INT. J. BIOL. BIOTECH., 23 (3): 565-571, 2026. *DOI:https://doi.org/10.65014/ijbb.v23iii.08*

GLYCINE ATTENUATES NOISE STRESS–INDUCED ALTERATIONS IN ANTIOXIDANT ENZYMES AND BRAIN NEUROTRANSMITTERS

Irfan Sajid*, Hafsah Khan, Munawar Abbas, Ayesha Farooq, Muhammad Sohail Khan and Zanobia Gulzar

Department of Biochemistry, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan
*Corresponding author: Irfan Sajid (irfan.sajid@fuuast.edu.pk)

Received: June 25, 2026; Accepted: July 30, 2026

ABSTRACT

Glycine, the simplest amino acid, acts as an inhibitory and excitatory neurotransmitter that regulates central nervous system functions. Other biochemical molecules that have an impact on bodily functions are metabolized with the help of glycine. Stress is a common challenge encountered during everyday activities. There has been a correlation between neurological functions and the perturbation of cerebral levels of neurotransmitters. The study was designed to find out that glycine supplementation on an antioxidant system under noise stress. Eighteen rats were randomly allocated into three groups: control, noise stress, and noise stress + glycine. Noise stress was given to the animals by exposing to the sound >110 dB for 3 hrs. After 15 days, rats were euthanized, and brain tissues were collected for antioxidant analysis including Malondialdehyde, Superoxide dismutase (SOD) and catalase while neurochemical estimations including Dopamine (DA) and Serotonin. Results showed that glycine attenuates stress effects and significantly ($p<0.05$) improves the antioxidant system with its neurochemical contents of rats. Antioxidant enzymes, dopamine and serotonin levels increased >95% following glycine administration. It is concluded that glycine in noise stressed rats significantly improved antioxidant defense system and improved neurochemical functions in rats.

Key words: Glycine, Malondialdehyde, Superoxide dismutase, Dopamine, Serotonin

INTRODUCTION

Glycine assists in facilitating the processing of both sensory and motor signals that enables motion, visual perception, and hearing at glycinergic circuits of retinal, spinal cord related and caudal brain type. It has been studied that Glycine, which is one of the high contents in glutathione as important factor to protect porcine oocytes in vitro. Further experiments demonstrate that its action is very similar to that of protecting the process of egg cell maturation and development from damage by bio membranes, due to lipid metabolism under the influence of ROS (Gao *et al*., 2023). Other studies also reported the antioxidant and anti-inflammatory properties of Glycine (Gly), and warned it to be associated with regulating apoptosis in different models and its implication in the functional amino acid with ability to protect liver from lipopolysaccharide induced-injury in mice models (Zhang *et al*., 2020). A study revealed that chemicals introduced into the body, especially benzene, will be detoxified. Unfortunately, at the detoxification process, sometimes benzene can produce free radicals. MDA compounds (malondialdehyde) are generated in the process of free radical oxidation of lipids. The body will react to these free radicals, in order to overcome them, it will form the Glutathione enzymes. They also said the workers should aim to consume foods rich in glutathione enzymes (broccoli or spinach), to reduce the impact of free radicals due to benzene inhalation and neutralize them (Tualeka *et al*., 2019). Janjira *et al.* (2023) in their work stated that functional decrease of physiological systems during ageing leads to age-related diseases. They suggested that dietary glycine increases healthy lifespan in model organisms and might decrease inflammation in humans, suggesting its Gero protective potential. longer-term glycine administration improved sleep in healthy populations. Previous studies also explained that chronic and degenerative diseases are caused by oxidatively damaged and dead cells due to the presence of toxic reactive oxygen species (ROS) and reactive nitrogen species in cigarette smoke (Korschelt *et al*., 2017). The synthesis of the Gly-Cu (OH)2 NPs, embedded in the cigarette filter, was a great success in removing ROS from the smoke, which prevented the cigarette filter cell lines from being affected by its cytotoxicity. Due to their stability, mass production and versatility, they are useful for many different applications in environmental chemistry, biotechnology and medicine (Korschelt *et al*., 2017). Different temporal noise patterns have been reported to be rising in aquatic environment, and different physiological processes and sensory function of the reference fish model are affected, showing that the overall acoustic energy of noise or environmental sound has the most important effect on the prediction of its impacts (Wong *et al*., 2022). Chronic stress appears to be linked to significant alterations in

neuronal morphology and function in several areas, which are linked to deficits in emotions, memory and learning. According to previous research, stress can cause rats to exhibit behaviors like anxiety and depression (Lee *et al*., 2013). Right after being exposed to persistent, unexpected moderate stress, researchers discovered a connection between behavioral modifications and the brain's amino acid metabolism (Chen *et al*., 2015). When rats are exposed to noise stress, the sympatho-adrenal medullary system and the hypothalamic-pituitary-adrenocortical axis are activated, and the rises of plasma adrenaline levels are decreased. Given that stress is only a reaction to stimuli that interrupts our state of equilibrium, either physically or mentally.

It has been studies that dopamine can activate trace amine receptors and that receptors are exclusively expressed on the trigeminal nucleus pars caudalis, Dopamine might act on putative pre-synaptic trace amine receptors, rather than classical DA receptors, to inhibit glycinergic transmission onto substantia gelatinosa neurons of the trigeminal nucleus pars caudalis (InSun *et al*.,2010). The goal of the current study is to assess how glycine attenuated a variety of antioxidant functions in stress treated animals as well as neurochemical performance, along with its influence on physiological variables.

MATERIAL AND METHODS

Eighteen albino Wister rats were locally bred obtained from Aga Khan University Hospital. Upon arrival, animals were housed individually in a peaceful environment with a standard light/dark cycle and maintained surrounding thermometric reading. Animals had ad libitum access to standard rodent diet and water. Initially rats habituated at least 3 days before experimentation. Animals have been split into three groups; control is given saline while one test group is exposed to noise stress (Rats were exposed to >110 dB noise 3 h daily) (Haider *et al.,* 2016) and second test group is given i.p. glycine (200mg/kg) and noise stress both. Saline was administered into control group of rats (1ml/kg). All protocols are approved by the institutional ethical care committee (Ref # EIRB-09008/2026).

Oxidative parameters:

MDA. SOD and catalase levels were estimated in brain sample. Brain homogenate was taken and subsequently, proceeded to reaction by centrifugation. The mixture centrifugation was carried out then cooled down and absorbance was measured at 532 nm utilizing the supernatant (Madiha *et al.,* 2023).

Determination of Brain DA and DOPAC levels:

For the determination of brain dopamine levels, homogenization of frozen brains was carried out in an extraction medium using an electrical homogenizer. The neurochemical analysis was done to assess the concentration of dopamine in brain as described by Madiha *et al.,* (2023).

Statistical Analysis:

Data of complete experiments are represented as values of means with standard deviations. SPSS software of version 20.0 used for statistical analysis. Data from antioxidant enzymes estimations and neurochemical experiments evaluated by using one-way ANOVA with Tukey's post hoc analysis subsequently applied. p values <0.05 were considered as significant values.

RESULTS

Effect of 14-day noise stress and intraperitoneal administration of glycine for 14 days on MDA Levels in rats shown in figure 1. Data was processed through one way ANOVA shows significant effect $F(2, 15) = 26.743$, $p<0.05$) of noise stress and glycine on MDA. Noise stress increases oxidative damage to membranes that showed a reversive effect by administration of glycine.

Effect of 14 days noise stress and intraperitoneal administration of glycine on SOD Levels in rats expressed in figure 2. Data processed through one way ANOVA shows significant effect $F(2,15) = 33.263$, $p<0.05$) of noise stress and glycine on superoxide dismutase. Noise stress increases the SOD levels showing protection response against oxidative stress and administration of glycine further increase and provide more protection against formation of oxidative radicals as shown in figure.

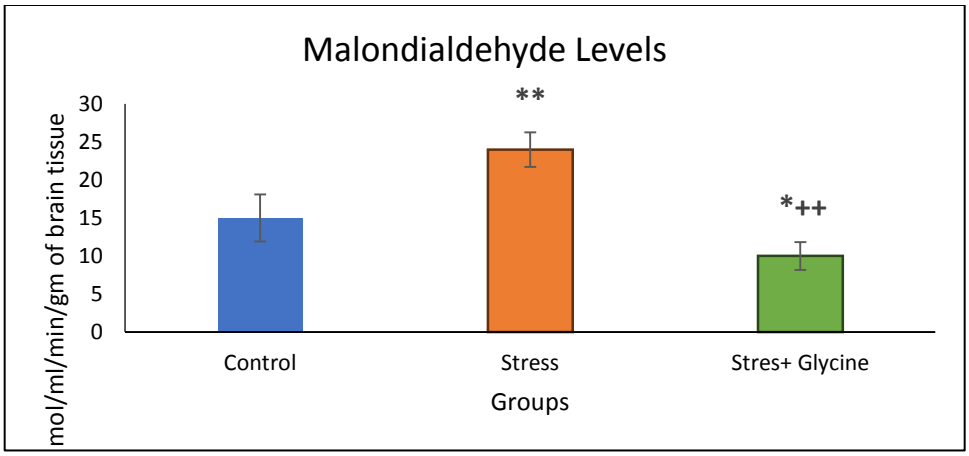

Fig. 1. Values are mean ± significant results by Tukey's test following One-way Anova **P<0.01>*P<0.05 vs Control, ++P<0.01 vs Stressed rats.

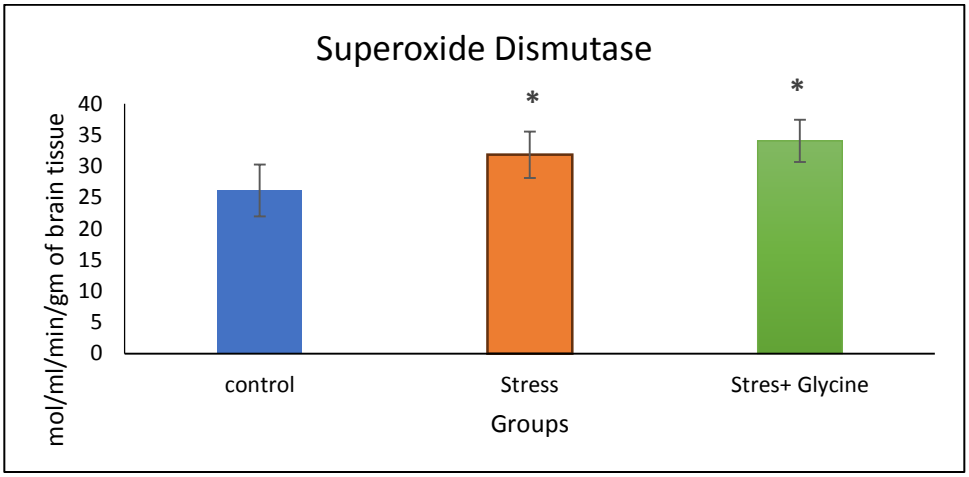

Fig. 2. Values are mean ± significant results by Tukey's test following One-way Anova *P<0.05 vs Control.

Effect of 14-day noise stress and intraperitoneal administration of glycine on Catalase activity in rats shows figure 3. Data processed through one way ANOVA shows significant effect F (2,15) = 160.368, p<0.05 of noise stress and glycine on depression. Noise stress was observed to lowering activity of Catalase as it was reversed by administration of glycine and protecting against oxidative damage.

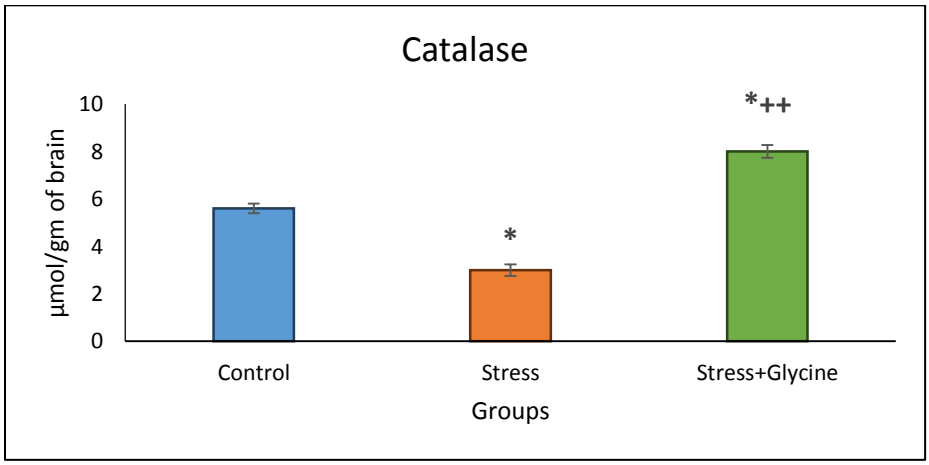

Fig. 3. Values are mean ± significant results by Tukey's test following One-way Anova *P<0.05 vs Control, ++P<0.01 vs Stressed rats.

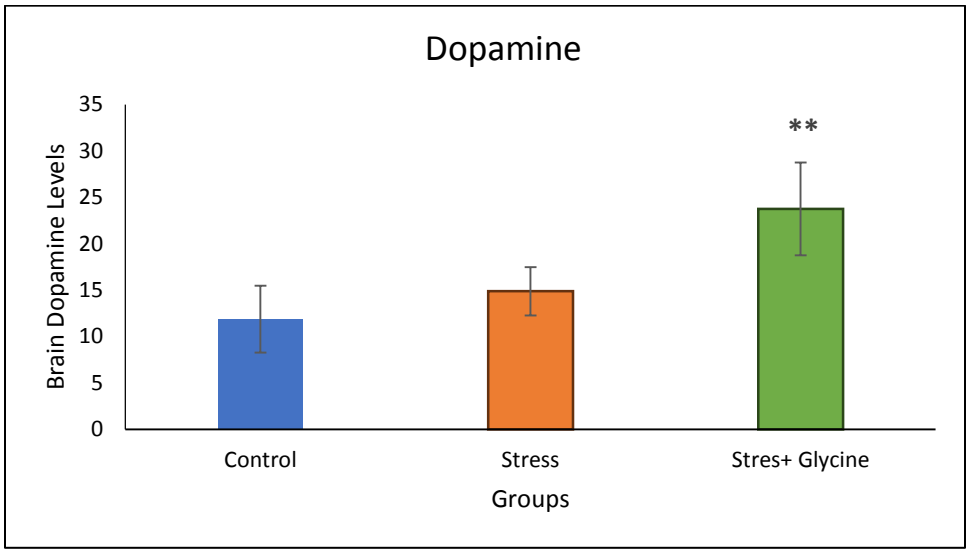

Fig. 4. Values are mean ± significant results by Tukey's test following One-way Anova **P<0.01 vs Control.

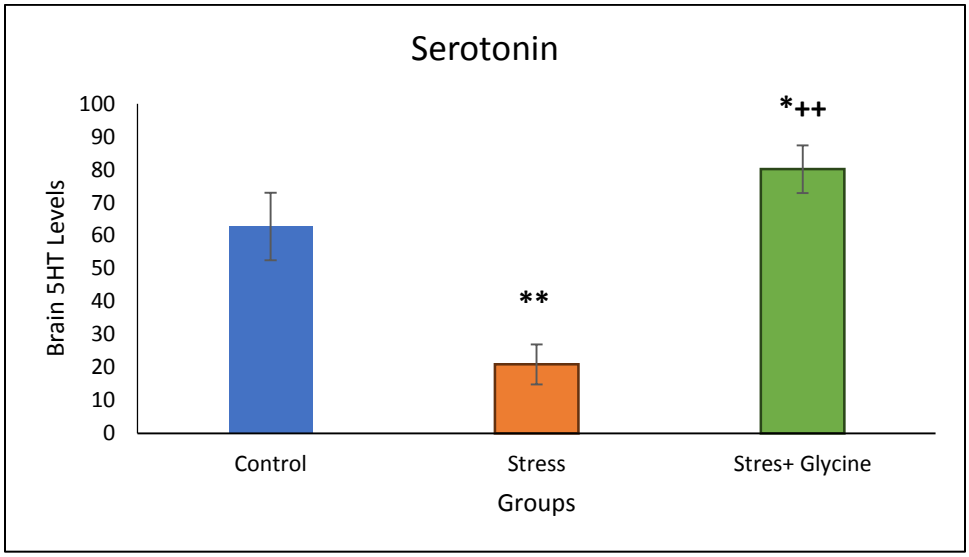

Fig. 5. Values are mean ± significant results by Tukey's test following One-way Anova **P<0.01>*P<0.05 vs Control, ++P<0.01 vs Stressed rats.

Effect of 14-day noise stress and intraperitonially administration of glycine on Brain Dopamine and 5HT levels show in figure 4 and 5 respectively. Data processed through 1-way ANOVA shows significant effect F (2,15) = 759.747, p<0.05 of noise stress and glycine on Brain Dopamine levels. It was observed that noise stress increased dopamine level but administration of glycine further increase the DA levels in brain. Data processed through 1-way ANOVA shows significant effect F (2,15) = 547.191, p<0.05 of noise stress and glycine on Serotonin levels. It was observed that noise stress increased serotonin level that was attenuated by administration of glycine.

DISCUSSION

The current research showed the effect of glycine on noise stress in animals through antioxidant and neurochemical estimations. Glycine at a dose of 200mg/kg administered intraperitoneally in rats showed attenuated effects on MDA levels as well as on catalase and SOD activities. As well as noise stress effect also altered by glycine administration in case of neurochemical analysis in rats.

Previous studies have documented that oxidative stress occurs very commonly after spinal cord injury and may lead to secondary injury to spinal cord and skeletal muscle atrophy. Research was also conducted that showed N-acetylcysteine and glycine to have anti-aging and anti-oxidative stress properties. This study indicated that after spinal cord damage, GlyNAC induced tissue protection in the spinal cord and functional recovery in rats and provided a delay of the development of skeletal muscle atrophy (Xu *et al*., 2024). Additionally, it has been shown that stress activates the hypothalamus-pituitary-adrenal axis and affects a wide range of neurological activities both centrally and peripherally. Moreover, many forms of stress have an impact on brain functioning and may contribute to several neurodegenerative illnesses (Esch *et al.,* 2003). Present studies show that glycine administration lowers MDA levels which reflects its protective action. Stress may produce alterations in neurological systems and most of the disorders result due to attack of free radicles on neuron results in damaging. As in current study administration of glycine attenuated effects of noise stress regarding antioxidant enzyme levels.

The study by Wong *et al*., (2022) revealed that anthropogenic noise, which varies considerably in temporal structure, is rising in aquatic habitats and can induce physiological stress and sensory impairment. But they also pursued the information they had at their disposal—and that is that there is little information to date available on how different noise time regimes affect a reference fish model, and how the overall acoustic energy relates to effects—important for noise sustainable management (Wong *et al*., 2022). Recent studies also explore the effect of noise stress on oxidative markers. Noise treated rats show alterations in antioxidant activity that are told about the deteriorations of stress in brain.

Adermark *et al*., (2011) reported that elevated levels of dopamine are thought to play a role in the reinforcing actions of ethanol, and that increased concentration of glycine can enhance the release of dopamine may play a role in the reinforcing effects of ethanol that occur through strychnine-sensitive glycine receptors in the nucleus accumbens. Others also accounted for the rewarding and reinforcing effects of ethanol by activation of the mesolimbic dopamine system, which is thought to be glycine receptor dependent within the nucleus accumbens (Loftén *et al*., 2023). Current study shows the effect of glycine administration results in increase in dopamine levels. Stress causes mild increase in dopamine levels that are increased further by glycine possibly activating the countering the mesolimbic dopamine system.

The researchers explained in prior studies that glycine transport across the blood brain barrier seems to be inefficient, but glycine containing dipeptides raises levels of dopamine in whole brain tissue of mice. The tentative correlation between dopamine baseline and subsequent response to glycinergic treatment and assumed direct interactions between glycine-containing dipeptides and the GlyR suggest ways for further optimizing the glycinergic approach to AUD (Olsson *et al*., 2022).

In some previous studies, CSF, serotonin and glycine were shown to be significantly correlated with the pain mechanism in body. These results indicate that serotonergic and glycinergic systems might contribute to a modulation mechanism in the spinal cord for visceral pain (Chalermkitpanit *et al*., 2017). It was suggested that serotonin and melatonin are molecules that play a role in signaling, as well as stress reducing. However, their role and molecular mechanism in the accumulation of isoflavones are not clearly defined. under serotonin and melatonin treatments, ethylene biosynthesis may play a role in the alterations in isoflavone content in plant culture (Kumar *et al*., 2021). Neurotransmitters are found to be very important in the nervous system and abnormalities in their level are known to be responsible for neurodegenerative diseases and some recent developments in the design of new organic receptors used for the detection of neurotransmitters such as monoamines, amino acids such as glycine (Chemchem *et al.,* 2022). Previous literature showed that glycine may interact by binding to insulin receptors (Caraiscos *et al.,* 2007). Moreover, the level of serotonin in restraint glycine treated animals is decreased and stressed animals showed increase serotonin level as compared to control. Present study also showed that noise stress results in increase in serotonin level which further enhances due to glycine administration.

CONCLUSION

The intraperitoneal administration of glycine reduced stress induced effects on antioxidants and neurochemicals. Present work showed that glycine enhances antioxidant system by attenuating the minimized effects of stress in animals. Current results explain that stress alters the neurochemical secretion that could impair the neuronal system this abnormal effect can be altered by glycine administration and improves the antioxidant defense system as well as neurochemical molecules that could improve the brain functions.

CONFLIUCT OF INTEREST

Authors declare no conflict of Interest

FUNDING

Authors receive no external funding

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