A comparison of the retrograde amnesic effects of Metrazol and electroconvulsive shock[1]

J. PETER KINCAID[2]
ROOSEVELT UNIVERSITY

Effects of Metrazol and electroconvulsive shock (ECS), each administered under the same conditions 5 min after one trial training were compared. Metrazol produced memory impairment while ECS did not. In all cases Metrazol produced submaximal seizures (clonic seizures or multiple jerks) while ECS produced the more intense tonic. extensor seizures. Therefore, maximum intensity of seizure was ruled out as an explanation of this particular case. However, the convulsive action of Metrazol lasted longer than that of ECS and this might have accounted for the results. The character and duration of a period of consolidation of memory cannot be explained unequivocally in terms of a single agent which produces retrograde amnesia.

Several recent studies demonstrated that electroconvulsive shock (ECS) must be administered within about 30 sec or less after one trial training to be effective in producing significant retrograde amnesia (Quartermain, Paolino, & Miller, 1965; Chorover & Schiller, 1966). Pearlman, Sharpless, & Jarvik (1961) reported that another agent, the convulsant drug pentylenetetrazol (Metrazol), produced interference with retention of a response learned in one trial when administered as long as four days after training. This observed difference between 30 sec and four days raises the question whether these two agents differ because of their intensity or because of some other factor relating to the duration of their action.

Paolino, Quartermain, & Miller (1966) compared the effects of ECS and CO_2 under the same conditions and found that CO_2 caused interference with retention when administered up to 4 min after one trial training while ECS had to be administered within 30 sec to be effective.

The purpose of the present experiment was to directly compare the effects of ECS and Metrazol in producing interference with retention of a response learned in one trial. It was decided to administer both the ECS and the Metrazol 5 min after training. This interval was chosen as one likely to show little effect of ECS; it was expected that Metrazol would interfere with retention. Since Metrazol causes a less intense maximum seizure but a longer lasting one than ECS, it was felt that a demonstrated difference between the two agents would give some insight into the mechanism of "consolidation."

Subjects

The Ss, 84 Sprague-Dawley rats of both sexes obtained from Abram's Animal Supply House in Chicago, were experimentally naive and 60 to 80 days old at the time of treatment. Of these 84 Ss, 24 were eliminated for three reasons described below, leaving 60 which completed the experiment.

Apparatus

The apparatus was modeled after the stepdown device described by Quartermain et al (1965) and consisted of a 16 x 16 x 16 in. Masonite and Plexiglas compartment into which a 5 x 5 x 7 in. startbox was fitted. The startbox was raised manually and lowered to the grid floor of the large compartment by means of a small motor. The S in the lowered startbox could easily step into the large compartment and was prevented from returning to the starting compartment during grid shock by means of a sliding door. A 60 cycle ac grid shock of approximately 0.5 mA could be delivered for a timer-controlled (Hunter Model 115) period of 2.0 sec. The ECS consisted of a 0.3 sec, 540 V, 60 cycle sine wave stimulus delivered to the ears through moist padded alligator clips. The duration of ECS was automatically controlled by means of another Hunter 115 timer.

Design

Six groups consisting of 10 animals each were run in a 3 by 2 orthogonal design with the posttrial treatments, ECS, Metrazol, and no treatment, superimposed on a grid shock or no grid shock training condition.

Procedure

The Ss were placed in the startbox and given a 1 min adaptation period, after which the startbox was lowered to the level of the large compartment. When a S in the grid shock group had stepped out and had placed all four feet on the grid floor, the sliding door was closed and grid shock was delivered for 2.0 sec. Ss in the control groups receiving no grid shock were required to step onto the grid floor and the sliding door was closed. Twelve of the original 84 Ss failed to step out of the starting compartment within 30 sec and were eliminated from the study. This insured that Ss had no initial reluctance to respond. Acceptable Ss were removed to a holding cage immediately after the training trial. ECS and Metrazol Ss received treatment 5 min after stepping out of the starting compartment, on a table adjacent to the training apparatus. ECS was administered under the conditions described. All ECS Ss had full tonic extensor seizures. The Metrazol Ss received 65 mg/kg of the drug through an IP route. This dose was selected to produce a high incidence of clonic seizures. Tonic seizures were fatal too frequently to be studied. Onset of convulsions occurred on the average of 75 sec after

Table 1. Number of Ss Stepping Down on Test Trial (N=10 in each group)

Grid Shock	Convulsive Treatment ECS	Metrazol	None
Present	3	8	1
Absent	8	9	10

injection and typically lasted 10 sec. Ss were then observed in a transparent holding cage for 5 min. Eight out of the surviving 28 Metrazol Ss did not manifest either multiple clonic jerks or a clonic seizure during the 5 min observation period following injection and were eliminated from the sample. "Multiple jerks" consisted of rapid, spasmodic movements of the head and neck. Eight of the original 84 Ss died. All ECS and Metrazol Ss were kept in a holding cage for about 30 min after treatment to permit recovery, before being returned to the home cage. The Ss were tested in the same apparatus 24 h after training. Failure to leave the starting compartment within 3 min was taken as evidence that the passive avoidance response had been learned and retained.

Results

Three of the 10 Ss receiving grid shock in training followed by ECS 5 min later left the starting compartment during the test trial; the other seven were considered to have retained the learned response. Eight of the 10 Ss receiving grid shock followed by Metrazol stepped down from the startbox leaving two which showed evidence of retention. This set of frequencies exhibited a significant lack of independence when evaluated by using Fisher's exact probability test. The probability of obtaining a discrepancy this large or larger was 0.03. Clearly, this response of stepping down was not independent of the type of convulsant agent used after training. The distribution of frequencies suggests that the Metrazol-treated group manifested the greater loss of retention.

Only one of the 10 control animals receiving grid shock and no posttrial convulsive treatment stepped down in the test, indicating strong retention of the response. This group was not independent of the grid shock-Metrazol group (the probability, using the same test, was .007), but it was independent of the grid shock-ECS group. The remaining control groups (the three groups not receiving grid shock) did not differ significantly from one another. In these groups, 8/10, 9/10, and 10/10 stepped down on the last trial, indicating that the ECS and Metrazol treatments by themselves had no aversive effects.

Discussion

The results of the experiment indicate that submaximal seizures produced by Metrazol at least 5 min after training resulted in interference with retention of a passive avoidance response. Full tonic extension seizures induced by ECS exactly 5 min posttrial did not do so. These results demonstrate that the intensity of the seizure per se was not responsible for the greater effectiveness of Metrazol at this posttrial interval. However, it is possible that the longer duration of action of Metrazol upon the central nervous system (as compared with the brief application of the ECS stimulus) may have contributed to its greater effect.

Maximum intensity of seizure cannot account for the present results. Duration of the action of the treatment, however, was directly related to the degree of interference with retention. ECS and Metrazol may affect memory through entirely different mechanisms. An improved "consolidation hypothesis" can be developed as more information becomes available about the mechanisms through which different agents affect memory.

References

Chorover, S. L., & Schiller, P. H. Short-term retrograde amnesia in rats. *J. comp. physiol. Psychol.*, 1965, 59, 73-78.

Paolino, R. M., Quartermain, D., & Miller, N. E. Different temporal gradients of retrograde amnesia produced by carbon dioxide anesthesia and electroconvulsive shock. *J. comp. physiol. Psychol.*, 1966, 62, 270-274.

Pearlman, C. A., Sharpless, S. K., & Jarvik, M. E. Retrograde amnesia produced by anesthetic and convulsant agents. *J. comp. physiol. Psychol.*, 1961, 54, 109-112.

Quartermain, D., Paolino, R. M., & Miller, N. E. A brief temporal gradient of retrograde amnesia independent of situation change. *Science*, 1965, 149, 1116-1118.

Notes

1. This research is based upon a thesis submitted by the author in partial fulfillment of the requirements for the M. A. degree in psychology at Roosevelt University. The author wishes to express his gratitude to Dr. J. A. Chevalier who contributed to all phases of this research. A preliminary report of this research (Kincaid and Chevalier) was presented at the 1966 meeting of the Midwestern Psychological Association in Chicago.

2. Now with the Personnel Subsystems Branch (SEG/SEMCP), Wright-Patterson Air Force Base, Ohio 45433.