Gonchar O.O.[1], Klyuchko O.M.[2], Mankovska I.M.[1]

N-acetylcysteine neuroprotective effect on restraint-induced oxidative stress in rat brain

[1]Bogomoletz Institute of Physiology National Academy of Sciences of Ukraine, Kiev, Ukraine

[2]National Aviation University, Kiev, Ukraine

Restraint as neuroendocrine stress leads to the elevation of stress hormones and increased metabolic rate, which is accompanied by oxidative damage, antioxidant disorders and disruption in cellular redox state. Glutathione is crucial for neuroprotection in brain under stressful conditions since directly reacts with reactive oxygen metabolites and electrophilic intermediates, maintains intracellular redox homeostasis [1]. Therefore compounds modulating GSH biosynthesis such as GSH precursor N- Acetylcysteine (NAC) can play more significant role in providing of oxidative insult protection. However, mechanisms of NAC positive effect were examined insufficiently. NAC influence on intensity of oxidative processes and glutathione system state of rat brain under restraint exposure was studied. Wistar rats were divided into groups: 1- served as control; 2- animals, which were exposed to restraint for 6h; 3- rats, which were exposed to restraint and received NAC. NAC (100mg/kg) was administered i.p.once per day for 1week prior to restraint exposure. The restraint was performed using plastic rodent restrainer that allowed limiting rat movement. In brain homogenates the contents of secondary products of lipid peroxidation (LPO) were determined. To assess the state of glutathione pool, an amount of oxidized (GSSG) and reduced (GSH) glutathione, as well as activity of GSH-dependent and $NADP^+$ -generating enzymes were measured. Protein expression of GSH-related enzymes was evaluated by Western blot analysis. We found that 6h restraint caused intensification of LPO, significant reduction of GSH content and GSH-related enzymes that denoted disorders in GSH biosynthesis, absence of adequate antioxidative defense in rat brain after restraint exposure. Our results indicated that prophylactic NAC administration weakened oxidative processes. Thus, we registered a decrease in content of secondary products of LPO and GSSG, an increase in ratio GSH/GSSG in comparison with restraint group. Pretreatment with NAC diminished stress-induced overactivation of MnSOD to control level. Gradual recovery of glutathione pool was promoted by increase in activity of glutathione reductase and $NADP^+$ -isocitrate dehydrogenase that confirm enhancement of NADPH level, required for regeneration of GSH from oxidized glutathione. Increased activity and protein expression of glutathione peroxidase and γ-glutamylcysteinyl ligase indicated both increase of antiperoxide protection and inductions of GSH recycle. Neuroprotective actions of NAC under re-

straint stress were also confirmed by significant decrease in corticosterone concentration, which was important indicator of stress state. Thus, NAC administration restored restraint-induced depleted antioxidant glutathione pool and free radical scavenging enzyme system in brain. Since glutathione is major antioxidant in brain, modulation of its biosynthesis by NAC through upregulating key enzyme for glutathione biosynthesis γ-glutamylcysteinyl ligase, recovery of GSH recycle and as consequence cellular redox state could be mechanisms that protect neuronal cells under oxidative stress conditions.

References

1. Gonchar O., Klyuchko E., Mankovskaya I. Role of complex nucleosides in the reversal of oxidative stress and metabolic disorders induced by acute nitrite poisoning. Indian Journal of Pharmacology, 38(6), 2006, p. 414-418.