

# The Effects of Several Anorexigenics on Monkey Social Behavior<sup>1</sup>

JOHN A. BEDFORD,<sup>2</sup> D. KAREN L. MARQUIS  
AND MARVIN C. WILSON

*Research Institute of Pharmaceutical Sciences and Department of Pharmacology  
University of Mississippi, University, MS 38677*

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BEDFORD, J. A., D. K. L. MARQUIS AND M. C. WILSON. *The effects of several anorexigenics on monkey social behavior.* PHARMACOL BIOCHEM BEHAV 20(3)317-321, 1984.—The effects of fenfluramine HCl, diethylpropion HCl, and methylphenidate HCl on social behavior were studied in a heterosexual group of stumptailed monkeys (*M. arctoides*). Subjects were treated concurrently (i.e., every monkey received the same treatment on a given day). The range of doses studied was: fenfluramine (1.0–10 mg/kg), methylphenidate (1.0–5.0 mg/kg), and diethylpropion (2.0–20 mg/kg). In general most drug/dose combinations produced decreases in social interactions. However, there was one notable exception; presenting was dramatically increased following dosing with methylphenidate and diethylpropion. Some of the solitary behaviors recorded were also observed to increase, notably, vocalization and self-grooming, which at the higher doses of diethylpropion and methylphenidate took the form of intensely idiosyncratic stereotypies. Finally, food consumption was observed to decrease in some subjects (more dominant) and increase in others (less dominant) indicating that social variables may interact with pharmacological variables.

Sociopharmacology	Grooming	Submissive behavior	Sexual behavior	<i>M. arctoides</i>
Fenfluramine	Diethylpropion	Methylphenidate	Stereotypy	Food competition

RECENTLY there have been numerous reports concerning the effect of d-amphetamine upon the social behavior of non-human primates [3, 12, 17, 19, 22]. In general amphetamine reduces social interaction between group housed monkeys. However, there have been reports of increases in social interaction [14,18]. Facilitation of human social interaction following treatment with d-amphetamine has also been reported in a clinical setting [10]. In addition, there have been several studies reporting on the use of primate social behavior as a measure of the effects of other psychotropic substances [3, 11, 14, 18].

A recent paper from our laboratory [1] reported the effects of acute pretreatment with d-amphetamine on the social behavior of a heterosexual group of stumptailed macaques (*M. arctoides*). Aside from one report [14] this was the first study involving both males and females. d-Amphetamine was shown, at low doses, to increase vocalization, self-grooming and aggression. At higher doses substantial decreases in most forms of social interaction occurred, although presenting was shown to increase dramatically in a dose-related fashion.

The present experiment was designed to assess the effects of three other appetite suppressants on the social behavior in

the same group of monkeys reported earlier [1]. The three drugs chosen (fenfluramine HCl, diethylpropion HCl, and methylphenidate HCl) were selected for study because each has some similar and some dissimilar effects when compared to d-amphetamine.

Fenfluramine, much like amphetamine, has been shown to reduce food consumption in animals [13] and has been shown to be effective in the treatment of obesity in man [24]. Unlike amphetamine it does not produce intense stereotypic behavior in animals nor does it engender typical psychomotor stimulant effects in man [2]. Fenfluramine was reported to be unlike amphetamine when its subjective effects were compared to those of amphetamine by experienced users [6]. Furthermore, unlike amphetamine, diethylpropion and methylphenidate, fenfluramine does not maintain self-administration behavior in rhesus monkeys [23]. Finally, fenfluramine has not found its way into the illicit drug culture, presumably because it lacks most of the typical psychomotor stimulant effects.

Diethylpropion is a stimulant with a profile very similar to that of amphetamine [10]; however, there is relatively little evidence relating to its abuse even though the drug has been available for some 20 years [8]. The foregoing would indicate

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<sup>2</sup>Reprints requests should be sent to: Dr. John Bedford, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677.

that for some reason other central stimulants are preferred, from an abuse standpoint, over diethylpropion. In a recent paper [9] diethylpropion and cocaine were studied in two intravenous self-administration procedures, one involving substitution of diethylpropion for cocaine and the other utilizing a choice between the same two drugs. Diethylpropion was shown to support self-administration; however, cocaine was always preferred. Finally, diethylpropion has a greater anorectic to stimulant ratio than amphetamine and is therefore, preferred over amphetamine in the treatment of obesity.

Methylphenidate is reported to have only minimal anorectic activity in man [4], however, its anorectic activity in animals is well known. Its apparent reduced anorectic efficiency and its lesser potential for producing other unwanted side effects (i.e., insomnia and tachycardia) have led clinicians to prefer methylphenidate over amphetamine in the treatment of hyperkinesis [20]. Like amphetamine, methylphenidate has been shown to elicit psychotic episodes in man, is self-administered intravenously by animals and produces amphetamine-like increases in locomotor activity.

#### METHOD

##### Subjects

The subjects used in the present study were six (three males, three females) sexually mature stump-tailed macaque (*M. arctoides*) weighing 4–7 kg. Subjects were fed appropriate amounts of monkey chow (Purina) twice daily and had free access to water. In addition, the subjects were each fed a multiple vitamin daily. Light and dark cycles were held at 12 hours on, 12 hours off for the duration of the experiment. All six subjects had been previously used in an experiment designed to assess the effect of chronic and acute amphetamine on group behavior [1]. However, all subjects had been drug free for at least two months prior to this study.

##### Apparatus

The group cage was divided into two areas, a main living area measuring 2.35×2.35×2.75 m and a similar dosing and treatment area measuring 1.17×2.35×2.75 m. The back and sidewalls of each chamber were covered with Formica<sup>®</sup> while the front wall ceiling were constructed of 2.5 cm<sup>2</sup>, 10 gauge wire. A watering device was located on the side wall of the living area 1.5 m up from the floor with a 30×30 cm perch located on the wall 30 cm below the watering device. A food hopper was centered on the front wall of the living area 60 cm up from the floor. In addition, the living area also contained a swing and several perches of various sizes located on the back wall.

##### Procedure

Subjects had been living in the group enclosure for approximately one year and remained in this cage for the duration of the study. Observation sessions were conducted daily five days per week and consisted of the following sequence [1]. The subjects were moved into the dosing and treatment area and each injected IM in a random order with either saline or a dose of one of the test substances, and returned to the living area. All subjects received the same treatment in a given session [2]. Fifteen minutes post injection, a feeding order determination was made by placing 75 biscuits (Purina<sup>®</sup> Monkey Chow) in the food hopper. The order in

which subjects removed the biscuits was recorded and then converted to the percentage of chows removed from the box for each subject [3]. Yielding behavior was recorded for 30 minutes from the onset of the feeding order. The term yield refers to the giving up of position at the water lick. This may or may not have occurred as a result of a facial threat or more hostile action on the part of an approaching monkey, but required that the positioned monkey be moving out of the area in response to another subject [4]. Finally, subject's interactive and solitary behaviors were observed continuously for 1 hour following the feeding order determination by a technician seated in the room.

The test compounds and doses employed in the present study were methylphenidate HCl (1.0, 2.0, 5.0 mg/kg), fenfluramine HCl (1.0, 5.0, 10 mg/kg) and diethylpropion HCl (2.0, 10, 20 mg/kg). All drugs were dissolved in sterile normal saline and injected IM. Dosing orders were randomized within drugs, with all doses of one drug given before testing with a new compound was begun. At least 72 hours separated succeeding drug days with saline being administered on intervening days.

The behavior categories recorded by the observer included the following:

*Vocalization.* When a subject emitted sounds other than those arising from rapid repetitive movements of the lips, jaws (teeth) or tongue or any combination thereof.

*Social grooming (allogrooming).* When a subject picks with hands, feet or mouth the skin, fur, or nails of another subject's body.

*Self-grooming (autogrooming).* When a subject picks with hands, feet or mouth the skin, fur or nails of his own body.

*Presenting.* When a subject directs his or her hindquarters to another subject with head and shoulders lowered and buttocks raised.

#### RESULTS

In this laboratory interrater reliability checks have demonstrated that the observational technique employed is quite reliable. Reliability coefficients have averaged around 0.9 and at times were greater than 0.95.

The results from the feeding order tests are presented in Table 1. The saline data indicates that the two most dominant positions in the hierarchy (as measured by the food competition test) were clearly established. The other four positions were not clearly established since there was considerable overlap between their standard errors. Yielding data indicated a similar effect with the first two positions in the hierarchy clearly established while the other four overlapped.

Methylphenidate was not included on the table since it produced a complete inhibition of food consumption by all animals at all doses. Both diethylpropion and fenfluramine were shown to produce a dose-related decrease in total biscuit consumption by the entire group. It is apparent that the effects varied greatly in different animals. The relative consumption of biscuits is about normal (i.e., similar to saline) for fenfluramine at the 1.0 mg/kg dose. The 5.0 mg/kg dose presents a somewhat different picture. The two highest ranking subjects, M-1 and F-1, didn't eat; however, F-2 and M-2 both consumed a greater percentage of biscuits than was observed under the saline condition. In terms of the absolute number of biscuits retrieved, F-2 consumed fewer (2 vs. 6)

TABLE 1  
EFFECTS OF SEVERAL ANOREXIGENICS ON FOOD COMPETITION IN GROUP-HOUSED *MACACA ARCTOIDES*\*

Subject <sup>‡</sup>	Saline	Diethylpropion mg/kg			Fenfluramine mg/kg		
		2.0	10	20	1.0	5.0	10
M-1	58 ± 0.5 (45)	45.2 (33)	0	0	42.0 (28)	0	0
F-1	23 ± 5 (17)	49.3 (36)	0	100 (2)	27.2 (18)	0	0
F-2	6 ± 2.5 (6)	43 (3)	0	0	18.8 (12)	16.6 (2)	0
M-2	3.8 ± 2.5 (3)	0	100 (11)	0	4.5 (3)	83.4 (10)	0
M-3	4.4 ± 1.9 (3)	1.2 (1)	0	0	7.5 (5)	0	0
F-3	1.3 ± 1.2 (1)	0	0	0	0	0	0
Absolute number of biscuits retrieved by all subjects	75	73	11	2	66	12	0

\*The numbers in the table represent the % of the total biscuits retrieved by the group which was obtained by that subject. Numbers in parentheses indicate the absolute number of chows retrieved by that subject. Under saline conditions all biscuits were retrieved. Saline values represent the mean ± SEM for 20 sessions in which all subjects were treated with saline.

<sup>‡</sup>Subject codes indicate the sex (M,F) and the relative dominance position of that subject within all subjects of the same sex. The lower the number the more dominant the subject. The descending order in which the subjects are listed indicates the decrease in dominance behavior exhibited by that subject in the group setting.

while M-2 consumed considerably more (10 vs. 3) than obtained under saline conditions. The highest dose of fenfluramine completely inhibited feeding.

Similar effects were seen with diethylpropion. The 2.0 mg/kg dose of diethylpropion reduced consumption in M-1 and increased consumption in F-1. The 10 and 20 mg/kg doses inhibited consumption in all, but one animal. M-2 obtained all biscuits retrieved following the 10 mg/kg dose; this represented an increase in the absolute number of biscuits retrieved compared to control conditions.

The effect of the three drugs studied on vocalization is shown in Table 2. Methylphenidate produced a slight decrease in vocalization at 1.0 mg/kg followed by substantial increases at 2.0 and 5.0 mg/kg. Diethylpropion produced a slight drop in vocalization at the higher two doses and was without effect at the lowest dose. Fenfluramine produced a dramatic increase in vocalization at 1.0 mg/kg followed by a smaller increase at 5.0 mg/kg. The 10 mg/kg dose of this drug almost completely suppressed vocalization. Vocalization scores during saline baseline sessions were fairly evenly distributed across subjects. The increases observed following treatment with fenfluramine can be attributed mainly to two subjects; M-1 and M-3. The increase observed with methylphenidate at 2.0 mg/kg was a result of increases in three animals, M-3, F-1 and F-3, while the increase observed after treatment with 5.0 mg/kg was a result of one subject, F-1.

Methylphenidate, diethylpropion (10, 20 mg/kg) and fenfluramine (10 mg/kg) completely suppressed social grooming while lower doses of diethylpropion and fenfluramine did not alter this behavior.

The effects of the three drugs on self-grooming times are presented in Table 3. The control numbers in the table represent the average (mean total for all six animals) amount of time spent self-grooming following treatment with saline (grand mean for 20 saline sessions). Methylphenidate produced substantial increases at all doses tested while fenfluramine produced a decrease at 1.0 mg/kg and com-

TABLE 2  
EFFECTS OF SEVERAL ANOREXIGENICS ON VOCALIZATION BEHAVIOR IN GROUP-HOUSED *MACACA ARCTOIDES*\*

Treatment (mg/kg)	Occurrences
Saline <sup>‡</sup>	39 ± 4
Methylphenidate 1.0	9
2.0	69
5.0	120
Diethylpropion 2.0	41
10	20
20	33
Fenfluramine 1.0	262
5.0	78
10	1

\*The numbers in the table represent the total vocalization for all six animals.

<sup>‡</sup>Saline value represents the mean ± SEM vocalization per day for 20 saline control sessions.

pletely eliminated this behavior at the 5.0 and 10 mg/kg doses. Diethylpropion produced a biphasic effect. The 2.0 and 10 mg/kg doses increased grooming times while the 20 mg/kg dose was without effect.

Table 4 presents the effects of these three drugs on presenting behavior. Methylphenidate and diethylpropion produced substantial increases in presenting at all doses tested. Fenfluramine, on the other hand, produced only a small increase at 1.0 mg/kg followed by a slight decrease at the two higher doses.

TABLE 3

EFFECTS OF SEVERAL ANOREXIGENICS ON SELF-GROOMING BEHAVIOR IN GROUP-HOUSED *MACACA ARCTOIDES*\*

Treatment (mg/kg)	Duration
Saline <sup>†</sup>	33.8 ± 3.1
Methylphenidate 1.0	103.2
2.0	70.6
5.0	91.1
Diethylpropion 2.0	119.3
10	114.6
20	31.3
Fenfluramine 1.0	23
5.0	3.7
10	0

\*The numbers in the table represent total minutes spent self-grooming by all subjects.

<sup>†</sup>Saline value represents the mean ± SEM time (min) spent self-grooming by the entire group per day for 20 saline control sessions.

The increase in presenting observed with diethylpropion and methylphenidate occurred predominantly in all three females and was directed almost entirely to the alpha male. However, as the dosage of each drug was increased, there was also a smaller increase in the incidence of presenting by lower ranking males toward the alpha male and also by these subjects toward females, noted. In contrast to these dyadic effects, the increase seen with 1.0 mg/kg fenfluramine occurred entirely in males who presented to other males.

## DISCUSSION

The results of the effects of the three drugs studied on food consumption support previous work done at this laboratory [1]. The complete suppression of eating by methylphenidate suggests that further testing should be conducted at substantially lower doses. The other two drugs produced dose-related decreases in food consumption based on overall group consumption; however, the subjects consuming the food varied from drug to drug and dose to dose. Although both drugs substantially reduced overall consumption, some subjects did eat greater amounts than were retrieved during control sessions. This effect was prominent in the beta male and two highest ranking females. One point clearly stands out, with diethylpropion at 10 and 20 mg/kg and fenfluramine at 5.0 and 10 mg/kg, the alpha male (M-1) did not eat. In fact, he didn't even approach the food hopper and, in addition, paid little attention to the other subjects in the group. This fact offers a potential explanation for the apparent social modification of the drug effect. During normal feeding tests, M-1 and F-1 retrieved most of the biscuits from the food hopper, smelling and biting pieces of each one, often followed by dropping them on the floor of the cage. The remaining subjects never approached the feeder while either one or both of these animals were in the vicinity of the feeder. The absence of the subjects at the feeder and their total disinterest with the colony probably explains the behavior of the lower ranking subjects. In a previous study [1] a similar ef-

TABLE 4

EFFECTS OF SEVERAL ANOREXIGENICS ON PRESENTING BEHAVIOR IN GROUP-HOUSED *MACACA ARCTOIDES*\*

Treatment (mg/kg)	Occurrences
Saline <sup>†</sup>	5.05 ± 0.93
Methylphenidate 1.0	86
2.0	163
5.0	63
Diethylpropion 2.0	50
10	78
20	305
Fenfluramine 1.0	26
5.0	
10	1

\*The numbers in the table represent the total number of presents for all six animals.

<sup>†</sup>Saline value represents the mean ± SEM of total number of presents per day for 20 saline control sessions.

fect was reported following pretreatment with several doses of d-amphetamine. Lower ranking subjects were observed to retrieve biscuits, but only when the dose of amphetamine was sufficient to inhibit the food-getting behavior of the higher ranking subjects.

The increases in vocalization following treatment with methylphenidate and to a lesser extent following treatment with fenfluramine agree with other published reports [7,21]. The authors reported increased vocalization in both grouped [7] and isolated [21] humans following treatment with psychomotor stimulants. Furthermore, this laboratory reported a similar effect of d-amphetamine on vocalization in this same group of subjects [1].

The rather dramatic decreases in social grooming reported seem to be a result of either an overall depression of all activity, as was the case with fenfluramine at the highest dose, or of other intensely stereotypic behaviors (presenting and self-grooming with diethylpropion and methylphenidate) taking precedent over normal social interactions. Treatment with d-amphetamine also suppressed social grooming in these same subjects [1]. Increased self-grooming occurred following treatment with methylphenidate and diethylpropion and took the form of intense stereotypic picking. These same effects have been reported in this colony following administration of d-amphetamine [1]. An interesting point is that the areas groomed by the various subjects following treatment here were the same areas stereotypically groomed in the earlier study following treatment with amphetamine [1]. In both instances, this grooming often produced severe irritation of the area groomed. Such idiosyncratic stereotypies have also been reported in squirrel monkeys [15] and cercopithecus monkeys [16] following psychomotor stimulant administration.

The dramatic increases in presenting observed following dosing with diethylpropion and methylphenidate can be viewed in at least two ways. Presenting can be considered as a sexual response leading to mating or it can also be construed as a submissive gesture directed toward a higher rank-

ing subject. As reported earlier [1] this group demonstrated considerable increases in presenting following the administration of d-amphetamine. Only slight increases in mounting were observed even though presenting was dramatically increased. The present results extend this finding to two more drugs of the psychomotor stimulant class. No increase in mounting behavior was observed even when presenting was occurring at 20–40 times the normal saline rate. These factors clearly support the argument that the increased presenting was likely an increase in submissive responses rather than sexual in context.

The results of the present study support those of other investigators reporting on the effects of stimulants (amphetamine, methamphetamine) on monkey social behavior [3, 11, 14, 19] and to a further extent the applicability of the model to three other anorexigenics. Decreases in social interactions appear to be a result of the interference of intense

stereotypic behavior patterns (self-grooming and presenting). It also appears that the increase in presenting is likely due to increased submissiveness on the part of the presenter. The source of this effect remains obscure since there was little to no evidence of an increase in aggression on the part of the more dominant subjects toward those subjects emitting the presents. Reports of others [3] concerning the fact that large doses of amphetamine can produce paranoid ideation in humans might offer some explanation for these effects.

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