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Disruption of FR-40 by 5-HT Agonists. II. Effects of Chronic Phenelzine or Isocarboxazid

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SHUKLA, R., J. GOUDREAU, D. MACKENZIE-TAYLOR AND R. H. RECH. *Disruption of FR-40 by 5-HT agonists. II. Effects of chronic phenelzine or isocarboxazid.* PHARMACOL BIOCHEM BEHAV **34**(2) 283–287, 1989.—Effects of chronic treatment with the monoamine oxidase inhibitors phenelzine and isocarboxazid on disruption of FR-40 operant responses by 5-HT agonists have been studied. Three groups of rats that were trained in the FR-40 operant schedule showed marked disruption by 0.1 mg/kg IP lysergic acid diethylamide (LSD), 2 mg/kg IP quipazine (Q), 0.05 mg/kg SC 8-hydroxy-2-(di-n-propylamino)tetralin (8-OHDPAT), and 1 mg/kg SC (m-trifluoromethyl-phenyl)piperazine (TFMPP), administered twice weekly in random order. Subsequently, one group received daily IP injection of phenelzine (5 and 10 mg/kg), the second group received 5 mg/kg IP of isocarboxazid, and the third group received vehicle (0.5% methyl cellulose) for 24 days (Period 1 and Period 2). For these periods and 12 days after discontinuing the MAOI treatments (Washout Period), test doses of 5-HT agonists were evaluated for their effects to decrease reinforcements (R) and increase pauses (P). No change in sensitivity to the LSD, Q and TFMPP effects on FR-40 behavior was observed in the vehicle-treated group. However, an attenuated effect of 8-OHDPAT was found in this group. In phenelzine- and isocarboxazid-treated rats the disruption of FR-40 responses by LSD and 8-OHDPAT were significantly reduced during Period 1, Period 2 and Washout Period. A significantly less effect on disruption in FR-40 responses by quipazine and TFMPP during Period 2 and the Washout Period was also seen. Since MAO inhibitors appear to down-regulate both 5-HT_1 and 5-HT_2 binding sites in brain, the attenuated effects of the 5-HT agonists were anticipated. However, the effects observed during Washout Period presumably reflect subsensitivity of brain 5-HT receptors that persists after discontinuing treatment with the MAO inhibitors.

5-HT agonists Phenelzine Isocarboxazid Lever-pressing FR-40 disruption Brain 5-HT receptors

THE assessment of biochemical and behavioral changes resulting from chronic antidepressant drug administration may provide insight into the therapeutic recovery from depression, since the clinical efficacy of these drugs generally requires 2 or more weeks of chronic administration. Chronic antidepressant therapy is known to produce changes in CNS monoamine receptors (26,27). In particular, chronic treatment with various types of antidepressants reduces the number of 5-HT receptors in the rat frontal cortex (20). An important question, then, is whether these drug-induced alterations in 5-HT receptors have specific functional consequences that may relate to the clinical utility of these agents.

The 5-HT receptor profiles following chronic administration of two types of antidepressants, tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI), have been documented. Chronic treatment with TCA has been shown to reduce the number of 5-HT_2 receptors in rat brain (12,20). In contrast, repeated administration of MAOI reduces the number of both 5-HT_1 and 5-HT_2 receptors in the brains of rats (4,24). Moreover, chronic administration of these two types of antidepressants attenuated several overt motor patterns induced by large doses of 5-HT agonists. Specifically, components of the 5-HT syndrome which relate to the activation of 5-HT_1 receptors (7,13) are attenuated by chronic pretreatment with MAOI, but not with chronic TCA (13,14). Conversely, "head shakes" mediated by 5-HT_2 receptors (14, 15, 28) were attenuated by chronic TCA as well as by chronic MAOI administration.

Although the above findings are of interest, they involve large doses of 5-HT agonists which produce an overt, yet still subjectively evaluated, indication of central 5-HT activity. On the other hand, the disruption of a high-demand fixed-ratio operant schedule by various hallucinogenic and nonhallucinogenic 5-HT agonists is a sensitive objective measure that has been known for many years (1). More recently, Rech and colleagues have quantified a "pause effect" in the fixed-ratio response pattern which is quite specific to the disruptive influence of 5-HT agonists (21–23). This "pause effect" was observed with a fixed-ratio paradigm requiring 40

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responses for each reinforcement (FR-40). The FR-40 may provide a more sensitive probe for the behavioral assessment of the changes in 5-HT receptors induced by chronic antidepressant therapy.

The FR-40 disruption by some 5-HT agonists, both hallucinogenic (LSD, DOM, mescaline) and nonhallucinogenic (quipazine), has been proposed to involve a critical activity at CNS 5-HT_2 receptors. Most 5-HT agonist-induced disruptions of the FR-40 schedule are attenuated by pretreatment with the nonspecific 5-HT antagonists meterogoline and pizotifen (17). The effects of indole-type and phenalkylamine-type hallucinogens, as well as those of quipazine, are also antagonized by the 5-HT_2-selective antagonists pirenperone and ketanserin (18). Work with drug discrimination procedures has indicated a very similar pattern regarding the ability of 5-HT antagonists to block drug discriminative cues of 5-HT agonists (2, 3, 6). The presumed involvement of 5-HT_2 receptors would suggest that the disruption of FR-40 responding by these 5-HT agonists may be a useful test of the functional influences of chronic MAOI and TCA to induce 5-HT_2 receptor down-regulation.

Recent work in this laboratory, however, did not support the hypothesis that chronic treatment with TCA would attenuate the behavioral disruption by 5-HT_2 but not 5-HT_1 agonists (25). In this first article in this series, chronic administration of imipramine and trazodone did not reduce the disruptive effects of the putative 5-HT_2 agonist quipazine (5, 14, 18), nor did these chronic treatments attenuate the effects of LSD. Interestingly, the most prominent changes in this initial study were observed during the washout period (after discontinuing the chronic antidepressants). After the interruption of chronic imipramine, there was an attenuation of the disruptive effects of LSD and 8-OHDPAT; i.e., two agonists with proposed 5-HT_{1A} activity (16). The possible involvement of 5-HT_1 receptor effects in the disruption of FR-40 responding by the above 5-HT agonists (as well as other 5-HT agonists) may be elucidated more clearly after chronic MAOI administration, since this latter treatment has been reported to down-regulate both 5-HT_1 and 5-HT_2 receptors in rat brain.

The present study examines the effect of chronic administration of two nonspecific MAOI, phenelzine and isocarboxazid, on the FR-40 disruption by four 5-HT agonists. The agonists were chosen to probe the various subtypes of 5-HT receptors that may relate to this behavioral disruption: 1) quipazine, a 5-HT_2 agonist (5, 7, 14, 15, 18); 2) TFMPP, a 5-HT_{1B} agonist (14); 3) 8-OHDPAT, a 5-HT_{1A} agonist (16,28); and 4) LSD, a mixed 5-HT_1 and 5-HT_2 agonist (2, 3, 13–15, 17, 18, 22). If the chronic dose of either aforementioned MAOI is sufficient to reduce both 5-HT_1 and 5-HT_2 receptor binding, then an attenuated response would be expected for all four 5-HT agonist probes. In any case, the data should provide quantifiable information on the proposed functional down-regulation of 5-HT receptors induced by MAOI.

METHOD

Animals

Male Sprague-Dawley rats (Harlan Inc., IN), weighing between 200–225 g, were used in this study. They were housed individually with unrestricted access to tap water. A twelve-hour light/drk cycle was maintained: light on from 7 a.m. to 7 p.m. Rats were fed 8 g/day of rat chow after the session to maintain them at 75–80% of their free-feeding weights. Training sessions occurred daily from 1 p.m. to 6 p.m.

Apparatus, Training and Behavioral Procedure

A total of 22 rats were trained in four operant cages placed in sound-attenuating compartments to press a lever (average force to active = 10–15 g) to obtain 45-mg food pellets (Dustless Precision Pellets, Bioserve, Inc.) as reinforcement. Animals were initially trained on a continuous reinforcement schedule. Subsequently, the required lever presses were gradually increased to 40 (FR-40) over a period of two weeks. Operant sessions were conducted daily in the afternoon and lasted 40 minutes per rat, with each rat being placed in the same cage for daily sessions. All programming was controlled by electromechanical circuits (Lehigh Valley Electronics, PA) and the data for reinforcements earned and number of 10-sec periods of nonresponding ["pause intervals," see (21,22)] were counted for each of four 10-min periods of the session.

The baseline data reflects the stable averaged values of reinforcements and pauses obtained on days when saline or vehicle was administered, with a day-to-day variation below 15 percent. Data of the Control Period were collected during the first twelve-day period after stable FR-40 responding was established. The four 5-HT agonists were administered in a randomized sequence to each animal every three days. No chronic treatment was given during this period. Eighteen rats were then randomly assigned to 3 groups of 6 animals each. The first group received chronic phenelzine (10 and 5 mg/kg/day), the second received chronic isocarboxazid (5 mg/kg/day), and the third group received vehicle during the next 24 days (the first 12 days labeled Period 1 and the second 12 days called Period 2). These subjects also received test doses of the four 5-HT agonists at 3-day intervals in Periods 1 and 2 as in the Control Period, beginning with the day after the first MAOI injection. The remaining 4 rats received a MAOI but not 5-HT agonists during Periods 1 and 2, to evaluate effects of the chronic drug treatment alone. At the end of Period 2, the chronic MAOI treatments were terminated and the next 12-day interval was designated the "Washout" Period, during which the 5-HT agonists continued to be tested on the FR-40 at 3-day intervals in the 3 groups of 6 rats each. However, subjects were tested for an additional 12 days beyond this period for the effects of the 5-HT agonists.

Drugs

The 5-HT agonists d-lysergic acid diethylamide (LSD, 0.1 mg/kg, NIDA, Rockville, MD), quipazine maleate (2 mg/kg, courtesy of Miles Labs, Inc.), 8-hydroxy3(di-n-propylamino)tetraline (8-OHDPAT, 0.05 mg/kg) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP, 1 mg/kg) were used to disrupt FR-40 responding to 20–40% of baseline levels. All the agonists were dissolved in saline at concentrations to allow a dose of 1 ml/kg. LSD and quipazine were injected intraperitoneally (IP), whereas 8-OHDPAT and TFMPP were prepared fresh on the day of use and administered subcutaneously.

The monoamine oxidase inhibitors phenelzine (initially 10 mg/kg, courtesy of Warner-Lambert Co., Morris Plains, NJ) and isocarboxazid (5 mg/kg, courtesy of Hoffmann-La Roche, Nutley, NJ) were injected IP daily, on alternating sides of the abdomen, after the session during the periods of chronic treatment. The dosage of phenelzine was reduced to 5 mg/kg in Period 2 after overt symptoms of hyperirritability developed. The control group received the 0.5% methyl cellulose vehicle daily during Periods 1 and 2.

Statistics

A repeated-measures ANOVA design was used to assess the effects of each 5-HT agonist separately on reinforcements and pausing in the three groups described above. Individual comparisons between two means were carried out using the least signifi-

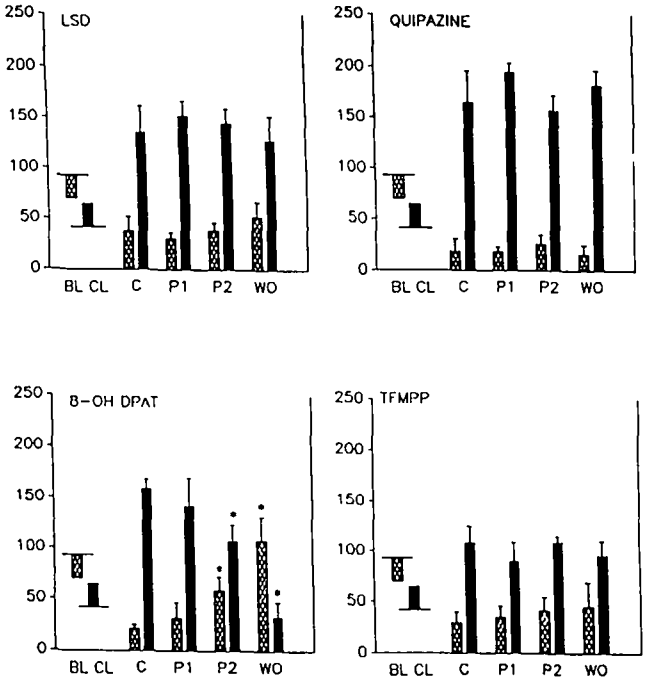

FIG. 1. Effects of 5-HT agonists to disrupt FR-40 operant responding in chronic vehicle- (0.5% methyl cellulose) treated rats. Doses (mg/kg) of agonists are: LSD, 0.1; quipazine, 2; 8-OHDPAT, 0.05; and TFMPP, 1. Reinforcements earned are depicted by hatched bars; pauses are indicated by filled bars. Baseline confidence limits (BL and CL) are shown as mean and downward deflection for reinforcements, and mean and upward deflection for pauses. Asterisks placed above a bar indicate that these values differ significantly ($p<0.05$) from Control Period (C) values.

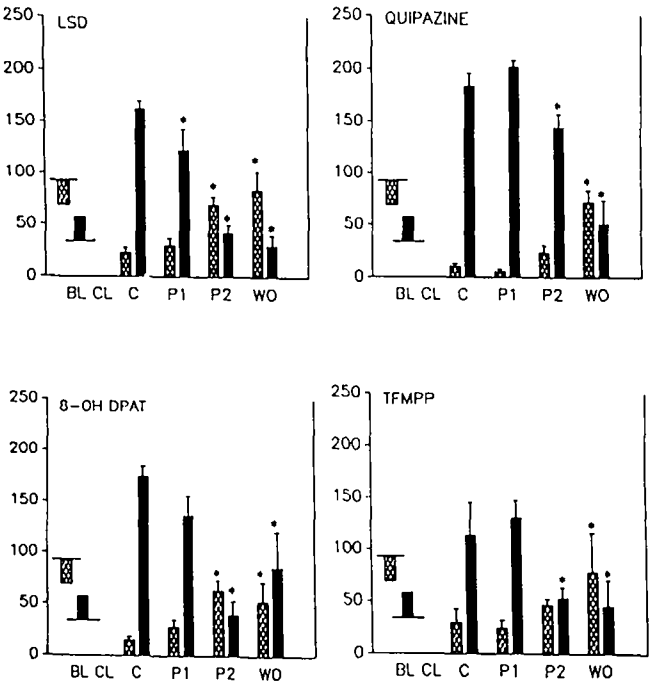

FIG. 2. Effect of 5-HT agonists to disrupt FR-40 operant responding before, during, and after chronic phenelzine. C = effect of the agonist before phenelzine. Period 1 (P1) = first 12 days of chronic phenelzine (10 mg/kg/day IP). Period 2 (P2) = second 12 days of chronic phenelzine (5 mg/kg/day IP). Washout Period (WO) lasted 12 days following the interruption of phenelzine treatment. Vertical lines on the bars show S.E.M. See legend to Fig. 1 for further clarification.

cant difference test where indicated. In all cases, the results were considered significant at $p<0.05$. In addition, all baseline measures of reinforcements and pauses for all periods, which were found to show no significant differences among Control Period, Period 1, Period 2 and Washout Period, were pooled. These mean values, with 95% confidence limits, afford an additional reference for assessing meaningful changes in the effects of the 5-HT agonists.

RESULTS

The chronic MAOI administration appeared not to have a prominent influence on baseline behavior. The effects of each 5-HT agonist on FR-40 reinforcements (R) and pauses (P) for each period in the Control rats (chronic vehicle treatment) are depicted in Fig. 1. The FR-40 disruption by 5-HT agonists in animals treated chronically with phenelzine and isocarboxazid at different periods are shown in Figs. 2 and 3, respectively. As anticipated, the administration of LSD, quipazine, and TFMPP at 12-day intervals (injected in random order with 8-OHDPAT every 3 days) did not result in a significant change in the FR-40 disruption pattern for these 3 agonists when chronic vehicle treatment followed daily behavioral measurements. On the other hand, the effects of 8-OHDPAT for reinforcements gradually diminished significantly, $F(2,10)=3.51$, $F>3.29=p<0.05$, in Period 2 and the Washout Period with repeated administrations in this control group, even when injected as infrequently as every 12 days.

Mean baseline values for R and P were as follows: in the vehicle-treated group $R=92$ and $P=32$, in the phenelzine group $R=90$ and $P=27$, and in the isocarboxazid group $R=95$ and $P=35$. During the Control Period in the phenelzine group, LSD decreased R to 23 ± 5 and increased P to 162 ± 8 (Fig. 2). In the isocarboxazid group (Fig. 3) during the Control Period, LSD decreased the R to 15 ± 5 and increased P to 179 ± 9. During Period 1, LSD's effect on R and P tended to be less in both groups, but a significant difference was found in pauses only [phenelzine: $R=30\pm7$ ($F=8.52$); $P=122\pm21$ ($F=35.4$); isocarboxazid: $R=38\pm10$ ($F=8.19$); $P=121\pm22$ ($F=11.77$), $df=3/15$]. Significantly less effect of LSD was observed on R and P in both MAOI groups during Period 2 and the Washout Period.

Quipazine disruption in FR-40 responding of the phenelzine group (Fig. 2) during the Control Period decreased R to 10 ± 3 and increased P to 184 ± 12. In isocarboxazid-treated rats (Fig. 3) during the Control Period, quipazine decreased R to 8 ± 2 and increased P to 197 ± 5. During Period 1 the values of R and P were not significantly different from the control Period in either group. During Period 2, the quipazine effect on P was significantly less in phenelzine-treated rats [$R=23\pm7$ ($F=21.7$) and $P=144\pm13$ ($F=27.6$)], while in isocarboxazid-treated rats the decrease in R was significantly lessened [$R=47\pm19$ ($F=6.77$) and $P=149\pm21$ ($F=7.66$)]. During the Washout Period the effects of quipazine on R and P were significantly attenuated in both MAOI groups.

The 5-HT_{1A} agonist 8-OHDPAT altered FR-40 responding during the Control Period by decreasing R to 15 ± 4 and increasing

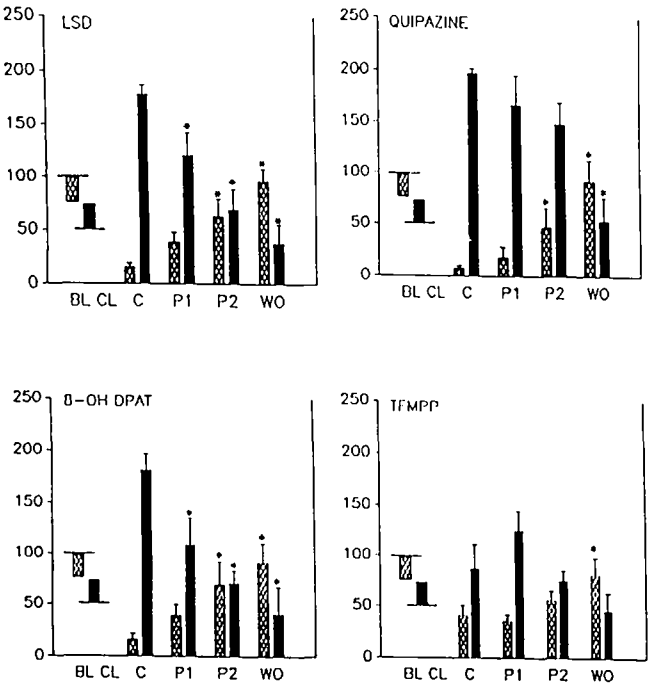

FIG. 3. Effects of 5-HT agonists to disrupt FR-40 operant responding before (C), during (P1 and P2), and after (WO) chronic isocarboxazid (5 mg/kg/day IP) treatment. See legends to Figs. 1 and 2 for further clarification.

P to 175 ± 10 in phenelzine-treated rats (Fig. 2). In the isocarboxazid group (Fig. 3) the values during the Control Period were altered by 8-OHDPAT to decrease R to 16 ± 6 ($F = 3.58$) and increase P to 181 ± 16 ($F = 8.21$). During Period 1 the values of R and P in phenelzine rats were not different from the Control Period, while a nonsignificant trend for lessened effect on P (109 ± 26) was found in isocarboxazid-treated rats. A significant attenuation of effects of 8-OHDPAT on R ($F = 3.45$) and P ($F = 6.78$) was obtained during Period 2 and the Washout period in both chronic treatment groups.

The 5-HT_{1B} agonist TFMPP caused somewhat variable levels of disruption of FR-40 patterns in the two MAOI groups during the Control Period (phenelzine group: R = 30 ± 14, P = 113 ± 32, Fig. 2; isocarboxazid group: R = 41 ± 10, P = 87 ± 24, Fig. 3). However, these trends for differences between the groups during the Control Periods were not significant. No significant change was found during Period 1 in either group. During Period 2, a trend for lessened effects on R and P was observed in both groups but a significant difference was observed only in P for the phenelzine rats [R = 47 ± 6 ($F = 5.26$); P = 53 ± 10 ($F = 6.01$)]. During the Washout Period, a significantly less effect on R was obtained in the phenelzine group only (phenelzine: R = 78 ± 37; isocarboxazid: R = 81 ± 17). A significant attenuation of the effect on pauses was also found only in phenelzine-treated rats (P = 46 ± 17).

In the 12-day period following Washout, the disruptive effects of 8-OHDPAT continued to be attenuated in the control, phenelzine and isocarboxazid groups (R = 108 ± 7, P = 33 ± 8; R = 102 ± 12, P = 26 ± 6; R = 100 ± 28, P = 53 ± 22, respectively). On the other hand, disruptive effects of LSD and quipazine returned during this period both in the phenelzine (R = 63 ± 16, P = 101 ± 25 for LSD; R = 42 ± 17, P = 152 ± 29 for quipazine) and isocarboxazid (R = 52 ± 12, P = 143 ± 14 for LSD; R = 28 ± 11, P = 174 ± 14 for quipazine) groups. There was a trend for recovery of the disruptive effects of TFMPP in both groups but this did not reach significance (R = 70 ± 5, P = 59 ± 13 for the phenelzine group; R = 61 ± 18, P = 89 ± 18 for the isocarboxazid group).

DISCUSSION

In the initial study in this series (25), neither chronic imipramine nor chronic trazodone over a 6-week period was effective in systematically reducing the potency of LSD, quipazine or TFMPP to disrupt the response pattern of rats performing in the FR-40 operant schedule. After discontinuing the chronic antidepressants (Washout Period), there was a reduction in the capacity of LSD to decrease reinforcers. Sensitivity to LSD gradually returned over 2–3 weeks following the Washout Period. During the latter period of chronic antidepressant treatment, and particularly during the Washout Period, 8-OHDPAT was less effective in disrupting FR-40 in both the imipramine and trazodone groups.

The above observations with 8-OHDPAT are put in question, however, by results of the present study. In Fig. 1, effects are indicated for repeated test doses of LSD, quipazine, 8-OHDPAT, and TFMPP in random order in subjects receiving vehicle during the chronic treatment phase. In this group 8-OHDPAT was noted to gradually lose potency for disrupting FR-40 both with regard to decrease in reinforcements and increase in pause intervals. Thus, it appears that 8-OHDPAT, when alternated with LSD, quipazine and TFMPP in a 3–4-day injection sequence, gradually becomes less effective for disrupting FR-40 performance. In preliminary studies with naive rats, we have tested repeated intermittent as well as daily dosings of 8-OHDPAT alone and found no clear indication of tolerance development to the effects on FR-40 behavior. Therefore, it appears that the loss of sensitivity observed in this study and the previous one reflects some interaction of 8-OHDPAT with the other 5-HT agonists as administered in this sequence.

Treatment with chronic imipramine or trazodone in the previous study did not alter baseline levels of responding of subjects in the FR-40. Baseline behavior of rats in the present study tended to be altered during chronic phenelzine, but a dose adjustment appeared to avoid a significant disruption. Neither chronic MAOI treatment alone (without intermittent test doses of 5HT agonists) altered baseline levels of FR-40 responding significantly. Nevertheless, chronic MAOI appeared to reduce the sensitivity of all four 5-HT agonists to disrupt FR-40, particularly with LSD and 8-OHDPAT. As noted above, the 8-OHDPAT changes are of questionable relevance since they occurred in controls in the absence of chronic antidepressant treatment. The more dramatic effects of chronic MAOI treatments on LSD (and to a lesser extent quipazine and TFMPP), compared to the lack of effects with chronic imipramine or trazodone in the previous study, may reflect the combined down-regulation of both 5-HT_1 and 5-HT_2 receptors by the MAOI.

The most dramatic effects of the chronic MAOI administration appeared in the Washout Period, during which there was less disruption of FR-40 by all 4 agonists. The significance of these changes, at least for effects of LSD, quipazine, and TFMPP, is obscure at this time, but prompts the need for further study of this phenomenon. For LSD and quipazine, sensitivity to FR-40 disruption was recovered during the 12-day period following Washout. Alterations in sensitivity of brain 5-HT systems following the termination of antidepressant drug treatment have been described previously (8–10). More documentation of the status of brain 5-HT mechanisms during and after various treatment regimens with antidepressants would be highly desirable.

The interactions of chronic antidepressant treatments with

effects of the 5-HT agonists in this operant behavior are less clear and consistent as compared with previous studies utilizing physiological measurements or gross motor patterns (9–11, 13–15, 19). Perhaps the more delicate balance of various 5-HT mechanisms involved in maintenance of this higher-order learned behavior is less readily reinstated when it is disrupted by drugs acting on these systems. Certainly it would be surprising if multiple mechanisms of these types, once disrupted by a drug, were exactly "returned" by a second drug treatment (that was not a direct receptor antagonist) to completely negate the effects of the first drug. Other complications relate to the potential actions of these 5-HT agonists and antidepressant drugs on non-5-HT mechanisms in the brain. These activities would probably be even less likely to interact in ways to reduce the disruptive effects of the 5-HT agonists on this operant behavior.

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