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# The effect of acute corticosterone administration on retrieval of remote and recent memory in the rat

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## ABSTRACT

**Background and Objective:** It is well known that stress and glucocorticoid, modulate memory processing, though the result is completely dependent on the time of stress induction. This study investigated the effect of acute corticosterone administration on memory retrieval of recent and remote memory in a 4 trials/day (low- intensity learning) or 8 trials/ day (high- intensity learning) Morris water maze protocol.

**Materials and Methods:** Sixty four adult male Wistar rats were used in this research study. Corticosterone was injected subcutaneously (3 mg/kg) 30 min before the probe trial test of Morris water maze. Control animals received the vehicle.

**Results:** Acute corticosterone, thirty minutes before probe test led to impairment of memory retrieval phase in recent ($p<0.01$) and remote memory ($p<0.001$). A high intensity learning protocol (eight trials/ day) was then used to show if an enhancement of learning could prevent corticosterone-induced memory impairment.

**Conclusion:** Apparently, learning enhancement was just effective for protecting deleterious effects of corticosterone in recent memory and had no effect on remote memory. Thus, acute stress may impair memory retrieval in a time-dependent manner.

## 1. Introduction

Memory is a process that can be divided into at least three different stages: acquisition phase, consolidation or stabilization phase, and retrieval phase which is the expression of memory (1). It is well established that glucocorticoids influence different phases of memory processing in different manners (2-4). While most of the time, acute corticosterone enhances acquisition and consolidation phases of learning in a dose-dependent manner (5, 6), it usually impairs the recall of previously acquired information (7). Acute stress or exogenous corticosterone administered shortly before memory retention has been shown to impair retrieval of spatial memory. The impairment effect of glucocorticoids on memory retrieval is dependent on different factors. It is time-dependent (8, 9) and additionally, it may be upon training intensity. In this study, we tried to reveal the role of acute stress on memory retrieval of recent and remote memory (when there is one day or one month interval between learning and retrieval phase, respectively). Additionally, we were also interested to show the effect of learning enhancement on memory retrieval.

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## 2. Materials and Methods

### 2.1. Animals and drugs

Sixty four adult male Wistar rats (200-250 g) were kept in a room with constant temperature (22±2°C) and a standard 12 hour light/dark cycle. Food and water were available *ad libitum*. All experiments were performed during the light phase of the cycle between 9:00 A.M. and 2:00 P.M. All procedures were conducted in agreement with Tehran University Guide for use of laboratory animals.

Corticosterone (Sigma, England) was dissolved in a vehicle containing 5% ethanol in normal saline and was injected subcutaneously (3.0 mg/kg) at a volume of 1 ml/kg 30 min before the probe trial test. Control animals received the vehicle.

### 2.2. Water maze training and testing

The water maze was a black round tank 120 cm in diameter and 60 cm in height, which was filled to a depth of 40 cm with water (21±2°C). The tank was divided into four equal quadrants and a platform was placed in one of the four maze quadrants. The platform could not be seen by the rats. Several visual extra-maze cues were placed on the wall of the room. For acquisition training, the rats were given four or eight trials in each daily session for 5 consecutive days. Each trial consisted of a ceiling time of 60 s and a trial interval of approximately 30 s. The time to reach the platform was measured as escape latency. Retention of the spatial training was assessed, either 24 h or one month after the acquisition phase, with a 60 s probe trial test. In the probe trial, the rat was placed in the pool, as in the training trial, except that the hidden platform was removed. The parameters measured in the probe trial were time spent in the target quadrant (containing the platform during training), and the frequency of entry into target quadrant (crossing).

### 2.3. Experimental protocol

Four different experiments were used in this study as the following:

Experiment 1: low intensity trial (4 trials/day) with recent memory retrieval testing (retention testing 24 h after training).

Experiment 2: high intensity trial (8 trials/day) with remote memory retrieval testing (retention testing 1 month after training).

Experiment 3: low intensity trial (4 trials/day) with remote memory retrieval testing (retention testing 1 month after training).

Experiment 4: high intensity trial (8 trials/day) with recent memory retrieval (retention testing 24 h after training).

In each experiment, two groups were examined. 1- normal control group (n=8 and 2- acute stress group which received corticosterone 30 min before probe test.

### 2.4. Statistical analysis

All data were expressed as the mean ± SEM and were analyzed by one way ANOVA followed by Tukey post hoc test. Data was considered significant when *p* value was less than 0.05.

## 3. Results

### 3.1. Acute corticosterone administration impairs remote and recent memory retrieval

Previous studies have shown that acute stress or corticosterone administration impairs spatial memory retrieval (7). Since the effect of stress on acquisition and retrieval is time- dependent (10), in this study we tried to reveal the effect of acute corticosterone administration on either recent memory with probe trial performance 24 h after learning, or remote memory with probe test performance one month after learning. The one-way ANOVA applied on data reflecting the time spent in target quadrant showed a significant impairment of both recent and remote memory retrieval when corticosterone administered before probe test, $p<0.01$ for recent memory and $p<0.001$ for remote memory, post hoc Tukey's test after ANOVA ($F(3,29)=11.642$; $p<0.001$; Fig.1). The results of crossing the location of hidden platform further confirmed that acute corticosterone administration before probe test, impaired both recent and remote memory retrieval ($p<0.05$ for recent memory and $p<0.01$ for remote memory, post hoc Tukey's test after ANOVA ($F(3,29)=10.470$; $p<0.001$; Fig.2).

For assessing the effects of enhancement learning, in corticosterone groups we used an eight trials protocol in each session of water maze task. According to the intensity principle; the more intense the material taught, the more likely it will be retained. However, the results showed that enhancement in learning phase only could reverse the deleterious effects of acute corticosterone in recent memory groups and had no effect on remote memory retrieval. ($p<0.05$ for recent memory, post hoc Tukey's test after ANOVA ($F(3, 29) = 2.081$; $p<0.05$ ; Fig.2).

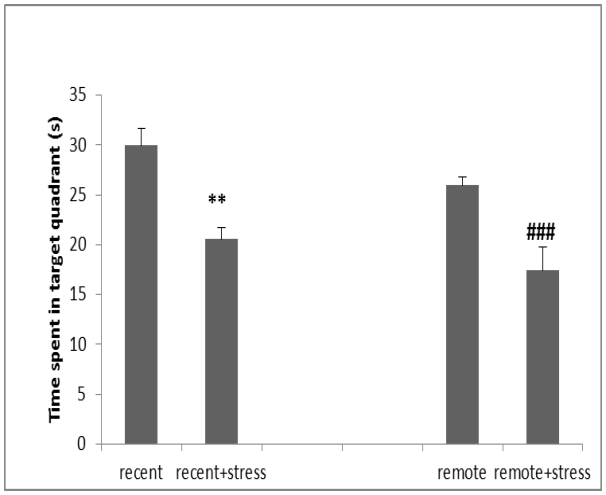


**Figure 1.** Histogram shows retrieval test performance of rats on day 6 for recent memory and on day 30 for remote memory. The stress groups received single injection of corticosterone 30 min before probe test. Acute corticosterone administration induced specific deficit on recent memory retrieval. * $p< 0.01$ and remote memory retrieval $p<0.001$, Tukey post hoc test after ANOVA ($F_{(3, 29)} = 10470$; $p<0.001$)

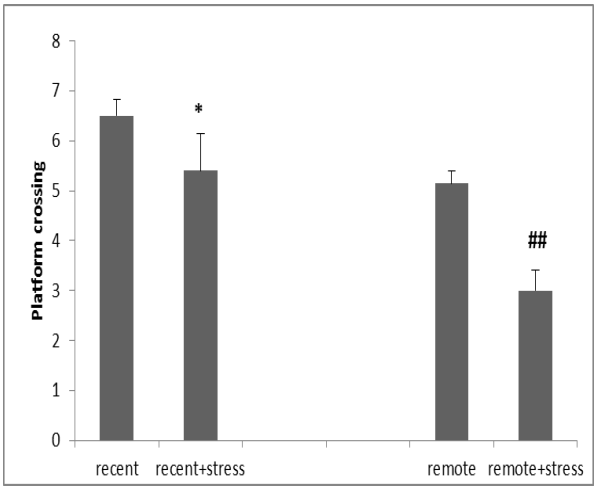


**Figure 2.** Histogram shows the numbers of crossings where the platform had been located in the probe test. * $p < 0.05$ recent stress groups vs. recent control and for remote stress groups vs. remote control groups. Tukey post hoc test after ANOVA ($F_{(3, 29)} = 11.642$; $p<0.001$)

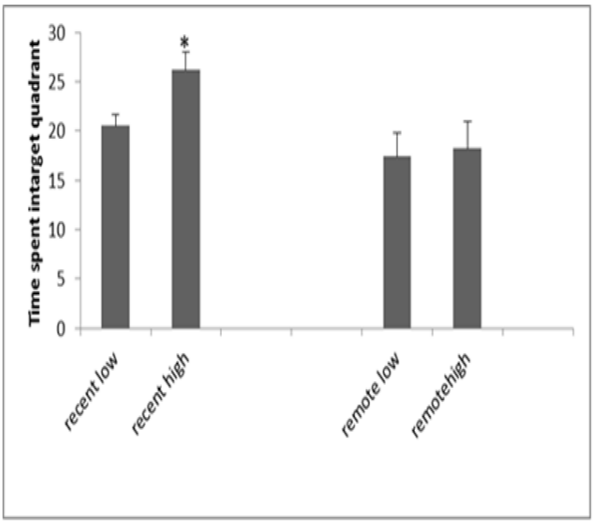


**Figure 3.** Histogram shows the effect of learning enhancement (high learning intensity) on recent and remote memory retrieval in corticosterone groups.More intense learning ameliorates the memory retrieval impairment-induced by corticosterone just in recent groups and had no effect on remote groups.

## 4. Discussion

Until recently, few studies manipulated acute stress or corticosterone administration on memory retrieval phase with mixed findings; while some data indicates that acute stress may impair memory, others believe that acute stress can actually enhance memory (11). An important factor in determining what will be impaired and what will be enhanced is the timing of the perceived stressful exposure and the timing of the retrieval phase (12). Animal studies showed that a decrease in baseline glucocorticoid levels could not affect retrieval when given on the second day of learning in spatial task (13). In a recent review article, it is well established that when a stressful episode immediately precedes or follows learning, such learning is enhanced. In contrast, when a stressful event is temporally separated from learning or is experienced before retrieval, learning or memory is impaired (10). In our study, acute corticosterone administration after acquisition phase and thirty minutes before probe test (memory retrieval phase) has led to impairment in memory retrieval in both recent and remote memory which is in accordance with Cadle et al results (10). However, the deleterious effect of acute stress on memory retrieval was more prominent when the timing between learning and memory retrieval was longer (remote memory compared with recent memory $P<0.001$ Vs. $P<0.01$). It is worth mentioning that the impairment of memory was not due to the effect of time per se as there was no significant difference between control groups in remote and recent memory. Probe test performance was evaluated in two measures: percent of time in target zone and the number of time rats cross target zone. It seems that the latter is more sensitive measure of water maze probe test (14). However, in our study, both measures were impaired by acute corticosterone administration (Fig. 1 & Fig. 2).

Further, to analyze the protective effect of enhanced learning against memory impairment-induced by acute stress, groups of high intensity were trained in an eight trials/day protocol. Our results showed that learning enhancement in high intensity groups could only ameliorate the deleterious effects of acute stress in recent memory groups and had no effects on remote groups. Other studies using protein synthesis inhibitors as memory-induced impairment revealed that memory consolidation impairment could be prevented, by enhanced learning. It seems that for memory retrieval, learning enhancement is not always effective, especially when there is long temporal interval between learning and memory retrieval.

Altogether we conclude that acute stress may interfere with memory retrieval both in recent and remote memory. In recent memory, this effect disappears when animals are submitted to an enhanced learning experience.

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