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Quipazine-Induced Stimulus Control in the Rat

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Abstract. The present investigation tested the hypothesis that quizapine, a drug thought to act directly or indirectly as an agonist at serotonergic (5-HT) receptors, mimics the stimulus properties of indoleamine and phenethylamine hallucinogens. In a group trained with mescaline (10 mg/kg) and saline in a single-lever response rate task, quipazine yielded intermediate results (58% mescaline-appropriate at 1 mg/kg), i.e., responding was fully appropriate for neither training condition. A second group was then trained with quipazine (3 mg/kg) and saline in a two-lever response choice task. Stimulus control was readily established with a mean of 22 sessions to achieve criterion performance (five consecutive sessions with at least 80% correct responses). When quipazine-trained rats were tested with LSD; responding was intermediate in nature (68% quipazine-appropriate) at a dose of 100 µg/kg but complete substitution was observed at 150 µg/kg (97% quipazine-appropriate). Similarly, subjects trained with LSD and saline in the two lever task and tested with quipazine responded in a fashion indistinguishable from the LSD training condition. The stimulus properties of quipazine alone and in cross tests in mescaline or LSD-trained subjects were blocked by the serotonergic antagonist, BC-105. Butaclamol, a dopaminergic antagonist, and the α-adrenergic antagonist, phentolamine, were without effect upon quipazine. The present data suggest that quipazine produces its stimulus effects by a serotonergic mechanism and that these effects are quite similar to those of LSD and mescaline.

Key words: Stimulus control – Quipazine – Mescaline – LSD – 5-Hydroxytryptamine

Stimulus control is said to exist when the dimensions of an antecendent stimulus determine the probability of occurrence of a conditioned response (Terrace, 1966). When stimulus control is demonstrable, the antecedent stimulus is called a discriminative stimulus (Kelleher and Morse, 1968). Following the initial report by Conger (1951), it has been demonstrated repeatedly that the effects of drugs can function as discriminative stimuli (for reviews, see Barry and Krimmer, 1978; Winter, 1978a).

The ability of mescaline, a phenethylamine hallucinogen (Heffter, 1896), and lysergic acid diethylamide (LSD), a hallucinogen of the indoleamine type (Stoll and Hofman, 1943), to serve as discriminative stimuli was reported by Hirschhorn and Winter (1971). Subsequent experiments in my laboratory (Winter 1975, 1978b) and elsewhere (Browne and Ho, 1975; Kuhn et al., 1978) demonstrated that the stimulus effects of both indoleamine and phenetylamine hallucinogens are blocked by antagonists of 5-hydroxytryptamine (5-HT, serotonin).

The hypothesis that LSD, mescaline, and related phenethylamines produce stimuli in the rat by mimicking, albeit in a distorted fashion, the actions of 5-HT (Winter, 1978b) predicts that other drugs able to act, directly or indirectly, as agonists at 5-HT receptors will substitute for LSD or mescaline in appropriately trained subjects. Furthermore, the LSD or mescaline-like stimulus effects would be expected to be blocked by serotonergic antagonists. The present experiments examine the stimulus properties of quipazine [2-(1-piperazinyl)quinoline maleate], a drug believed to act as an agonist at both peripheral and central 5-HT receptors (Hong and Pardo, 1966; Rodriguez et al., 1973). A recent study of the stimulus properties of quipazine by White et al. (1977) is discussed later in this paper.

Material and Methods

All subjects were CFN strain rats (Carworth Farms, Wilmington, MA). They were housed in pairs and had free access to dry food in the

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home cage. With the exception of weekends, water intake was limited to that obtained during experimental sessions. The equipment used were standard two-lever operant test chambers equipped with a dipper for delivery of the water reinforcer. Solid state programming equipment and electromechanical counters were used to control and record the sessions.

Before the present experiments began, all subjects in groups I and II had acquired a reliable discrimination between the effects of mescaline (·HCl, 10 mg/kg) and saline in a response rate task (Winter, 1978a) using methods previously described (Winter, 1973). All injections were i.p., 15 min before training. In group I, saline served as S^D, the stimulus in whose presence responses were reinforced on a fixed ratio (FR8) schedule and mescaline as S^Δ, the stimulus in whose presence responses had no programmed consequences. The stimulus conditions were reversed for subjects in group II, i.e., mescaline = S^D and saline = S^Δ. Subjects were trained in 15-min sessions, 5 days per week with the stimulus conditions alternating each day. The continued presence of discriminated responding was regularly tested in sessions in which responses for a 2-min period, which began with the emission of the first response, had no programmed consequence. Such sessions are hereafter referred to as test sessions.

The ability of quipazine to substitute for mescaline and the interaction of BC-105 with quipazine in mescaline-trained subjects were determined in sessions that were terminated 2 min after emission of the first response and with no responses having been reinforced. Such sessions are referred to as cross tests. Quipazine was injected (i.p.) 15 min before testing and the interaction of BC-105 and quipazine was determined by administering BC-105 (3 mg/kg) 60 min before the testing of quipazine.

Subjects in group III ($N = 4$) were trained with quipazine (3 mg/kg) and saline in a two-lever response choice task (Hirschhorn and Winter, 1971; Winter, 1978a) using a fixed-ratio 10 schedule of reinforcement. After the rats learned to drink from the dipper, they were trained to depress first one and then the other of the two levers. After responding was established on both levers, discrimination training was begun. Each 10-min session was preceded by one of two treatments; following quipazine, every tenth response on the quipazine-appropriate lever was reinforced and in a similar fashion, responses on the saline-appropriate lever were reinforced following the injection of saline. For two subjects, the left lever was designated as quipazine appropriate and for the remaining subjects, responses on the right lever were reinforced following quipazine. During discrimination training, quipazine was administered on Monday, Wednesday, and Friday; saline was injected on Tuesday and Thursday. The distribution of the first ten responses between the two levers was recorded each day. Quipazine-induced stimulus control was presumed to be present when, in five consecutive sessions, eight or more of the initial ten responses were upon the appropriate lever.

To determine the degree of similarity of the stimulus properties of LSD to those of quipazine, cross tests were conducted in which LSD was administered to quipazine-trained subjects. Cross tests as well as tests of antagonism were conducted each Friday so long as previous performance in the same week did not fall below a criterion of 80% correct responding. During cross tests, no responses were reinforced and the cross test session was terminated after the emission of ten responses. Response distribution during cross tests was compared with the distributions in the immediately preceding quipazine and saline sessions (henceforth referred to as control sessions). Sessions in which the ability of a drug to antagonize the stimulus properties of quipazine are similar to cross tests in that the session is terminated after ten responses and the results are compared with the preceding quipazine and saline control sessions.

Prior to the beginning of the present experiments, the rats of Group IV had been trained with LSD (100 µg/kg) and saline in the 2-lever response choice task. Cross tests of quipazine and of quipazine plus BC-105 or butaclamol were conducted as described above for Group III.

All cross test data were subjected to analysis of variance in a single-factor design with repeated measures (Winer, 1971). Simultaneous comparisons of mean response rates or choices in cross tests with drug and saline control values were made by means of the studentized range test (Winer, 1971), in which k, the minimum significant range is calculated. Observed ranges in excess of the k-values given in the present tables would be expected to arise by random sampling alone with a probability < 0.05. Tests of antagonism were analyzed by means of Student's t-test for paired observations.

Mescaline·HCl (NIDA, Washington, D.C.), D-LSD tartrate (NIDA), BC-105 [4-(1-methyl-4-piperidylidene)-9,10-dihydro-4H-benzo(4,5) cyclohepta(1,2-b) thiophene maleate, also known as pizotyline or pizotifen; Sandoz Pharmaceuticals, East Hanover, N.J.], quipazine [2-(1-piperazinyl) quinoline maleate; Miles Laboratories, Elkhart, Indiana], phentolamine mesylate (CIBA, Summit, N.J.), and butaclamol·HCl (Ayerst Research Laboratories, Montreal) were dissolved in 0.9% saline solution and injected on a constant volume of 1 ml/kg body weight.

Results

Figure 1A shows the effects of a range of doses of quipazine in rats trained with saline as S^D and mescaline as S^Δ (Group I). The rates of responding following doses of 1 and 3 mg/kg were comparable to those observed in tests of the mescaline condition. When subjects were pretreated with BC-105 and then given quipazine, the response rate was significantly increased ($P < 0.01$) compared with quipazine alone and was statistically indistinguishable from the saline condition. The suppression of responding seen in Fig. 1A could be due to (a) the similarity of the stimulus properties of quipazine and mescaline or (b) non-specific rate-depressant effects. The data of Fig. 1B permit the selection of the more appropriate of these interpretations. Rats of Group II were trained with mescaline (10 mg/kg) as S^D and saline as S^Δ and tested with quipazine. It is seen in Fig. 1B that the doses of quipazine that were mescaline-like in Group I (0.3, 1.0, and 3.0 mg/kg) were followed in Group II by rates of responding that were intermediate in nature. At 1 mg/kg, the response rate was significantly different ($P < 0.01$) from the rate in either training condition.

The subjects of Group III were trained with quipazine (3 mg/kg) in the two-lever choice task. Stimulus control was rapidly established with a mean of 22 sessions to the onset of criterion performance ($N = 4$; range = 13 – 27). Group III was then cross tested with LSD (Table 1). The lowest dose tested yielded saline-appropriate responding and the highest dose (300 µg/kg) abolished responding. However, following a dose of 100 µg/kg, responding was of an intermediate nature ($k = 27$), i.e., significantly different from both the saline and the quipazine training condition ($P < 0.05$) and at 150 µg/kg, complete substitution was observed ($k = 15$). When the same doses of LSD were

preceded by BC-105 (3 mg/kg), quipazine-appropriate responding was significantly reduced ($P < 0.01$). Also shown in Table 1 are the effects of butaclamol, phentolamine, and BC-105, purported antagonists at dopaminergic, α-adrenergic, and serotonergic receptor sites, respectively, upon quipazine-induced stimulus control. Of the three drugs, only BC-105 produced significant antagonism of quipazine ($P < 0.01$).

The subjects of Group IV were trained with LSD (100 µg/kg) in the two-lever choice task and then cross tested with quipazine (Table 2). At a dose of 3 mg/kg, quipazine was followed by responding which was indistinguishable from the LSD training condition ($k = 8$), i.e., quipazine substituted for LSD. When quipazine was tested in the presence of either BC-105 or butaclamol, only the former had an obvious effect in that quipazine-induced LSD-appropriate responding was significantly reduced ($P < 0.01$) by pretreatment with BC-105.

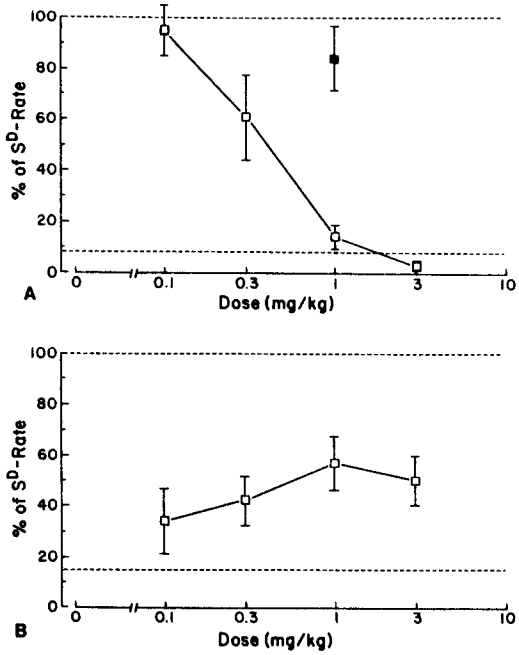

Fig. 1 A and B. The effects of quipazine in rats trained with mescaline (10 mg/kg) as a discriminative stimulus. Mescaline and quipazine were injected 15 min before testing. *Dotted lines* indicate mean control performance. Each quipazine point represents the mean of two determinations in each four subjects. *Ordinate:* mean rate of responding (± SE) expressed as a percentage of the S^D-rate. *Abscissa:* doses of quipazine and mescaline plotted on a log scale. **A** Rats trained with saline as S^D and mescaline as S^Δ. Closed square represents experiments in which BC-105 (3 mg/kg) was injected 60 min before testing with quipazine. **B** Rats were trained with mescaline as S^D and saline as S^Δ

Discussion

The present data indicate that quipazine only partially mimics mescaline in rats trained in a single lever response rate task (Fig. 1) but substitutes completely for LSD in rats trained in a two-lever response choice task (Table 2). One possible explanation for this discrepancy concerns the comparability of the stimulus properties of mescaline and LSD. Although several studies strongly suggest that they are quite similar (Hirschhorn and Winter, 1971; Schechter and Rosecrans, 1972; Winter, 1978b), subtle differences might exist and become apparent when cross tests with an appropriate drug are conducted. Alternatively, the quipazine cross tests may be influenced by the nature of the discrimination task. In an earlier investigation (Winter, unpublished), it was found that rats trained with either LSD or *d*-amphetamine were much more likely to respond in a drug-appropriate fashion when tested with p-methoxyamphetamine in a choice task than in a rate

Table 1. Effects of LSD, butaclamol, phentolamine, and BC-105 in rats trained with quipazine in a 2-lever choice task

Test drugs[a]	Dose (mg/kg)	N[b]	Quipazine control[c] (3 mg/kg)	Test[c]	Saline control[c]
LSD	0.05	4	97	7	0
LSD	0.1	4	98	68	5
LSD	0.15	3	93	95	2
LSD + BC-105 (3 mg/kg)	0.1	4	98	10	4
	0.15	3	96	9	6
Butaclamol + quipazine (3 mg/kg)	1	3	97	100	7
	3	3	90	97	10
Phentolamine + quipazine (3 mg/kg)	10	3	92	77	0
BC-105 + quipazine (3 mg/kg)	3	3	97	13	0

[a] LSD and quipazine administered i.p. 15 min before testing. All other drugs injected 60 min before testing
[b] Number of subjects
[c] Mean percentage of responses on the quipazine-appropriate lever

Table 2. Effects of quipazine alone and in combination with butaclamol and BC-105 in LSD-trained rats[a]

Test drugs	Dose quipazine (mg/kg)	Dose of antagonist (mg/kg)	N[b]	LSD control (100 µg/kg)	Cross test	Saline control
Quipazine	1	–	8	93	19	3
Quipazine	3	–	13	96	89	3
Quipazine + Butaclamol	3	0.3	4	94	96	2
	3	1.0	4	91	95	4
Quipazine + BC-105	3	3	4	91	8	0

[a] All details are as in Table 1
[b] Number of subjects

task. Nonetheless, if we assume that intermediate results indicate a partial similarity of the stimulus properties of a tested drug to those of the trained drug (Frey and Winter, 1978; Winter, 1978a), then all of the present cross test data are compatible with the conclusion that quipazine shares a significant proportion of the stimulus properties of indoleamine and phenethylamine hallucinogens. This conclusion is in substantial agreement with that of White et al. (1977), who found in a two-lever choice task that LSD (80 and 100 µg/kg) completely mimicked quipazine in rats trained with 2.5 mg/kg of the latter drug.

Various pharmacologic mechanisms have been invoked to explain the effects of quipazine. The bulk of evidence suggests an interaction with serotonergic receptors whether as a direct agonist (Jacoby et al., 1976; Quock et al., 1976; Malick et al., 1977), as a releaser of 5-HT (Hamon et al., 1976), or by blocking reuptake of the amine (Medon et al., 1973). In the present investigation, antagonism by BC-105 of quipazine-induced stimulus control (Table 1) and the diminution by BC-105 of the LSD and mescaline-like actions of quipazine (Table 2, Fig. 1) likewise implicate a serotonergic mechanism. Although a few workers have suggested a dopaminergic action of quipazine (Grabowska et al., 1974; Kruse, 1976; Medon et al., 1973), the failure of either phentolamine or butaclamol to modify the stimulus effects of quipazine (Table 1) indicates that neither adrenergic nor dopaminergic factors are of primary importance with respect to these effects. In contrast, a dose of 1 mg/kg butaclamol completely blocks apomorphine-induced stimulus control (Winter, unpublished). Similar results were obtained by White et al. (1977), who blocked quipazine-induced stimulus control with three different 5-HT antagonists (methysergide, cyproheptadine, and methiothepin) but found no effects with dopaminergic antagonists (haloperidol and fluphenazine).

As yet, no report of the effects of quipazine in human subjects has been published. The implications of the present findings and those of White et al. (1977) for the clinical pharmacology of quipazine are obvious. One would expect the drug to produce at least a portion of the mescaline-LSD syndrome. In a preliminary clinical investigation (H. Daumier, personal communication) normal human subjects reported 'low dose mescaline-like' effects at a dose of 0.5 mg. The study of higher doses was precluded by the onset of dysphoric effects including nausea.

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