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NMDA Receptor Antagonist MK-801 Selectively Impairs Learning of the Contiguity of the Conditioned Stimulus and Unconditioned Stimulus in Goldfish

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XU, X. *NMDA receptor antagonist MK-801 selectively impairs learning of the contiguity of the conditioned stimulus and unconditioned stimulus.* PHARMACOL BIOCHEM BEHAV **58**(2) 491–496, 1997.—Previous experiments have shown that administration of intracranial MK-801 blocks learning of classical fear conditioning in goldfish. The impairment of learning was decreased when fish received limited pretraining, suggesting that only the early phase of conditioning may be sensitive to disruption by MK-801. The present studies investigated the possibility that classical conditioning in goldfish consists of two successive phases and that only the initial phase depends critically on *N*-methyl-D-aspartate receptor function. A series of experiments showed that the anterograde amnestic effect of MK-801 is decreased or eliminated when fish received pretraining consisting of 6 or 12 conditioning trials, respectively. MK-801-sensitive learning is inferred to be completed within 12 trials. The neural mechanism of the learning which occurs during the later trials is manifestly insensitive of MK-801. Furthermore, MK-801 impaired learning when fish received pretraining consisting of six pseudoconditioning trials. The results indicate that MK-801-sensitive learning is associative or depends on the contiguity of the conditioned stimulus (CS) and unconditioned stimulus (US) and that MK-801 selectively impairs learning of the CS–US contiguity. © 1997 Elsevier Science Inc.

Learning Memory Classical conditioning Goldfish Excitatory amino acid receptor antagonist *N*-methyl-D-aspartate

INVESTIGATIONS of the role of excitatory amino acid (EAA) receptor functions in activity-induced synaptic plasticity and in learning from behavioral experience suggest that the mechanism of associative learning may be mediated by EAA receptors that are activated by *N*-methyl-D-aspartate (NMDA) (3,11,13,14). Administration of selective antagonists of NMDA receptor functions impairs learning in various associative learning paradigms, including visual spatial learning (6,12,19,21), olfactory discrimination (20), passive avoidance (2,15) and classically conditioned fear (7,10,17,25).

The amnestic effects of a noncompetitive NMDA receptor antagonist, MK-801, has been investigated in goldfish by using visually mediated, classical fear conditioning as a model of associative learning (25). The experiments showed that administering an intracranial (IC) injection of MK-801 prior to the first training session results in anterograde amnesia (AA) for fear conditioning in that session. The AA was not the result of a disruption of memory consolidation or state-dependent learning or of an impairment of performance processes, suggesting that MK-801 produces AA by specifically blocking learning processes (25). The experiments thus supported the proposal that neural mechanisms of associative learning critically depend on NMDA receptor functions.

An unanticipated finding was that the AA effect of MK-801 was decreased or eliminated in fish that received limited pretraining, consisting of a few conditioning trials. The results suggested that learning, which was disrupted by MK-801, occurred during the first few trials before fish showed any conditioned response. To investigate further the possibility that classical conditioning consists of two successive phases and that only the initial phase critically depends on NMDA receptor function, the present study examined how the AA effects

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of MK-801 change as the number of conditioning trials in the pretraining session is increased. The study also investigated the nature of the initial phase of classical conditioning and insensitivity of the later phase of learning to disruption by MK-801.

MATERIALS AND METHODS

Subjects and Experimental Drug

Goldfish (*Carassius auratus* L.), 11–15 g, obtained from Grassy Forks Fisheries (Martinsville, IN) or Ozark Fisheries (Stoutland, MO), were kept in large tanks for several weeks prior to experiments and in individual glass tanks during experiments at 25 ± 1°C, as previously described (1,18). MK-801 [(+)-MK-801 maleate, Research Biochemicals Inc.] was dissolved in 10 μl water and administered IC with the aid of a 30-gauge needle and a 100-μl Hamilton syringe (1). Control injections of water were not employed because previous studies have shown that they do not affect learning or memory in goldfish [e.g. (25)].

Fear Conditioning Apparatus

Fish were conditioned individually in three, brightly illuminated tanks (18,25). The conditioned stimulus (CS) was a spot of red light from a light-emitting diode that was turned on for 2.7 s. The unconditioned stimulus (US) was a 0.2 s of an electrical bodyshock produced by 7–8-mA 60-Hz constant current. The conditioned response was the occurrence of a decrease of breathing, or branchial movements, during the CS interval, which was denoted as the branchial suppression response (BSR). Branchial activity was detected by sensing water movements in frontal of the fish's mouth with a thermistor.

The BSR was visualized with an ink-writing polygraph and measured by digital conversion of the analog of the thermistor output (18). A microprocessor calculated the average rate of branchial activity/second during the 4-s interval (A) immediately prior to the CS and the rate during the 2-s interval beginning 0.5 s after the CS onset (B). BSR magnitude was expressed as the percentage of change in activity per second in B vs. A: BSR = $100 \times [1-(B/A)]$, where BSR = 100% signified the maximum response.

Behavioral Screening and Conditioning

Fish were prescreened within several days prior to the experiment to exclude individuals that showed irregular patterns of branchial movements or persistent unconditioned BSRs to the CS (25). In the prescreening session, the fish was placed in the experimental tank for 5 min and then given six pseudoconditioning trials consisting of unpaired presentations of the CS and US. The CS and US occurred at different intervals of 90–120 s in duration. Fish showing an average BSR < 25% in the last four trials were retained for learning experiments.

In a conditioning session, the fish was placed in the experimental tank for 5 min prior to the first trial. In a trial, the fish received a paired presentation of the CS and US. The US was delivered during the last 0.2 s of the CS interval and terminated with the CS. Trials were initiated by the investigator at times when the fish's branchial movements were regular. The intertrial interval was 90–120 s in duration.

EXPERIMENT 1

Trial Dependence of MK-801-Sensitive Learning

The aim of this experiment was to examine the AA effects of MK-801 as a function of the amount of prior conditioning experience. A total of 128 prescreened fish received a sequence of three semiweekly sessions of conditioning trials that were given on experimental days 1, 4 and 8. Individuals received 3 (n = 32), 6 (n = 32), 12 (n = 32) or 0 conditioning trials (n = 32) in session 1, 20 trials in session 2 and 5 trials in session 3. Following session 1, the fish in each of the four groups were distributed into an experimental and a control subgroup that were matched for similar average BSRs in that session. The experimental fish received 2 μg MK-801 30 min prior to the first trial in Session 2, and the controls received no injection. Session 3 served for measuring retention of learning from sessions 1 and 2. The AA effects of the MK-801 were assessed by contrasting BSR scores of the experimental and control fish in session 3.

Results

The results are presented in Fig. 1. A two-way analysis of variance (ANOVA) of data from session 3 indicated that retention differed significantly with the presence of MK-801 in session 2 [$F(1,20) = 8.01$, $p < 0.01$] but not with the number of trials in session 1 [$F(3,120) = 1.37$, $p > 0.05$]. The relationship between the number of trials in session 1 and the AA effects of MK-801 was evaluated by contrasting the mean BSRs of the experimental and control fish with independent Student t-tests. The results showed that MK-801 produced significant retention deficits in the fish that received 0 or 3 trials in session 1 but not in the fish that received 6 or 12 trials. Thus, although the presence of MK-801 extensively inhibited performance of BSRs in session 2, it did not block learning in that session in fish that had 6 or 12 prior conditioning trials in session 1. These results suggest that the learning which is sensitive to disruption by 2 μg MK-801 was completed within 6–12 trials.

The mean BSR of the controls in the first 5 trials of Session 2 revealed that presenting 6 or 12 trials in session 1 resulted in behavioral learning but that 3 trials did not (Fig. 2). A one-way ANOVA, with multiple contrasts, on the mean BSR for the four control subgroups revealed a significant trial effect [$F(3,60) = 2.413$, $p < 0.05$] and that 6 or 12 trials produced an increased mean BSR over that of the 0-trial subgroup and 3 trials did not. Thus, the onset of behavioral learning occurred between trials 6 and 12, coincident with the completion of the MK-801-sensitive learning.

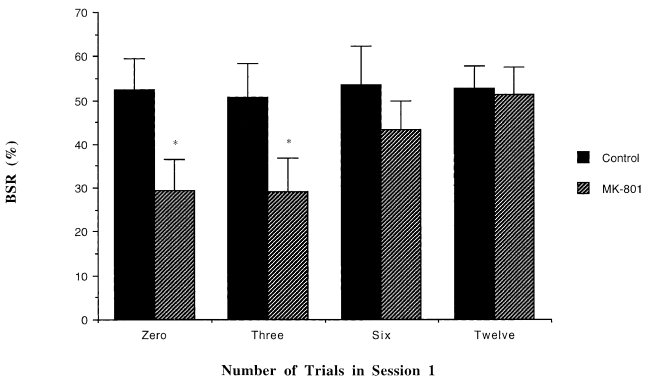

FIG. 1. Trial dependence of MK-801-sensitive learning. Different groups received a different number of conditioning trials in session 1 and MK-801 or no injection 30 min prior to session 2, which consisted of 20 conditioning trials. Each bar represents the mean BSR ± SE in session 3 for 16 fish. *$p < 0.05$ vs. controls.

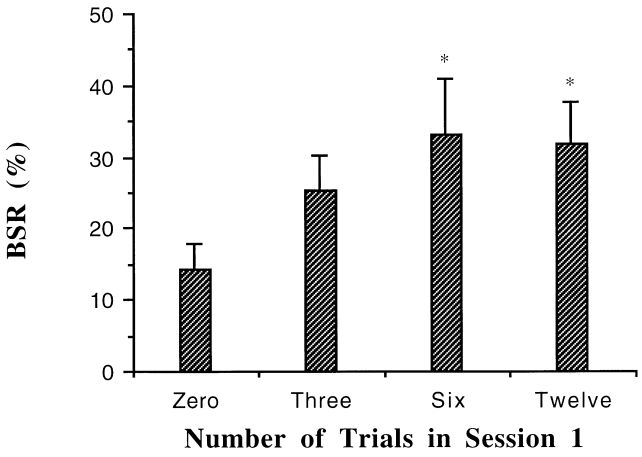

FIG. 2. The mean BSR of four control groups in the first 5 trials of session 2. Each bar represents mean BSR ± SE for 16 fish. *$p < 0.05$ vs. the 0-trial group.

EXPERIMENT 2

Temporal Contiguity of the CS and US and the Occurrence of MK-801-Sensitive Learning

The present experiment was carried out to investigate whether the learning that is disrupted by MK-801 is associative, that is, dependent on the contiguity of the CS and the US. To do this whether MK-801 blocks learning when the fish receive pretraining consisting of six pseudoconditioning trials was examined. A total of 30 prescreened fish received 6 unpaired presentations of the CS and the US in session 1, which was the same procedure used in screening session, followed by 20 conditioning trials in session 2 and 5 conditioning trials in session 3. At the end of session 1, fish were distributed among an experimental and a control group that were matched for similar average BSRs. The experimental group received 2 μg MK-801 30 min prior to session 2, and the control group received no injection. The AA effects of the MK-801 were assessed by contrasting the mean BSRs of the experimental and control groups in session 3.

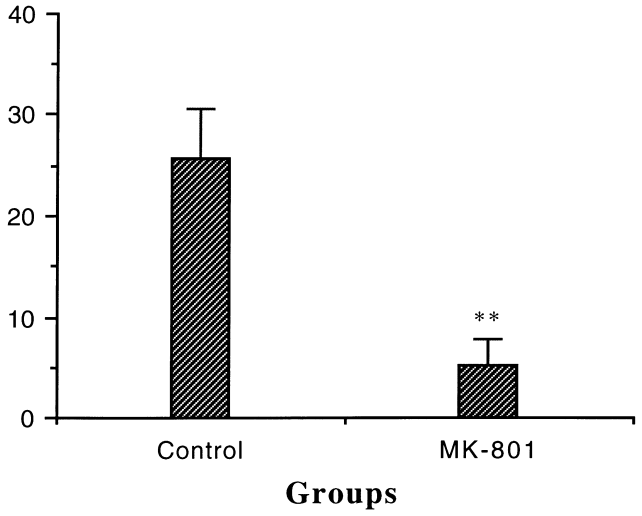

FIG. 3. Dependency of MK-801-sensitive learning on the contiguity of the CS and US. The two groups received 6 pseudoconditioning trials in session 1 and MK-801 or no injection 30 min prior to session 2, which consisted of 20 conditioning trials. Each bar represents the mean BSR ± SE in session 3 for 15 fish. **$p < 0.01$ vs. controls.

Results

An independent, one-tailed *t*-test contrasting the BSRs of the control and experimental fish in session 3 revealed that retention was significantly decreased in the experimental fish (Fig. 3). Thus, learning in session 2 was impaired by the presence of MK-801, indicating that, in contrast to 6 conditioning trials as used in experiment 1 (Fig. 1), 6 pseudoconditioning trials did not produce MK-801-sensitive learning. This result implies that MK-801-sensitive learning is associative and not nonassociative. Because every fish in the experiments received unpaired CS–US trials in the prescreening session and because that session did not produce MK-801-sensitive learning (Fig. 1), the learning is apparently associative. The fish in this experiment exhibited lower BSRs, as indicated by the mean BSR of the controls in session 3, than the fish in experiment 1 (Fig. 1). The lower BSR may result from receiving pseudoconditioning trials in session 1.

EXPERIMENT 3

Insensitivity of Learning After Trial 12 to MK-801

Experiment 1 showed that the learning that occurred after the first 6–12 trials is not significantly impaired by 2 μg of MK-801. If the MK-801-sensitive phase of learning is completed within 12 trials, increasing the dose should not result in AA until the dose reaches the threshold, at which time performance processes that enable learning are blocked. The 2-μg dose is near the threshold for producing AA in the initial training session and was the primary dose used in the previous experiments (25). Doses above 15 μg produce increasingly severe behavioral toxicity and might block learning nonspecifically (25). To investigate whether learning after trial 12 is insensitive to more than 2 μg MK-801, the AA effects of 10 and 30 μg were examined. It was anticipated that 30 μg would significantly impair performance processes affecting learning nonspecifically and that 10 μg would not.

A total of 57 prescreened fish were administered 12 conditioning trials in session 1, followed by 20 trials in session 2 and 5 trials in session 3. Following session 1, fish were divided into three groups matched for similar average BSRs. Groups received 10 or 30 μg MK-801 30 min prior to session 2 or no injection. The AA effects of MK-801 were evaluated by contrasting the BSRs of the three groups in session 3.

Results

The results are presented in Fig. 4. A one-way ANOVA, with multiple comparisons, on the session 3 scores revealed a significant drug effect [$F(2,54) = 5.4866$, $p < 0.01$] and that 30 μg produced a retention deficit but that 10 μg did not (Fig. 4). The evidence that a fivefold increase in the amount of MK-801 did not produce AA indicated that the learning processes during session 2 were insensitive to MK-801. Because learning was normal, a further conclusion is that the 10 μg dose does not significantly impair performance processes. The AA effect of 30 μg MK-801 can be interpreted as a result of a disruption of performance processes that are necessary for learning to occur (25). The dose of 30 μg results in severe ataxia

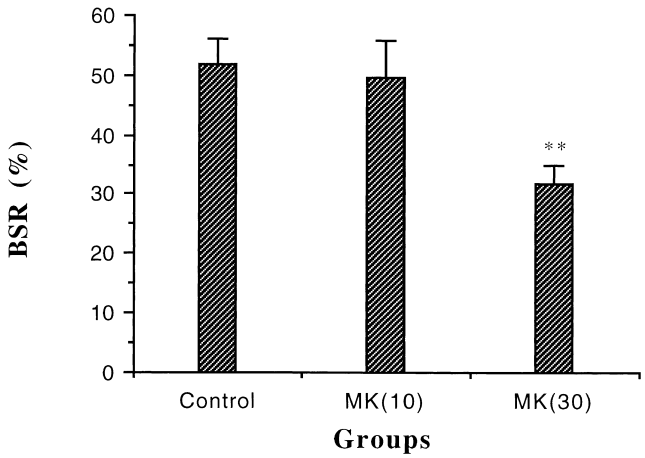

FIG. 4. Insensitivity of learning after trial 12 to MK-801. The fish received 12 trials in session 1 and different amounts of MK-801 or no injection prior to session 2, which consisted of 20 conditioning trials. Control group received 0 μg MK-801, MK(10) group received 10 μg MK-801 and MK(30) group received 30 μg MK-801. Each bar represents the mean BSR ± SE in session 3 for 19 fish. $^{**}p < 0.01$ vs. controls.

and intense struggling against handling but does not impair breathing patterns. Both doses resulted in greatly decreased BSRs during session 2, but only 30 μg produced amnesia.

DISCUSSION

The foregoing results support and expand the previous findings (25) in indicating that MK-801 inhibits classical fear conditioning in goldfish by selectively blocking learning processes that are completed during the first 6–12 conditioning trials. The presence of MK-801 during session 2 blocked learning in that session when fish had experienced three trials in session 1. The retention deficit in session 3 was similar to the deficit shown by the fish exposed to contextual stimuli in the conditioning apparatus during session 1 but had received no conditioning trials. Thus, 3 trials were insufficient to produce MK-801-sensitive learning. When fish received 6 or 12 trials in session 1, MK-801 did not significantly impair learning in session 2. Thus, the results that the presence of MK-801 during session 2 blocked learning when fish received 0 or 3 pretraining trials cannot be due to an injection artifact because the same injection did not impair learning when fish received 6 or 12 pretraining trials. The retention scores in session 3 suggest that learning in session 2 may have been inhibited by the MK-801 in some of the 6-trial fish. These findings imply that learning that is disrupted by MK-801 (2 μg) occurs before trial 12. The evidence that the learning that occurs after trial 12 is not inhibited by a five fold higher dose (10 μg) indicates that MK-801-sensitive learning is completed by trial 12.

The present data also show that the learning that is disrupted by MK-801 is associative and that it occurs prior to the onset of explicit, or behavioral, learning. The term "behavioral learning" is used to denote the learning that is manifested in the trial-dependent increase in the magnitude of the BSR. Behavioral learning ensued between trials 6 and 12 on average, which is concomitant with the decrase in the susceptibility of learning to disruption by MK-801. The comparative insensitivity of the behavioral learning to disruption suggest that learning that is blocked by MK-801 might be nonassociative learning. However, this possibility was ruled out by the finding that MK-801 impaired learning when fish received pretraining consisting of 6 pseudoconditioning trials. The implication is that the learning disrupted by MK-801 may be mainly implicit, or silent, learning that precedes behavioral learning. The study comparing anticonvulsant effects of NMDA antagonists with their amnestic effects suggests that MK-801 impairs learning through its antagonism to the NMDA receptors (26). Thus, NMDA receptor functions that are blocked by MK-801 may be necessary for the silent learning phase of classical fear conditioning but not for behavioral learning phase. Although the behavioral learning also depends on the contiguity of the CS and US, what is learned may relate primarily to the probability of the reinforcement and not to the temporal contiguity of the CS and US.

Comparisons With the Effects of Atropine on Learning in Rats

Following the completion of these experiments, the behavioral effects of MK-801 on classical fear conditioning in goldfish resembled the behavioral effects of atropine sulfate on instrumental learning in rats. Intraperitoneal administration of atropine 20 or 30 min prior to daily training sessions in a swimming maze severely impairs learning of spatial and nonspatial discrimination tasks in rats (5,23). Atropine given immediately following the daily session does not produce retrograde amnesia (RA). Similarly, MK-801 does not produce RA for BSR conditioning (25). Most significantly, Whishaw and Petrie (23) showed that atropine inhibits nonspatial, visual discrimination learning by selectively disrupting the initial, or "presolution" (8), phase of maze learning.

Studies of discrimination learning in rats by Lashley (9) and Krechevsky (8), who used a jumping stand paradigm, have indicated that the exploratory behavior which rats exhibit at the start of maze training, although essential for the successful solution of the problem, is functionally distinct from the discrimination learning process. Kreschevsky proposed that maze learning in rats consists of a presolution phase and a solution phase. He successfully dissociated the two phases in experiments showing that during the first few daily sessions of maze training, each consisting of 20 trials, the rat adopted, or learned to employ, patterns of behavior that were prerequisite for solving the discrimination problem but did not learn to discriminate between the relevant visual stimuli until later sessions. The design of the atropine experiments of Whishaw and Petrie (23) was patterned after the experiments of Kreschevsky. Administering atropine did not impair learning of a black–white discrimination problem when the rats received pretraining on a pattern discrimination problem in the maze. Similarly, learning the pattern discrimination was not impaired by atropine when the rats received pretraining in the maze in which the reinforcement was switched from one discriminative stimulus to the other in successive trials to prevent learning.

How atropine acts in disrupting the presolution phase of maze learning is unclear. It might act by blocking access to, or the use of, the various behavioral patterns, or "hypotheses" (8) or "strategies" (23,24), that rats exhibit in exploring a new maze. The atropine could conceivably produce disorganized exploratory behavior by preventing the rat from learning about the maze from its exploratory experience. The relevant implication of this interpretation is that the learning processes in the presolution and the solution phases have fundamentally different neural mechanisms. The atropine data imply that activation of cholinergic pathways, specifically of muscarinic re-

ceptors, is necessary for learning in the presolution but not in the solution phase.

In BSR conditioning, the inferred period of silent learning and the subsequent behavioral learning can be seen to correspond to the presolution and solution phases, respectively. Whether atropine blocks learning of classical fear conditioning in goldfish is unknown. The experiments with MK-801 indicate that learning during the presolution phase critically depends on glutamatergic neurotransmission, specifically that which is mediated by NMDA receptor activation, and that the learning during the solution phase is not. In showing that learning can be divided into two different phases involving different neural mechanisms, the atropine studies in rats and the MK-801 studies in goldfish strongly support Krechevsky's thesis and suggest that it applies to both instrumental and classical conditioning. In rats, NMDA receptor antagonists block some forms of maze learning, [e.g. (12,18,21)] but whether their amnestic effects are decreased or eliminated by pretraining in the maze is unclear.

MK-801-Sensitive and -Insensitive Learning in BSR Conditioning

If during the atropine-sensitive, presolution phase of discrimination learning, the rat learns movement patterns that are prerequisite for solving the experimental problem, what might the goldfish learn during the MK-801-sensitive, presolution phase of BSR conditioning? The presolution phase of maze learning is completed relatively slowly, over several daily sessions of trials, presumably reflecting the difficulty of the problem (8,23). BSR conditioning may present a much simpler learning problem, consisting of cue learning in which a highly salient CS is associated with a punishing US, and the presolution phase is completed within a few trials.

During the presolution phase, the fish might learn the elemental contiguity of the CS and the US, such that the CS is a signal of the US. Recognition of the CS–US relationship could conceivably occur within a few trials and be completed before the fish exhibits a significant increase in conditioned fear or behavioral learning. What is learned during the presolution phase may be relatively general and not specific to the particular CS and US. For example, the fish may learn that in the experimental tank the periodic occurrence of pain or fear is preceded by a conspicuous but comparatively neutral cue. Whether MK-801 blocks conditioning of the body-shock US to the light CS when the fish receive pretraining with different US and/or CS, which would be a variation of the Krechevsky procedure, remains to be investigated. However, the results that the AA effects of MK-801 on learning of an acoustical CS were eliminated when fish were pretrained on a light-off CS (4) support this interpretation.

During the MK-801-insensitive solution phase, the fish exhibited a trial-dependent increase in BSR magnitude. The fish may learn that the CS is a consistent, or reliable, predictor of the US and may express proportionately increasing defensive freezing behavior during the CS interval. The magnitude of response to the CS classical conditioning changes in part with the probability that the US will occur given a CS and inversely with the probability of a US given no CS (16). Thus, the solution phase of BSR conditioning may consist of behavioral learning related to the probability of a US given a CS, that is, the contingency of the CS and US. Although this learning and the MK-801-sensitive phase of learning both depend on the contiguity of the CS and US, they are clearly mediated by difficult neural mechanisms.

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