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High Dose Pimozide Does Not Block Amphetamine-Induced Euphoria in Normal Volunteers

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BRAUER, L. H. AND H. DE WIT. *High dose pimozide does not block amphetamine-induced euphoria in normal volunteers.* PHARMACOL BIOCHEM BEHAV **56**(2) 265–272, 1997.—Studies with laboratory animals have shown that dopamine antagonists block the rewarding and interoceptive effects of amphetamine. However, studies using dopamine antagonists with humans have not consistently shown blockade of amphetamine-induced euphoria. The unexpected results in humans may relate to the low doses of dopamine antagonists tested. The purpose of this study was to evaluate the effects of a relatively high acute dose (8 mg) of the dopamine receptor antagonist, pimozide, on responses to *d*-amphetamine (10 and 20 mg) in normal volunteers. Male and female volunteers ($N = 12$) attended six sessions on which they received pimozide or placebo (7:30 am) followed by *d*-amphetamine or placebo (9:30 am). Subjective, physiological and behavioral measures were obtained at baseline (7:15 am) and hourly over a 5 h period. *d*-Amphetamine and pimozide, when administered alone, produced significant and opposite effects on ratings of Elation and Vigor, as well as on psychomotor performance and physiological measures. However, there were few significant interactions between pimozide and *d*-amphetamine. Thus, pimozide failed to consistently antagonize the effects of *d*-amphetamine, even at doses of pimozide that had behavioral and physiological effects when administered alone. Possible reasons for lack of robust dopamine antagonism of amphetamine-induced euphoria in humans are discussed.

Amphetamine Dopamine Subjective effects Normal volunteers Antagonism Drug mechanism Drug interaction Euphoria Dopamine antagonists Neuroleptics

STUDIES with laboratory animals strongly suggest that the effects of amphetamine that are related to its abuse are mediated by the neurotransmitter dopamine (8,22,28,32,34,42). In laboratory animals, dopamine antagonists such as haloperidol and pimozide attenuate the discriminative stimulus (i.e., the interoceptive) effects of amphetamine (8,22,28,34), and they also alter amphetamine self-administration in ways that are suggestive of reduced reinforcing efficacy (32,42). Reinforcing and discriminative stimulus effects of drugs are thought to be closely associated with their subjective effects in humans. However, few studies have directly examined the neurochemical mechanisms underlying euphoria in humans. Those studies that have investigated interactions between dopamine antagonists and amphetamine in humans have yielded inconsistent results (6,7,14,18,21,30,36). Although two early studies reported that the relatively selective D2 dopamine receptor blocker, pimozide (5-20 mg), attenuated the euphorigenic effects of high doses (200 mg) of intravenous amphetamine in drug abusers (14,21), we have found that doses of pimozide up to 4 mg do not attenuate the euphorigenic effects of lower doses of oral *d*-amphetamine (10 and 20 mg; (6,7)) in healthy, normal (i.e., non-drug-abusing) volunteers. Other investigators have shown that these doses of pimozide (up to 4 mg) also do not attenuate *d*-amphetamine-induced arousal in normal volunteers (18,36).

The reasons for the differences between studies may be related to several factors, including the drug doses, dosing procedures, pretreatment intervals, or populations tested. The most likely methodological reason for the lack of antagonism in our own studies is that the doses of pimozide tested were too low to effectively block post-synaptic dopamine receptors. Although acute administration of 4 mg pimozide has been shown to occupy 80% of brain dopamine receptors in schizophrenic patients maintained on neuroleptics (9), it is not

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known whether a single dose of 4 mg pimozide, such as we used in our previous study, would yield similar levels of receptor occupancy in normal volunteers. Since the doses of pimozide used in our previous studies did not produce significant subjective or behavioral effects when administered alone, we could not rule out the possibility that higher doses might be needed to produce the expected attenuation.

The purpose of this study was to extend our previous findings by evaluating the effects of a higher dose of pimozide (8 mg) on responses to *d*-amphetamine (10 and 20 mg) in normal volunteers. This dose of pimozide was tested because lower doses (up to 4 mg) failed to alter responses to *d*-amphetamine. Only a single higher dose of pimozide was tested to minimize the likelihood of adverse drug reactions. Subjects attended six laboratory sessions on which they received pimozide or placebo followed 2 h later by *d*-amphetamine or placebo. Subjective, physiological and behavioral measures were collected prior to pimozide administration and over a 5-h period thereafter.

METHODS

Subjects

Fifteen normal, healthy males ($N = 6$) and females ($N = 9$) between the ages of 21 and 35 were recruited from the University of Chicago community. Non-smokers who consumed at least one alcoholic beverage per week came to the laboratory for a physical examination, electrocardiogram (ECG), and face-to-face psychiatric interview. Cigarette smokers were excluded from the study to minimize potential interactions between nicotine and the study drugs, and to eliminate the possibility that smoking withdrawal symptoms during the 5-h session would confound the assessment of drug effects on mood. Individuals who had serious medical conditions or abnormal ECGs were excluded from the study, as were those with past or current major Axis 1 disorders [DSMI-IIR (1)].

Procedures

Prior to their participation, subjects attended an orientation session during which study procedures were explained and informed consent was obtained. Subjects were told that they might receive a stimulant/appetite suppressant, sedative/minor tranquilizer, major tranquilizer, or placebo during the study, but that they would not be informed of the actual drug(s) they received until after the study. They were instructed not to use drugs, medications or alcohol for 24 h before and after each session, and not to eat or to drink caffeine one hour prior to the session. Routine breath alcohol concentration and random urine drug screens were conducted to verify abstinence from alcohol and drugs, respectively. Subjects were advised not to drive or operate machinery for 8 h after leaving the laboratory. This study was approved by the University of Chicago Institutional Review Board.

This study was conducted according to a within-subjects design. Subjects attended six laboratory sessions lasting from 7:15 am until 12:30 pm. On each session, they received some combination of pimozide (8 mg) or placebo, followed 2 h later by *d*-amphetamine (10 and 20 mg) or placebo. Sessions were conducted at one week intervals due to the long half-life of pimozide [18 h (31)]. The 2-h pretreatment interval was chosen based on previous studies and on the pharmacokinetic profiles of pimozide and *d*-amphetamine (3, 5, 6, 7, 18, 31, 36). Subjects arrived at the laboratory at 7:15 am and completed baseline subjective, physiological and behavioral measures (see below). These measures were repeated hourly for the duration of the session. At 7:30 am, subjects ingested a capsule containing pimozide or placebo. Two hours later they ingested a second capsule containing *d*-amphetamine (10 or 20 mg) or placebo. All drugs were administered in opaque capsules with dextrose filler. Drug administration was double-blind, and the order of conditions was counterbalanced across subjects. At approximately 12:30 pm, after the last set of measures, subjects left the laboratory. Before leaving, they were given a tablet of the anticholinergic drug, benztropine mesylate (Cogentin), under single-blind conditions, and instructed to use it as needed to reverse any drug-induced side effects experienced outside the laboratory. Typical neuroleptic-induced side effects (e.g., muscle spasms or rigidity) were described as examples of effects that could be reversed by the benztropine, but pimozide was not specifically mentioned during this explanation. No subjects used the benztropine at any time during the study.

Dependent Measures

Subjective effects of the drugs were measured with the 49-item version of the Addiction Research Center Inventory [(ARCI; 1(15,25)] and with several visual analog scales (VAS). The ARCI is a true/false questionnaire that measures mood effects representative of several drug classes, including euphoria. Visual analog scales are 100 mm lines labeled with an adjective and tagged at either end with opposites, such as "not at all" and "extremely". Subjects respond by placing a line along the 100 mm continuum reflective of their current mood with respect to each adjective (''feel drug'', ''like drug'', ''feel high'', ''want more drug'', ''anxious'', ''sedated'', ''stimulated'', ''down'', ''high'', ''hungry''). Momentary mood states were evaluated with an experimental version of the Profile of Mood States (POMS; 20, 27), a 72-item questionnaire on which subjects rate their mood on a scale of 0 (not at all) to 4 (extremely). These items have been factor analyzed to yield eight composite scores on dimensions of Anger, Anxiety, Confusion, Depression, Elation, Fatigue, Friendliness, and Vigor. Two additional scales have been intuitively derived, Arousal {(Anxiety + Vigor) - (Fatigue + Confusion)} and Positive Mood {(Elation - Depression)}. Global drug effects and drug identification were assessed at the end of the session. Subjects rated the overall strength of drug effect on a Likert-type scale (1 = "I felt no effect at all" to 5 = "I felt a strong drug effect"), and overall liking on a 100 mm visual analog scale. They also attempted to identify the class of drug they received (stimulant, sedative, major tranquilizer, or placebo) and rated whether they would take the drug again if they had the opportunity (0 = no, 1 = yes).

Behavioral effects of pimozide and *d*-amphetamine were measured with the Digit Symbol Substitution Test [DSST (38)], a pencil and paper test of psychomotor performance, and with a computerized test of eye-hand coordination (16, 29). The DSST requires subjects to substitute symbols for numbers over a 1-min period and speed and accuracy are measured. In the eye-hand coordination test, subjects use the computer mouse to track the movement of a circle on the computer screen. The primary variable of interest in this study was the number of mistakes, defined as the number of times the subjects had the cursor more than 1 cm from the middle of the circle on the screen. Physiological effects of *d*-amphetamine and pimozide were measured using a digital blood pressure and heart rate monitor (Omron Healthcare, Inc., Vernon Hills, IL). Each of the measures used in this study is sensitive

TABLE 1

F VALUES FOR MEASURES ON WHICH SIGNIFICANT DRUG EFFECTS WERE OBSERVED

Measure	Pim	Amp	Hr	Pim × Amp	Pim × Hr	Amp × Hr	Pim × Amp × Hr
ARCI							
A (stimulant-like)		5.43†	5.45†			6.05§	
BG (stimulant-like)		6.16‡	13.53§			3.65†	
LSD (dysphoria)			4.40†				
MBG (euphoria)		8.95§	5.78§			3.76†	
PCAG (sedation)		6.18†	14.13§			3.57†	
POMS							
Anxiety		5.33†					
Arousal	4.2*	4.12†	7.50§			3.85†	
Confusion	6.83†		4.19†				
Elation	8.09†		5.89‡			3.29†	
Fatigue		3.47*	7.40§				
Friendliness			2.93†			3.29†	
Positive Mood	8.45†		4.93†			2.75*	
Vigor	8.68†	4.48†	7.11§		3.02*	3.99†	
VAS							
"Feel drug"	6.52†					4.91§	
"Feel high"						2.61*	
"Like drug"		7.82§	2.74*		3.66†	2.47*	
"Want more"		7.13‡	3.35†	3.80†		2.80*	2.35*
"High"		3.32*	2.70*			2.52*	
"Hungry"		5.74†	10.88‡				
"Stimulated"	17.54§	7.37†	9.27§			5.06‡	2.82†
DSST			6.85§		7.98§	3.14†	
Mistakes		4.44†	5.18§		2.66*	3.07†	
Systolic BP		4.66†	5.88§		4.30†		
Diastolic BP		4.08†	2.30*				
Heart Rate		2.94*	5.17§		2.41*	3.45†	

Pim (pimozide); Amp (*d*-amphetamine); Hr (hour); *$p < .10$; †$p < .05$; ‡$p < .01$; §$p < .005$

to the dose-related effects of a variety of drugs, including stimulants (e.g., 6, 12).

Data Analysis

Subjective, physiological, and behavioral data collected during the session were analyzed with 2 (pimozide dose) × 3 (*d*-amphetamine dose) × 6 (Hour) repeated-measures analyses of variance. Geisser-Greenhouse degrees of freedom corrections for within-subjects designs were used (23). Alpha levels of less than or equal to .05 were considered significant. End-of-session ratings of drug strength, overall liking, and willingness to take the drug again were analyzed with two-way repeated-measures ANOVAs with pimozide dose and *d*-amphetamine dose as factors. For the drug identification question, the percent of subjects correctly identifying each drug was calculated.

RESULTS

Subject Characteristics

Three of the original 15 subjects (2 males and 1 female) experienced unpleasant side effects from pimozide and dropped out of the study (see below). The remaining 12 subjects (5 males and 7 females) were a mean age of 24.7 years old, and drank an average of 4.1 alcoholic beverages per week (range = 1-10). In general, subjects were only occasional users of recreational drugs, typically marijuana.

d-Amphetamine

d-Amphetamine produced robust and dose-related effects on a number of measures when administered alone (i.e., when placebo, rather than pimozide, was the pretreatment drug, see Table 1). As expected, *d*-amphetamine produced dose- and time-dependent increases in scores on the POMS Arousal (*d*-amphetamine × hour interaction; $F(10, 110) = 3.8, p < 0.02$), Elation ($F = 3.3$, $p < 0.05$), and Vigor ($F = 4.0$, $p < 0.02$) scales, and on visual analog ratings of stimulation ($F = 5.1$, $p < 0.006$) and drug liking (main effect of *d*-amphetamine; $F(2,22) = 7.8, p < 0.004$) relative to placebo. *d*-Amphetamine also increased heart rate, blood pressure and the number of substitutions completed on the DSST (*d*-amphetamine × hour interaction; $F(10, 110) = 3.2$, $p < 0.02$), and decreased the number of mistakes made on the eye-hand coordination test (*d*-amphetamine × hour interaction; $F(10, 110) = 3.1$, $p < 0.03$). $^{F\text{and}}p$ values for significant effects of *d*-amphetamine are shown in Table 1, and representative plots of *d*-amphetamine's effects over time are presented in Fig. 1. The data points shown represent the time point immediately prior to *d*-amphetamine administration and the three subsequent time points. End-of-session ratings were dose-dependently increased by *d*-amphetamine. The mean ratings of drug strength on a scale of 1("I felt no effect at all") to 5 ("I felt a strong drug effect") in the placebo, 10 and 20 mg conditions were 2.0, 2.5, and 3.0, respectively (main effect of *d*-amphetamine: $F(2, 20) = 5.1$, $p < 0.05$). Mean ratings of liking on a scale of 0 ("dislike very

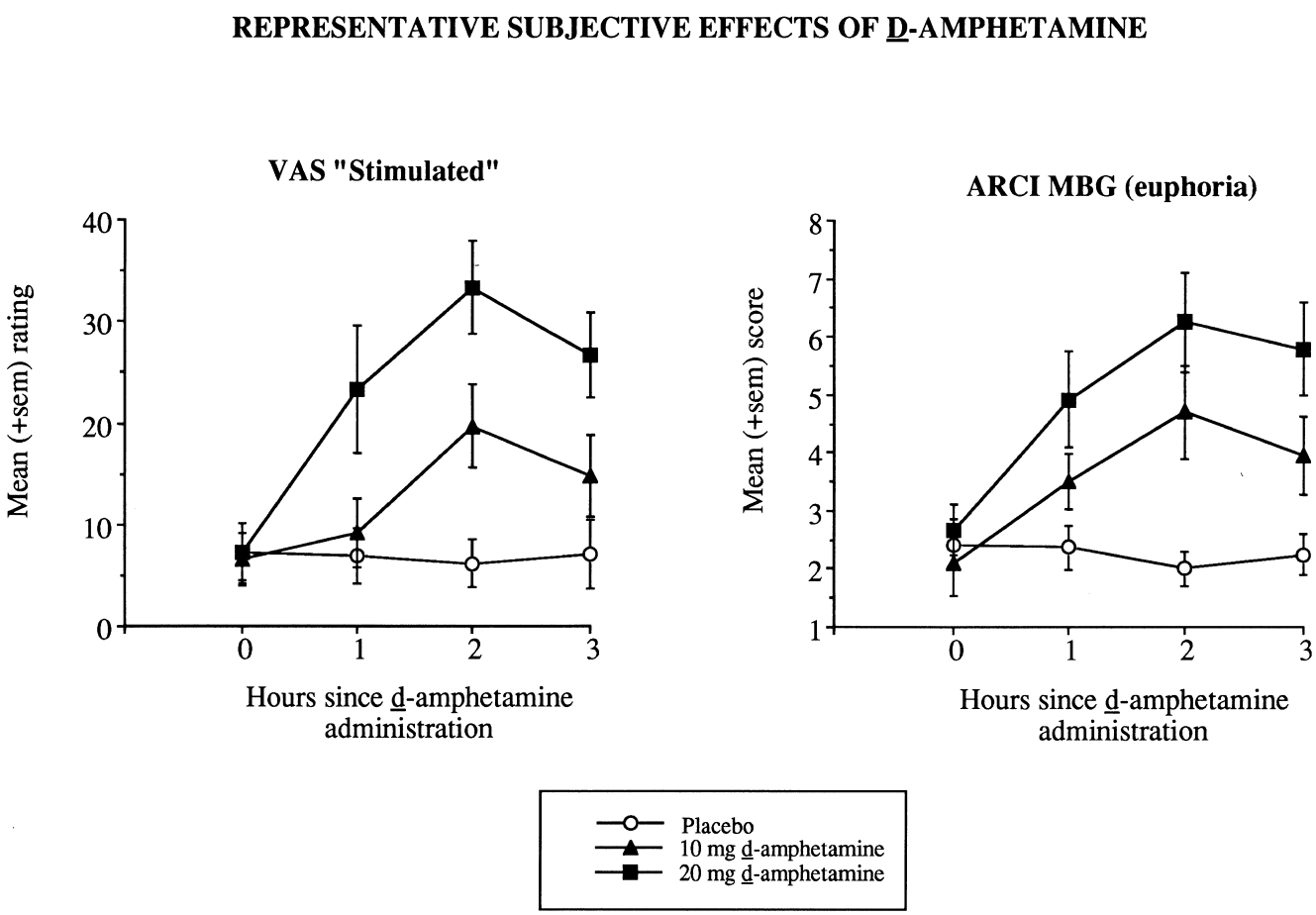

FIG. 1. Significant effects of *d*-amphetamine on ratings of stimulation and euphoria. Scores shown are mean (+sem) values. Ratings after placebo and 10 and 20 mg *d*-amphetamine are shown in open circles, and closed triangles and squares, respectively. The axes have been expanded to illustrate small differences between conditions. Visual analog ratings of "Stimulated" can range from 0 to 100. Scores on the MBG scale of the Addiction Research Center can range from 0 to 16.

much") to 100 ("like very much") increased with dose, yielding mean values of 48.8, 60.4, and 73.3 (main effect of *d*-amphetamine; $F(2, 22) = 9.7$, $p < 0.001$). Twenty-five percent of subjects identified placebo as a stimulant, compared to 58% and 75% who identified 10 and 20 mg *d*-amphetamine, respectively, as stimulants. Although subjects reported being less likely to take the drug again in the placebo (0.43 on a 0 = no to 1 = yes scale) or 10 mg (0.58) *d*-amphetamine as compared to the 20 mg *d*-amphetamine condition (0.67), this effects was not statistically significant.

Pimozide

Pimozide produced significant subjective, physiological, and behavioral effects, which were generally opposite in direction to those of *d*-amphetamine (see Table 1). For example, pimozide significantly decreased scores on the POMS Elation (main effect of pimozide; $F(1,11) = 8.1$, $p < 0.02$), Positive Mood ($F = 8.4$, $p < 0.02$), and Vigor ($F = 8.7$, $p < 0.02$) scales, and on visual analog ratings of stimulation ($F = 17.5$, $p < 0.002$), relative to placebo. Pimozide also significantly decreased scores on the Digit Symbol Substitution Test relative to placebo (pimozide × hour interaction; $F(5,55) = 8.0$, $p < 0.0004$) and decreased systolic blood pressure ($F = 4.3$, $p < 0.02$) late in the session. In contrast, pimozide increased scores on the Confusion scale of the POMS (main effect of pimozide; $F(1,11) = 6.8$, $p < 0.03$), and unexpectedly, also increased visual analog ratings of drug liking relative to placebo. The effects of pimozide on liking ratings were small, and appear to have been accounted for by one time point (h 4). In addition to these effects, there were trends ($p < 0.10$) for pimozide to decrease Arousal (POMS) and heart rate, and to increase the number of mistakes on the eye-hand coordination test. Fig. 2 shows the time course of pimozide's effects on selected measures. There were no significant differences between placebo and 8 mg pimozide on end-of-session ratings of drug strength (mean for placebo = 2.0 vs. mean for pimozide = 1.9), liking (mean placebo = 48.8 vs. mean pimozide = 50.0), or willingness to take the drug again (mean placebo = 0.42 vs. mean pimozide = 0.33). Subjects identified pimozide as a sedative 42% of the time, and as placebo 50% of the time.

Three of the original 15 subjects experienced adverse side effects from pimozide and dropped out of the study. Over a two day period, the first subject, a male, felt very sedated and disoriented, then agitated, irritable, and restless. In addition, he had trouble sleeping and concentrating. The second subject, also male, felt jittery, anxious and restless after the laboratory

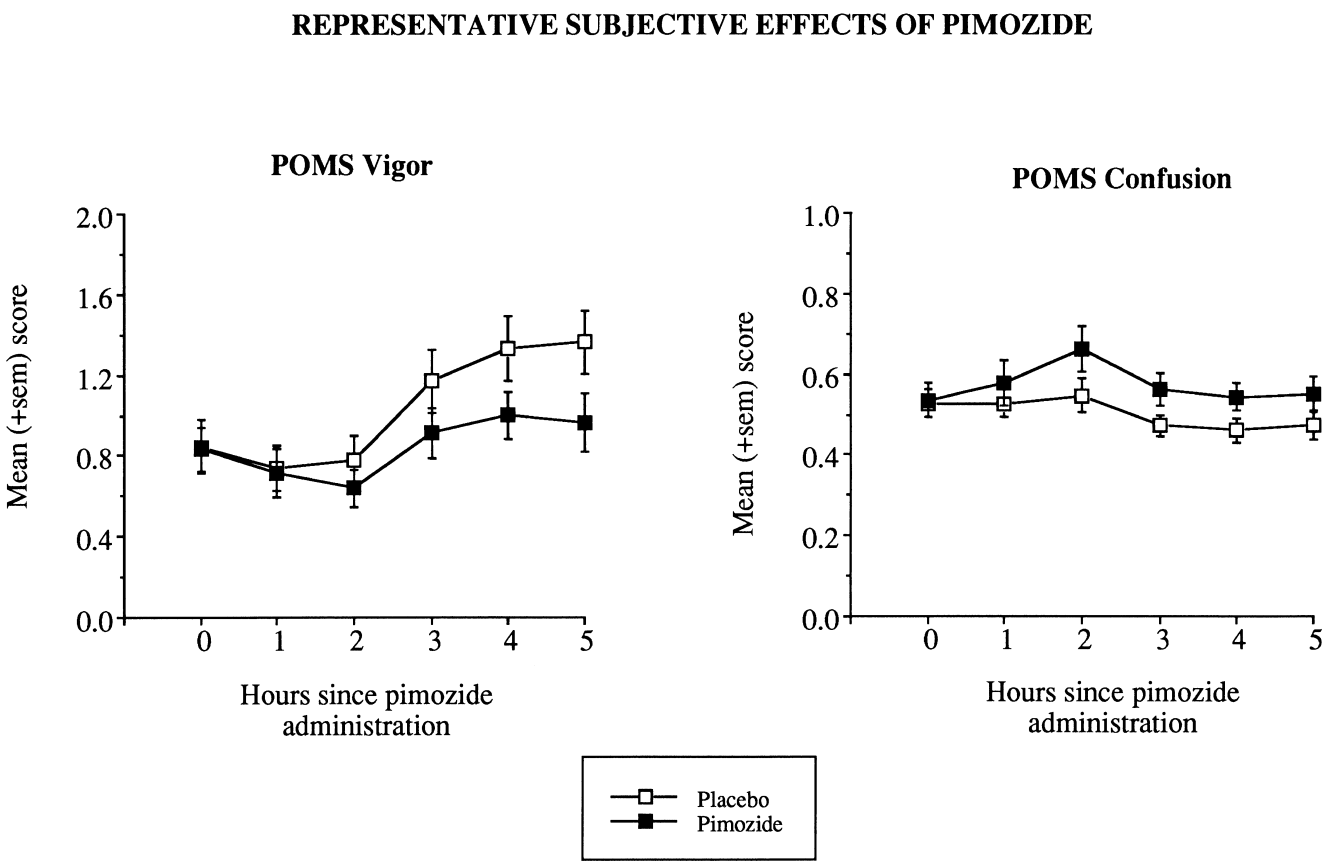

FIG. 2. Significant effects of pimozide on Profile of Mood States (POMS) of Vigor and Confusion scales. Scores shown are mean (+sem) values. Ratings after placebo and pimozide are shown in open and closed squares, respectively. The axes have been expanded to illustrate small differences between conditions. Scores on the Vigor and Confusion scales can range from 0 to 4. Both of the effects shown are statistically significant (main effects of pimozide, $p < 0.05$).

session, and experienced facial spasms and rigidity. These effects also lasted 2-3 days. The last subject, a female, reported feeling sleepy, emotional, and moody for two days following ingestion of pimozide. No other side effects were reported.

Pimozide plus d-*amphetamine*

Pimozide did not significantly alter responses to *d*-amphetamine on most measures (see Table 1). Fig. 3 shows mean ratings on representative measures, collapsed across all time points (i.e., data from the pimozide × *d*-amphetamine interaction term). Visual inspection of Fig. 3 shows that the dose-response relationship for *d*-amphetamine is comparable in the placebo and pimozide pretreatment condition. In addition, there were few apparent differences between responses to individual doses of *d*-amphetamine in the placebo as compared to the pimozide pretreatment condition. For ratings of wanting more drug and stimulation, there were slight but statistically significant interactions between *d*-amphetamine and pimozide. As can be seen from the figure, these interactions are likely due to main effects of pimozide: For example, for ratings of stimulation, responses to 10 mg *d*-amphetamine appear to be lower in the pimozide pretreatment condition than in the placebo pretreatment condition. However, the same is true of responses when pimozide was given with no *d*-amphetamine, suggesting that a main effect of pimozide accounted for the lower scores in the pimozide relative to the placebo pretreatment condition. Indeed, there was a highly significant effect of pimozide on this measure (see above). End of session ratings of *d*-amphetamine effects were similar in the pimozide pretreatment condition as in the placebo pretreatment condition.

We conducted two additional analyses to examine whether individual differences in responses to *d*-amphetamine interacted with the effects of pimozide. First, we conducted a regression analysis examining subjects' responses to pimozide + *d*-amphetamine on ratings of "feel drug" and the POMS Elation scale, using responses to *d*-amphetamine alone as a covariate. Second, we derived the slope of the *d*-amphetamine dose-response curve with and without pimozide for each subject, and then entered these slopes into a simple one-way repeated measures ANOVA. There was wide inter-subject variability in dose-response slopes, with *d*-amphetamine alone curves ranging from -0.05 to 4.4 and *d*-amphetamine + pimozide slopes ranging from -2.5 to 4.2. However, neither of these analyses suggested that the results with pimozide were related to individual differences in responses to *d*-amphetamine.

DISCUSSION

The results of the study suggest that the lack of effect of pimozide in our previous studies was not due to the doses of pimozide tested. Even though the dose of pimozide used in this

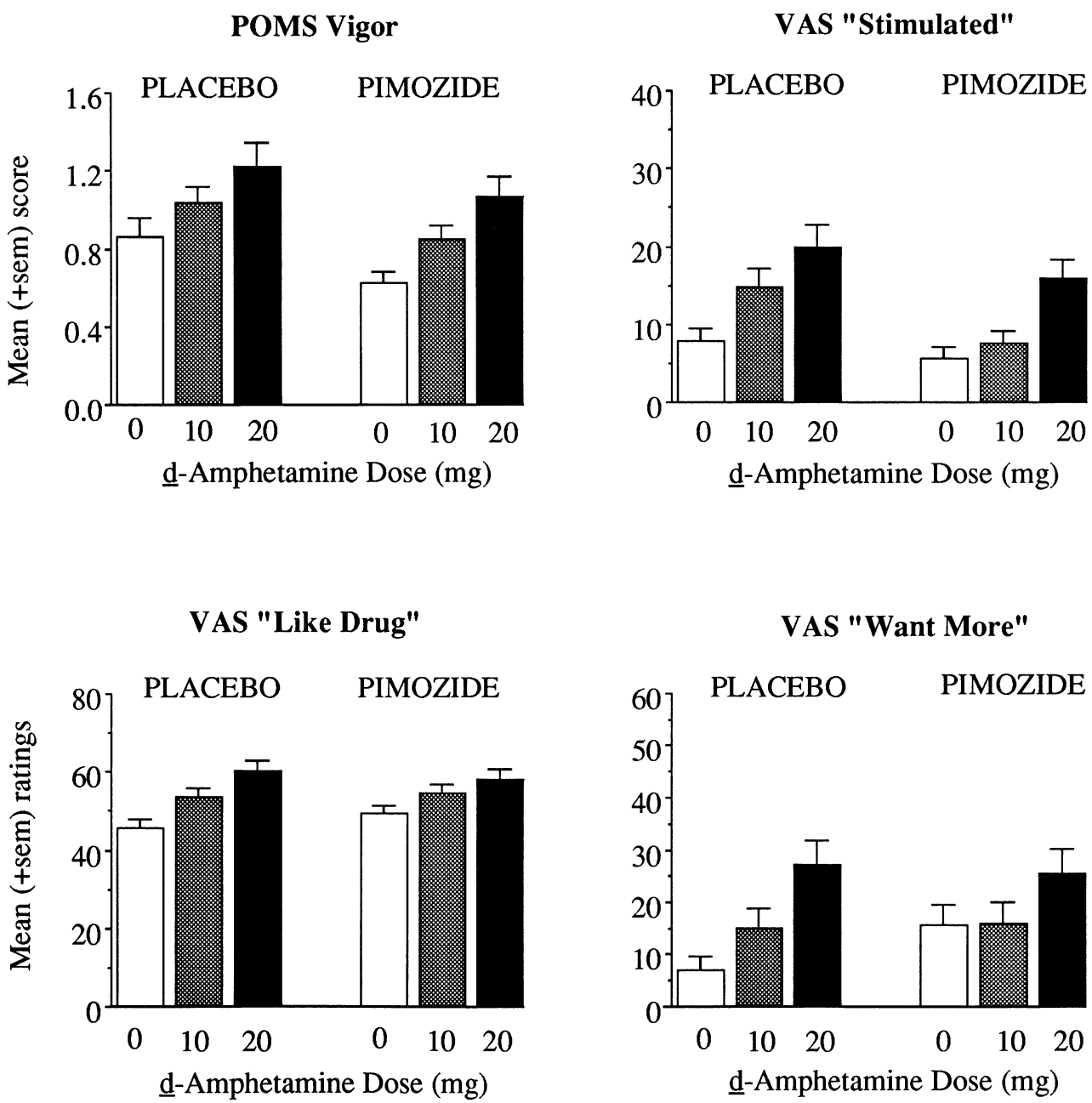

FIG. 3. Effects of *d*-amphetamine and pimozide, alone and in combination, on ratings of Vigor, stimulation, drug liking, and desire for drug. Scores shown are mean (+sem) values collapsed across all time points. The left side of each panel shows ratings of *d*-amphetamine after pretreatment with placebo, whereas the right side shows ratings after pretreatment with pimozide. Ratings for placebo, 10 and 20 mg of *d*-amphetamine are represented by open, shaded, and filled bars, respectively. The axes have been expanded to illustrate small differences between conditions. Scores on the Profile of Mood States Vigor scale can range from 0 to 4, and scores on visual analog scales can range from 0 to 100. The interaction between pimozide and *d*-amphetamine was significant for visual analog ratings of stimulation (pimozide × *d*-amphetamine × hour, $p < 0.05$) and "want more drug" (pimozide × *d*-amphetamine, $p < 0.05$) drug but not for ratings of Vigor or drug liking.

study (8 mg) produced significant effects when administered alone (e.g., decreases in Elation, Positive Mood, and Vigor, and increases in Confusion), it did not consistently antagonize responses to *d*-amphetamine. Therefore, even a clearly behaviorally active dose of pimozide did not attenuate responses to a low or moderate dose of *d*-amphetamine.

On the surface, these findings suggest that pimozide and *d*-amphetamine do not interact at the receptor level. However, this is unlikely considering the large body of data to the contrary from laboratory animal studies and a few human studies (e.g., 8,14,21,22,41). Moreover, *d*-amphetamine is known to increase dopaminergic activity and to produce rewarding effects (20,35), whereas pimozide blocks dopamine receptors and produces aversive subjective effects (2,31). Thus, in this

experiment, each of the two drugs produced direct subjective effects that are consistent with their known actions on the dopamine system.

An alternative possibility is that higher and even more behaviorally active doses of pimozide are needed to block the effects of *d*-amphetamine. That is, it is possible that the blockade of *d*-amphetamine-induced euphoria may only occur at doses of pimozide that produce significant dysphoria. The presence of "dysphoria" might be easily overlooked in laboratory animals, without special procedures designed to detect it. In humans, aversive psychological states can readily be reported, but ethical and practical considerations make it difficult to investigate this possibility. It is possible that only those subjects who experience marked dysphoria from pimozide alone would show evidence of attenuated responses to *d*-amphetamine. Interestingly, a recent examination of the effects of classical and atypical antipsychotics on amphetamine discrimination in laboratory animals raised the possibility that the apparent antagonism observed in animals might also be related to neuroleptic-induced dysphoria (4).

It is also possible that the unique pharmacological profile of pimozide accounts for our results. Although pimozide has been shown to reduce the reinforcing effects of amphetamine in laboratory animals, it does so less reliably than other dopamine antagonists (22,28). One reason may relate to the receptor profile of pimozide. Pimozide is a relatively selective D2 dopamine receptor blocker (17), and there is evidence that blockade of D1 receptors may also be important in altering the interoceptive effects of amphetamine (e.g., 13). Another characteristic of pimozide that may account for our results is that it has variable and delayed effects at receptors despite its ready entry into the brain (26,31). Thus, in some subjects, the central effects of pimozide may have peaked after the final measures in the session were obtained. That fact that pimozide-induced dystonia and akathisia did not occur until later in the day supports this notion. Therefore, a longer pretreatment interval may be needed.

A related issue is that of acute vs. chronic dosing. It is possible that chronic exposure to amphetamine, pimozide, or both, is necessary in order for a drug interaction to be apparent. In antagonism studies using laboratory animals both the agonist (i.e., the self-administered drug) and the antagonist are usually administered several times. In previous studies using human subjects, low doses of pimozide (e.g., 5 mg) blocked amphetamine-induced euphoria in amphetamine abusers who had been chronically exposed to the amphetamine (14,21). It is possible that long-term changes in receptor number or sensitivity are needed to observe the antagonism of amphetamine's effects by neuroleptics. However, a recent study explicitly examined the effects of dopamine antagonists after acute vs. chronic treatment with cocaine in rats and found that dopamine antagonists had a greater effect on locomotor responses to cocaine in naive rats compared to rats with prior exposure to cocaine (37). These findings suggest that the brain and behavioral mechanisms which underlie drug-taking during early exposure may be distinct from the processes underlying chronic use (see also 33).

Notwithstanding the possible methodological limitations, our data have important implications for current theories of drug reward and of the generalizability of animal models of drug effects to human drug taking. Several assumptions are often made when extrapolating data from animal models to human drug-taking, or between different measures of drug effect within a species. One assumption often made (implicitly or explicitly) is that both drug self-administration and drug discrimination in animals are in some way related to the experience of drug-induced "euphoria" in humans. Our data indirectly call into question this assumption by failing to demonstrate a role for dopamine in the acute euphorigenic effects of amphetamine, despite convincing demonstrations of its role in animal self-administration and drug discrimination studies. Another assumption is that interoceptive effects of drugs are related to their reinforcing effects. That is, it is often assumed that drug-taking is related to positive drug effects on mood (e.g., 11). However, there are several examples in the animal and the human literature in which the subjective or interoceptive effects of drugs appear to be dissociable from their reinforcing effects (e.g., 10,13,19,22,24,32,39,40,42).

Taken together these data suggest that traditional models of drug taking and drug-induced interoceptive effects may need to be modified. Additional studies on this topic are urgently needed to elucidate the relationship between animal and human data and between different measures of drug effect within species. The present study evaluated only the subjective, or interoceptive, effects of amphetamine, and thus does not address the possible role of dopamine in drug reinforcement, or drug taking. Future studies should attempt to evaluate the effects of dopamine and other pharmacological antagonists on drug reinforcement or drug taking, and should evaluate the effects of antagonists on stimulant self-administration and subjective responses in the same individuals in a controlled setting. In this way, the role of dopamine in human drug-taking can be systematically assessed and evaluated in the context of animal models.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (3rd ed., Revised). Washington DC: American Psychiatric Association; 1987.
2. Anden, N.; Butcher, S.; Corrodi, H.; Fuxe, K.; Ungerstedt, U. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. Eur. J. Pharmacol. 11:303–314; 1970.
3. Angrist, B.; Corwin, J.; Bartlik, B.; Cooper, T. Early pharmacokinetics and clinical effects of oral *d*-amphetamine in normal subjects. Biol. Psychiatry 22:1357–1368; 1987.
4. Arnt, J. Inhibitory effects on the discriminative stimulus properties of *d*-amphetamine by classical and newer antipsychotics do not correlate with antipsychotic activity. Relation to effects on the reward system? Psychopharmacology 124:117–125; 1996.
5. Brauer, L.; Ambre, J.; de Wit, H. Acute tolerance to subjective but not cardiovascular effects of *d*-amphetamine in normal, healthy volunteers. J. Clin. Psychopharmacol. 16:72–76; 1996.
6. Brauer, L.; de Wit, H. Role of dopamine in *d*-amphetamine-induced euphoria. Experimental and Clinical Psychopharmacology 3:1995.
7. Brauer, L.; de Wit, H. Subjective responses to *d*-amphetamine alone and after pimozide pretreatment in normal, healthy volunteers. Biol. Psychiatry 39:26–32; 1996.

8. Colpaert, F.; Niemegeers, C.; Janssen, P. Discriminative stimulus properties of cocaine and *d*-amphetamine, and antagonism by haloperidol: A comparative study. Neuropharmacology 17:937–942; 1978.
9. Farde, L.; Nordstrom, A.; Wiesel, F.; Pauli, S.; Halldin, C.; Sedvall, G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Arch. Gen. Psychiatry 49:538–544; 1992.
10. Fischman, M. Relationship between self-reported drug effects and their reinforcing effects: Studies with stimulant drugs. In: Fischman, M.; Mello, N., eds. Testing for abuse liability of drugs in humans. Washington, DC: US Government Printing Office;1989:211–230.
11. Fischman, M.; Foltin, R. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. Br. J. Addict. 86:1563–1570; 1991.
12. Foltin, R.; Fischman, M. Assessment of abuse liability of stimulant drugs in humans: A methodological survey. Drug Alcohol Depend. 28:3–48; 1991.
13. Goudie, A. Discriminative stimulus properties of amphetamine, cathinone, and related agents. In Glennon, R. A.;Jarbe, T. U. C.; Frankenheim, J., eds. Drug discrimination: Applications to drug abuse research. Washington DC: U.S. Government Printing Office;1991:45–60.
14. Gunne, L.; Anggard, E.; Jonsson, L. Clinical trials with amphetamine-blocking drugs. Psychiatr. Neurol. Neurochirugia 75:225–226; 1972.
15. Haertzen, C.; Hill, H.; Belleville, R. Development of the Addiction Research Center Inventory (ARCI): Selection of items that are sensitive to the effects of various drugs. Psychopharmacology 4:155–166; 1963.
16. Hindmarch, I.; Kerr, J.; Sherwood, N. The effects of alcohol and other drugs on psychomotor performance and cognitive function. Alcohol Alcoholism 26:71–79; 1991.
17. Hyttel, J.; Larsen, J.; Christensen, A.; Arnt, J. Receptor-binding profiles of neuroleptics. Psychopharmacology Supplementum 2:9–18; 1985.
18. Jacobs, D.; Silverstone, T. Dextroamphetamine-induced arousal in human subjects as a model for mania. Psychol. Med. 16:323–329; 1986.
19. Johanson, C.; Kilgore, K.; Uhlenhuth, E. Assessment of dependence potential of drugs using multiple indices. Psychopharmacology 81:1983.
20. Johanson, C.; Uhlenhuth, E. Drug preference and mood in humans: *d*-amphetamine. Psychopharmacology 71:275–279; 1980.
21. Jonsson, L. Pharmacological blockade of amphetamine effects in amphetamine dependent subjects. Eur. J. Clin. Pharmacol. 4:206–211; 1972.
22. Kamien, J.; Woolverton, W. A pharmacological analysis of the discriminative stimulus properties of *d*-amphetamine in rhesus monkeys. J. Pharmacol. Exper. Ther. 248:938–946; 1989.
23. Keppel, G. Design and analysis: A researcher's handbook. (2nd ed.). Englewood Cliffs, NJ: Prentice-Hall, Inc.; 1982.
24. Lamb, R.; Preston, K.; Schindler, C.; Meisch, R.; Davis, F.; Katz, J.; Henningfield, J.; Goldberg, S. The reinforcing and subjective effects of morphine in post-addicts: A dose-response study. J. Pharmacol. Exper. Ther. 259:1165–1173; 1991.
25. Martin, W.; Sloan, J.; Sapira, J.; Jasinski, D. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin. Pharmacol. Ther. 12:245–258; 1971.
26. McMillen, B.; Geman, D.; Sanghera, M.; Warnack, W.; Shore, P. Pimozide: Delayed onset of action at rat striatal pre- and postsynaptic receptors. J. Pharmacol. Exper. Ther. 215:150–155; 1980.
27. McNair, D.; Lorr, M.; Droppleman, L. Profile of Mood States (Manual). San Francisco: Educational and Industrial Testing Service; 1971.
28. Nielsen, E.; Jepsen, S. Antagonism of the amphetamine cue by both classical and atypical antipsychotic drugs. Eur. J. Pharmacol. 11:167–176; 1985.
29. Nuotto, E.; Kortilla, K. Evaluation of a new psychomotor test battery: Effects of alcohol. Pharmacol. Toxicol. 68:360–365; 1991.
30. Nurnberger, J.; Simmons–Alling, S.; Kessler, L.; Jimerson, S.; Schreiber, J.; Hollander, E.; Tamminga, C.; Nadi, N.; Goldstein, D.; Gershon, E. Separate mechanisms for behavioral, cardiovascular, and hormonal responses to dextroamphetamine in man. Psychopharmacology 84:200–204; 1984.
31. Pinder, R.; Brogden, R.; Sawyer, P.; Speight, T.; Spencer, R.; Avery, G. Pimozide: A review of its pharmacological properties and therapeutic uses in psychiatry. Drugs 12:1–40; 1976.
32. Risner, M.; Jones, B. Role of noradrenergic and dopaminergic processes in amphetamine self-administration. Pharmacol. Biochem. Behav. 5:477–482; 1976.
33. Robinson, T.; Berridge, K. The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain Res. Rev. 18:247–291; 1993.
34. Schechter, M.; Cook, P. Dopaminergic mediation of the interoceptive cue produced by *d*-amphetamine in rats. Psychopharmacology 42:185–193; 1975.
35. Seiden, L.; Sabol, K.; Ricuarte, G. Amphetamine: Effects on catecholamine systems and behavior. Ann. Rev. Pharmacol. Toxicol. 32:639–377; 1993.
36. Silverstone, T.; Fincham, J.; Wells, B.; Kyriakides, M. The effect of the dopamine receptor blocking drug pimozide on the stimulant and anorectic actions of dextroamphetamine in man. Neuropharmacology 19:1235–1237; 1980.
37. Tella, S. Differential blockade of chronic versus acute effects of intravenous cocaine by dopamine receptor antagonists. Pharmacol. Biochem. Behav. 48:151–159; 1994.
38. Wechsler, D. The Measure and Appraisal of Adult Intelligence. (4th ed.). Baltimore: Williams & Wilkins; 1958.
39. Woolverton, W. Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol. Biochem. Behav. 24:531–535; 1986.
40. Woolverton, W.; Kamien, J.; Kleven, M. Blockade of the discriminative stimulus effects of cocaine and *d*-amphetamine in rhesus monkeys with the D1 dopamine antagonist SCH 23390. Pharmacologist 29:158; 1987.
41. Yokel, R.; Wise, R. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. Science 187:547–549; 1975.
42. Yokel, R.; Wise, R. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology 48:311–318; 1976.