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State-dependency of Conditioning and Extinction of an Appetitive Response with Amphetamine and Midazolam

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MAES, J. H. R. AND J. M. H. VOSSEN. *State-dependency of conditioning and extinction of an appetitive response with amphetamine and midazolam.* PHARMACOL BIOCHEM BEHAV **58**(2) 305–310, 1997.—Rats received a single conditioning session in which unsignaled food pellets were delivered to the food magazine of a training box, followed by a single extinction session without pellet presentations. Groups of rats differed in the drug state induced prior to conditioning and extinction according to a 2 × 2 design using *d*-amphetamine sulphate (AMP, 0.5 mg/kg, SC) and midazolam (MID, 0.1 mg/kg, SC). Subsequently, all rats received nonreinforced test sessions under AMP and MID. The dependent measure was the frequency of magazine visits during selected portions of each session. Rats that received extinction in the same drug state as had been present during conditioning did not respond significantly more during the extinction session than rats extinguished in a different drug state. This implies that conditioning was not state dependent. However, during the AMP tests, the rats extinguished under MID responded more under AMP than under MID, whereas the rats extinguished under AMP did not respond differentially during the tests under AMP vs. MID. These results were interpreted as reflecting the joint operation of state-dependent extinction and unconditioned drug effects. As in studies manipulating external contextual stimuli, extinction proved to be more vulnerable to becoming context dependent than conditioning. © 1997 Elsevier Science Inc.

State-dependent extinction State-dependent conditioning Appetitive conditioning Amphetamine Midazolam Rats

PREVIOUS animal research shows that associations acquired during a conditioning phase of a learning experiment generally transfer very well to an environmental, or external, context that is distinctively different from that used during conditioning [e.g., (1,2)]. Accordingly, the strength of a conditioned response, as measured in a test context that is distinctively different from the context used for conditioning, more often than not is equal to that observed upon testing in the former conditioning context [e.g., (4,6,13), but see, e.g., (10,11)].

Interestingly, it is the retrieval of the information acquired during an extinction phase, in which no biologically significant stimuli are presented, that frequently has been shown to become dependent on the contextual cues present during that phase [see (1,2), for a review]. This means that after conditioning of a response in one context, Context A, and subsequent extinction of that response in a distinctively different context, Context B, the response re-occurs upon testing the subject in the original training Context A ("ABA renewal"). Moreover, renewed responding also occurs during testing in Context C, after conditioning in Context A and extinction in Context B ("ABC renewal"), and upon testing in Context B, after conditioning and extinction in Context A ["AAB renewal"; (5)]. Thus, retrieval of an extinction experience by an animal is context dependent, whereas retrieval of a conditioning experience is not, or at least much less so than is the case for extinction.

Interoceptive cues, such as those induced by different levels of food deprivation or pharmacologically active agents, can be considered to constitute an "internal" context. In experiments examining state dependent learning (SDL), a change in this type of context after a conditioning phase often has been found to have no, or only a weak, negative effect on the retrieval of associations acquired during conditioning [see (17), for review, and also, e.g., (3,15); but see, e.g., (7,12)].

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These results resemble the context-independent conditioning frequently found in studies manipulating external contexts.

Much less research has been conducted to examine whether or not the context dependency found for extinction in studies manipulating external contexts also appears in procedures with different internal contexts. In the first three experiments of a relatively recent study (3), groups of rats of major interest were first injected with saline. Subsequently, they received unsignaled electric foot shocks in a conditioning box to condition a fear response to that box on the basis of an association between box and shock. The animals were then injected with either saline or a drug (chlordiazepoxide or diazepam) and placed in the conditioning box without receiving any foot shocks. This was done to extinguish the fear response. During a final test session, which was conducted after the administration of saline, the rats that had received extinction in the drug state showed more fear upon being placed in the conditioning box than was the case for the rats extinguished under saline. In Experiment 4 of this same study, rats that had been conditioned under saline and extinguished under a drug were tested under both saline and the drug (within-subjects design). The rats showed more fear in tests under saline than in tests under the drug. Collectively, these results suggest that retrieval of the extinction experience (box–no shock association) was dependent on the internal context being present during extinction, a phenomenon hereafter referred to as state-dependent extinction (SDE).

The present experiment was intended to pursue the generality of SDE and to assess whether extinction is more dependent on internal states than conditioning. A procedure was used that differed in a number of respects from the basic design used in the study described above (3). First, rats were used in an appetitive conditioning procedure instead of an aversive one. Second, a 2×2 design was used, with one factor being the internal drug state present during conditioning [*d*-amphetamine sulphate (AMP) or midazolam (MID)], and the other one being the state present during extinction (also AMP or MID). These drugs were chosen on the basis of the results of previous research showing that, at least in an aversive discrimination procedure, they acquire retrieval properties [e.g., (14)]. Two explicit drug states were induced, rather than a salient drug state and a nonsalient saline state, to increase the chance of detecting both SDL and SDE (if present). The latter issue also bears on a third difference, namely, that the present study intended to examine explicitly the strength of SDL and SDE in one and the same study. A fourth, and final, difference was that the number of conditioning and extinction sessions was held equal and at a minimum, namely only one of each.

For the sake of clarity it must be noted that, by referring to these differences between studies, we by no means intend to suggest that the previous study was in some way incomplete. The former study mainly addressed the issue of the extent of transfer of extinction in a drug state to an undrugged state. The question of interest in the present study was whether, using two different drug states, the rats would show SDE but no SDL, as is expected in case the retrieval properties of internal contexts are similar to those of external contexts. An absence of SDL would be expressed most clearly in an equal level of conditioned responding during the extinction session under a same-drug condition, that is, in the same drug state as present during conditioning, and a different-drug condition, that is, in a drug state different from that present during conditioning. SDE would be reflected in the animals showing less responding after extinction when tested under the same drug condition as previously in effect during extinction, than when tested in another drug state.

METHODS

Subjects

The subjects were 32 experimentally naive female Wistar rats. Their mean free-feeding body weight ranged from 182 to 244 g. They were housed individually in Makrolon cages (type 3) and gradually reduced to 85% of their free-feeding body weight by being fed a restricted amount of food each day. The rats were maintained at this weight throughout the experiment. On each of the experimental days, the animals received their daily food approximately 0.5 h after the experimental treatments. Water was available continuously in the home cage. The animals were maintained on a 12 h/12 h dark/light cycle. Experimental manipulations took place 6–7 h into the dark phase of this cycle.

Apparatus

Training and testing were conducted in eight identical operant-conditioning chambers from which the levers had been retracted. Each chamber measured $24.5 \times 25 \times 20$ cm and was made of a clear Plexiglas front wall, back wall, and ceiling, and aluminium side walls. The floor was constructed of 3-mm stainless-steel rods, spaced 1.3 cm apart. One side wall contained a $5 \times 5 \times 3$ cm recessed food magazine to which 45-mg food pellets could be delivered. The magazine had an infrared emitter and photodiode sensor that was used for detecting magazine visits. Each interuption of the beam was counted as a magazine visit. The chambers were housed in sound- and light-attenuating shells. The shells were located in a room illuminated dimly by one red strip light. Presentation of pellets and the recording of magazine visits were controlled by a Macintosh/Performa 460 computer.

Drugs

The drugs used were 0.5 mg/kg *d*-AMP sulphate (RBI Research Biochemicals International; dose expressed as salt), or 0.1 mg/kg MID, a short-acting, water-soluble benzodiazepine agonist (Roche Netherlands). These drugs were dissolved in saline (0.9% NaCl). All substances were administered subcutaneously. The drugs and doses were chosen on the basis of previous drug-discrimination research [e.g., (8,14,18)].

Procedure

The experiment was run in two replications with 16 subjects in each. The rats were divided into four equal groups ($n = 4$ in each replication), matched on body weight. The experiment was run using squads of eight subjects that were counterbalanced for group. All animals received six 30-min sessions: one conditioning, one extinction session, and four test sessions. Immediately prior to each of these sessions, the rats were injected with either AMP or MID.

On the first day of the experiment, the conditioning session, the rats in group AA (the first and second letter of each group's designation refer to the drug state during conditioning and extinction, respectively) were injected with AMP and placed individually in the conditioning chambers. During this session, 10 unsignaled pellets were presented according to a variable time 3-min schedule. All rats received the pellets at exactly the same times into the session. Recordings of the frequency of magazine visits were made during each minute im-

mediately prior to each pellet presentation. Thus, there were 10 1-min samples of magazine responding during the session. On all other subsequent sessions (see below), the samples for all rats were always taken at the same times as had been the case for the conditioning session.

The second session, the extinction session, was conducted 24 h later. The rats of group AA were placed in the chambers while under AMP; no food was presented. Finally, a nonreinforced test session was performed in the chambers on each of the next four experimental days. Two test sessions were performed under AMP, and two test sessions under MID. For one half of the animals in group AA, the schedule of the induced drug states on the test sessions was AMP, MID, AMP, MID, on test day 1, 2, 3, and 4, respectively. For the other half of the rats in this group, the corresponding test order was MID, AMP, MID, AMP. The time interval between tests 1 and 2 and between tests 3 and 4 was 24 h, whereas the interval between tests 2 and 3 was 72 h (week-end).

The rats in groups MM, AM, and MA received an identical treatment as did the rats in group AA, with the induced drug state during the conditioning and extinction session corresponding with each group's name. Thus, the animals in group MM were under MID on both the conditioning and extinction sessions, those in group AM were under AMP during conditioning and under MID during extinction, etc.

Dependent measure and statistical analysis

The dependent measure for each of the sessions and groups was the mean number of magazine visits during two-sample blocks, or the mean number of visits based on all 10 1-min samples. The data were subjected to analyses of variance (ANOVAs). Where appropriate, interactions between main factors were analyzed by tests for simple main effects. The error terms and degrees of freedom used in these latter tests were based on the overall ANOVA following Satterthwaite's approximation (19). A rejection criterion of $p < 0.05$ was used throughout.

To examine whether the training procedure used resulted in a gradual increase in magazine responding, reflecting acquisition of conditioned responding, and whether the drug states had a differential effect thereupon, we analyzed the data from the conditioning session separately using an ANOVA with Conditioning Drug (AMP vs. MID) as a between-subjects factor and Block (of two samples each) as a within-subjects factor.

To assess whether the omission of food during the extinction session resulted in a significant decrease in responding for all groups, relative to responding displayed at the end of the conditioning session, the frequency of magazine responding during the final block of two samples of the conditioning session was compared with the frequency of magazine visits observed during the final block of two samples of the extinction session using a Group × Type of Session ANOVA. The former factor was a between-subjects factor and the latter a within-subjects factor. Successful extinction in each group would be reflected in a main effect for type of session, and no interaction between this factor and the group factor.

Potential SDL effects were examined using the data from the extinction session. A Conditioning Drug (AMP vs. MID) × Nature of Extinction Drug (same as conditioning drug vs. different from conditioning drug) × Block (two-sample blocks) ANOVA, with the first two factors being between-subjects factors, and the last one a within-subjects factor, was performed. This analysis was expected to reveal no significant effects involving the extinction-drug factor in case the present drugs do not induce state-dependent learning. In the first session after conditioning, responding in a different-drug condition should cause as much responding as in a same-drug condition.

Possible SDE effects were evaluated by means of a Conditioning Drug (AMP vs. MID; between-subjects factor) × Extinction Drug (AMP vs. MID; between-subjects factor) × Test Drug (AMP vs. MID; within-subjects factor) × Test Cycle (1 vs. 2; within-subjects factor) ANOVA using the mean frequency of responses observed during the 10 samples of each of the test sessions. It must be noted that we also performed an ANOVA including Test Order (first test session conducted under AMP or MID) as an additional between-subjects factor. However, we excluded this factor from all further analyses because it did not exert a significant main effect; nor did it interact significantly with any other factor. Furthermore, for the sake of brevity, the test data were not separated on the basis of blocks of two 1-min samples, as was done in the previous analyses. An analysis including a block factor gave rise to the same conclusions as presented hereafter.

A symmetrical SDE effect would be reflected in a significant interaction between extinction drug and test drug, which would have to be caused by more test responding under AMP than under MID for the rats extinguished under MID, and more responding under MID than under AMP for the rats extinguished under AMP. Finally, in view of the hypothesized absence of SDL, such an interaction effect should hold irrespective of the specific conditioning drug used. In other words, there should be no reliable effects involving the conditioning drug factor in this analysis.

RESULTS

In none of the analyses reported below did the effect of the factors of main interest differ for the various levels of the replication factor. Therefore, the data were collapsed across replications.

Conditioning

The left panel of Fig. 1 shows the mean number of magazine visits emitted by the different groups during blocks of two 1-min samples of the conditioning session.

As can be seen, the rats in all groups increased their frequency of magazine visits in the course of the conditioning session. Moreover, there did not appear to be substantial differences between rats as a function of the drug state that was induced during this session (AMP or MID). A Conditioning Drug × Block ANOVA using the conditioning data indeed only found a highly significant block effect [$F(4,120) = 20.73$, $p < 0.001$; other Fs < 1.11, ps > 0.30].

Extinction

The right side of Fig. 1 depicts the group's mean number of magazine visits across two 1-min sample blocks of the extinction session. During the first block, the rats made more magazine responses than was the case during the corresponding block of the conditioning session. However, they also (already) made less responses than was observed during the last block of the conditioning phase. Furthermore, during the last extinction block, the rats that were under AMP, groups AA and MA, appeared to make more magazine visits than did the rats extinguished under MID, groups MM and AM. A Conditioning Drug × Extinction Drug × Type of Session (condi-

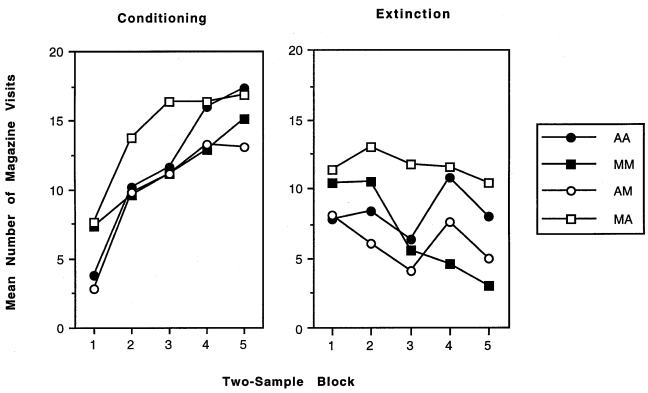

FIG. 1. Mean number of magazine visits during blocks of two 1-min samples of the conditioning session (left) and the extinction session (right). Groups differed in the drug state induced prior to conditioning and extinction (AMP, A, and/or MID, M).

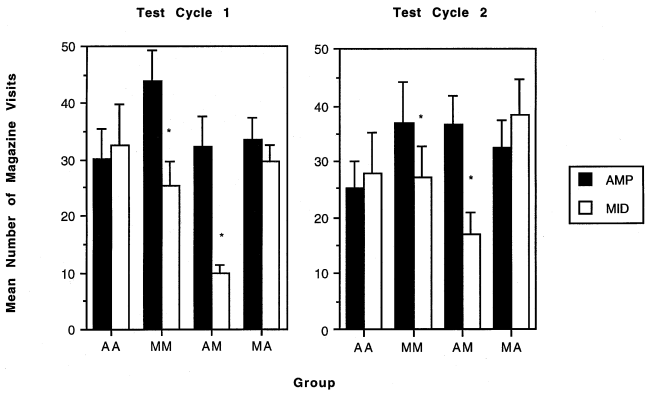

FIG. 2. Mean number of magazine visits (+SEM) during each of the two test cycles performed after the extinction session. Each group was tested twice under AMP and twice under MID. Groups had previously been conditioned and extinguished according to a 2 × 2 design using AMP (A) and MID (M).

tioning vs. extinction) ANOVA using the data of the last block of the conditioning and extinction session revealed a significant main extinction drug effect [$F(1,28) = 5.14$, $p < 0.05$], and a highly reliable main effect for type of session [$F(1,28) = 32.87$, $p < 0.001$]. Each of the remaining main and interaction effects were not significant [Fs$(1,28) < 1.19$, ps > 0.28].

SDL

The extinction data displayed in Fig. 1 suggest that the rats that were extinguished in a state that was the same as that present during conditioning, groups AA and MM, did not make more magazine visits relative to those extinguished in a state different from the conditioning drug state, groups AM and MA. A Conditioning Drug × Nature of Extinction Drug (same as vs. different from conditioning drug) × Block ANOVA on the extinction data only revealed a significant interaction between conditioning drug and nature of extinction drug [$F(1,28) = 7.48$, $p < 0.05$]. The main effect for nature of extinction drug did not approach statistical significance [$F(1,28) = 1.21$, $p > 0.28$]; neither did the remaining effects [Fs < 2.55, ps > 0.12]. The significant interaction between conditioning drug and nature of extinction drug is a consequence of the fact that the rats in one of the groups that was extinguished under AMP, namely group MA, responded more than those extinguished under MID, groups MM and AM.

SDE

Figure 2 presents the results of the test sessions. The figure shows that, in each of the test cycles, the rats that had been extinguished under MID, groups MM and AM, responded less during testing under MID than during testing under AMP, whereas the rats extinguished under AMP, groups AA and MA, did not differ much in responding under AMP and MID.

A Conditioning Drug × Extinction Drug × Test Drug × Test Cycle ANOVA on the test data revealed only a significant main effect for test drug [$F(1,28) = 11.15$, $p < 0.01$], and a highly reliable interaction between extinction drug and test drug [$F(1,28) = 17.05$, $p < 0.001$]. The other main and interaction effects were not significant (ps > 0.05). Simple main effect analyses were performed to further examine the significant interaction. These revealed that, across test cycles, animals extinguished under MID responded less under MID than under AMP [$F(1,28) = 27.89$, $p < 0.001$], whereas rats extinguished under AMP did not respond differentially under AMP vs. MID [$F < 1$]. Furthermore, animals extinguished under MID responded less than those extinguished under AMP during the tests under MID [$F(1,49) = 8.73$, $p < 0.01$], whereas there was no difference between these types of subject during the test under AMP [$F(1,49) = 2.89$, $p > 0.05$].

DISCUSSION

The results of the training session imply successful conditioning of a magazine-approach response in all groups of rats. Acquisition of this response was not affected differentially by the drugs employed.

From the initial phase of the extinction session on, the absence of food pellets caused a decrease in the number of magazine visits, relative to the number of visits observed at the end of the conditioning session, that is, after repeated exposure to pellet deliveries. Although this response decrease held for the animals in all groups, it did so to a larger extent for the rats that were extinguished under MID than for those extinguished under AMP. Thus, under the present extinction conditions, AMP enhanced magazine responding relative to MID. This is an effect that must be taken into account when interpreting the test results (see below).

More importantly for present purposes is the finding that the rats that, during the extinction session, were replaced in the training box while in the same drug state as present during conditioning did not emit more magazine responses than those replaced while in another drug state. Also, in none of the critical analyses was there a significant effect involving the conditioning drug factor. Thus, no reliable SDL effect was observed. This supports the notion of identical effects of internal and external contextual cues as far as SDL is concerned.

During testing under the two drug conditions, only the rats that were extinguished under MID displayed less magazine visits in the drug state that corresponded with their extinction drug state (MID) than in the other drug state (AMP). The rats extinguished under AMP did not respond differentially in the different drug states. Thus, only for one half of the subjects did the extinction drug state appear to promote less responding compared with the other drug state. This finding implies asymmetrical SDE.

However, in view of the differential drug effect found during the extinction session, with AMP yielding more magazine

responses than MID, the test results may be interpreted as reflecting the joint operation of conditioned (SDE) and unconditioned drug effects in all groups. That is, if only an unconditioned drug effect were operative during the test sessions, which were also performed under extinction, one would have expected more magazine visits under AMP than under MID in all groups of rats. The fact that such a difference was absent for the rats extinguished under AMP implies the presence of a second process. This process prevented the unconditioned drug effect from exerting a significant behavioral effect, or, alternatively, the unconditioned drug effect prevented this second process from reliably influencing the rat's behavior. It is conceivable that this second process concerned the potential of AMP-induced cues to signal the extinction experience (SDE). Thus, for the AMP-extinguished rats, AMP at the same time increased magazine responding as a result of its unconditioned effect and decreased it because it signaled extinction. In this regard, it is interesting to note that, at least numerically, the rats extinguished under AMP during the second test cycle also responded less in their previous extinction-drug state than in the other drug state. According to our analysis, this reflects a suppressed SDE effect.

Following this same line of reasoning, it must be assumed that, for the rats extinguished under MID, the observed test results reflect the mutual effect of unconditioned and conditioned (SDE) effects that both worked in the direction of more responding under AMP than under MID. For these rats, MID unconditionally suppressed responding (relative to AMP) and functioned as a signal for the absence of the food reinforcer [see also (14), for independent evidence for a similar line of reasoning in an aversive conditioning preparation].

It must be noted that the empirical SDE effect displayed by the MID-extinguished rats, and the proposed masked SDE effect for AMP-extinguished animals, did not manifest themselves as a complete "renewal" of conditioned responding during the tests in the nonextinction drug state [e.g., (4,5)]. For comparison purposes, the group's mean number of magazine visits based on all 10 1-min samples of the conditioning session were: group AA, 58.9; group MM, 56.0; group AM, 50.0; and group MA, 71.0, whereas, during the extinction session, the corresponding means dropped to, respectively, 41.3, 34.1, 31.0, and 58.1. As can be seen in Fig. 2, the frequency of responding during the test sessions ranged from 9.8 to 44.0. This means that renewal took the form of a prevention of a further reduction of conditioned responding that was expected as a result of continued extinction of the conditioned response during testing ("extinction" and "test" sessions were identical and were all nonreinforced sessions), rather than inducing response frequencies that were at about the same level as observed during conditioning. Although this is a somewhat weaker SDE effect than is usually found in studies on context-dependent extinction manipulating external contexts, the principle remains the same: Relative to other internal contextual cues, the extinction context most powerfully signals extinction.

It is also important to note that any other direct, or unconditioned, effects that the drugs might have, aside from the unconditioned effect mentioned above, cannot have played a critical role in the present experiment. For instance, in principle, one could argue that the pattern of responding during the extinction session reflects a direct deleterious effect of AMP on extinction learning, relative to MID, without referring to the notion of SDE. However, if this was the primary effect, one would have expected between-group differences in magazine responding on both MID and AMP tests, reflecting overall enhanced responding during the test phase for the rats extinguished under AMP. However, a between-group difference was not observed on AMP tests.

The results of the present experiment extend the generality of SDE effects in previous studies [e.g., (3)]. SDE also occurs in female rats (most previous studies were performed with male rats) in appetitive conditioning using a 2×2 factorial design with explicit drug cues during both conditioning and extinction. The current finding that rats are more likely to show SDE than SDL, or, to put it differently, that rats do not demonstrate SDL under conditions where they do show SDE, can be added to the growing list of studies indicating that internal and external contextual cues become involved in conditioning procedures in a comparable way [see also, e.g., (9,14–16)].

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