THE DEVELOPMENT OF CONTEXT-SPECIFIC OPERANT
SENSITIZATION TO \textit{d}-AMPHETAMINE

by

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ABSTRACT

The Development of Context-Specific Operant Sensitization to \(d\)-Amphetamine

by

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Utah State University, 2009

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Animal models have previously been used to study tolerance and sensitization using two different procedures that are difficult to compare. Tolerance has been studied by administering a drug to a subject that is engaged in an operant behavior, and sensitization by administering a drug to a subject that is not engaged in an operant behavior. Previous research has shown that sensitization can occur when \(d\)-amphetamine is administered to rats emitting an operant behavior for a food presentation. The first goal of the experiment was to show operant sensitization using dose response curves. The second goal of the present experiment was to determine if operant sensitization is context specific. These goals were addressed by administering \(d\)-amphetamine to rats engaged in an operant behavior in two stimulus contexts and creating dose-response curves. Sensitization occurred but was not found to be context-specific, with the dose-response curves not being significantly different between the two contexts. It is not clear whether
this result was due to the drug administration procedure or the counterbalancing assignments used. Further research is needed to determine whether operant sensitization is context specific.
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9. Individual response-rate data expressed as proportion-control responses per minute in the context the same as and different from the one in which chronic administration of \(d\)-amphetamine occurred. Other details as in Figure 8.
CHAPTER I
INTRODUCTION

Drug addiction is a persistent problem in today's society. Many factors have been shown to play a role in the development of addiction, including the environment in which one uses a drug, tolerance to the effects of a drug (a decrease in the effectiveness of a drug), and sensitization to the effects of a drug (an increase in the effectiveness of a drug). Animal models have been created to study the role of the environment in the development of tolerance and sensitization. These findings, in turn, may be generalizable to humans and ultimately prove to be useful in helping a person overcome drug addiction.

Tolerance is a key element of drug addiction because as one continues to use a drug, the effectiveness of the drug tends to decrease, thus resulting in the user taking larger and larger doses to achieve the same effect. This in turn may lead the user to start abusing the drug. In experiments with nonhuman subjects, tolerance typically occurs when the animal is required to engage in purposeful (operant) behavior. This is true for various topographies of responding, lever pressing as well as head movement (Wolgin & Wade, 1995). Previous research suggests that the development of tolerance may be seen as a compensatory mechanism, counteracting any drug-induced effects that interfere with an animal’s ability to receive food (Wolgin, 2000). In Carlton and Wolgin (1971), tolerance to the initial suppressive effects of amphetamine on feeding occurred when amphetamine was administered in an environment containing food but not in an environment where food was absent.
Tolerance does not typically occur in arrangements where the animal does not have to work for food. Instead sensitization, a second key element of drug addiction, occurs. After repeated administrations of a drug, incentive motivation and reward systems in the brain become hypersensitive to drugs and drug-associated stimuli, increasing the likelihood that an individual will engage in drug-seeking and drug-taking behavior (incentive sensitization; Robinson & Berridge, 2000). Behavioral sensitization in nonhumans is studied in open field experiments in which a drug is administered and the animal’s activity is recorded (Kilbey & Sannerud, 1985). Behavioral sensitization has also been shown to occur in an operant chamber when the animal is not presented with an operant task and instead its behavior is recorded as if it were in an open field experiment (Pinkston & Branch, 2003).

Both behavioral sensitization and operant tolerance have been shown to only occur under circumstances similar to those when the drug was administered repeatedly. For example, in Smith (1990), tolerance to the rate-decreasing effects of cocaine occurred only in that context that cocaine was administered when rats completed three different tasks in three different chambers. The same is true of sensitization. When subjects receive a drug in a context in which they were previously exposed to a drug, then an increase in the effects of the drug is seen. Likewise, if a subject receives a drug in a context where the drug was not previously administered, then an increase in the effects of the drug does not occur (e.g., Rademacher, Napier, & Meredith, 2007).

Previous research has shown that under some circumstances sensitization may also develop when subjects complete an operant task, as observed by Odum and Shahan (2004). In their experiment, sensitization to the rate-decreasing effects of d-amphetamine
developed when the drug was administered to rats pressing a lever for food. However, sensitization was assessed by observing how a single dose of $d$-amphetamine administered daily over a period of time affected lever pressing. Dose-response curves were not used to analyze the drug’s effects.

The purpose of the present experiment is to demonstrate the development of sensitization using dose-response curves and to show that operant sensitization is context specific. The same strain of rats will respond on the same schedule of food delivery that was arranged in Odum and Shahan (2004) and will receive $d$-amphetamine injections. Dose response curves will be created and postchronic effects will be compared to prechronic effects. Rats will respond in two different contexts signaled by visual and auditory stimuli on alternating days and will only receive chronic $d$-amphetamine injections in one of these contexts. It is expected that sensitization will develop in the context in which the chronic injections occur and will not generalize to the other context.
CHAPTER II

LITERATURE REVIEW

Drug addiction, defined as a compulsive pattern of drug-seeking and drug-taking behavior that takes place to the exclusion of other activities, is a persistent problem (Hasin, Hatzenbuehler, Keyes, & Ogburn, 2006). It is estimated that drug abuse costs America more than $484 billion a year (National Institute of Drug Abuse, 2008). However, research shows that addiction is not an inevitable outcome of drug abuse (Robinson & Berridge, 2000). For instance, individuals who use drugs frequently in one situation may be able to cease this use in another situation. For example, many soldiers who had used heroin in Vietnam returned to America, their heroin taking ceased (Zinberg, 1974). This is just one example of how important the environment is in influencing drug-taking behavior.

Taking a drug repeatedly can result in either tolerance or sensitization. Tolerance is a decrease in the effectiveness of the drug after chronic administration; sensitization is an increase in the effectiveness of the drug after chronic administration (Stewart & Badianai, 1993). A change in the effectiveness of a drug is determined by administering a variety of doses immediately prior to and immediately after chronic administration in order to create dose response curves. The effectiveness of each dose after chronic administration is compared to its effectiveness before chronic administration. Tolerance is defined as a shift to the right in the dose-response curve after repeated administrations of a drug and sensitization as a shift to the left. Therefore, if tolerance to the effects of a drug develops, then more of the drug is needed to produce the original effects of the drug.
If sensitization develops, then less of a drug is needed to produce the original effects of the drug.

Tolerance has been shown to be one process involved in the development of drug addiction. Tolerance can result in more of a drug being needed to achieve the same initial effect. Tolerance can either occur passively or be conditioned. Passive tolerance occurs when changes occur to any of the mechanisms that come into play between when a drug was administered and when the drug has its pharmacological effects (Stewart & Badiani, 1993). Unlike passive tolerance, contingent tolerance results when earning a reward depends on the development of tolerance to counteract those effects of a drug that interfere with the individual obtaining that reward.

Sensitization is another process that has been shown to play a role in compulsive drug seeking. Robinson and Berridge (2000) have postulated that incentive-sensitization may provide some insight into drug addiction. They argue that potentially addictive drugs are able to produce long-lasting changes in the incentive motivation and reward systems in the brain. These systems become hypersensitive to drugs and drug-associated stimuli and result in the individual engaging more frequently in drug-seeking and drug-taking behavior.

Animal models have been created to study tolerance and sensitization in the laboratory. Stimulant drugs such as cocaine and amphetamine are a common type of drug used when tolerance and sensitization are studied in the laboratory. The use of amphetamines is common to research investigating the behavioral effects of drugs due to these drugs acting on the central nervous system (Stewart & Badiani, 1993). The conditions arranged in an experiment may play a role in determining whether tolerance or
sensitization to the effects of a drug will occur. Tolerance has typically been studied by administering a drug and then requiring the subject to engage in some kind of operant behavior, such as having pigeons peck a key or rats press a lever for food presentation (e.g., Wolgin, 1989). Sensitization has typically been studied by administering a drug and then not requiring the subject to engage in purposeful behavior; the experimenter simply observes the effects of a drug on behavior, such as repeated circling of the cage (locomotor activity) or repetitive body movements (stereotypy; e.g., Kilbey & Sannerud, 1985).

According to Eikelboom and Stewart (1982), feedback systems in the central nervous system regulate whether or not tolerance or sensitization will occur. If environmental stimuli do not signal a drug administration will occur, the drug effect will not be attenuated. If however the environmental stimuli signal a drug administration, the central nervous system will attempt to attenuate the drug effect. It is difficult to predict if the drug effect will be attenuated by tolerance or by sensitization.

Factors Involved in the Development of Tolerance

Schuster, Dockens, and Woods (1966) formulated the reinforcement density hypothesis in an effort to explain the development of tolerance. This hypothesis states that when the effects of a drug result in a diminished ability to emit the operant behavior, such that food presentations occur less frequently, then tolerance develops. For example, in Smith (1986), rats received chronic injections of amphetamine for 30 days while responding on a two-component multiple schedule. In a multiple schedule, two schedules of food presentation that alternate are signaled by unique stimuli, such as a particular
colored cue light above the response lever (Ferster & Skinner, 1957). In one of the components, a random-ratio (RR) schedule operated, such that 2.5% of the responses emitted resulted in food presentation (see Lattal, 1991). In the other component, a differential-reinforcement-of-low-rates (DRL) schedule operated: food presentations only occurred when the rat responded at a slow pace (Ferster & Skinner).

Smith (1986) found that tolerance developed in the RR component, but not in the DRL component. He concluded that this effect occurred because RR responding decreased as a result of d-amphetamine administration, resulting in a decreased rate of food presentations. In the DRL component, d-amphetamine administration resulted in a decreased rate of food presentations and tolerance was not observed. Smith concluded that tolerance was not observed because even though the amount of food presentations in the DRL component was reduced, the rat could still earn a high rate of food in the RR component. However, when the RR component was removed, tolerance developed during the DRL component. This is because when the rate of food presentations depended solely on the DRL component, tolerance developed in the DRL component to increase the rate of food presentations. Interestingly, when the RR component was reinstated, tolerance occurred once again in the RR component but was lost in the DRL component.

Tolerance has also been shown to develop in behavior maintained on a fixed-ratio (FR) schedule. In Experiment 1 of Pinkston and Branch (2003), pigeons pecked a key that resulted in food presentation after every 20th response, an FR 20 schedule (Ferster & Skinner, 1957). When cocaine was administered chronically, tolerance developed to the response-rate decreasing effects. Because the relation between the rate of responding and
the rate of reinforcement in an FR schedule is a linear function, the rate of reinforcement was also disrupted, which presumably lead to the development of tolerance.

Tolerance will also develop when a requirement is placed on body movement. For example, in Salisbury and Wolgin (1985), one group of rats obtained milk by drinking out of a bottle; another group of rats obtained milk via an intraoral cannula. When amphetamine was administered, tolerance to the drug’s stereotypy-inducing effects developed in only that group of rats who obtained milk by drinking out of a bottle. It was concluded that tolerance developed because amphetamine interfered with the rat’s ability to drink out of the bottle, and thus resulted in reinforcers lost. In the intraoral cannula group however, the rats could still obtain milk even when emitting stereotypy because the device delivered milk directly into their mouths and so no reinforcers were lost. These results were further investigated in Wolgin and Wade (1995). In this experiment, two groups of rats were implanted with intraoral cannulas that delivered milk. For one group of rats, milk was delivered regardless of what behavior was emitted. For the other group, milk was delivered only if the rats held their heads still (i.e., emitted no stereotypy). When amphetamine was administered, tolerance to the drug’s stereotypy-inducing effects developed only in rats in which milk deliveries were contingent on the absence of stereotypy. This is presumably because the stereotypy caused by the amphetamine resulted in a decrease in the rate of milk presentations obtained. Hughes, Popi, and Wolgin (1998) showed that it is possible to suppress stereotypy, even sensitized stereotypy, by requiring the animal to emit a specific response to obtain a reward.
Sensitization of Locomotor Activity and Stereotypy

Sensitization of locomotor activity and stereotypy typically develops when a stimulant is administered to an animal that is not required to work for food but whose activity is observed instead (Kilbey & Sannerud, 1985). After repeated administrations, the amount of locomotor activity and stereotypy is greater than what was initially observed. In general, the amount of drug that is administered is proportional to the amount of stereotypy and inversely related to the amount of locomotor activity observed. Stereotypy has also been found to develop in a standard operant chamber. In Experiment 2 of Pinkston and Branch (2003), naïve pigeons were placed in an operant chamber with no programmed consequences. When cocaine was administered chronically, sensitization to cocaine's activity-inducing effects occurred for all pigeons in this part of the experiment.

Context-specific Tolerance

The development of tolerance to those effects of a drug that result in a loss of food has been shown to be context dependent. For example, if a rat presses a lever to receive food in two contexts and drug is administered in only one context, then tolerance to the effects of the drug that interfere with lever pressing will only occur in the context in which the drug was administered. In other words, the environmental context acquires control over the drug response being expressed (Wolgin, 2000). When the drug is first administered in the second context, it will have a greater effect in this context than in the first context, thus indicating that tolerance did not transfer to this new context.
For example, in Smith (1990), subjects completed a Sidman avoidance preparation in one chamber, a fixed-interval (FI) task in a second chamber, and an FR task in a third chamber daily. In the Sidman avoidance preparation, a rat presses a lever to delay the delivery of shocks (Sidman, 1953). It is possible for the rat to respond in such a way that no shocks are delivered during the session. In an FI task, the first response after a specified time interval elapses results in the presentation of food (Ferster & Skinner, 1957). Responding before the interval elapses has no programmed consequences. Rats received cocaine every day for 4 weeks immediately after FR responding. Cocaine was then administered daily for 4 weeks before FR responding, then daily for 4 weeks before FI responding, and finally daily for 4 weeks before avoidance responding. Tolerance developed in the FI and FR tasks only when cocaine was administered prior to those tasks. This result may be explained by the reinforcement density hypothesis. Cocaine resulted in decreased response rates during the FI and FR tasks, and thus a loss in the rate of food presentations obtained, presumably leading to the development of tolerance. Neither tolerance nor sensitization developed in the avoidance task. Cocaine administration in the avoidance task resulted in an immediate two-fold increase in response rates compared to baseline, and consequently a decrease in the number of shocks experienced. These response rates remained elevated. Smith concluded that the development of tolerance that results when food presentations are lost is context specific. This is because tolerance developed in the FI and FR tasks, but only when cocaine was administered immediately before each task.
Context-specific Sensitization

The development of sensitization that occurs in an open field is also context specific. In Rademacher and colleagues (2007), pairing d-amphetamine injections with one context increased motor activity, even when subjects were tested with saline. Rats received d-amphetamine on alternating days and were placed in either the left or right outer compartment of a three-compartment operant chamber. Saline injections were given on intervening days and the rats were then placed in the opposite outer compartment. On the fifth day, one group of rats received d-amphetamine before being placed in the d-amphetamine-paired compartment, one group received d-amphetamine before being placed in the saline-paired compartment, one group received saline before being placed in the d-amphetamine-paired compartment, and the last group received saline before being placed in the saline-paired compartment. An increase in the amount of motor activity was observed after the rat was placed in the d-amphetamine-paired compartment, regardless of whether d-amphetamine or saline had been administered. An increase in the amount of motor activity was not observed after the rat was placed in the saline-paired compartment, regardless of whether d-amphetamine or saline had been administered. Not only was the expression of sensitization context specific, it appears that the d-amphetamine-paired compartment elicited a conditioned sensitization response and the saline-paired compartment did not. The presence or absence of this conditioned response did not depend on whether d-amphetamine or saline had been administered immediately before the test.
Sensitization has been frequently observed with subjects in open-field experiments but rarely documented in operant research. In Odum and Shahan (2004), sensitization was observed when rats responded on a random-interval (RI) 30-s schedule (Millenson, 1963). On this schedule, food presentation set up with a probability of 0.025 every 0.75 seconds. Food was delivered when the rat pressed the lever after a food presentation was set up. When 3.0 mg/kg of \(d\)-amphetamine was administered chronically before sessions for 7 days, sensitization developed, as indicated by response rates decreasing through chronic administration. However, the development of sensitization was not systematically evaluated using dose-response curves.

The development of operant sensitization in Odum and Shahan (2004) may be explained by the reinforcement density hypothesis postulated in Wolgin (1989). Despite the fact that response rates were decreased, if the rate of food presentations that the rat obtained was not substantially impacted, then one would expect for tolerance not to occur, which was the case in Odum and Shahan. As shown in Figure 1, when a rat responds on an interval schedule, a high rate of food presentations can be earned even though the rat may be responding at a low rate. This is because the relationship between number of responses made and number of food presentations earned is nonlinear at the beginning of the function with an asymptote relatively early. However, how many food presentations are earned is dependent on the number of responses made on a ratio schedule. Presumably, for an RI schedule, the drug must substantially decrease response rates for tolerance to develop. Likewise, with a ratio schedule, the decrease in response rates should not have to be nearly as pronounced for tolerance to develop. When the number of food pellets earned by the organism is directly proportional to the number of
responses made by the organism, as in a RR schedule, then decreased-response rates results in a decreased food rate. Tolerance may then develop to enable the rat to earn the lost reinforcers.
CHAPTER III

STATEMENT OF THE PROBLEM

Previous research has shown that tolerance is the likely outcome when a drug disrupts the rate of responding and results in a diminished rate of food presentations. Odum and Shahan (2004) reported that sensitization developed when rats responded on an RI schedule where the subject could make few responses but still earn all the available food. The present experiment will attempt to show that sensitization develops when a rat responds on an RI schedule. The development of sensitization will be analyzed using dose-response curves, which were not used in Odum and Shahan. In addition, this experiment will investigate whether the development of sensitization that results from responding on an RI schedule is context specific, as has found to be the case with operant tolerance. Because human behavior is so complex and drugs have different effects in different situations, it is important that situations that result in sensitization when an operant behavior is made are investigated more in depth so that better treatments for drug addiction can be devised.
CHAPTER IV

METHOD

Subjects

Eight male Long-Evans rats (Charles River, Portage, Michigan, USA), approximately 90 days old at the start of the experiment, were maintained at 85% of their free-feeding weight. Rats were housed individually under a 12:12 hr light/dark cycle and had free access to water when not in experimental sessions. Sessions were conducted daily at the same time. In addition to pellets obtained during the session, supplemental feedings were given after the sessions as necessary.

Apparatus

Four modified Med-Associates modular operant chambers (24-cm long, 30-cm wide, 22-cm high) in sound-attenuating enclosures were used. The left and right walls and the ceiling of the chamber were constructed of Plexiglas. The front and rear walls and the rods making up the floor were constructed of stainless steel. The floor rods, 0.5 cm in diameter, were spaced 1.3 cm apart center to center. The front wall was equipped with two response levers, each with a 28V DC lamp overhead and centered 13 cm apart, and a 28V DC houselight was located at the top center. A feeder, which when operated was accompanied by the houselight being turned off for 0.1 s, delivered 45-mg Bio-Serv pellets. Control of experimental events and data recording was conducted with Med-Associates interfacing and programming. The chambers were modified by removing 4 cm from the bottom of each Plexiglas wall and replacing it with steel that was sanded,
primed, and painted. Two photobeam sensors, spaced 10 cm from the sides of the
chamber and 3 cm from the grid floor, were attached to each piece of steel. Two
photobeam sensors were also placed on the front and rear walls 3 cm from the grid floor,
spaced 6.5 cm from the sides of the chamber.

Procedure

Rats first completed magazine training for two sessions, in which a food pellet
was delivered on a random-time (RT) 30-s schedule. That is, a food delivery was set up
with a probability of 0.025 every 0.75 s, such that a mean of 30 s elapsed between food
deliveries. Rats then responded on an FR 1 schedule on the right lever for one session,
wherein every response resulted in the delivery of a food pellet. The next day, a RR 2
schedule operated, in which each response had a 50% chance of being reinforced, so that
a food pellet was delivered after a mean of two responses. Rats then responded on an RI
5-s schedule, in which a food delivery occurred after an average of 5 s. The value of the
RI schedule was increased in 5-s increments over 6 days until an RI 30-s schedule was
reached.

During baseline, rats responded on the RI schedule in two stimulus contexts that
alternated daily (each stimulus context was experienced by all 8 subjects on an every-
other-day basis). In one stimulus context, context A, no alterations were made to the
operant chamber. In the other stimulus context, context B, two changes were made. The
tone sounded on and off every 0.5 s. Also, a second houselight with a green cap was
added to the ceiling of the sound-attenuating shell and red construction paper was
attached to the outsides of the Plexiglas walls.
Rats responded under baseline conditions for at least 55 days and until response rates were judged stable (minimal trend and variability across sessions, as judged by visual inspection). The number of baseline sessions each rat experienced before drug administration is shown in Table 1. *d*-Amphetamine sulfate (Sigma-Aldrich, St. Louis, MO) was dissolved in 0.9% NaCl (saline) solution and administered intraperitoneally in a volume of 1.0 ml/kg of the 85% free-feeding weight. Prior to drug administration, three saline injections were given, two in one stimulus-context, and the third in the other, to accustom the subjects to the injection procedure. Rats first received acute administration of saline and three doses of *d*-amphetamine (saline, 1.0, 3.0, and 5.6 mg/kg, in that order) in one of the stimulus contexts. Rats then received acute administration in the other stimulus context. Drug administration was separated by 3 sessions, during which time no injections were given. Rats then received chronic administration of a 3.0 mg/kg dose of *d*-amphetamine for 10 sessions in one of the stimulus contexts to see if prolonged exposure to *d*-amphetamine in one of the contexts would result in sensitization to the effects of the drug in that context as well as the other. Acute administrations were given again in both stimulus contexts using the same procedure as already outlined. Table 2 shows the order and the context in which the acute and chronic administrations occurred.

Locomotor activity was recorded when two spatially adjacent photobeams were broken (Feifel et al., 2008). Stereotypy was measured by recording sessions using a small camera and scoring the sessions later using the same procedure used in Ellinwood and Balster (1974), as shown in Table 3. One adjustment to this rating scale was made: lever pressing and magazine checking were added to the description for “in place activities.” Sessions were divided into 20-s blocks, and the behavior that predominated each 20-s
Table 1

**Number of Days Under Baseline Conditions**

*Before Drug Administration for Each Rat*

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Table 2

**Drug Administration Procedure**

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<tr>
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<th>Context A</th>
<th>Context B</th>
<th>Rat</th>
<th>Context A</th>
<th>Context B</th>
</tr>
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*Note.* Shown for each rat are the order and stimulus context of acute and chronic administrations.
Table 3

*Rating Scale for the Behavioral Effects of Psychomotor Stimulants in Rats*

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1</td>
<td>Asleep</td>
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<tr>
<td>2</td>
<td>Inactive</td>
</tr>
<tr>
<td></td>
<td>In place activities</td>
</tr>
<tr>
<td>3</td>
<td>(Grooming consummatory)</td>
</tr>
<tr>
<td>4</td>
<td>Normal, alert, active</td>
</tr>
<tr>
<td>5</td>
<td>Hyperactive</td>
</tr>
<tr>
<td>6</td>
<td>Slow patterned</td>
</tr>
<tr>
<td>7</td>
<td>Fast patterned</td>
</tr>
<tr>
<td>8</td>
<td>Restricted</td>
</tr>
<tr>
<td>9</td>
<td>Dyskinetic-reactive</td>
</tr>
</tbody>
</table>

*Note.* Score represents activity that predominates in a given 20-s interval, except for 8, which is second only when observed for an entire 20-s interval. (From Ellinwood & Balster, 1974).

Block was recorded. At the conclusion of the experiment, 10% of the 344 recordings were randomly selected and used to assess interobserver agreement during the experiment. Interobserver agreement for each session was calculated by dividing the number of agreements by the total number of agreements and disagreements and multiplying this result by 100 (Cooper, Heron, & Heward, 1987). Sessions were scored independently by
two observers only after interobserver agreement was 80% or higher on preliminary test recordings, as recommended by Hersen and Barlow (1976). The calculated interobserver agreement was 92%.

Measures

Five dependent measures were analyzed to determine whether sensitization to the effects of d-amphetamine occurred: response and reinforcer rates, locomotor activity counts, stereotypy score, and percent time spent engaging in normal activity. Proportion-control data are not shown because the control days from the two contexts were not significantly different from each other. Response and reinforcer rates were calculated as the average number of responses or reinforcers, respectively, per minute during each session. Locomotor activity counts were calculated as the number of spatially adjacent photobeam breaks that occurred during the session. The stereotypy score was calculated by averaging the score given to each 20-s interval over the course of the session. The percent of the intervals with normal activity was calculated by dividing the number of intervals that were coded in the 1-4 range by the number of intervals for that session and multiplying the result by 100. The data for each dependent measure were averaged across rats according to context (same or different), phase (pre- or postchronic) and dose (saline, 1.0, 3.0, and 5.6 mg/kg d-amphetamine). The same context (hereafter “same”) refers to the context in which chronic administration occurred, while the different context (hereafter “different”) refers to the context in which chronic administration did not occur.
Analyses

Data from the pre- and postchronic tests in the same and different contexts with the order in which the contexts were experienced as a between-subjects factor were analyzed using a 2 x 2 x 4 x 2 (context x phase x dose x context order) mixed-model ANOVA. The order that the conditions were experienced was also analyzed as a within-subject variable by comparing data from the context experienced first to the context experienced second. The 2 x 2 x 4 (condition order x phase x dose) repeated-measures ANOVA was carried out in the same manner, but with condition order instead of context. Follow-up tests were conducted when a significant interaction occurred. A linear regression was performed on the data from the chronic phase to determine if there was an effect of session. Because there was no linear trend across days of chronic administration, data are averaged across session. Data are presented as a proportion of baseline for chronic administration so that the effects of d-amphetamine on the various measures can be compared to each other. Proportion of baseline was calculated for each measure by dividing the mean of that measure from the day immediately preceding chronic administration by the 10-day mean of that measure during chronic for each rat.
CHAPTER V
RESULTS

Figure 2 shows responses per minute as a function of dose of \textit{d}-amphetamine for pre- and postchronic tests in the same and different contexts. In both the same and different contexts, the dose-response curve from postchronic shifted to the left of the dose-repose curve from prechronic, with response rates decreasing as a function of dose. However, a mixed-model ANOVA with context order as a between-subjects factor did not find a significant difference between the two contexts, $F(1, 6) = .704, p > .05, h_p^2 = .105$. The main effect of context order was not significant, $F(1, 6) = .963, p > .05, h_p^2 = .138$. The difference between prechronic and postchronic response rates was significant, $F(1, 6) = 9.105, p < .05, h_p^2 = .603$. The main effect of dose was also significant, $F(3, 18) = 19.370, p < .000, h_p^2 = .763$. Additionally, the phase by dose by context order interaction was significant, $F(3, 18) = 5.034, p < .01, h_p^2 = .456$. The phase by dose interaction was also significant, $F(3, 18) = 4.417, p < .05, h_p^2 = .424$. Pairwise comparisons revealed that at 1.0 and 3.0 mg/kg, postchronic response rates were significantly different from prechronic rates.

Figure 3 shows reinforcer rates as a function of dose of \textit{d}-amphetamine for pre- and postchronic tests in the same and different contexts. In both the same and different contexts, the dose-response curve from postchronic shifted to the left of the dose-repose curve from prechronic, with reinforcer rates decreasing as a function of dose. However, a mixed-model ANOVA with context order as a between-subjects factor did not find a significant difference between reinforcer rates in the two contexts, $F(1, 6) = .146, p > .05,$
Figure 2. Mean responses per minute averaged across all 8 rats in the context the same as (top panel) and different from (lower panel) the one in which chronic administration of d-amphetamine occurred. Vertical bars represent one standard error above and below the mean. Unconnected points show means for all control (C) and saline (S) sessions. Lines connect points showing mean responses per minute across doses of d-amphetamine. Closed squares represent prechronic responses per minute and open squares represent postchronic responses per minute.
Figure 3. Mean reinforcers per minute averaged across all 8 rats in the context the same as (top panel) and different from (bottom panel) the one in which chronic administration of $d$-amphetamine occurred. Closed squares represent prechronic reinforcers per minute and open squares represent postchronic reinforcers per minute. Other details as in Figure 2.
$h_p^2 = .024$. The main effect of context order was not significant, $F(1, 6) = .345, p > .05, h_p^2 = .054$. The difference between prechronic and postchronic reinforcer rates was significant, $F(1, 6) = 26.494, p < .01, h_p^2 = .815$. The main effect of dose was also significant, $F(3, 18) = 29.732, p < .000, h_p^2 = .832$.

Figure 4 shows locomotor activity counts as a function of dose of $d$-amphetamine for pre- and postchronic tests in the same and different contexts. In both the same and different contexts, the dose-response curve from postchronic shifted to the left of the dose-repose curve from prechronic, with locomotor activity counts decreasing as a function of dose. However, a mixed-model ANOVA with context order as a between-subjects factor did not find a significant difference between locomotor activity counts in the two contexts, $F(1, 6) = .495, p > .05, h_p^2 = .076$. The main effect of context order was not significant, $F(1, 6) = .006, p > .05, h_p^2 = .001$. The difference between prechronic and postchronic reinforcer rates was not significant, $F(1, 6) = 2.508, p > .05, h_p^2 = .295$. The main effect of dose, however, was significant, $F(3, 18) = 19.914, p < .000, h_p^2 = .768$.

Figure 5 shows stereotypy score as a function of dose of $d$-amphetamine for the pre- and postchronic tests in the same and different contexts. In both the same and different contexts, the dose-response curve from postchronic shifted to the left of the dose-repose curve from prechronic, with stereotypy score increasing as a function of dose. A mixed-model ANOVA with context order as a between-subjects factor did not find a significant difference between stereotypy score in the two contexts, $F(1, 5) = .235, p > .05, h_p^2 = .045$. The main effect of context order was not significant, $F(1, 5) = .109, p > .05, h_p^2 = .021$. The difference between prechronic and postchronic stereotypy was significant, $F(1, 5) = 14.753, p < .05, h_p^2 = .747$. The main effect of dose was also
Figure 4. Mean locomotor activity counts averaged across all 8 rats in the context the same as (top panel) and different from (bottom panel) the one in which chronic administration of d-amphetamine occurred. Closed squares represent prechronic locomotor activity counts and open squares represent postchronic locomotor activity counts. Other details as in Figure 2.
Figure 5. Mean stereotype scores averaged across all 8 rats in the context the same as (top panel) and different from (bottom panel) the one in which chronic administration of d-amphetamine occurred. Closed squares represent prechronic stereotypy scores and open squares represent postchronic stereotypy scores. T4’s postchronic 3.0 dose from the context different from chronic is missing due to an error with the camera. Other details as in Figure 2.
significant, \(F(3, 15) = 103.528, p < .000, h_p^2 = .954\). The phase by dose interaction was significant, \(F(3, 15) = 8.503, p < .01, h_p^2 = .63\). Pairwise comparisons revealed that at 1.0 and 3.0 mg/kg, postchronic stereotypy scores were significantly different from prechronic.

When stereotypy scores were analyzed using the within-subject factor of condition order instead of context, the main effect of order was significant, \(F(1, 6) = 20.366, p < .01, h_p^2 = .772\). The difference between prechronic and postchronic stereotypy scores was significant, \(F(1, 6) = 18.197, p < .01, h_p^2 = .752\). The main effect of dose was also significant, \(F(3, 18) = 123.936, p < .000, h_p^2 = .954\). The condition order by phase by dose interaction was significant, \(F(3, 18) = 3.081, p < .05, h_p^2 = .388\). The phase by dose interaction was significant, \(F(3, 18) = 10.013, p < .000, h_p^2 = .625\). Pairwise comparisons revealed that at 1.0 and 3.0 mg/kg, postchronic stereotypy scores were significantly different from prechronic.

Figure 6 shows the percent of intervals with normal activity as a function of dose of \(d\)-amphetamine for pre- and postchronic tests in the same and different contexts. In both the same and different contexts, the dose-response curve from postchronic shifted to the left of the dose-repose curve from prechronic, with percent of intervals with normal activity decreasing as a function of dose. A mixed-model ANOVA with context order as a between-subjects factor did not find a significant difference between the two different contexts, \(F(1, 5) = .024, p > .05, h_p^2 = .005\). The main effect of context order was not significant, \(F(1, 5) = .653, p > .05, h_p^2 = .116\). The difference between prechronic and postchronic percent of intervals with normal activity was significant, \(F(1, 5) = 8.754, p < .05, h_p^2 = .636\). The main effect of dose was also significant, \(F(3, 15) = 68.675, p < .000, h_p^2 = .864\).
Figure 6. Mean percent of intervals coded as normal activity averaged across all 8 rats in the context the same as (top panel) and different from (bottom panel) the one in which chronic administration of \textit{d}-amphetamine occurred. Closed squares represent prechronic percent of intervals coded as normal activity and open squares represent postchronic percent of intervals coded as normal activity. Other details as in Figures 2 and 5.
The context by dose by context order interaction was significant, \( F(3, 15) = 3.889, p < .05, h_p^2 = .438 \). The phase by dose interaction was significant, \( F(3, 15) = 8.227, p < .01, h_p^2 = .622 \). Pairwise comparisons revealed that at 1.0 mg/kg, postchronic percent of intervals with normal activity was significantly different from prechronic.

When the percent of intervals with normal activity were analyzed using the within-subject factor of condition order instead of context, the main effect of condition order was significant, \( F(1, 6) = 6.919, p < .05, h_p^2 = .536 \). The difference between prechronic and postchronic stereotypy scores was significant, \( F(1, 6) = 10.662, p < .05, h_p^2 = .64 \). The main effect of dose was also significant, \( F(3, 18) = 144.366, p < .000, h_p^2 = .96 \). The phase by dose interaction was significant, \( F(3, 18) = 10.173, p < .000, h_p^2 = .628 \). Pairwise comparisons revealed that at 1.0 mg/kg, postchronic percent of intervals with normal activity were significantly different from prechronic.

Difference scores were also calculated for all five measures in both contexts by subtracting the postchronic value for each dose from the prechronic value. A 2 x 4 (context x dose) repeated-measures ANOVA did not find a statistically significant main effect of context and as a result these data are not shown. The data were also analyzed in terms of the immediacy with which acute dosing in the same context occurred after chronic as a between-subjects factor. A 2 x 2 x 4 x 2 (context x acute x dose x immediacy) mixed-model ANOVA did not find a significant main effect of context and these data are not shown.

Figure 7 shows the mean chronic response rate, reinforcer rate, locomotor activity counts, stereotypy score, and percent of intervals with normal activity as a proportion of baseline so that the effects of the chronic dose of 3.0 mg/kg \( d \)-amphetamine can be
related to the baseline performance. Response rates as well as reinforcer rates were roughly half of what they were during baseline. In comparison, \(d\)-amphetamine had a greater effect on locomotor activity counts, with approximately a quarter of the baseline amount observed. Chronic administration resulted in two-and-half-fold increase in stereotypy compared to baseline. Consequently, very few intervals with normal activity occurred during chronic administration. To allow examination of the response rate data in detail, Figure 8 shows the individual subject data for response rates as responses per minute, while Figure 9 shows these data as a proportion of control so that the effects of each dose of \(d\)-amphetamine can be related to the control performance.
Figure 8. Individual response-rate data expressed as responses per minute in the context the same as and different from the one in which chronic administration of d-amphetamine occurred. Unconnected points show means for all control (C) and saline (S) sessions. Lines connect points showing mean responses per minute across doses of d-amphetamine. Closed squares represent prechronic responses per minute in the context the same as chronic administration, open squares postchronic responses per minute in the context the same as chronic administration, closed triangles prechronic responses per minute in the context different from chronic administration, and open triangles postchronic responses per minute in the context different from chronic administration.
Figure 9. Individual response-rate data expressed as proportion-control responses per minute in the context the same as and different from the one in which chronic administration of d-amphetamine occurred. Other details as in Figure 8.
CHAPTER VI
DISCUSSION

In the present experiment, sensitization to the effects of d-amphetamine occurred when d-amphetamine was administered to rats that were required to work for food deliveries. This is evidenced by the postchronic dose response curve being shifted to the left in comparison to the prechronic dose response curve for response rates, reinforcer rates, stereotypy scores, and percent of intervals with normal activity. However, the development of sensitization was not context-specific. For all five measures, the dose-response curves in both the same and different contexts were not statistically different from each other. When the data were further analyzed according to which context was experienced first, the main effect of order was significant for stereotypy score and percent of intervals with normal activity. This result suggests that the order of the contexts may have had an effect on the expression of context-specific sensitization.

The development of operant sensitization, indicated by a leftward shift in the dose-response curve for the response rate and reinforcer rate measures, is in concordance with the results of Odum and Shahan (2004). In their experiment, sensitization of the response-rate decreasing effects of d-amphetamine occurred when d-amphetamine was administered to rats responding on an RI schedule. Sensitization was observed as the drug decreased response rates more strongly as chronic administration progressed and not by comparing pre- and postchronic dose-response curves. The present experiment was successful in replicating operant sensitization and measuring this effect using dose
response curves, the preferred method for showing sensitization (e.g., Stewart & Badiana, 1993).

According to the reinforcement density hypothesis (Schuster et al., 1996), tolerance develops when food presentations occur less frequently as a result of a drug effect. As shown in Figure 6, in the chronic phase of the present experiment, the mean number of food presentations that each rat received during chronic administration was reduced to 50% of the baseline rate. However, the mean response rate during chronic administration was 60% of what it was during baseline. This suggests that tolerance to those effects of d-amphetamine did not occur, even when food presentations were reduced by 50%. However, tolerance to the rate-decreasing effects of d-amphetamine occurred in Smith (1986) in the ratio component when the mean reinforcement rate during initial administration of chronic d-amphetamine was reduced to 40% of the baseline rate. Reinforcement and response rates recovered to baseline levels by the end of the ninth session. Reinforcement-rate data during chronic administration from Smith (1990) and Pinkston and Branch (2003) were not presented. Therefore, it may be that tolerance did not occur in the present experiment because the reinforcement rates were not impacted substantially enough, although this explanation seems unlikely.

The finding in the present study that operant sensitization was not context specific is in contrast to the results of Wolgin (2000) and Smith (1986), in which operant tolerance was found to be context specific. The present results also deviate from the findings of Rademacher and colleagues (2007), who found that locomotor sensitization was context specific. One possible explanation for why sensitization was not specific to the context in the present experiment is that the contexts were not different enough. However, this does
not seem likely considering several aspects of the present data. For T3, T7, and T8, sensitization occurred in the same context but neither tolerance nor sensitization occurred in the different context. Nor does it explain why T2’s response rates increased in the same context but decreased in the different context. Also, it does not explain why sensitization occurred in the different context for T1 and T4, but neither tolerance nor sensitization occurred in the same context. In summary, there are a number of indicators that the contexts were discriminably different, yet the sensitization observed was not context specific.

Another possible explanation why context-specific operant sensitization was not found in the present experiment is the complex design used for the counterbalancing arrangements. The order of the contexts as well as the context for chronic administration was counterbalanced across rats. Because of this, it is possible that additional order effects than those already discussed occurred. However, not enough subjects may have been used to detect this effect. Future research using the same design could employ more subjects to increase the power to investigate all possible order effects.

Previous research investigating locomotor sensitization has used group designs when testing for context-specific sensitization. For example, in Rademacher and colleagues (2007), both groups were placed in opposite outer chambers of a three-chamber operant chamber on alternate days, but were broken up into four different groups when the context-specific effects of d-amphetamine were analyzed. Future research investigating context-specific operant sensitization may need to incorporate a group design to investigate context-specific operant sensitization. Both groups of rats would respond for food in two stimulus contexts on alternate days, with amphetamine injections being paired
with only one of these contexts and saline with the other. On the test day, the rats would be
broken up into four groups: one group would be administered saline and respond in the
saline-paired context, one group would be administered saline and respond in the $d$-
amphetamine-paired context, one group would be administered $d$-amphetamine and
respond in the $d$-amphetamine-paired context, and the last group would be administered
saline and respond in the $d$-amphetamine-paired context. In this way, the procedure for
testing for context-specific operant sensitization would be modeled after the procedure for
testing for context-specific locomotor sensitization. One limitation of this procedure
however is that dose-response curves could not be created to measure sensitization.
Within-subject designs instead of group-designs have been successful in creating dose-
response curves to measure context-specific tolerance (Pinkston & Branch, 2003).

The drug administration procedure used in the present study is different from the
one that has been used to study operant tolerance. In Pinkston and Branch (2003), chronic
dosing did not cease when the postchronic acute phase began. Instead, various doses were
substituted in place of the chronic dose after the chronic dose had been administered 50
sessions. This procedure is different from that of the present study in which three baseline
(no-injection) sessions intervened between each postchronic injection. Future research
should investigate how the drug administration procedure affects the development of
tolerance and sensitization and the context-specificity of these drug effects.

Context-specific operant sensitization may not have occurred because a 3.0 mg/kg
$d$-amphetamine was used as the chronic dose. Much of the research investigating context-
specific locomotor sensitization has used a 1.0 mg/kg dose of $d$-amphetamine (e.g.,
Rademacher et al., 2007). According to Tirelli, Laviola, and Adriani (2003), sensitization
can be context-independent when a high drug dose is administered. However, in Odum and Shahan (2004), sensitization occurred for the group that received a 3.0 mg/kg dose of \( d \)-amphetamine before the session but not for the group that received \( d \)-amphetamine after the session. Further research is needed to determine if context-specific sensitization is dose dependent.

Operant sensitization may not have been context specific in the current experiment because the two different contexts did not predict a change in the contingency maintaining lever pressing. For example, in Experiment 1 of Jenkins and Harrison (1960), one group of pigeons responded on a VI schedule while a tone at 1000 cycles per second (cps) sounded; for a second group of pigeons, periods of tone alternated with periods of no tone, during which reinforcement did not occur. When generalization testing took place, the group of pigeons that experienced extinction when the tone was not presented was able to discriminate the 1000 cps tone, while the group that always experienced the tone did not. In the present experiment, the same contingency was in place in the two contexts on alternate days before drug administration began. This similarity may have led operant sensitization to generalize across contexts.

The results of the present experiments suggest that future research examining how drugs affect operant behavior should incorporate other measures in addition to response rates to assess what, if any, drug effects occur. The majority of the previous research studying operant drug effects has focused predominately on response rate and reinforcer rate (e.g., Odum & Shahan, 2004; Smith, 1986, 1990). In Pinkston and Branch (2003), a video camera was used to monitor the sessions but only to measure locomotor activity. Measuring locomotor activity and stereotypy can give a clearer picture of what
behavior is actually occurring during a session. In the present experiment, in some cases drug-induced stereotypies may have competed with or facilitated lever pressing. For example, stereotypy facilitating lever pressing occurred when many rats remained stationary in front of the lever and bobbed their heads, occasionally bumping the lever and earning a food presentation. Additionally, alternating between making a response and checking the hopper over the entire session instead of exploring the chamber is another way that stereotypies facilitated lever pressing. In essence, this may have resulted in a lever press being recorded when a type of stereotypy was occurring. Stereotypies competing with lever pressing occurred when the rat would instead stay stationary in one part of the chamber for the entire session and not press the lever. Because stereotypies can compete with or facilitate response rates, future research investigating drug effects on behavior could take a more in-depth look at what behavior the rat is emitting during the session.

In conclusion, the present experiment found that operant sensitization and not operant tolerance occurred when rats received repeated injections of d-amphetamine while responding on an RI schedule. Tolerance and sensitization have previously been studied using two different procedures: tolerance through operant procedures and sensitization in locomotor-activity procedures. Operant sensitization allows one type of drug effect that was not previously documented to be studied. Studying all possible drug effects can lead to more effective treatments of drug addiction. In the present experiment, operant sensitization was not found to be context specific. Future research should be conducted to see if a group design would find that operant sensitization is context specific and what effects the counterbalancing arrangements had in the present experiment. Although
context-specific operant sensitization was not found in the present experiment, future research incorporating these changes may have this result.
REFERENCES


