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# Antagonism of the Behavioral Effects of 2,5-Dimethoxy-4-Methylamphetamine (DOM) and Quipazine by Metergoline

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COMMISSARIS, R. L. AND R. H. RECH. *Antagonism of the behavioral effects of 2,5-dimethoxy-4-methylamphetamine (DOM) and quipazine by metergoline.* PHARMAC. BIOCHEM. BEHAV. 15(4)659–662, 1981.—The present study examined the disruptive effects of the phenethylamine hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) and the putative 5-hydroxytryptamine (5-HT) agonist quipazine on fixed ratio-40 (FR-40) operant responding alone or after pretreatment with the putative 5-HT antagonist metergoline. Food-deprived male rats were trained to bar press on a FR-40 schedule for food reinforcements; control responding under this schedule is characterized by a rapid, constant rate of responding (approximately 100 responses/min). In control animals, both DOM and quipazine produced dose-dependent disruptions of FR-40 performance characterized by periods of non-responding or "pausing." Following pretreatment with 1.0 mg/kg, and to a lesser extent 0.1 mg/kg, metergoline (180 min prior to the session) the dose-response curves for the "pausing" produced by both DOM and quipazine were shifted significantly to the right. Moreover, increasing the dose of DOM about 16-fold and that of quipazine about 8-fold appears to completely override the antagonism by 1 mg/kg metergoline. These results suggest that the "pausing" produced by DOM or quipazine is the result of activation of 5-HT receptors.

Hallucinogens 5-Hydroxytryptamine DOM Quipazine Metergoline

HALLUCINOGENS produce a number of effects which are presumed to be mediated through 5-hydroxytryptamine (5-HT) neurons. These agents produce an exaggerated extensor reflex in reserpine-treated rats [1,2] and generate stimulus control cues in rats which generalize to one another and the putative 5-HT agonists, quipazine [7, 9, 14, 16, 17]; these stimulus cues are blocked by cinanserin and methysergide, putative 5-HT antagonists [9, 14, 16].

The disruptive effects of hallucinogens on fixed ratio operant behavior (FR) have been well-characterized, as agents of this class typically produce periods of non-responding or "pausing" [4–6,10]. Quantitation of this pausing can be attained by the use of a pause interval timer [4,6]. This pausing effect can differentiate hallucinogens from a number of other psychoactive agents, including the stimulant *d*-amphetamine, the depressant phenobarbital, and the neuroleptic chlorpromazine. While hallucinogens invariably produce pausing at doses which decrease overall responding up to 50%, doses of these non-hallucinogens which reduce response rates comparably typically produce slowed and erratic response rates not characterized by pausing [4–6] and Commissaris *et al.*, unpublished). The effects of quipazine on FR behavior have not been assessed using this quantitative measure for pausing.

Metergoline (1-methyl-8-carbobenzyloxyaminomethyl-10α-ergoline) is a relatively potent and selective 5-HT antagonist when aministered in doses of 0.5–2.0 mg/kg with a 3 hr pretreatment [12,13]. Higher doses of this compound have been shown to antagonize the capacity of both the phenethylamine and indolealkylamine hallucinogens to produce a "5-HT behavioral syndrome" characterized by side-to-side headweaving or head tremor, forepaw treading and splayed hindlimbs [15]. However, the efficacy of metergoline to antagonize the pause-producing effects of the phenethylamine hallucinogens is considerably greater than the efficacy of this compound against the indolealkylamine hallucinogens [5]. The purpose of the present study was to further characterize the metergoline antagonism of the FR-40 pause produced by the phenethylamine hallucinogen 2,5- dimethoxy-4-methylamphetamine (DOM) and to extend these observations to the 5-HT agonist quipazine.

## METHOD

### *Subjects*

The subjects were drug-naive male Sprague-Dawley (Spartan Farms, Haslett, MI) rats weighing between 200–225 g at the

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start of the experiments. All subjects were housed singly in a room with a 12-hr light-dark cycle (lights on 0700–1900 hr).

*Behavioral Apparatus*

Behavioral training and testing was conducted between 1400 and 1800 hr in four standard operant chambers (LVE No. 143-20-215) equipped with food pellet dispensers; these chambers were located in sound-attenuating boxes. Each chamber contained a single lever which required a force of 10–15 grams to activate. All experimental events were controlled by electromechanical programming circuits and responses were recorded on electromagnetic counters and cumulative recorders. Two parameters were monitored in the operant sessions: (1) the number of reinforcements obtained, a reflection of the average response rate; and (2) the period of non-responding, or "pausing." To quantify the period of non-responding during operant sessions, a 10-sec pause interval counter was incorporated into the program as described by Commissaris *et al.* [4–6].

*Behavioral Procedure*

All subjects were maintained at approximately 70–80% of their free-feeding weights. The subjects were first trained to respond on a continuous reinforcement (CRF) schedule for food (45 mg Noyes pellets). Daily sessions were 40 min in duration. Each animal was run at the same time of day and in the same cage seven days a week. After the subjects were responding on the CRF schedule (approximately 2–4 days) a fixed ratio (FR) schedule was introduced and gradually (2–3 weeks) increased to FR-40. After FR-40 responding had become stable for all rats (2–3 weeks) the effects of various doses of DOM (0.125–16.0 mg/kg) and quipazine (0.5–16.0 mg/kg) were determined alone or following pretreatment with 0.1 or 1.0 mg/kg metergoline. In addition, the effects of metergoline administration alone (0.1 and 1.0 mg/kg) were determined. Metergoline was injected 180 minutes prior to testing. DOM and quipazine were administered immediately prior to the start of the FR-40 session.

*Statistical Analysis*

Drug effects were determined by comparing the data from test days to the average of the three days prior to the test. Student's *t*-tests for paired data were used to evaluate the effects of individual doses of the agents used. Dose-response relationships were examined by analysis of variance. In all statistical evaluations $p<0.05$ was used as the criterion for significance.

*Drugs*

DOM hydrochloride was obtained from NIDA; quipazine hydrochloride was obtained from Miles Laboratories (Elkhart, IN). Doses of these agents refer to the salts dissolved in saline. Metergoline was received as a gift from Farmitalia Labs (Milan, Italy); doses of this agent refer to the free base suspended in a 0.5% corn starch solution.

## RESULTS

Control FR-40 responding is characterized by a rapid, constant rate of responding with brief pauses throughout the session. These pauses usually, but not always, follow the delivery of a food pellet. Metergoline pretreatment alone slightly increased response rates and decreased pausing at both the 0.1 mg/kg and the 1.0 mg/kg doses. These effects are indicated in Table 1. The hallucinogen DOM produced a dose-dependent disruption of FR-40 responding characterized by periods of non-responding (Fig. 1). Quipazine also produced a dose-dependent increase in pause intervals (Fig. 2). Pretreatment with 1.0 mg/kg metergoline significantly antagonized the pause-producing effects of DOM (Fig. 1) and quipazine (Fig. 2), although the effects of this metergoline pretreatment could be overcome by increasing the doses of these agents. The lower dose of metergoline (0.1 mg/kg), although effective, did not produce as great an antagonism of

TABLE 1

EFFECTS OF METERGOLINE ON FR-40 OPERANT RESPONDING

| Treatment | Pause Intervals | Reinforcements |
|---|---|---|
| Control | 47 ± 4 | 116 ± 7 |
| 0.1 mg/kg Metergoline | 32 ± 6* | 129 ± 7* |
| | (68) | (111) |
| 1.0 mg/kg Metergoline | 28 ± 5* | 126 ± 7* |
| | (60) | (108) |

Values represent mean ± S.E.M. for 8 subjects. Metergoline was administered 180 min prior to the start of the operant session. Numbers in parentheses represent the effects of metergoline treatment expressed as a percent of control values.

*$p<0.05$, Student's *t*-test for paired values. Reinforcement data was normalized by square root transformation prior to statistical analysis.

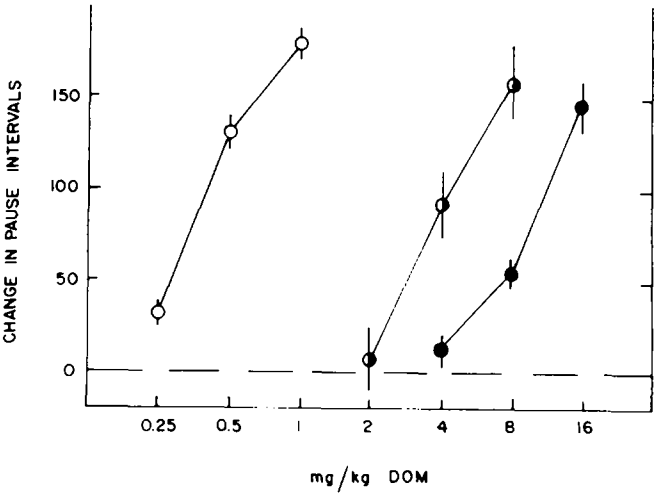


FIG. 1. Antagonism of the effects of DOM by metergoline. The change in pause intervals produced by various doses of DOM alone (open symbols) or in combination with 0.1 mg/kg (half-filled symbols) or 1.0 mg/kg (filled symbols) metergoline (180 min pretreatment) are shown. One pause interval represents a ten-second interval without a response. Change in pause intervals was determined comparing the data obtained on the test day with scores of the 3 prior days (baseline). Each symbol and vertical bar represent the mean ± SEM obtained from 5–9 animals. One mg/kg, and to a lesser extent 0.1 mg/kg, metergoline produced a significant shift to the right in the dose-response curve for DOM ($p<0.05$, factorial analysis of variance).

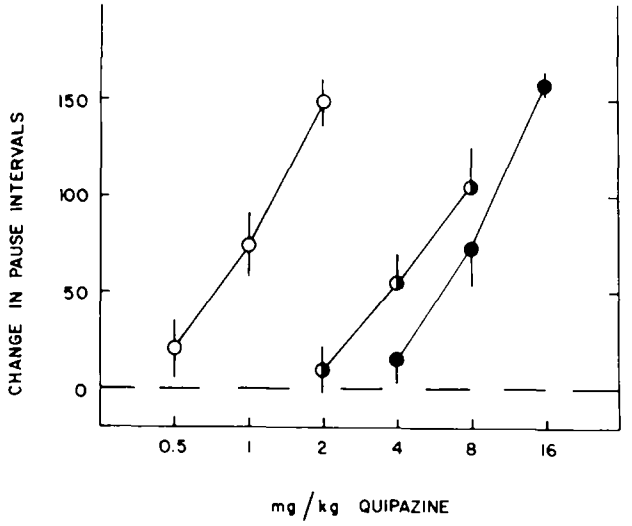


FIG. 2. Antagonism of the effects of quipazine by metergoline. The change in pause intervals produced by various doses of quipazine alone (open symbols) or incombination with 1.0 mg/kg (filled symbols) or 0.1 mg/kg (half-filled symbols) metergoline (180 min pretreatment) are shown. Each symbol and vertical bar indicate the mean ± SEM obtained from 5–9 animals. One mg/kg, and to a lesser extent 0.1 mg/kg, metergoline produced a significant shift to the right in the dose-response curve for quipazine.

the pause-producing effects of DOM and quipazine as the 1.0 mg/kg dose.

## DISCUSSION

The production of "pausing" by quipazine in the FR-40 operant paradigm was quantified and found to be similar to the pausing produced by the hallucinogen DOM. These periods of non-responding by quipazine and DOM differ from the pattern of FR-40 disruption produced by the stimulant *d*-amphetamine, the depressant phenobarbital and the neuroleptic chlorpromazine, with which erratic and slowed response rates without clear-cut pausing (at least at the lower dose range) are generally observed ([4–6] and Commissaris *et al.*, unpublished). It has been proposed that quipazine produces many of its behavioral effects through activation of 5-HT receptors in the brain [11,17]. These data suggest that the pause-producing effects of the hallucinogens may be mediated through the activation of 5-HT receptors in the brain. The capacity of metergoline administration alone to significantly decrease the slight degree of pausing in control FR-40 sessions further supports the contention that this pausing produced by the hallucinogens and quipazine is the result of 5-HT receptor activation, although other interpretations may apply.

The 1.0 mg/kg metergoline dose produced a greater than 16-fold shift in the dose-response pattern for the FR-40 disruptive effects produced by DOM. This antagonism by metergoline of the effects of DOM and quipazine appears to be competitive in nature, since the 0.1 mg/kg dose provides less protection against the disruptive effects of these agents and increases in the DOM and quipazine doses completely reverse the blockade.

We have previously reported differences between the indolealkylamine and phenethylamine hallucinogen classes in the antagonism of their FR-40 disruptive effects by metergoline [5]. The blocker in a dose of 1.0 mg/kg shifts the dose-response of LSD and DMT to the right about 2 fold, whereas the DOM and mescaline dose-response patterns were shifted by a factor of at least 8-fold (confirming in part the present results). Thus, in terms of its antagonism by metergoline, quipazine appears to resemble the phenethylamine hallucinogens rather than the indoles.

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