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Effects of d-Amphetamine on Human Aggressive Responding Maintained by Avoidance of Provocation[1]

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CHEREK, D R , J L STEINBERG, T H KELLY AND C S SEBASTIAN *Effects of d-amphetamine on human aggressive responding maintained by avoidance of provocation* PHARMACOL BIOCHEM BEHAV **34**(1) 65–71, 1989 —Male subjects were administered placebo and three doses of d-amphetamine (5, 10 and 20 mg per 70 kg of body weight) under double-blind conditions in a laboratory setting which provided both aggressive and nonaggressive response options The nonaggressive response was button pressing maintained by the presentation of points which were exchanged for money The aggressive response was pressing another button which ostensibly resulted in the subtraction of points from a fictitious person Aggressive responding was initiated by subtracting points from the subject Point subtractions were attributed to the other person Aggressive responding was maintained by an avoidance contingency between aggressive responses and scheduled provoking point subtraction presentations d-Amphetamine increased nonaggressive responding, while aggressive responding was increased at the 10 mg dose and 20 mg resulted in significant decreases in aggressive responding relative to the 10 mg dose Comparisons with previous research indicate that the contingency relationship between aggressive responses and presentation of provoking point subtractions can alter the effects of d-amphetamine on aggressive responding

Aggressive d-Amphetamine Human Operant

THE relationship between d-amphetamine self-administration and human aggression has been discussed in a number of clinical articles. Intravenous self-administration of large doses of d-amphetamine (100–1000 mg per day) has been associated with instances of violence (4). Oral self-administration of large doses of d-amphetamine has also been linked to homicide and other aggressive behavior (11,24). In contrast, clinical doses of d-amphetamine administered to Attention Deficit Disorder children resulted in diminished aggressive behavior (1, 2, 22).

Biphasic effects of d-amphetamine on aggressive behavior have been reported in nonhuman subjects, with low doses increasing and high doses decreasing aggressive behavior [see review (16)] Inverted-U-shaped dose-response curves for the effects of d-amphetamine on aggressive and threat behaviors have been reported in stumptail macaque monkeys (3, 25, 26) Similar effects of d-amphetamine on shock-elicited biting has been observed in squirrel monkeys (12) Attacks against a resident intruder were also increased by low doses and decreased by high doses of d-amphetamine administered to rats and mice (18,21)

Our previous research indicated that human aggressive responding occasioned by provoking point subtractions had also evidenced inverted-U-shaped dose-response curves (7). Typically, aggressive responding was increased at low doses (5 and 10 mg/70 kg) and decreased to at or near placebo values following the administration of the highest dose (20 mg/70 kg). These biphasic effects were observed on aggressive responding occasioned by provoking point subtractions presented independently of the subject's aggressive responding In a subsequent study (8), the effects of d-amphetamine were determined on aggressive responding maintained by escape from scheduled provoking point subtractions. In that study (8), an escape contingency was stipulated between aggressive responses and provocations, and aggressive responding initiated intervals in which subjects were not provoked Under these circumstances, d-amphetamine produced small decreases in aggressive responding and no biphasic effects were observed

Behavioral studies in our laboratory, indicated that aggressive responding can be maintained by an avoidance contingency and

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under these experimental conditions subjects received very few provoking point subtractions (6) The present experiment sought to determine the effects of d-amphetamine on aggressive responding maintained by avoidance of schedule provocations

METHOD

Subjects

Eight male volunteers (age range 18–36 years) participated after giving their informed consent Subjects were recruited by newspaper advertisement soliciting participation in behavioral research projects In order to minimize possible interactions among subjects, volunteers that were students or employees of the medical center were not allowed to participate Subjects were given a complete physical examination, including EKG, a mental status examination and a structured psychiatric interview using the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-L) Subjects were excluded if any physical illness, or current or historical psychiatric disorder, including alcoholism and substance abuse, was detected Subjects that reported the use of any licit or illicit drug (except alcohol, caffeine and tobacco) were also excluded Urine samples were obtained at the beginning and periodically during participation and a complete drug screen analysis was performed to provide an objective assessment of the subject's current drug usage Detection of any drug in this sample resulted in the removal of the subject from the study Daily alcohol intake was monitored by assessment of the subject's blood alcohol level prior to each daily session using an Intoximeter Model 3000 III If the subject's expired air sample contained alcohol, the scheduled daily session was cancelled and the subject received no compensation If alcohol was detected prior to another session, the subject was removed from the study

Instructions

The advertisements and consent forms did not refer to aggressive behavior, since we did not want to imply that the subjects were required to respond aggressively in order to participate or earn money Subjects were told that the project for which they had volunteered involved the study of the effects of d-amphetamine on motor performance and physiological responses Subjects were shown a response console containing two push buttons and a counter, and were told that pushing button A would result in the addition of points to the counter which would be exchanged for money at the end of each session Subjects were informed that they would be paired with other individuals participating in the research project at the same time, but in different locations The term paired referred to hypothetical connections between the subject's console and the other person's console As a result of these connections, subjects were told that they could influence the amount of money earned by the other person by subtracting points from his counter Similarly, subjects were informed that these other people could choose to subtract points from them Subjects were instructed that pushing button B resulted in the subtraction of points from the other people, and these points were not added to the subject's point total Subjects were assured that these instructions were provided only for information, and they were not to assume that they were expected to push either button

To divert attention from the aggressive response option, subjects were given information about responding to earn money and the measurement of body temperature and peripheral blood flow Subjects were instructed that the number of times they pressed button A determined the amount of money they could earn However, there was an optimal rate of button pressing which would result in the accumulation of the maximum number of points The number of accumulated points could be reduced by responding too slowly or too rapidly Responding very rapidly reduced the number of points earned because an added time contingency stipulated that button presses occurring less than 125 msec apart would not count toward the accumulation of points Subjects were told that the investigators were interested in how efficiently subjects responded on this motor task In addition, at the beginning of each session, the middle finger of the subject's left hand was wiped with alcohol and a thermistor was attached with paper adhesive tape Subjects were told that this thermistor monitored their body temperature, pulse rate and peripheral blood flow throughout each experimental session These diversions served to emphasize that monetary reinforced responses and physiological measures provided valid experimental data and deemphasized aggressive responses as the primary dependent variable

Response Measures

Subjects were able to press either button A or B mounted on a response console (HTC-603, BRS/LVE) during daily experimental sessions The nonaggressive response option was pressing button A which resulted in the accumulation of points exchangeable for money Pressing button A was maintained by a fixed ratio (FR) 100 schedule of point presentation, i e , 100 consecutive presses produced one point Subjects were paid ten cents for each point on the counter at the end of each session

The aggressive response option was pressing button B which ostensibly delivered an aversive stimulus, i e , a point subtraction, to another person The completion of each fixed ratio (FR) 10 on button B ostensibly resulted in the subtraction of one point or ten cents from the other person

These two response options were concurrently available as nonreversible options The first response on either button A or B illuminated the button pressed and inactivated the other button When the ratio requirement for the illuminated button was completed (either 10 or 100 responses), the stimulus light on that button was extinguished and both response options became available

Provocations (Subtraction of Points)

Aggressive responses were initiated by the subtraction of previously accumulated points from the research subject These provoking point subtractions were attributed to the other person Each point subtraction decreased the display counter by one unit, i e , ten cents, and was signalled by an audible click and brief illumination of a stimulus light at the bottom of the counter Point subtractions were scheduled to occur at random times throughout the daily experimental session

Consequences of the Subject's Aggressive Responses

In this experiment, we specified a consequence contingent upon completion of a fixed ratio (FR) 10 on button B, i e , aggressive responding The consequence was an interval of time free from subsequent point subtractions ostensibly presented by the other person This interval was termed a provocation-free interval or PFI

Approximately forty (40) point subtractions were scheduled for presentation at random times throughout each session In addition to ostensibly subtracting a point from the other person, ten aggressive responses on button B initiated a provocation-free interval (PFI) during which point subtractions were not presented Subjects were assigned to PFI durations of either 125 or 500

seconds. When the PFI had elapsed, point subtractions were again scheduled to occur at random time points Subjects were not informed of these contingencies.

The contingent relationship between aggressive responses and the PFI was avoidance Under this avoidance contingency, each completion of an FR 10 on button B initiated a PFI, or if the ratio was completed during a PFI the duration of the PFI was reset to zero Thus, with this avoidance contingency, it was possible for subjects to avoid all scheduled point subtractions

d-Amphetamine

All research subjects came into the medical center for daily 50 minute sessions, 5 days per week Thirty minutes before daily sessions, subjects were required to drink twelve ounces of tonic water which contained either placebo or d-amphetamine elixir The placebo consisted of tonic water and 10 ml of wine, since the d-amphetamine elixir is a wine base Since the d-amphetamine elixir was orange, two drops of food coloring were added to each drink to give the beverage the same orange color.

The d-amphetamine was administered in doses of 5, 10 and 20 mg per 70 kg of body weight The equivalent doses in mg/kg were 0 07, 0 14 and 0 28 mg/kg Successive drug doses were separated by at least 48 hours and were administered when the frequency of aggressive and nonaggressive responses during placebo sessions were within variability ranges observed prior to drug administration All placebo and drug doses were administered double-blind Drug doses were presented initially in an ascending sequence and then randomly over successive sessions, with each drug dose presented three times

Profile of Mood States (POMS)

Subjects completed the Profile of Mood States (POMS) questionnaire at the end of each session Scores from the POMS were combined into six categories Tension, Depression, Confusion, Vigor, Anger and Fatigue (18)

Debriefing

Prior to debriefing, subjects completed a series of brief questionnaires to determine if the instructional deception had been successful and subjects thought that they were paired with other subjects during the experiment While subjects were required to complete these questionnaires, there were no consequences, i e , monetary payments, attached to the content of their answers Research subjects were not actually paired with other people, and they were debriefed and informed of this at the end of the experiment Subjects were informed that responding aggressively to provocation was an expected reaction

Statistical Analysis

An analysis of variance (ANOVA) was performed for each response option with repeated measures on the factors d-amphetamine dose and sessions (31) If the main effect of d-amphetamine dose was significant, then post hoc comparisons between each dose were performed using the Tukey Honestly Significant Difference (HSD) Test (31) If the main effect of d-amphetamine dose was not significant, then planned comparisons were made between placebo and the highest d-amphetamine dose. Comparisons between d-amphetamine effects upon aggressive responding maintained by escape from scheduled provocations (previous study) and aggressive responding maintained by avoidance of provocation (this experiment) were made by split-plot ANOVA analysis (31)

RESULTS

Answers to the questionnaires at the end of the experiment indicated that three subjects (S-171, S-182 and S-242) were not certain that they had been paired with other individuals during the experiment These three subjects attributed this uncertainty to the lack of aggressive responding (point subtractions) by the other people in the presence of the subject's button B responding Although these subjects periodically provoked the other person, the other subjects did not retaliate This problem of maintaining instructional deception was not observed when an escape contingency was specified (8) The avoidance contingency ensured that the subjects would continue to respond on button B, however, this contingency did not ensure that subjects would attribute point subtractions to another person and believe that they were paired with another person

During the initial sessions, subjects emitted aggressive responses shortly after provocation As the subjects began to emit aggressive responses in the immediate absence of provocation (during a PFI), the avoidance contingency altered aggressive responding so that it began to occur with increased probability in the absence of provocation. Subjects appeared to use the addition of points to the counter as a discriminative stimulus, in that, they would typically complete a number of successive ratios (4–8) on button A and then switch to the aggressive response option (button B) Typically, subjects would complete only a single FR 10 on button B (subtract a single point from the other person), and then switch back to nonaggressive responding (button A)

The effects of placebo (0) and three doses of d-amphetamine (5,10 and 20 mg per 70 kg of body weight) on the number of aggressive responses per session for all subjects are shown in Fig 1 The dose-response curves are expressed as percent changes from the mean placebo value set at zero. d-Amphetamine generally increased aggressive responding at the 10 mg per 70 kg dose Five of the eight subjects increased aggressive responding following administration of the 10 mg per 70 kg dose Following administration of the highest d-amphetamine dose (20 mg per 70 kg), aggressive responding typically decreased, relative to the 10 mg per 70 kg dose, to or below placebo values Two subjects (S-238 and S-242) emitted the highest number of aggressive responses following the 5 mg per 70 kg dose, and the higher d-amphetamine doses reduced aggressive responding to placebo levels Seven of the eight subjects evidenced inverted-U-shaped dose-response curves, with peaks at 5 or 10 mg per 70 kg doses. Only one subject (S-182) consistently decreased aggressive responding following d-amphetamine administration A repeated measures ANOVA indicated that the main effect of d-amphetamine dose was significant, $F(3,21) = 3\ 22$, $p < 0\ 04$. Post hoc comparisons using Tukey's Honestly Significant Difference (HSD) Test (31) indicated that although the increase in aggressive responding was highest following the 10 mg per 70 kg d-amphetamine dose these changes were not significantly different from placebo The only significant difference indicated by Tukey HSD Test was between aggressive responses at 10 and 20 mg per 70 kg doses ($p < 0\ 05$)

Under placebo conditions, subjects typically switched to the aggressive response option after completing a number of FR 100 ratios on button A Subjects usually completed an FR 10 ratio, i.e , subtracted one point from the other person, and then returned to the nonaggressive response option The frequency of switching was related to the duration of the PFI, with subjects switching to the aggressive response option more frequently at PFI of 125 seconds Occasionally subjects would receive a provoking point subtraction, and these occurred more frequently among subjects assigned to a PFI duration of 125 seconds. Subjects assigned to the PFI of 500 seconds, had a much larger decrease in aggressive

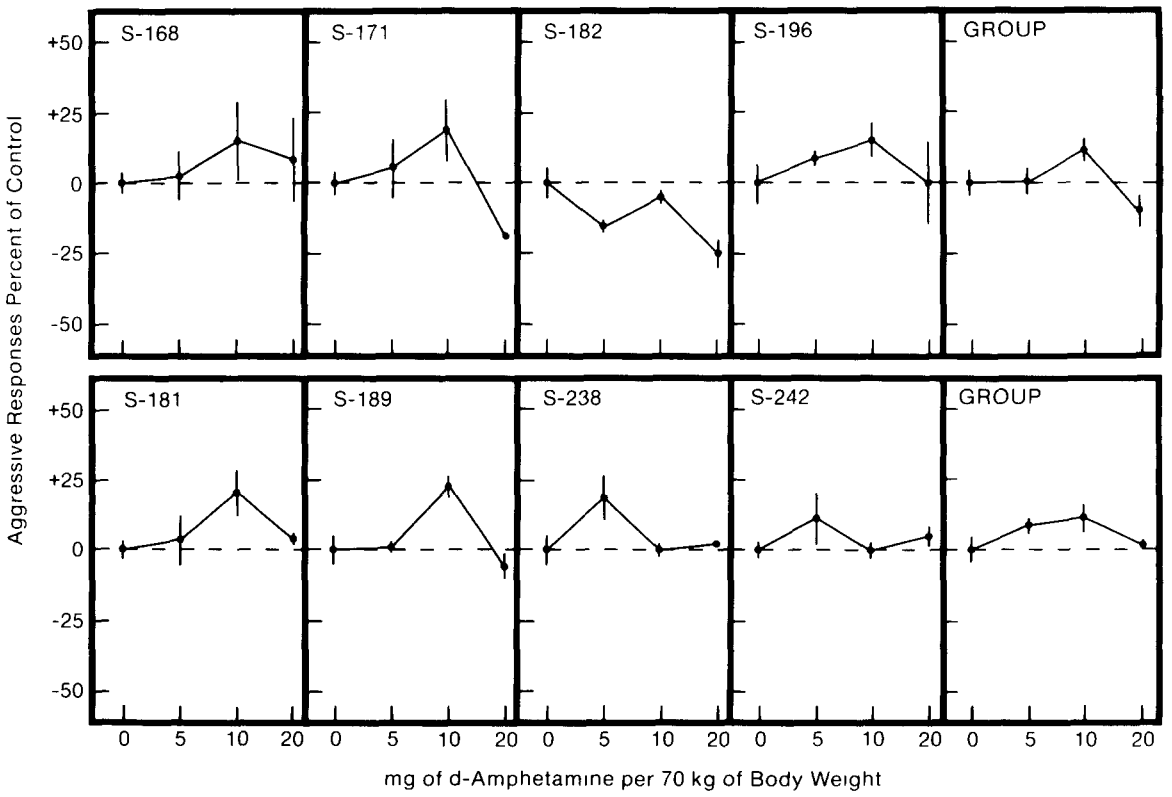

FIG 1 The effects of placebo (0) and three doses of d-amphetamine (5, 10 and 20 mg per 70 kg of body weight) on aggressive responding Data points are expressed as percentage changes from mean placebo session values set at zero Drug data points represent the mean of three different sessions Vertical lines at all data points represent ± S E M Subjects assigned to PFI durations of 500 seconds are shown in the top half of the figure, and those assigned to PFI durations of 125 seconds are shown in the bottom half of the figure Group data are shown in the extreme right column

responding relative to placebo following the administration of the highest d-amphetamine dose Because of the longer PFI duration (relative to 10 mg per 70 kg dose) frequency of aggressive responding could decrease more without coming into contact with the point subtractions

The effects of placebo (0) and the three doses of d-amphetamine (5, 10 and 20 mg per 70 kg) on the number of nonaggressive responses per session for all subjects are shown in Fig 2 The dose-response curves are expressed as percent changes from the mean placebo value set at zero Nonaggressive responding was increased particularly at 10 and 20 mg per 70 kg d-amphetamine doses A repeated measures ANOVA indicated that the main effect of d-amphetamine dose on nonaggressive responding was significant, $F(3,21) = 17\ 70$, $p<0\ 0001$ Post hoc comparisons using Tukey's HSD Test (31) indicated that both the 10 and 20 mg per 70 kg d-amphetamine doses resulted in increased nonaggressive responding that was significantly different from placebo levels ($p<0\ 01$) The 20 mg per 70 kg d-amphetamine dose also resulted in increased nonaggressive responding which was significantly different from the 5 mg per 70 kg d-amphetamine dose ($p<0\ 01$)

Subjects completed the Profile of Mood States (POMS) questionnaire at the end of each session MANOVA analysis indicated that there were no significant changes in the six categories of the POMS as a function of d-amphetamine dose

Figure 3 depicts the group results for all subjects in the present study showing the effects of d-amphetamine dose on aggressive responding maintained by avoidance of provocation (closed circles) In addition, the results of a previous study (8) showing the effects of d-amphetamine dose on aggressive responding maintained by escape from provocation are also shown (open circles) All methods and procedures in this earlier study (8) were the same as the current study, except aggressive responding was maintained by an escape rather than an avoidance contingency The two dose-response curves indicate that the effects of d-amphetamine are altered by the specified contingency between aggressive responding and provoking point subtractions which set the occasion for such responding A split-plot ANOVA indicated that the effect of the contingency (avoidance vs escape) was significant, $F(1,3) = 6\ 61$, $p<0\ 02$, indicating that the effects of d-amphetamine on aggressive responding varied as function of contingency stipulated between that responding and scheduled provocations

DISCUSSION

The effects of d-amphetamine on aggressive responding maintained by the avoidance of scheduled provocations produced inverted-U-shaped dose-response curves The administration of 10 mg of d-amphetamine per 70 kg of body weight increased aggressive responding, while the 20 mg per 70 kg dose decreased aggressive responding relative to the effects of 10 mg, to at or near placebo values Similar results have been previously reported using the same methodology (7), when provoking point subtractions were presented independent of the subject's aggressive responding Previous animal research has also observed inverted-U-shaped dose-response relationships between aggressive behavior and d-amphetamine dose (3, 12, 16, 21, 25, 26) These results

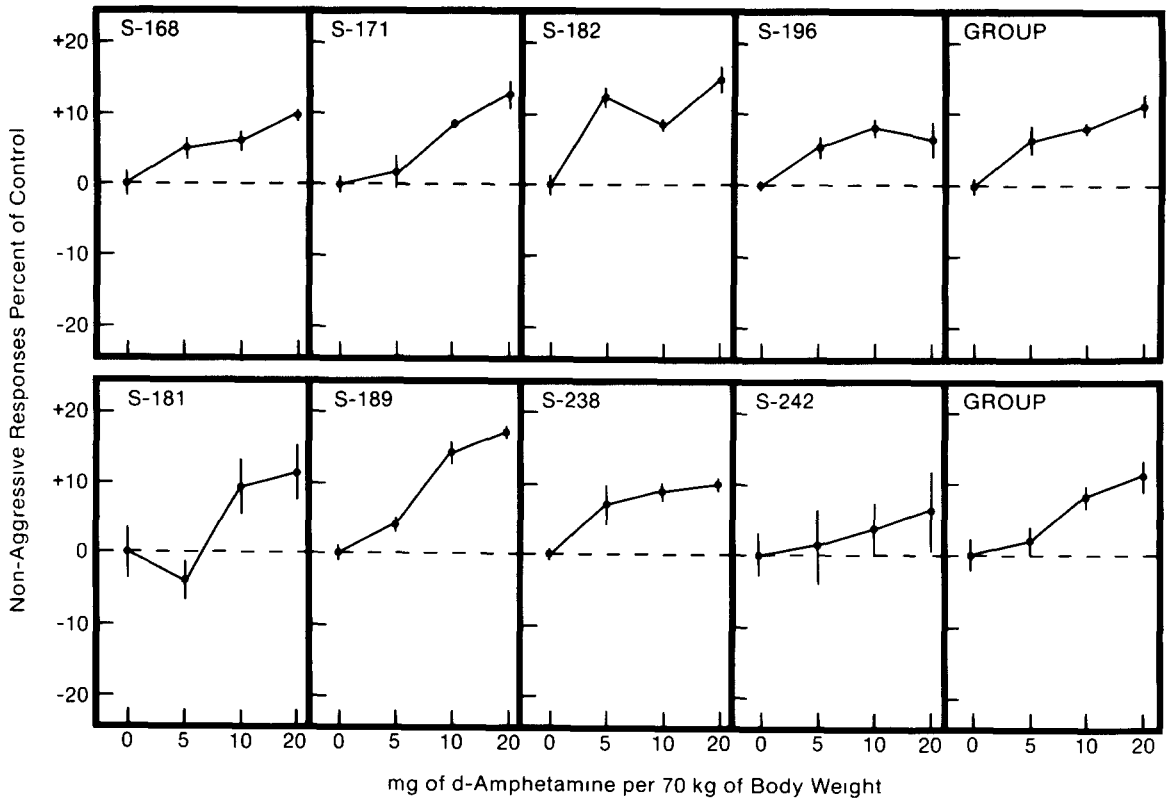

FIG 2 The effects of placebo (0) and three doses of d-amphetamine (5, 10 and 20 mg per 70 kg of body weight) on nonaggressive responding Data points are expressed as percentage changes from mean placebo session values set at zero Drug data points represent the mean of three different sessions Vertical lines at all data points represent ± S E M Subjects assigned to PFI durations of 500 seconds are shown in the top half of the figure, and those assigned to PFI durations of 125 seconds are shown in the bottom half of the figure Group data are shown in the extreme right column

are quite different from the effects of d-amphetamine on aggressive responding maintained by escape from schedule provocations (8), where aggressive responding decreased slightly following d-amphetamine administration

The administration of d-amphetamine resulted in dose-dependent increases in nonaggressive responding, an effect which we have reported in two previous studies (7,8) Similar increases have also been observed on point maintained responding in humans at smaller fixed ratio (FR) values (28). These effects are in marked contrast to the effects on concurrent aggressive responding

In evaluating the effects of any drug on aggressive behavior, it is important to consider the specificity of action (9, 20, 29) One method used to evaluate the specificity of drug effects and to identify a general nonspecific stimulant or depressant action is to determine the effects on more than one response option available to the subject (23). When contrasting the effects of d-amphetamine on aggressive and nonaggressive responding, there is an apparent specificity detected at the highest d-amphetamine dose (20 mg per 70 kg) At this dosage, nonaggressive point maintained responding continued to increase relative to the lower doses, while aggressive responding decreased and returned to placebo levels As discussed in our previous research (8), the decreased aggressive responding at the 20 mg per 70 kg dose cannot be attributed to a generalized depressant effect since nonaggressive responding was increased Likewise, this decrease cannot be explained by induction of behavior incompatible with aggressive responding, since button pressing maintained by point presentation was not disrupted

The behavioral effects of d-amphetamine are influenced by the ongoing rate of responding prior to drug administration (10,15) However, in this experiment similar rates of responding were maintained on both the aggressive and nonaggressive response options Rate of responding refers to running rate of button pressing, i e , the rate of responding between the initial choice response (which illuminates the button selected) and the completion of the ratio requirement for that button. Button pressing was maintained at very stable and high rates (3 5 to 5.0 responses per sec) and was not influenced by manipulanda (A vs. B) Subjects maintained a uniform rate of button pressing throughout each session and occasionally switched from one manipulanda to the other Postreinforcement pausing following either point presentation or ostensible point subtraction from the other person were absent

The pattern of aggressive responding engendered by an avoidance contingency are different than those occurring under an escape contingency In our previous research (7,8), we have reported that aggressive responding typically involves a pattern of completing several fixed ratio (FR) 10 on button B, i e , subtracting multiple points from the other person, before returning to the nonaggressive response option when an escape contingency was stipulated between aggressive responses and scheduled provocations Under these conditions, the pattern of aggressive responding and nonaggressive responding are similar As discussed in the Results section, the pattern of aggressive responding under an avoidance contingency typically involves the completion of a single FR 10 ratio on button B, and the immediate return to nonaggressive responding. This difference in pattern of aggressive

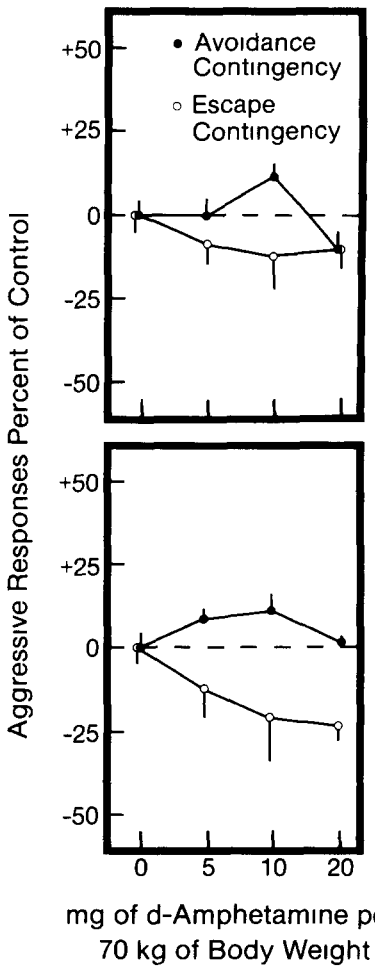

FIG 3 The effects of placebo (0) and three doses of d-amphetamine (5, 10 and 20 mg per 70 kg of body weight) on aggressive responding maintained by avoidance of scheduled provocations (closed circles) or escape from scheduled provocations (open circles) Data points are expressed as percentage changes from mean placebo session values set at zero Data points represent mean values of four different subjects Vertical lines at all data points represent ±S E M Subjects assigned to PFI durations of 500 seconds are shown in the top half of the figure, and those assigned to PFI durations of 125 seconds are shown in the bottom half of the figure Avoidance contingency data is from the present study, and escape contingency data from a previous study (8)

responding may contribute to the differences in effects of d-amphetamine on aggressive responding maintained by avoidance versus an escape contingency (Fig 3) However, previous research indicates that d-amphetamine has similar effects on fixed ratio (FR 30) (24) and fixed ratio (FR 100) responding (7,28)

The type of stimulus control evidenced under avoidance and escape contingencies also differs Under the escape contingency, aggressive responding occurred shortly after provocation and rarely in the immediate absence of provocation Under the avoidance contingency, aggressive responding occurred in the absence of provocation, and provocation was very infrequent d-Amphetamine decreased the number of successive ratios completed on the B button (aggressive responding) maintained by an escape contingency which resulted in a decreased frequency of aggressive responding which did not alter the frequency of provocation (8) The provocation still reliably set the occasion for aggressive responding, but the frequency of aggressive responding per instance of provocation was reduced Also, following d-amphetamine administration, subjects would occasionally not respond aggressively following provocation Under the escape contingency, d-amphetamine decreased the stimulus control exerted by provocation on aggressive responding Under the avoidance contingency, both aggressive and nonaggressive responding were increased at low doses, and aggressive responding was decreased at the higher doses These effects reflected changes in frequency of switching from the nonaggressive option, rather than effects upon the frequency of aggressive responding per episode which remained unchanged

The demonstration that d-amphetamine effects upon aggressive responding using the free-operant methodology (5) were altered by the contingency stipulated between these responses and scheduled provocation asserts that the observed drug effects were altered by environmental contingencies, i e , a behavioral mechanism of drug action (29,30)

The effects of d-amphetamine on aggressive responding were determined while such responding was maintained by an avoidance contingency Studies of continuous avoidance responding with nonhuman subjects indicated that d-amphetamine increased avoidance responding at lower doses, while higher doses decreased avoidance responding (13, 14, 27) These results are similar to the effects of d-amphetamine on aggressive responding maintained by an avoidance contingency in the present experiment However, the effects of d-amphetamine on simultaneously occurring nonaggressive responding, indicated that this decrease was specific to aggressive responding and was not the result of a nonspecific depressant effect of high doses of d-amphetamine

One problem which developed with the avoidance contingency, was maintenance of the instructional deception With the avoidance contingency in place, the subject receives little or no provocation, i e , aggressive responding by the other person directed at the subject, although the subject periodically provokes the other person throughout the session Some subjects indicated during postexperiment interviews that they began to question the presence of another person, because they failed to retaliate

Both nonaggressive and aggressive responding increased at low d-amphetamine doses indicating a possible nonspecific effect At higher doses the lower probability aggressive response began to decrease Similar types of inverted-U-shaped dose-response relationships have been described for a variety of response classes [e g , (17)] If one assumes that at higher doses d-amphetamine acts to reduce the array of response classes which the organism will engage in, then one would expect lower probability responses to diminish, and higher probability responses to be maintained or increased A narrowing of the behavior repertoire of the organism would occur, as the result of drug action Such an interpretation of d-amphetamine effects on aggressive responding in the present experiment may indicate that decreased aggressive responding observed with d-amphetamine might represent an effect upon a lower probability behavior, rather than a particular response class

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