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Dopaminergic Activity of Quipazine

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SCHECHTER, M. D. AND J. T. CONCANNON. *Dopaminergic activity of quipazine*. PHARMAC. BIOCHEM. BEHAV. 17(3) 393–397, 1982.—Rats were trained to discriminate between the stimulus properties of intraperitoneal 0.16 mg/kg apomorphine and saline in a two-lever, food-motivated operant task. Administration of 1.0 mg/kg quipazine, a putative serotonin agonist, produced apomorphine-appropriate responding with a maximal effect occurring at 45 min post-injection. Pretreatment with either 2.0 mg/kg methysergide or 0.4 mg/kg haloperidol reduced quipazine-induced responding upon the apomorphine-appropriate lever to levels observed with methysergide or haloperidol administered alone. These results evidence a dopaminergic action for quipazine and suggest that central serotonergic and dopaminergic pathways may interact cooperatively to control behavior.

Drug discrimination Dopamine Apomorphine Serotonin Quipazine Methysergide Haloperidol

THE corpus striatum and substantia nigra are innervated by serotonergic neurons and both serotonin (5HT) and its synthesizing enzyme tryptophan hydroxylase have been found there [6, 7, 11]. The physiological role of these projections is still not clear, although it has been proposed that the serotonergic systems influence the function of the nigrostriatal pathway by producing an opposing, tonic effect upon central dopaminergic systems. Thus, pretreatment with the serotonin receptor antagonist methysergide has been reported to potentiate, whereas pretreatment with either of the 5HT precursors L-tryptophan or 5-hydroxytryptophan was found to antagonize amphetamine- and apomorphine-induced stereotypy in animals [1,22]. Furthermore, pretreatment with para-chlorophenylalanine, a specific depletor of brain 5HT, was found to potentiate amphetamine-induced stereotypy in rats [14].

However, not all reports are consistent with the notion of a reciprocal dopamine-serotonin function in the striatum. For example, lesions of the serotonergic raphé nuclei have been reported to reduce the stereotyped effects of dopaminergic agonists in rats [5] and pretreatment of rats with para-chlorophenylalanine has been reported to antagonize amphetamine-induced stereotypy [19]. These data suggest a facilitory influence of serotonergic systems upon central dopaminergic systems.

Numerous reports have indicated that apomorphine is capable of producing a discriminative stimulus complex in rats [3,18] and it appears that the action underlying the ability of apomorphine to produce discriminative control of rat behavioral responding is consistent with its dopamine-mimicking activity at dopamine receptors. Thus, discriminative control by apomorphine joins other behavioral paradigms that have been employed to access the dopaminergic activity of drugs, such as apomorphine-induced stereotypy [10] and rotational behavior in rats with unilateral 6-hydroxydopamine lesions in the substantia nigra [21]. The initial aim of the present study was to investigate the influence of the serotonergic agonist, quipazine, and the serotonergic antagonist, methysergide, upon on-going dopaminergically-mediated apomorphine discrimination.

GENERAL METHOD

The subjects were 5 experimentally-naive male Sprague-Dawley (Charles River) rats weighing 380±15 g at the beginning of experimentation. They were housed in individual living cages and their weights were adjusted (by daily rationing of rat chow) to approximately 85±5% of their free feeding values as determined by daily weighing of a control free-feeding rat. Water was continuously available.

The experimental space was a standard rodent Skinner box (Lafayette Instrument Co.) equipped with 2 operant manipulanda (levers) placed 7 cm apart and 7 cm above the grid floor. A food pellet receptacle was mounted 2 cm above the grid floor at an equal distance between the levers. The test cage was housed in a sound-attenuating cubicle equipped with an exhaust fan and house light. Solid-state programming equipment (LVB Corp.) was used to control and record the sessions and was located in an adjacent room.

The procedure used to train rats to discriminate between apomorphine and saline has been detailed elsewhere [3,18]. Daily discrimination training started after initial shaping to lever press on both levers on a FR10 schedule of food reinforcement. Thirty min prior to placement into the test chamber, the rats were injected intraperitoneally (IP) with either freshly prepared 0.16 mg/kg apomorphine hydrobromide (as base) or an equal volume (1 ml/kg) of saline. Depending on whether the rat was administered apomorphine or saline, it obtained reinforcement by pressing either the apomorphine lever (AL) or the saline level (SL), respectively. After every tenth press (FR10) on the appropriate lever, a 45 mg Noyes pellet was delivered through the food receptacle. Responses on the incorrect lever (i.e., on the SL after apomorphine administration or on the AL after saline

TABLE 1

APOMORPHINE DOSE-RESPONSE AND THE EFFECT OF QUIPAZINE AND METHYSERGIDE UPON APOMORPHINE DISCRIMINATION

Pretreatment (Dose; mg/kg)	Treatment* (Dose; mg/kg)	% Apomorphine-Lever Selections
	Apomorphine (0.16)	90.5
	Saline	4.8
	Apomorphine (0.24)	95.0
	(0.08)	50.0
	(0.04)	30.0
Methysergide (1.0)	Saline	0.0
Methysergide (1.0)	Apomorphine (0.16)	80.0
Methysergide (1.0)	Apomorphine (0.08)	60.0
Quipazine (1.0)	Saline	80.0†
Quipazine (1.0)	Apomorphine (0.16)	100.0
Quipazine (1.0)	Apomorphine (0.08)	70.0
Saline	Apomorphine (0.08)	50.0

*Treatments followed pretreament administrations by 15 min and preceded testing by 30 min in all cases.

†Not significantly different from % Apomorphine-lever selection after administration of Apomorphine training dose; χ^2 test.

administration) were recorded but produced no programmed consequence.

Every week, each rat was run once a day for 5 consecutive days in a session of 15 min duration. Daily apomorphine (A) and saline (S) injections were given according to a 2 weekly-alternating sequence: A-S-S-A-A and S-A-A-S-S. The number of responses made on either of both levers before obtaining the first food pellet (and, thus, before having made 10 correct responses) was recorded after each session and the lever pressed 10 times first was designated the selected lever. The training criterion was reached when the animal selected the appropriate lever, according to the drug state imposed, on 8 of 10 consecutive sessions.

EXPERIMENT 1: APOMORPHINE DOSE-RESPONSE AND INTERACTION WITH SEROTONERGIC DRUGS

METHOD

Once all rats attained the training criterion, testing and maintenance sessions of 15 min duration, with alternating administrations of freshly prepared 0.16 mg/kg apomorphine and saline, were continued on Mondays, Wednesdays and Fridays. This procedure was used to insure and maintain behavioral discrimination to the trained drug conditions and it was intended that if a rat was observed to fall below the criterion of 8 out of 10 consecutive correct lever selections on these maintenance sessions, the data on that rat's performance would be deleted from the results.

On Tuesdays and Thursdays, the well-trained rats were injected with various doses of apomorphine, i.e., 0.04, 0.08 and 0.24 mg/kg IP in a volume (1 ml/kg) identical to that used for initial discrimination training. Each dose was tested 30 min post-injection in a random order on 2 occasions with each session preceded by both an apomorphine and a saline maintenance session. Upon making 10 responses on either lever with the doses of apomorphine different from the training dose, the rat was immediately removed from the test chamber without receiving reinforcement. This dose-response procedure generated an ED50 of apomorphine.

Subsequently, test sessions were conducted after pretreatment with quipazine or methysergide 15 min prior to administration of either saline, the training dose, or the ED50 of apomorphine. As before, all test administrations were randomized and preceded by one apomorphine and one saline maintenance session. The rats were removed immediately after 10 responses on either lever were made.

RESULTS

The 5 rats required a mean of 20 sessions with each of 0.16 mg/kg apomorphine and saline to attain criterion training performance. Subsequently, the dose-response trials indicated that decreasing doses of apomorphine produced decreased number of first choice selections upon the apomorphine-correct lever and the ED50 was observed to be 0.08 mg/kg (Table 1). Pretreatment with a 1.0 mg/kg dose of methysergide, previously reported to antagonize LSD-appropriate discrimination responding [12], was observed to have little or no effect on the discrimination of saline or the two doses of apomorphine. In contrast, the 1.0 mg/kg dose of quipazine produced 80% apomorphine-appropriate responding when administered prior to saline and this pretreatment elevated the percent of apomorphine-correct responses after administration of both the ED50 and training dose of apomorphine.

EXPERIMENT 2: DOSE-RESPONSE AND TIME-COURSE OF QUIPAZINE IN APOMORPHINE-TRAINED RATS

Since quipazine produced apomorphine-appropriate responding, experiments were designed to determine the dose-effect and time-course nature of the quipazine-induced

apomorphine-like interoceptive cue. Experiment 2 immediately followed Experiment 1 without interspersing any drug-free days.

METHOD

Maintenance sessions with 0.16 mg/kg apomorphine and saline continued on Mondays, Wednesdays and Fridays. On Tuesdays and Thursdays, the rats were injected with one of four doses of quipazine, 0.5, 1.0, 2.0 and 4.0 mg/kg (IP), and 45 min later were placed into the test chamber. Once either lever was pressed 10 times, the rat was removed without receiving reinforcement. Each dose was tested on two occasions, in a random order, preceded by one apomorphine and one saline maintenance session.

Once the most effective quipazine dose was determined, this dose (1.0 mg/kg) was administered and testing (as above) was conducted at various times, i.e., 15, 30, 45, 60 and 90 min, post administration.

RESULTS

Criterion responding in all rats to the training dose of apomorphine and saline was maintained throughout these experiments. Administration of the 0.5 and 2.0 mg/kg doses of quipazine produced intermediate results, whereas 1.0 mg/kg elicited 70% of first lever selections on the apomorphine-correct lever (Table 2A).

When 1.0 mg/kg quipazine was tested at various times post-administration, the peak effect for producing apomorphine-appropriate lever selection occurred at 45 min post-injection (Table 2B).

TABLE 2

DOSE-RESPONSE (A) AND TIME-COURSE OF ACTION (B) OF QUIPAZINE IN APOMORPHINE-TRAINED RATS

		% Apomorphine-Lever Selection
A.	Quipazine Dose (mg/kg) at 45 min post-administration	
	0.5	40.0
	1.0	70.0
	2.0	50.0
	4.0	33.3*
B.	Time after 1.0 mg/kg Quipazine administration (min)	
	15	0.0
	30	10.0
	45	80.0
	60	40.0
	90	40.0

*Behavioral disruption observed where only 6 of 10 tests conducted resulted in any responding.

EXPERIMENT 3: EFFECT OF HALOPERIDOL AND METHYSERGIDE UPON QUIPAZINE-INDUCED APOMORPHINE RESPONDING

Given the results of Experiment 2, indicating that 1.0 mg/kg quipazine tested at 45 min post-administration produced 80% apomorphine-appropriate responding, this series of experiments was designed to determine whether pretreatment with the dopaminergic antagonist haloperidol or with the serotonergic antagonist methysergide could affect the quipazine-induced apomorphine responding. The initial dose of haloperidol chosen, i.e., 0.02 mg/kg, has been reported to effectively block apomorphine discrimination [3] and the 1.0 mg/kg dose of methysergide has been shown to block LSD discrimination [12].

METHOD

Maintenance and testing sessions were conducted as in Experiment 2. On test days, haloperidol (0.02 or 0.04 mg/kg) was administered, on 2 occasions each, 15 min prior to saline, the training dose of apomorphine, or the 1.0 mg/kg dose of quipazine. Testing of saline and apomorphine took place 30 min post-administration, whereas quipazine was tested 45 min after its administration. Likewise, pretreatment with saline and 2 doses of methysergide occurred 15 min prior to quipazine or saline administration and testing was conducted 45 min after the second injection.

RESULTS

Haloperidol, at doses of 0.02 and 0.04 mg/kg, had little effect upon saline discrimination but the lower dose reduced apomorphine-lever selection after 0.16 mg/kg apomorphine administration to 10% (Table 3A). The administration of this dose of haloperidol prior to quipazine produced 6 of 10 first choice selections on the apomorphine-correct lever, whereas pretreatment with 0.04 mg/kg haloperidol reduced quipazine responding to 10%. During the testing of methysergide pretreatments one of the five rats did not attain criterion performance and the data on that animal do not appear in Table 3B. Saline administered prior to quipazine produced 87.5% apomorphine lever selections, whereas pretreatment with 1.0 or 2.0 mg/kg methysergide reduced apomorphine-lever selection after 1.0 mg/kg quipazine administration to 50% and 12.5%, respectively, without affecting saline discrimination.

GENERAL DISCUSSION

The results of the present experimentation indicate that quipazine can produce apomorphine-appropriate responding in rats trained to discriminate the interoceptive cue produced by 0.16 mg/kg apomorphine. Quipazine has been reported to act primarily as a serotonin agonist in the central nervous system [16]. These central serotonin-like actions of quipazine were abolished by the antiserotonergic drugs, cyproheptadine, cinancerin [16] and methysergide [8]. In addition, quipazine may also be a dopamine agonist as indicated by its ability to induce stereotyped behavior and to antagonize the catalepsy produced by dopamine receptor blockers in rats [8]. Furthermore, biochemical evidence indicates that quipazine elevates striatal dopamine at a time (30 min post-injection) when decreasing brain serotonin levels and peak behavioral effects are observed [15].

Quipazine has previously been shown to acquire and maintain control of choice responding in a drug-discrimination paradigm [23–26]. The interoceptive cue produced by quipazine was reported to transfer to (150 μg/kg) LSD [25], but not transfer significantly to (1.0 mg/kg)

TABLE 3

EFFECT OF PRETREATMENT WITH HALOPERIDOL AND METHYSERGIDE UPON QUIPAZINE-INDUCED APOMORPHINE RESPONDING

	Pre-treatment (Dose; mg/kg)	Treatment (Dose; mg/kg)	% Apomorphine-Lever Selection
A.	Haloperidol (0.02)	Saline	10.0
	Haloperidol (0.04)	Saline	10.0
	Haloperidol (0.02)	Apomorphine (0.16)	10.0
	Haloperidol (0.02)	Quipazine (1.0)	60.0
	Haloperidol (0.04)	Quipazine (1.0)	10.0
B.	Methysergide (1.0)	Saline	12.5
	Methysergide (2.0)	Saline	12.5
	Saline	Quipazine (1.0)	87.5*
	Methysergide (1.0)	Quipazine (1.0)	50.0
	Methysergide (2.0)	Quipazine (1.0)	12.5

*No significant difference from % Apomorphine-lever selection after administration of 0.16 mg/kg Apomorphine dose, χ^2 test.

apomorphine [23] and to be significantly reduced by pretreatment with (1 mg/kg) methysergide [23] but not after pretreatment with (0.05 mg/kg) haloperidol [24]. These studies employed larger apomorphine doses that may confound direct comparisons. However, the authors suggest the serotonergic mediation of the quipazine-produced interoceptive cue. The present study, employing rats trained to discriminate dopaminergically-mediated interoceptive cues produced by a low apomorphine dose, suggests that there may be an asymmetrical transfer between quipazine and apomorphine, i.e., quipazine trained rats will transfer to the effects of a large apomorphine dose only partially (37%; [23]) but rats trained to a lower apomorphine dose will transfer more completely (87.5%, this study) to quipazine. This asymmetrical generalization of discriminative stimulus properties has previously been reported to occur between fentanyl and apomorphine [2].

The transfer of apomorphine discrimination to quipazine at 45 min post-administration closely parallels the time course of quipazine-induced head twitches [14], hypermotility [9], and antinociception [17]. More pertinent is the report that at 30 min post-injection, quipazine causes a 23% increase in dopamine content in rat striata [15]. A close functional relationship has been reported to exist between serotonin and dopamine in this brain area [5] and quipazine has been observed to increase apomorphine-induced turning behavior in rats [20] suggesting cooperative serotonin-dopaminergic functioning.

The present observation that methysergide blocks quipazine effects confirms previous evidence [8]. However, the ability of haloperidol to block quipazine suggests that quipazine may have direct dopaminergic activity as has previously been suggested [8]. Quipazine given to rats in which a hyperkinetic syndrome had been produced by administration of $\beta\beta'$-iminodipropionitrile exacerbated their hyperactive behavior. This effect was antagonized by both methysergide and haloperidol suggesting a functional dependence of 5HT pathways on intact dopamine neurons [13]. The present study suggests that rather than being mutually antagonistic, central serotonergic and dopaminergic pathways may, in fact, interact synergistically to control certain body movements and behaviors. The serotonergic raphé-striatal and dopaminergic nigro-striatal pathways may be the anatomical focus of this relationship [4].

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