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The Relation of Central 5-HT_{1A} and 5-HT_2 Receptors: Low Dose Agonist-Induced Selective Tolerance in the Rat[1]

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PRANZATELLI, M. R. AND R. S. PLUCHINO. *The relation of central 5-HT_{1A} and 5-HT_2 receptors: Low dose agonist-induced selective tolerance in the rat.* PHARMACOL BIOCHEM BEHAV **39**(2) 407–413, 1991.—To study the purported relation of 5-HT_{1A} and 5-HT_2 receptors, we chronically injected rats with a low dose of selective 5-HT agonists to induce behavioral tolerance and then tested for cross-tolerance. Acutely, in naive rats, both the putative 5-HT_2 agonist DOI and the 5-HT_{1A} agonist 8-OH-DPAT induced some behaviors of the "serotonin syndrome" but the two drugs could be differentiated. Only DOI evoked shaking behavior, "skin jerks" (spinal myoclonus), and hyperthermia. Only 8-OH-DPAT induced flat body posture, head weaving, hypothermia, and occasional hindlimb hyperextension (dystonic posture). Both drugs, especially 8-OH-DPAT, evoked forepaw tapping. Chronic (21 day) treatment with DOI prevented DOI-evoked behaviors but not behaviors evoked by 8-OH-DPAT. Behaviors evoked by 8-OH-DPAT and not DOI decreased significantly after chronic 8-OH-DPAT treatment. Development of selective tolerance suggests that putative selective 5-HT_2 and 5-HT_{1A} agonists exert both shared and distinctive behavioral effects through separate sites whose relation is behavior-specific. For some behaviors (forepaw myoclonus, shaking behavior, thermoregulation), there is a functional interaction between 5-HT_{1A} and 5-HT_2 sites, while for other behaviors (skin jerks, flat body posture, head weaving), there is no interaction.

5-HT_{1A} receptors 5-HT_2 receptors Tolerance Serotonin syndrome Skin jerks Shaking behavior

SHAKING behavior, hyper- or hypolocomotion, dyskinesias, stereotypies, hyperreactivity, postural abnormalities, and thermoregulation are some of the behaviors or functions described as "serotonergic." Identification of which of the multiple types of serotonin receptors mediate these behaviors is of potential clinical and pharmacologic importance. The "serotonin syndrome" (20,38) and shaking behavior have been linked to 5-HT_{1A} (23,41) and 5-HT_2 (5, 26, 46) sites, respectively. However, some observations from acute comparative studies of agonists or antagonists are difficult to reconcile. The 5-HT_2 agonist, quipazine (10), induces both shaking behavior and the serotonin syndrome, and its effects can be blocked with the selective 5-HT_2 antagonist ritanserin (14,44). The putative 5-HT_{1A} agonist 8-OH-DPAT also evokes only some features of the serotonin syndrome (forepaw myoclonus, head weaving, flat body posture) (42) which are blocked by the 5-HT_1 antagonist l-propranolol but not by ritanserin (14). We found that the putative 5-HT_2 agonist, DOI (12), evokes shaking behavior and some behaviors of the serotonin syndrome (forepaw myoclonus) which are blocked by both ritanserin and l-propranolol, and also skin jerks, or paraspinal muscular contractions, which are blocked by ritanserin but not l-propranolol (27,28). Is there more than one classical serotonin syndrome, or is there an interaction between 5-HT_{1A} and 5-HT_2 sites? Goodwin and Green (14) postulated that the 5-HT_{1A} site is interposed between the 5-HT_2 site and behavioral effectors.

To test the hypothesis of an interaction between 5-HT_{1A} and 5-HT_2 agonist sites more directly, we chronically treated rats with DOI, 8-OH-DPAT or saline to produce behavioral tolerance. Tolerance develops following repeated administration of 5-HT agonists (4, 25, 37, 43). Once rats exhibited tolerance to a low test dose of the agonist given chronically, they were then tested for cross-tolerance with a low dose of the other agonist. If 5-HT_2 and 5-HT_{1A} sites are linked in the manner suggested by Goodwin and Green (14), tolerance induced by 8-OH-DPAT should also decrease responses to DOI. If cross-tolerance to either drug does not develop, however, their respective behavioral effects are probably mediated by different 5-HT receptors. Our study also included a controlled comparison of the behavioral effects of 8-OH-DPAT and DOI, as selective putative 5-HT_{1A} and 5-HT_2 agonists, which has not been previously reported. The inferences about receptors are based on a 1000-fold greater selectivity of 8-OH-DPAT at 5-HT_{1A} than 5-HT_2 receptors, and 100-fold greater selectivity of DOI at 5-HT_2 than 5-HT_{1C} recep-

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tors in radioligand binding studies (12,40).

METHOD

Animals

Male (200–250 g) Sprague-Dawley rats were obtained from Charles River and housed three to a cage (18 × 34 × 51 cm) with access to food and water at room temperature under a 12-hour light/12-hour dark cycle.

Chemicals

8-OH-DPAT [8-hydroxy-2-(di-n-propylamino)tetralin HBr, RBI] and DOI [1-(2,5-dimethoxy-4-iodo-phenyl aminopropane)-2 HCl, RBI] were dissolved in 0.9% saline just prior to use (dose/ml). Dosages were calculated as salts according to the body weight determined on the day of testing.

Behavioral Scoring

Rats were injected with drug or saline intraperitoneally and immediately placed in clear plastic test cages for behavioral observations. An observer blind to drug treatment evaluated forelimb myoclonus (reciprocal forepaw treading or tapping), truncal myoclonus (paraspinal muscle contractions or skin jerks), flat body posture, hindlimb abduction, Straub (stiff or snake-like) tail, backing, pivoting (tight circling), reactivity (to handling), lateral head weaving, and vertical head movements or sniffing (34). Rearing and mobility were included not as features of the serotonin syndrome but as behaviors often affected by the syndrome. Scores were awarded each 5 minutes for 30 minutes for individual behaviors by the following scale: 0 = absent, 1 = rare or trace, 2 = mild or infrequent, 3 = moderate or intermittent, 4 = severe or continuous. Shaking behavior (head shakes or wet-dog shakes) (18) was counted for 30 minutes following drug injections (31). Body temperature was taken rectally with a Becton-Dickinson digital thermometer 15 minutes before and 30 minutes after drug injections.

Studies of Tolerance

Different groups of rats (n = 5) were injected for consecutive days intraperitoneally with 0.9% saline, DOI (3 mg/kg), or 8-OH-DPAT (3 mg/kg). Doses were chosen from previous studies (28,32). Each rat received only one chronic drug treatment. After 14 days, rats were injected with a smaller dose of the same chronic drug as a test of behavioral tolerance. This dose was chosen from dose-response studies to be the minimum effective dose to evoke the complete behavioral syndrome (28). At the end of the testing session, rats received their usual daily injection. In tests of tolerance, the principal reference behavior was hypothermia for 8-OH-DPAT (14,41) and shaking behavior for DOI (28). If there was no significant tolerance for reference behaviors, as determined by interim statistics, rats were treated for 3 more days and then retested, repeating the sequence, if necessary, until behavioral tolerance was achieved. Only then were rats tested for cross-tolerance. A minimum of 3 days elapsed between testing sessions. Each rat received only one other drug as a test of cross-tolerance.

Injection of DOI, 8-OH-DPAT or saline in rats injected chronically with saline allowed controlled comparison of acute drug effects.

Statistics

Means of the behavioral scores for six time points were used for data analysis. The effect of independent variables (chronic drug, test drug, dose, length of treatment) and their interactions on dependent variables (behaviors) were tested by analysis of variance (ANOVA) using the General Linear models (PROC GLM) of the Statistical Analysis System (SAS) (35). For all significant main effects, groups were then compared by pairwise *t*-tests (pdiff).

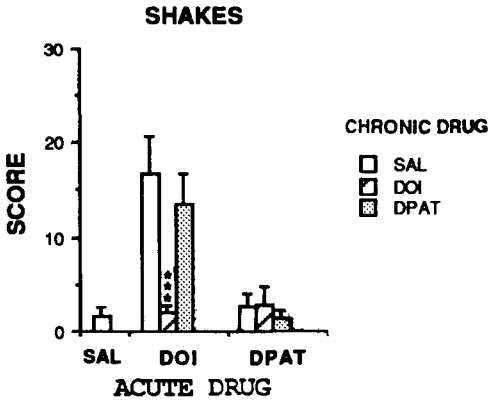

FIG. 1. Comparative acute effects of shaking behavior of saline (SAL) (n = 9), 2 mg/kg DOI (n = 5), or 0.5 mg/kg 8-OH-DPAT (DPAT, n = 5) (as shown on X-axis) in rats treated chronically with saline, DOI or DPAT (as indicated in legend). Shaking behavior was counted by an observer for 30 minutes after subcutaneous injection of test drugs. Rats were shown to be tolerant to the effects of chronic drug prior to testing for cross-tolerance. Statistical comparisons of chronic drug treatments are shown for each test drug. Other statistical comparisons are described in the Results section. $*0.01<p<0.05$; $**0.001<p\leq0.01$; $***0.0001<p\leq0.001$.

RESULTS

Comparison of Acute Drug Effects in Drug-Naive Rats

The effects of DOI and 8-OH-DPAT were compared to saline and to each other for shaking behavior (Fig. 1), body temperature (Fig. 2), core serotonin syndrome behaviors (Fig. 3), and other syndrome behaviors (Fig. 4).

In comparisons of acute drug effects with saline, there were significant statistical main effects for rearing, $F(2,58) = 28.68$, $p = 0.0001$, skin jerks, $F(2,58) = 86.29$, $p = 0.0001$, forepaw myoclonus, $F(2,58) = 57.41$, $p = 0.0001$, head weaving, $F(2,58) = 50.81$, $p = 0.0001$, flat body posture, $F(2,58) = 36.49$, $p = 0.0001$, sniffing, $F(2,58) = 8.49$, $p = 0.001$, body temperature change, $F(2,58) = 90.69$, $p = 0.0001$, and shaking behavior, $F(2,58) = 11.97$, $p = 0.0001$. Pivoting and backing were dropped from analysis since all scores were less than 0.33 and 0.17, respectively.

DOI induced significantly more (+869%) forepaw myoclonus ($p = 0.0001$), (+3,350%) skin jerks ($p = 0.0001$), (+806%) shaking behavior ($p = 0.0001$), (+77%) change in body temperature ($p = 0.02$) compared to saline. DOI significantly reduced (−26%) rearing ($p = 0.008$).

8-OH-DPAT, compared to saline, evoked significant increases in (+67%) flat body posture ($p = 0.0001$), (+1,315%) forepaw myoclonus ($p = 0.0001$), and (+450%) head weaving ($p = 0.0001$). 8-OH-DPAT significantly reduced (−351%) body temperature ($p = 0.0001$), (−68%) rearing ($p = 0.0001$), and (−28%) sniffing ($p = 0.0001$). We also observed that a hindlimb of 8-OH-DPAT-injected rats infrequently became arrested in hyperextension, halting locomotion (hindlimb hyperextension).

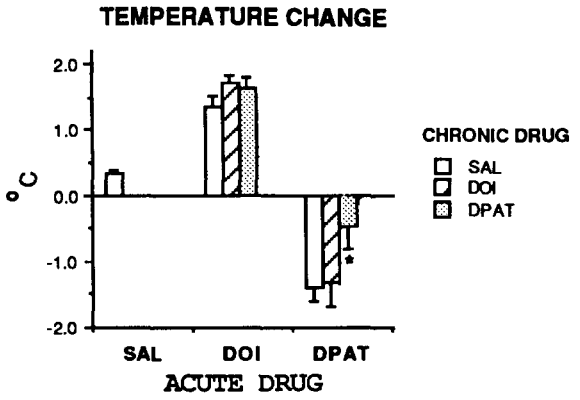

FIG. 2. Effects of chronic agonist or saline (SAL) injection (shown in legend) on change in body temperature (°C) in response to DOI (2 mg/kg), DPAT (0.5 mg/kg) or saline (labelled on X-axis). Presence of tolerance was verified prior to testing for cross-tolerance. Statistical comparisons of chronic drug treatments are shown for each test drug. See the Results section for other comparisons. *$0.01<p<0.05$; **$0.001<p\leq0.01$; ***$0.0001<p\leq0.001$.

Compared to 8-OH-DPAT, DOI evoked significantly more (+6,800%) skin jerks ($p=0.0001$) and (+94%) shaking behavior ($p=0.008$).

8-OH-DPAT induced significantly greater (+82%) flat body posture ($p=0.0001$), (+45%) forepaw myoclonus ($p=0.002$), (+100%) head weaving ($p=0.0001$), and (+42%) temperature change ($p=0.0001$) than DOI.

Chronic Treatment—Statistical Main Effects

There were significant main effects of chronic treatment on skin jerks, $F(2,22)=4.98$, $p=0.02$, forepaw myoclonus, $F(2,22)=4.53$, $p=0.02$, head weaving, $F(2,22)=5.56$, $p=0.01$, flat body posture, $F(2,22)=9.33$, $p=0.001$, and shaking behavior, $F(2,22)=4.61$, $p=0.02$.

There were also significant main effects of test drug on rearing, $F(1,22)=7.51$, $p=0.01$, skin jerks, $F(1,22)=26.62$, $p=0.0001$, forepaw myoclonus, $F(1,22)=15.17$, $p=0.0008$, head weaving, $F(1,22)=33.60$, $p=0.0001$, flat body posture, $F(1,22)=242.58$, $p=0.0001$, body temperature change, $F(1,22)=214.62$, $p=0.0001$, and shaking behavior, $F(1,22)=13.98$, $p=0.001$, but not other behaviors.

Significant interactions between chronic treatment and test drugs occurred for skin jerks, $F(2,22)=4.98$, $p=0.02$, forepaw myoclonus, $F(2,22)=8.28$, $p=0.002$, head weaving, $F(2,22)=4.95$, $p=0.02$, shaking behavior, $F(2,22)=5.92$, $p=0.009$, flat body posture, $F(2,22)=6.23$, $p=0.007$, but not other behaviors.

Tests for Tolerance

Chronic 5-HT agonist treatment desensitized several agonist-evoked behaviors. Treatment with DOI (compared to saline) significantly reduced only DOI-evoked skin jerks ($p=0.0002$), forepaw myoclonus ($p=0.0007$), and shaking behavior ($p=0.0001$).

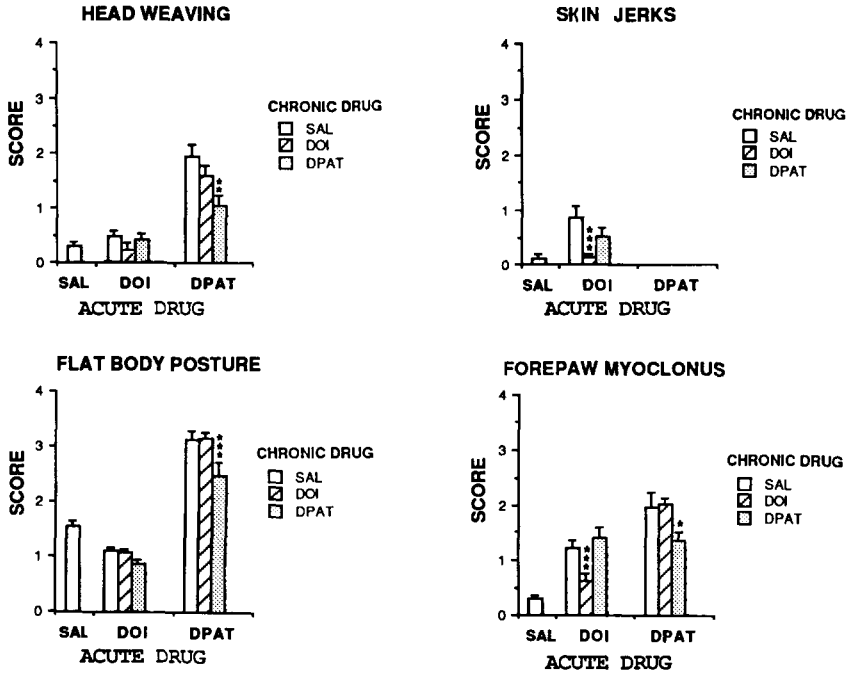

FIG. 3. Comparative effects on core serotonin syndrome behaviors of test doses of DOI, 2 mg/kg, DPAT, 0.5 mg/kg, and saline (SAL) (labelled on X-axis) in rats treated chronically with saline, DOI, or DPAT (as indicated in the legend). Behaviors were scored on a scale of increasing severity or frequency, as described in the Method section. Rats were shown to be tolerant to the effects of chronic drugs prior to testing for cross-tolerance. Pivoting and backing had values too close to 0 to be shown. Statistical comparisons of chronic drug treatments are shown for each test drug. Other statistical comparisons are described in the Results section. *$0.01<p<0.05$; **$0.001<p\leq0.01$; ***$0.0001<p\leq0.001$.

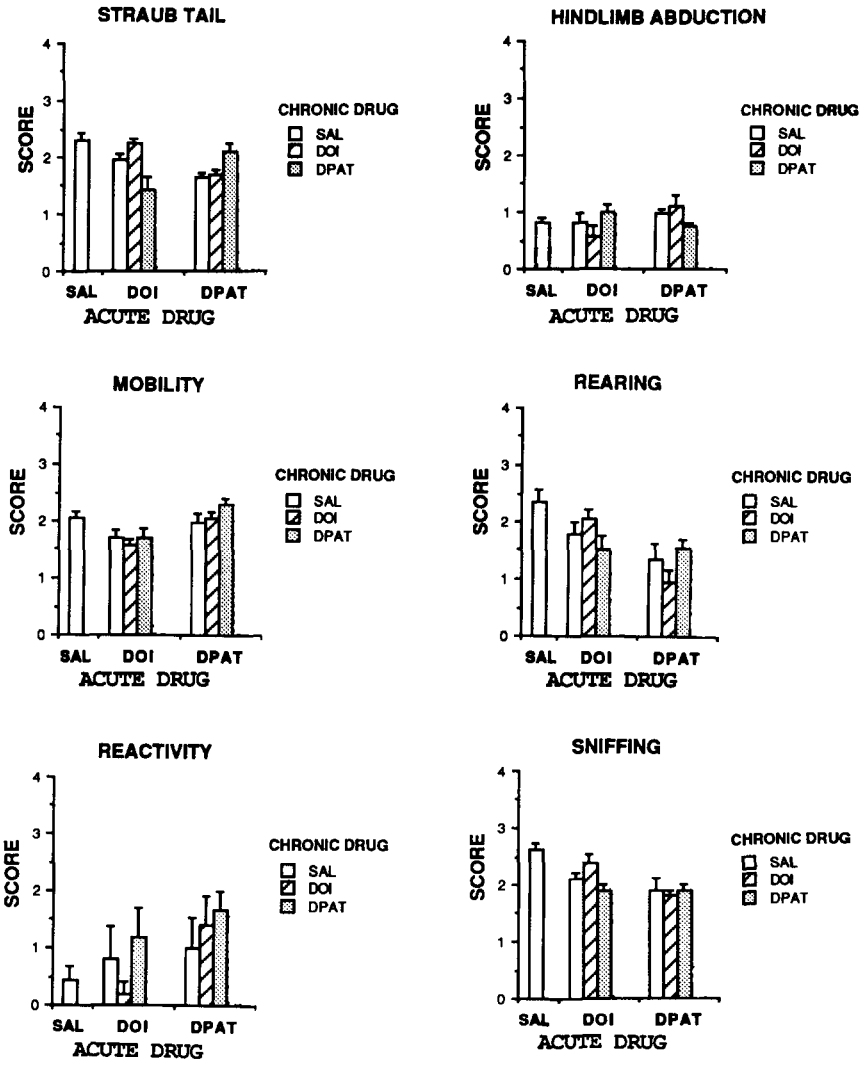

FIG. 4. Effects of chronic drug treatment (shown in legend) on other serotonin syndrome and related behaviors evoked by test doses of the same drugs: DOI, 2 mg/kg, DPAT, 0.5 mg/kg or saline (SAL). Behaviors were scored on a scale of increasing severity or frequency from 0 to 4, as described in the Method section. Presence of tolerance was verified prior to testing for cross-tolerance. Statistical comparisons of chronic drug treatments are shown for each test drug. See the Results section for other comparisons. $*0.01<p<0.05$; $**0.001<p\leq 0.01$; $***0.0001<p\leq 0.001$.

Chronic treatment with 8-OH-DPAT (compared to saline) significantly reduced only 8-OH-DPAT-evoked head weaving ($p=0.0007$), hypothermia ($p=0.009$), forepaw myoclonus ($p=0.04$), and flat body posture ($p=0.0006$).

Tests for Cross-Tolerance

In rats treated chronically with DOI, there were no significant changes in behaviors evoked by 8-OH-DPAT.

In rats treated chronically with 8-OH-DPAT, there were no significant changes in behaviors evoked by DOI.

DISCUSSION

The main finding of the acute drug comparisons was that the putative selective 5-HT_{1A} agonist 8-OH-DPAT and the putative selective 5-HT_2 agonist DOI evoked distinctive behaviors as well as some of the same behaviors. The most distinctive features of DOI were shaking behavior, skin jerks, and hyperthermia, while 8-OH-DPAT uniquely evoked flat body posture, lateral head weaving, and hypothermia. However, both drugs, especially 8-OH-DPAT, evoked forepaw myoclonus. The experiments on tolerance extended these findings by demonstrating that forepaw myoclonus evoked by either agonist could be desensitized by chronic treatment with that agonist, but there was no cross-tolerance. Shaking behavior evoked by DOI was reduced by chronic DOI treatment. These data do not support the hypothesis that the 5-HT_{1A} site is interposed between the 5-HT_2 site and effector pathways for behaviors of the serotonin syndrome. Rather, they suggest that 5-HT-evoked behaviors are mediated by distinct recognition sites which show an interaction for some behaviors but not others. Interactions are suggested by shared behaviors (forepaw myoclonus) and by reciprocal behaviors (tem-

perature effects, shaking behavior).

Although pharmacokinetic (dispositional tolerance) and behavioral interacting mechanisms (15) may have contributed to the tolerance we observed, the principal factor is probably the pharmacodynamic mechanism of autologous desensitization and receptor down-regulation. Cross-tolerance to other 5-HT agonists has occurred in the absence of a significant pharmacokinetic or metabolic component (43,45). We have found a selective 60–75% down-regulation of cortical 5-HT_2 sites in rats treated chronically with DOI using a treatment regimen similar to this study (30). The cortex may not be relevant to the 5-HT syndrome, however, and there is no information about the response of subcortical 5-HT_2 sites to chronic DOI treatment. For 5-HT_{1A} receptors, in contrast, no reduction in receptor density in cortical or subcortical regions accompanies the behavioral tolerance to 5-HT_{1A} agonists in the rat, suggesting changes instead in the postsynaptic cell (22).

Opposing Behaviors

Thermoregulation. Several studies now suggest opposing roles for 5-HT_2 and 5-HT_{1A} receptors in thermoregulation in the rat: 5-HT-induced hyper- and hypothermia are mediated by 5-HT_2 and 5-HT_{1A} receptors, respectively (11, 17, 24). Our data support that hypothesis. Although both pre- and postsynaptic mechanisms have been ascribed to 8-OH-DPAT-induced hypothermia (13,19), there is agreement that chronic treatment with 8-OH-DPAT in the rat (22) or mouse (7) attenuates 8-OH-DPAT-evoked hypothermia. An unexpected finding was that DOI increased body temperature but no tolerance developed to this effect following chronic DOI administration. A similar lack of attenuation of 5-HT_2 receptor-mediated hyperthermia evoked by the 5-HT agonist MK-212 was reported following DOI treatment (1 mg/kg for 7 days) in the rat (24). A conditioning phenomenon has been proposed, but this finding is unexplained. Chronic DOI injection did not alter 8-OH-DPAT-induced hypothermia (24).

Shaking behavior. 8-OH-DPAT inhibits DOI-induced shaking behavior (2,27). 8-OH-DPAT and other 5-HT_{1A} agonists also inhibit quipazine-induced head shakes (47). While these observations suggest an interaction between 5-HT_{1A} and 5-HT_2 receptors, there are a number of conflicting observations in the literature. In the rat, chronic treatment with 8-OH-DPAT or the partial 5-HT_{1A} agonists gepirone or buspirone reduced quipazine-evoked head shakes (9,47), and chronic gepirone reduced cortical 5-HT_2 receptor density (9). In contrast, mice treated chronically with 8-OH-DPAT exhibited increased 5-MeO-DMT-evoked head twitches despite reduced cortical 5-HT_2 receptors, and chronic ipsapirone treatment reduced 5-HT_2-mediated head twitches but not cortical 5-HT_2 receptors (7). Differences in drug selectivity for pre- or postsynaptic 5-HT_{1A} sites and other 5-HT receptors, drug doses (5–40 mg/kg), species, method of drug delivery (single or multiple daily injection, continuous pump infusion), duration of treatment (7–28 days) introduce a number of variables which prevent exact comparisons among these studies or with our data. These factors have been shown to be important to tolerance, such as the different responses of pre- and postsynaptic 5-HT_{1A} receptors to repeated administration of 8-OH-DPAT (21,22). While all of these data support an interaction between 5-HT_{1A} and 5-HT_2 sites for shaking behavior, the mechanism of the interaction remains unclear. We have also found that 8-OH-DPAT elicits dose-dependent inhibition of shaking behavior evoked by TRH (31) and by certain benzodiazepine agonists (29), which was not 5-HT_2 receptor mediated. We also demonstrated that inhibition by 8-OH-DPAT of shaking behavior was not due to behavioral response-competition because ipsapirone, which does not evoke the 5-HT syndrome, was also an effective inhibitor of shaking behavior.

Behaviors Evoked Both by 5-HT_{1A} and 5-$HT_{2,1C}$ Agonists

Forepaw myoclonus. In contrast to a previous report (2), we found that DOI did evoke forepaw myoclonus in a dose-dependent manner (27,28), although significantly less than 8-OH-DPAT. The putative 5-HT_2 agonist, quipazine, similarly evokes forepaw myoclonus, also referred to as reciprocal forepaw treading or forepaw tapping (14). These observations suggest that not only 5-HT_{1A} but 5-HT_2 agonists evoke forepaw myoclonus, an essential or core feature (34) of the 5-HT syndrome.

Behaviors Evoked by Either But Not Both 5-HT_{1A} or 5-$HT_{2,1C}$ Agonists

Skin jerks. DOI-evoked skin jerks or paraspinal muscular contractions showed tolerance only to DOI. Skin jerks may be a pharmacologic model of spinal myoclonus (28). It is of considerable interest whether this behavior is induced by the effects of DOI at 5-HT_2 or 5-HT_{1C} receptors. Skin jerks do not exhibit an interaction with 5-HT_{1A} receptors. Differentiation of the role of 5-HT_2 and 5-HT_{1C} receptors in skin jerks awaits drugs selective for 5-HT_{1C} but not 5-HT_2 receptors.

Head weaving. Lateral head weaving was evoked only by 8-OH-DPAT and showed tolerance only to 8-OH-DPAT. Our initial impression that DOI induced vertical head movements in association with sniffing, rather than lateral movements, was not confirmed.

Flat body posture. Flattening of the back in response to 8-OH-DPAT has been previously described (42). Arching of the back or hunching results from injection of 5-hydroxy-L-tryptophan in rats with 5,7-dihydroxytryptamine lesions (33). Our hypothesis that 5-HT_{1A} receptors mediated flattening whereas 5-$HT_{2,1C}$ receptors mediated arching was not confirmed. Other receptors may participate in hunching.

Behaviors Evoked in Trace Amounts or by Neither 5-HT_{1A} nor 5-$HT_{2,1C}$ Agonists

Behaviors without a clear relation either to 5-HT_{1A} or 5-$HT_{2,1C}$ receptors include pivoting, Straub tail, altered reactivity, hindlimb abduction, and vertical head movements with sniffing. The low frequency of backing obscures its receptor mediation. There is little information available concerning the mechanism of hindlimb abduction except that it is prominent in the behavioral syndrome evoked by nonselective 5-HT agonists and 5-HT neurotoxins (20,34). The 8-OH-DPAT-evoked hindlimb hyperextension, which was also observed by Tricklebank et al. (42), is a dystonic posture, but, unfortunately, it is too episodic to provide a pharmacologic model of dystonia. These behaviors contrast others not studied here for which interactions between 5-HT_1 and 5-HT_2 receptors have been suggested, including locomotor activity, motor habituation (32), and feeding behavior (4,36).

Several different molecular mechanisms may explain the interaction or lack of interaction between 5-HT_{1A} and 5-$HT_{2,1C}$ receptors for a given 5-HT agonist-induced behavior. 5-HT_{1A} sites may be pre- or postsynaptic depending on brain region, whereas 5-HT_2 sites are apparently postsynaptic (39). 5-HT_{1A} sites are presynaptic (somatodendritic autoreceptors) in brainstem and postsynaptic in hippocampus (16), and the regional effect of 8-OH-DPAT may reflect this (3). Regional agonist effects may be important since some behaviors of the serotonin syndrome originate from different brain regions (8,43). Further, 5-HT_{1A} and 5-HT_2 receptors may coexist on the same cell in some regions, such as frontal cortex (1) and brainstem (6), and electro-

physiologic studies demonstrate interactions.

Therefore, there may be a physical basis for 5-HT receptor subtype interactions in regions which mediate certain serotonergic behaviors but not others. Other possible levels of interaction between 5-HT_{1A} and 5-$HT_{2,1C}$ receptors include coupling to second messengers and transducer/effector systems. Further studies will be necessary to elucidate the specific mechanisms involved in the behavioral interactions we and others report.

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