Curr Neurobiol 2019; 10(3): 123-129 *ISSN 0975-9042*

Effect of erythropoietin administration on schizophrenic-like behavior induced by Ketamine in BALB/C mice

Masood AS, Ahmed AA, AlBuainain NY, Alalaiwi OJ, Albinali AM, Bucheery YA, AlQasimi AR, Yousif AM, Kamal A

Arabian Gulf University/ College of Medicine and Medical Sciences, Manama/Bahrain

Abstract

Schizophrenia is a severe mental disorder described as a chronic, relapsing disease with a heterogeneous course and outcome which is characterized by episodic positive and negative symptoms. Ketamine (Ket) in our study was used to induce schizophrenic-like behavior in mice with attempts to study erythropoietin (Epo) neuroprotective properties in preserving normal functions against ketamine administration by assessing learning and memory, motor coordination, anxiety, and social behavior. Six weeks old male BALB/C mice where divided into four groups: control, ketamine induced schizophrenia, Erythropoietin treated, and erythropoietin-treated ketamine-administered groups (Ket+Epo). A rotarod test for motor coordination showed no difference between the four groups. Regarding learning and memory water maze test showed that ketamine group had a significantly prolonged time to reach the platform in contrast to the other groups. However, erythropoietin treatment in ketamine administered animals improved their performance. In elevated plus maze test, ketamine showed an antianxiety effect in comparison to the three tested groups. The social behavior in mice was not affected among the four groups when tested by the three chambers test. We conclude that erythropoietin has neuroprotective properties against ketamine-induced schizophrenia by enhancing learning and memory functions. Thus, providing new possible approaches in treating neuropsychiatric diseases.

Keywords: mice, ketamine, schizophrenia, learning and memory, anxiety, social behavior, motor coordination

Introduction

Schizophrenia is a severe mental disorder, typically beginning in late adolescence or early adulthood, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. Schizophrenia has been described as a chronic, relapsing disease with a heterogeneous course and outcome [1]. It's characterized by episodic positive symptoms such as delusions, hallucinations, paranoia, and psychosis and/or persistent negative symptoms such as flattened affect, impaired attention, social withdrawal, and cognitive impairments [2]. Dopaminergic deregulation, hypofunction of NMDA receptor and GABAergic activity, diminished cholinergic firing, neuroinflammation and increased oxidative stress has been demonstrated to play a pathophysiological role in schizophrenia [2-5]. The lifetime risk of schizophrenia is ~1% and typically manifests in early adulthood [4]. The lifespan of schizophrenic patients may be shortened by at least 20 years. The cause of schizophrenia is not known and current treatments for the illness do not reduce disability. Thus, research on the causes of schizophrenia, including factors such as genetics and environmental experiences are critically important. Similarly, research on treatments that reduce disability are also critical. Cognitive training that targets specific deficits seen in most schizophrenia patients are associated with different levels of brain activity.

It was proven previously by many studies that Ketamine (Ket), a non-competitive NMDA receptor antagonist was found to induce schizophrenia-related alterations in human as well as animal models. Ket is widely being used as a dissociative anesthetic [6,7]. It was found that in addition to its anesthetic function, Ket can induce psychotic symptoms when it is given in subanesthetic doses, this led to the substance being used to create an animal model of schizophrenia, assessing it's positive and negative symptoms. Ket effects can be explained by its antagonism (on the Phencyclidine binding site) to the NMDA receptor [8], resulting in blockade of the receptor, reduction in Ca^{+} ion flux, and decreasing glutaminergic signals transmission and subsequent effects [7,9,10]. Also, it has been implicated that other neuronal pathways (cholinergic and GABAergic pathways) can be altered when increased doses Ket are administered [11,12]. Beside the decrease in glutamate signals

transmission, several studies have reported dysfunction of the GABAergic neurons as a possible mechanism for inducing schizophrenia, this can be attributed to the NMDA receptor antagonism as well [13-15].

Erythropoietin (Epo), a hormone known for its erythropoietic effect through binding to its receptor EPO-R, was also reported to have a neuroprotective role in ischemic and traumatic CNS conditions [16] It was found that Epo is expressed in astrocytes and neurons, and increased in response to hypoxia, promoting neuronal cell survival, neurogenesis and migration of regenerating neurons. A study done on rats receiving intra-peritoneal Epo injection 24 hours post-ischemic stroke showed an increase in levels of vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) in the brain, leading to enhancement of angiogenesis and neurogenesis in ischemic brain tissue, and an increase in neuroblast migration towards the ischemic region [17,18]. Epo receptor is not only expressed on erythroid progenitor cells, but is also expressed in brain cells, including neural progenitor cells (NPC), neurons, glial cells and endothelial cells [19]. EPO and EPO-R were found to be expressed in the cerebral cortex, cerebellum, hippocampus, pituitary gland, and spinal cord5. EPO was shown to be responsible for an augmentation of hippocampus dependent memory through modulating synaptic connectivity, plasticity, and activity of memory-related neuronal networks [20]. EPO administration was associated with an increase in number of pyramidal neurons and oligodendrocytes in the hippocampus of mice [21]. EPO levels are present efficiently in the human brain, and more distinctly in schizophrenic patients, and the EPO-R is expressed in hippocampus and cortex of schizophrenic subjects more than in controls. Furthermore, EPO was found to be responsible for the improvement in cognitive functions, which are apparently affected by schizophrenia [22] A recent study showed that adjunctive EPO could improve schizophrenia-related cognitive performance in humans [23].

In our study, Ket, an NMDA receptor antagonist, was used to induce schizophrenic like behavior in BALB/C mice along with preceding doses of Epo aiming to study both their schizophrenic like effect and neuroprotective properties respectively regarding learning and memory defects, motor coordination anxiety like behavior, and social behavior.

Materials and methods

Animals

The animals used in this experiment are 6 weeks old male BALB/C mice. They are kept in Arabian Gulf University animal house facility and are fed as often as necessary.

Four groups of animals were used for the trials; each group is composed of 8 mice:

Group 1: Control (Cont), neither Ket nor Epo administered.

Group 2: Ket-induced schizophrenia (Ket). These animals were injected with Ket 24 hours prior to each water maze test.

Group 3: Epo (Epo). Healthy animals were injected with Epo for 7 days and tested on the 8th day.

Group 4: Epo-treated Ket-administered animals (Ket+Epo). Epo was administered for 7 days prior to the experiments, and Ket was given 24 hours prior to the water maze tests.

All animals from the four groups were subjected for the following behavioral tests:

1. Rotarod test: testing for motor coordination
2. Morris Water maze test: testing for memory and learning
3. Three-chambers social apparatus test: testing for sociability and social novelty
4. Elevated Plus Maze: testing for anxiety

Morris Water Maze Test (MWM)

Spatial learning and memory functions were assessed using the Morris water maze. The water maze is composed of a circular tank, 140 cm in diameter, 50 cm in height, and filled up to 30 cm with water; kept at a temperature of 26 C to 28 C. The circular maze was divided into four equal quadrants by two imaginary lines set by the program; each quadrant had a visual cue. The maze was kept in a dark room and illuminated by one source of red light. In the northwest quadrant, a fixed 'escape' platform was submerged 1cm below the surface of water; each mouse was given 5 trials on the first day to learn the location of the hidden platform. The trial consisted of releasing the mice, starting from the northeast quadrant, moving successively to the next quadrant, and finally coming back again to the northeast quadrant. Each mouse was given a maximum of 2 minutes to swim and find the platform, and was given 20 seconds to remain on the platform, whether it found it or not, in order to form a memory of its location. After 48 hours, the mice were given 3 test trials, in order to determine the memory of each mouse in locating the hidden platform. The latency to reach platform and mouse movement and position were recorded and analyzed by a video-camera computer system, and ANY-maze video-tracking system (Stoelting CO., Wood Dale, IL, USA). The outcome measures are the latency time and distance swum to reach the platform, as well as the speed of swimming during the experiment.

After the 3 testing trials, a probe test was performed, in which the platform was removed and each mouse is allowed to explore the water maze for 2 minutes, and the percentage of time spent in each quadrant was then recorded.

Rotarod test

Using an accelerating rotarod, the mice were assessed for balance and motor coordination. The mice were placed on a cylinder rod, which rotates with a speed that progressively increases 0.5 cm/s every 5 seconds. Each mouse was given 3 practice trials prior to being tested 3 times. Both trials and tests were a maximum of 5 minutes each, and the latency to fall from the rotating rod was recorded by the rotarod timer. The cylinder

rod was cleaned by 70% Ethanol mixed with water after each mouse. The experiment, comprising the trials and tests, was done in one day. Results were obtained by the mean time of the 3 tests.

3 chambers social apparatus test

This test aims to measure sociability and social novelty. A rectangular, 3 chambered apparatus was used. It is separated by plexiglass made walls with small openings in each wall to allow the mice to roam freely. Each chamber is (20 cm x 40 cm x 22 cm). A circular wire cage that is (11 cm) in height and a bottom diameter of (9 cm) and bars spaced (0.5 cm) apart is present in the right and left chambers. The subject mouse was first introduced into the middle chamber alone for 5 minutes to allow for habituation. The test is composed of two main sessions. Sociability of each animal was estimated in session 1, where a complete stranger mouse to the subject mouse (stranger 1) was introduced to one of the empty chambers and locked inside the wired cage, the subject mouse was allowed to explore the apparatus for 10 minutes and spend time whether in stranger mouse chamber, empty chamber or middle chamber. The time spent in each chamber was recorded. The second session investigated the social novelty. The first investigated stranger mouse (stranger 1) was introduced to the same chamber it was previously in, and another complete stranger mouse (stranger 2) was added to the other empty chamber and locked inside the wire cage. The subject mouse was introduced to the middle chamber and allowed to explore the apparatus for 10 minutes. The time spend in the chamber with the already explored mouse in session one together with time spent in the chamber containing new mouse were calculated. Between each session, the apparatus was cleaned by 70% ethanol and water. Three sessions (including the habituation) are done for each mouse. Session 1 tests social motivation, that is represented by time spent with the first mouse. Session 2 tests for social novelty, which is represented by preference in spending time in the chamber containing the novel mouse, more than time spent with the previously investigated mouse.

Elevated plus maze test

The elevated plus maze tests for anxiety like behavior in mice. It consists of two open arms (25 cm x 5 cm) opposed to each other, crossed, forming a shape of a plus by the two closed arms (25 cm x 5 cm) with (15 cm) high walls. The whole apparatus is elevated 55 cm above the ground, and is made of a wooden material. The subject mouse was placed on the central area, facing the closed arms and allowed to explore all arms freely. Each mouse had 1 session lasting for 10 minutes. An open arm or closed arm entry is defined as all four paws in one arm. The apparatus was cleaned be 70% ethanol and water between each mouse to avoid olfactory cue. Open arm duration and closed arm duration were recorded. Time spent in open arms indicated anti-anxiety like behavior, with time spent in the closed arms indicates anxiety like behavior.

The experimental procedures were approved by the Research and Research Ethics Committee, Arabian Gulf University, Bahrain.

Statistical analysis

Data are presented as mean ± standard error of mean (SEM) unless mentioned otherwise. Intergroup significance was measured using Analysis of variance (ANOVA) for repeated measures. Between specific groups analysis, a t-test was used. All statistical analyses were performed with Microsoft EXCEL (version 2010)

Results

Rotarod test: no significance between the groups tested

ANOVA test for repeated measures revealed no statistical significant differences between all the four groups (control; 20.55 ± 1.4, Ket;18 ± 3.09, Epo18.8 ± 2, and Epo treated, Ket administered; 18.1 ± 2.1 groups, ANOVA, $p > 0.05$, $F = 0.3185$, F crit= 2.6815) groups **(Figure 1).**

EPM: Anti-anxiety in ketamine treated mice

The results illustrated a decrease in the anxiety level of the Ket treated mice by spending more time in the opened arm (325.3 ± 17.3 s, t test, p value>0.05, t critical 1.76131) **(Figure 2)** when compared to the other three groups (control 252.4 ± 23.1; Epo 263.9 ± 8.2; and Ket + Epo 265.6 ± 18.3 s). No significant difference ($p>0.05$, t-test) was calculated between the Con, Epo and ket+ Epo groups.

Morris water maze: neuroprotective properties of erythropoietin noted in ketamine induced schizophrenic mice

Morris water maze test was used to assess the spatial memory function of the tested mice **(Figure 3A).** The latency to reach a hidden platform as a function of learning and memory,

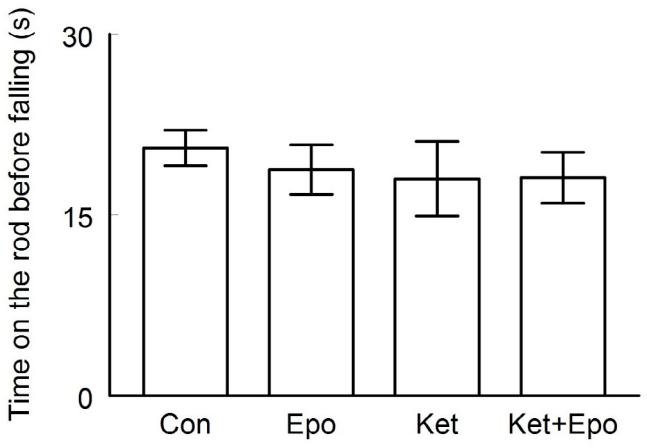

Figure 1. *Latency to fall (mean ± SEM seconds) in the rotarod test for the control, Epo, Ket, and Ket + EPO groups. There was no statistically significant difference between the four groups (ANOVA, $p< 0.05$). Con: control; Epo: erythropoietin; Ket: ketamine; Ket+Epo: ketamine + erythropoietin.*

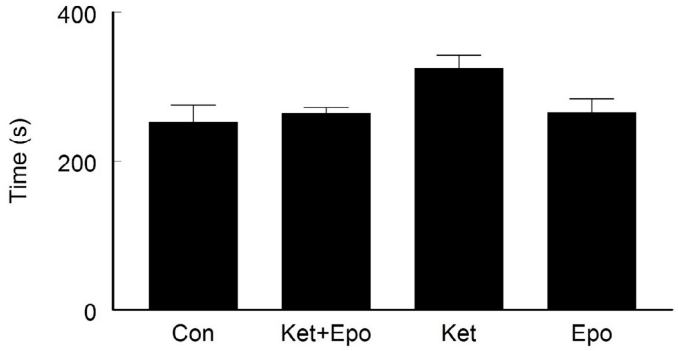

Figure 2. *Elevated plus maze test to evaluate anxiety effect corresponding to the amount of time spent on the open arm. Ket administered animals showed statistically significant decrease in anxiety levels (325.3 ± 17.3 s) in comparison to the other three groups.*

was calculated and compared between the group. No significant difference in the performance between the control group (45.8 ± 5.6s, t-test, t-Critical 1.6, p-value >0.05) when compared to the Epo group (56.3 ± 5.6s). As for the Ket group (108.2 ± 5.24), there was a significant increase in time when compared to all the other groups. However, Epo-treated Ket-administered group (65.6 ± 5.6s) improved their performance in the water maze test when compared to the Ket group (108.2 ± 5.2s, t-test, t-Critical 1.6, p-value <0.000005). No significant difference was calculated between control, Epo and Epo-treated Ket-administered groups.

Figure 3B shows that there were no significant differences in the speed of swimming in the pool between the groups (ANOVA test, p>0.05, F= 0.8136, F crit= 1.411). This implies that the changes in latency to reach the hidden platform was not due to swimming speed differences but rather to learning and memory capabilities.

Moreover, in the probe experiment **(Figure 4),** the percentage of time spent in the disc zone was more than 25% of the trial duration, which is more than what would be expected by chance. The time spent in the disc zone by the Ket group (24.92 ± 3.89) was significantly less than the control (45.2 ± 5.15s, t test, p value <0.05, t critical 1.6) and Epo groups (39.23 ± 4.90s t test, p value < 0.05, t critical 1.6). However, treatment of the Ket-administered animals with EPO (38.39 ± 5.59) enhanced their performance and their time spent in the disc zone is not significantly different from control (t test, p-value > 0.05, t critical 1.6) and Epo groups (t test, p-value > 0.05, t critical 1.6).

Three chambers test: Effect on Sociability and Preference for Social Novelty in Ketamine administered alone and in Erythropoietin-treated ketamine-administered mice

In the three chambers test, the control group displayed normal sociability by favoring to be in the chamber with another mouse rather than being alone in the empty chamber (315.4 ± 17.9s versus 217 ± 22.4s, respectively). They also exhibited a

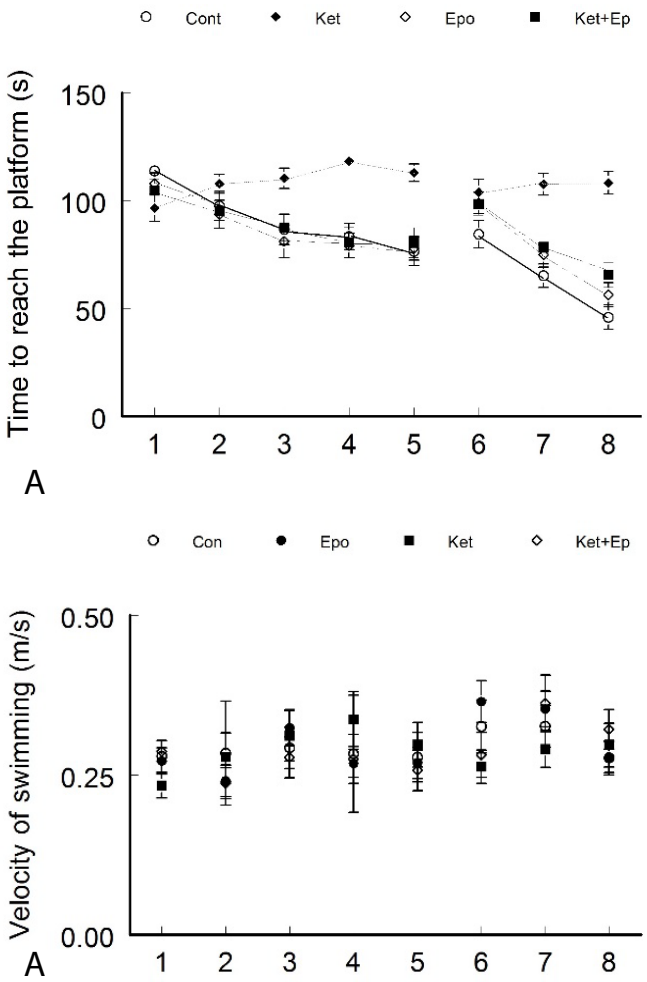

Figure 3. *Morris water maze test used to assess cognitive function of the control, erythropoietin, ketamine, and erythropoietin-treated ketamine administered groups.* ***(A)*** *Time to reach the platform.* ***(B)*** *Velocity of swimming.*

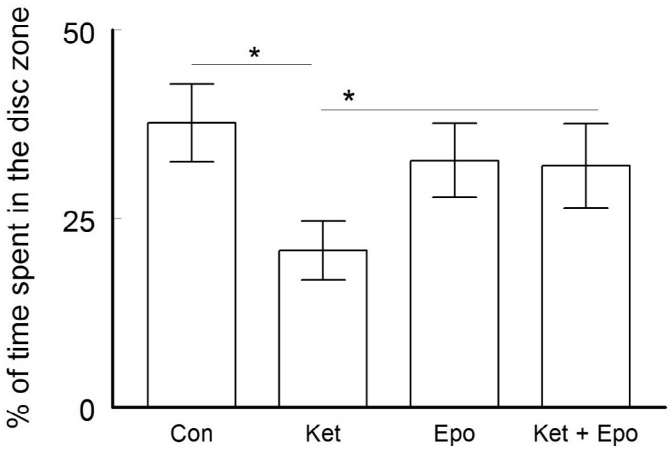

Figure 4. *Percentage of time spent in the disc zone. ket (24.92 ± 3.89) showed significant decrease in time spent in disc zone in comparison with other groups. (cont 45.24 ± 5.15, Epo 39.23 ± 4.9, Ket+Epo 38.39 ± 5.59).*

normal preference for social novelty by spending more time in the chamber containing the novel mouse than with the socially familiar mouse (347 ± 38.1s versus 184.8 ± 29.5s, respectively). This behavior was also recorded in the Epo group **(Figure 5A).**

However, the Ket group animals spent significantly more time in the empty chamber when compared to the time spent in chamber containing the mouse (244.38 ± 42.6 in empty chamber, and 108.8 ± 41.7 in the chamber with another mouse, t-test; $p<0.05$).

The Epo-treated Ket-administered mice showed almost equal time spent in both chambers (154 ± 51s with another mouse, and 150.8 ± 43.5s in empty chamber).

On the other hand, test of preference for social novelty in the Ket administered group showed a tendency preference (although not statistically significant) to the old mouse rather than the new mouse (278.4 ± 62.2s versus 195 ± 45.6s respectively, t-test; $p>0.05$) in comparison to the control group, which showed preference to spend time with the new mouse, as mentioned previously. Furthermore, the Epo-treated Ket-administered mice spent more time with the new mouse (220.5 ± 22.7s) instead of the old (209.5 ± 28.1s), showing improvement in preference for social novelty in contrast to Ket administered mice group **(Figure 5B).**

Discussion

Many studies were concerned with memory and learning observed in mice model of schizophrenia. Of which, impairment in hippocampal-dependent cognition and long-term memory was found in Ket mice model of schizophrenia [24-27]. *N*-methyl-*D*-Aspartate receptor (NMDAR) blockade resulted in cognitive and behavioral impairment [24], as well as sub-anaesthetic Ket induced impairment in all aspects of episodic-like memory formation [26] in addition to deficits in attention, working, and long-term memory [25]. Conversely, different opinion illustrated that Ket exposure in neonatal rats did not affect their adulthood's spatial memory. However, exposure to Ket for 3 days and intraperitoneal injection of Ket resulted in long-term memory dysfunction and decline in spatial memory ability, respectively [28]. Our study's results support the findings shown in most of the previous studies, for which the mice showed a decline in memory function after administration of intra-peritoneal Ket. This was represented as an increase in time required by the mice to find the platform after repetitive trials in the Morris Water-maze test. Furthermore, the mice spent less amount of time in the disc zone during the probe test, which also demonstrates memory deficit in the Ket-administered mice. In addition, no significant difference in swimming velocity was recorded between the groups. This implies that any differences in latency to reach the hidden platform were not because of differences in the swimming velocity but rather to the processes of learning and memory.

Recently, it has been reported that Epo is expressed in the nervous system and found to enhance hippocampal long-term potentiation and memory. Studies concluded that a certain amount of Epo is required to improve cognitive performance [29]. Moreover, Epo has shown significant improvement in recovery of memory function and brain plasticity when brain ischemia was induced [30]. However, our results showed that when administered to healthy mice subjects, Epo showed no significant enhancement in learning and memory. Results from this study further demonstrated that Epo-treated Ket-administered mice spent less time to find the platform and more time in the disc zone in comparison to Ket administered mice group. This suggests that Epo given to mice simultaneously with Ket exhibits preservation of memory function, which

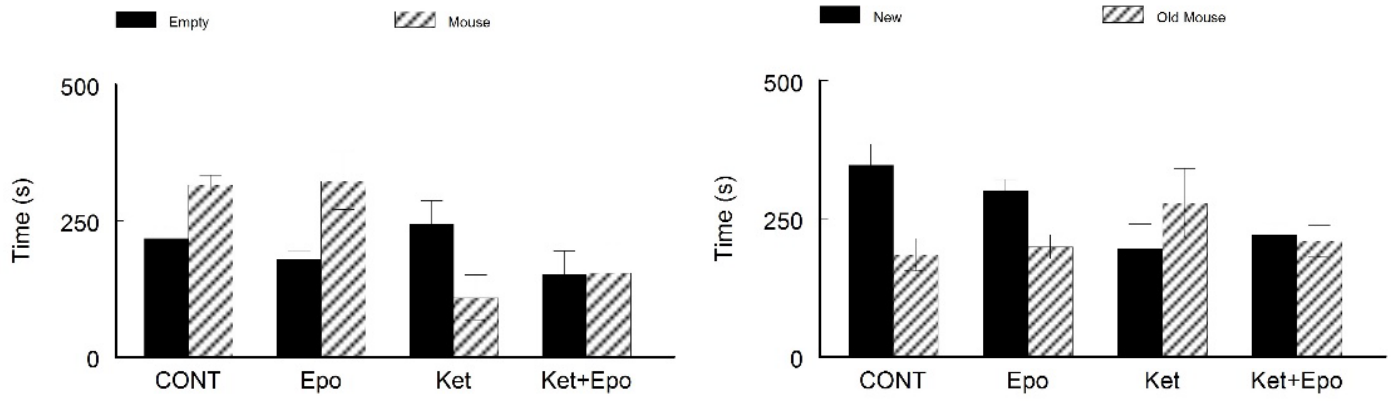

Figure 5. *Assessment of Sociability and Preference for Social Novelty by the Three-Chambers test.* ***(A)*** *Sociability expressed as seconds spent in the empty chamber alone, in comparison to time spent in chamber with another mouse for all groups.* ***(B)*** *Preference for Social novelty expressed as seconds spent with old mouse (stranger 1) versus with new mouse (stranger 2). All groups of mice showed normal sociability except for Ket group, which showed significantly higher preference to stay in the empty chamber. Test of preference for social novelty in the Ket-administered group showed a tendency preference to the old mouse rather than the new, compared to the control group and Ket+Epo, which showed social preference for the new mouse.*

would have been deteriorated if Ket was to be given alone, indicating that Epo could be protective against schizophrenic like behavior. This presented a similar finding in a study where memory impairment was induced by scopolamine and intracerebroventricular streptozotocin, following which the mice were injected with Epo, and an enhancement in memory and cognitive function was noted [31].

In relation to studying anxiety related behavior in schizophrenic model mice, our research established that Ket has an antianxiety influence, in opposition to other studies that stated that Ket has no effect on anxiety behavior [32,33]. Furthermore, when elevated plus maze test was performed on Epo given alone mice, the results showed no improvement from the control group. Likewise, different studies supported this findings, for which Epo did not have any effect in treating or reversing anxiety like behavior in normal mice model, in addition to preserving normal fear and protecting fear conditioning performances [34,35]. Our results also showed that when given to Ket-administered mice, Epo was found to be responsible for preserving normal anxiety behavior, which shared a similar result in a study that used a stressor as an insult [36].

In the three-chamber sociability and social novelty testing, Ket injected mice group showed abnormal results compared to the other groups. Some studies found that Ket had no effect on the social interaction, however other studies reported reduced social interaction when given in low doses [37,38,39]. Furthermore, regarding Epo administered group, result in our study demonstrated familiar sociability as seen in different studies, in which Epo can restore social interaction after an injury that caused social interaction impairment [40]. Epo+ Ket group mice on the other hand showed almost equal time spent in both chambers. Furthermore, concerning preference for social novelty, Epo+Ket group showed improvement for social novelty in the three-chamber test, in contrast to Ket-alone administered group in which a preference for old mice was seen. This was proved in a previous study which showed that using Epo and melatonin reduces social interaction deficiency, as well as significant modification in social drive and behavior in sham and injured rats [41].

Regarding locomotor activity, our study showed no difference noted in all groups tested. However, in contrast to previous studies, EPO was found to increase locomotor activity when cellular edema is induced, and decreases it before this insult [42]. An increase is also notable when EPO was given to mice known to have ischemia [43]. Concerning Ket administration, it was found to induce locomotor hyperactivity in mice [24,44-46]. Moreover, a study demonstrated that when Ket is given in a dose dependent manner it showed different results, in which high dose can cause locomotor hyperactivity, whereas 15mg/kg results in locomotor hypoactivity [26].

In conclusion, there was a positive consequence when using Epo in protecting against Ket-induced impairment in learning and memory and profound anti-anxiety behavior. Ket administered mice whom have been treated with Epo exhibited almost normal results regarding memory and learning, social preference and novelty, along with restoring normal anxiety-like behavior in comparison with Ket-administered alone. This supports our hypothesis that Epo has neuroprotective properties against schizophrenic-like behavior induced by Ket.

Acknowledgment

We acknowledge the help offered by the Arabian Gulf University to make this work possible.

Source of funding

This work has been funded by the Arabian Gulf University/ College of Medicine.

References

1. Haro JM, Novick D, Suarez D, Ochoa S, Roca M. Predictors of the course of illness in outpatients with schizophrenia: A prospective three-year study. Prog Neuro-Psychopharmacology Biol Psychiatry. 2008; 32: 1287-1292.
2. Foussias G, Remington G. Negative symptoms in schizophrenia: Avolition and occam's razor. Schizophr Bull. 2010; 36: 359-369.
3. Messinger JW, Trémeau F, Antonius D, Mendelsohn E, Prudent V, et al. Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. Clin Psychol Rev. 2011; 31: 161-168.
4. Keating D, McWilliams S, Schneider I, Hynes C, et al. Pharmacological guidelines for schizophrenia: A systematic review and comparison of recommendations for the first episode. BMJ Open. 2017; 7: 1-10.
5. Clemmensen L, Vernal DL, Steinhausen H. A systematic review of the long-term outcome of early onset schizophrenia - 1471-244X-12-150.pdf. 2012.
6. Gowravaram MR, Gallop MA. "Traceless" solid-phase synthesis of furans via 1,3-dipolar cycloaddition reactions of isomunchnones. Tetrahedron Lett. 1997; 38: 6973-6976.
7. World Health Organization. Expert Committee on Drug Dependence. Ketamine. Update Review. 2014.
8. Ellison G. The N-methyl-d-aspartate antagonists phencyclidine, ketamine and dizocilpine as both behavioral and anatomical models of the dementias. Brain Res Rev. 1995; 20: 250-267.
9. Thomson AM, West DC, Lodge D. An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: A site of action of ketamine? Nature. 1985; 313: 479-481.
10. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol. 1983; 79: 565-575.
11. Castellani S, Adams PM. Effects of dopaminergic drugs on phencyclidine-induced behavior in the rat. Neuropharmacology. 1981; 20: 371-374.
12. Adinolfi M. Life Sciences, Vol. 29, pp. 1607-1615 Printed in the U.S.A. Pergamon Pres~. 1981;29(c):1607-1615.
13. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 2005; 6: 312-324.
14. Eyles DW, McGrath JJ, Reynolds GP. Neuronal calcium-binding proteins and schizophrenia. Schizophr Res. 2002; 57: 27-34.

15. Akbarian S, Huang HS. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. Brain Res Rev. 2006; 52: 293-304.

16. Catania MA, Marciano MC, Parisi A, Sturiale A, Buemi M, et al. Erythropoietin prevents cognition impairment induced by transient brain ischemia in gerbils. Eur J Pharmacol. 2002; 437: 147-150.

17. Wang L, Zhang Z, Wang Y, Zhang R, Chopp M. Treatment of stroke with erythropoietin enhances neurogenesis and angiogenesis and improves neurological function in rats. Stroke. 2004; 35: 1732-1737.

18. Wang L. Matrix Metalloproteinase 2 (MMP2) and MMP9 Secreted by Erythropoietin-Activated Endothelial Cells Promote Neural Progenitor Cell Migration. J Neurosci. 2006; 26: 5996-6003.

19. Noguchi CT, Asavaritikrai P, Teng R, Jia Y. Role of erythropoietin in the brain. Crit Rev Oncol Hematol. 2007; 64: 159-171.

20. Al-Qahtani JM, Abdel-Wahab BA, Abd El-Aziz SM. Long-term moderate dose exogenous erythropoietin treatment protects from intermittent hypoxia-induced spatial learning deficits and hippocampal oxidative stress in young rats. Neurochem Res. 2014; 39: 161-171.

21. Hassouna I, Ott C, Wüstefeld L, Offen N, Neher RA, et al. Revisiting adult neurogenesis and the role of erythropoietin for neuronal and oligodendroglial differentiation in the hippocampus. Mol Psychiatry. 2016; 21: 1752-1767.

22. Ehrenreich H, Degner D, Meller J, Brines M, Béhé M, et al. Erythropoietin: A candidate compound for neuroprotection in schizophrenia. Mol Psychiatry. 2004; 9: 42-54.

23. Li XB, Zheng W, Ning YP, Cai DB, Yang XH, et al. Erythropoietin for cognitive deficits associated with schizophrenia, bipolar disorder, and major depression: a systematic review. Pharmacopsychiatry. 2018; 51: 100-104.

24. Shepard R, Heslin K, Hagerdorn P, Coutellier L. Downregulation of Npas4 in parvalbumin interneurons and cognitive deficits after neonatal NMDA receptor blockade: relevance for schizophrenia. Transl Psychiatry. 2019; 9.

25. Chatterjee M, Verma R, Kumari R, Singh S, Verma AK, et al. Antipsychotic activity of standardized Bacopa extract against ketamine-induced experimental psychosis in mice: Evidence for the involvement of dopaminergic, serotonergic, and cholinergic systems. Pharm Biol. 2015; 53: 1850-1860.

26. de Souza IBMB, Meurer YDSR, Tavares PM, Pugliane KC, Lima RH, et al. Episodic-like memory impairment induced by sub-anaesthetic doses of ketamine. Behav Brain Res. 2019; 359: 165-171.

27. Koh MT, Shao Y, Sherwood A, Smith DR. Impaired hippocampal-dependent memory and reduced parvalbumin-positive interneurons in a ketamine mouse model of schizophrenia. Schizophr Res. 2016; 171: 187-194.

28. Guo D, Gan J, Tan T, Tian X, Wang G, Ng KTP. Neonatal exposure of ketamine inhibited the induction of hippocampal long-term potentiation without impairing the spatial memory of adult rats. Cogn Neurodyn. 2018; 12: 377-383.

29. Adamcio B, Sargin D, Stradomska A, Medrihan L, Gertler C, et al. Erythropoietin enhances hippocampal long-term potentiation and memory. BMC Biol. 2008; 6: 1-16.

30. Undén J, Sjölund C, Länsberg JK, Wieloch T, Ruscher K, et al. Post-ischemic continuous infusion of erythropoeitin enhances recovery of lost memory function after global cerebral ischemia in the rat. BMC Neurosci. 2013; 14.

31. Kumar R, Jaggi AS, Singh N. Effects of erythropoietin on memory deficits and brain oxidative stress in the mouse models of dementia. Korean J Physiol Pharmacol. 2010; 14: 345-352.

32. Vivek A, Christopher J, Alyssa D, Kroener S. Ac Ce p Te d Cr T. Elsevier B.V; 2015.

33. Trofimiuk E, Wielgat P, Braszko JJ, Car H. PT. Behav Brain Res. 2018.

34. Leconte C, Bihel E, Lepelletier FX, Bouët V, Saulnier R, et al. Comparison of the effects of erythropoietin and its carbamylated derivative on behaviour and hippocampal neurogenesis in mice. Neuropharmacology. 2011; 60: 354-364.

35. Miu AC, Olteanu AI, Chiş I, Heilman RM. Have no fear, erythropoietin is here: Erythropoietin protects fear conditioning performances after functional inactivation of the amygdala. Behav Brain Res. 2004; 155: 223-229.

36. Osborn M, Rustom N, Clarke M, Litteljohn D, Rudyk C, et al. Antidepressant-Like Effects of Erythropoietin: A Focus on Behavioural and Hippocampal Processes. PLoS One. 2013; 8: 1-9.

37. Onaolapo OJ, Paul TB, Onaolapo AY. Comparative effects of sertraline, haloperidol or olanzapine treatments on ketamine-induced changes in mouse behaviours. Metab Brain Dis. 2017; 32: 1475-1489.

38. Ximenes NC, Dos Santos Júnior MA, Vasconcelos GS, Dias KCF, Jucá MM, et al. Ethanolic extract of Erythrina velutina Willd ameliorate schizophrenia-like behavior induced by ketamine in mice. J Complement Integr Med. 2018: 1-8.

39. Onaolapo OJ, Ademakinwa OQ, Olalekan TO, Onaolapo AY. Ketamine-induced behavioural and brain oxidative changes in mice: an assessment of possible beneficial effects of zinc as mono- or adjunct therapy. Psychopharmacology (Berl). 2017; 234: 2707-2725.

40. Robinson S, Corbett CJ, Winer JL, Chan LAS, Maxwell JR, et al. Neonatal erythropoietin mitigates impaired gait, social interaction and diffusion tensor imaging abnormalities in a rat model of prenatal brain injury. Exp Neurol. 2018; 302: 1-13.

41. Jantzie LL, Oppong AY, Conteh FS, Yellowhair TR, Kim J, et al. Repetitive neonatal erythropoietin and melatonin combinatorial treatment provides sustained repair of functional deficits in a rat model of cerebral palsy. Front Neurol. 2018; 9.

42. Marešová D, Kozler P, Miletínová E, Zima T, Pokorný J. Locomotion in young rats with induced brain cellular edema – effects of recombinant human erythropoietin article abstract. 2018; 39: 310-314.

43. Hralová M, Plaňanská E, Angerová Y, Jadwiszczoková A, Bortelová J, et al. Effects of a single dose of erythropoietin on motor function and cognition after focal brain ischemia in adult rats. Prague Med Rep. 2014; 115: 5-15.

44. Yadav M, Parle M, Sharma N, Jindal DK, Bhidhasra A, et al. Protective effects of Spinacia oleracea seeds extract in an experimental model of schizophrenia: Possible behavior, biochemical, neurochemical and cellular alterations. Biomed Pharmacother. 2018; 105:1015-1025.

45. Chatterjee M, Ganguly S, Srivastava M, Palit G. Effect of "chronic" versus "acute" ketamine administration and its "withdrawal" effect on behavioural alterations in mice: Implications for experimental psychosis. Behav Brain Res. 2011; 216: 247-254.

46. Chatterjee M, Singh S, Kumari R, Verma AK, Palit G. Evaluation of the antipsychotic potential of panax quinquefolium in ketamine induced experimental psychosis model in mice. Neurochem Res. 2012; 37: 759-770.

Correspondence to:

Prof. Amer Kamal
Arabian Gulf University
College of Medicine and Medical Sciences
P.O. Box 26671
Manama. Bahrain
Tel: (+) 973 36622801
Fax: (+) 973 17271090
e-Mail: amerha@agu.edu.bh