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BRIEF COMMUNICATION

8-OH-DPAT and Buspirone Analogs Inhibit the Ketanserin-Sensitive Quipazine-Induced Head Shake Response in Rats

FRANK D. YOCCA,*[1] ROBERT N. WRIGHT,* RUSSELL R. MARGRAF† AND ARLENE S. EISON‡

**Preclinical CNS Research, Pharmaceutical Research and Development Division*
Bristol-Myers Company, P.O. Box 5100, Wallingford, CT 06492
†Department of Biology, Hall-Atwater Labs
Wesleyan University, Middletown, CT 06457
‡Section of Pharmacology and Toxicology, School of Pharmacy
University of Connecticut, Storrs, CT 06268

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YOCCA, F. D., R. N. WRIGHT, R. R. MARGRAF AND A. S. EISON. *8-OH-DPAT and buspirone analogs inhibit the ketanserin-sensitive quipazine-induced head shake response in rats.* PHARMACOL BIOCHEM BEHAV **35**(1) 251–254, 1990.— Behavioral syndromes mediated by serotonergic mechanisms may reflect interactions between distinct effects initiated by specific 5-HT receptors, such as the 5-HT_{1A} and the 5-HT_2 receptor. This hypothesis was tested by examining the effect of various 5-HT_{1A} agonists on the 5-HT_2 receptor-mediated quipazine-induced head shake response in rats. Subcutaneous administration of 8-OH-DPAT, buspirone, gepirone, and ipsapirone produced a dose-dependent inhibition of the ketanserin-sensitive quipazine-induced head shake response. These effects were produced by doses of agonists which did not induce reciprocal forepaw treading. Furthermore, pretreatment with a partial 5-HT_{1A} agonist (±)pindolol blocked the inhibitory effects of 8-OH-DPAT to the level of inhibition produced by (±)pindolol itself. These results suggest that stimulation of central 5-HT_{1A} receptors can modulate the expression of a central 5-HT_2 receptor-mediated behavior.

5-HT_{1A} agonists 5-HT_{1A} receptors 5-HT_2 receptors Quipazine-induced head shake response

CLASSIFICATION of functional serotonin (5-HT) receptors has been aided in recent years by the discovery of selective agonists and antagonists of the 5-HT_{1A}, 5-HT_2 and 5-HT_3 receptor subtypes (5). Not only have these agents been useful for classification of 5-HT receptor systems studied in vitro, but they have also become valuable tools for delineating responses mediated by various 5-HT receptors in vivo. It is plausible to assume that in vivo, the firing of 5-HT-containing raphe neurons results in the release of 5-HT and activation of multiple 5-HT receptor subtypes by endogenous 5-HT throughout the central nervous system (CNS). Therefore, it is of particular importance to utilize selective agents to elucidate putative interactions between responses mediated by simultaneous activation of different 5-HT receptors in the CNS. We chose to study possible interaction(s) resulting from simultaneous stimulation of central 5-HT_{1A} and 5-HT_2 receptors, two well-defined subtypes of 5-HT receptors which mediate specific behavioral syndromes in rat (14,19).

Several lines of evidence suggest that responses mediated by central 5-HT_2 receptors can be modulated by simultaneous activation of central 5-HT_{1A} receptors. Chronic administration with gepirone, a selective 5-HT_{1A} agonist (20), down-regulated (20%) cortical d-bromo-LSD-sensitive [^{3}H]spiperone binding sites, while attenuating ketanserin-sensitive quipazine-induced behavior (7). The antidepressant imipramine, while dose-dependently inhibiting

[1]Requests for reprints should be addressed to Frank D. Yocca.

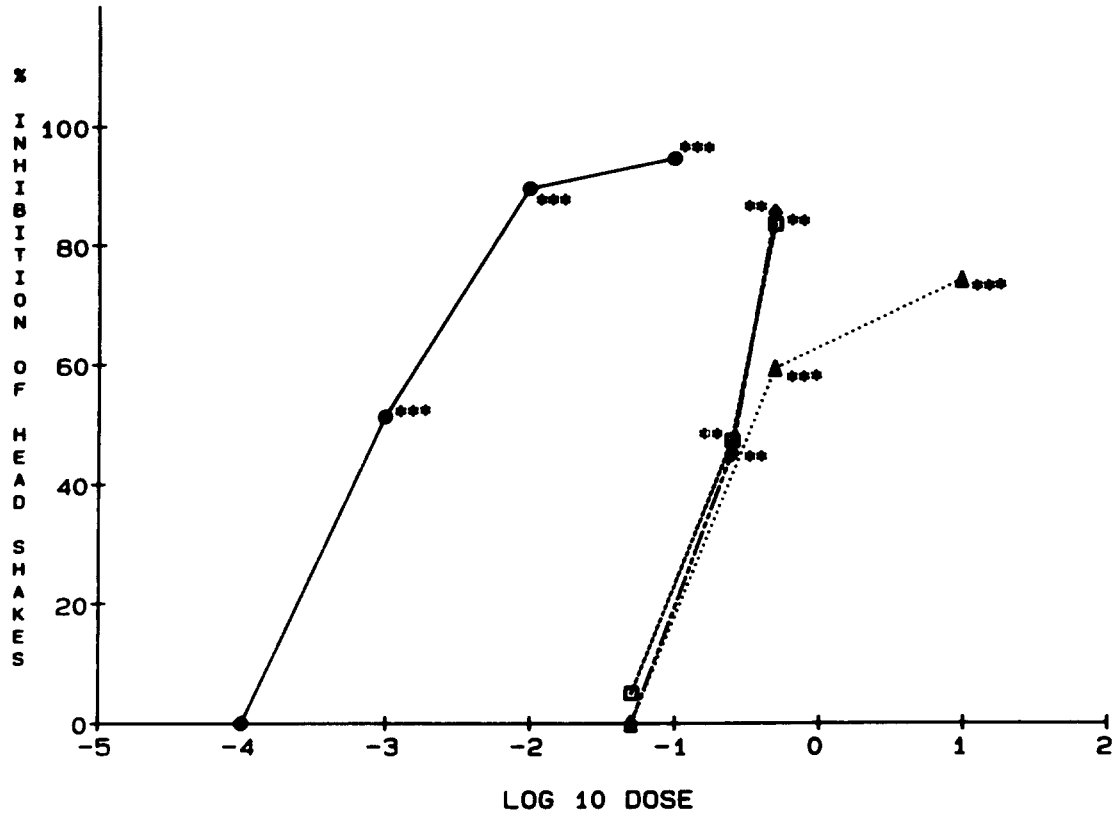

FIG. 1. Dose-dependent inhibition of the quipazine-induced head shake response by 8-OH-DPAT and buspirone analogs. Rats (N = 6 per dose) were pretreated with various doses of 8-OH-DPAT (●), buspirone (◇), gepirone (□), and ipsapirone (▲), 15 min prior to the administration of quipazine maleate (see text), and the frequency of head shake responses were quantified for 30 min commencing immediately after injection. Results are expressed as percent inhibition of the quipazine-induced head shake response where the mean total number of head shakes for control rats was 18 ± 1. The ID_{50} values (μg/kg, SC; 8-OH-DPAT, 1.3; gepirone 240; buspirone, 270; and ipsapirone, 470) were generated using the Finney Dose Response Analysis method.

5-HT_2-mediated behavior in mice, stimulated the 5-HT syndrome in rats (16), a behavioral syndrome proposed to be mediated in part by 5-HT_{1A} receptors (19). In order to determine if an interaction(s) exists between responses mediated by 5-HT_{1A} and 5-HT_2 receptors, we examined the effect of the selective 5-HT_{1A} agonists 8-OH-DPAT [8-hydroxy-2-(di-N-propylamino)-tetralin], buspirone, gepirone (20), and ipsapirone (18) on the quipazine-induced head shake response. Studies have demonstrated that the head shake response to quipazine in rats is a simple, quantifiable and reliable behavior mediated by central 5-HT_2 receptor activation which is ketanserin-sensitive (14).

METHOD

Animals

Male Sprague-Dawley (CD) rats (Charles River, Kingston, NY, 200–300 g) were group housed (5/cage) and maintained 2 weeks on a 12-hour light cycle in a temperature- and humidity-controlled room with food and water ad lib prior to testing.

Procedures

In studies where the effect of various 5-HT_{1A} agonists on quipazine-induced head shakes were examined, animals were pretreated with either test drug or saline 15 min prior to the subcutaneous administration of 5 mg/kg quipazine. The rats were then placed in individual clear Plexiglas chambers (34 × 28 × 17 cm) with wood shavings covering the chamber floor. Observations were then made on the frequency of head shake responses over 30 min commencing immediately following quipazine injection. Quipazine-induced head shakes were characterized as rapid side to side twitches of the head and ears, as previously described (4).

To determine if the 8-OH-DPAT-induced inhibition of the quipazine-induced head shake response could be antagonized by (±)pindolol, rats were pretreated 30 min prior to quipazine with (±)pindolol (8.0 mg/kg, SC) or saline (2 ml/kg, SC). Fifteen min prior to quipazine the rats were dosed again with either 8-OH-DPAT (0.2 mg/kg, SC) or saline (1 ml/kg, SC). The rats were then observed for head shake responses over 30 min beginning 5 min after quipazine injection. The experiments were conducted over 3 consecutive days between the hours of 10:30 a.m. and 4:00 p.m. and were randomized in a balanced fashion to control for day effect, time of day effect, and order of testing effect.

Drugs

8-OH-DPAT-HBR (RBI), gepirone and buspirone HCl (Bristol-Myers Co.), ipsapirone HCl and quipazine maleate (Miles Laboratories) were dissolved in 0.9% saline. (±)Pindolol (Sandoz Ltd.) was dissolved in water to which 1–2 drops of glacial acetic acid had been added. All drugs were injected subcutaneously in a volume of 2 ml/kg.

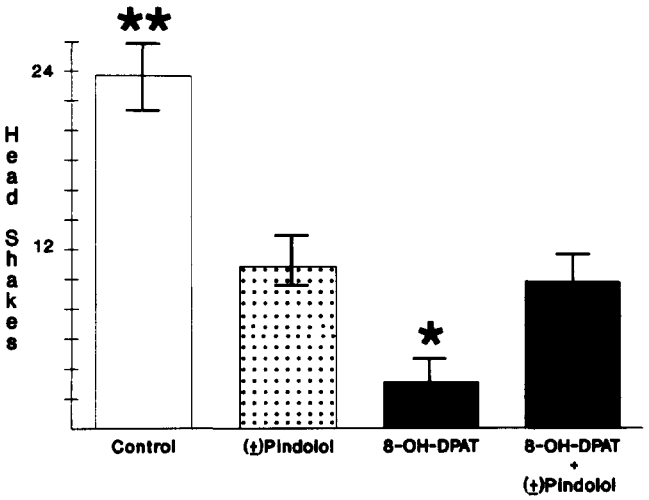

FIG. 2. Pindolol antagonism of 8-OH-DPAT-induced inhibition of the quipazine head shake response. Four groups of rats (n = 9 per group except 8-OH-DPAT + (±)pindolol group n = 8) were pretreated 30 min prior to quipazine with either 8 mg/kg (±)pindolol or saline and again 15 min prior to quipazine with either 0.2 mg/kg 8-OH-DPAT or saline. The frequency of head shake responses were quantified for 30 min commencing 5 min after 5 mg/kg quipazine injection. $^{**}p \leq 0.01$, $^{*}p \leq 0.05$ vs. 8-OH-DPAT + (±)pindolol, Tukey Kramer Method.

Statistical Analysis

The ID_{50} values (dose necessary to inhibit the quipazine-induced head shake response by 50%) were generated using the Finney Dose Response Analysis method. In the antagonism experiments, a one-way ANOVA was performed to determine the overall treatment effect. This was followed by a Tukey Kramer Method for comparisons of means.

RESULTS

Figure 1 displays the dose-dependent inhibition of the quipazine-induced head shake response by 8-OH-DPAT, buspirone, gepirone, and ipsapirone. The ID_{50} values in rank order were: 8-OH-DPAT (1.3 μg/kg), gepirone (240 μg/kg), buspirone (270 μg/kg), and ipsapirone (470 μg/kg).

Treatment of rats with a high dose of (±)pindolol (8 mg/kg) produced a moderate inhibition (54%) of the quipazine-induced head shake response (Fig. 2). In a study designed to antagonize the effects of 0.2 mg/kg 8-OH-DPAT (which produces an 87% inhibition of the quipazine-induced head shake response), pretreatment with (±)pindolol followed by 8-OH-DPAT administration resulted in a significant antagonism (33%, $p<0.05$) of the 8-OH-DPAT-induced inhibition of the quipazine-induced head shake response to the level produced by (±)pindolol alone.

DISCUSSION

Distinct behavioral syndromes induced by selective 5-HT_{1A} and 5-HT_2 agonists in rats are mediated by selective stimulation of central 5-HT_{1A} or 5-HT_2 receptors (14,19). Recently however, a number of studies support the possibility of an interaction between responses mediated by central 5-HT_{1A} and 5-HT_2 receptors. Pericic and Manev (16) showed that imipramine which dose-dependently inhibited 5-HT_2-mediated behaviors in mice, stimulated the 5-HT syndrome in rats which has been proposed to be mediated in part by 5-HT_{1A} receptors (19). Interestingly, the behavioral syndrome induced by the 5-HT_{1A} agonist 8-OH-DPAT can be potentiated in a dose-dependent fashion by the selective 5-HT_2 antagonist ritanserin (3) and the 5-HT_2 agonist DOI (2). Furthermore, the behavioral evidence suggesting an interaction between 5-HT_{1A} and 5-HT_2 receptors is corroborated by physiological and biochemical studies. For example, Araneda and Andrade (1) demonstrated that when 5-HT_{1A} and 5-HT_2 receptors coexisted on the same cell in rat prefrontal cortex, the activation of 5-HT_2 receptors reduced the ability of 5-HT_{1A} receptors to hyperpolarize these cells. Similarly, treatment in humans with ritanserin potentiated the prolactin response to L-tryptophan (6), an effect which is thought to be mediated by 5-HT_1 receptors.

In the present study, 8-OH-DPAT, buspirone, gepirone and ipsapirone, agents which demonstrate selective 5-HT_{1A} agonist activity (11, 18, 20), dose-dependently attenuated the ketanserin-sensitive quipazine-induced head shake response thought to be mediated by 5-HT_2 receptors (14). This effect occurred with relatively low doses of agonists which did not induce reciprocal forepaw treading behavior in reserpinized rats (F. Yocca, unpublished results), an effect which was proposed to be mediated by postsynaptic 5-HT_{1A} receptors (19). This is in agreement with the findings of Arnt and Hyttel (2), who demonstrated that the head shake response induced by the 5-HT_2 agonist DOI was inhibited in a dose-dependent fashion by 8-OH-DPAT. Interestingly, the doses of 8-OH-DPAT and buspirone analogs required to inhibit the quipazine-induced head shake response are similar to those required for inhibition of central 5-HT synthesis (10,17), an effect which appears to be mediated by presynaptic 5-HT_{1A} autoreceptors residing on 5-HT cell bodies (13). This dose-related congruency suggests that the inhibition of the 5-HT_2-mediated behavior by 5-HT_{1A} agonists may be mediated by presynaptic 5-HT_{1A} receptors (autoreceptors). The stimulation of presynaptic 5-HT_{1A} autoreceptors by 5-HT_{1A} agonists reduce 5-HT impulse flow and synthesis which may alter the degree of postsynaptic receptor stimulation by 5-HT in the presence of quipazine. Alternatively, if stimulation of postsynaptic 5-HT_{1A} receptors is responsible for inhibition of 5-HT_2 receptor-mediated behaviors, then putative cross-talk between receptors may be initiated by low concentrations of agonist that cannot elicit a behavioral response (i.e., 5-HT_{1A} syndrome in rats). This hypothesis will be the focus of future investigations which involve removal of presynaptic 5-HT neuronal activity with the neurotoxin 5,7-dihydroxytryptamine.

While behavioral and biochemical studies have demonstrated that (−)pindolol possesses 5-HT_{1A} receptor antagonist activity (15,19), racemic (±)pindolol appears to be a partial 5-HT_{1A} agonist, weakly inhibiting the forskolin stimulation of rat hippocampal adenylyl cyclase (DeVivo and Maayani, unpublished results). In the present study, a high dose of (±)pindolol produced a modest, but significant inhibition of the quipazine-induced head shake response. This effect was probably mediated by either stimulation of a presynaptic 5-HT_{1A} or 5-HT_{1B} receptor, and not by antagonism of 5-HT_2 receptors, since (±)pindolol demonstrates little affinity for 5-HT_2 binding sites (9). Furthermore, the beta-adrenergic antagonism component of (±)pindolol's pharmacology is probably not involved in this effect, since it has been demonstrated that the quipazine-induced head shake response in rats was unaffected by pretreatment with (±)propranolol (8). Interestingly, similar doses of (−)pindolol have been found to inhibit hippocampal synthesis (12) in a manner similar to selective 5-HT_{1A} agonists (13,17), but to a lesser degree. Pretreatment with (±)pindolol antagonized the inhibition of the quipazine-induced head shake response by 8-OH-DPAT to the level of activity produced by (±)pindolol alone. This result supports the idea that the 5-HT_{1A} agonist-induced inhibition of the quipazine head shake

response is mediated by stimulation of 5-HT_{1A} receptors. Furthermore, the similarities between the doses of 8-OH-DPAT and enantiomeric and racemic pindolol that are required to inhibit 5-HT synthesis and are necessary for antagonism of the quipazine-induced head shake response, respectively, suggest that stimulation of presynaptic 5-HT_{1A} receptors may modulate the expression of a 5-HT_2 receptor-mediated behavior.

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