Different temporal gradients of retrograde amnesia produced by metrazol or electroconvulsive shock

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Temporal gradients of amnesic effects produced by Metrazol or electroconvulsive shock (ECS) treatment were compared in the same step down experimental situation. Both ECS and Metrazol convulsions, occurring approximately 90 sec after one-trial passive avoidance training, caused retrograde amnesia (RA) in rats. When administered 5 min after training, Metrazol caused RA while ECS did not. This and other evidence suggests that the two treatments produce RA via different mechanisms.

The purpose of the present experiment was to compare the temporal gradients of retrograde amnesia produced by two convulsive agents, Metrazol or ECS, both administered after the same passive avoidance one-trial learning situation. Several recent studies have demonstrated different temporal gradients of retrograde amnesia (RA) produced by various treatments given after this step down task. Quartermain, Paolino, & Miller (1965) found the disruptive half time of electroconvulsive shock (ECS) to be about 30 sec. Paolino, Quartermain, & Miller (1966), using the same procedure and apparatus, found the disruptive half time of CO_2 to be about 2-3 min. In contrast to these rather short time periods, other treatments have been found to be effective amnesiacs when administered at much longer times after training Alpern & Kimble (1967) reported heat-potentiated ether to be effective when administered 24 h after training and Indokol to be effective when administered 4 h post trial. Pearlman, Sharpless, & Jarvik (1961) found Metrazol to be effective when administered four days post trial. Considering the similarities in the training situations employed in these studies, it seems reasonable to suggest that the different temporal gradients obtained reflect different disruption processes.

The Ss were 118 naive Sprague-Dawley rats of both sexes, 60-80 days old at the time of this experiment. The apparatus was a step down device consisting of a 5 x 5 x 7 in. motorized descending startbox separated from a 16 x 16 x 10 in. compartment by a sliding door. Grid shock was a 60 cycle alternating current of approximately 0.5 mA intensity delivered for a timer controlled period of 2.0 sec. ECS was delivered through moist padded alligator clips and consisted of an automatically timed 0.3 sec, 540 V, 60 cycle sine wave stimulus.

The training session consisted of a 1 min adaptation period after which the S was lowered to the level of the large compartment and the sliding door was closed if the S placed all four feet on the grid floor. Eighteen out of the original 118 Ss that failed to step out of the starting compartment within 30 sec were eliminated from the study. Four control groups and four experimental groups were employed with 10 Ss in each group. One experimental group received grid shock followed immediately by 65 mg/kg IP injections of Metrazol. Onset of Metrazol convulsions occurred on the average of 90 sec following grid shock with 8/10 Ss in this group manifesting seizures between 72 and 105 sec following grid shock. Another experimental group received ECS at latencies following grid shock matched with the onset of Metrazol seizures of the above group. Two other experimental groups received either Metrazol or ECS treatments 5 min following grid shock. ECS or Metrazol treatments were administered on a table adjacent to the training apparatus. All ECS Ss had tonic extension seizures. Eight out of the surviving Metrazol animals did not manifest either multiple clonic jerks or a clonic seizure during a 5 min observation period following injection and were eliminated. "Multiple clonic jerks" consisted of rapid spasmodic movements of the head and neck. Twelve out of the original 118 Ss died. Control groups included: (1) a group receiving no grid shock or convulsive treatment; (2) a group receiving only grid shock; (3) a group

receiving Metrazol injections 5 min after stepping down; (4) a group receiving ECS 5 min after stepping down. The Ss were tested in the same apparatus 24 h after training. Failure to leave the starting compartment was taken as evidence that the passive avoidance response had been learned and retained.

Three of the 10 Ss receiving grid shock in training followed 5 min later by ECS left the starting compartment during the test trial; the other seven were considered to have retained the learned response. This group showed a significant lack of independence, when evaluated using Fisher's Exact Probability Test, when compared to the group receiving ECS approximately 90 sec after training in which eight Ss responded ($p = .03$). The group receiving a Metrazol injection 5 min following grid shock (in which seven Ss responded) was not independent of the group manifesting Metrazol convulsions approximately 90 sec following grid shock (in which eight Ss responded).

The Metrazol and ECS groups demonstrating convulsions at approximately 90 sec following training did not significantly differ from one another as nine and eight Ss, respectively, stepped down during the test. However, the Metrazol and ECS groups receiving treatment 5 min after grid shock did significantly differ from one another as eight and three Ss, respectively, responded ($p = .03$).

Only one of the 10 control Ss receiving grid shock and no post trial convulsive treatment stepped down in the test, indicating strong retention of the response. This group was not significantly different from the group receiving ECS 5 min after grid shock ($p = .25$). However, this control group was not independent of the other three experimental groups. The probabilities of obtaining discrepancies this large or larger were: (1) $p = .003$ in the case of the group receiving Metrazol 5 min after grid shock; (2) $p = .005$ in the case of the group manifesting Metrazol convulsions approximately 90 sec following grid shock; and (3) $p = .01$ in the case of the group given ECS approximately 90 sec following grid shock. The distribution of frequencies suggests that the group receiving ECS 5 min after grid shock demonstrated far less interference with retention than did the other three experimental groups.

The control groups did not differ significantly from one another. In these groups, 8/10, 9/10, and 10/10 Ss responded during the test trial indicating that the ECS and Metrazol treatments by themselves had no aversive effects.

Fig. 1. Temporal gradients of retrograde amnesia caused by Metrazol or ECS.

The results which are depicted in Fig. 1 indicate that ECS produced a much steeper gradient of RA than did Metrazol. While both agents produced RA when convulsions occurred approximately 90 sec after training, only Metrazol was capable of interfering with retention when either agent was administered 5 min post trial.

The results cannot be explained in terms of maximum strength of treatment; Metrazol, which was the more effective amnesiac, produced clonic seizures while ECS produced the more intense tonic extension seizures. However, Metrazol had a longer lasting effect than did the ECS stimulus which was applied only briefly. While the Metrazol seizures lasted about 10 sec, this treatment has been observed by the present experimenter to cause RA in Ss which manifested no visible seizures indicating that the amnesiac action of the drug lasts longer than the duration of visible symptoms. Jarvik & Kopp (1967) have demonstrated a similar effect with ECS; intensities of ECS insufficient to produce clonic-tonic seizures produced RA in mice.

The results are compatible with the explanation offered by Alpern & Kimble (1967); namely, that severity of treatment may extend the duration of amnesic effects. In the present experiment, "severity" would refer to the duration of action of the amnesiac. The temporal gradient of RA produced by various amnesiacs is a function of the nature and the duration of trauma to the nervous system.

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NOTE

1. This research was done while the author was at Roosevelt University. It has been identified by the Aerospace Medical Research Laboratories as AMRL-TR-68-92. Further reproduction is authorized to satisfy needs of the U. S. government.

2. The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965, prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council; the regulations and standards prepared by the Department of Agriculture; and Public Law 89-544, "Laboratory Animal Welfare Act," August 24, 1967.