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The Role of Dopamine in the Effects of Pentazocine and Tripelennamine[1,2]

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HUDZIK, T. J. AND B. L. SLIFER. *The role of dopamine in the effects of pentazocine and tripelennamine.* PHARMACOL BIOCHEM BEHAV **36**(3) 547–554, 1990.—CNS dopamine has been suggested as a mediator in the effects of many drugs of abuse. The present study was conducted to assess the potential dopaminergic activity of pentazocine and tripelennamine combinations (T's and Blues). The effects of pentazocine and tripelennamine, administered alone and in combination with several dopaminergic drugs, on milk drinking were assessed in the rat. Both the opioid and antihistamine were tested in combination with apomorphine and haloperidol. Pentazocine was also tested in combination with the D_1- and D_2-receptor selective antagonists SCH 23390 and raclopride, and with the D_2-receptor agonist quinpirole. Tripelennamine was additionally tested in combination with methamphetamine. Haloperidol and quinpirole pretreatment produced leftward shifts in the pentazocine dose-effect curve while raclopride and SCH 23390 shifted the opioid curve to the right. Doses of apomorphine shifted tripelennamine's dose-effect curve to the left, tripelennamine enhanced the effects of methamphetamine, but haloperidol did not alter the antihistamine's effects. These data suggest dopaminergic involvement in the effects of the opioid and antihistamine.

Pentazocine Tripelennamine Dopamine Milk drinking Rats Drug interactions Isobolographic analysis Apomorphine Methamphetamine Haloperidol SCH 23390 Raclopride Quinpirole

ABUSE of combinations of the antihistamine tripelennamine and the opioid pentazocine presented a significant public health problem in the latter 1970's and early 1980's (21). The interaction between these two agents results in a euphoriant effect that is not obtainable by use of either drug alone (22). This interaction may be the result of the antihistamine directly increasing the euphoriant effects of the opioid or by attenuating the dysphoric effects of high doses of the opioid (29,30). Overcoming the low abuse potential of pentazocine or other opioids by combination with other agents presents a problem for the health care community because of the potential for increased toxicity as well as complications involved in intravenous drug use.

Pentazocine is a mixed agonist/antagonist benzomorphan opioid which has complex properties. It shares discriminative stimulus effects with the opioid mu agonist morphine and produces partial generalization from the sigma agonist n-allylnormetazocine and the dissociative anesthetic phencyclidine (38). The benzomorphan has affinity for the mu and kappa receptors as well as for the sigma binding site (25, 35, 36). Some of its activity is thought to be mu-mediated because of its naltrexone-reversible morphine-like stimulus properties (38) and respiratory depression associated with its administration (18). The psychotomimetic or dysphoric effects of higher doses may be mediated by the kappa receptor or the sigma binding site (20,26).

There are several lines of evidence for dopaminergic involvement in the effects of pentazocine. The opioid produces release of dopamine from in vitro synaptosomal preparations (6). Pentazocine administration to rats with unilateral lesions of the dopamine-containing cell bodies of substantia nigra results in ipsilateral rotational behavior (7), an effect thought to be attributable to dopaminergic release from neurons of the intact, unlesioned side. Haloperidol attenuation of the analgesic (15) and discriminative stimulus effects (1) of pentazocine has also been reported, providing further evidence for dopaminergic involvement in the effects of the opioid.

In addition to its reported sedative effects (9), tripelennamine produces a profile of behavioral effects which resembles that of agents which facilitate dopamine transmission such as CNS stimulants. The antihistamine shares discriminative stimulus effects with d-amphetamine (12) and with cocaine (39). Tripelennamine is self-administered by squirrel monkeys at levels comparable to that of cocaine (4), and increases response rates in squirrel monkeys responding under fixed-interval schedules of either food presentation or stimulus-shock avoidance (3, 4, 24).

Activity in central dopamine-containing neurons has been repeatedly implicated in the neurophysiology of substance abuse

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(32). It is possible that if pentazocine and tripelennamine each interact with this neurotransmitter system, then perhaps the enhanced reinforcing efficacy of the drug combination may be mediated by this system.

One method of collecting information regarding CNS activity of an agent is through analysis of the interaction of the agent with other drugs with known activity in the neurotransmitter system of interest. Isobolographic analysis provides a useful means of interpretation of drug interactions (23,41). There are several advantages to the isobolographic approach to drug interactions. It allows for a quantitative description of the interaction of agents, particularly as applied to leftward shifts in the dose-effect curves of one agent after combination with a range of doses of a second drug. Additionally, isobolograms are particularly useful when two agents studied in combination have similar effects (drugs which are homergic). The nature of the observed interactions provides evidence for hypothesized mechanisms of action of two agents (2).

The purpose of the present study was to provide further evidence for dopaminergic mediation of the effects of pentazocine and tripelennamine, which would in turn implicate the neurotransmitter system as a possible site of interaction between the two agents. The effects of either drug alone and in combination with several dopamine agonists and antagonists were studied using drinking behavior in the rat as a baseline. Data were interpreted in terms of relative potency estimates and, where applicable, isobolographic analyses were applied to results.

METHOD

Animals

The subjects were 23 experimentally naive male Sprague-Dawley rats (300–355 g), which were individually housed and tested in standard stainless steel rodent cages. Animals were maintained at 80–85% of ad lib feeding weights by postsession feedings of Purina Rodent Chow. Tap water was available at all times except during test sessions. Animals were housed in the Department of Psychology animal colony which was illuminated from 7 a.m. to 7 p.m. The rats were divided into two groups of 13 and 10 animals.

Procedure

Sessions were conducted seven days per week at 11 a.m. Each week included at least two control sessions (no injections or vehicle injections) and two experimental sessions. During experimental sessions the rats were allowed to drink from graduated drinking tubes containing a solution of Borden's sweetened condensed milk and water (a 1:2 ratio). The daily sessions consisted of a total of 4 discrete periods of access to the solution each 3 min long, followed by a 13-min time-out during which the tubes were removed and milk intake recorded. Intraperitoneal drug or vehicle injections were administered during time-outs, 10 min prior to the next drinking period (see exceptions below), resulting in cumulative dosing within a session.

When intake stabilized (varied by less than 10% on 3 consecutive days) cumulative dose-effect functions were determined. Group one received injections of pentazocine (1–30 mg/kg), tripelennamine (3–17 mg/kg), apomorphine (0.03–1 mg/kg), haloperidol (0.1–1 mg/kg), SCH 23390 (0.03–1 mg/kg), raclopride (0.1–3 mg/kg) and quinpirole (0.01–0.3 mg/kg). A time-effect function for apomorphine was conducted by administering a single dose of the drug (0.3 mg/kg) and measuring intake 10, 26, 42 and 58 min after the injection. The effects of a single dose of haloperidol (0.1 mg/kg) in combination with a range of cumulative doses of apomorphine (0.03–1 mg/kg) were assessed. Dose-effect functions for pentazocine and tripelennamine were then redetermined in the presence of fixed doses of haloperidol (0.1 and 0.3 mg/kg) and of apomorphine (0.03 and 0.1 mg/kg). The opioid was further tested in combination with fixed doses of SCH 23390 (0.03 and 0.1 mg/kg) and raclopride (0.1 and 0.3 mg/kg). The pentazocine dose-effect curve was redetermined after these assessments in order to determine if tolerance to the effects of the opioid was present. The effect of quinpirole (0.03 mg/kg) on the pentazocine dose-effect function was determined. Subject attrition prevented testing of a second dose of quinpirole. In the second group (N = 10), the effects of tripelennamine (1 and 3 mg/kg) on a methamphetamine dose-effect curve (0.1–3 mg/kg) were determined.

An IP injection of drug or vehicle preceded each 3-min milk exposure by 10 min, with the exception of the dopamine antagonists (30 min). The necessity of a longer pretreatment for haloperidol, raclopride and SCH 23390, than the time-out interval allowed, limited the cumulative doses to two doses per session for these drugs. Because of its short duration of action, the dose-effect functions with apomorphine included only two cumulative doses of drug as well. When drug combinations were tested, two independent injections were administered into opposite sides of the peritoneal cavity. Vehicle control sessions were conducted one or two days prior to test sessions and had identical injection and pretreatment parameters as the following test sessions.

Drugs

Apomorphine hydrochloride (Sigma Chemical, St. Louis, MO) was prepared prior to each use in distilled water. Tripelennamine hydrochloride (a gift from Ciba-Geigy, Summit, NJ), methamphetamine hydrochloride (National Institutes on Drug Abuse, Rockville, MD), raclopride tartrate (donated by Astra-ALAB, Sodertalje, Sweden) and quinpirole (a gift from Eli Lilly, Indianapolis, IN) were dissolved in sterile saline. SCH 23390 maleate (a gift from Schering Corp., Bloomfield, NJ), haloperidol (Sigma) and pentazocine hydrochloride (donated by Sterling Winthrop, Rensselaer, NY) were dissolved in a solution of 8.5% lactic acid (2 parts) and 1 N NaOH (3 parts), pH titrated to 6.5–7.0. Dosages are expressed in terms of the weights of the forms of the drugs listed.

Data Analysis

Milk intake per 3-min exposure was converted to ml/kg body weight for individual animals and averaged across animals. Drug effects are expressed as percent of intake under the previous vehicle condition. The ED_{50}, ED_{16} (the doses estimated to reduce intake by 50% and 16%, respectively, relative to control) and corresponding 95% confidence limits were determined by least squares regression of the linear portions of the curves. The log of the ratio of the potency of a drug combination to the potency of a drug alone was used as a measure of the magnitude of the dose-effect curve shifts.

Isobolograms were employed in analyses of leftward shifts in dose-effect functions. Estimated ED_{50}'s of agents alone were plotted on isobolograms (23) and connected with a line, forming the dose-additivity region. The calculated ED_{50}'s and 95% confidence limits of one agent in the presence of the second drug were then plotted. Intersection of 95% confidence limits of ED_{50}'s with the additivity line represents additive interactions. Points

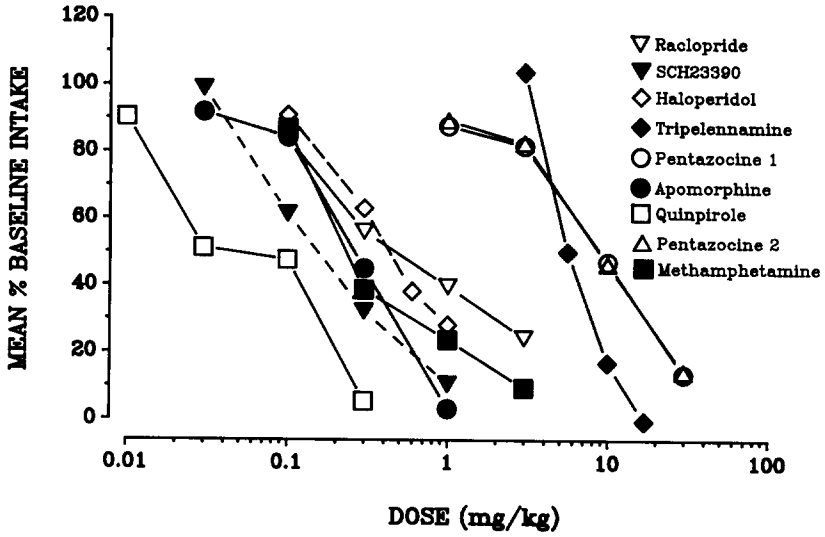

FIG. 1. Cumulative dose-effect functions for each of the agents tested. Data are presented as mean % baseline ml/kg intake (error bars omitted for clarity). Means are based upon data from 13 animals.

falling below the additivity line are denoted supra-additive, which indicates that the shifts in the dose-effect curves are greater than would be predicted by dose-additivity. The ED_{50}'s which remain above the additivity line denote infra-additive shifts, which indicates that dose-effect curve shifts are less than would be predicted by additivity.

RESULTS

Milk intake stabilized within 12 sessions and remained stable throughout the following 14 weeks. Control intake following saline or vehicle administrations ranged throughout the experiment from 23.7 (±0.8) ml/kg to 25.4 (±1.9) ml/kg. During sessions in which no injections were administered prior to exposures, intake ranged from 22 (±1.3) ml/kg to 26.6 (±0.6) ml/kg.

Dose-effect curves for each of the agents tested alone are shown in Fig. 1. The ED_{50}'s, ED_{16}'s and 95% confidence limits for these curves and for drug interaction curves are shown in Table 1. All drugs produced dose-dependent, monotonic decreases in ml/kg intake relative to control, with the following rank order of potency: SCH 23390 > apomorphine > methamphetamine > haloperidol > raclopride >> tripelennamine > pentazocine. The possibility that tolerance to the effects of pentazocine may have contributed to the observed effects on the opioid curve was investigated. Redetermination of the pentazocine dose-effect function near to the conclusion of the study indicated that tolerance was not a factor. Combination of 0.1 mg/kg haloperidol with cumulative doses of apomorphine resulted in a rightward shift in the apomorphine dose-effect curve, increasing the ED_{50} of apomorphine from 0.26 to 0.53 mg/kg (Table 1). The corresponding ED_{16}'s shifted by a comparable amount.

Apomorphine's predictably short duration of action was demonstrated in the present assay. The effect of 0.3 mg/kg apomorphine was stable at 10 and 26 min after injection, where intake averaged 10.2 (±1.3 S.E.M.) and 11 (±1.5) ml/kg, respectively. However, at 42 min postinjection, mean intake increased to 16.3 (±1.9) ml/kg and finally reached 22 (±0.71) ml/kg 58 min postinjection. Intake at 58 min was not different from baseline intake.

When combined with tripelennamine, apomorphine (0.1 mg/kg) shifted the antihistamine dose-effect curve to the left (Fig. 2) while the lower dose of the dopamine agonist (0.03 mg/kg) was ineffective in altering the tripelennamine dose-effect function. These interactions were isobolographically defined as infra-additive (Fig. 2, inset).

Haloperidol did not alter the ED_{50} of tripelennamine (Table 2). Casual observation of rats treated with higher tripelennamine doses (>10 mg/kg) revealed stereotyped, repetitive motor behaviors such as "head weaving" and gnawing which resembled those which are characteristically noted at higher CNS stimulant doses (11). Although not quantified in the present study, haloperidol did not appear to noticeably affect these antihistamine-induced behaviors.

Tripelennamine (1 and 3 mg/kg) produced dose-dependent shifts to the left in the methamphetamine dose-effect curve (Fig.

TABLE 1

POTENCY ESTIMATES AND 95% CONFIDENCE LIMITS OF THE AGENTS TESTED ON MILK INTAKE IN THE RAT, AND THE EFFECTS OF HALOPERIDOL ON THE APOMORPHINE DOSE-EFFECT FUNCTION

Test	Doses	ED_{50} (95% C.L.)	ED_{16} (95% C.L.)
Apomorphine	0.03–1 mg/kg	0.26 (0.24–0.29)	0.10 (0.09–0.11)
Haloperidol	0.1–3 mg/kg	0.44 (0.35–0.56)	0.13 (0.10–0.16)
Tripelennamine	1–17 mg/kg	6.36 (4.43–9.13)	3.53 (2.46–5.07)
Pentazocine	1–30 mg/kg	8.95 (7.29–10.9)	2.83 (2.31–3.48)
SCH 23390	0.03–1 mg/kg	0.18 (0.11–0.29)	0.05 (0.03–0.08)
Raclopride	0.1–3 mg/kg	0.58 (0.31–1.07)	0.08 (0.04–1.48)
Quinpirole	0.01–0.3 mg/kg	0.05 (0.016–0.17)	0.01 (0.003–0.04)
Haloperidol	Apomorphine		
0.1 mg/kg +	0.03–1 mg/kg	0.53 (0.007–36.9)	0.18 (0.003–12.4)

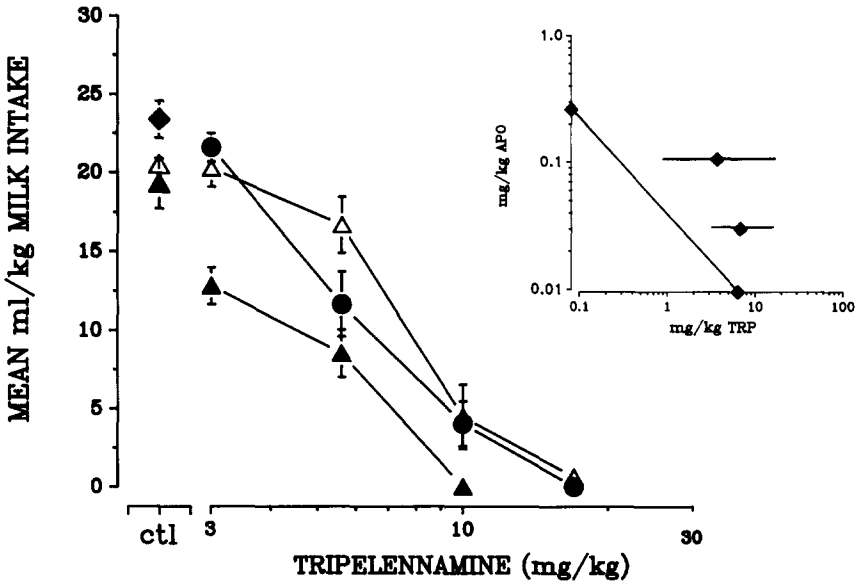

FIG. 2. Effects of tripelennamine alone and in combination with apomorphine (left figure) and isobolographic representation of the interaction (inset to right). CTL axis: filled diamond = saline control; effect of 0.03 (open triangle) and 0.1 mg/kg (filled triangle) apomorphine alone. X-axis: dose-effect function for tripelennamine alone (filled circles) and in combination with 0.03 (open triangle) and 0.1 mg/kg (filled triangle) apomorphine. Variability about the means is expressed as standard errors. Isobologram: ED_{50}'s and 95% confidence limits of tripelennamine (TRP) and apomorphine (APO) alone (connected by the diagonal line) and of tripelennamine when combined with apomorphine.

3). The lower dose of tripelennamine (1 mg/kg) produced a ¼ log shift to the left while 3 mg/kg tripelennamine produced a greater than ⅔ log shift to the left in the methamphetamine dose-effect curve (Table 2). Both of these interactions were isobolographically additive (Fig. 3, inset).

When pentazocine (1–30 mg/kg) was tested in combination with apomorphine (Table 3), the lower apomorphine dose (0.03 mg/kg) produced a 1/10 log-dose increase and the higher dose (0.1 mg/kg) a similar degree of decrease in the ED_{50} of pentazocine. Combination with haloperidol (Fig. 4), on the other hand, resulted in additive, dose-dependent shifts to the left in the pentazocine dose-effect function.

Pentazocine was subsequently tested in combination with SCH 23390 and raclopride (Table 3). SCH (0.03 mg/kg) was ineffective in altering the pentazocine dose-effect function while the higher dose (0.1 mg/kg) flattened it, resulting in a slight increase in the ED_{50} of pentazocine from 8.9 to 10.6 mg/kg. Combination of pentazocine with the higher dose of raclopride (0.3 mg/kg) also flattened the curve and produced a ½ log-unit shift to the right. This shift was great enough to necessitate an increment in the dose of pentazocine to 56 mg/kg in order to derive an ED_{50} from the curve.

A single dose of quinpirole (0.03 mg/kg) was administered in combination with pentazocine (1–30 mg/kg; Fig. 5).This quinpirole dose produced a 1.3 log-unit shift to the left in the ED_{50} of pentazocine and a 2 log-unit shift in the ED_{16} value (Table 3).

DISCUSSION

Agents with activity in the dopamine system modified the

TABLE 2

THE EFFECTS OF HALOPERIDOL AND APOMORPHINE ON THE PENTAZOCINE DOSE EFFECT FUNCTION

Test	ED_{50}	Log Shift	ED_{16}	Log Shift
Tripelennamine	6.36 (4.43–9.13)	—	3.53 (2.45–5.07)	—
+ Haloperidol 0.1	7.48 (6.64–8.44)	0.07	4.26 (3.78–4.81)	0.08
+ Haloperidol 0.3	6.59 (2.97–14.62)	0.015	3.54 (1.6–7.86)	0.001
+ Apomorphine 0.03	6.78 (4.32–10.66)	0.03	3.64 (2.32–5.72)	0.013
+ Apomorphine 0.1	3.72 (0.89–15.5)	−0.23	1.82 (0.44–7.55)	−0.29

Listed are potency estimates and 95% confidence limits. Log shift refers to the changes in the dose-effect curves relative to that of pentazocine alone.

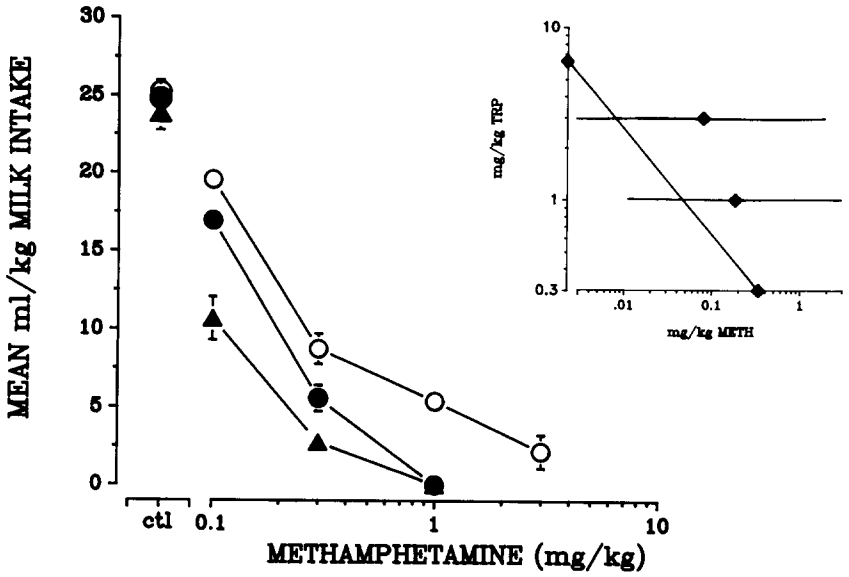

FIG. 3. Effects of methamphetamine alone and in combination with tripelennamine (left figure) and isobolographic representation of the interaction (inset to right). CTL axis: open circle = saline control; effect of 1 (filled circle) and 3 mg/kg (filled triangle) tripelennamine alone. X-axis: dose-effect function for methamphetamine alone (open circles) and in combination with 1 (filled circles) and 3 mg/kg tripelennamine (filled triangle). Isobologram: ED_{50}'s and 95% confidence limits of tripelennamine (TRP) and methamphetamine (METH) alone (connected by diagonal line) and of methamphetamine when combined with tripelennamine.

effects of both tripelennamine and pentazocine. Leftward shifts in dose-effect curves indicative of dose-additive interactions were noted after combinations of pentazocine and quinpirole, tripelennamine and methamphetamine, and haloperidol and pentazocine. The dopamine D_2 receptor blocker raclopride produced rightward shifts in the dose-effect curve for pentazocine. SCH 23390 also produced rightward shifts in the pentazocine dose-effect function, the degree of which was less than one-half that resulting from combination with raclopride. This may suggest that the dopaminergic involvement in the effects of pentazocine is more related to dopamine D_2 than D_1 activity. Consistent with this interpretation, the dopamine D_2 agonist quinpirole produced an additive shift in the pentazocine dose-effect curve while the nonselective dopamine agonist, apomorphine did not. These findings also concur with reports that dopamine blockers antagonize the effects of pentazocine upon shock detection in the rat (15) and partially antagonize its discriminative stimulus effects (1,39). Of the two types of dopamine receptors described in brain (34), the D_2 receptor is thought to be involved in the reinforcing effects of dopamine agonists (40). This observation also agrees with raclopride's

TABLE 3

THE EFFECTS OF APO MORPHINE, HALOPERIDOL, SCH 23390, RACLOPRIDE AND QUINPIROLE ON THE PENTAZOCINE DOSE-EFFECT FUNCTION

Test	ED_{50}	Log Shift	ED_{16}	Log Shift
Pentazocine	8.95 (7.29–10.99)	—	2.83 (2.31–3.48)	—
+ Apomorphine 0.03	11.6 (3.86–35.0)	0.11	3.05 (1.01–9.20)	0.03
+ Apomorphine 0.1	7.34 (2.31–23.3)	−0.09	1.51 (0.48–4.8)	−0.27
+ Haloperidol 0.1	1.53 (0.31–7.61)	−0.77	0.12 (0.024–0.61)	−1.37
+ Haloperidol 0.3	0.44 (0.03–7.11)	−1.31	0.04 (0.005–0.7)	−1.85
+ SCH 23390 0.03	8.43 (1.22–58.2)	−0.03	3.21 (0.46–22.18)	0.05
+ SCH 23390 0.1	10.76*	0.08	2.93*	0.015
+ Raclopride 0.1	11.67*	0.11	5.14*	0.26
+ Raclopride 0.3	26.46 (1.74–403)	0.47	7.86 (0.51–119.7)	0.44
+ Quinpirole 0.03	0.44 (0.005–35)	−1.3	0.034 (0.0004–2.7)	1.92
Pentazocine Redetermined	9.05 (8.37–9.79)	0.005	2.88 (2.66–3.11)	0.008

*Accurate confidence limits of potency estimates could not be determined due to the nonlinear shapes of the dose-effect curves.

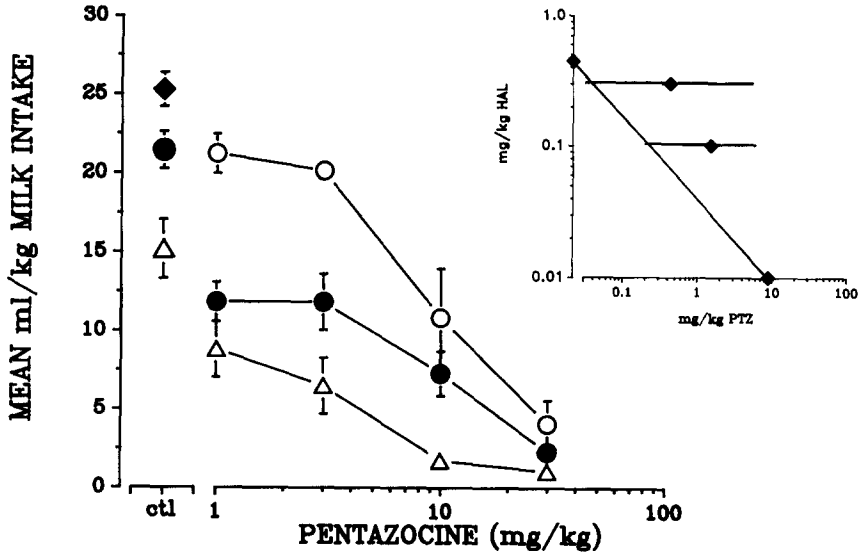

FIG. 4. The effects of haloperidol on the pentazocine dose-effect function. CTL axis: filled diamond = vehicle control; effect of 0.1 (filled circle) and 0.3 mg/kg (open triangle) haloperidol alone. X-axis: effects of cumulative doses of pentazocine alone (open circles) and in combination with 0.1 (filled circles) and 0.3 mg/kg (open triangles) haloperidol. Isobologram: ED_{50}'s and 95% C.L. of pentazocine (PTZ) in the presence of the two doses of haloperidol (HAL).

antagonism of pentazocine.

The additive effects of combinations of haloperidol with pentazocine on the present behavioral measure are more difficult to interpret in reference to the raclopride and SCH 23390 antagonism of the effects of pentazocine discussed above. Raclopride is thought to possess a greater degree of selectivity for the dopamine D_2 receptor than haloperidol (28). It is therefore possible that haloperidol's broader spectrum of activity may have contributed to its additive effects in combination with pentazocine. For example, both agents share a common, nondopaminergic binding site in brain, which has been termed the sigma site (35). Because haloperidol binds to this site with a higher affinity than pentazo-

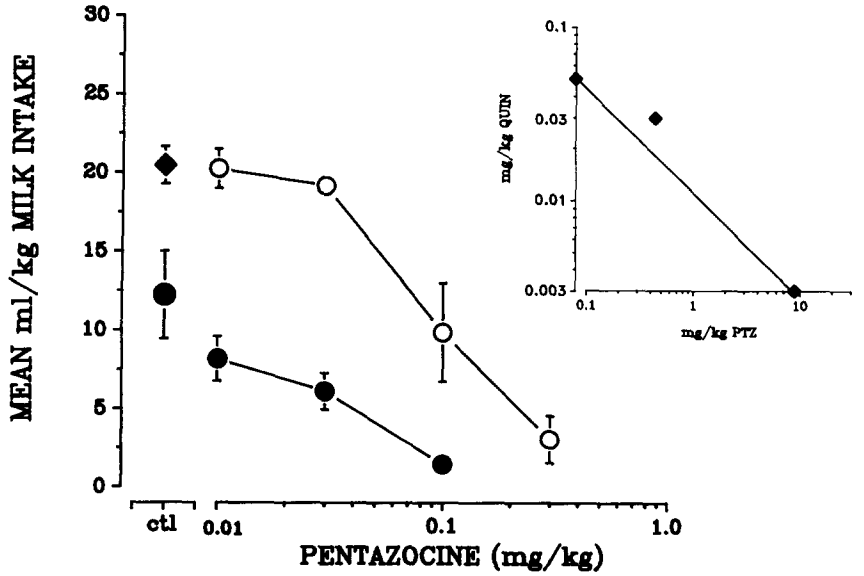

FIG. 5. The effect of quinpirole on the pentazocine dose-effect function. CTL axis: filled diamond = vehicle control; filled circle = effect of 0.03 mg/kg quinpirole alone. X-axis: the effects of pentazocine alone (open circles) and in combination with 0.03 mg/kg quinpirole (filled circles). Isobologram: ED_{50}'s and 95% C.L. of quinpirole (QUIN) and pentazocine (PTZ) alone and of pentazocine in combination with 0.03 mg/kg quinpirole. Due to the large size of the confidence limits about the potency estimate of pentazocine in combination with quinpirole, this measure of variability is excluded from the graph.

cine (33), it is possible that pretreatment with the dopamine antagonist allowed for greater pentazocine interaction with other binding sites (i.e., mu or kappa receptors). Given this type of interaction, the result would be the functional equivalent of administration of higher doses of pentazocine.

When tripelennamine was tested in combination with haloperidol, the dopamine antagonist did not significantly alter the effects of the H1 antagonist. This finding was somewhat surprising because haloperidol has been found to antagonize the response-rate increasing effects of antihistamines on operant fixed-interval responding in squirrel monkeys (4). However, both the species and procedures used between the two studies differ, which may have contributed to the differences in the findings. On the other hand, haloperidol has also been reported to attenuate the discriminative stimulus effects of tripelennamine in the rat (39). It may, however, be the case that the dopaminergic component of the tripelennamine discriminative stimulus is dissociable from its effects on response rate, since haloperidol did not antagonize the antihistamine's effects upon response-rate decreases in the latter study.

A moderate dose of apomorphine (0.1 mg/kg) enhanced the effects of tripelennamine. The degree of this leftward shift was small, and it was isobolographically defined as infra-additive. However, tripelennamine interacted with the indirect dopamine agonist methamphetamine in an additive manner. There are at least two possible reasons for the differences between the methamphetamine and apomorphine interactions with tripelennamine. First, methamphetamine has effects which include central release of norepinephrine and serotonin (27) while apomorphine may be only weakly active in these systems (5). It may therefore be that tripelennamine's effects on the drinking measure are mediated by effects in nondopaminergic systems. On the other hand, if tripelennamine acts by inhibition of dopamine reuptake (8), its differences in mechanism from that of apomorphine may have been sufficient to result in infra-additive as opposed to additive interactions. Consistent with this interpretation, Foltin and colleagues reported that d-amphetamine and cocaine (which are thought to be primarily a dopamine releaser and a reuptake inhibitor, respectively) produced infra-additive effects upon drinking behavior (14).

The drinking procedure used in the present study proved to be a stable and rapid method of assessing dose-effect relationships, particularly as applied to drug interactions. Cumulative administration of all agents tested in the present study produced orderly, dose-dependent decreases in milk intake. Drinking behavior may be as sensitive an index of drug effects as some operant behaviors. For many of the agents tested in the present study, potency to decrease milk intake and fixed-ratio response rates by 50% are very similar. For example, the ED_{50} of pentazocine to decrease intake in the present study is 8.8 mg/kg and is 12 mg/kg for fixed-ratio response rate decreases in rats trained to discriminate morphine from saline (17). However, the degree of sensitivity of the procedure may depend upon the drug class studied because both apomorphine and haloperidol were considerably less potent (¾ to 1 log-unit) in the present study than in operant assays in the rodent (10,37). The fact that the pentazocine dose-effect curve did not shift over the course of repeated dose-effect determinations lends further support to the suggestion of the assay's stability. A similar drinking procedure has been previously used in the evaluation of the interaction of haloperidol with d-amphetamine (13) and in the interaction of the psychomotor stimulants cocaine, l-cathinone and d-amphetamine (14). Isobolographic analysis was a useful tool in the present study and in those cited above for the interpretation of the effects of drug combinations. The analysis provides a useful description of shifts in dose-effect curves.

If dopaminergic mechanisms mediate the behavioral effects that result from combinations of pentazocine and tripelennamine, the mediation is likely indirect since clear antagonism of the effects of either drug by dopamine antagonists was not demonstrated. It is also likely that the drugs' potential effects upon dopamine systems are via different mechanisms because when combined (16), their effects on intake are not indicative of an interaction of two forms of the same substance (small, infra-additive shifts were observed). This could possibly explain the differential interaction of pentazocine and tripelennamine with the dopaminergically active agents.

In summary, the results of the present study suggest dopaminergic involvement in the effects of pentazocine and tripelennamine. Apomorphine and methamphetamine enhanced the effects of tripelennamine, and quinpirole enhanced those of pentazocine. Additionally, the D_2-antagonist raclopride attenuated the effects of pentazocine. The results do, however, indicate that dopamine is unlikely to be the only neurochemical system underlying the behavioral effects of combinations of pentazocine and tripelennamine.

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