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DISCRIMINATIVE STIMULUS PROPERTIES OF QUIPAZINE: DIRECT SEROTONERGIC MEDIATION*

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Summary—Rats were trained to discriminate intraperitoneal injections of quipazine (1.0 mg/kg) from saline in a two-lever drug discrimination task. After reliable levels of accuracy (>85%) were attained, various agents which alter the functional activity of serotonergic (5-HT) neuronal systems were tested either alone or in combination with quipazine. Neither the 5-HT precursor, *l*-tryptophan, nor the 5-HT re-uptake inhibitors, fluoxetine and citalopram (Lu 10-171), either alone or in combination, elicited responding on the quipazine-appropriate lever. However, fenfluramine, a drug which releases endogenous 5-HT from nerve terminals, produced 84% quipazine-like responding. The dopamine (DA) agonists, apomorphine and amphetamine, did not transfer to quipazine. Of the several neurotransmitter antagonists tested, those which block 5-HT were also found to block the quipazine cue. *Para*-chlorophenylalanine (PCPA), which depletes central 5-HT by inhibiting its synthesis, significantly potentiated a sub-threshold dose (0.25 mg/kg) of quipazine and reduced the transfer of fenfluramine to quipazine, suggesting that quipazine exerts its discriminatory effect by directly stimulating central 5-HT receptors.

Since the potent hallucinogen, D'lysergic acid diethylamide (LSD), has been shown to transfer to a relatively high dose of quipazine (2.5 mg/kg), this compound and other known hallucinogens were tested for transfer to the dose of quipazine (1.0 mg/kg) used in the present experiment. Mescaline, LSD, and psilocybin all produced strong transfers to the quipazine cue. These data suggest the possibility that quipazine may possess hallucinogenic properties.

In a previous report, evidence was presented that quipazine (2-(1-piperazinyl)-quinoline maleate) can serve as an effective discriminative stimulus in rats and that the discriminative properties of this compound are similar to those of D-lysergic acid diethylamide (LSD) (White, Kuhn and Appel, 1977). Since the serotonin (5-HT) antagonists, methiothepin, methysergide and cyproheptadine, blocked the quipazine-saline discrimination while the dopamine (DA) antagonists, fluphenazine and haloperidol, did not, it was suggested that interaction with 5-HT neurotransmitter systems might be the neural mechanism mediating the quipazine (as well as the LSD) cue (Kuhn, White and Appel, 1978) and that DA involvement was not indicated.

Although these data, as well as those from other laboratories, involving behavior such as hyperactivity (Green, Youdim and Grahame-Smith, 1976), stereotypy (Costall and Naylor, 1975), antinociception (Samanin, Bernasconi and Quattrone, 1976), head-twitching (Malick, Doren and Barnett, 1977) and food intake (Samanin, Bendotti, Miranda and Garattini, 1977), suggest that the primary action of quipazine is direct stimulation of central 5-HT receptors, this hypothesis has been difficult to prove directly (Fuller, Snoddy, Perry, Rousch, Molloy, Bymaster and Wong, 1976) and other serotonergic mechanisms have been proposed; two of these are inhibition of 5-HT re-uptake (Hamon, Bourgoin, Enjalbert, Bockaert, Hery, Ternaux and Glowinski, 1976; Jacoby, Howd, Levin and Wurtman, 1976; Fuller *et al.*, 1976; Medon, Leeling and Phillips, 1973) and stimulation of release of 5-HT from pre-synaptic terminals (Malick *et al.*, 1977; Hamon *et al.*, 1976). In addition, quipazine has been found to inhibit monoamine oxidase *in vitro* (Hamon *et al.*, 1976; Fuller *et al.*, 1976; Green *et al.*, 1976) but, since very weak (Fuller *et al.*, 1976; Green *et al.*, 1976; Rodriguez and Pardo, 1971) or no inhibition of this enzyme (Hamon *et al.*, 1976; Jacoby *et al.*, 1976) occurs *in vivo*, this mechanism would not appear to have much behavioral significance.

The present experiment was designed to confirm and extend the previous findings using a lower, less behaviorally disruptive training dose of quipazine (1.0 mg/kg) and to explore further the synaptic mechanisms underlying its discriminatory effect. This was accomplished first by testing for transfer of the quipazine cue to several compounds which alter the functional activity of 5-HT [that is, agents which either increase the synthesis of serotonin (*l*-tryptophan), inhibit its re-uptake (fluoxetine, citalopram) or stimulate its release (fenfluramine)], and second, by adminis-

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tering various neurotransmitter antagonists (5-HT, alpha and beta noradrenergic (NE) and acetylcholine (Ach) blockers) in conjunction with quipazine. Since the potent hallucinogen, LSD, was shown to transfer to quipazine, the stimulus properties of other classes of hallucinogens (indole amine, phenylethylamine, anticholinergic drugs) were compared to those of quipazine. Finally, parachlorophenylalanine (PCPA), a drug which depletes 5-HT by inhibiting tryptophan hydroxylase (Koe and Weissman, 1966), was administered and effects on the quipazine cue and the ability of fenfluramine to mimic this cue were investigated.

METHODS

Subjects. Twenty-three experimentally naive male albino rats (Sprague–Dawley) were maintained at 80% of their free-feeding weight by limiting water intake. They were housed individually in a room at constant temperature (21–23°C) and humidity (40–50%) on a 12-hr light–dark cycle (07:00 a.m.–07:00 p.m.).

Apparatus. Four commercially available two-lever operant chambers (Lehigh Valley Electronics Model 143-24) contained in sound and light attenuating cubicles (LVE Model 137-04) were used for all phases of the experiment. Water (0.01 ml/reinforcement) was delivered by a dipper mounted equidistant between the two levers. Boxes were illuminated by a 28 V white house light. All programming and data recording were controlled electromechanically in an adjacent room.

Discrimination Training. The procedure used to train the discrimination between quipazine (1.0 mg/kg) and saline (in equivalent volume) was the same as that previously reported (White *et al.*, 1977; Kuhn *et al.*, 1978). Thirty minutes prior to testing, rats were injected intraperitoneally (i.p.) with either quipazine or saline. Training began on a continuous schedule of water reinforcement (FR 1) with only the stimulus-appropriate lever present. To control for possible position preference, the quipazine-correct lever was the right lever for 12 rats and was the left lever for the other 11 rats. The order of quipazine or saline administration was random with the restriction that no condition be present for more than three consecutive days. Bar-pressing requirements were gradually increased until all animals showed stable performance on an FR 32 schedule on both levers. When this was achieved, both levers were presented simultaneously and discrimination training was begun. The animals were reinforced only for responding on the stimulus-appropriate lever; there were no programmed consequences for incorrect responses.

Table 1. Mean % responding on the quipazine lever after injection of 5-HT and DA "agonists"

Drug	Dose*	Time†	*N*	Percentage ± S.E.M.
Quipazine	1.0	30	23	95 ± 1
Saline		30	23	5 ± 1
d-Amphetamine	0.75	30	12	26 ± 12‡
Apomorphine	1.0	30	11	37 ± 10‡
l-Tryptophan	100.0	30	11	9 ± 4‡
	100.0	60	12	12 ± 3‡
	100.0	120	12	27 ± 9‡
Fluoxetine	10.0	30	5	18 ± 12‡
	10.0	60	11	22 ± 10‡
	10.0	120	11	31 ± 10‡
	10.0	240	12	32 ± 12‡
Citalopram	2.5	30	12	34 ± 11‡
	2.5	60	12	37 ± 13§
	5.0	60	11	20 ± 10‡
	5.0	240	11	21 ± 10‡
l-Tryptophan +	50.0	60		
Citalopram	2.5	60	22	25 ± 8‡
l-Tryptophan +	50.0	120		
Citalopram	2.5	120	11	19 ± 5‡
l-Tryptophan +	100.0	60		
Fluoxetine	10.0	30	14	28 ± 10‡
l-Trytophan +	100.0	60		
Fluoxetine	10.0	60	12	27 ± 8‡
Fenfluramine	1.0	30	18	84 ± 7‖

* All doses are mg/kg, intraperitoneal (i.p.).
† Interval between injection and testing.
‡ Not significantly different from saline.
§ Significantly different from both saline and quipazine ($P < 0.01$).
‖ Not significantly different from quipazine.

All discrimination sessions were 30 min long and were conducted five days per week (Mon. through Fri.). Discrimination training continued until the average percentage of correct responses for the 23 rats was consistently 85% or higher. The percentage of correct responses for each rat during discrimination training was calculated as the number of correct responses, either saline or quipazine depending on which was injected, divided by the total number of responses on both levers before the first reinforcer was delivered.

Test for transfer of the quipazine cue to other compounds. The 5-HT precursor *l*-tryptophan (100 mg/kg), the 5-HT re-uptake inhibitors citalopram (Lu 10-171) (2.5 and 5.0 mg/kg) and fluoxetine (10 mg/kg) and the 5-HT releaser fenfluramine (1.0 mg/kg) were given at various time intervals before behavioral testing. Combinations of *l*-tryptophan with both citalopram and fluoxetine were also tested at various time intervals (Table 1). The DA agonists *d*-amphetamine (0.75 mg/kg) and apomorphine (1.0 mg/kg) were given 30 min prior to testing.

The indole amine hallucinogens, LSD (0.04 and 0.08 mg/kg) and psilocybin (0.5 and 1.0 mg/kg), the phenethylamine hallucinogen, mescaline (10 mg/kg), the anticholinergic drugs, atropine (1.0 and 2.0 mg/kg) and ditran (1.0 and 2.0 mg/kg) and the dissociative anesthetic, phencyclidine (0.05 and 1.0 mg/kg) were given in random order, all 30 min prior to behavioral testing. All transfer tests were conducted during extinction sessions to avoid possible confounding effects of additional learning. Data from all test sessions are expressed as percentage responding on the quipazine lever (see below).

Tests for antagonism of the quipazine cue. The putative central 5-HT antagonists, methysergide (1.0 mg/kg), cyproheptadine (1.0 mg/kg), methiothepin (1.0 mg/kg), 2-bromo-D-lysergic acid diethylamide (BOL) (0.55 and 1.0 mg/kg), and the peripheral 5-HT antagonist, xylamidine tosylate (1.0 mg/kg); the alpha-NE antagonist, phentolamine (10.0 mg/kg), the beta-NE antagonist, propranalol (20 mg/kg), and the muscarinic cholinergic antagonist, atropine (2.0 mg/kg) were administered 60 min (BOL-30 min) before quipazine (1.0 mg/kg); animals were tested for lever-choice 30 min after the quipazine injection. As always, these tests were conducted during extinction sessions. In addition, all antagonists (at the same doses) were tested in combination with saline (rather than quipazine) to control for possible synergistic effects.

Effects of PCPA on the discriminatory action of quipazine. Following all other testing, PCPA methyl ester in a dose of 100 mg/kg (calculated as the free base) was administered to 12 rats for three consecutive days (i.e. a total of 300 mg/kg of PCPA was given). The other 10 rats received control injections of the PCPA vehicle (NaCl). On the fourth day after the last injection, one half of the rats in both the PCPA and vehicle groups were given the training dose of quipazine (1.0 mg/kg), while the other half were given one-quarter of this dose (0.25 mg/kg). The following day the injections were reversed, such that the animals which had been given 1.0 mg/kg of quipazine on the first test day received 0.25 mg/kg and the animals which had had 0.25 mg/kg on the first test day were given 1.0 mg/kg. The percentage of quipazine-appropriate responses was recorded during extinction sessions and the data from the two days for each group of rats were pooled. After a saline practice session, fenfluramine (1.0 mg/kg) was tested for transfer in the two groups (PCPA and vehicle).

Drugs. Doses of the following drugs were based on the weight of the salt: apomorphine HCl, atropine sulfate, BOL tartrate, citalopram HBr, cyproheptadine HCl, *d*-amphetamine sulfate, LSD tartrate, ditran, fenfluramine HCl, fluoxetine HCl, mescaline HCl, methiothepin maleate, methysergide maleate, phencyclidine HCl, phentolamine HCl, propranolol HCl, psilocybin, quipazine maleate and xylamidine tosylate. Doses of *l*-tryptophan methyl ester HCl and PCPA methyl ester refer to free acid or base. Cyproheptodine was prepared in 15% aqueous propylene glycol. Apomorphine was dissolved in 0.2% ascorbic acid. All other drugs were dissolved in 0.9% NaCl and, except for quipazine, were prepared immediately before use. All injections were given intraperitoneally.

Analysis of data. During extinction testing, the animals were removed from the chamber as soon as they made a total of 32 responses on one of the two levers or, in those cases when disruption of responding occurred, after 10 min. All test data are expressed as the per cent of responding on the quipazine lever. Therefore, the number of total responses for any animal during a test session was always between 32 and 63. Planned comparison correlated *t*-tests were used to analyze differences between means. Since all animals were not given the same treatment on each test day, comparisons were made between the data of rats given particular treatment and the data of the same rats from the quipazine or saline session held most recently before that test session. This was done to insure equal sample sizes in all comparisons. Test sessions were held on Tuesdays and Fridays with saline sessions always held the previous day (i.e. Mondays and Thursdays) to minimize possible residual drug effects. Quipazine retraining (practice) sessions were held every Wednesday.

RESULTS

The acquisition of the quipazine–saline (1.0 mg/kg) discrimination is shown in Figure 1. Attainment of criterion (85% correct) took considerably longer than in a previous experiment, when 2.5 mg/kg of quipazine was used (White *et al.*, 1977). Nevertheless, by block 6 (sessions 26–30), accuracy of responding reached 90% and remained above 90% through block 9, after which extinction tests began. As might be expected, inter-session variability decreased as accuracy increased. Throughout the remainder of the

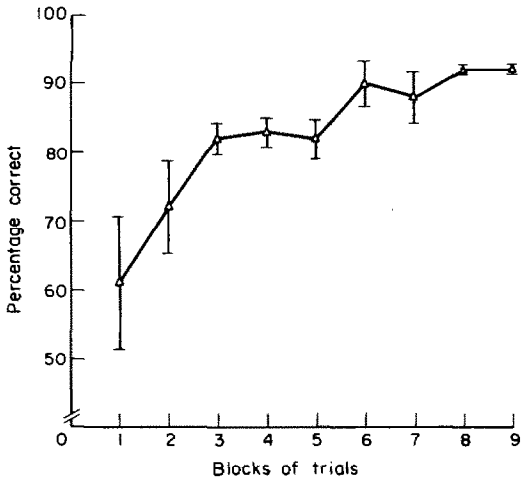

Fig. 1. Acquisition of quipazine-saline discrimination. Each block represents the mean of five acquisition sessions including both saline and quipazine sessions. Data are presented as the percentage of correct responding. Standard errors of the mean across the five sessions are indicated by vertical lines.

experiment, the percentage of correct responses remained above 85% during weekly re-training sessions. In contrast to a previous study, there was no significant response rate difference between saline and quipazine sessions during the 45 days of discrimination training (*t*-test for correlated measures), probably because of the lower dose used (1.0 mg/kg).

Transfer of the quipazine cue to other compounds. The results of transfer tests with neurotransmitter 'agonists' are presented in Table 1. Of the drugs which increase the synaptic availability of 5-HT, only fenfluramine (1.0 mg/kg), a drug which releases 5-HT from pre-synaptic terminals (Duhault and Boulanger, 1977; Buczko, De Gaetano and Garattini, 1975), resulted in a significant (84%) transfer to the quipazine cue ($P < 0.01$). Although some of the doses of the 5-HT reuptake inhibitors, fluoxetine (Fuller, Perry and Molloy, 1974) and citalopram (Hytell, 1977), produced 32–37% quipazine-like responding, only the 2.5 mg/kg dose of citalopram, given 30 min prior to testing, was significantly different from saline control ($P < 0.01$); a higher dose of the same compound (5.0 mg/kg), given at the same time interval, did not produce responding significantly different from saline controls.

Neither of the DA agonists, amphetamine nor apomorphine, produced responding which was significantly different from saline control values, although apomorphine at 1.0 mg/kg produced 37% quipazine responding. Unfortunately, higher doses of this compound produced behavioral disruption and therefore could not be tested.

The results of transfer tests with various hallucinogens are presented in Table 2. As found previously (White *et al.*, 1977), LSD transferred to the discriminative cue produced by quipazine and this transfer is dose-related. Thus, 0.08 mg/kg of LSD produced 81% while 0.04 mg/kg produced only 66% transfer. In addition, another indoleamine hallucinogen, psilocybin (0.05 and 1.0 mg/kg) produced 84–85% quipazine responding; the phenylethylamine hallucinogen, mescaline (10.0 mg/kg) produced 74% transfer. The anticholinergic hallucinogen, ditran, produced a dose-dependent transfer which reached 70% at 2.0 mg/kg. Both atropine and phencyclidine produced intermediate responding (i.e. 40–80%) at the highest doses that were not disruptive. This amount of responding on the quipazine-appropriate lever dif-

Table 2. Mean % responding on the quipazine lever after injection of various hallucinogens

Drug	Dose*	Time†	*N*	Percentage ± S.E.M.
Quipazine	1.0	30	23	95 ± 1
Saline		30	23	5 ± 1
LSD	0.04	30	11	67 ± 13§
	0.08	30	12	81 ± 10‖
Psilocybin	0.5	30	11	84 ± 5‖
	1.0	30	5	85 ± 7‖
Mescaline	10.0	30	12	74 ± 9‖
Ditran	1.0	30	20	46 ± 9§
	2.0	30	9	70 ± 9
Atropine	1.0	30	11	31 ± 12‡
	2.0	30	21	40 ± 9§
Phencyclidine	1.0	30	22	26 ± 6‡
	2.5	30	10	42 ± 10§

* Doses are mg/kg, intraperitoneal (i.p.).
† Interval between injection and testing.
‡ Not significantly different from saline.
§ Significantly different from both saline and quipazine ($P < 0.01$).
‖ Not significantly different from quipazine.

Table 3. Mean % responding on quipazine lever following administration of neurotransmitter antagonists

Treatment	Dose of antagonist	Time†	N	Percentage
Saline + quipazine		60	23	94 ± 1
Saline + saline		60	23	6 ± 1
Methysergide + quipazine	1.0	60	15	54 ± 11§
Methysergide + saline	1.0	60	7	17 ± 12‡
Methiothepin + quipazine	1.0	60	21	24 ± 7‡
Methiothepin + saline	1.0	60	10	9 ± 4‡
Cyproheptadine + quipazine	1.0	60	15	8 ± 6‡
Cyproheptadine + saline	1.0	60	8	7 ± 5‡
BOL + quipazine	0.55	30	6	65 ± 18§
BOL + quipazine	1.1	30	5	63 ± 21§
BOL + saline	0.55	30	5	4 ± 3‡
BOL + saline	1.1	15	6	14 ± 7‡
Propranalol + quipazine	20.0	60	15	92 ± 8‖
Propranalol + saline	20.0	60	7	8 ± 2‡
Phentolamine + quipazine	10.0	60	15	95 ± 6‖
Phentolamine + saline	10.0	60	8	6 ± 3‡
Atropine + quipazine	2.0	60	22	90 ± 6‖
Atropine + saline	See Table 2			
Xylamidine + quipazine	1.0	60	7	97 ± 4‖
Xylamidine + quipazine	2.0	60	8	100 ± 0‖
Xylamidine + saline	2.0	60	7	2 ± 1‡

* Quipazine was always given at 1.0 mg/kg.
† Time refers to the interval between antagonist injection and quipazine injection. Tests were always conducted 30 min after quipazine injection.
‡ Not significantly different from saline.
§ Significantly different from both saline and quipazine ($P < 0.01$).
‖ Not significantly different from quipazine.

fered significantly from that following both quipazine and saline.

Antagonism of the quipazine cue. Results obtained during antagonism test sessions are presented in Table 3.

All the putative central 5-HT antagonists (at doses of 1.0 mg/kg) blocked the discriminatory action of quipazine. The order of potency of antagonism was cyproheptadine > methiothepin > methysergide > BOL. The peripheral serotonin antagonist, xylamidine tosylate, did not block the quipazine cue. No other neurotransmitter blocker had any effect on the quipazine–saline discrimination.

Effects of PCPA on the discriminatory action of quipazine. *Para*-chlorophenylalanine had no effect on the discriminatory effect of the normal training dose of quipazine, i.e. the rats which received PCPA responded 92% on the quipazine lever while those which received vehicle responded 91%. However, PCPA significantly potentiated ($P < 0.01$) the effect of the lower dose of quipazine (0.25 mg/kg); that is, the PCPA-treated animals exhibited 65% quipazine-like responding while the vehicle rats exhibited only 21%. There was some suggestion that PCPA might inhibit the transfer of fenfluramine to quipazine. Although the difference between the two groups was not significant at $\alpha = 0.01$, the percentage difference was 29% (82% to 53%) and was significant at $\alpha = 0.17$. The PCPA data are presented in Table 4.

DISCUSSION

The results of this experiment confirm and extend the earlier findings (White *et al.*, 1977); that is, quipa-

Table 4. Mean responding on quipazine lever following *para*-chlorophenylalanine treatment

Group	Quipazine 1.0	Quipazine 0.25	Fenfluramine 1.0
PCPA $n = 12$	92 ± 2	65 ± 10*	53 ± 14†
Vehicle $n = 10$	91 ± 3	21 ± 9	82 ± 14

* Significantly different from vehicle control $\alpha = 0.01$.
† Significantly different from vehicle control $\alpha = 0.17$.

zine is an effective discriminative stimulus that controls the choice-responding of rats in a two-lever barpressing task. The fact that the acquisition of discrimination to 1.0 mg/kg of quipazine required more sessions (25) than that to 2.5 mg/kg quipazine (12) is consistent with many other reports that the rate of acquisition of discrimination to a drug is dependent upon the dose used to establish the discrimination (Appel, Kuhn and White, 1978; Barry and Krimmer, 1978; Chance, Murfin, Krynock and Rosecrans, 1977; Jarbe, Johansson and Henriksson, 1975; Overton, 1971). However, once discrimination is attained, different doses of the same drug can exert the same amount of stimulus control, in this case >85% correct responding after both 2.5 mg/kg (White *et al.*, 1977) and 1.0 mg/kg (present results). It should be noted that, in the present experiment, there were no differences in response rates between quipazine and saline sessions as was the case in the earlier study involving the higher dose. Therefore, there is no possibility that the rats were simply discriminating their own rates of responding on the two different levers.

The results of the transfer tests with the agents altering 5-HT functioning are similar to those seen with rats trained to discriminate LSD from saline (Kuhn *et al.*, 1978). Neither the 5-HT precursor, *l*-tryptophan, nor the 5-HT uptake inhibitors, fluoxetine and citalopram (alone or in combination) transferred to quipazine at doses which are known to increase the synaptic availability of 5-HT (Gallager and Aghajanian, 1976; Trulson and Jacobs, 1976; Fuller and Steinberg, 1976; Hytell, 1977). This suggests that at least one behavioral effect of quipazine is not the result of changes in 5-HT synthesis or inhibition of 5-HT re-uptake. Even if quipazine does inhibit 5-HT re-uptake *in vivo* as it does *in vitro* (Fuller *et al.*, 1976), re-uptake inhibition is not sufficient to produce its discriminative effects.

In contrast to *l*-tryptophan and the uptake inhibitors, fenfluramine (1.0 mg/kg) produced predominant responding on the quipazine-appropriate lever (84%). Fenfluramine is a drug which stimulates the release of 5-HT from nerve terminals as well as inhibiting its re-uptake (Buczko *et al.*, 1975; Carruba, Picotti, Zambotti and Mantegazza, 1977; Duhault and Boulanger, 1977). These data, along with those reported above, support the hypothesis that quipazine might produce its behavioral effects by releasing serotonin from pre-synaptic terminals (Hamon *et al.*, 1977; Malick *et al.*, 1977).

A previous finding that the 5-HT antagonists, methysergide (UML), methiothepin and cyproheptadine blocked the discriminatory action of 2.5 mg/kg quipazine was confirmed with a lower training dose (1.0 mg/kg); in addition, BOL was found to antagonize the quipazine (1.0 mg/kg)-saline discrimination. Cyproheptadine and methiothepin were extremely potent in blocking the quipazine as well as the LSD cue (Kuhn *et al.*, 1968). Since xylamidine tosylate did not block the quipazine cue, the discrimination appears to be mediated centrally. No other neurotransmitter antagonists had an effect on the discriminatory action of quipazine (or LSD). These data, along with the transfer data and the data from a previous study (White *et al.*, 1977), lead to the conclusion that quipazine produced its discriminatory effect either by directly stimulating post-synaptic 5-HT receptors or by increasing the release of 5-HT from pre-synaptic vesicles.

Para-chlorophenylalanine (PCPA), a drug which depletes 5-HT by inhibiting the enzyme involved in its synthesis, tryptophan hydroxylase (Koe and Weissman, 1966), was administered to differentiate between these two possibilities. If quipazine directly stimulates 5-HT receptors, depletion of 5-HT should potentiate discrimination of a sub-threshold dose of quipazine since it should have easier access to the post-synaptic 5-HT receptor sites. Conversely, if quipazine releases endogenous 5-HT, depletion of 5-HT by PCPA should disrupt the discrimination by the usual (training) dose. When the PCPA-treated animals in this study were given a lowered dose (0.25 mg/kg) of quipazine, they made 65% of their responses on the quipazine lever, while the animals which received vehicle made only 21% of their responses on the quipazine lever, a 42% difference. When both groups received the normal dose of quipazine (1.0 mg/kg), there was no difference in the percent of quipazine responding (PCPA = 92% vs vehicle = 91%). These data agree with those of other investigators who reported that PCPA either enhanced quipazine-induced responding such as hyperactivity (Green *et al.*, 1976) and disruption of FR responding (Appel, Joseph, Utsey, Hernandez and Boggan, 1977) or failed to disrupt quipazine-induced stereotypy (Grabowska, Antkiewicz and Michaluk, 1974) and head-twitches (Malick *et al.*,

1977). Thus, it seems likely that the behavioral effects of quipazine are mediated by a direct stimulation of 5-HT receptors rather than by indirectly promoting the release of 5-HT. The fact that PCPA pretreatment reduced rather than enhanced the transfer of fenfluramine to quipazine (above) further supports this contention.

Another interesting finding is the consistent transfer of the stimulus properties of known hallucinogenic drugs to those of quipazine. That the indole amine hallucinogens, LSD (0.04 and 0.08 mg/kg) and psilocybin (0.5 and 1.0 mg/kg), and the phenylethylamine hallucinogen, mescaline (10.0 mg/kg) produced significant transfers to quipazine is not surprising since both mescaline and psilocybin also transfer to LSD (Cameron and Appel, 1973; Schechter and Rosecrans, 1972; Kuhn, White and Appel, 1977) and the discriminative stimulus properties of LSD and quipazine are very similar, if not identical (White *et al.*, 1977; Kuhn *et al.*, 1978). Also, the LSD, mescaline and quipazine cues appear to be mediated, at least in part by a similar mechanism; that is, stimulation of 5-HT receptors (Browne and Ho, 1975; Browne, 1978; Greenberg, Kuhn and Appel, 1975a; Kuhn, White and Appel, 1976; Kuhn *et al.*, 1977; White *et al.*, 1977; Winter, 1978). Although psilocybin has been reported to possess discriminatory properties (Greenberg, Kuhn and Appel, 1975b; Harris and Balster, 1971), no systematic attempt has yet been made to discern the mechanism of action underlying these specific effects. In other respects, however, psilocybin is pharmacologically very similar to, though less potent than, LSD. It should also be noted that fenfluramine, which like the (other) hallucinogens, transferred to quipazine, has been shown to produce vivid hallucinogenic episodes in man (Griffith, Nutt and Jasinski, 1975) and to possess strong discriminative stimulus properties in rats (Goudie, 1977).

The two known anticholinergic drugs, atropine and ditran, and the dissociative anesthetic, phencyclidine, a compound that also has anticholinergic properties (Finnegan, Kanner and Meltzer, 1976; Garey and Heath, 1976; Maayani, Weinstein, Ben-Zvi, Cohan and Sokolovsky, 1974) produced intermediate responding on the quipazine lever, i.e. 40–70% quipazine responding. Such "partial transfers" are a well known problem in drug discrimination research in that they are extremely difficult to interpret (Overton, 1974; Colpaert, 1977). The method of analyzing transfer data dictates the interpretation. Comparing transfer data to training drug performance levels, as the present authors have chosen to do, can result in "over-inclusiveness", i.e. classifying drugs as similar when they may be pharmacologically different in other assays (Overton, 1974). However, the consistency of the partial transfers of these anticholinergic hallucinogens to the quipazine cue, and the dose-related increase in quipazine responding seen with ditran, might be indicative of some pharmacological similarity between these drugs. Quipazine has been reported to increase indirectly levels of ACh in certain areas of the striatum, possibly as a result of decreased ACh release in striatal interneurons which are under the inhibitory control of serotonergic neurons originating in the raphe nuclei (Euvrard, Javoy, Herbert and Glowinski, 1977; Guyenet, Euvrard, Javoy, Herbert and Glowinski, 1977). However, the doses of quipazine in these studies (30 mg/kg) were extremely large in comparison to that used in this study (1 mg/kg). Because of this large difference in dose, the inherent difficulty in interpreting partial transfers, and the fact that phencyclidine can be discriminated from ditran (Jarbe *et al.*, 1975), the hypothesis that these partial transfers represent some indirect pharmacological similarity between anticholinergic drugs and quipazine is tentative. Further research may directly test this notion.

The fact that all of the hallucinogenic drugs which were tested in this study produced at least a partial and usually a significant transfer to quipazine suggests the possibility that quipazine possesses hallucinogenic properties. The fact that BOL, a non-hallucinatory congener of LSD, does not transfer to quipazine (Table 3) also supports this possibility. Another research worker (J. C. Winter, personal communication), has also found that hallucinogens such as mescaline and LSD transfer to a quipazine discrimination and vice versa and has reached the same conclusion.

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