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Ketamine: Acquisition and Retention of Classically Conditioned Responses During Treatment With Large Doses

M. M. GHONEIM,[1] PING CHEN, H. M. EL-ZAHABY AND ROBERT I. BLOCK

Department of Anesthesia, University of Iowa, Iowa City, IA 52242

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GHONEIM, M. M., P. CHEN, H. M. EL-ZAHABY AND R. I. BLOCK. *Ketamine: Acquisition and retention of classically conditioned responses during treatment with large doses.* PHARMACOL BIOCHEM BEHAV **49**(4) 1061–1066, 1994.—Two experiments were conducted in rabbits to examine the effects of ketamine (0, 100, and 200 mg/kg) on the acquisition and retention of the classically conditioned nictitating membrane response (NMR). Classical conditioning of the NMR was accomplished by pairing tone and light conditioned stimuli (CS) with paraorbital shock as the unconditioned stimulus (UCS). Experiment 1 assessed the effects of the drug on acquisition and retention of conditioned responses (CR) and determined the role of previous exposure to the experimental environment. Ketamine blocked the display of CR. However, data from subsequent retention testing under nondrug conditions revealed that rabbits that had previously received 100 mg/kg ketamine learned faster than saline-treated rabbits during the acquisition phases. Rabbits that received 100 mg/kg ketamine and were placed in the experimental chambers, but not presented with stimuli during the acquisition phase, did not learn faster during the retention phase than naive rabbits. Experiment 2 controlled further for the effects of nonassociative, unlearned processes. Control groups were presented with unpaired CS and UCS training after drug administration, and subsequently received conventional acquisition sessions under nondrug conditions. Their data indicated that the ketamine group's rapid acquisition during retention testing could not be attributed to nonassociative factors. We conclude that, although it was impossible directly to observe acquisition in rabbits under the influence of ketamine, it was possible that learning occurred as manifested by "savings" in subsequent learning trials.

Anesthetic Ketamine Classical conditioning Memory Learning Retention Rabbit Nictitating membrane response

THE possible occurrence during general anesthesia of conscious or unconscious perception and retention of information is of substantial clinical concern and theoretic interest. Unfortunately, the results of published studies contain a litany of conflicting, inconclusive, and ambiguous findings that defy attempts to draw strong conclusions (7). This is particularly true with respect to implicit memory—that is, the influence of a response by the memory of a previous experience without the subject's knowing that he is being influenced. Studies in anesthetized surgical patients, subject to multitudes of extraneous influences, may not decisively advance our knowledge. One alternative is to study other species in scientifically rigorous, tightly controlled studies. Such studies also avoid the ethical dilemma of anesthetizing healthy human volunteers. The tasks used to test implicit memory in humans under anesthesia probe for "priming" effects (24) rather than the learning of motor skills, which is obviously impossible in an unconscious subject. Unfortunately, the dissociations between priming and recall or recognition in humans have not been demonstrated in animals. This probably reflects the difficulties inherent in adapting to animal studies paradigms from the human literature that permit experimental separation of priming from other forms of memory (15).

In the present study, we investigated the possibility of showing learning after the administration of large doses of ketamine in rabbits. We used as our model classical conditioning of the nictitating membrane response (NMR). This model is widely used for studying associative learning and its interaction with drugs (9,12). Classical conditioning is one basic category of associative learning whose essential feature is a set of

[1] To whom requests for reprints should be addressed at the Department of Anesthesia, College of Medicine, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242-1079.

experimental operations involving an unconditioned stimulus (UCS) that reliably evokes a measurable unconditioned response (UCR). The UCS is paired with a conditioned stimulus (CS) that has been shown by test not to elicit the UCR. After the CS and UCS are presented repeatedly to the organism in a specified order and temporal spacing, a response similar to the UCR develops to the CS, called the conditioned response (CR). For example, when the CS is a tone and the UCS is an electric shock to the paraorbital region, the tone comes to elicit extension of the nictitating membrane (11).

We used ketamine to produce unconsciousness because of the absence of significant cardiovascular and respiratory depressions after its administration, thus eliminating the need for cardiorespiratory support; the maintenance of a patent airway without artificial devices because of the presence of adequate skeletal muscle tone; and a report that classical conditioning may occur under anesthesia with the drug and its retention can last at least 7 days (6). Two sets of experiments were carried out after approval from the institutional animal care committee. Both experiments assessed the effects of the drug on acquisition and retention of the NMR. Control groups in Experiments 1 and 2 assessed the influences on performance of previous exposure to the experimental environment and unpaired presentations of the CSs and UCS, respectively.

EXPERIMENT 1

Experimental Groups

The effects of 100- and 200-mg/kg doses of ketamine administered subcutaneously on the rate and level of acquisition of CR were examined.

We had determined in preliminary studies that the righting reflex was lost within 5 min after treatment with 100- and 200-mg/kg doses and that they produced about 90 min and over 2 h, respectively, of unconsciousness, defined as an absent or sluggish pinna reflex and absence of spontaneous movements, with the animal remaining on its side.

Method. Experimentally naive, 80–100-day-old, male and female New Zealand white albino rabbits were purchased from Knapp Creek Rabbitry (Amana, IA). Each rabbit weighed approximately 1.9 kg on arrival and was housed individually under consistent light, with free access to water and 90 g of food daily.

Apparatus and general procedure. The apparatus and procedures used in conditioning of the rabbit NMR have been described in detail elsewhere (8,10). In brief, a small loop of surgical nylon (Ethilon 6.0, Ethicon, Somerville, NJ) was sutured into the right nictitating membrane (NM), and the surrounding hair was removed. One day later, the rabbit was placed in a Plexiglas restrainer, and two stainless-steel wound clips were applied to the skin over the paraorbital region. The rabbit was fit with a headmount that supported a photoresistive assembly for recording the NMR by physical coupling with a length of thread to the nylon loop in the NM. The transducer assembly converted NM movements into electrical signals that were subjected to an analog-to-digital conversion using a 5-ms sampling rate and a resolution of 0.06 mm actual membrane extension. The animal was then positioned in a ventilated, sound-attenuated chamber facing a stimulus panel containing an 11.4-cm speaker and two 6-W, 24-V DC house lights, one mounted on each side of the speaker. During the course of the experiment, two stimuli were employed as CS: a) a 1000-ms, 1-kHz, 84-dB tone (0.002 dyne/cm reference); b) a 1000-ms, intermittently presented light produced by interruption of the house lights at 10 Hz to yield a change in illumination, measured at the eye level of the rabbit from 32.1 1× to 8.0 1×. The UCS was a 100-ms, 3-mA, 60-Hz shock delivered to the two wound clips by a constant current shock generator. Analog-to-digital conversion, response analysis, and experimental control were all accomplished by an Apple II/First operating system (16) (Cupertino, CA).

Drugs. The doses of ketamine (Ketalar, Parke-Davis, Morris Plains, NJ) employed in the experiments were 0 (saline), 100, and 200 mg/kg. The drug solutions and saline were injected subcutaneously into the cervical area of the rabbit via a Harvard infusion pump in a volume of 2 ml/kg at a rate of 3 ml/min, 30 min before behavioral testing.

Procedure. Experimentally naive rabbits were randomly assigned in equal numbers to each of the three treatments (n = 10 per treatment). The experiment consisted of two phases: Phase 1 was an adaptation day followed by 9 days of acquisition training. No stimuli were presented during the 60-min adaptation session. Subjects were injected with their assigned treatment 30 min before each acquisition session. Each acquisition session consisted of 30 tone-shock and 30 light-shock trials presented in a randomized sequence within 10 trial blocks, with the restriction that no more than three consecutive tone or light trials could occur. On each CS-UCS trial, the offset of the 1000-ms tone or light CS occurred simultaneously with the onset of the 100-ms shock UCS. The intertrial interval averaged 60 s (range 50–70). A response was defined as at least a 0.5-mm extension of the NM. Responses occurring during the tone or light CS, but before UCS onset, were recorded as CR; those occurring after the UCS onset were recorded as UCR.

After the completion of phase 1, the rabbits were given 3 days of rest in their home cages without treatments. On the fourth day, the rabbits entered phase 2, which consisted of five additional days of conditioning identical to that described before, except that no ketamine or saline was administered. These sessions assessed retention and/or additional learning of the CR.

Data analysis. The data were analyzed by repeated measures analyses of variance and Tukey tests (28). The data of phases 1 and 2 were analyzed separately, with days (the 9 days of phase 1 or 5 days of phase 2) serving as a repeated-measures factor. The significance level was set at $p < 0.05$.

Results. Analysis of variance revealed a significant effect of dose [$F(2, 27) = 301.3$, $p < 0.001$], which the Tukey test localized to the saline group's higher level of CR acquisition than the ketamine-injected groups. The latter groups did not differ from each other. The left panel of Fig. 1 (solid lines) presents the mean percentage of CR across the 9 days of acquisition training of phase 1 as a function of ketamine dosage (0, 100, and 200 mg/kg). Examination of the panel shows that ketamine at both 100 and 200 mg/kg completely blocked the display of acquisition of CR. By the first day of training, the saline group acquired a level of 9.1% CR, whereas the ketamine-injected groups showed CR levels of < 2%. Over subsequent acquisition days, the rate and level of CR of the saline group steadily increased, reaching an asymptote of 91.1% on the fifth day of training and averaging 73.8% across days; the ketamine-injected groups showed no such pattern, reaching a terminal CR level of only 2.7%, a response level that was no greater than the baseline responding level (4.3%) that occurred during the 800-ms pre-CS onset period.

The right panel of Fig. 1 (solid lines) presents the mean percentage of CR across the 5 days of phase 2. Inspection of the panel reveals that the saline group maintained its asymp-

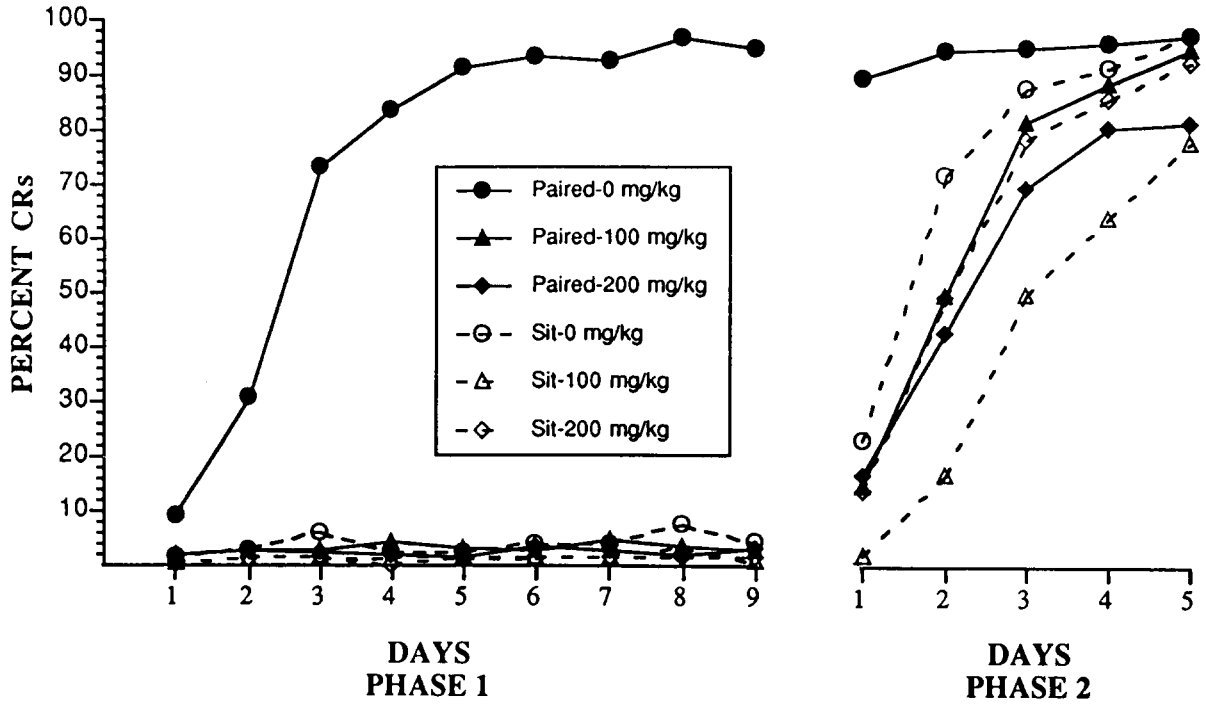

FIG. 1. Left panel: Effects of ketamine on acquisition of conditioned responses (CRs) by the experimental groups (solid lines denoted "Paired") and percentages of responses by the control groups (dashed lines, denoted "Sit") in phase 1 of Experiment 1. Data are expressed as mean percentages of CR calculated for the 60 daily trials, irrespective of CS modality, for the experimental groups, or responses during corresponding time intervals for the control groups, to whom stimuli were not presented during phase 1. Each point represents the mean of either 10 or eight control animals. Right panel: Effects of ketamine on retention and/or additional acquisition of CR (experimental groups), and acquisition of CR (control groups) in phase 2 of Experiment 1. Data are expressed as mean percentages of CR in the same manner as in the left panel.

totic level of CR that was attained in phase 1. The analysis of variance revealed significant effects of dose [F (2, 27) = 15.99, $p < 0.001$] and days [F (4, 108) = 76.76, $p < 0.001$]. Tukey tests indicated that the saline group's mean level of CR was significantly greater than the other two groups. The 100- and 200-mg/kg groups did not appear to differ from each other.

An examination of Fig. 1 suggests that CR acquisition of the 100- and 200-mg/kg ketamine groups during the first 2 days of phase 2 was superior to that of the saline group during the first 5 days of phase 1—that is, that rabbits in the former two groups acquired CR faster than rabbits that had never been exposed to any conditioning. On the first day of phase 2, the 100- and 200-mg/kg groups showed 14.9 and 17.1% CR, respectively, compared with 9.1% CR for the saline group on the corresponding day of phase 1 (left panel of Fig. 1). On the second day, the 100- and 200-mg/kg groups showed 49.9 and 42.8% CR, respectively, compared with only 30.5% CR for the saline group on the corresponding day of phase 1 (left panel of Fig. 1). Learning under the influence of ketamine seemed likely to be so faint, and its retention so fragile, that we judged it appropriate to perform comparisons by days, because one would expect an effect to be observable only on early days of acquisition training and to become obscured on later days, as learning approached asymptotic levels. Tukey tests indicated that the percentage of CR on the second day was significantly greater for the 100-mg/kg group than the saline group, whereas the superiority of the 200-mg/kg group to the saline group was only marginally significant.

Control Groups

The data of the experimental groups suggested that although ketamine blocked the display of CR, the treated rabbits showed faster CR acquisition in phase 2 than naive rabbits in phase 1. The control groups helped to determine whether this faster acquisition was attributable to the previously paired CS-UCS training—that is, whether the drugged rabbits acquired CR during training under ketamine, although they were not able to exhibit this learning—or whether their faster acquisition during phase 2 was simply attributable to their previous exposure to the experimental environment—that is, the setting within the experimental chambers.

Method. The experiment employed 24 rabbits similar to those of the experimental groups. The animals were purchased and housed as described for the experimental groups.

Procedure. The rabbits were randomly assigned in equal numbers to one of the three drug treatments administered to the experimental groups (n = 8 per treatment). After an adaptation session identical to that of the experimental groups, the rabbits received either saline or ketamine in one of its two doses 30 min before each of nine sessions in the experimental chambers. These sessions lasted 60 min, the same duration as in the experimental groups, but no stimuli were presented. Responses occurring during the intervals in which CS would have been presented to the experimental groups were recorded.

After the ninth session, the rabbits were given 3 days of rest in their home cages without treatments. On the fourth

day, the rabbits were exposed to phase 2, which consisted of 5 days of paired CS-UCS training, without drug administration. Each conditioning session consisted of 30 tone-shock and 30 light-shock trials. The total numbers and parameter values of tone, light, and shock presentations, and durations of the session were identical to those for the experimental groups. Drug injections and statistical analyses were performed as described previously.

Results. The dotted lines in the left panel of Fig. 1 represent the mean percentages of NMR for the control groups during the 800-ms period when CS would have been presented to the experimental groups. Examination of the panel reveals that percentages of responses were very low for all three groups. Analyses of variance, however, showed a main effect of dose [$F(2, 20) = 5.3, p < 0.05$]. The saline group showed a slightly higher percentage of NMR (3.7%) than the other two groups (1.4 and 1.0%).

Comparison of responses of the experimental and control groups during phase 1 showed a large difference for the rabbits to which saline was administered, as a result of CR acquisition by the experimental animals, but no apparent differences between the experimental and control groups to which 100 and 200 mg/kg ketamine were administered.

The right panel of the same figure (dotted lines) shows the percentages of CR for the control groups during phase 2, which involved paired CS-UCS training. Analysis of variance revealed a significant effect of dose [$F(2, 20) = 6.29, p < 0.01$], which was localized by Tukey tests to significant differences between the saline and 100-mg/kg groups on days 2-4, and between the 200-mg/kg group and the 100-mg/kg group on days 2 and 3. The 100-mg/kg group showed lower percentages of CR than both of the other groups.

An analysis of variance comparing the experimental and control groups during phase 2 showed significant effects of group [$F(4, 132) = 5.37, p < .001$] and interaction effects of group × dose [$F(8, 132) = 2.92, p < 0.01$], group × days [$F(16, 528) = 4.39, p < 0.001$], and group × dose × days [$F(32, 528) = 4.48, p < 0.001$]. Tukey tests indicated that experimental animals showed greater percentages of CR than control animals on days 2-5 for the 100-mg/kg groups and days 1 and 2 for the saline groups. No such differences occurred for the 200-mg/kg groups.

EXPERIMENT 2

Experimental Groups

Procedures for the experimental groups of Experiment 2 were identical to those for the corresponding groups of Experiment 1, but only two doses, 0 or 100 mg/kg ketamine, were administered. We used 24 rabbits. The 200-mg/kg group was eliminated; it did not differ from the 100-mg/kg group in Experiment 1 with respect to CR acquisition in phase 1, and showed less evidence than the latter group that paired CS-UCS training during phase 1 led to faster acquisition during phase 2.

Results. Data were similar to those of Experiment 1 (Fig. 2). During phase 1 (left panel, solid lines), the 100-mg/kg dose maintained a low level of CR across the 9 days of acquisition training, whereas the saline group showed gradual CR acquisition (average CR levels of 3.0 and 73.8%, respectively). Analysis of variance showed a significant effect of dose [$F(1, 20) = 386.05, p < 0.001$.]

The results of phase 2 also resembled those of Experiment 1. The saline group maintained its asymptotic level of CR (96.5%) across the 5 days, and the 100-mg/kg group showed CR acquisition that appeared to be faster than that of the saline group during the first 5 days of phase 1.

Control Groups

The purpose of the control groups was to examine whether the rapid CR acquisition by the 100-mg/kg experimental group in phase 2 of both experiments was due to true associative learning during the previously paired CS-UCS training of phase 1, or merely to previous exposure to the CS and UCS, without necessarily involving any learning of their association.

Method. We employed 24 rabbits similar to those used in Experiment 1. The animals were purchased and housed as described previously.

Procedure. After 1 day of adaptation, rabbits were injected with either saline or ketamine (100 mg/kg) about 30 min before sessions started on each of nine consecutive days of phase 1. After being placed in the experimental chambers, they were presented with 30 tone, 30 light, and 60 shock trials in a nonpaired fashion. Each session lasted 60 min. We recorded responses occurring during the intervals in which tones and lights were presented.

After the completion of phase 1, the rabbits were given 3 days of rest in their cages. On the fourth day, they entered phase 2 of the experiment, during which paired CS-UCS training was conducted as previously described.

Results. The left panel of Figure 2 (dotted lines) shows the mean percentages of NMR during the periods when tones and lights were presented. The frequencies of NMR were low, averaging 3% across the 0- and 100-mg/kg groups. An analysis of UCR conducted to see whether ketamine affected motor functioning showed no effect of dose on UCR frequency or latency. However, a dose effect on UCR amplitude was observed [$F(1, 22) = 61.16, p < 0.001$]. The saline group showed larger UCR amplitudes (5.68 mm) than the 100-mg/kg group (2.51 mm).

The right panel of the same figure (dotted lines) shows percentages of CR during phase 2, which involved paired CS-UCS training. An analysis of variance revealed a significant effect of dose [$F(1, 22) = 5.48, p < 0.05$] and interaction effect of dose × days [$F(1, 22) = 4.70, p < 0.05$]. Tukey tests localized the differences to the 100-mg/kg group's higher levels of CR than the saline group on days 3-5. These results indicated that exposure to the unpaired CS and UCS in phase 1 produced a slower acquisition rate and lower level of CR during phase 2 in the saline group than the 100-mg/kg group. Comparisons with performance of the saline group in phase 1 suggested that prior exposure to the unpaired CS and UCS had no effect on rabbits receiving 100 mg/kg ketamine, but a detrimental effect on those receiving saline.

An analysis of variance comparing experimental and control groups revealed a significant group × dose × days interaction [$F(4, 168) = 18.32, p < 0.001$]. Tukey tests indicated that CR levels were higher in the experimental than the control group on days 1-3 among rabbits receiving 100 mg/kg ketamine.

DISCUSSION

In both experiments, ketamine used in large doses appeared to block the display of conditioned responses (CR) to both tone and light CS during the 9 days of acquisition training of phase 1, probably as a result of an inability to perform in the unconscious state. However, data from phase 2 revealed that the rabbits previously receiving 100 mg/kg ketamine showed faster CR acquisition than naive rabbits during later condi-

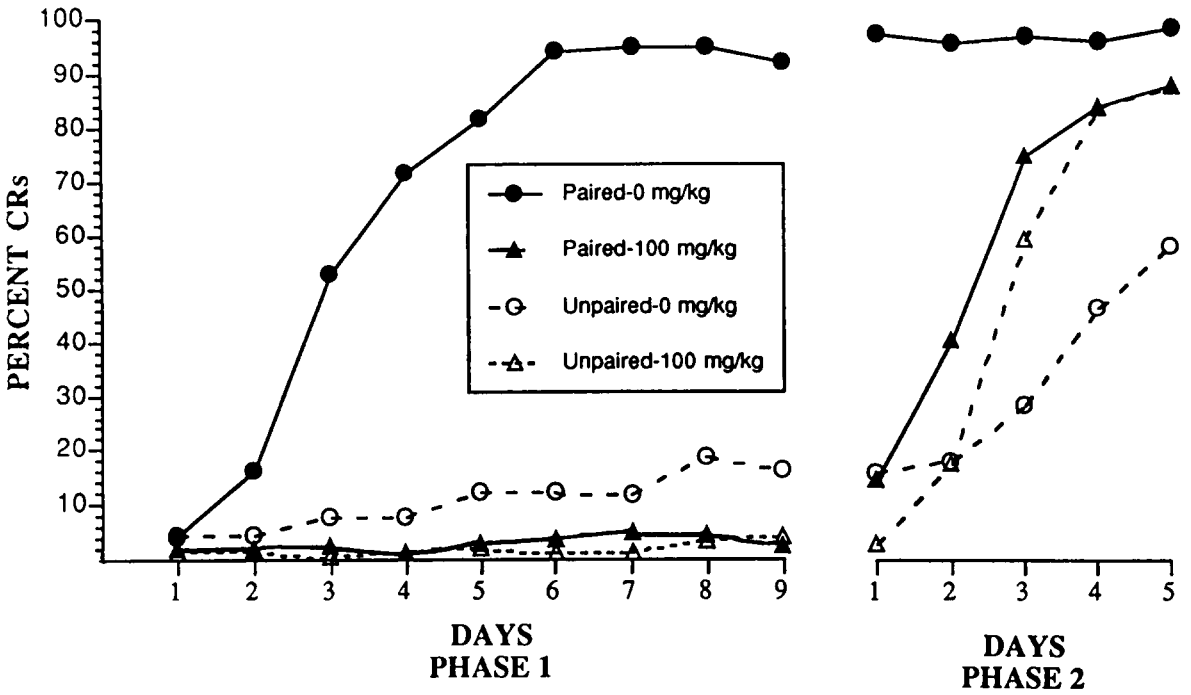

FIG. 2. Left panel: Effects of ketamine on acquisition of controlled repsonses (CRs) by the experimental groups (solid lines, denoted "Paired"), and percentages of responses by the control groups (dashed lines, denoted "Unpaired") in phase 1 of Experiment 2. Data are expressed as mean percentages of CR calculated for the 60 daily trials, irrespective of CS modality, for the experimental groups, or responses during tone and light stimuli for the control groups, for whom these stimuli were not paired with the unconditioned stimuli during phase 1. Each point is the mean of 12 animals. Right panel: Effects of ketamine on retention and/or additional acquisition of CR (experimental groups), and acquisition of CR (control groups) in phase 2 of Experiment 2. Data are expressed as mean percentages of CR, as in the left panel.

tioning, a "savings" effect indicating that prior associative conditioning might have occurred during phase 1.

The control conditions of both experiments helped determine whether this finding reflected true associative conditioning—that is, learning of the contingency between the CS and the UCS. Control rabbits were placed in the experimental chambers during phase 1, but not presented with the CS and UCS (Experiment 1), or presented with these stimuli in a nonpaired fashion (Experiment 2). The effects of these experiences on the performance of the control rabbits during phase 2 were related to doses of ketamine administered during phase 1 in a complex fashion; in other words, the 100-mg/kg group showed lower percentages of CR than the 200-mg/kg and saline groups in Experiment 1, but better performance than the saline group in Experiment 2. The most important pattern, however, that emerged consistently in both experiments was that, for rabbits receiving 100 mg/kg ketamine, CR levels during phase 2 were higher in the experimental than the control groups. This finding in both experiments indicated that mere exposure to the experimental chambers or presentation of the CS and UCS in a nonpaired fashion during phase 1 did not produce the beneficial effects on "savings" in learning the previously presented task.

Among saline-treated control rabbits, learning during phase 2 appeared to be improved by exposure to the experimental chambers during phase 1 in Experiment 1, but retarded when such exposure during phase 1 was also accompanied by exposure to the unpaired CS and UCS in Experiment 2. Relative to learning of the saline-treated control rabbits, that of the control rabbits treated with 100 mg/kg ketamine showed a much smaller effect of exposure conditions and appeared inferior in Experiment 1, but superior in Experiment 2. Why the saline-treated control rabbits showed such a large effect of exposure conditions is unclear, but because this phenomenon was not as apparent among the control rabbits treated with 100 mg/kg ketamine, it does not alter the interpretation of the savings shown by the experimental rabbits treated with 100 mg/kg ketamine. Our analyses were intended to determine whether savings could occur at all—that is, exceed zero—as a consequence of prior exposure to the conditioning task under the influence of ketamine, and not to compare this savings with that arising from exposure to the experimental chambers among saline-treated rabbits.

In Experiment 1, the effects of associative conditioning during phase 1 under the influence of 200 mg/kg ketamine on phase 2 performance were less clear. There was one marginally significant difference, suggesting superior performance by the 200-mg/kg group during phase 2, relative to experimentally naive rabbits, or the saline group during phase 1. But experimental and control rabbits that had received 200 mg/kg ketamine during phase 1 did not differ in performance during phase 2. Any beneficial effect on subsequent acquisition of prior associative conditioning under the influence of 200 mg/kg ketamine did not seem attributable to true associative learning.

Patients suffering from organic amnesias have a severely impaired ability to remember new events; yet, some forms of learning, denoted implicit memory, show little impairment (17). One example of implicit memory is classical condition-

ing. Classical conditioning can be acquired and retained over long periods, even though these patients will deny any memory of the experiment (5,25).

Two animal studies suggested that classical conditioning can also occur under anesthesia. Edeline and Neuenschwander-El Massioui (6) reported retention of a CS-UCS association that was learned under ketamine anesthesia in rats. Weinberger et al.(26) demonstrated that epinephrine enabled the learning of a Pavlovian conditioned fear response during pentobarbital and chloral hydrate anesthesia. Our present report adds to these two and suggests a new model for future studies in this area. We think our model, the rabbit's NMR, has distinct advantages over the conditioning paradigm used in the other two reports, tone paired with foot shock in rats. These are: a) The parameters governing the acquisition of the response are well defined and understood (10). b) Behavioral and neurobiologic substrates of this form of learning in rabbits may generalize to all mammals, including humans (19,22,29). c) The model permits fine experimental control of the stimuli and the responses. Effects on sensorimotor or motivational changes, which might affect learning and memory proper, can be precisely controlled. Evaluation of drugs' effects on learning vs. performance is feasible. d) The neural circuitry for the learned response is beginning to be well understood (23), and some of the cellular and molecular changes that accompany learning have been described (1). Such is not the case for any other aspect of learning and memory in the mammalian brain.

The hippocampus is an important site for memory storage. It is also one of several locations in the brain where short bursts of high-frequency stimulation have been shown to induce a sustained enhancement in synaptic efficacy—a property termed long-term potentiation (LTP) (3,18). LTP has therefore been proposed as a neurophysiologic mechanism for associative learning or memory storage in general (2,20). The induction of LTP in several hippocampal pathways is dependent on the activation of *N*-methyl-D-aspartate (NMDA) receptors (4). Unlike the volatile anesthetics (13), ketamine is a noncompetitive NMDA receptor antagonist (27). It is possible that drugs acting on the NMDA receptor complex may selectively disrupt learning and memory in a manner different from the volatile anesthetics. Future studies should address this issue. Equally intriguing is the fact that a large, 100-mg/kg dose of a drug with a well-defined action on NMDA receptors allowed some associative learning to occur. Perhaps the type of learning that we examined is pertinent. The cerebellum and its associated brainstem circuitry contains the necessary circuitry for the elaboration of the conditioned response. The hippocampus is essential under some training conditions, but not those involved in the present study (14,21,23).

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