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Evidence for Antiserotonergic Properties of Yohimbine[1]

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DWOSKIN, L. P., B. S. NEAL AND S. B. SPARBER. *Evidence for antiserotonergic properties of yohimbine*. PHARMACOL BIOCHEM BEHAV 31(2) 321–326, 1988.—Yohimbine (YOH) is a widely used pharmacological tool employed to produce a selective blockade of alpha$_2$-adrenergic receptors. In the present study operant behavior was used as a biobehavioral assay to determine the activity of YOH at serotonergic receptors, as indicated by its ability to antagonize the behavioral effects of a serotonergic agonist, lysergic acid diethylamide (LSD). Rats were trained to respond on a Fixed Ratio 15 schedule for food reinforcement. YOH (0.5–5.0 mg/kg) or vehicle and LSD (50 μg/kg) were administered (IP) 30 min and immediately prior, respectively, to the 30-min operant session. In a separate study, the ability of YOH (0.5–2.5 mg/kg) to antagonize a higher dose of LSD (100 μg/kg) was examined. Relatively low doses of YOH (0.5–1.0 mg/kg) were able to partially, but significantly antagonize the LSD-induced suppression and typical hallucinogen-induced disruption of schedule-controlled responding. These results suggest that YOH, even at moderate doses, may act nonselectively as an antagonist at 5-HT receptors, in addition to its antagonist action at alpha$_2$-adrenergic receptors. This study demonstrates the utility of operant behavior as a biobehavioral assay to study the receptor mediated action of drugs.

Yohimbine Serotonin Lysergic acid diethylamide Operant behavior

YOHIMBINE (YOH) is widely used as a pharmacological tool to obtain selective blockade of alpha$_2$-adrenergic receptors [for review (13,38)]. In biochemical studies, YOH has been reported to increase norepinephrine (NE) turnover (2), NE release from nerve terminals (17) and NE metabolite levels in cerebrospinal fluid [CSF (22)]. In binding studies, YOH has been reported to have a high affinity for alpha$_2$-receptors (23,28). In behavioral studies, we have found that low doses of YOH block the behavioral suppression produced by the alpha$_2$-receptor agonist clonidine; however, clonidine did not antagonize the behavioral suppression induced by higher doses of YOH (10). Therefore, the behavioral effect of yohimbine is not apparently due to an alpha$_2$-receptor mediated event.

Using operant behavior as a bioassay, we recently reported that only behaviorally active, moderate to high doses of YOH were able to partially antagonize the suppressant effect of apomorphine, a dopamine (DA) receptor agonist (9). Therefore, at least part of the behavioral effect of YOH may be the result of a DA receptor mediated event. These results are in agreement with the findings from neurochemical studies which support a role for DA in the action of YOH (25, 34, 40).

YOH is an indole alkaloid and has a functional group in common with serotonin (5-HT), an indoleamine. Therefore, the involvement of 5-HT receptors in the action of YOH might be predicted. Relatively high doses and concentrations of YOH have been reported to increase 5-HT and reduce 5-hydroxyindoleacetic acid concentrations (24,33), decrease 5-HT synthesis (30) and decrease evoked [^{3}H]5-HT release from rat brain slices (12). In behavioral studies, relatively high doses of YOH have been reported to produce a protective effect against electroconvulsive shock-induced seizures in mice. Moreover, this effect of YOH was antagonized by methysergide and metergoline, but not by clonidine (21). Additionally, YOH has been reported to produce generalization in rats trained to discriminate LSD (6) and tetrahydro-beta-carboline, a condensation product of tryptamine and formaldehyde (35). The neurochemical basis of the discriminative stimulus effects of these compounds have been reported to involve serotonergic neurons (7,35). Therefore, YOH may have multiple effects, including interaction(s) as either an agonist or antagonist at 5-HT receptors.

The interaction of YOH with 5-HT function was examined in the present study by determining its ability to antagonize the behavioral effect of 5-HT receptor agonist lysergic

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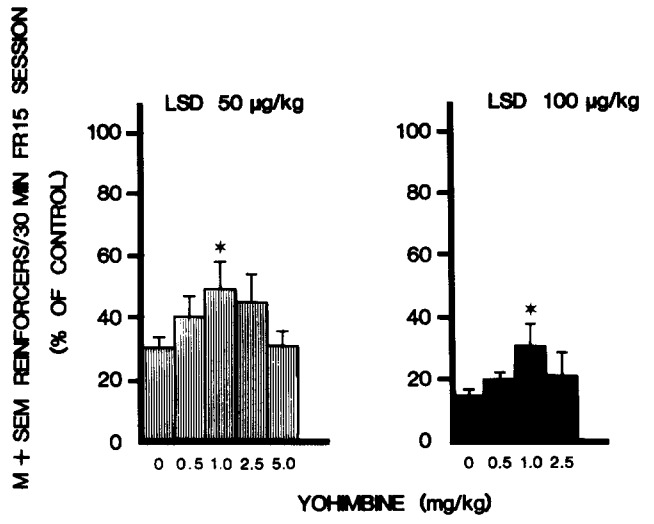

FIG. 1. Partial antagonism of the behavioral suppressant effect of LSD by yohimbine HCl. Data are expressed as a percent of the control day prior to drug administration when vehicles were administered 30 min and immediately prior to the 30 min operant session. Yohimbine HCl partially antagonizes the behavioral suppression induced by LSD (50 µg/kg, left panel; 100 µg/kg, right panel). The effect of the 0 mg/kg doses of yohimbine and LSD was 99.51±2.09% of control in left panel and 103.5±1.20% of control in right panel (not shown). In both experiments, repeated measures ANOVA revealed a significant main effect of yohimbine HCl [LSD 50 µg/kg, $F(5,25)=31.472$, $p<0.001$; and, LSD 100 µg/kg, $F(4,20)=105.425$, $p<0.001$]. *$p<0.05$, Dunnett's test compared to LSD alone.

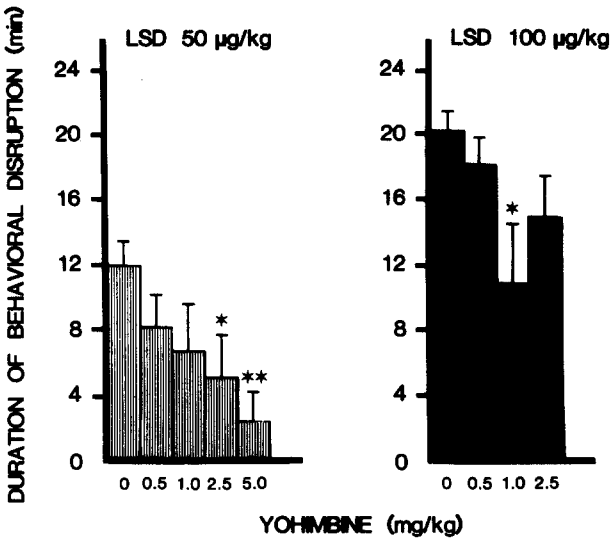

FIG. 2. Yohimbine partially antagonizes the disruption of responding induced by LSD. The measure of behavioral disruption is the number of minutes taken to receive 5 reinforcers after a period of at least 2 min during which no reinforcers were received. Yohimbine HCl partially antagonizes the disruption of responding induced by LSD (50 µg/kg, left panel; 100 µg/kg, right panel). The effect of the 0 mg/kg doses of yohimbine and LSD was 0±0 in both experiments (not shown). In both experiments, repeated meausures ANOVA revealed a significant main effect of yohimbine HCl [LSD 50 µg/kg, $F(5,25)=5.641$, $p<0.001$; LSD 100 µg/kg, $F(4,20)=19.568$, $p<0.001$]. *$p<0.05$, **$p<0.01$ by Dunnett's test compared to LSD alone.

acid diethylamide (LSD). LSD was chosen because the preponderance of evidence, including biochemical (32), binding (26), electrophysiological (1) and brain perfusion data (19,39) support a role for 5-HT receptors in producing LSD's effect. The present study demonstrates that even low to moderate doses of YOH appear to have effects at multiple receptor sites, and therefore, do not act selectively as an alpha$_2$-adrenergic receptor antagonist.

METHOD

Subjects

Male Sprague-Dawley rats (n=6; 325–460 g free-feeding; Holtzman Laboratories) were individually housed in a controlled environment (24°C; 40–50% humidity) under a 12 hr light-dark cycle (lights on from 0700 hr). Body weight was reduced to 80% of free-feeding weight and was maintained by a 23 hr schedule of food deprivation with small supplements of Purina Rat Chow, as necessary. Water was freely available in the home cage.

Apparatus

Behavioral sessions were conducted in operant chambers (Model No. 143-22 BRS/LVE) equipped with a lever which could be depressed by at least a 25 g weight, a dispenser which delivered 45 mg food pellets (Bio Serv) and a speaker for introduction of a white masking noise. House and cue lights provided low level illumination. A specially constructed outer chamber provided sound and light attenuation. Experimental events and contingencies were controlled and recorded by a Nova-2/10 minicomputer (Data General Corp.) and Interact System interfacing (BRS/LVE). Continuous records of behavior were made on cumulative recorders (Ralph Gerbrands).

Yohimbine-LSD Behavioral Interaction

Rats were trained during daily 30 min sessions of a Fixed Ratio 15 (FR 15) schedule for food reinforcement. Stable response rates were obtained for the group within 30 days after initiation of the behavioral training sessions. In the first experiment, injections (1 ml/kg, IP) of yohimbine HCl (YOH; 0.5–5.0 mg/kg; Sigma) or vehicle (distilled water) and of LSD (50 µg/kg; d-LSD tartrate, National Institute on Drug Abuse) or vehicle (0.9% saline) were administered 30 min prior and immediately prior, respectively, to the session. In the second experiment using the same group (n=6) of animals, injection of YOH (0.5–2.5 mg/kg) or vehicle and of LSD (100 µg/kg) or vehicle were administered 30 min prior and immediately prior, respectively, to the session. Since it was determined that there was no greater attenuation of the effect of the 50 µg/kg dose of LSD by the 5.0 mg/kg dose of yohimbine (in fact, an inverted U-shape function was observed in terms of reinforcers earned), we subsequently omitted the 5 mg/kg dose of yohimbine in the second experiment examining the higher dose of LSD. In both experiments, at least 72 hr separated drug sessions, thereby controlling for development of tolerance. Each drug session was preceded by two drug-free sessions, including a control session the day before in which vehicles were administered. When the experimental design called for two injections of vehicle on one of the treatment days, responding was com-

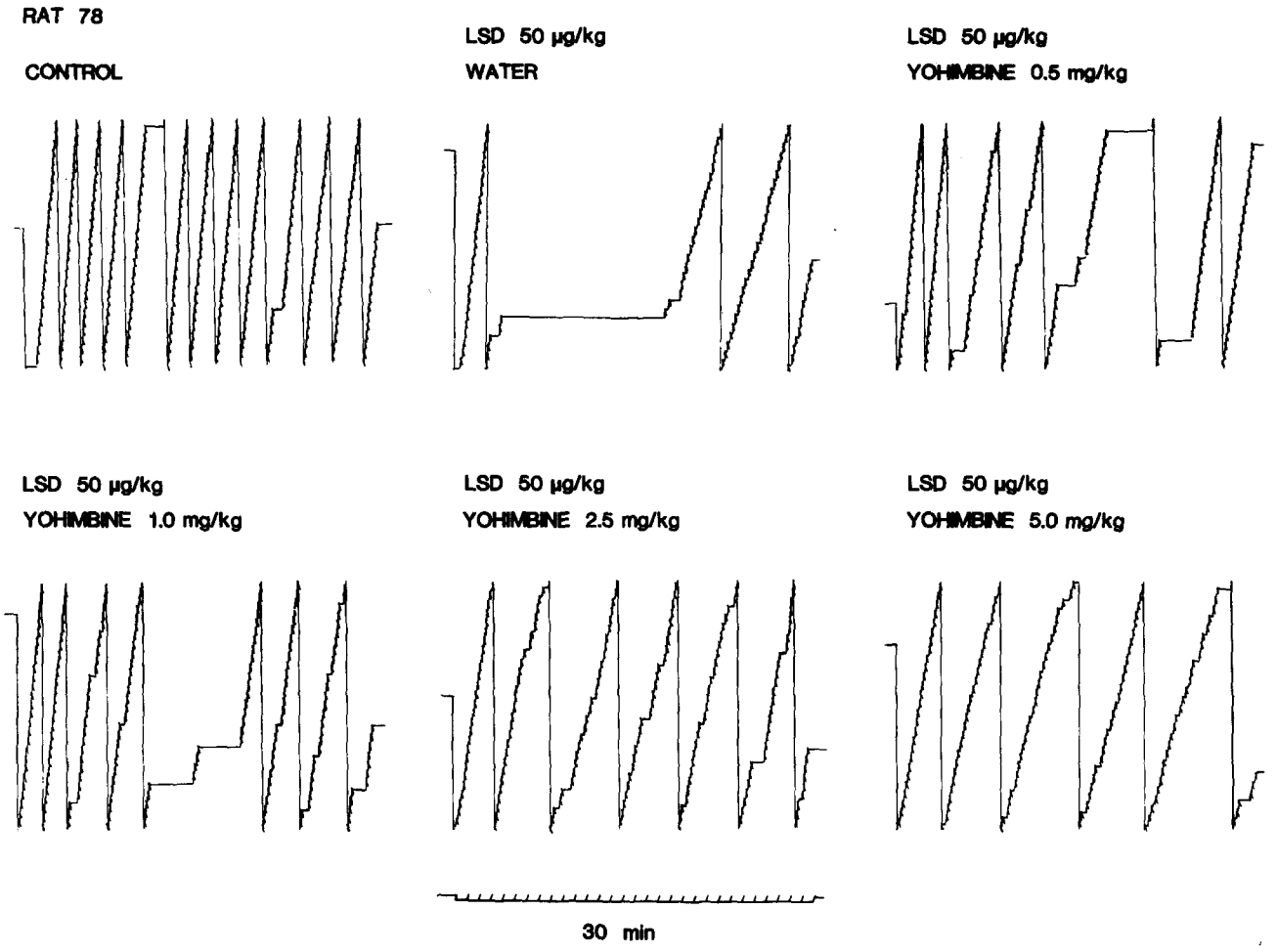

FIG. 3. Represenative cumulative records for rat 78 illustrating the effect of LSD (50 µg/kg), and the partial antagonism of the effect of LSD by pretreatment with yohimbine HCl (0.5–5.0 mg/kg). The length of the stepping pen traversed before reset represents 400 responses on the lever.

pared with that obtained 24 hr previously, at which time the rats were likewise given two vehicle injections. Treatment order (including the control session on one of the experimental days in which one rat received two vehicle injections while the other rats received drug) was based upon random assignment to subject and latin square dose sequence. Time of administration and doses of drugs were based on previous experiments in which we demonstrated that YOH suppressed FR 15 responding at doses greater than 1.0 mg/kg (9,10). Based on these studies, doses of YOH were chosen over a range which included behaviorally inactive (0.5 and 1.0 mg/kg) and active (2.5 and 5.0 mg/kg) doses.

Data Analysis

Group data are expressed as the number of reinforcers earned following drug as a percent of those earned during the previous day's control session in which vehicles were administered. The use of control sessions 24 hr before experimental sessions provides normalization of individual differences in response rate and for potential baseline shifts during the course of a protracted experiment. FR responding is characteristically abruptly disrupted following administration of hallucinogenic drugs (3). Duration of disruption was defined as the amount of time (min) taken to receive 5 reinforcers after a period of 2 min in which no reinforcers were received (37). Data were analyzed using one factor repeated measures ANOVA and Dunnett's *t*-test.

RESULTS

YOH partially antagonized the suppression of responding produced by LSD (Fig. 1). Administration of LSD (50 µg/kg) altered responding to a degree whereby subjects earned 31% of the reinforcers ordinarily earned under control conditions. Pretreatment with YOH (1.0 mg/kg) significantly antagonized the effect of this dose of LSD, such that responding was "suppressed" to only 50% of control. Similarly, YOH significantly antagonized the suppression of responding produced by a higher dose of LSD (100 µg/kg; Fig. 1). LSD (100 µg/kg) "suppressed" responding to 15% of control. YOH (1.0 mg/kg) also antagonized this effect of LSD, such that rats earned twice as many reinforcers (31% of control).

YOH also partially antagonized the duration of abrupt behavioral disruption induced by LSD (Fig. 2). Pretreatment with YOH (2.5 and 5.0 mg/kg) significantly reduced the duration of disruption from an average of 12 min after LSD (50

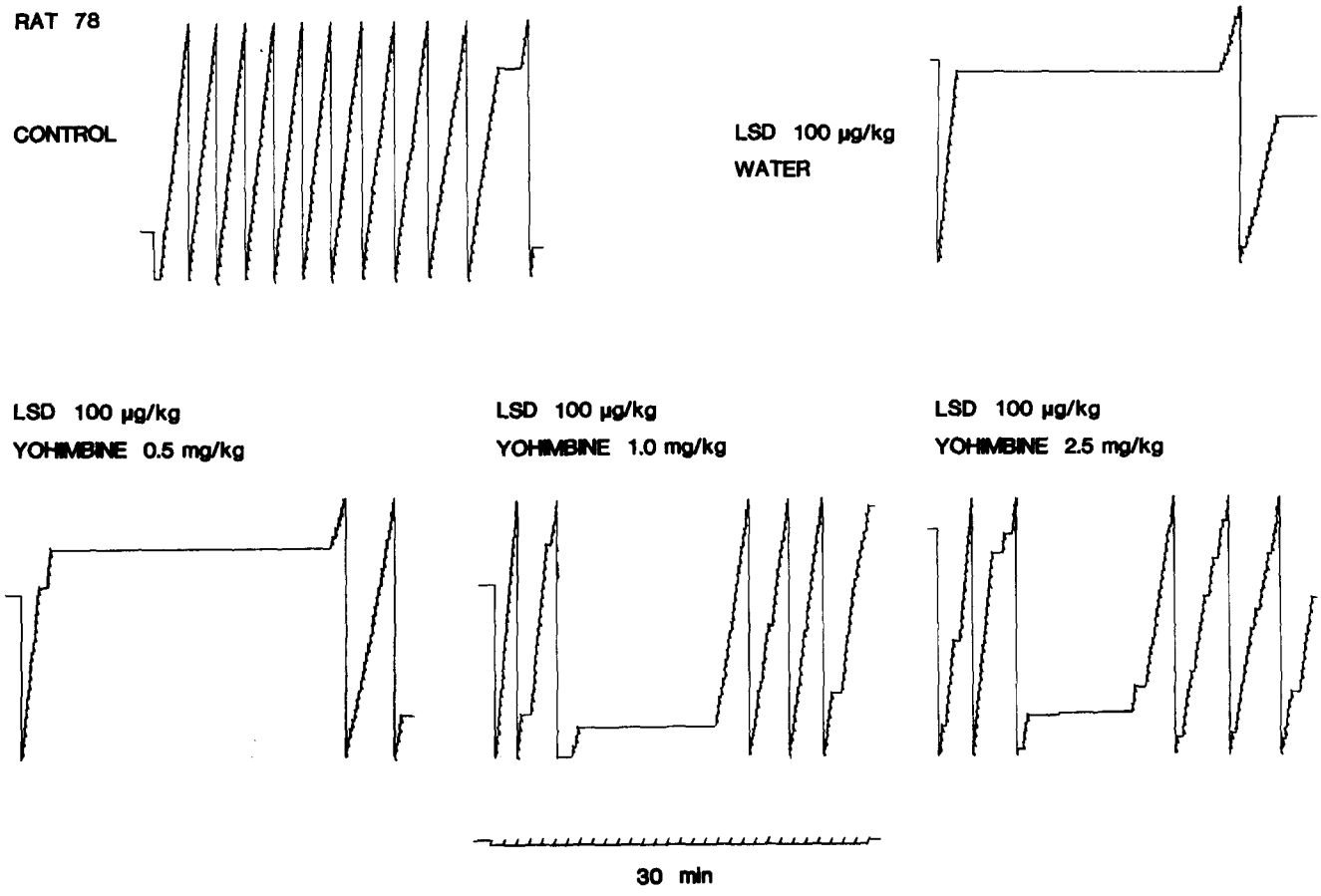

FIG. 4. Representative cumulative records for rat 78 illustrating the effect of LSD (100 µg/kg), and the partial antagonism of the effect of LSD by pretreatment with yohimbine HCl (0.5–2.5 mg/kg). The length the stepping pen traversed before reset represents 400 responses on the lever.

µg/kg) alone to 5 and 3 min, respectively. Following administration of a higher dose of LSD (100 µg/kg), the duration of disruption was 20 min. Pretreatment with YOH (1.0 mg/kg) significantly reduced this disruption to 11 min. The higher dose (2.5 mg/kg) was less effective after 100 µg LSD/kg.

Cumulative response records for a representative subject (rat 78) administered vehicle, LSD (50 µg/kg) alone and the same dose of LSD following pretreatment with various doses of YOH are illustrated in Fig. 3. When LSD was administered immediately prior to the session, 4 min after the session began rat 78 ceased responding for a period of 16 min. Pretreatment with YOH (0.5 and 1.0 mg/kg) clearly reduced the duration of the disruption in responding induced by this dose of LSD. Following pretreatment with YOH (2.5 and 5 mg/kg), no extended pause in responding, by definition (see the Method section) is apparent for this subject. Intermittent postreinforcement pauses occurred throughout the session in which YOH and LSD were administered. The cumulative records illustrate that postreinforcement pauses, not necessarily the rate of depressing the lever, is what is probably responsible for the decreased number of reinforcers obtained (and therefore the decreased overall response rate) as illustrated in Fig. 1.

Cumulative response records for the same animal are illustrated (Fig. 4) after administration of vehicle, the higher dose of LSD (100 µg/kg) and this dose of LSD following pretreatment with various doses of YOH. When LSD was administered immediately prior to the behavioral session, 2 min after the start of the session, rat 78 ceased responding and did not resume for 20 min. Administration of YOH (1.0 and 2.5 mg/kg) prior to LSD reduced the period of no responding to 11 and 8 min, respectively. Therefore, the cumulative records for this particular subject revealed that the behavioral disruption produced by LSD was antagonized to a greater extent by 2.5 mg/kg than by 1.0 mg/kg of YOH. Note that for the group, the optimal antagonist dose of YOH was 1.0 mg/kg (Fig. 2). The pause in responding was not reduced after pretreatment with the lowest dose of YOH (0.5 mg/kg).

DISCUSSION

In the present study, the behavioral interaction of YOH and LSD was examined to test the hypothesis that YOH, a presumed selective alpha$_2$-antagonist, acts nonselectively as an antagonist at 5-HT receptors. Drug interaction experiments revealed that low doses of YOH were able to partially antagonize the LSD-induced reductions in the total number of reinforcers obtained during the 30-min behavioral session. The low doses of YOH which were effective against LSD in the present study have been previously shown (9,10) to produce no discernable effect on the same schedule of responding. Therefore, one possible interpretation of the results is that YOH, at behaviorally inactive, low doses also acts

as an antagonist at 5-HT receptors. However, a complete antagonism or reversal of this effect of LSD was not obtained. Higher doses of YOH failed to attenuate the LSD-induced reductions in the total number of reinforcers obtained. Doses of YOH above 1.0 mg/kg themselves have been shown to suppress FR 15 response rate by inducing short postreinforcement pauses (9,10), suggesting that the effects of YOH alone may be a limiting factor in determining its effectiveness as an LSD antagonist. Therefore, using the measure of total number of reinforcers obtained may underestimate the ability of YOH to interact with 5-HT receptors.

Behaviorally suppressant doses of YOH do not alter FR 15 responding in the characteristic manner (dose-related disruption of responding or pausing) of LSD (9–11). Therefore, the effectiveness of YOH as an LSD antagonist may not be self-limiting or due to partial LSD-like agonist properties when examining this component (pausing) of LSD's effect. Indeed, YOH produced a striking, although partial, antagonism of the LSD-induced disruption of responding. The partial antagonism produced by YOH and the inverted U-shaped dose-response curve obtained in the experiment examining the higher dose of LSD (Fig. 2) may be explained by a further loss of selectivity at the higher doses of YOH. At doses greater than 1.0 mg/kg, YOH may interact either with other 5-HT receptor subtypes or with receptors other than 5-HT, which in turn may counteract its ability to antagonize the behavioral disruption produced by LSD.

Complications in discerning the involvement of 5-HT receptors arise when one considers the recent proliferation in the number of subtypes of 5-HT receptors (4). Nevertheless, several of the subtypes (16, 20, 26, 27) have been demonstrated to affect neuronal function (i.e., modulate the release of 5-HT from 5-HT neurons and inhibit or excite postsynaptic effectors). Similarly, more than a single 5-HT receptor may be involved in LSD's behavioral effect. Separating LSD's behavioral effect into disruption and depressed response rate enabled us to demonstrate that low doses of mianserin, a 5-HT_2 antagonist, was able to completely reverse both components of LSD's behavioral effect, whereas methysergide blocks the disruption of responding, without blocking the decreased response rate (11,36). Therefore, these two separate components of LSD's behavioral effect can be selectively antagonized and may reflect an interaction with different 5-HT receptor subtypes. YOH produced a partial antagonism of both components of LSD's effect, and therefore, its effect may be the result of interactions with more than one 5-HT receptor subtype(s). Exactly which subtypes(s) of 5-HT receptor is responsible for the constellation of behaviors induced by LSD, and which subtype(s) interact with YOH will require further study.

The above interpretation of the data relies on the assumption that LSD acts selectively as an agonist at 5-HT receptors; however, this may not be the case. Evidence from binding (5,14) and biochemical (8, 15, 29, 31) studies indicate that LSD may also affect dopaminergic and histaminergic systems. However, the preponderance of evidence support a role for 5-HT receptors in producing the action of LSD, especially at low doses (see Introduction).

The results of the present study are in agreement with biochemical and behavioral studies (see Introduction) which suggest that YOH interacts with central 5-HT receptors. The present study extends these findings by demonstrating that even low doses of YOH appear to have multiple effects, and therefore, do not act selectively as an alpha_2-adrenergic receptor antagonist. This information may in part explain recently obtained paradoxical results that a low dose (0.5 mg/kg) of YOH enhanced learning in a food motivated delayed reinforcement autoshaping task, whereas a higher dose (1.5 mg/kg) retarded acquisition (18). Perhaps different receptor systems are involved in the YOH-induced enhancement and retardation of learning. In conclusion, caution must be used when YOH is employed as a pharmacological tool to determine specific alpha_2-adrenergic receptor-mediated events, because it interacts with 5-HT receptors as well.

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