ELSEVIER

European Journal of Pharmacology 319 (1997) 5–11

ejp

Short communication

Conditional control by midazolam and amphetamine in a rapid appetitive discrimination procedure

J.H. Roald Maes *, Jo M.H. Vossen

Department of Comparative and Physiological Psychology, University of Nijmegen, P.O. Box 9104, 6500 HE Nijmegen, Netherlands

Received 9 September 1996; revised 29 November 1996; accepted 3 December 1996

Abstract

The present two experiments examined conditional control by midazolam and amphetamine cues in an appetitive discrimination procedure. In each of two experiments, male Wistar rats were subjected to a small number of two types of training session in a conditioning box. During one type of session, a stimulus was consistently followed by food in a magazine, whereas during the other type of session, this very same stimulus was followed by nothing. Groups of rats were injected with either midazolam (0.1 mg/kg, s.c.) or amphetamine (0.5 mg/kg, s.c.), prior to each food-reinforced session, and with saline prior to each food non-reinforced session. Other groups received the reverse treatment. Subsequent non-reinforced test sessions showed that, in both experiments, only the rats that had been food reinforced in a drug state displayed shorter magazine-response latencies in their previously reinforced than in their previously non-reinforced state, both prior to and during the stimulus. This finding was interpreted as reflecting the joint operation of unconditioned and conditioned drug effects, with the latter being based on occasion setting by the drug cues that was induced by the relatively short discrimination training procedure. The present results parallel those of previous aversive drug-discrimination experiments adopting a similar short discrimination procedure.

Keywords: Appetitive discrimination; Occasion setting; Midazolam; Amphetamine; Unconditioned drug effect; Conditioned drug effect

1. Introduction

Recently, Maes et al. (1996) reported the results of a series of rat experiments in which internal cues arising from the administration of various drugs (midazolam, amphetamine and flesinoxan) were shown to acquire the potential to modulate conditioned immobility in an aversive conditioning procedure. Specifically, rats were subjected to a discrimination procedure in which two types of session were given: sessions in which an electric footshock was presented some time after placement in a conditioning box, and sessions which merely consisted of placement in that same box without subsequently presenting a shock. Groups of rats differed in the internal state that was induced prior to each of these types of session. Some groups were under the influence of a drug in shock sessions and under saline in non-shock sessions. For other groups, the reverse was true. The discrimination procedure consisted of only three sessions of each type, presented in a semi-random order. The conditioned response observed was immobility. During this short training phase, no differential immobility was observed between and within groups during the two session types. However, during a subsequent test phase, in which no shocks were presented, animals of some groups showed more immobility in the conditioning box when they were in the same state as they were during previous shock sessions than when they were in the alternative state. Other groups did not show differential responding on the basis of the induced internal state.

The response profiles observed during testing were accounted for by referring to the notions of conditional control by drug cues (conditioned effect) and unconditioned, or non-associative, effects of the various drugs on the response measure used. The latter effects were assessed in a separate experiment. Accordingly, drug states either somehow signalled the presence (positive control) or the absence (negative control) of shock, depending on whether the drug had been present in the shock or in the non-shock sessions. Positive conditional control was reflected in the rats showing more immobility during test sessions under the drug than in those under saline. However, this effect only appeared if the unconditioned effect that the specific drug had on immobility was also in the direction of an

* Corresponding author. Tel.: (31-24) 361-2544; Fax: (31-24) 361-6066; e-mail: maes@nici.kun.nl

PII S0014-2999(96)00953-3

enhancement of immobility. If not, the conditioned effect was masked by the unconditioned drug effect (or vice versa). A similar line of reasoning was adopted regarding the drug states that were assumed to exert negative conditional control. Induction of these latter states yielded less immobility than induction of a saline state, but only if the drug did not by itself have an unconditioned immobility-promoting effect.

Concerning the nature of the associations underlying the conditional potential of the drug cues, it must be noted that these cues did not prove to function as 'simple' signals for the presence or absence of shock (schematically: drug → shock, or drug → no shock associations), but as occasion setters, indicating a specific relationship between drug states and the occurrence or non-occurrence of shock after placement in the conditioning box (schematically: drug → [box → shock], or drug → [box → no shock]; see, e.g., Bouton, 1993). This conclusion was based on separate test sessions in a novel box. The response pattern observed during these novel context tests reflected the influence of unconditioned drug effects. All subjects showed more, or less, immobility in the novel test context under the specific drug examined than under saline, irrespective of the training history with that drug in the training box. Occasion setting by drug cues, which in the training context gave rise to the observed differential immobility between and/or within groups, was assumed to be eliminated in the novel context because these cues did not provide any information regarding the relationship between that novel context and the occurrence of shock.

Because of the consistent results regarding conditional control by the various drugs investigated, the training procedure adopted in the above-described experiments has been promoted as a relatively rapid technique to be used in future drug discrimination research. The present paper was intended to examine the generality of these previous findings. Specifically, it was assessed whether a demonstration of drug discrimination learning is also possible using a similar rapid training procedure in an appetitive conditioning paradigm. Such a procedure could be more advantageous, relative to the aversive conditioning procedure. For instance, the present appetitive procedure does not require the fairly elaborate and subjective observation technique necessary when using immobility as the dependent variable. As will be described hereafter, the various potential conditioned and unconditioned effects that drugs may have on the appetitive response measure can be evaluated using standard analyses of variance.

2. Materials and methods

2.1. Subjects

The subjects were 32 experimentally naive male Wistar rats. Sixteen rats were used in each of two experiments. At the start of the experiments, the body weights ranged from 405 to 567 g. The animals were individually housed in Makrolon cages in a vivarium maintained on a 12-h-light/12-h-dark cycle (lights out at 8 a.m.). The experimental sessions were run midway through the dark phase. Before the start of the experiments, the rats were gradually reduced to 85% of their free-feeding weight and were maintained at this level for the remainder of the experiments by being given a restricted amount of food several minutes after termination of each training and test session.

2.2. Apparatus

The apparatus consisted of four boxes, each measuring $24.5 \times 25 \times 20$ cm. The front wall, back wall and ceiling of each box were made of clear Plexiglas; the side walls were aluminium. The floor consisted of 3-mm stainless-steel rods, spaced 1.3 cm apart. Each of the boxes contained a recessed food magazine to which 45-mg precision food pellets (Campden Instruments) could be delivered. A light bulb located behind the food magazine providing a green light. A 1.1-kHz, 70 dB(A) tone could be presented through two speakers. One of these speakers was mounted 10 cm to the left of the food magazine; the other 10 cm to the right of the magazine. The speakers were 2 cm above the grid floor. The green magazine light served as a conditioned stimulus in the first experiment, whereas in the second experiment, a stimulus consisting of the green magazine light and the tone served that same role. The purpose of using a more salient conditioned stimulus in Experiment 2 was to assess whether, under this condition, the effects of the factors of major interest would still apply to both pre-conditioned stimulus and conditioned stimulus periods, as was the case in Experiment 1 (see following sections). The magazine contained an infrared emitter and photodiode sensor. Interruption of the infrared beam was recorded as the start of a magazine visit, which was considered to last until the beam was no longer interrupted. The boxes were housed in sound- and light-attenuating shells; masking noise was provided by the operation of ventilation fans contained in these shells. The apparatus was controlled by a Macintosh/Performa 460 computer.

2.3. Drugs

The drugs used were midazolam (Roche Netherlands) and *d*-amphetamine sulphate (RBI Research Biochemicals International). The midazolam dose used was 0.1 mg/kg and amphetamine was injected at a dose of 0.5 mg/kg. Each of these drugs was dissolved in saline (0.9% NaCl) and injected subcutaneously. Midazolam, amphetamine and saline were administered in a volume of 2 ml/kg. These drugs and doses were chosen because they had also been used in the aversive conditioning experiments by Maes et al. (1996).

2.4. Procedure

2.4.1. Pre-training

In each of the two experiments, two 30-min training sessions were given in which each animal was trained to retrieve food pellets from the food magazine. During each session, ten food pellets were delivered according to a variable time 3-min schedule. No drugs were administered during this phase.

2.4.2. Discrimination training

In Experiment 1, the subjects were divided into two equal-sized groups, Group M^+ (reinforcement under midazolam) and Group S^+ (reinforcement under saline). These groups were matched for body weight. Training session 1, which was given to each rat, was identical to each of the pre-training sessions, except that the green magazine light was on for 30 s prior to each pellet delivery. Thus, there were 10 conditioned stimulus-pellet trials. Training session 2 was identical to training session 1, except that the number of conditioned stimulus-pellet trials was reduced to five in order to decrease inter-trial responding. The mean interval between onset of conditioned stimuli was 5 min. Training sessions 3–6 were identical to training session 2, except that no pellets were delivered on sessions 3, 4 and 6. The difference between groups was that the animals in Group M^+ were injected with midazolam immediately prior to each of the three food-reinforced training sessions (Sessions 1, 2 and 5), and with saline immediately prior to each of the three non-reinforced sessions (Sessions 3, 4 and 6). For the animals in Group S^+, the reverse relationship was in effect between internal state and the availability of a pellet after each conditioned stimulus. Thus, for this group, a pellet was delivered after each conditioned stimulus under saline (Sessions 1, 2 and 5), but not under midazolam (Sessions 3, 4 and 6).

The discrimination training procedure adopted in Experiment 2 was identical to that used in Experiment 1, except that there were only five reinforced trials in the first training session instead of ten. Our impression from the results of Experiment 1 was that five trials would be sufficient to already induce a strong conditioned response to the conditioned stimulus on the very first training session. Moreover, by reducing the number to five trials, we equated the total number of reinforced and non-reinforced trials given during discrimination training. However, due to equipment failure, the rats only received three of the intended five trials during this first training session. However, as will be described below, the response profile was the same in the two experiments, suggesting no differential effects of the different number of training trials presented in the first training session. In Experiment 2, Group A^+ received a food pellet after each conditioned stimulus presentation after amphetamine, but not after saline, whereas the reverse relationship between internal state and conditioned stimulus reinforcement held for the rats in Group S^+.

2.4.3. Test

The test phase in both experiments consisted of two sessions that each were identical to non-reinforced training sessions (five non-reinforced conditioned stimulus presentations). In Experiment 1, one half of the animals in each group was first tested under midazolam during the first test session, and under saline during the second. For the remaining animals in each group, the test order was reversed. In Experiment 2, one session was conducted under amphetamine; the other under saline. In this experiment too, test order was counterbalanced within groups. The purpose of these test sessions was to examine whether or not the rats would respond faster (see Section 2.5) in their previously reinforced state than in their previously non-reinforced state. A positive finding would reflect successful discrimination learning.

2.5. Dependent measure

The dependent measures were the latency between onset of each conditioned stimulus and the first magazine visit during that conditioned stimulus presentation, and the latency between the start of each 30-s pre-conditioned stimulus period and the first magazine visit during that period. A latency of 30 s was taken if no magazine response had occurred and the latency was considered to be 0 s if the rat already had its head in the food magazine at the very start of a pre-conditioned stimulus or conditioned stimulus period. The mean pre-conditioned stimulus and conditioned stimulus latency scores for each test session were based on the five pre-conditioned stimulus and five conditioned stimulus ‘trials’ of each session.

2.6. Data analysis

The data from the test sessions were first evaluated using analyses of variance (ANOVAs) that also included the factor ‘Test Order’ (first drug state or first saline state) as a between-subjects factor. In neither experiment did this factor exert a significant main effect; neither did it significantly interact with any other factor. Therefore, this factor was excluded from all further analyses.

We were interested in assessing three different types of (potential) drug effects. The first is an unconditioned effect that each of the two drugs might have on magazine responding. This effect was examined by performing an ANOVA with Group as a between-subjects factor, and Drug (midazolam or saline in Experiment 1, and amphetamine or saline in Experiment 2) and Period (pre-conditioned stimulus or conditioned stimulus) as within-subjects factors. A reliable unconditioned performance effect would be expressed in a significant main drug effect, reflecting an overall response-enhancing or -attenuating effect of a drug during testing, irrespective of the training history concerning that drug.

Second, using this same ANOVA we could also assess whether the drugs have an unconditioned effect on learning processes that take place during the discrimination training phase (acquisition effect). Such an effect would be reflected in a significant group main effect. For instance, if a drug used to induce the internal state during reinforced sessions has a non-specific detrimental effect on the acquisition of new associations, response latencies during testing should be longer in the drug-reinforced than in the saline-reinforced group, regardless of the induced drug state (main group effect).

Third, and of primary importance for our purpose, the drug cues might come to act as conditional stimuli, signalling food reinforcement or non-reinforcement. A sensitive test for uncovering conditional control is an ANOVA using the test latencies, with Group, Type of Test (in previously reinforced state or in previously non-reinforced state) and Period as factors. The ability to discriminate between internal states, and to relate these in some way to the presence or absence of food (in short: discrimination learning), would be reflected in significant effects involving the type of test factor.

Significant interactions between main factors in the ANOVAs mentioned above were examined further by simple main effect analyses, with the error terms and degrees of freedom based on the overall ANOVA (Winer, 1971). A rejection criterion of $P < 0.05$ was used throughout.

3. Results

Fig. 1 displays the results of the test sessions of Experiment 1. The figure shows that, overall, the rats showed faster magazine responses in conditioned stimulus than in pre-conditioned stimulus periods. Furthermore, both groups showed shorter latencies during pre-conditioned stimulus and conditioned stimulus periods when tested under midazolam than when tested under saline. Most importantly, the rats in Group M^+ responded faster in both pre-conditioned stimulus and conditioned stimulus periods when tested in their previously reinforced state (midazolam) than when tested in their previously non-reinforced state (saline). However, the animals in Group S^+, if anything, responded faster in their former non-reinforced than in their former reinforced state. A Group × Drug × Period ANOVA on the data displayed in Fig. 1 revealed that, overall, the rats in Group M^+ showed longer response latencies than those in Group S^+ (main effect for group, $F(1,14) = 8.80$, $P < 0.05$), that rats responded faster under midazolam than under saline (main drug effect, $F(1,14) = 7.38$, $P < 0.05$) and that the rats responded faster during conditioned stimulus than during pre-conditioned stimulus periods (main period effect, $F(1,14) = 12.87$, $P < 0.01$). The interactions between the main factors were not significant ($Fs(1,14) < 3.33$, $Ps > 0.05$). A Group × Type of Test × Period ANOVA on these data revealed a significant Group × Type of Test interaction ($F(1,14) = 7.38$, $P < 0.05$), aside from, of course, the same main group and period effects reported above. All other terms were not significant ($Fs(1,14) < 3.33$, $Ps > 0.09$). The significant Group × Type of Test interaction was caused by the fact that the effect of type of test was significant in Group M^+ ($F(1,14) = 5.82$, $P < 0.05$), but not in Group S^+ ($F(1,14) = 1.82$, $P > 0.05$). Furthermore, the rats in Group M^+ responded slower in their previously non-reinforced state (saline) than the rats in Group S^+ did in their previously non-reinforced state (midazolam).

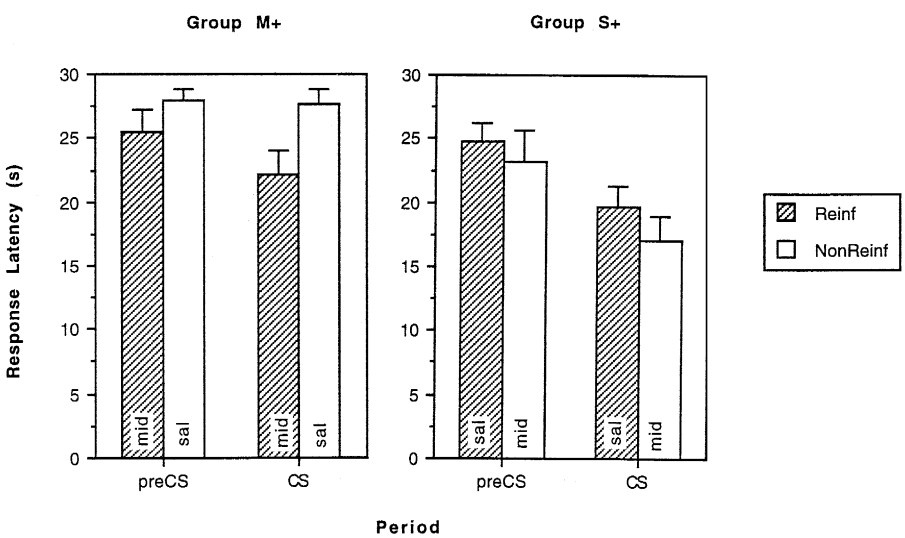

Fig. 1. Mean response latencies (+S.E.M.) of the groups during both pre-conditioned stimulus (preCS) and conditioned stimulus (CS) periods of the tests of Experiment 1, which were performed in the previously reinforced and non-reinforced states. During training, the animals in Group M^+ had been reinforced under midazolam (mid), but not under saline (sal), whereas for the rats in Group S^+, the reverse conditions had been in effect.

Fig. 2 shows the results of Experiment 2. As in Experiment 1, in both groups the response latencies were shorter in conditioned stimulus than in pre-conditioned stimulus periods. Moreover, the rats displayed shorter latencies under amphetamine than under saline. This was true during both pre-conditioned stimulus and conditioned stimulus periods. Most importantly, however, only the rats in Group A^+ responded faster when tested in their previously reinforced state, as compared to their previously non-reinforced state. A Group × Drug × Period ANOVA using the test latencies from Experiment 2 revealed that, overall, rats showed shorter latencies under amphetamine than under saline (main drug effect, $F(1,14) = 24.85$, $P < 0.001$) and shorter latencies during conditioned stimulus than during pre-conditioned stimulus periods (main period effect, $F(1,14) = 14.58$, $P < 0.01$). The interaction between group and drug was also significant ($F(1,14) = 5.68$, $P < 0.05$) and reflects the fact that the rats in Group A^+ responded faster under amphetamine than under saline ($F(1,14) = 27.15$, $P < 0.001$), whereas there was no significant difference in response latency under amphetamine versus saline in Group S^+ ($F(1,14) = 3.38$, $P > 0.05$). None of the other main or interaction effects reached statistical significance ($Fs(1,14) < 2.97$, $Ps > 0.05$). A Group × Type of Test × Period ANOVA on these same data revealed that, aside from the main effect of period mentioned above, rats responded faster in their reinforced state than in their non-reinforced state (main type of test effect, $F(1,14) = 5.68$, $P < 0.05$). Interestingly, this effect of the type of test was solely due to Group A^+, as was reflected in a significant Group × Type of Test interaction ($F(1,14) = 24.85$, $P < 0.001$). This interaction was caused by the fact that the effect of the type of test was significant in Group A^+ ($F(1,14) = 27.15$, $P < 0.001$), but not in Group S^+ ($F(1,14) = 3.38$, $P > 0.05$). None of the remaining main or interaction effects were significant.

4. Discussion

In each of the two experiments, the factor 'period' did not significantly interact with any other factor. Although the rats consistently showed shorter response latencies during conditioned stimulus than during pre-conditioned stimulus periods, which reflects successful conditioning to the conditioned stimulus, the effects of the factors of main interest were similar in pre-conditioned stimulus and conditioned stimulus periods. This means that the different drug effects found in the present experiments extended to magazine responding that was evoked by both the conditioned stimulus and the stimuli that were present in the absence of that conditioned stimulus, such as, for instance, those related to the food magazine.

Three different types of drug effect were found in the present experiments. First, an unconditioned effect of the drugs was found on magazine responding (unconditioned performance effect), as reflected in a main drug effect in each of the two experiments. Faster magazine responding was observed in the drug state than in the saline state. With respect to midazolam, this effect could be caused by the drug's anxiolytic and/or hyperphagic properties (e.g., Yerbury and Cooper, 1987). The reduced response latencies in the amphetamine state might well be a consequence of the drug's stimulating property.

Second, an unconditioned drug effect on learning processes taking place during discrimination training appeared in Experiment 1, as reflected in a main group effect. Rats that had been reinforced during training sessions under

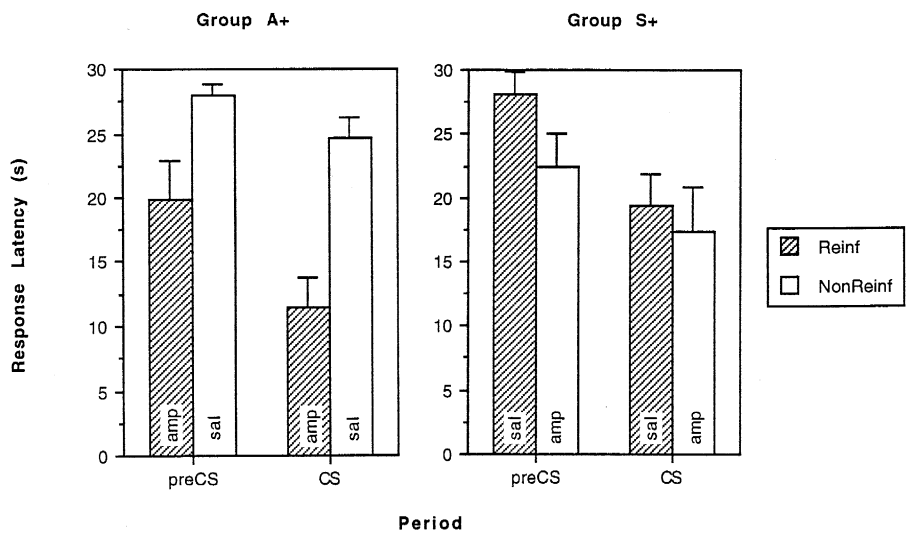

Fig. 2. The results of the tests in Experiment 2. Mean response latencies (+S.E.M.) during pre-conditioned stimulus (preCS) and conditioned stimulus (CS) periods of the test session in the formerly reinforced drug state, and the previously non-reinforced state. For the rats in Groups A^+, the reinforced state during training had been induced by amphetamine (amp), whereas the non-reinforced state had been induced by injecting saline (sal). The reverse conditions held for the animals in Group S^+.

midazolam responded slower than those reinforced under saline, regardless of the state induced during testing. There are several possible mechanisms underlying this drug effect. First, midazolam might have decreased the reinforcing value of food, which, in turn, resulted in a weaker conditioned response in Group M^+ than in Group S^+. However, this is a somewhat unlikely possibility in view of the benzodiazepine-induced hyperphagia already referred to above. Second, midazolam might have impaired the formation of an associative link between relevant stimuli and food, which also resulted in a weaker conditioned response. However, midazolam has previously been found not to primarily exert an effect on acquisition, but rather on the effect of a subsequent learning phase on originally acquired associations. For instance, midazolam reduces the effect of extinction treatment after the formation of an associative link between stimuli (e.g., Pereira et al., 1989). Therefore, we favour a third possibility, namely that in Group S^+, the effect of the non-reinforced training sessions (extinction sessions) had a less adverse effect on the strength of the original association(s) formed during the reinforced training sessions than was the case for the rats in Group M^+. This was the case because, during extinction sessions, the subjects in Group S^+ were under midazolam, whereas those in Group M^+ were under saline.

The third drug effect, namely conditional control by drug cues, is currently of primary importance and was manifest as a significant interaction between group and type of test, which was found in each of the two experiments. The rats that had been reinforced during training under the drug (Groups M^+ and A^+) responded faster in their previously reinforced (drug) state than in their previously non-reinforced (saline) state, whereas the rats reinforced during training in the saline state (Groups S^+) did not show differential responding upon testing in the drug versus saline state. This response profile resembles that found by Maes et al. (1996). In both series of experiments, asymmetrical drug discrimination performance was observed, in that only one of the two groups in each experiment responded more in the previously reinforced state than in the previously non-reinforced state. Also as was the case in the previous experiments, this asymmetrical effect can be explained in terms of the combined unconditioned performance and conditional stimulus effects of the drugs. Accordingly, in the present experiments, both midazolam and amphetamine decreased response latencies, irrespective of the training history (main drug effect). This performance effect worked for finding shorter latencies in the reinforced state than in the non-reinforced state for the rats in each of the Groups M^+ and A^+. In these groups, the drug cues promoted shorter response latencies as a result of their conditioned and unconditioned effects. Instead, in the two saline-reinforced groups, Groups S^+, the unconditioned, latency-reducing, drug effect worked against finding shorter latencies in the previously reinforced state (saline) than in the previously non-reinforced state (midazolam/amphetamine), which would be expected on the basis of a conditioned effect alone. Consequently, null results were obtained for these groups.

Because of the primary research interest of the present experiments, namely, to test the generality of the findings of previous drug discrimination experiments, no explicit test was included to examine the nature of the associations that underlie the conditioned drug effect (simple associations vs. occasion setting). However, we do have some data that indirectly bear on this issue. After the tests of major interest, we continued Experiment 1 using the animals that did show state-dependent responding, namely those from Group M^+. Specifically, animals first received four retraining sessions, two standard midazolam (reinforced) and two standard saline (non-reinforced) training sessions. Subsequently, one half of the animals, Group M^+/Ext (extinction), received five sessions. Each of these sessions consisted of injecting the rats with midazolam and placing them back in the home cage. The other half of the rats of Group M^+, Group M^+/noExt (no extinction), received an identical treatment, except for the administration of saline instead of midazolam. Following this differential treatment, all animals were tested for magazine responding in two test sessions, which were identical to the test sessions conducted prior to the differential home-cage treatment.

The logic behind these treatments is as follows. If, for the rats in Group M^+, midazolam cues had acquired a direct associative link with the food reinforcer, the home-cage treatment in sub-Group M^+/Ext can be considered to be an extinction treatment that should eliminate, or at least weaken, a midazolam-food association. This would be reflected in a reduction in the difference between response latencies under midazolam versus saline. Instead, the home-cage treatment in sub-Group M^+/noExt should have no effect on the strength of the midazolam-food association, which implies that the difference in responding, namely, faster responding under midazolam than under saline, should be unaffected. However, if the cues arising from the midazolam injection were functioning as occasion setters, indicating that food would be delivered in the training context, then the manipulations in the home cage should have no effect whatsoever on the discrimination performance in either group.

The result of the test sessions after the differential home-cage treatment was that the discrimination performance was left completely intact in both sub-groups, which is expected if the midazolam cues were operative as occasion setters.

A final issue that deserves some discussion is the possibility that the external stimuli present during pre-conditioned stimulus and conditioned stimulus periods were not primarily functioning as Pavlovian conditioned stimuli, whose response-evoking ability was modulated or occasion set by the internal drug cues (schematically: drug → [stimuli → food/no food]. It is conceivable that these ex-

ternal stimuli instead were themselves operative as conditional or discriminative stimuli that indicated that a visit to the food magazine would be food reinforced or not (stimuli → [approach response → food/no food]; see, e.g., Colwill and Rescorla, 1990). If so, one would then have to assume that the drug cues in turn modulated the discriminative-stimulus function of these external cues (drug → [stimuli → [approach → food/no food]). It is important to note that, whatever the exact nature of the associations, each of the two possibilities outlined implies a form of hierarchical control by the drug cues. This is in accordance with the conclusion drawn on the basis of the experiments by Maes et al. (1996).

To summarize, the previous and present experimental results indicate that drug cues can be shown to very rapidly acquire controlling properties with respect to both discrete and non-discrete stimuli in both aversive and appetitive conditioning preparations. Furthermore, it is very likely that this control is based on occasion setting.

Acknowledgements

The Netherlands Organization for Scientific Research (NWO) is gratefully acknowledged for funding this research. The experiments were conducted while J.H.R.M. was supported by a grant of the Foundation for Behavioural and Educational Sciences of this organization (575-58-056). We thank R. ten Tusscher for his assistance in collecting part of the data of Experiment 2. We also thank Roche Nederland b.v., Mijdrecht, Netherlands, for providing midazolam.

References

Bouton, M.E., 1993, Context, time, and memory retrieval in the interference paradigms of Pavlovian learning, Psychol. Bull. 114, 80.

Colwill, R.M. and R.A. Rescorla, 1990, Evidence for the hierarchical structure of instrumental learning, Anim. Learn. Behav. 18, 71.

Maes, J.H.R., C.M. Van Rijn and J.M.H. Vossen, 1996, Drug states as modulators of conditioned immobility in a latent discrimination procedure, Eur. J. Pharmacol. 309, 131.

Pereira, M.E., R. Rosat, C.H. Huang, M.G.C. Godoy and I. Izquierdo, 1989, Inhibition by diazepam of the effects of additional training and of extinction on the retention of shuttle avoidance behavior in rats, Behav. Neurosci. 103, 202.

Winer, B.J., 1971, Statistical Principles in Experimental Design, 2nd edn. (McGraw-Hill, New York, NY).

Yerbury, R.E. and S.J. Cooper, 1987, The benzodiazepine partial agonists, Ro16-6028 and Ro17-1812, increase palatable food consumption in nondeprived rats, Pharmacol. Biochem. Behav. 28, 427.