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Effects of d-Amphetamine and Diazepam on Paired and Grouped Primate Food Competition

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LOVELL, D. K., J. A. BEDFORD, L. GROVE AND M. C. WILSON. *Effects of d-amphetamine and diazepam on paired and grouped primate food competition.* PHARMAC. BIOCHEM. BEHAV. 13(2) 177–181, 1980.—Two male and two female rhesus monkeys (*Macaca mulatta*) were the subjects of an experiment designed to assess the effect of d-amphetamine (DA; 0.125, 0.5 and 2.0 mg/kg, IM) and diazepam (DZP: 0.5 and 2.5 mg/kg, IM) on food-getting behavior in paired and group competition. Paired competition results show that in some cases submissive animals, that had previously failed to obtain apple pieces, were successful in obtaining some apple pieces when either the dominant animal of the pair or both subjects were given 0.5 mg/kg DA or 2.5 mg/kg DZP. Results revealed the same effect when all animals (group competition) were given 0.125 and 2.0 mg/kg DA and 2.5 mg/kg DZP. These results appear to indicate that the effect of drugs on food-getting behavior in competitive situations is in some manner influenced by the social status of the animal.

Dominance hierarchy Competition d-Amphetamine Diazepam Food-getting Monkey Social behavior

ALTHOUGH there have been surprisingly few experimental investigations in this area, there is evidence [3] that the effect of drugs on food-getting behavior of primates in social settings may depend on the social status of the subject. Paired food competition has often been used as a measure of dominance-submissive relationships [9, 10, 12], also it has been demonstrated as an experimental procedure sensitive to the effects of social status on the response to drug administration in a food competition situation [3]. The effects of oral diazepam on pellet-taking, mobility and aggression in rhesus monkeys, *Macaca mulatta*, that were either alone or paired with another monkey has been investigated [3]. When paired, the monkeys were tested as both the dominant and the submissive animal of a pair. Only one animal of a pair was dosed and the apparatus was designed with two feeders so that both animals of a pair could obtain pellets. Pellet taking decreased significantly in the submissive monkey, whereas pellet taking in the dominant monkey was not as drastically affected. Thus these results revealed that the same monkey would respond differently to the competitive situation depending on whether the monkey was the dominant or submissive monkey in the pair. Furthermore, the submissive position was far more sensitive to the drug effect than the dominant position.

However, published data from this laboratory [13] have indicated that only submissive macaques, *Macaca arctoides*, in a group-housed situation, will eat after the administration of an anorexic dose of d-amphetamine to all animals. In light of these results further experimentation was undertaken to examine the effect of this drug and diazepam on group-housed food-getting behavior and on paired competition for food. In addition, the effects on food competition were tested when either the submissive or dominant animal of a pair was dosed as well as when both were dosed. Rhesus monkeys were selected as subjects because of their extensive and well known behavioral repertoire and the aggressiveness of the species in a group situation [8] and more importantly, because this species has been used previously [3].

EXPERIMENT 1

METHOD

Subjects

Four captive bred rhesus monkeys (*Macaca mulatta*), 2 male and 2 female, served as subjects. The subjects were approximately 3 years old, and weighed between 2.4 and 3.0 kg at the start of the experiment. Subjects were named Arthur, Henry, Catherine and Ann. During the course of the experiment, the animals were fed appropriate amounts of monkey chow (Purina®) and a multiple vitamin after each test session. Access to water was ad lib. The subjects were housed in individual stainless steel cages (Hoeltge, Cincinnati, OH).

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TABLE 1

THE NUMBER OF APPLE PIECES WON BY ANIMAL 1 WHEN PAIRED WITH ANIMAL 2 UNDER FOUR TREATMENT CONDITIONS INVOLVING INTRAMUSCULAR INJECTIONS OF EITHER D-AMPHETAMINE, DIAZEPAM OR VEHICLE

	Subject	Treatment* condition	Animal 2: Henry	Arthur	Catherine	Ann	Total
0.5 mg/kg d-amphetamine							
Animal 1	Henry	Cont	—	10	10	10	30
		Sub	—	10	10	10	30
		Dom	—	10	10	10	30
		Both	—	10	10	10	30
	Arthur	Cont	0	—	10	10	20
		Sub	0	—	10	10	20
		Dom	0	—	8	9	17
		Both	0	—	8	8	16
	Catherine	Cont	0	0	—	10	10
		Sub	0	0	—	10	10
		Dom	0	2	—	1	3
		Both	0	2	—	0	2
	Ann	Cont	0	0	0	—	0
		Sub	0	0	0	—	0
		Dom	0	1	9	—	10
		Both	0	2	10	—	12
2.5 mg/kg diazepam			Animal 2				
Animal 1	Henry	Cont	—	10	10	10	30
		Sub	—	10	10	10	30
		Dom	—	10	10	10	30
		Both	—	10	8	10	28
	Arthur	Cont	0	—	10	10	20
		Sub	0	—	10	10	20
		Dom	0	—	10	10	20
		Both	0	—	10	5	15
	Catherine	Cont	0	0	—	10	10
		Sub	0	0	—	10	10
		Dom	0	0	—	5	5
		Both	2	0	—	9	11
	Ann	Cont	0	0	0	—	0
		Sub	0	0	0	—	0
		Dom	0	0	5	—	5
		Both	0	5	1	—	6

*Cont—Both animals given vehicle.
Sub—Submissive animal given drug and dominant animal given vehicle.
Dom—Dominant animal given drug and submissive animal given vehicle.
Both—Both animals given drug.

Procedure (Paired Food Competition)

The dominance hierarchy was established prior to testing and was based on the number of apple pieces obtained in all possible pairs without any injections. The subjects of a pair were moved from their respective home cages to the test cage (a stainless steel home cage) and allowed to adapt to the cage and to each other for 15 min. Following the adaptation period, 10 apple pieces (each approximately 1/32 of a whole apple) were made available in a food hopper mounted on the cage door, one at a time at 1 min intervals. With each subject appearing 3 times in the 6 possible pairs, the maximum possible number of pieces that could be obtained was 30. The number of apple pieces obtained from the hopper was recorded for each animal, and certain other individual and interactive behaviors were noted.

Following this determination of the hierarchy, all possible pairs of the four subjects were tested for the effects of d-amphetamine (0.125 and 0.5 mg/kg, IM) and diazepam (Injectable Valium,® Hoffman-LaRoche, Nutley, NJ; 0.5 and

2.5 mg/kg, IM) on food competition. Injections were given in the respective home cages. Subjectives were immediately moved to the test cage where the same procedure was followed for adaptation and collection of number of apple pieces obtained. Subjects were tested in only one pair a day. Four testing situations existed: both animals given vehicle; both animals given drug; dominant animal given drug with the submissive animal given vehicle; submissive animal given drug with the dominant animal given vehicle. The vehicle for d-amphetamine control was saline. The vehicle for diazepam control was a solution of 10% ethanol, 40% propylene glycol and 50% water. Injection volumes ranged from 0.3 to 0.5 ml. Dosing was scheduled so that no animal received a drug more frequently than every 3 days. All possible combinations involving a single dose of a drug were tested before going on to the next dose.

RESULTS

Table 1 presents the results of the paired competition in all testing situations with both drugs. Results for only the high dose of each drug are presented, since the low dose of both drugs did not produce any change in the variable tested. From control sessions (both animals given vehicle) the dominance hierarchy in the paired competition situation (based on the number of apple pieces obtained) was determined to be the same as when no injections were given and was Henry, Arthur, Catherine and Ann in descending order.

The number of apple pieces obtained by each subject was altered from control only when the dominant animal of the pair or both animals were treated with d-amphetamine (0.5 mg/kg, IM) or diazepam (2.5 mg/kg, IM). In addition it was noted by the observer, that under control conditions, as well as when given either drug, Ann was usually competitive with Catherine. However, Catherine was defined as the dominant animal in control sessions since she obtained the greater number of apple pieces. In addition, it was noted that when dosed with d-amphetamine Catherine circled about the cage area almost constantly. Arthur also exhibited this behavior, but to a lesser extent than Catherine. There were some signs of CNS depression at both doses of diazepam tested.

EXPERIMENT 2

METHOD

Subjects

The same four animals that were used in the first procedure also served as subjects for this procedure. The same feeding regimen applied; however, less control was possible over the amount of chow consumed by each individual animal since the animals were fed as a group. Throughout the experiment, the animals were housed in a group cage (1.5 m wide, 2.1 m long, 2.1 m high). A food hopper was mounted on the outside of the front wall of the cage 35.6 cm above the floor and was easily accessible through the cage wire.

Procedure (Group Food Competition)

The effects of d-amphetamine (0.125, 0.5, and 2.0 mg/kg, IM) and diazepam (0.5 and 2.5 mg/kg, IM) on competition for food were recorded in this group situation. A random dosing schedule across both the doses used in paired competition and across drugs was employed. The highest dose of d-amphetamine, 2.0 mg/kg, was included as the last dose tested since results up to that point had revealed some effect at the 0.125 mg/kg dose, but not at the 0.5 mg/kg dose. Dosing was scheduled so that no animal received a drug more frequently than every 3 days. All animals were immobilized and given the same dose of a drug 15 minutes prior to an experimental session. On the intervening days, all animals received an intramuscular injection of the vehicle appropriate to the drug being tested. Subsequently 20 apple pieces were made available in the food hopper, one at a time at 1 min intervals. The number of apple pieces obtained by each animal was recorded. In addition the number of Purina® chows obtained by each subject from the food hopper was recorded after all the apple pieces had been presented. The chow was made available in the food hopper, one piece at a time at 1 min intervals up to 40 pieces of chow or 40 minutes. Following this, more chow was made available in the hopper to insure that all subjects had an opportunity to obtain food. The dispensation of these additional chows wasn't recorded.

RESULTS

Table 2 presents the results of the effects of diazepam and d-amphetamine on group competition for apple pieces. Table 3 presents the results on the number of monkey chows obtained from the food hopper by each monkey after all apple pieces had been presented.

The dominance hierarchy as determined from Table 3 agrees with the dominance hierarchy determined in paired competition for apple pieces. However, Table 2 indicates that Arthur was the most dominant animal when apple was presented to the group. The most striking deviation from control occurred when all subjects were dosed with 2.0 mg/kg d-amphetamine (Table 2). During this test Ann obtained all the apple pieces.

In addition it can be seen from Table 3 that changes occurred in the number of monkey chows obtained when the animals were dosed with both d-amphetamine and diazepam.

DISCUSSION

The control values shown in Table 1 for d-amphetamine and diazepam indicate that there was a consistency in the number of apple pieces obtained by each animal when paired against the other 3 animals. This would suggest that changes in the variable measured during test sessions were not due to variability in the behavior, but rather due to a pharmacological effect.

The paired competition data indicates that a submissive animal obtained some or all of the apple pieces in competition with a more dominant animal when the dominant animal was dosed or when both animals were dosed with the higher dose of either drug. This was particularly true for the pairing of Catherine vs Ann under the influence of d-amphetamine. There was normally some competition between these 2 animals even though Catherine always won in control sessions. Thus, perhaps the probability was greater that a change might occur in the number of apple pieces obtained when these two animals competed.

The same effect was also seen in the group competition though perhaps not as strongly, with the greatest effect being observed at the 2.0 mg/kg dose of d-amphetamine. The number of monkey chows obtained by individuals of the group in control sessions appears to correlate well with the paired competition data. However, Arthur obtained the greatest number of apple pieces in the group situation, not Henry. This alteration from the paired to the group control

TABLE 2

THE NUMBER OF APPLE PIECES OBTAINED BY EACH SUBJECT FROM THE FOOD HOPPER IN A GROUP SITUATION WITH A MAXIMUM OF 20 APPLE PIECES TOTAL POSSIBLE FOR ALL SUBJECTS

	D-amphetamine (mg/kg, IM)				Diazepam (mg/kg, IM)		
Subject	*Control	0.125	0.5	2.0	†Control (± SE)	0.5	2.5
Arthur	19.6 ± 0.4	15	19	0	20 ± 0	18	12
Henry‡	0 ± 0	0	0	0	0 ± 0	0	4
Catherine	0 ± 0	0	0	0	0 ± 0	2	4
Ann‡	0.4 ± 0.4	5	1	20	0 ± 0	0	0

*Mean (± SE) of 5 control sessions interspersed between experimental sessions.
†Mean (± SE) of 4 control sessions interspersed between experimental sessions.
‡Died within 24 hr after receiving 2.0 mg/kg, IM d-amphetamine.

TABLE 3

THE NUMBER OF PURINA® MONKEY CHOW OBTAINED FROM THE FOOD HOPPER IN A GROUP SITUATION WITH A MAXIMUM OF 40 CHOWS POSSIBLE FOR ALL SUBJECTS TOTAL‡

	D-amphetamine (mg/kg, IM)				Diazepam (mg/kg, IM)		
Subject	Control*	0.125	0.5	2.0	Control†	0.5	2.5
Henry	12.8 ± 2.4	4	18	22	19.0 ± 1.2	7	3
Arthur	7.8 ± 0.9	4	8	0	10.8 ± 0.6	8	10
Catherine	6.8 ± 1.4	1	0	0	6.8 ± 0.5	4	2
Ann	1.0 ± 0	1	12	14	1.8 ± 0.8	1	1

*Mean (± SE) of 5 control sessions interspersed between experimental sessions.
†Mean (± SE) of 4 control sessions interspersed between experimental sessions.
‡In some cases the total chow may not equal 40 if the chow was not retrieved from the food hopper in the 40 minute interval allowed for chow consumption.

situation indicates that the dominance-submissive relationships in a group are not simply one on one interactions, but are influenced by the presence of other members of the group. The reader should be reminded that the data in Table 3 (chow) was collected after the data in Table 2 (apple) and it is quite likely that, because Arthur normally obtained most of the apple pieces in control group competition, there was some effect on the number of chows that he obtained. Therefore, whereas the deprivation state was equal across subjects in the grouped apple competition, it was not equal for the grouped chow competition. In addition, since generally only one animal obtained apple pieces in the group control situation, the intricacies of the dominance-submissive relationships are not revealed by the presentation of the apple pieces. However, it is clear that under the effects of both d-amphetamine and diazepam in the group situation, animals which had previously failed to obtain apple pieces succeeded. These data suggest that social status may play an important role in determining the effects of drugs on food getting behavior in two different social situations (paired and group competition).

The data from both the paired and grouped competition indicate that diazepam and d-amphetamine exert similar effects on food-getting behavior. The manner in which these drugs exert their effects is not known; however, it is unlikely that they work via the same mechanism. In addition, differing effects generated in dominant and submissive animals may combine to yield the observed results, although the primary effect appears to be in the dominant animal. d-Amphetamine exerts an anorexigenic action; however, one or more animals continued to eat all the apple pieces available. Diazepam, on the other hand, is thought to stimulate food intake [1, 4, 14]. It is unclear from the data the degree to which these actions affect the results.

It is possible that, rather than affecting appetite, motivational factors are altered. Diazepam has been shown [5] to increase lever responding in rats during conflict periods in which food was paired with shock, and diazepam also increased consumption in rats naive to sweetened condensed milk as opposed to experienced subjects. It is postulated that these data indicate a disinhibition effect of diazepam. Motivational factors can also be affected by the presence of another animal and whether or not that animal blocks food-getting behavior, i.e., a dominant animal. It has been suggested that a stimulus "informational" exchange occurs between a competing pair such that that behavior of a dominant animal elicits fear in a submissive subject and thus depresses food-getting behavior. When only dominant animals are dosed with chlorpromazine [7], submissive animals obtained a greater than normal number of food pellets. These data are consistent with the results of this experiment and imply that the drug effect is primarily in the dominant animal and possibly is due to a breakdown in the "informational" exchange when the dominant animal is dosed. Diazepam, like chlorpromazine, exerts behavioral effects which may interfere with informational exchange. d-Amphetamine, on the other hand, is a CNS stimulant which elicits stereotypic behavior. When dosed with d-amphetamine, stereotypic behavior (circling cage area) was exhibited by Catherine and, to a lesser extent, by Arthur. At the highest dose administered (2.0 mg/kg, group competition) Ann was very active, whereas all the other members of the group were relatively inactive during the initial competition period. Stereotypic behavior might cause a more dominant animal to fail to occupy a position that he or she normally occupied when competing for apple pieces and thus cause a disruption in normal competition or informational exchange.

Other properties of diazepam may contribute to its effects on food-getting behavior. Diazepam has been shown to be an anti-anxiety agent by increasing responding in a conflict situation in squirrel monkeys [2]. Another study indicates that diazepam alleviates socially induced suppression of a behavior in cynomolgus monkeys [6]. In addition diazepam has been shown to decrease aggressive behaviors in rhesus monkeys [3].

It should be noted that the results of this experiment do not appear at first to agree with those of other investigators [3] although both experiments are based on the same premise. Other experimentation has determined that food pellet intake was decreased in submissive animals dosed with diazepam; however, both animals of a pair were not concurrently dosed. In our experiment it cannot be determined whether food intake decreased when only the submissive animal was dosed because the submissive animal of a pair did not obtain any apple pieces in the control sessions. However, when both animals were dosed, the submissive animals increased their food intake. Therefore the apparent differences could be due to differences in experimental procedure.

Of particular interest is the fact that 2 of the subjects, Henry and Ann, died within 24 hours after the administration of 2.0 mg/kg d-amphetamine. At this dose, Ann, the lowest ranking animal, obtained all the apple pieces and significant amounts of chow during competition. Furthermore she continued to eat from the daily ration of chow delivered to the group after the experimental session. Henry, although not eating any apples, consumed half of the initial 40 chows and also ate a larger than normal amount of chow after the experimental session. A necropsy revealed that in both cases the stomach was severely dilated. The cause of death was attributed to overeating. It has recently been reported [11] that the deaths of 18 non-human primates of various species were due to gastric dilatation.

In conclusion, it appears that the effect of drugs on food-getting behavior in competitive situations is in some manner influenced by the social status of the treated monkey. Furthermore this interaction was complicated by the social setting of the test situation. This is evidenced by the fact that whereas 0.5 mg/kg of d-amphetamine enhanced consumption by submissive subjects during paired competition, a similar effect did not result when this dose of d-amphetamine was administered in the group competition paradigm. It is quite conceivable that other pharmacological and toxicological measures may also vary depending on the social situation in which the treated subject is placed. Thus, results of experimentation in this area may be particularly applicable to the therapeutic uses of many agents affecting social behavior, as well as to the determination of the behavioral toxicology of abuse drugs used in a social setting.

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