both behavioral responses are a consequence of central 5-HT receptor activation, the head shake response was not included as a symptom of the 5-HT syndrome (Grahame-Smith, 1971a,b; Jacobs, 1976). Furthermore, because the head shake response and the 5-HT syndrome have now been shown to involve different 5-HT receptors, additional confusion between these two behavioral models should be avoided.

The involvement of different types of 5-HT receptors with the head shake response and the 5-HT syndrome emphasizes the differences in effects of 5-HT antagonists that can be obtained using different measures of serotonergic response. Other functional models have been suggested that are associated with the activation of 5-HT_1 (Ennis and Cox, 1982; Lucki and Frazer, 1982b; Peroutka *et al.*, 1983) or 5-HT_2 receptors (Leysen *et al.*, 1982). The physiological importance of such a classification of 5-HT receptors that was initially proposed on the basis of ligand binding studies (Peroutka and Snyder, 1979) is supported by the separate functional roles that have been found for the two types of receptors. The present study demonstrates that behavioral models in the rat can be used to examine responses that are linked to these different types of 5-HT receptors in the CNS.

Note added in proof: while this paper was in review, Yap and Taylor published a report (Neuropharmacology **22:** 801–804, 1983) showing that the head shake response produced by 5-HTP in rats was blocked by the selective 5-HT_2 antagonists ketanserin and pirenperone. Colpaert and Janssen (Neuropharmacology **22:** 993–1000, 1983) showed similar results with pirenperone and other 5-HT antagonists on the head shake response in rats. These reports are in basic agreement with the data presented in this paper.

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