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Metoclopramide Potentiates *d*-Amphetamine-Induced Hypermotility and Stereotypy in Rat

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HOWARD, J. L., G. T. POLLARD, R. M. CRAFT AND K. W. ROHRBACH. *Metoclopramide potentiates d-amphetamine-induced hypermotility and stereotypy in rat.* PHARMACOL BIOCHEM BEHAV **27**(1) 165–169, 1987.— The substituted benzamide metoclopramide has been reported to block the behavioral effects of dopamine agonists, whereas its congener sulpiride potentiates these effects. We injected metoclopramide 2.0, 4.0, or 8.0 mg/kg PO into rats 2 hr before *d*-amphetamine 1.5 mg/kg IP and measured locomotion for 3 hr. We injected metoclopramide 8.0 mg/kg PO into rats 2 hr before *d*-amphetamine 1.5, 3.0, or 6.0 mg/kg IP and measured stereotypy for 3 hr. Metoclopramide potentiated the effects of all doses of *d*-amphetamine on both measures; peak effects occurred in the second or third hr after *d*-amphetamine injection. Metoclopramide alone tended to reduce behavior. The results suggest that metoclopramide is qualitatively similar to sulpiride in its interaction with *d*-amphetamine, and that metoclopramide's mechanism of action is not a simple dopaminergic antagonism. Clinicians are advised that metoclopramide, which is prescribed extensively for gastrointestinal and other disorders, may interact adversely with drugs that affect dopaminergic function.

Metoclopramide Sulpiride Benzamide Amphetamine Locomotor activity Stereotypy Drug interaction

The substituted benzamide metoclopramide is widely prescribed for its effect on the gastrointestinal tract. Because it increases peristalsis, thereby decreasing transit time through stomach, duodenum, and jejunum, metoclopramide is useful in clearing the stomach before general anesthesia, dissolving gastric bezoars, and facilitating intubation and radiological examination. It has been used also in the treatment or prevention of neurogenic bladder, orthostatic hypotension, tumor-associated gastroparesis, nonprolactinemic amenorrhea, failure to thrive, Tourette's syndrome, anorexia nervosa, hiccups, nausea, tardive dyskinesia, aspiration pneumonitis, and migraine (see [1] and [15] for reviews).

Metoclopramide is thought to produce its gastrointestinal effects by antagonizing dopaminergic function [1]. However, there is disagreement about the precise mechanism of action of these and other effects. Results from in vivo models suggest that the compound blocks dopamine receptors, but results from in vitro models suggest little antagonism [2]. Data have been interpreted as showing antagonism of D-2 receptors specifically or of D-1 and D-2 receptors [9,10]. Explanations invoking antagonism of presynaptic dopamine receptors [6] and of an unidentified subpopulation of dopamine receptors [17] have been offered.

The behavioral literature is consistent in that the compound antagonizes the effects of dopamine agonists in mouse and rat. Doses in the 1 to 5 mg/kg range IP or SC antagonized apomorphine-induced stereotypy [5, 9, 10] and hypermotility [9] in rat. It antagonized these behaviors in mouse also, as well as other apomorphine-induced behaviors in rat and mouse [5, 9, 10]. However, there is one study in which it did not reverse stereotypies and dyskinesias induced by dopamine agonists in guinea pig [4].

Metoclopramide 1.0 to 2.0 mg/kg SC antagonized the stereotypy induced by *d*-amphetamine 10 mg/kg IP given 1 hr before; behavior was scored for 3 hr, but the measure of interest was inhibition, not potentiation, and the observation periods reported did not much exceed 30 min post-injection [3]. In the 0.5 to 4.0 mg/kg range SC it antagonized the stereotypy induced by *d*-amphetamine 2.5 or 5.0 mg/kg IP given 10 min later, as well as other *d*-amphetamine-induced behaviors, during a 1-hr observation period [13]. Metoclopramide's congener sulpiride, on the other hand, enhanced *d*-amphetamine-induced stereotypy [13].

We wanted to know whether procedural differences could account for the opposite effects reported for metoclopramide and sulpiride. We injected metoclopramide before *d*-amphetamine and measured behaviors for 3 hr after *d*-amphetamine injection. Under this regimen, metoclopramide's effect was qualitatively the same as that reported

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for sulpiride: It enhanced *d*-amphetamine-induced hypermotility and stereotypy.

METHOD

Subjects

Subjects for the primary locomotor activity experiment (Fig. 1) were naive male Long-Evans rats from Blue Spruce Farms, Altamont, NY, that weighed about 220 g. Subjects for stereotypy were naive male Wistar rats from Charles River Breeding Laboratories, Wilmington, MA, that weighed about 385 g. Subjects for additional locomotor activity experiments (Table 1) were naive male CD rats from Charles River Breeding Laboratories, Wilmington, MA (about 285 g) or naive male Harlan SD rats from ARS/Sprague-Dawley, Madison, WI (about 220 g). All subjects were group housed in temperature- and humidity-controlled animal quarters on a regular light/dark cycle (lights on 0600 to 1800) with free access to food and water. They were tested during the light portion of the cycle. Each subject was tested once.

Apparatus

Locomotor activity was measured in 12 individual doughnut-shaped chambers (Woodard). A chamber was 31 cm in diameter and had six evenly spaced photocells 1 cm from the wire mesh floor. These chambers are presumed to measure primarily locomotion, because doses of *d*-amphetamine that cause repetitive non-locomotary movement produce low counts; but it is physically possible for non-locomotary movement to register as counts. Interruption of a photocell beam was registered on a Data General NOVA 3/12 minicomputer via an INTERACT interface. Observation of stereotypy was done in a rack of single rat housing cages with wire mesh floors and fronts; the area of each floor was 429 cm^2.

Drugs

In the primary experiments (Figs. 1 and 2), metoclopramide HCl (Beecham) was suspended in 0.5% methyl cellulose and injected at 2.0, 4.0, or 8.0 mg/kg PO for locomotor activity and 8.0 mg/kg PO for stereotypy. *d*-Amphetamine SO_4 (SK&F) was dissolved in isotonic saline and injected at 1.5 mg/kg IP for locomotor activity and 1.5, 3.0, or 6.0 mg/kg IP for stereotypy. Injection volumes were 1.0 ml/kg of body weight. Treatments in the additional locomotor activity experiments (Table 1) differed only as indicated in the Procedure section.

Procedure

Subjects in the primary experiments (Figs. 1 and 2) were transported to the laboratory in plastic group cages and injected with metoclopramide or its vehicle about 0900. In the locomotor activity experiment, they were placed in the photocell cages 1 hr later for 1 hr of habituation. For both locomotor activity and stereotypy, *d*-amphetamine was injected 2 hr after metoclopramide, and behavior was measured for 3 hr.

Locomotor activity. In the primary experiment (Fig. 1), twelve subjects were tested in each daily run, six with one dose of metoclopramide and six with its vehicle. The sample size was doubled and chamber bias controlled for by testing the same treatments in 12 more subjects on another day.

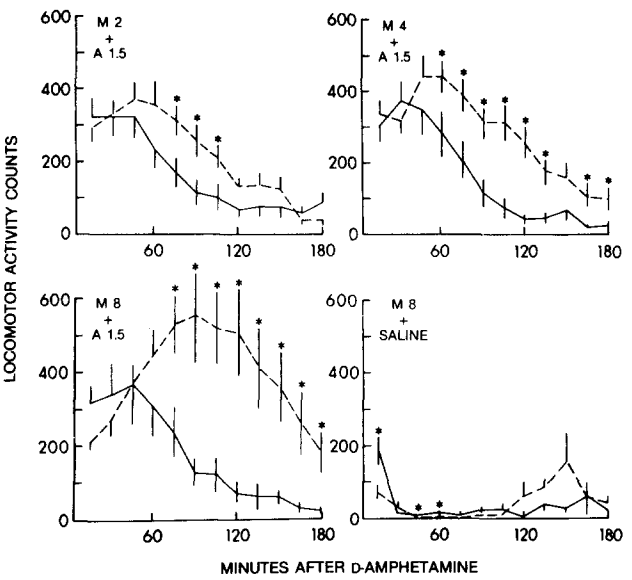

FIG. 1. Effects of three doses of metoclopramide on *d*-amphetamine-induced hypermotility in photocell cages. Metoclopramide 2.0, 4.0, or 8.0 mg/kg (M, broken curves) or its vehicle (solid curves) was injected PO 120 min before *d*-amphetamine (A) 1.5 mg/kg IP, and activity was recorded in 15-min bins for 180 min. The lower right panel shows activity when no A was given. Each point represents the mean effect in 12 rats; vertical lines represent 1 S.E. *Indicates $p<0.05$, *t*-test.

Each interruption of a photocell beam was registered by the computer as one count. Counts for each subject were gathered into 15-min bins. In the additional experiments (Table 1), procedure was the same except that one factor was varied in each: Metoclopramide 8.0 mg/kg was injected PO 1 hr before *d*-amphetamine, metoclopramide 8.0 mg/kg was injected PO simultaneously with *d*-amphetamine, metoclopramide 4.0 mg/kg was injected SC 2 hr before *d*-amphetamine, and sulpiride 32 mg/kg was injected PO 2 hr before *d*-amphetamine; also the sample size for the additional metoclopramide experiments was not doubled as in the primary experiment.

Stereotypy. The experiment was done in 2 days, procedure on the second day being a replica of that on the first, thus doubling the sample size to 10. Half of the subjects received metoclopramide 8.0 mg/kg and the other half received vehicle. Each half was divided into four groups, and 2 hr later a group received *d*-amphetamine at one of the following doses: 0 (saline), 1.5, 3.0, or 6.0 mg/kg. Behavior was scored on a scale adapted from Costall and Naylor [3]: 0=immobility, locomotion, or other non-stereotyped behavior; 1=repetitive sniffing with locomotion; 2=repetitive sniffing without locomotion; 3=licking, biting, or gnawing with locomotion; 4=licking, biting, or gnawing without locomotion. (Repetitive sniffing was defined as sniffing that occurred over and over in a set pattern, e.g., from side to side.) Behavior for each subject was observed for 10 sec every 15 min; the score assigned was that of the behavior with the highest value observed (e.g., if the subject exhibited both sniffing and licking, the score for licking was recorded). The observer did not know which groups had received which drugs or doses.

TABLE 1

POTENTIATION OF *d*-AMPHETAMINE-INDUCED HYPERMOTILITY: ADDITIONAL DATA

	Activity Counts (Mean ± SE)					
	Hour 1		Hour 2		Hour 3	
Treatment	Drug + Amphet[b]	Vehicle + Amphet[c]	Drug + Amphet	Vehicle + Amphet	Drug + Amphet	Vehicle + Amphet
Metoclopramide 8 mg/kg PO 1 hr pretreatment (Charles River CD)[a]	2001 ±591	1951 ±345	3077 ±639	1287 ±300	2632 ±481	128 ±29
	$t=0.07$		$t=2.54$*		$t=5.19$*	
Metoclopramide 8 mg/kg PO 0 hr pretreatment (Charles River CD)[a]	3086 ±457	1751 ±414	3188 ±404	1113 ±237	2341 ±522	255 ±123
	$t=2.17$		$t=4.43$*		$t=3.89$*	
Metoclopramide 4 mg/kg SC 2 hr pretreatment (Harlan SD)[a]	3263 ±426	2268 ±610	4035 ±845	1398 ±295	1814 ±651	519 ±215
	$t=1.34$		$t=2.95$*		$t=1.89$	
Sulpiride 32 mg/kg PO 2 hr pretreatment (Harlan SD)[a]	2913 ±460	1802 ±283	1890 ±435	663 ±173	524 ±115	281 ±55
	$t=2.06$		$t=2.62$*		$t=1.90$	

[a]Strain of rat.
[b]Drug (metoclopramide or sulpiride) followed by *d*-amphetamine SO_4 1.5 mg/kg IP.
[c]Vehicle (0.5% methyl cellulose) followed by *d*-amphetamine SO_4 1.5 mg/kg IP.
*$p<0.05$, Drug + Amphet vs. Vehicle + Amphet.

Data Analysis

Data were subjected to analysis of variance (CRISP, Crunch Software, San Francisco, CA), with post-hoc *t*-tests at individual time points.

Locomotor activity. For the primary experiments (Fig. 1), metoclopramide was the between-subjects factor with three levels (2.0, 4.0, and 8.0 mg/kg), and time was the within-subjects factor with 12 levels (15-min bins). Metoclopramide followed by saline (lower right panel of Fig. 1) was analyzed separately, with two levels of the drug factor (0 and 8.0 mg/kg). For the additional locomotor activity experiments (Table 1), analysis was similar except that the within-subjects factor had three levels (1-hr bins).

Stereotypy. Metoclopramide with two levels (0 and 8.0 mg/kg) and *d*-amphetamine with four levels (0, 1.5, 3.0, and 6.0 mg/kg) were the between-subjects factors, and time with 12 levels (15-min bins) was the within-subjects factor.

RESULTS

Locomotor Activity

In the primary experiments, both main effects (metoclopramide with three levels, time with 12 levels) and their interaction were significant. For metoclopramide, $F(3,71)=9.770$, $p<0.00001$; for time, $F(11,792)=44.268$, $p<0.00001$; and for the metoclopramide × time interaction, $F(33,792)=7.030$, $p<0.00001$. These data appear in the first three panels of Fig. 1. In the experiment in which metoclopramide 8.0 mg/kg or its vehicle was followed by saline (*d*-amphetamine's vehicle), for metoclopramide, $F(1,21)=0.128$, $p=0.72$; for time, $F(11,242)=4.063$, $p<0.00001$; and for the metoclopramide × time interaction, $F(11,242)=2.146$, $p=0.0182$. These data appear in the lower right panel of Fig. 1. An asterisk in the first three panels indicates that rats pretreated with metoclopramide 2.0, 4.0, or 8.0 mg/kg emitted significantly more activity counts following *d*-amphetamine injection than did vehicle pretreated rats in the same time period (*t*-test). An asterisk in the lower right panel indicates that rats pretreated with metoclopramide 8.0 mg/kg emitted significantly fewer activity counts following saline injection than did vehicle pretreated rats in the same time period. Metoclopramide at all doses significantly potentiated the hypermotility produced by *d*-amphetamine in some time periods after *d*-amphetamine injection, but metoclopramide 8.0 mg/kg alone had only a depressant effect.

Time was collapsed into 1-hr bins to facilitate further analysis of the potentiating effects of metoclopramide. Application of ANOVA to 1-hr bins indicated significant overall effects of metoclopramide, $F(3,204)=15.105$, $p<0.001$, and time, $F(2,204)=24.575$, $p<0.001$, and a metoclopramide × time interaction, $F(6,204)=4.444$, $p<0.001$. Because of the significant interaction, one-way ANOVAs were used to compare vehicle, 2.0, 4.0, and 8.0 mg/kg to each other during each of the 3 hr following *d*-amphetamine injection. No dose of metoclopramide significantly potentiated the hypermotility during the first hr. During the second and third hr, 2.0, 4.0, and 8.0 mg/kg differed significantly from 0 mg/kg. 2.0 mg/kg did not differ significantly from 4.0 mg/kg in either the second or third hr; and 4.0 mg/kg did not differ significantly

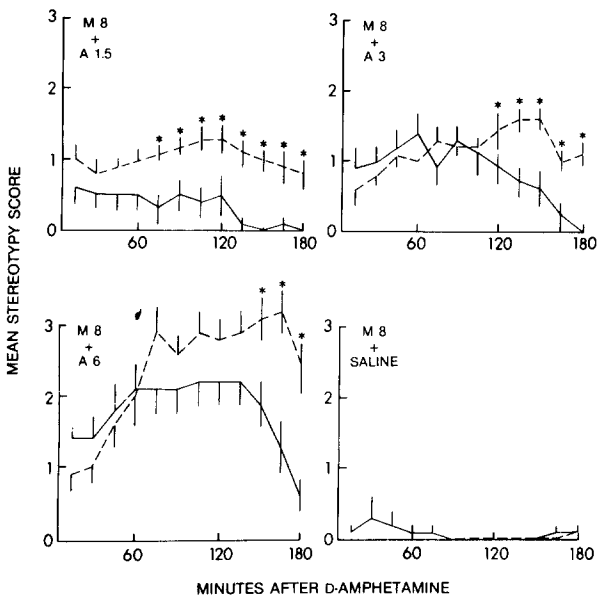

FIG. 2. Effects of metoclopramide on *d*-amphetamine-induced stereotypy. Metoclopramide 8.0 mg/kg (M, broken curves) or its vehicle (solid curves) was injected PO 120 min before *d*-amphetamine (A) 1.5, 3.0, or 6.0 mg/kg IP, and stereotypy was scored for 10 sec every 15 min over a period of 180 min. The lower right panel shows stereotypy when no A was given. Each point represents the mean effect in 10 rats; vertical lines represent 1 S.E. *Indicates $p<0.05$, *t*-test.

from 8.0 mg/kg, although the probabilities were close ($p=0.07$ and $p=0.06$). However, 2.0 and 8.0 mg/kg were significantly different from each other, $F(1,22)=8.025$, $p=0.009$ in the second hr, $F(1,22)=7.230$, $p=0.012$ in the third hr, which suggests that the potentiation of hypermotility was dose-dependent.

Results of the additional locomotor activity experiments are given in Table 1. Metoclopramide 8.0 mg/kg PO given 1 hr before *d*-amphetamine yielded significant main effects of metoclopramide, $F(1,11)=6.743$, $p=0.0267$, time, $F(2,24)=5.221$, $p=0.0149$, and the interaction of the two, $F(2,24)=11.974$, $p=0.0004$. Metoclopramide 8.0 mg/kg PO given simultaneously with *d*-amphetamine yielded significant main effects of metoclopramide, $F(1,11)=19.200$, $p=0.0014$, and time, $F(2,24)=7.545$, $p=0.0036$. Metoclopramide 4.0 mg/kg SC given 2 hr before *d*-amphetamine yielded significant main effects of metoclopramide, $F(1,11)=5.926$, $p=0.0353$, and time, $F(2,24)=14.324$, $p=0.00001$. Sulpiride 32 mg/kg PO given 2 hr before *d*-amphetamine yielded significant main effects of sulpiride, $F(1,23)=6.022$, $p=0.0225$, time, $F(2,48)=48.639$, $p<0.00001$, and the interaction of the two, $F(2,48)=3.668$, $p=0.0334$.

Metoclopramide 8.0 mg/kg significantly reduced motility during the 1-hr period of habituation to the activity chambers (data not shown).

Stereotypy

Figure 2 shows the effects of metoclopramide 8.0 mg/kg pretreatment on the stereotypy produced by three doses of *d*-amphetamine. Three-way ANOVA yielded significance of all main effects and all interactions. For metoclopramide, $F(1,79)=13.781$, $p=0.0004$; for *d*-amphetamine, $F(3,79)=67.599$, $p<0.00001$; for time, $F(11,880)=10.213$, $p<0.00001$; for the metoclopramide × *d*-amphetamine interaction, $F(3,79)=2.803$, $p=0.0455$; for the metoclopramide × time interaction, $F(11,880)=11.379$, $p<0.00001$; for the *d*-amphetamine × time interaction, $F(33,880)=6.057$, $p<0.00001$; for the metoclopramide × *d*-amphetamine × time interaction, $F(33,880)=2.425$, $p<0.00001$.

Because interactions were significant, data for each dose of *d*-amphetamine were subjected to two-way ANOVAs with metoclopramide as the between-subjects factor (two levels, 0 and 8.0 mg/kg) and time as the within-subjects factor (12 levels). When the dose of *d*-amphetamine was 0, no factor or interaction was significant. When the dose of *d*-amphetamine was 1.5 mg/kg, metoclopramide was significant, $F(1,19)=43.377$, $p<0.00001$. When the dose of *d*-amphetamine was 3.0 mg/kg, time, $F(11,220)=3.926$, $p<0.00001$, and the metoclopramide × time interaction, $F(11,220)=4.872$, $p<0.00001$, were significant. When the dose of *d*-amphetamine was 6.0 mg/kg, time, $F(11,220)=14.823$, $p<0.00001$, and the metoclopramide × time interaction, $F(11,220)=8.007$, $p<0.00001$, were significant. An asterisk in Fig. 2 indicates that rats pretreated with metoclopramide 8.0 mg/kg had a higher mean stereotypy score following *d*-amphetamine injection than did vehicle pretreated rats in the same time period. Metoclopramide significantly potentiated the stereotypy produced by all doses of *d*-amphetamine in some time periods after *d*-amphetamine injection. Saline produced a negligible stereotypy score, and metoclopramide did not change it.

DISCUSSION

Metoclopramide pretreatment significantly increased the duration of *d*-amphetamine-induced hypermotility and stereotypy. This effect is opposite to the effects in all studies found in a literature search (except [4]), where the only action of metoclopramide on dopamine agonist-induced behaviors was antagonism. Except for the length of time during which behavior was recorded, procedural differences between this and previous studies seem insufficient to account for the difference in results. Strain of rat is unlikely to be critical; we have observed potentiation in four strains. Route of administration is unlikely to be critical; we found a qualitatively similar effect in hypermotility after SC injection of metoclopramide 4.0 mg/kg. Nor is the behavioral measure likely to be critical; we have preliminary data showing potentiation of *d*-amphetamine's effects on operant responding.

In previous studies metoclopramide was given shortly before (e.g., 10 min [13]) or even after [3] the dopamine agonist; we gave it 2 hr before and saw a strong effect in the second hr after *d*-amphetamine injection—that is, 3 to 4 hr later. Pretreatment time seems not to be critical beyond the point at which metoclopramide ceases to show a measured (perhaps nonspecific) depressant effect: We found qualitatively similar potentiation of hypermotility when metoclopramide 8.0 mg/kg was given 2 hr before, 1 hr before, or simultaneously with *d*-amphetamine. This potentiation could have resulted from a simple blockade of the metabolism of *d*-amphetamine; however, it should be noted that the effect occurred at about the same time after *d*-amphetamine injection irrespective of pretreatment time (2 hr, 1 hr, or 0 hr). The delay in expression of the interaction suggests that a metabolite of metoclopramide could be producing the effect, but four metabolites

were inactive in a test in which metoclopramide (2.5 mg/kg, 1 hr pretreatment) reversed apomorphine-induced stereotypy and in receptor binding assays [18]. The effect may be specific to *d*-amphetamine: We have seen no effect on several hypermotility-inducing doses of methylphenidate.

Given that metoclopramide binds weakly or not at all to dopamine receptors in some assays [2,18], its antagonism of dopamine agonist-induced behaviors in previous studies could be nonspecific. Specificity is generally difficult to prove when the measure is reduction of behavior, especially if the behavior is induced by a manipulation such as the injection of a dopamine agonist: If the behavior (e.g., stereotypy) is not present in the absence of the agonist, then how does one demonstrate that pretreatment with an antagonist has any effect upon it except a nonspecific depressant one? The argument that metoclopramide specifically antagonizes dopamine agonists needs in vitro support or other evidence. In the absence of such evidence, a more satisfying position is that metoclopramide acts the same as its congener sulpiride, which in the literature and in our hands potentiates *d*-amphetamine's effects.

There are reports of untoward clinical effects associated with metoclopramide: tardive akathisia and agitated depression [16], mania [11], and phantom dyskinesia [8]. There are two clinical reports of drug synergy: potentiation of chlorpromazine's effect [7] and induction of severe extrapyramidal disturbances in a patient being treated with chlorpromazine and lithium [14]. Motor disturbance indicates an effect on dopamine neurons.

These results suggest that metoclopramide's effect on *d*-amphetamine-stimulated behavior is similar to that of its congener sulpiride, that the apparent blockade of *d*-amphetamine-stimulated behavior in previous studies was a nonspecific depression, and that the absence of potentiation in previous studies resulted from the shortness of the measurement period. All the evidence indicates dopaminergic involvement in metoclopramide's action, but the nature of the mechanism remains unclear.

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