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Do Functional Relationships Exist Between 5-HT_{1A} and 5-HT_2 Receptors?

NISSAR A. DARMANI,* BILLY R. MARTIN,*[1] U. PANDEY*
AND RICHARD A. GLENNON†

*Departments of *Pharmacology/Toxicology and †Medicinal Chemistry*
Virginia Commonwealth University/Medical College of Virginia, Richmond, VA 23298

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DARMANI, N. A., B. R. MARTIN, U. PANDEY AND R. A. GLENNON. *Do functional relationships exist between 5-HT_{1A} and 5-HT_2 receptors?* PHARMACOL BIOCHEM BEHAV 36(4) 901–906, 1990.—To investigate the possible functional relationship between 5-HT_1 and 5-HT_2 receptors, we studied the effects of a nonselective 5-HT agonist (5-MeO DMT), a 5-HT_{1A}-selective (8-OH-DPAT) and a 5-HT_{1B}/5-HT_{1C}-selective (TFMPP) agonist on the head-twitch behavior induced by the putative 5-HT_2-selective receptor agonist (±)-DOI. In the mouse (±)-DOI produced the head-twitch response in a dose-dependent manner and (−)-DOI was twice as potent as the (+) isomer. Selective 5-HT_2 antagonists, ketanserin and spiperone, dose-dependently inhibited the (±)-DOI-induced head-twitch response. The nonselective and the 5-HT_{1A}-selective agonists also dose-dependently reduced the behavior, whereas 5-HT_{1B}/5-HT_{1C}-selective agonist (TFMPP) failed to affect the (±)-DOI-induced response. Taken together with previously published literature data, we propose a 5-HT_{1A} inhibitory action on the 5-HT_2 receptor-mediated response when induced by its selective agonist (±)-DOI.

Head-twitch Functional interaction 5-HT_{1A} receptor 5-HT_2 receptor DOI 8-OH-DPAT TFMPP 5-MeO DMT Ketanserin Spiperone

SEVERAL types of 5-HT binding sites (5-HT_1, 5-HT_2, 5-HT_3) have been identified by radioligand binding studies [for reviews see (3, 5, 8, 20)]. The 5-HT_1 and 5-HT_3 sites appear to consist of a number of subtypes, of which 5-HT_{1A} sites are perhaps the best studied (8,20). Biochemical and other functional correlates have been identified for some of these sites (3, 5, 8, 20). 5-HT-mediated behaviors are also important pharmacological tools for examining the effects of drugs on 5-HT receptor function, and the discovery of multiple populations of 5-HT binding sites has stimulated efforts to determine what functional relationships exist between these sites and the various behavioral responses (9). In reviewing the recent literature on 5-hydroxytryptamine, it becomes apparent that there may be functional interactions among 5-HT-receptor subtypes. Receptor subtype interactions have already been reported for dopamine D_1 and D_2 receptors [i.e., stimulation of D_1 receptors is a necessary component for the expression of the behavior induced by D_2-specific agonists; for review see (4)], and the possibility exists that such interactions may also be important with regard to other neurotransmitters.

One of the most often used models of 5-HT_2 receptor function is the head-twitch behavior induced in rodents by direct- or indirect-acting 5-HT agonists (9, 13, 17). Although a head-twitch response may be mediated by multiple neurotransmitter systems (12), the head-twitch produced by 5-HT agonists can be antagonized by 5-HT_2-selective antagonists (16). In fact, there is a significant correlation between antagonist potency and 5-HT_2-site affinity (19). The serotonin syndrome is a behavioral response which is induced by stimulation of 5-HT_{1A} receptors by selective (8-OH-DPAT) and nonselective (5-MeO DMT) 5-HT agonists in rodents (23). Although in the past some authors have considered the head-twitch response to be a component of the serotonin syndrome, there are mechanistic distinctions that allow them to be considered as separate functional entities (16). There are a number of studies indicating possible interactions between 5-HT_{1A} and 5-HT_2 receptor function (11). For example, 8-OH-DPAT, which displays very low affinity for 5-HT_2 sites (8), inhibits the head-twitch response induced by precursor (5-hydroxytryptophan) loading but not the behavior produced through direct stimulation of postsynaptic 5-HT_2 receptors by the nonselective agonist 5-MeO DMT. Moreover, the putative 5-HT_{1A} partial agonist ipsapirone increases 5-MeO DMT-induced, but not 5-hydroxytryptophan-induced head-twitch response in rats (10). The nonselective ergoline derivative LSD reportedly induces both the 5-HT syndrome (22) and head-twitch behavior in rats (25). However, at doses lower than those that induce the 5-HT syndrome, LSD inhibits the head-twitch response induced by 5-hydroxytryptophan (7).

Since no adequate explanation has been offered for these

[1]Requests for reprints should be addressed to Dr. Billy R. Martin, Ph.D., Department of Pharmacology & Toxicology, Medical College of Virginia, Richmond, VA 23298.

possible 5-HT_{1A}/5-HT_2 receptor interactions, the aim of the present study was to determine whether the 5-HT_2-selective agonist (±)-DOI would produce head-twitch behavior, and whether 5-HT_1 agonists could modulate the head-twitch response induced by (±)-DOI.

METHOD

Male albino mice of the ICR strain, weighing 16–18 g, were housed in groups of five on a 12-hour light-dark cycle and were allowed food and water ad lib. In order to habituate animals to the test environment, each animal was randomly transferred 30 minutes prior to treatment to a 40 × 25 × 16 cm plastic cage lined with a thin layer of sawdust. Mice were injected intraperitoneally with doses of (±)-DOI (0.63, 1.25, 2.5 and 5 mg/kg), 5-MeO DMT (2, 4, 8, 16, and 32 mg/kg) or distilled water (6 mice per group). The head-twitch response was scored every 2 minutes for the first 30 minutes following (±)-DOI injection or for the first 10 minutes after 5-MeO DMT injection. Total mean scores (±S.E.M.) over the 10- or 30-minute periods, as well as the mean scores (±S.E.M.) in each 2-minute interval, were calculated.

In order to determine which isomer of (±)-DOI is the more potent, each isomer was tested at a dose of 2.5 mg/kg. For drug interaction studies, (±)-DOI was used at a dose of 2.5 mg/kg. Doses of 5-MeO DMT (0, 2, 4 and 8 mg/kg) were coadministered with a dose of 2.5 mg/kg of (±)-DOI. They were injected together via the intraperitoneal route (4 mice per group). The selective 5-HT_{1A} agonist 8-OH-DPAT was administered intraperitoneally at doses of 0, 0.5, 1 and 2.5 mg/kg 10 minutes prior to injection of (±)-DOI (6–8 animals per group). The selective 5-HT_{1B}/5-HT_{1C} agonist TFMPP (0, 0.313, 0.625 and 1.25 mg/kg) was injected intraperitoneally 5 minutes prior to administration of (±)-DOI (5–7 animals per group). Doses of the 5-HT_2 antagonists ketanserin (0, 0.125, 0.25 and 1 mg/kg subcutaneously) and spiperone (0.025, 0.05, 0.125 and 0.5 mg/kg IP) were administered 30 minutes prior to (±)-DOI injection (4 animals per group). In each case, the head-twitch response was recorded in 2-minute intervals for 30 minutes after (±)-DOI injection as described above.

The following drugs were obtained from Research Biochemicals Inc. (Natick, MA): (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl [(±) DOI HCl], (±)-8-hydroxy-2-(di-n-propylamino)tetralin HBr (8-OH-DPAT), 1-(3-trifluoromethylphenyl) piperazine HCl (TFMPP), ketanserin tartrate and spiperone. The (+) and (−) isomers of DOI previously were synthesized in our facilities. Unless otherwise stated, all drugs were dissolved in distilled water and given at a volume of 10 ml/kg.

Statistical Analysis

Data were analyzed by one-way analysis of variance and post hoc analysis by Dunnett *t*-test. ED_{50} values were calculated by method of Finney (6).

RESULTS

(±)-DOI caused an increase in head-twitch response in mice in a dose-dependent manner when observed for 30 minutes after injection (Fig. 1). The drug appears to be absorbed very quickly from intraperitoneal injection since maximal effects were observed 2 minutes after administration (Fig. 2). The induced response persists up to 30 minutes after the injection. The R(−)-isomer of DOI, which possesses twice the 5-HT_2 receptor affinity of S(+)-DOI, was approximately twice as potent as the S(+) isomer when tested at 2.5 mg/kg (Fig. 3). Due to limited quantities of the available isomers, a full dose-response effect study was not practical. The nonselective 5-HT agonist 5-MeO DMT also dose-dependently induced the head-twitch response. However, unlike the (±)-DOI-induced response, the 5-MeO DMT effect subsided to insignificance 10 minutes after its administration (Fig. 9).

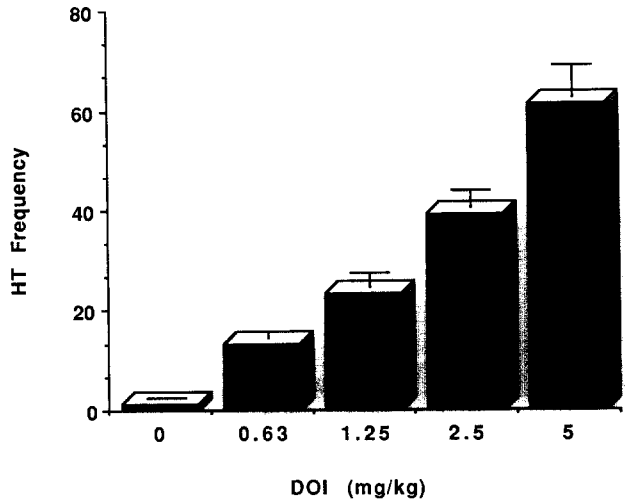

FIG. 1. The effect of (±)-DOI administration (IP) on the production of head-twitch (HT) response in mice. The behavior was observed for 30 minutes immediately after injection. Results are given as means ± SEM.

The selective 5-HT_2 antagonist ketanserin dose-dependently inhibited the head-twitch response induced by 2.5 mg/kg (±)-DOI with a 50% inhibition dose (ID_{50}) of 0.17 mg/kg (Table 1 and Fig. 4). Similarly, spiperone, another 5-HT_2 antagonist, inhibited the response in a dose-dependent manner (ID_{50} = 0.08 mg/kg) (Table 1 and Fig. 5).

The 5-HT nonselective agonist 5-MeO DMT reduced the head-twitch response induced by 2.5 mg/kg (±)-DOI in a dose-dependent manner (ID_{50} = 1.52 mg/kg); the head-twitch response,

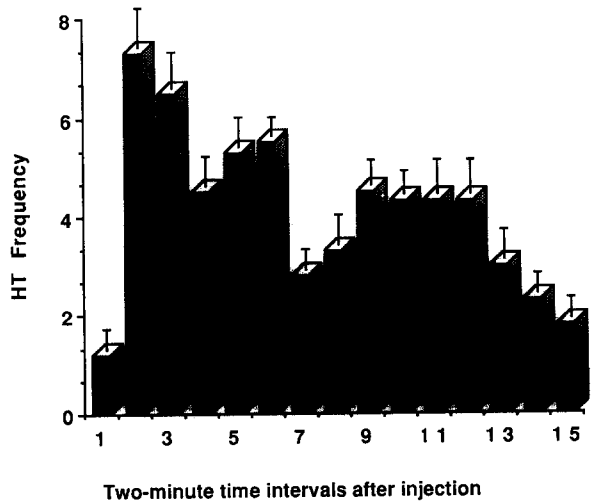

FIG. 2. Time course of head-twitch frequency in mice observed at 2-minute intervals for 30 minutes after an intraperitoneal injection of 5 mg/kg (±)-DOI. Results are given as means ± SEM at each time point.

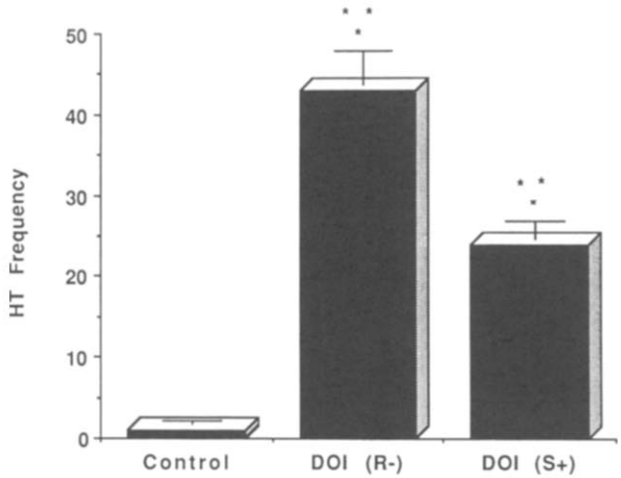

FIG. 3. The effects of intraperitoneal administration of R(−)- and S(+)-DOI isomers on the production of head-twitch response observed in mice for 30 minutes after injection. Results are given as means ± SEM. (*$p<0.05$ significantly different from control; **significant difference between the isomers.)

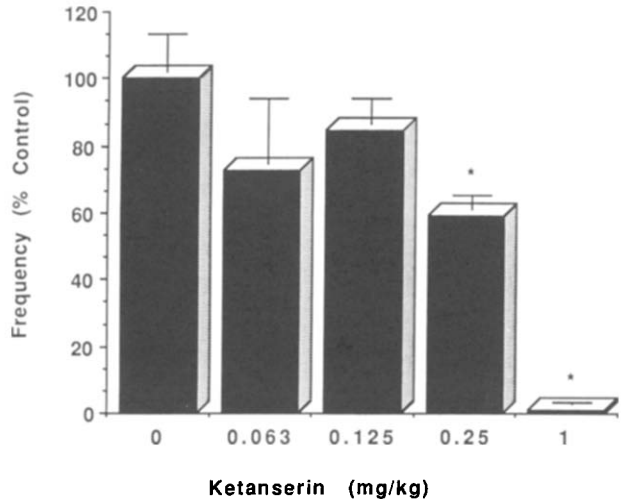

FIG. 4. Dose-dependent inhibitory effect of ketanserin on head-twitch frequency induced by 2.5 mg/kg (±)-DOI. Data are presented as percent control head-twitch response (± SEM) (*$p<0.05$).

however, was not totally inhibited (Table 1 and Fig. 6). The selective 5-HT_{1A} agonist 8-OH-DPAT (ID_{50} 0.25 mg/kg) was approximately six times more potent than the nonselective agent 5-MeO DMT (Table 1 and Fig. 7). Similar to the effect of 5-MeO DMT, the inhibition was not complete and significant head-twitches were observed even with a 2.5 mg/kg dose of 8-OH-DPAT (Fig. 7). The 5-HT_{1B}/5-HT_{1C} agonist TFMPP caused a nonsignificant increase in the (±)-DOI-induced head-twitch response (Fig. 8).

DISCUSSION

Consistent with the hypothesis that head-twitch response is a 5-HT_2-mediated phenomenon, the putative 5-HT_2-selective agonist (±)-DOI induced a dose-dependent increase in this behavior, and R(−)-DOI was twice as potent as its S(+) enantiomer. Furthermore, the (±)-DOI-induced increase in head-twitch response was completely antagonized by the 5-HT_2 receptor antagonists ketanserin and spiperone at very low doses. However, the nonselective 5-HT agonist 5-MeO DMT and the selective 5-HT_{1A} agonist 8-OH-DPAT also dose-dependently attenuated the (±)-DOI-induced response. The selective 5-HT_{1A} agonist was over six times more potent than 5-MeO DMT. Unlike the complete inhibition exhibited by the 5-HT_2 receptor antagonists, the selective and nonselective 5-HT agonists failed to cause a complete inhibition of the behavior induced by (±)-DOI. However, the 5-HT_{1B}/5-HT_{1C} agonist TFMPP failed to cause a significant effect ($p>0.05$) on the (±)-DOI-induced head-twitch response at all doses evaluated.

Several explanations may be offered to account for the attenuation of the (±)-DOI-induced effect by 5-MeO DMT. By itself, 5-MeO DMT induces head-twitch behavior (Fig. 9). Therefore, a combination of suboptimal doses of 5-MeO DMT and (±)-DOI might produce a bell-shaped dose-response curve (i.e., an "apparent" antagonistic effect) similar to that produced by administration of LSD (25). This seems unlikely, however, on the basis of several lines of reasoning: (a) The head-twitch produced by 5-MeO DMT subsides approximately 10 minutes postinjection, whereas antag-

TABLE 1

THE ID_{50} VALUES (50% INHIBITORY DOSE) WITH 95% CONFIDENCE LIMITS OF THE VARIOUS 5-HT AGONISTS AND ANTAGONISTS IN INHIBITING THE (±)-DOI-INDUCED HEAD-TWITCH RESPONSE

Drug	ID_{50} (mg/kg)	Corr. Coeff.	ID_{50} Ratio
Spiperone	0.08 (0.03–0.28)	.98	1.0
Ketanserin	0.17 (0.05–0.93)	.93	2.1
8-OH DPAT	0.25 (0.05–1.33)	1.0	3.1
5-MeO DMT	1.52 (0.2–11.91)	.98	19

Ratios of the ID_{50}s of the various drugs to that of spiperone is also given.

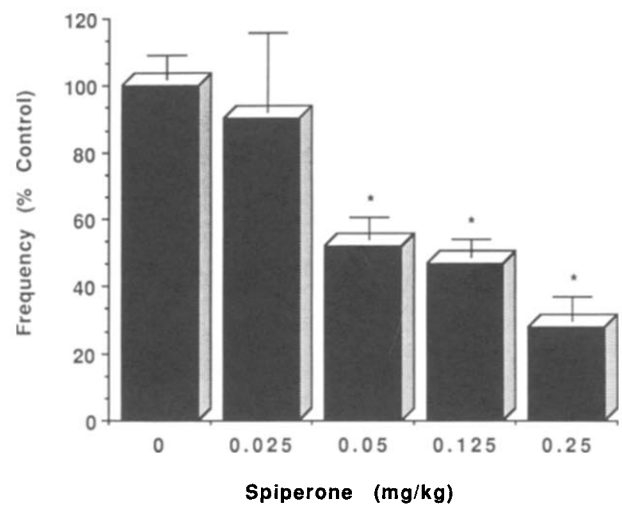

FIG. 5. Dose-dependent inhibition of (±)-DOI-induced head-twitch response (2.5 mg/kg) by spiperone. Data are presented as percent control head-twitch response (± SEM) (*$p<0.05$).

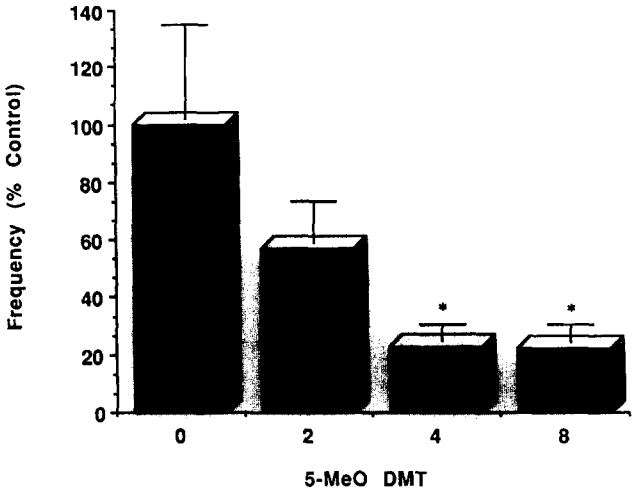

FIG. 6. Effects of the nonselective 5-HT agonist 5-MeO DMT on (±)-DOI-induced head-twitch response (2.5 mg/kg) in mice. Data are presented as percent head-twitch response observed in control mice (±SEM) (*$p<0.05$).

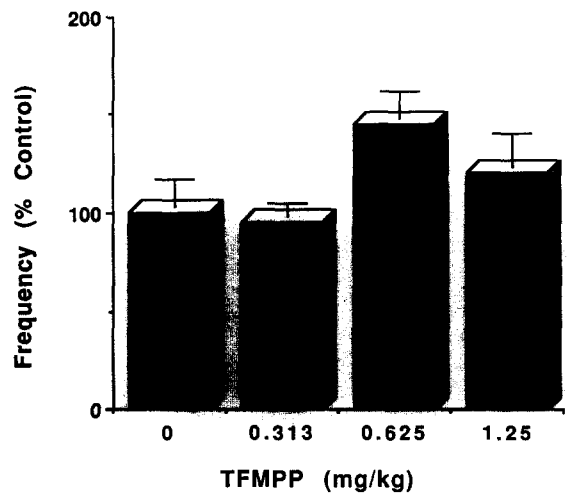

FIG. 8. Effects of the selective 5-HT_{1B}/5-HT_{1C} agonist TFMPP on head-twitch frequency induced by 2.5 mg/kg (±)-DOI. Data are presented as percent response in control mice (±SEM) (*$p>0.05$).

onism of the (±)-DOI-induced effect is still evident 30 minutes postinjection. Furthermore, signs of the serotonin syndrome, such as hind-limb abduction, persist beyond the 30-minute postinjection period. (b) There is no evidence that either agent, given alone, produces a bell-shaped curve. That is, although 5-MeO DMT ($ED_{50}=1.52$ mg/kg) antagonizes the effect produced by 2.5 mg/kg (±)-DOI, higher doses of either agent produce the head-twitch response. For example, 5 mg/kg of (±)-DOI produces head-twitch (Fig. 1); 10 mg/kg and 20 mg/kg of (±)-DOI (data not shown) produce a frequency of head-twitch that is not significantly different than that produced by the 5 mg/kg dose. Doses of 5-MeO DMT of up to 32 mg/kg also produce head-twitch dose dependently without a bell-shaped dose-effect curve (Fig. 9). Although a 20 mg/kg dose of (±)-DOI produces a substantial decrease in ambulation and in disruption of behavior, and doses of 5-MeO DMT greater than 32 mg/kg produce an extreme amount of tremor, making it nearly impossible to objectively quantitate head-twitch frequency, it is evident that doses much higher than those shown in Fig. 6 can be administered without evidence of a bell-shaped curve. Furthermore, because the frequency of head-twitch observed for administration of the combination is less than that of (±)-DOI administered alone, the effects do not appear to be additive.

A second explanation for the apparent antagonism is that the (±)-DOI-induced effect can be modulated by a 5-HT_1 agonist mechanism. To further explore this possibility, and because 5-MeO DMT is a nonselective 5-HT_1 as well as a 5-HT_2 agonist, we examined the effects of the 5-HT_{1A} agonist 8-OH-DPAT and the 5-HT_{1B}/5-HT_{1C} agonist TFMPP. By themselves, neither compound produced the head-twitch response. Given in combina-

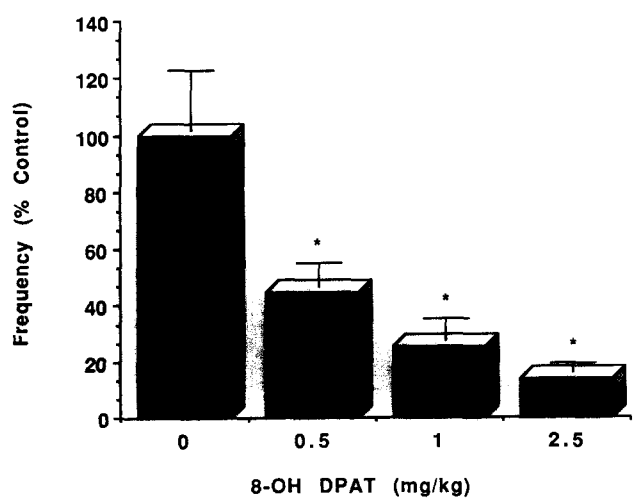

FIG. 7. Effects of the selective 5-HT_{1A} agonist 8-OH-DPAT on head-twitch frequency induced by 2.5 mg/kg (±)-DOI. Data are presented as percent response in control mice (±SEM) (*$p<0.05$).

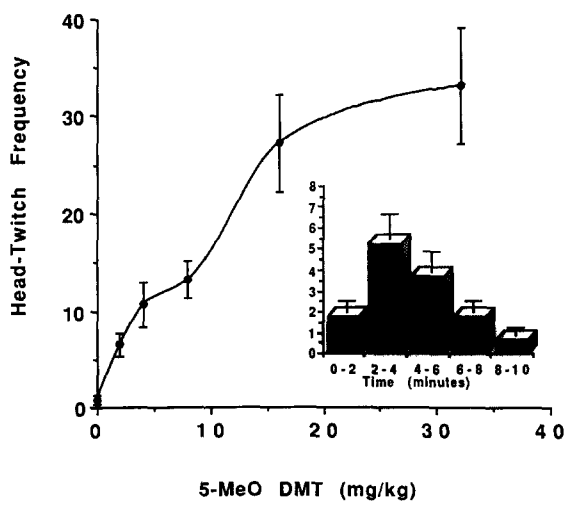

FIG. 9. The effect of 5-MeO DMT administration (IP) on the production of head-twitch (HT) response in mice. The behavior was observed for 10 minutes immediately after injection. Results are given as means±SEM. The inset represents a time course for head-twitch response in two-minute intervals for a dose of 8 mg/kg 5-MeO DMT.

tion with (±)-DOI, 8-OH-DPAT (Fig. 7), but not TFMPP (Fig. 8), results in attenuation of (±)-DOI-induced head-twitch.

The present results indicate that there may be a possible pharmacological interaction between 5-HT_{1A} and 5-HT_2 receptors, and that simultaneous costimulation of 5-HT_{1A} receptors by 8-OH-DPAT or 5-MeO DMT would lead to the inhibition of head-twitch response induced by the direct selective agonist (±)-DOI. Indirect support for such a notion is evident from the reported increase (196%) in head-twitch frequency induced by the direct nonselective agonist 5-MeO DMT upon administration of the 5-HT_{1A} partial agonist ipsapirone (10). However, ipsapirone failed to increase the head-twitch response induced by 5-hydroxytryptophan (precursor loading). Furthermore, 8-OH-DPAT, which displays very low affinity for 5-HT_2 sites, inhibits the head-twitch behavior induced indirectly by precursor loading, but not the behavior produced by direct stimulation of 5-HT_2 receptors by 5-MeO DMT (11). Since the latter study also reports that 8-OH-DPAT inhibits 5-HT synthesis through a presynaptic 5-HT_{1A} mechanism, it obviously can inhibit 5-hydroxytryptophan-precursor-induced head-twitch behavior. Under such nonphysiological conditions as precursor loading, where 5-HT is synthesized and released at a much greater rate than normal, antagonism of the inhibitory presynaptic 5-HT_{1A} mechanism by ipsapirone may not lead to a further increase in 5-HT synthesis and therefore head-twitch response (10). In light of the present investigation, it is difficult to explain the reported inability of 8-OH-DPAT to inhibit 5-MeO DMT-induced head-twitch produced by direct stimulation of 5-HT_2 receptors (11). It may be that the dose of 5-MeO DMT (5 mg/kg) used in that particular study reduced its own maximal 5-HT_2 effects (i.e., head-twitching frequency) by simultaneously stimulating inhibitory postsynaptic 5-HT_{1A} receptors. This stimulation of 5-HT_{1A} receptors would explain the inability of 8-OH-DPAT to further reduce the induced head-twitch frequency.

As discussed in the introduction, LSD not only induces the 5-HT syndrome and head-twitch behavior (5-HT_{1A}- and 5-HT_2-mediated behaviors, respectively), but also inhibits 5-hydroxytryptophan-induced head-twitch response (22,25). LSD is a known nonselective 5-HT agonist and can therefore induce both behaviors. It also inhibits 5-HT release, probably through activation of presynaptic 5-HT_{1B} autoreceptors (18) and thus can reduce precursor-induced head-twitch. It should be noted, however, that this inhibition is different from that described for 8-OH-DPAT. The latter drug has no direct effect on 5-HT release (18), but inhibits synthesis and therefore release through presynaptic 5-HT_{1A} receptors (11). Furthermore, as with 8-OH-DPAT and 5-MeO DMT in the present study, LSD may stimulate the inhibitory postsynaptic 5-HT_{1A} receptors to reduce the frequency of head-twitch behavior. Further increases in dose may even lead to inhibition of attained maximal head-twitch response as has been reported for LSD and quipazine, i.e., bell-shaped dose-response curves (25).

While this manuscript was in preparation we became aware of studies by Arnt and Hytell (1) and by Yocca and co-workers (26) that complement the results of the present investigation. In the latter study, it was demonstrated that quipazine-induced head-twitch in rats could be attenuated by pretreatment of the animals with 8-OH-DPAT. Arnt and Hytell (1) showed that 8-OH-DPAT could also attenuate (±)-DOI-induced head-twitch in rats. Both papers conclude that 5-HT_{1A} agonists may influence the behavioral effects of 5-HT_2 agonists. There is, however, one significant difference between the Arnt and Hytell study and the present investigation. Whereas they found that 1.3 mg/kg of TFMPP was able to antagonize by 50% the effect of 2.5 mg/kg of (±)-DOI, we found that doses of 0.3 to 1.25 mg/kg were without significant effect on (±)-DOI-induced head-twitch. The discrepancy may be related to the different species of animals used in the two studies.

Although a (±)-DOI effect is discussed in terms of being a selective 5-HT_2 agonist, DOI also shows appreciable affinity for 5-HT_{1C} sites. (±)-DOI is reported to have a similar (15) or up to 40-fold higher affinity (24) for 5-HT_2 than 5-HT_{1C} sites. Ketanserin also binds at 5-HT_{1C} sites but has a 50-fold selectivity for 5-HT_2 versus 5-HT_{1C} (15). Spiperone possesses 600–2000-fold selectivity for 5-HT_2 over 5-HT_{1C} receptors (14,21); and is considered to be more selective than ketanserin for 5-HT_2 relative to 5-HT_{1C} sites. Because spiperone was more potent than ketanserin in inhibiting DOI-induced head-twitch behavior, it seems likely that the head-twitch is 5-HT_2-mediated. Further support for this hypothesis is the observation that the 5-HT_{1B}/5-HT_{1C} agonist TFMPP did not produce head-twitch.

In summary, we have demonstrated (a) that racemic DOI and both of its optical isomers induce head-twitch in mice, (b) that R(−)-DOI is about twice as potent as S(+)-DOI, (c) that, consistent with a 5-HT_2 mechanism, ketanserin is capable of attenuating (±)-DOI-induced head-twitch, (d) that the nonselective 5-HT agonist 5-MeO DMT dose-dependently attenuates the (±)-DOI-induced effect, (e) that the selective 5-HT_{1A} agonist (8-OH-DPAT) produces a similar antagonism of DOI-induced head-twitch, and (f) that the 5-HT_{1B}/5-HT_{1C} agonist TFMPP did not affect the (±)-DOI-induced response. Furthermore, (±)-DOI-induced head-twitch appears to be 5-HT_2-mediated, on the basis that TFMPP does not produce the effect and because spiperone is essentially equipotent with ketanserin in antagonizing (±)-DOI-induced head-twitch. Thus, taken together with the previously published literature, we propose that costimulation of 5-HT_{1A} receptors has a modulating role on 5-HT_2-mediated head-twitch behavior. At this time, the exact nature of this relationship is unknown.

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