Comparing the Effect of Dexmedetomidine and Etomidate Administration with Acute Height Stress on Spatial Memory in Male Mice

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Research

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Abstract

Background: Nowadays, anesthetic drugs are widely used in anesthesia and surgical procedures and their effects on memory have been the focus of attention for a very long time. The effects of these common drugs include Dexmedetomidine (DEX) and Etomidate (ETO), on memory are controversial. In this study, the effects of these two drugs, co-administrated with heights stress, were evaluated on short-term and long-term spatial memory. 48 male mice were divided into 6 experimental groups consisting of Control, Control+heightstress (H.S), ETO, ETO+H.S, DEX+H.S. Drugs were administered Intra-peritoneal with doses of 0.3-0.4 mg/kg and 11 mg/kg for DEX and ETO respectively, and spatial memory was assessed using the Barnes Model.

Results: DEX improved acquisition and retention of spatial reference memory, whereas ETO showed no such effects. In addition, DEX and ETO showed excitatory effects on short-term spatial memory, however DEX was more effective than ETO.

Conclusion: the results suggested the neuoprotective, synaptic plasticity and memory improving effects of DEX on spatial reference and working memory. However, the precise neuronal and molecular mechanisms of these effects and their relation to the anti-stress system is still unknown and requires further research.

Background:

Anesthetic drugs are widely used in anesthesia and surgical procedures and their effects on memory have been the focus of attention for a very long time. The experience of height stress may result in stress-related psychiatric disorders such as Post-traumatic stress disorder (PTSD). Which is a psychiatric disease that occurs after serious accidents, anxiety and fright(1). The symptoms of PTSD include increased sensitivity to stress, intrusive memory, hyperarousal, and avoidance (1, 2).

During recent years, improvement of behavioral tasks which assess spatial learning and memory in rodents has us comprehend the role of the hippocampus in these cognitive functions (3). Allocentric navigation involves different parts such as the hippocampus, entorhinal cortex, and its surrounding structures while in the human body this system encodes allocentric, semantic, and episodic memory. This form of memory is assessed in laboratory animals in many ways, but one form of assessment is the Barnes maze (4).

The primary aim of the pharmacotherapeutic agents for PTSD is to disrupt the memory consolidation and the associated fear conditioning response after exposure to an event (5, 6).

The risk of PTSD occurrence in patients exposed to stressful medical conditions associated with perioperative awareness or Intensive Care Unit (ICU) treatment is moderately high (7-9). Patients treated in ICU for life-threatening medical events have multiple traumatic experiences and often develop severe

PTSD symptomatology, including vivid memory of traumatic experiences, anxiety, panic, hallucinations and nightmares (10, 11).

Commonly used anesthetics/sedatives, such as ETO and the α2-adrenoceptor agonist Dexmedetomidine (DEX) interact with several neurotransmission systems importantly involved in the regulation of emotional memory formation (12).

DEX is an α2 adrenoceptor agonist that has been used as an anesthetic agent and sedative for several years (13). DEX produces dose-dependent sedation, anxiolysis, and analgesia without respiratory depression. DEX triggers and maintains natural sleeping status without eye movement by stimulating the locus coeruleus in the brain stem, so it increases the activity of inhibitory gamma aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus (14). Experimental and clinical practices have revealed that DEX is neuroprotective on delirium, stress and inflammatory response (15-18). Based on previous studies, DEX may suppress memory formation only at doses reducing central nervous system activity in response to sensory inputs(19). Previous studies reported that DEX reduced fear memory consolidation in an inhibitory avoidance task (20). DEX treatment after trauma at sub-anesthetic doses reduced fear memory and anxiety behavior in a rat PTSD model (21).Use of DEX after experiencing a traumatic event might prevent the occurrence of emotional distress(12).

GABAA receptors (GABAARs) are heteropentameric ligand-gated anion channels responsible for the majority of inhibitory synaptic transmission in the brain (22). GABAARs are considered important targets of a variety of agents, including Etomidate (ETO) (23-25).

ETO is an ultra short-acting agent which in contrast to ketamine, induces only transient apnea with good cardiovascular stability in animals and humans (26-28). It also can cause nausea, vomiting, myoclonus, pain on injection and impairment of endocrine system function (29). Cardiovascular stability is attributed to the stimulation of central adrenergic receptors, with a lack of myocardial depression and little change in the heart rate or blood pressure (30). Because of its favorable hemodynamic profile, ETO is used in the clinical setting to induce anesthesia in patients at risk for cardiovascular compromise, and in other select circumstances such as electroconvulsive therapy (31).The inverse agonist effects of α5-containing $GABA_AR$s were also found to reduce the amnestic and intraoperative-awareness effects experienced with some anesthetic drugs such as ETO, but without affecting the long-term plasticity and sedative-hypnotic side effects of anesthesia (32).

In this study, the effects of these two drugs, in addition to fear of heights stress, using Barnes maze were evaluated on short-term and long-term spatial memory in mice.

Results:

3 – 1: Effect of acute stress with DEX and ETO on reference spatial learning in Barnes maze model:

Figure 1A shows the comparison between number of errors on learning days in experimental groups. ANOVA showed significant statistical difference between groups. Post hoc test shows significant difference between DEX + H.S with CON + H.S and CON groups($P < 0.05$, $p < 0.01$respectively).

Figure 1B shows the comparison of the time spent on finding the target hole on learning days between experimental groups. ANOVA showed significant statistical difference between groups. Post hoc test shows significant difference between DEX and DEX + H.S with CON groups ($P < 0.05$, $p < 0.01$respectively) and also DEX + H.S with CON + H.S and ETO + H.S ($P < 0.05$).

Figure 1C shows the comparison of Distance traveled to finding target hole on learning days between experimental groups. ANOVA showed no significant statistical difference between groups ($P < 0.05$).

These results indicate that DEX could facilitate special reference learning while ETO had no such effect; in addition, DEX shows anxiolytic effect which enhanced learning.

3 – 2: Effect of acute stress with DEX and ETO on spatial reference memory in Barnes maze model:

Figure2A shows the comparison of number of errors on spatial reference memory between experimental groups. ANOVA showed significant statistical difference between groups. Post hoc test shows significant difference between DEX and DEX + H.S with CON groups ($P < 0.01$, $p < 0.001$respectively), between DEX and DEX + H.S with CON + H.S groups ($P < 0.01$, $p < 0.05$respectively), between DEX and DEX + H.S with ETO groups ($P < 0.01$), between DEX and DEX + H.S with ETO + H.S groups ($P < 0.01$).

Figure2B shows the comparison of distance traveled to finding target hole on spatial reference memory between experimental groups. ANOVA showed significant statistical difference between groups. Post hoc test shows significant difference between DEX and DEX + H.S with CON groups ($P < 0.05$), between DEX and DEX + H.S with CON + H.S groups ($P < 0.01$), between DEX and DEX + H.S with ETO groups ($P < 0.05$), between DEX and DEX + H.S with ETO + H.S groups ($P < 0.001$).

Our results indicate that DEX could facilitate spatial reference memory whereas ETO had no effect, height stress had no significant effect on spatial reference memory.

3–3: Effect of acute stress with DEX and ETO on acquisition of spatial working memory in Barnes maze model:

Figure3A shows the comparison of number of errors on acquisition spatial working memory between experimental groups. ANOVA showed no significant statistical difference between groups ($P < 0.05$).

Figure 3B shows the comparison of distance traveled to finding target hole on acquisition spatial working memory between experimental groups. ANOVA showed significant statistical difference between groups. Post hoc test shows significant difference between DEX with CON groups ($P < 0.05$), between DEX and DEX + H.S with CON + H.S groups ($P < 0.05$), between DEX with ETO groups ($P < 0.05$).

In this protocol animals should extinct the farmer goal place and acquire new place. There was no significant difference of number of errors between groups but traveled distance was significantly different between experimental groups and showed that in the DEX group the mice immediately looked for a new place after finding the replacement of the goal box, which indicates facilitating effects of DEX on acquisition of spatial working memory.

3–4: Effect of acute stress with DEX and ETO on retention spatial working memory in Barnes maze model:

Figure4A shows the comparison of number of errors on retention spatial working memory between experimental groups. ANOVA showed significant statistical difference between groups. Post hoc test shows significant difference between DEX and DEX + H.S with CON groups ($P < 0.05$), between DEX and DEX + H.S with CON + H.S groups ($P < 0.001$), between ETO and ETO + H.S with CON + H.S groups ($P < 0.001$, $p < 0.01$respectively), between CON with CON + H.S groups ($P < 0.05$).

Figure 4B shows the comparison of distance traveled to finding target hole on retention spatial working memory between experimental groups. ANOVA showed significant statistical difference between groups. Post hoc test shows significant difference between DEX with CON groups ($P < 0.01$), difference between DEX with CON + H.S groups ($P < 0.05$), DEX, DEX + H.S and ETO + H.S with ETO groups ($P < 0.001$, $P < 0.001$, $p < 0.01$respectively).

Our results indicate that both DEX and ETO have facilitating effect on spatial working memory.

Discussion:

Our main findings areas follow: A) DEX strengthened the reference spatial learning in Barnes maze model whereas ETO had no effect. B) DEX also improved the recall of long-term and Short-term spatial memory. C) Both DEX and ETO improved short-term spatial memory recall, although the effect of DEX was relatively greater than ETO. D) DEX showed facilitating effects on acquisition of spatial working memory. E) In our study, the used height stress model was less effective on most spatial memory parameters, which seems to be because of the sensitivity of our experimental model.

The Barnes maze is broadly used for the evaluation of learning and memory function in mice, particularly spatial learning and memory (33, 34). In the present study, the Barnes maze test was used to determine the effect of DEX and ETO on Spatial memory. GABAA receptors (GABAARs) are heteropentameric ligand-gated anion channels responsible for the majority of inhibitory synaptic transmission in the brain (22). GABAARs are considered to be important targets of a variety of agents, including Etomidate (ETO) (23–25). Because the majority of α5-GABAARs are located extra-synaptically on pyramidal cells, where they mediate a persistent conductance termed “tonic inhibition” (35), and tonic inhibition is strongly enhanced by amnestic drugs, it was proposed that the effect of ETO on synaptic plasticity is due to its enhancement of tonic inhibition (36–38). It is also possible that ETO controls synaptic plasticity and memory by targeting interneurons (39). Based on these findings we can conclude that the effect of ETO

to improve short-term spatial memory can be explained through these receptors and their role on synoptic plasticity, which is the fundamental mechanism for memory traces.

Cheng and colleagues, using whole cell patch clamp technique on hippocampal pyramidal cells, have shown the ETO-induced amnesia through selective modulation of α5β2-containing GABAARs (38). In addition, it has been shown that ETO at doses that impair memory may causes sedation, as indicated by a decrease in exploratory activity (40). Considering that sedation is attributed to the modulation of β2-containing GABAARs (41, 42), it seems likely that it has contributed to the β2-GABAAR-mediated learning impairment (43). In the present study, we could not observe any memory impairment in ETO group compare with control group. This discrepancy may be because of the different experimental protocol and dosage of ETO compared to other studies.

Previous studies demonstrated that pretreatment with DEX could reduce learning and memory impairment, and decrease neuronal cell apoptosis, inflammation and oxidative stress. Moreover, the neuroprotective effects of DEX was reversed by yohimbine, an α2adrenoceptor antagonist, suggesting that the effects of DEX may be mediated by α2 adrenoceptors(13). DEX increases extracellular signal regulated kinases (ERK) ½ phosphorylation, a key mitogen-activated proteinkinase involved in cell survival and memory by the activation of proteinkinase C, andprobably imidazoline receptors (44, 45). DEX also increases the expression of growth factors such as epidermal growth factor and brain-derived neurotrophic factors, and then participates in neuroprotection. These molecular properties of DEX may underlie its anti-inflammatory and anti-apoptotic effect (46).Some of these effects of DEX may be explained by the anti-inflammatory and neuroprotective action of this agent. The anti-inflammatory effect ofDEX is achieved by inhibiting the TLR4/NF-κB (47),JAK2-STAT3 (48, 49), and NF-κB/COX-2 pathways (50, 51); activating the ERK1/2 pathway (52); and releasing acetylcholine(ACh) through anti-sympathetic effects via the cholinergic pathway (53). DEX also reduces neuronal apoptosis via myriad mechanisms that enhance the viability of the neurocyte. The brain is quite sensitive to the annihilation of oxygen-free radicals, and ischemia reperfusion injuries produce an intracorporal antioxidant-peroxidationstate imbalance. The excessive free radicals in the body are eliminated by DEX and this pathological chain-reaction is reduced by decreasing malondialdehyde and improving the activity of superoxide dismutase(54, 55).

In addition, it has been reported that DEX reduces fear memory consolidation without altering symptoms associated with PTSD in animal models. Also, it is reported that DEX reduces fear memory consolidation in an inhibitory avoidance task (12, 20)which is suggested that this effect may result from anxiolytic effect of DEX. Furthermore, it has been shown that DEX treatment after acute stress at sub-anesthetic doses reduces fear memory and anxiety behavior in a mice stress full model(21). In our results, we found facilitating effects of DEX on short term and long term spatial memory which may be because of anxiolytic effect of DEX at sedative dose which was reported in previous studies. In this study, for the first time, we compared the effect of DEX and ETO on reference and working spatial memory together with height stress as an acute stress model. In this study our acute stress model could not affect spatial memory and it means that this point should be examined using different stress models such as

immobility stress or swimming stress which remain to be elucidated. On the other hand, some discrepancieswith previous findings concerning the role of this agent in learning and memory may be explained by the different behavioral task models which were used (fear memory task or passive avoidance task versus Barnes spatial memory).

Conclusion

Our results suggest that DEX administration after experiencing a stress event might prevent the occurrence of emotional distress and subsequent stress disorder development. The results showed that the neuron protection, synaptic formation and memory improving effects of DEX positively affect on learning and remembering reference spatial memory and also remembering working memory. However, the precise neuronal and molecular mechanisms of these effects and their relation to the anti-stress system is still unknown and requires further research.

Materials And Methods:

Animals:

Animal care and experimentation were performed in accordance with protocols approved by the Science and Animal Experimentation ethics Committee no. IR.UMSHA.REC.1397.064 (Hamadan University of medical sciences).

Forty-eight mice (25–30 g) were purchased from the Neuroscience Research Center of Laboratory Animals, Each group contained 8 animals. Only males were chosen to reduce variability due to endocrine cycling. All mice were kept in a controlled air-conditioned room with food and water available ad-libitum with a controlled temperature (22 ± 2°C) under a 12-hr light/dark cycle with lights on 7:00 A.M.–7:00 P.M..The adaptability phase for the Mice was at least 7 days before the onset of experiments. Training and testing was performed during the light phase of the cycle between 9:00 AM and 5:00 PM

Drug preparation and administration

Etomidate (11mg/kg; B.Braun Medical S.R.L) and Dexmedetomidine (0.3 or 0.4 mg/kg; Exir, Tehran, Iran) were dissolved in saline solution (0.9%). Drugs solutions were freshly prepared the day of the experiment and were administered by intraperitoneal injection 30 minutes before trial (43). Drug doses were chosen based on previous studies performed (12, 40).

Experiment protocol

Barnes Maze model:

Spatial learning and working memory were evaluated using the Barnes maze (56). The maze consists of a circular platform (92-cm diameter) surrounded by 20 holes (5- cm diameter, equidistant), one providing

an escape route and was elevated 90 cm above the floor. The mice were placed in a dark chamber in the center of the maze and aversive stimuli subsequently triggered (bright light and noise). The animal was then given the opportunity to leave the maze by crawling through the hole allowing the escape. There was a small dark recessed “goal box” (20x 9 x 9 cm) located under one of the holes where mice can escape the aversive stimulus (bright light) and hide. Charts were pasted on the walls to act as visual cues and were kept permanently in their positions throughout the days of the study. A videocamera was positioned about 150 cm above the platform to record the activities (57).

Behavioral procedures:

In the spatial acquisition phase, animals were subjected to five trials per day for four consecutive days, with a constant inter-trial interval time of 20 min. The number of holes explored and the time required for the mice to locate the escape hole, were quantified. For the reference memory phase or probe trials, animals were tested on the 24hr and7th day (short-term retention) following the first trials, omitting training sessions between test trials. At some point in the probe trial, the escape hole was removed and replaced with a standard hole which the animal could not enter through. The cut off time was300-s period and mice were located in the box for 30s. The latency to reach the virtual target hole and number of errors were recorded, the outcome measure corresponding to the spatial memory capacity of the animal(33). For the purpose of the spatial working memory test, the escape hole was moved 180 degrees from its original location and the first working trial were done. In the second trial (working memory test) escape latency were measured when animal reached to the escape hole.

Elevated platform (EPF) exposure (Height stress):

For height stress, animal were exposed to EPF before Barnes maze session for 5 min (58). Each mouse was individually placed in the center of the EPF (diameter 18 cm; elevation 75 cm; room light 160 lux) and then the Barnes maze test was carried out.

Experimental groups:

For the study a total of 48 male mice (age 8-10 weeks) were obtained from the Experimental Animal Center of Hamadan University of Medical Sciences. The study groups included control 1, control 2 (Control+H.S), DEX, ETO, DEX+H.S and ETO+H.S; the control group received saline, DEX received Dexmedetomidine and ETO received Etomidate intraperitoneally.

Statistical analysis

The tests were carried out by a person who was blinded to the condition of the animals. The results are presented as the means ± standard error of the mean (SEM). Comparisons between the experimental and control groups were performed using two-way analysis of variance (ANOVA), followed by Bonferroni or Tukeys post hoc tests when appropriate. A value of $p< 0.05$ was considered as significant.

Declarations

Ethics approval and consent to participate:

all experimental procedures using mices were conducted in accordance with the animal care and use guidelines approved by the institutional ethics com-mittee at Hamadan University of Medical Sciences (Code of Ethics Committee: Grant Number: IR.UMSHA.REC.1397.064) and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals

Consent for publication:

Not applicable.

Availability of data and materials:

The data are available for any scientific use with kind permission.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

A.Emam and A. Sarihi conceived of the presented idea. M. Tarbiat. developed the theory and performed the computations. M. Rezaei. verified the analytical methods. A. Emam Drafted or provided critical revision of the article and A. Sarihi Provided final approval of the version to publish. All authors discussed the results and contributed to the final manuscript.

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Figures

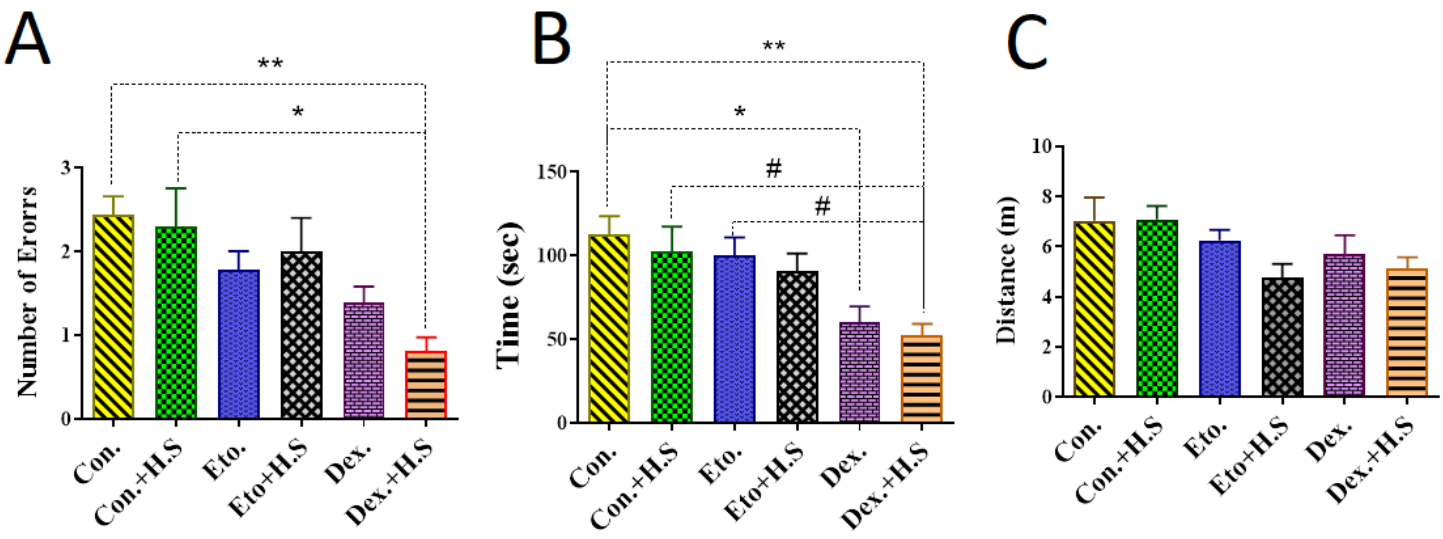

Figure 1

Effect of acute stress with DEX and ETO on Reference spatial learning A: comparison number of errors (* P<0.05, ** P<0.01), B: comparison of spended time to finding target hole (*, # P<0.05, ** P<0.01) C: comparison of Distance traveled.

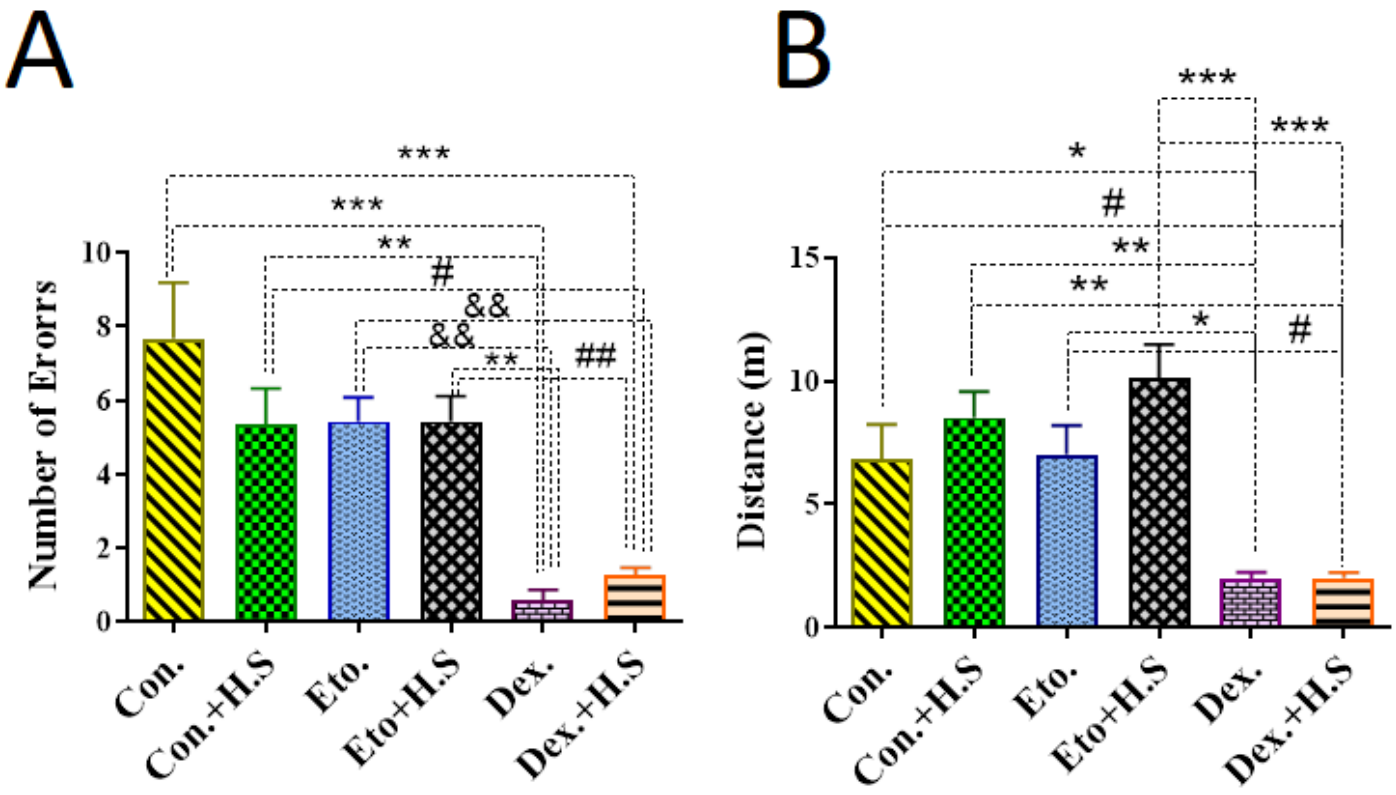

Figure 2

Effect of acute stress with DEX and ETO on recalling reference spatial memory A: comparison number of errors (# P<0.05 , ***,**,##,&& P<0.01) B: comparison of distance traveled to finding target hole (#,* P<0.05 ** P<0.01 *** P <0.001).

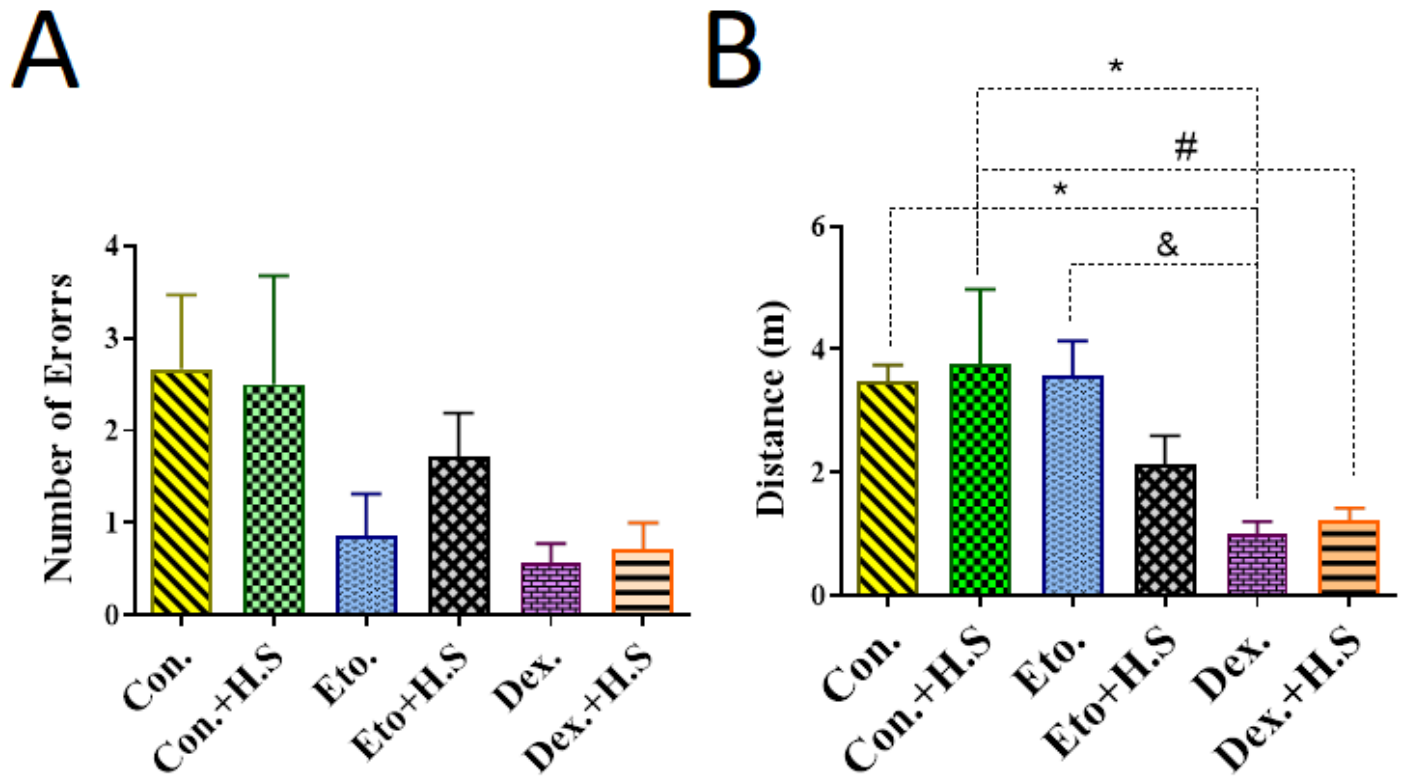

Figure 3

Effect of acute stress with DEX and ETO on learn spatial working memory A: comparison number of errors B: comparison of distance traveled to finding target hole (#,*, & P<0.05).

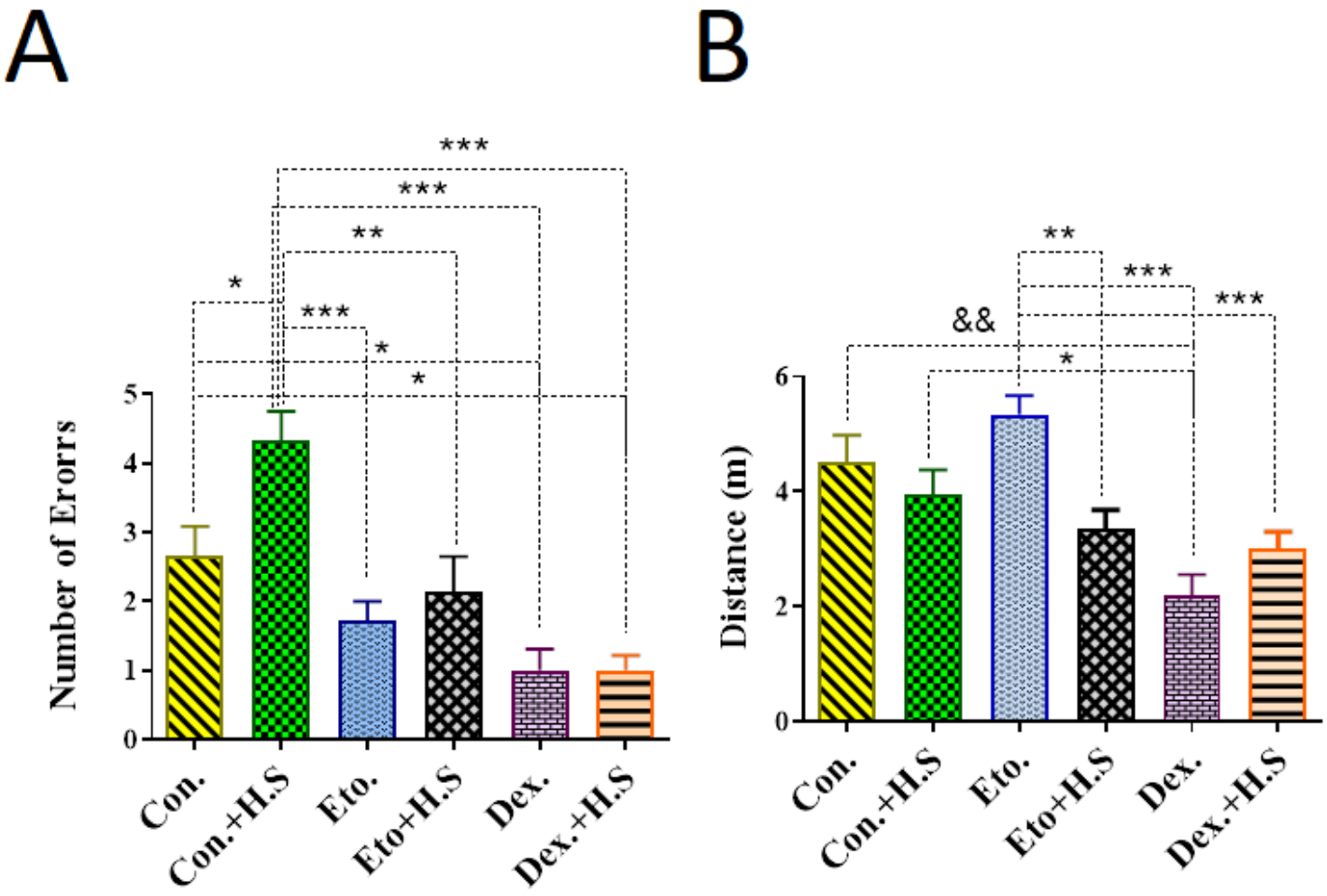

Figure 4

Effect of acute stress with DEX and ETO on recalling spatial working memory A: comparison number of errors (* P<0.05 ** P<0.01 *** P <.0.001) B: comparison of distance traveled to finding target hole (* P<0.05 &&, ** P<0.01, *** P <0.001).