Pharmacology Biochemistry & Behavior, Vol. 34, pp. 275–281. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Disruption of FR-40 by 5-HT Agonists. I. Effects of Chronic Imipramine or Trazodone

R. SHUKLA, V. DAVE, D. MACKENZIE-TAYLOR AND R. H. RECH[1]

Department of Pharmacology and Toxicology
Michigan State University, East Lansing, MI 48824

Received 3 October 1988

SHUKLA, R., V. DAVE, D. MACKENZIE-TAYLOR AND R. H. RECH. *Disruption of FR-40 by 5-HT agonists. I. Effects of chronic imipramine or trazodone*. PHARMACOL BIOCHEM BEHAV **34**(2) 275–281, 1989.—Doses of LSD, quipazine, 8-OHDPAT and TFMPP were established that prominently disrupted FR-40 operant response patterns in two groups of rats. Subsequently, one group received daily intraperitoneal (IP) injections of imipramine, 2.5 mg/kg, for 4 weeks, then 10 mg/kg for 2 additional weeks. The second group received 5 mg/kg/day, IP, of trazodone for the first 4 weeks, then 20 mg/kg/day for the next two weeks. For these periods and the 3 weeks after discontinuing the chronic drug treatments (washout), test doses of the 4 agonists were evaluated twice weekly in random order for their effects to decrease FR-40 reinforcements and increase pauses. No consistent, systematic changes in sensitivity to the agonist effects on FR-40 behavior were observed during chronic drug treatments, although significant effects were at times observed. However, during the washout period in the imipramine group, both LSD and 8-OHDPAT effects on reinforcements were reversed to baseline levels. The effect of 8-OHDPAT on pauses during washout in this group was also attenuated. During washout in the trazodone group, the 8-OHDPAT-induced pausing and loss of reinforcements was reduced so as to be not significantly different from baseline values. Previous studies have demonstrated antagonism of LSD- and quipazine-induced disruption of FR-40 by pretreating with the 5-HT_2-selective antagonist pirenperone (28). Since chronic antidepressants down-regulate brain 5-HT_2 binding sites, the effects of LSD and quipazine were expected to be attenuated, which was not the case. However, the effects observed during the washout period, especially in the imipramine group, may reflect some modulation of 5-HT_{1A} sites during treatment with and recovery from the chronic antidepressant effect, as several recent studies have proposed.

5-HT agonist Imipramine Trazodone Lever-pressing FR-40 disruption Brain 5-HT receptors

THE sensitivity of a high-demand fixed-ratio operant schedule to the disruptive effects of indole-type and phenalkylamine-type hallucinogens has been known for many years (2). More recently, Rech and colleagues (34,36) have quantified the "pause" effect induced by these hallucinogens in the fixed-ratio response pattern and have equated it with an influence of 5-HT agonists of various types.

The FR-40 disruption by some 5-HT agonists, including hallucinogens, is attenuated by pretreatment with the nonspecific 5-HT antagonists metergoline and pizotifen (27) as well as by the 5-HT_2-selective antagonists pirenperone and ketanserin (28). Work with drug discrimination procedures has indicated a very similar pattern regarding the efficacy of 5-HT antagonists to block drug discrimination cues (4, 6, 15). Therefore, the mechanism of central nervous influences of indole-type and phenalkylamine-type hallucinogens and some nonhallucinogenic 5-HT agonists such as quipazine (11,15) has been proposed to involve a critical activity at brain 5-HT_2 receptors.

Large doses of various 5-HT agonists, including hallucinogens, induce several types of overt motor patterns in rodents: the "5-HT syndrome" and 5-HT-induced "head shakes" (16,21). Components of the 5-HT syndrome relate to the activation of 5-HT_1 receptors, while head shakes appear to depend on effects mediated via brain 5-HT_2 receptors (24,40). Some manifestations of the 5-HT syndrome appear to be mediated by 5-HT_{1A} as opposed to 5-HT_{1B} receptors. Drug discrimination properties of 5-HT_{1A} (8-OHDPAT), 5-HT_{1B} (TFMPP) and 5-HT_2 (quipazine) agonists appear to be distinctive (7, 14, 25). The 5-HT syndrome induced by 5-MeODMT was attenuated by chronic pretreatment with monoamine oxidase inhibitors (22) as was the depression of locomotor activity exerted by mCPP (23), but chronic pretreatment with tricyclic antidepressants was not active in reversing these effects of 5-MeODMT or mCPP. On the other hand, head shakes caused by quipazine or hallucinogens were attenuated after chronic pretreatment with monoamine oxidase inhibitors, desipramine or iprindole (23). Effects of 5-HT agonists on body

[1]Requests for reprints should be addressed to Dr. Richard H. Rech.

temperature of rats were examined by Gudelsky *et al.* (18,19) after chronic monoamine oxidase inhibitors or other antidepressants. Monoamine oxidase inhibitors attenuate the hypothermia by 5-HT_{1A}-specific agonists and the hyperthermia of 5-HT_2-specific agonists. However, antidepressants that selectively down-regulated 5-HT_2 receptors attenuated the hyperthermia of the 5-HT_2 agonist, but not the hypothermia of the 5-HT_{1A} agonist. Among other behaviors attenuated by chronic treatment with tricyclic antidepressants are learned helplessness behavior (33) and stress-induced suppression of daily running activity in rats (9).

Both tricyclic antidepressants and monoamine oxidase inhibitors administered chronically cause a reduction in brain 5-HT_2 receptor number (31,38), while only chronic monoamine oxidase inhibitors will down-regulate 5-HT_1 receptors (23,38). Trazodone is an atypical antidepressant characterized as a 5-HT_2 antagonist (12) and which on chronic treatment results in the down-regulation of brain 5-HT_2 receptors (37). Since evidence is available that chronic treatment with tricyclic antidepressants and trazodone reduce brain 5-HT_2 (but not 5-HT_1) receptor count, we explored the consequences of these drug treatments on the FR-40 disruption by four 5-HT agonists. LSD and quipazine were chosen as agents exerting 5-HT_2 effects important to this behavioral disruption (28); it was postulated that the above chronic drug treatments with imipramine or trazodone should attenuate the effects of these agonists. The other two agonists were 8-OHDPAT and TFMPP, putative 5-HT_{1A} and 5-HT_{1B} agonists, respectively (23); disruptive effects of these latter drugs on the FR-40 would not be expected to be attenuated by the chronic antidepressant treatments.

METHOD

Animals

Drug-naive, three-month-old male Sprague-Dawley rats (Harlan Inc., IN), weighing between 175–225 g, were applied to this study. The animals were housed individually in approved animal quarters with controlled temperature and a 12-hour day-night light cycle, light being present from 7 a.m. to 7 p.m., and were allowed unrestricted access to tap water. They were food deprived throughout the duration of the study in order to maintain them at 75–80% of their free-feeding weights, being fed an appropriate amount of preweighed rodent food blocks following the FR-40 sessions.

Behavioral Apparatus and Procedure

A total of 14 animals were trained in operant cages to bar-press a lever requiring an average force between 10–15 g in order to obtain 45-mg food pellets (Dustless Precision Pellets, Bioserv Inc.) as reinforcers, initially on a continuous reinforcement schedule. Four operant cages placed inside sound-attenuating chambers were available. The number of bar presses required to obtain a reinforcement was then gradually increased to 40 (the FR-40 schedule) over a period of four weeks. Operant sessions were conducted five times a week in the mornings and lasted for 40 minutes per subject, each animal being placed into the same allotted cage. All programming was controlled by electromechanical circuits (Lehigh Valley Electronics, PA) and the two parameters described below were recorded in four sets of 10 min each.

Reinforcements

The delivery of a food pellet following 40 bar presses constituted a "reinforcement." The total number of reinforcements obtained per session was registered on a counter and reflected the average response rate per 10 min period, although reinforcements per 40 min daily session are generally reported.

Pausing

A 10-second period in which no bar pressing occurred was considered a "pause," and the total number of such periods of nonresponding were recorded on a second counter (pause interval counter). Previous work from this laboratory has established that the extent of pausing, when reciprocal to the extent to which reinforcers are decreased, is a particularly valid measure of serotonergic agonist activity (5,27).

Baseline Measures

These refer to the averaged values of reinforcements and pausing obtained on days when saline or vehicle injections were administered before placing subjects into the operant cages. They derive from a week or more of measurements, once stable response patterns are established in each animal, with a day-to-day variation below 15 percent. These measures were determined before the testing of 5-HT agonists and over each period during the testing of 5-HT agonist drugs on FR-40 behavior.

Control Period Drug Effects

Following the collection of the initial week of baseline performance data, testing with the 5-HT agonists was initiated for a four-week period in a randomized sequence. Drugs were administered just prior to placement of the animals into the operant cages and the change in reinforcers earned and pauses generated were recorded. Throughout the study, the 5-HT agonists were administered only on Tuesdays and Fridays. Observations recorded on the other days enabled an assessment of recovery from acute drug treatments. In later periods scores on days other than Tuesdays and Fridays were used not only to indicate the presence of residual agonist drug effects, but also any change in baseline behavior related to chronic antidepressant drug treatment.

Drugs

The 5-HT agonists were dissolved in saline, the dose contained in 1 ml/kg, and the doses adjusted to disrupt responding to 20–40% of baseline levels. The final test doses chosen were 0.1 mg/kg d-lysergic acid diethylamide IP (LSD, NIDA, Rockville, MD), 2 mg/kg quipazine maleate IP (Miles Labs Inc., USA), 0.05 mg/kg 8-hydroxy-2(di-n-propylamino)tetralin (8-OHDPAT), and 1 mg/kg of 1-(3-trifluoromethylphenyl)piperazine (TFMPP). Both 8-OHDPAT and TFMPP, obtained from RBI, Inc., USA, were prepared fresh on the day of use and administered subcutaneously.

Daily injections of imipramine HCl (2.5 mg/kg, courtesy of Ciba-Geigy Corp., Ardsley, NY) and trazodone HCl (5 mg/kg, courtesy of Bristol-Myers Co., Evansville, IN), dissolved in saline, were initiated in two randomly assigned groups of animals ($n = 7$ each) at the end of the Control Period. The antidepressants were injected at these lower doses IP on alternate sides of the abdomen on alternating days, following completion of the operant sessions during the week and also on Saturday and Sunday for 4 weeks. The pattern of bar-pressing in response to the test doses of 5-HT agonists was assessed twice weekly. Since preliminary observation indicated that 5-HT agonist activity was little changed by the lower chronic doses of antidepressants, the dose of imipramine was increased to 10 mg/kg and of trazodone to 20 mg/kg for an additional period of 2 weeks. The data were analyzed in sets of 2 weeks each, with the first 4 weeks at the low dose constituting Periods 1 and 2, and the last 2 weeks at the high dose

TABLE 1

INITIAL DOSES OF 5-HT AGONISTS USED TO DISRUPT FR-40 PERFORMANCE*

LSD	Quipazine	8-OHDPAT	TFMPP
	Reinforcements		
0.085 (0.03–0.2)	1.6 (0.5–4.0)	0.04 (0.02–0.1)	0.7 (0.3–2.0)
	Pause Intervals		
0.081 (0.03–0.25)	1.6 (0.5–5.0)	0.045 (0.02–0.1)	0.73 (0.3–2.0)

*Values are approximate ED_{50} doses with the range of active doses in parentheses. All others are mg/kg. Values for LSD and quipazine were taken from Mokler *et al.* (27).

constituting Period 3.

Washout Period

The 3-week period immediately following cessation of antidepressant treatment, labeled the "Washout Period," was included to assess any rebound effects during recovery from chronic antidepressant treatment that could interact with the activity of the 5-HT agonists, which continued to be evaluated during this period.

Statistics

A repeated-measures ANOVA design was used to assess the effects of each 5-HT agonist separately on reinforcements and pausing in both the imipramine and trazodone groups. Individual comparisons between two means were carried out using the least significant differences test where indicated. In all cases the results were considered significant at $p<0.05$. In addition, all baseline measures of reinforcements and pauses, which were observed not to change significantly during the course of chronic antidepressant treatment, were pooled for the Control Period, Periods 1–3, and the Washout Period. These mean values, with 95% confidence limits, afford an additional reference for assessing meaningful changes in the effects of the 5-HT agonists.

RESULTS

Table 1 lists the approximate ED_{50}'s of LSD, quipazine, 8-OHDPAT and TFMPP to decrease reinforcements (R) and increase pauses (P) in FR-40 behavior. LSD and quipazine data were taken from a previous study, while 8-OHDPAT and TFMPP values were derived from preliminary tests prior to this study.

The chronic drug administrations appeared not to have a prominent influence on baseline (vehicle before daily FR-40) determinations. Baseline values prior to drug testing and for all periods during agonist drug testing are shown, for both R and P, in Table 2.

The effects of each 5-HT agonist on FR-40 R and P for each period in the rats treated chronically with imipramine are depicted in Fig. 1. The effects of these agonists in animals receiving chronic trazodone are indicated in Fig. 2.

LSD during the Control Period decreased R to 26 ± 6 and increased P to 161 ± 19 in the imipramine group and decreased R to 26 ± 5 and increased P to 166 ± 12 in the trazodone group. During Periods 1 and 2 of chronic drug treatment, no significant effects were noted in either group receiving LSD. During Period 3, LSD appeared to be more active for both measures in imipramine animals ($R = 11 \pm 4$, $P = 186 \pm 3$), but not in trazodone subjects

TABLE 2

BASELINE VALUES OF FR-40 REINFORCEMENTS AND PAUSES PRIOR TO AND DURING DRUG TESTING*

	Imipramine Group		Trazodone Group	
Time Period	Reinforcements	Pauses	Reinforcements	Pauses
1. Before drug testing	111 ± 43	30 ± 6	99 ± 16	23 ± 8
2. Control	105 ± 22	58 ± 11	101 ± 14	51 ± 9
3. Period One	101 ± 20	57 ± 14	104 ± 12	46 ± 18
4. Period Two	128 ± 17	52 ± 12	107 ± 13	59 ± 12
5. Period Three	90 ± 13	63 ± 12	78 ± 9	80 ± 10
6. Washout	116 ± 16	52 ± 8	92 ± 9	68 ± 8

*Values are means ± S.E. for all baseline values for each period before and during the testing of 5-HT agonist effects.

($R = 41 \pm 7$, $P = 129 \pm 7$). During the Washout Period with the imipramine group, LSD was significantly ($F = 3.99$) less active in disrupting R, relative to Control, and less active against both FR-40 measures, relative to Periods 2 and 3 ($R = 68 \pm 22$, $P = 112 \pm 25$). LSD affected the trazodone group during the Washout Period no differently than in the Control Period ($R = 39 \pm 8$, $P = 144 \pm 8$).

Quipazine altered FR-40 responding during the Control Period by decreasing R to 13 ± 7 and increasing P to 191 ± 24 in imipramine rats. In the trazodone group, values during Control were altered by quipazine to decrease R to 12 ± 5 and increase P to 213 ± 6. During Period 1, quipazine effects on R were more intense, with little change in pauses, in both chronic groups (imipramine: $R = 5 \pm 3$, $P = 206 \pm 9$; trazodone: $R = 5 \pm 3$, $P = 208 \pm 6$). In both imipramine and trazodone groups, Period 2 measurements showed trends for a lessened effect of quipazine (imipramine: $R = 27 \pm 8$, $P = 174 \pm 7$; trazodone: $R = 48 \pm 22$, $P = 144 \pm 35$), but this reached significance ($F = 2.54$) for both R and P only in the trazodone group. In Period 3, both groups responded to quipazine about the same as in the Control Period (imipramine: $R = 9 \pm 6$, $P = 204 \pm 10$; trazodone: $R = 14 \pm 6$, $P = 191 \pm 3$). During the Washout Period there was again a trend for lessened effects of quipazine in both groups, but without reaching significance (imipramine: $R = 25 \pm 13$, $P = 177 \pm 27$; trazodone: $R = 37 \pm 17$, $P = 159 \pm 27$).

The 5-HT_{1A} agonist 8-OHDPAT altered responding during the Control Periods by decreasing R to 37 ± 9 and increasing P to 116 ± 26 in imipramine animals, and decreasing R to 16 ± 4 and increasing P to 60 ± 16 in trazodone rats. In Period 1, the effects of 8-OHDPAT tended to lessen in the imipramine group ($R = 50 \pm 13$, $P = 95 \pm 26$), but not significantly so. In the trazodone subjects the extent of FR-40 disruption was significantly ($F = 3.88$) less during Period 1 compared to Control ($R = 69 \pm 20$, $P = 75 \pm 27$). Effects of 8-OHDPAT during Period 2 were not significantly different from controls in either group (imipramine: $R = 31 \pm 9$, $P = 122 \pm 29$; trazodone: $R = 29 \pm 12$, $P = 145 \pm 25$). In Period 3, the effect on pauses in the imipramine group and on reinforcements in the trazodone group was significantly ($F = 3.53$, 3.12) less than for controls (imipramine: $R = 62 \pm 9$, $P = 59 \pm 16$; trazodone: $R = 59 \pm 17$, $P = 107 \pm 28$). During the Washout Period, both groups demonstrated a prominent ($F = 5.45$ and 3.53 in the imipramine group, $F = 3.88$ and 3.12 in the trazodone group) reduction in effects (imipramine: $R = 118 \pm 32$, $P = 50 \pm 15$, trazodone: $R = 81 \pm 4$, $P = 67 \pm 17$).

The 5-HT_{1B} agonist TFMPP caused similar disruptions of

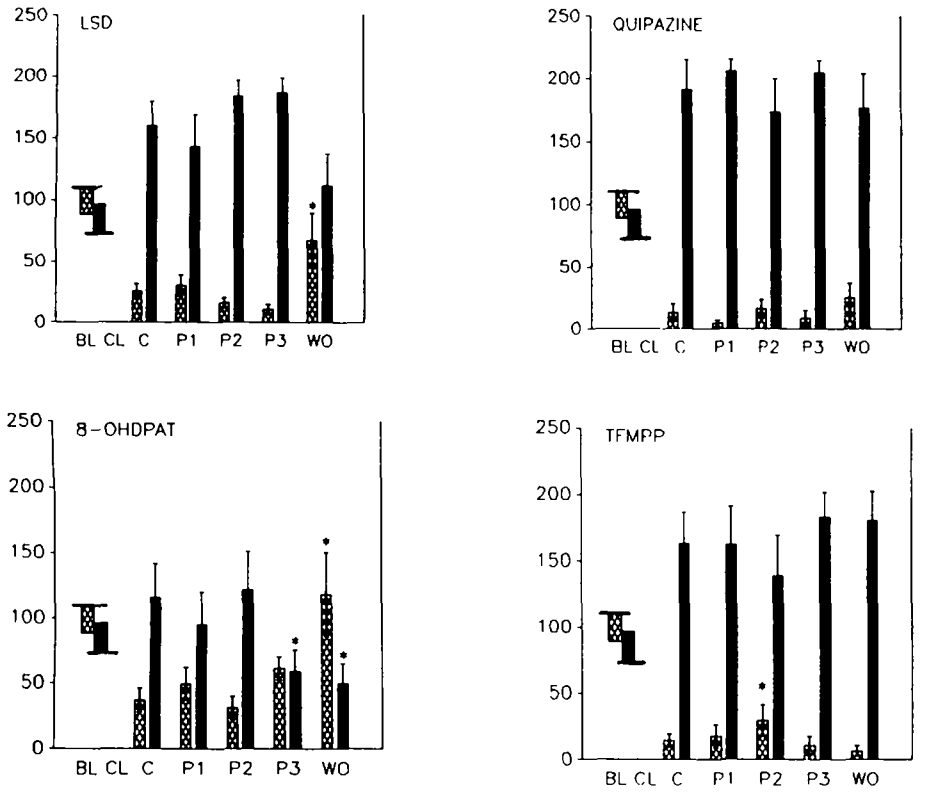

FIG. 1. Effects of 5-HT agonists to disrupt FR-40 operant responding before, during, and after chronic imipramine. Doses (mg/kg) of agonists are: LSD, 0.1; quipazine, 2; 8-OHDPAT, 0.05; and TFMPP, 1. Reinforcements earned are depicted by hatched bars; pauses are indicated by filled bars. Baseline confidence limits (BL and CL) are shown as mean and downward deflection for reinforcements, and mean and upward deflection for pauses. C = effect of the agonist before imipramine. Period 1 (P1) = first 2 weeks of chronic imipramine (2.5 mg/kg/day). Period 2 (P2) = second 2 weeks of chronic imipramine (2.5 mg/kg/day). Period 3 (P3) = last 2 weeks of chronic imipramine (10 mg/kg/day). Washout (WO) = 3 weeks following the interruption of imipramine treatment. Vertical lines on the bars show S.E.M.

FR-40 patterns in both groups during the Control Periods (imipramine: $R = 15 \pm 5$, $P = 163 \pm 23$; trazodone: $R = 28 \pm 9$, $P = 184 \pm 21$). There was little change in either group on chronic treatment with the antidepressants during Periods 1 (imipramine: $R = 18 \pm 9$, $P = 163 \pm 28$; trazodone: 23 ± 9, $P = 138 \pm 26$). In Period 2 there was a significantly ($F = 2.91, 2.78$) less effect on R in the imipramine group and on P in the trazodone group (imipramine: $R = 30 \pm 12$, $P = 139 \pm 30$; trazodone: $R = 40 \pm 13$, $P = 134 \pm 19$; Washout: $R = 7 \pm 4$, $P = 181 \pm 22$), but the trend was not significant, while trazodone subjects showed effects of TFMPP in the same range as Controls (Period 3: $R = 23 \pm 9$, $P = 155 \pm 23$; Washout: $R = 18 \pm 7$, $P = 171 \pm 21$).

The above results as subjected to repeated measures ANOVA demonstrated effects of chronic antidepressant treatment primarily on the activity of 8-OHDPAT during the Washout Period, although LSD activity in the imipramine animals also appeared to be affected during Washout. The pooled means and 95% confidence limits (CL) for all periods of agonist drug testing are depicted in Figs. 1 and 2 for reference (CL for R in the downward direction only and CL for P in the upward direction only). Comparing disruptive effects of the agonists on drug test days with the variability in values of baseline FR-40 responding during the same period offers another criterion for evaluation of changes in agonist activity. In both the imipramine and trazodone groups, both R and P changes induced by 8-OHDPAT in the Washout Period did not differ significantly from baseline values. In Period 1 for the trazodone rats, the change in P after 8-OHDPAT yielded a value that was no different from the baseline value.

Following the Washout Period, both groups of rats were evaluated for dose-response patterns of 8-OHDPAT and TFMPP disruption of FR-40 behavior. The results (Table 3) demonstrated a continued subsensitivity to 8-OHDPAT relative to Control Period values, both for R and P. However, TFMPP affected R and P in about the same dose range as observed during the Control Period.

DISCUSSION

Previous studies have defined LSD as a drug that binds with high affinity to all classes of 5-HT receptors (32). Large doses of LSD in rats evoke motor patterns called the "serotonin syndrome," related to brain 5-HT_{1A} receptor activity (23,24), as well as "head twitches" or "wet-dog shakes," identified with activation of central 5-HT_2 sites. Drug discrimination cues and disruption of FR-40 operant response patterns by LSD are attenuated by 5-HT_2-specific antagonists (4,28). Quipazine is a 1-arylpiperazine derivative that has modest affinity for all 5-HT receptors, but which induces head twitches, drug discrimination cues, and interactions in FR-40 behavior that suggest effects also mediated through brain 5-HT_2 sites (11, 23, 28).

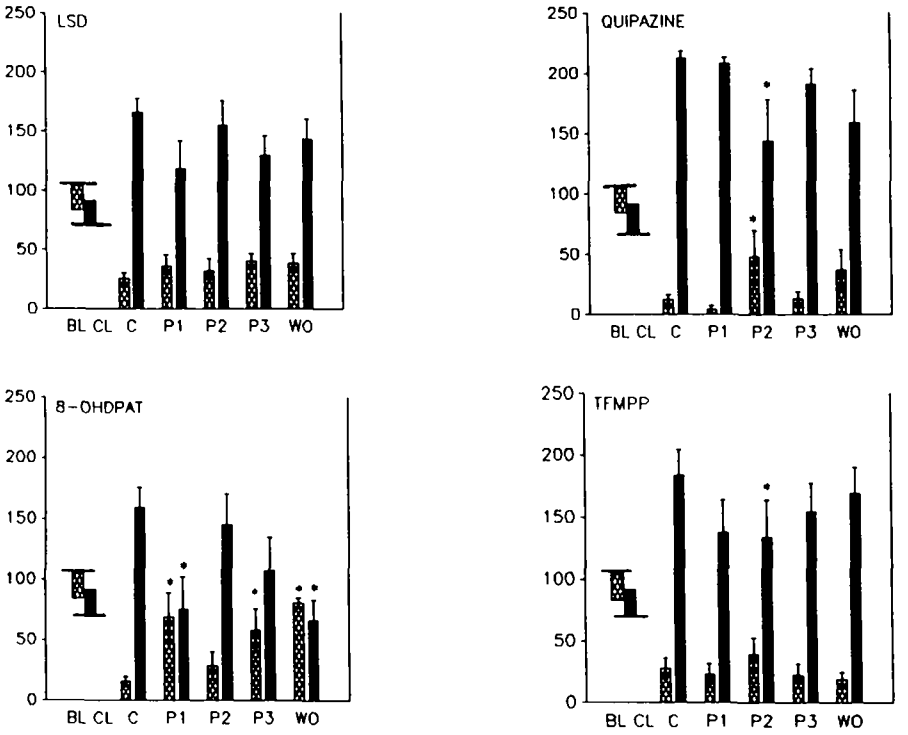

FIG. 2. Effects of 5-HT agonists to disrupt FR-40 operant responding before, during and after chronic trazodone. Period 1 (P1) = first 2 weeks of chronic trazodone (5 mg/kg/day). Period 2 (P2) = second 2 weeks of chronic trazodone (5 mg/kg/day). Period 3 (P3) = last 2 weeks of chronic trazodone (20 mg/kg/day). Washout (WO) = 3 weeks following the interruption of trazodone treatment. See Fig. 1 legend for further clarification.

TFMPP is another 1-arylpiperazine derivative which binds with high affinity to 5-HT_{1B} brain sites, somewhat lower to 5-HT_2 sites, and poorly to 5-HT_{1A} sites (13,39). TFMPP and a closely related drug mCPP are anorectics and depressants of motor activity, effects likely to be mediated by brain 5-HT_{1B} receptors (3,23). 8-OHDPAT, an aminotetralin derivative, was found to have high selectivity for the 5-HT_{1A} subtype (26) and in its tritiated form is a preferred ligand for these sites (10,13). Functionally, 8-OHDPAT induces components of the serotonin syndrome identified with 5-HT_{1A} receptors, has anticonflict activity, causes hypothermia, and generalizes to other drugs considered to be 5-HT_{1A} agonists (6, 10, 18, 30, 40, 41).

The tricyclic antidepressants, while acutely blocking reuptake of norepinephrine and 5-HT into monoaminergic nerve terminals, provoke on chronic administration a down-regulation of β-adrenergic and 5-HT_2 binding sites in brain tissue (23,32). Trazodone, a second-generation antidepressant with 5-HT_2 antagonist properties (20) but only weak activity to block monoamine uptake, also down-regulates 5-HT_2 receptors when administered chronically (1,13).

TABLE 3

DOSE-RESPONSE PATTERNS OF 8-OHDPAT AND TFMPP TO DISRUPT FR-40 DETERMINED AFTER THE WASHOUT PERIOD*

Drug	Reinforcements	Pause Intervals
8-OHDPAT	0.18 (0.025–0.25)	0.13 (0.025–0.25)
TFMPP	1.0 (0.5–2.0)	0.7 (0.3–2.0)

*Values are approximate ED_{50} doses to decrease reinforcements or increase pause intervals, with the range of active doses in parentheses, expressed as mg/kg.

The results obtained in this study were not in accord with the initial expectations. No consistent time-related changes in the effects of any agonist was apparent over the course of chronic treatment with imipramine or trazodone. However, the repeated measures ANOVA did demonstrate some significant differences in agonistic effects during the chronic administration phases and during Washout. In the imipramine group the decrease in reinforcements by LSD was significantly lessened during the Washout Period. The effects on pausing by LSD during imipramine Washout tended to be less than for the LSD effect in other periods, but differed significantly by ANOVA only in comparison to the values of Periods 2 and 3. The quipazine effects were quite variable, but significant for both reinforcements and pauses (lessened effect) during Period 2 in the trazodone group. These effects of quipazine during Period 2 in the trazodone group may relate a missed injection, since one outlier dramatically altered the group means and increased variability for both reinforcements and pauses. TFMPP caused a significantly lessened effect on reinforcements during Period 2, as compared to Control, in the imipramine group. In the trazodone rats, a significantly reduced effect of TFMPP on pauses was observed during Period 2, but this was due to a lack of effect in one subject, probably due to a faulty drug injection.

The most remarkable changes were seen in the effects of 8-OHDPAT. This agonist was less effective (in fact not different from baseline values) in both groups during Washout. In fact, the reduced sensitivity to 8-OHDPAT outlasted the Washout Period, being still obvious when the dose-response parameters were again

examined following the Washout (Table 3). Both the decrease in reinforcements and increase in pauses by 8-OHDPAT during Period 1 in trazodone rats were also attenuated. TFMPP and quipazine appeared not to show such changes in sensitivity during Periods 1, 3 or Washout.

Recently, Green (17) and Pandey *et al.* (29) demonstrated that chronic desipramine and trazodone, as well as other antidepressant treatments, caused subsensitivity of 5-HT_{1A} receptors as well. Therefore, a course of chronic treatment either with imipramine or trazodone would be expected to attenuate effects of drugs acting prominently through a 5-HT_2 or a 5-HT_{1A} mechanism, i.e., 8-OHDPAT, LSD or quipazine. On the contrary, an agonist exerting its actions predominantly by way of 5-HT_{1B} receptors (TFMPP) should not be attenuated in its effects after chronic exposure to these antidepressants. The most prominent changes were observed during the Washout Periods, after discontinuing chronic treatment with either antidepressant, and appeared to be most obvious as attenuated activity of LSD and 8-OHDPAT, agonists proposed to have 5-HT_{1A} activity. The reduced effects of 8-OHDPAT during chronic antidepressant treatment and in the Washout Period (and LSD during Washout) may very well be a reflection of 5-HT_{1A} receptor down-regulation during and following the chronic treatments, as recently described (17,29). The lack of effect of chronic antidepressant treatment to systematically alter the activity of quipazine, a presumed 5-HT_2 agonist in this behavior, may have related to a failure of the chronic drug regimens to affect brain 5-HT_2 sites. This seems unlikely, since the doses and time-courses of both imipramine and trazodone administration exceeded those found by other investigators (9, 18, 23, 31, 33, 37) to induce 5-HT_2 down-regulation. Therefore, the effects observed did not support the original hypothesis that chronic treatment with antidipressants would attenuate the behavioral disruption by 5-HT_2 but not 5-HT_1 agonists.

The previously demonstrated attenuation of 5-HT_2 agonistic activity by chronic exposure to antidepressants has related to physiological actions or overt motor patterns induced by rather large doses of agonists. It may be that disruption of an associative behavior of this high order (FR-40 operant responding) relates to the disturbance of delicately balanced interactions between regional brain 5-HT receptor subtypes and/or with other types of neurotransmitters. If this were the case, attempting to reverse that process with a chronic drug treatment that broadly affects 5-HT as well as non-5-HT mechanisms throughout the brain may be an unrealistic goal. In any case, it is clear that chronic imipramine or chronic trazodone does not systematically attenuate the disruptive effects of LSD and quipazine in the FR-40 behavior. These treatments, therefore, do not replicate the effects of acute pretreatment with the mixed 5-HT antagonists metergoline and pizotifen or 5-HT_2-specific antagonists pirenperone and ketanserin to block the disruption of FR-40 responding by LSD and quipazine (27, 28, 35). Therefore, 5-HT receptor antagonism and down-regulation may not result in the same types of functional alterations in brain 5-HT neuronal activities. Alternatively, the FR-40 effects of LSD and quipazine could be induced by actions on a proportion of brain 5-HT_2 receptors resistant to down-regulation by antidepressants.

ACKNOWLEDGEMENT

A postdoctoral fellowship to R.S. by Pradhan Foundation, Washington, DC, is gratefully acknowledged.

REFERENCES

1. Anderson, J. L. Serotonin receptor changes after chronic antidepressant treatments: Ligand binding, electrophysiological, and behavioral studies. Life Sci. 32:1791–1801; 1983.
2. Appel, J.; Freedman, D. Tolerance and cross-tolerance among psychotomimetic drugs. Psychopharmacologia 13:267–274; 1968.
3. Bendotti, C.; Samanin, R. The role of putative 5-HT_{1A} and 5-HT_{1B} receptors in the control of feeding in rats. Life Sci. 41:635–642; 1987.
4. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J. A drug discrimination analysis of LSD: In vivo agonist and antagonist effects of purported 5-HT antagonists and of pirenperone, a LSD-antagonist. J. Pharmacol. Exp. Ther. 221:206–214; 1982.
5. Commissaris, R. L.; Lyness, W. H.; Moore, K. E.; Rech, R. H. Differential antagonism by metergoline of the behavioral effects of indolalkylamine and phenethylamine hallucinogens in the rat. J. Pharmacol. Exp. Ther. 219:170–174; 1981.
6. Cunningham, K. A.; Appel, J. B. Neuropharmacological reassessment of the discriminative stimulus properties of d-lysergic acid diethylamide (LSD). Psychopharmacology (Berlin) 91:67–73; 1987.
7. Cunningham, K. A.; Callahan, P. M.; Appel, J. B. Discriminative stimulus properties of the serotonin agonist MK 212. Psychopharmacology (Berlin) 90:193–197; 1986.
8. Cunningham, K. A.; Callahan, P. M.; Appel, J. B. Discriminative stimulus properties of 8-hydroxy-2-(di-n-propylamino) tetraline: Implications for understanding the actions of novel anxiolytics. Eur. J. Pharmacol. 138:29–36; 1987.
9. Desan, P. H.; Silbert, L. H.; Maier, S. F. Long-term effects of inescapable stress on daily running activity and antagonism by desipramine. Pharmacol. Biochem. Behav. 30:21–29; 1988.
10. Frazer, A.; Offord, S. J.; Lucki, I. Assessment of the selectivity of serotonin receptor agonists and antagonists for subtypes of the serotonin-1 receptor. In: Rech, R. H.; Gudelsky, G. A., eds. 5-HT agonists as psychoactive drugs. Ann Arbor, MI: NNP Books; 1988: 107–126.
11. Friedman, R. L.; Barrett, R. J.; Sanders-Bush, E. Discriminative stimulus properties of quipazine: Mediation by serotonin-2 binding sites. J. Pharmacol. Exp. Ther. 228:628–635; 1984.
12. Fuller, R. W.; Snoddy, H. D.; Cohen, M. L. Interaction of trazodone with serotonin neurons and receptors. Neuropharmacology 23:539–544; 1984.
13. Glennon, R. A. Central serotonin receptors as targets for drug research. J. Med. Chem. 30:1–12; 1987.
14. Glennon, R. A.; McKenney, J. D.; Young, R. Discriminative stimulus properties of the serotonin agonist 1-(3-trifluoromethylphenyl) piperazine (TFMPP). Life Sci. 35:1475–1480; 1984.
15. Glennon, R. A.; Young, R.; Rosecrans, J. A. Antagonism of the effects of the hallucinogen DOM and the purported serotonin agonist quipazine by 5-HT-2 antagonists. Eur. J. Pharmacol. 91:189–196; 1983.
16. Green, A. R.; Shanghnessy, K. O.; Hammond, M.; Schachter, M.; Grahame-Smith, D. G. Inhibition of 5-hydroxytryptamine-mediated behavior by the putative 5-HT_2 antagonist pirenperone. Neuropharmacology 22:573–578; 1983.
17. Green, A. R. Evolving concepts on the interactions between antidepressant treatments and monoamine neurotransmitters. Neuropharmacology 26:815–822; 1987.
18. Gudelsky, G. A.; Koenig, J. I.; Jackman, H. Suppression of the hypo- and hyperthermic responses to 5-HT agonists following the repeated administration of monoamine oxidase inhibitors. Psychopharmacology (Berlin) 90:403–407; 1986.
19. Gudelsky, G. A.; Koenig, J. I.; Meltzer, H. Y. Selective desensitization of serotonin (5-HT) receptor-mediated hyperthermia by mianserin and other 5-HT antagonists. Neuropharmacology 26:707–712; 1987.
20. Hingtgen, J. N.; Hendrie, H. C.; Aprison, M. H. Postsynaptic serotonergic blockade following chronic antidepressive treatment with trazodone in an animal model of depression. Pharmacol. Biochem. Behav. 20:425–428; 1984.
21. Lucki, I.; Frazer, A. Behavioral effects of indole and piperazine type serotonin receptor agonists. Soc. Neurosci. Abstr. 8:101; 1982.
22. Lucki, I.; Frazer, A. Prevention of the serotonin syndrome in the rat by repeated administration of monoamine oxidase inhibitors but not tricyclic antidepressants. Psychopharmacology (Berlin) 77:205–211; 1982.
23. Lucki, I.; Frazer, A. Changes in behavior associated with serotonin

receptors following repeated treatment of rats with antidepressant drugs. In: Seiden, L. S.; Balster, R. L., eds. Behavioral pharmacology: Current status. New York: Alan Liss Co.; 1985:339–357.
24. Lucki, I.; Nobler, M. S.; Frazer, A. Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. J. Pharmacol. Exp. Ther. 228:133–139; 1984.
25. McKenney, J. D.; Glennon, R. A. TFMPP may produce its stimulus effects via a 5-HT_{1B} mechanism. Pharmacol. Biochem. Behav. 24:43–47; 1986.
26. Middlemiss, D. N.; Fozard, J. R. 8-Hydroxy-2(di-n-propylamino) tetralin discriminates between subtypes of the 5-HT_1 recognition site. Eur. J. Pharmacol. 90:151–153; 1983.
27. Mokler, D. J.; Commissaris, R. L.; Warner, M. R.; Rech, R. H. Blockade of the behavioral effects of LSD, DOM, quipazine and lisuride by 5-hydroxytryptamine antagonists. J. Pharmacol. Exp. Ther. 227:557–562; 1983.
28. Mokler, D. J.; Stoudt, K. W.; Rech, R. H. The 5-HT_2 antagonist pirenperone reverses disruption of FR-40 by hallucinogenic drugs. Pharmacol. Biochem. Behav. 22:677–682; 1985.
29. Pandey, G. N.; Pandey, S. C.; Schlemmer, R. F.; Kerkstran, J.; Davis, J. M. Effect of treatment with trazodone on serotonin and β-adrenergic receptors and LSD induced behavior in rats. FASEB J. 5:1384; 1988.
30. Peroutka, S. J. Selective interaction of novel anxiolytics with 5-HT_{1A} receptors. Biol. Psychiatry 20:971–979; 1985.
31. Peroutka, S. J.; Snyder, S. H. Long term antidepressant treatment decreases spiroperidol-labelled serotonin receptor binding. Science 210:87–89; 1980.
32. Peroutka, S. J.; Snyder, S. H. Recognition of multiple serotonin receptor binding sites. In: Ho, B. T.; Schoolar, J. C.; Usdin, E., eds. Serotonin in biological psychiatry. New York: Raven Press; 1982: 155–172.
33. Petty, F. A.; Sherman, A. D. Reversal of learned helplessness by imipramine. Commun. Psychopharmacol. 3:371–373; 1980.
34. Rech, R. H.; Commissaris, R. L. Neurotransmitter basis of the behavioral effects of hallucinogens. Neurosci. Biobehav. Rev. 6: 521–527; 1982.
35. Rech, R. H.; Commissaris, R. L.; Mokler, D. J. Hallucinogenic 5-hydroxytryptamine agonists characterized by disruption of operant behavior. In: Rech, R. H.; Gudelsky, G. A., eds. 5-HT agonists as psychoactive drugs. Ann Arbor, MI: NPP Books; 1988:185–215.
36. Rech, R. H.; Mokler, D. J. Disruption of operant behavior by hallucinogenic drugs. Psychopharmacol. Bull. 22:951–952; 1986.
37. Riblet, L. A.; Taylor, D. P. Pharmacology and neurochemistry of trazodone. J. Clin. Psychopharmacol. Suppl. 1:175–225; 1981.
38. Savage, D. D.; Mendels, J.; Frazer, A. Monoamine oxidase inhibitors and serotonin uptake inhibitors: Differential effects on [^{3}H] serotonin binding sites in rat brian. J. Pharmacol. Exp. Ther. 212:259–263; 1980.
39. Sills, M. A.; Wolfe, B. B.; Frazer, A. Determination of selective and nonselective compounds for the 5-HT_{1A} and 5-HT_{1B} receptor subtypes in the rat frontal cortex. J. Pharmacol. Exp. Ther. 231:480–487; 1984.
40. Tricklebank, M. D.; Forler, C.; Fozard, J. R. The involvement of subtypes of the 5-HT_1 receptor and of catecholaminergic systems in the behavioral responses to 8-hydroxy-2-(di-n-propylamino) tetralin in the rat. Eur. J. Pharmacol. 106:271–282; 1984.
41. Young, R.; Glennon, R. A. Second generation anxiolytics and serotonin. In: Rech, R. H.; Gudelsky, G. A., eds. 5-HT agonists as psychoactive drugs. Ann Arbor, MI: NPP Books; 1988:239–258.