ORIGINAL ARTICLES

Brain oxidative stress in the syndrome of mutual aggravation on the model of combined injury in Mongolian gerbils

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General reaction of an organism (survival, body temperature, hematocrit, glycemia) was followed in Mongolian gerbils subjected to isolated head injury (brain ischemia – LD_5), to peripheral injury (ischemia of both hind limbs – LD_{20}), and to combined injury (head injury + peripheral injury). In the early period (1 hour) after the injury, parameters of oxidative stress were followed in the brain cortex (superoxide anion, index of lipid peroxidation, activity of superoxide dismutase and glutathione reductase). Obrained results indicate that the combined peripheral and central injury of low lethality leads to the worsening of general response of the organism with high lethality of experimental animals (LD_{80}). Likewise, the increased cortical production of superoxide anion and index of lipid peroxidation, as well as the disturbances of antioxidative enzymes activity suggest on an important role of brain oxidative stress in the development of the syndrome of mutual aggravation in animals subjected to combined injury.

Key words: **multiple trauma; brain ischemia; extremities; ischemia; oxidative stress; superoxide dismutase; glutathione peroxidase; lipid peroxidation.**

Introduction

Nowdays, in modern life conditions, combined injury as a form of polytrauma with the same etiological factor (mostly mechanical force) inducing the damage of different parts of an organism, represents one of the most frequent ways of injury. The specificity of combined injury includes the changes in the severity, duration or patterns of general response induced by the basic injury, due to the simultaneous reaction of the organism to the associated injury (1). The most frequent result of the combined injury is potentiation, because of additive effects. It means that the effects of associated activity of two injuries exceed the addition of isolated effects of these injuries acting separately, which represents the syndrome of mutual aggravation (1, 2).

One of the most severe forms of combined injury develops when, besides the damage of peripheral tissues, head injury is also present (3). Changes in peripheral tissue damage could influence the central nervous system (CNS) by neural (afferent impulses from injured region, muscles or blood vessels), and humoral (transmission of toxic metabolites and mediators by the circulation) interaction periphery-CNS-periphery (4, 5). These changes cause the increased activity of neuronal cells, i. e. enhanced metabolic activities and oxygen utilization (6). However, developed hypovolemia and reduced brain circulation induce the disbalance between supply and neuronal demand for oxygen (7). Besides, it has been shown that more than 90% of patients with head injury have brain ischemic lesion distributed in the territory vascularized by some of the main brain arteries (4, 8).

Disturbance of cell energy metabolism is one of the earliest changes induced by tissue ischemia: contents of ATP, glucose and P-creatine are decreasing, and processes of anaerobic metabolism are enhancing (7, 9, 10). There is a tissue overproduction of the reduced equivalents that is characterized as the reductive stress (11). Superoxide anion

is released from the places of oxygen transport in mitochondrial respiratory chain. The xanthine oxidase reactions are also the source of hydrogen peroxide, superoxide radical and "singlet" oxygen (12, 13). Reactions between these reactive oxygen metabolites with biological macromolecules generate secondary molecules with characteristics of free radicals, which mediate the damage of membranes, enzymatic and other cell systems (14). Resuscitation of circulation in the previous ischemic brain region leads to relative tissue hyperoxia, which initiates the production of active oxygen metabolites, making the conditions for spatial and temporal propagation of free radical reactions (oxidative stress) (15). Oxidative damage of polyunsaturated fatty acids from cellular and subcellular membrane phospholipids induces the formation of lipid peroxides, which cause the disturbances in membrane permeability and receptors, as well as in enzymatic systems, including the enzymes of antioxidative defense (superoxide dismutase – SOD, glutathione peroxidase – GP, glutathione reductase – GR etc.) (11).

According to the represented facts we have proposed that brain oxidative stress caused by head injury could be one of the possible mechanisms leading to disturbances of central regulation of general response to the injury of peripheral tissues, with consequent development of mutual aggravation syndrome in combined injuries. Based on the importance of preserved CNS functional and morphological integrity, the aim of our investigation was to define the general protective response of the organism (survival, body temperature, hematocrit, glycemia) and brain oxidative stress (production of superoxide anion, activity of antioxidative enzymes, index of lipid peroxidation) in animals subjected to isolated head and peripheral tissue injury, as well as to both injuries simultaneously (combined injury).

Methods

Mongolian gerbils (*Meriones unguiculatus*) of both sexes, body mass from 60–80 g, and mean age of 15 weeks were used in all experiments (16). As a model of brain ischemia (correlate of head injury) was used the ligation of the both common carotid arteries (17). Mutual ischemia of hind limbs, according to Rosenthal, was the model of peripheral trauma (18). Simultaneous application of head and peripheral tissue injuries was the model of combined injury.

The investigation comprised three experimental and two control groups with 10 animals in each group:

Group I: animals subjected to head injury (brain ischemia with duration of 5 minutes – LD_5).

Group II: animals subjected to peripheral tissue injury (ischemia of hind limbs in duration of 32 minutes – LD_{20}).

Group III: animals subjected to combined injury (brain ischemia was induced during the last 5 minutes of hind limbs ischemia, which lasted 32 minutes).

Control for the experimental group II were intact animals, and for groups I and III were sham operated animals (neck incision).

Samples of blood and tissues (brain cortex) for the appropriate analysis were collected 1 hour after the each treatment.

The survival and body temperature were followed during 48 hours. Temperature of the room in which animals stayed, as well as of the room for the experiments was maintained on 20–22°C. Values of hematocrit were determined in the blood obtained during the decapitation of animals. Glycemia was measured by enzymatic method with glucose oxidase (19).

Activity of SOD and GR, superoxide anion production, and index of lipid peroxidation were measured in brain tissue homogenate (cortex). After the decapitation, heads of animals were immediately frozen and stored on −70°C. During the tissue preparation brain cortex was separated on cold and homogenized in the cold sucrose medium (0.25 mol/L sucrose and 1 mmol/l EDTA in 10 mmol/l K,Na- phosphate buffer pH 7.4). Obtained homogenate was centrifuged on 2000 x g during 15 minutes on +4°C; supernatant was separated and sediment resolved in 1 ml of the sucrose medium and centrifuged again. Afterwards, supernatant was centrifuged on 3200 x g during 30 minutes on + 4°C and obtained sediment was resolved in 1 ml of deionized water. After the incubation of 1 hour, sample was centrifuged on 3000 x g during 15 minutes on +4°C and supernatant (crude mitochondrial fraction) was stored on −70°C (20). Protein content in samples was determined according to the method of Lowry (21).

Activity of SOD was measured as % of inhibition of epinephrine autooxidation with sample of crude mitochondrial fraction, in basic conditions (22).

Activity of GR was determined fluorimetrically: in the presence of NADPH, glutathione reductase reduced glutathione disulfide with generation of reduced glutathione and $NADP^+$; oxidized form of coenzyme was transformed in highly fluorescent derivative by strong base (23).

Index of lipid peroxidation was determined spectrophotometrically by measurement of products concentration, generated in the reaction of thiobarbituric acid with degradation products of polyunsaturated fatty acids (malondialdehyde – MDA), after the *in vitro* stimulation of peroxidaton (24–26).

Student's t-test for the independent samples was used for the evaluation of statistical differences between the examined parameters. Correlation between single measured parameters was determined by measurement of linear correlation coefficient.

Results

Survival of 48 hours duration was observed in 95% of animals subjected to brain ischemia, 80% of animals with hind limbs ischemia, and only 20% in the group with combined injury (Fig. 1). Differences in animal survival, obtained by associating of head and peripheral tissues injuries of low lethality, was highly significant ($p<0.001$).

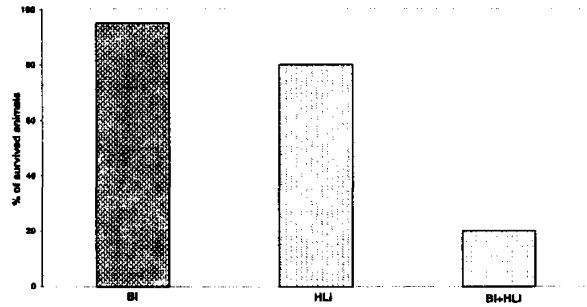

Fig. 1 – Survival of Mongolian gerbils after brain ischemia (BI), hind limb ischemia (HLI), and combined injury (BI + HLI).

Body temperature, 1 hour after the injury of peripheral tissues, was 93% of control value (37.3 ± 0.1 °C), but it was 86% of controls in the group with combined injury (Fig. 2).

Increase of hematocrit was the most pronounced in the group subjected to combined injury, and was about 150% of control values (Fig. 2).

Values of glycemia were increased about 113% in the group with head injury, 370% in peripheral injury, and 394% in combined injury, compared to control (5.5 ± 0.5 mM/l) (Fig. 2).

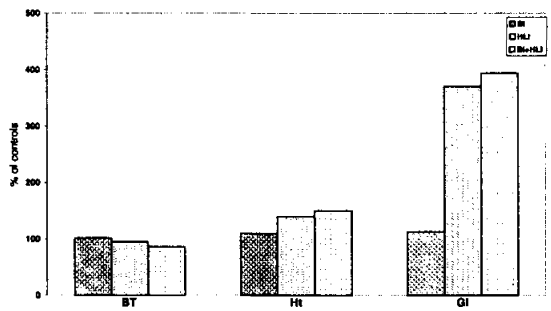

Fig. 2 – Values of body temperature (BT), hematocrit (Ht), and glycemia (Gl) in Mongolian gerbils 1 hour after brain ischemia (BI), hind limb ischemia (HLI), and combined injury (BI + HLI). Presented values are significant, compared to control values (Student's t-test; $p < 0.001$).

Increase in superoxide anion production was significant in all examined groups, compared to control values (90.5 ± 6.5 nM/min/mg prot.) (Fig. 3).

Also, compared to controls (82.2 ± 6.7 nM/h/mg prot.), index of lipid peroxidation 1 hour after the injury showed significant increase in all groups, with maximal values (190% of controls, $p<0.01$) in combined injury (Fig. 3).

Increased activity of SOD in brain cortex of animals subjected to combined injury was about 122% of the control (302.6 ± 19.9 U) ($p<0.01$) (Fig. 4).

Activity of GR was increased about 172% in the group with head injury, 152% in peripheral injury, and 151% in combined injury, compared to controls (40.1 ± 6.9 nM/min/mg prot.) (Fig. 4).

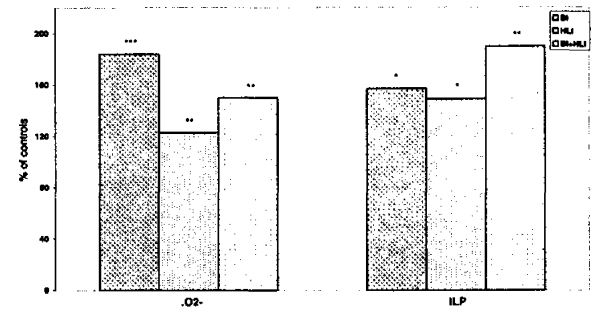

Fig. 3 – Production of superoxide anion ($.O_2^-$) and index of lipid peroxidation (ILP) in the brain cortex of Mongolian gerbils 1 hour after brain ischemia (BI), hind limb ischemia (HLI), and combined injury (BI + HLI). Presented values are significant compared to control values (Student's t-test; * $p< 0.05$, ** $p< 0.01$, *** $p< 0.001$).

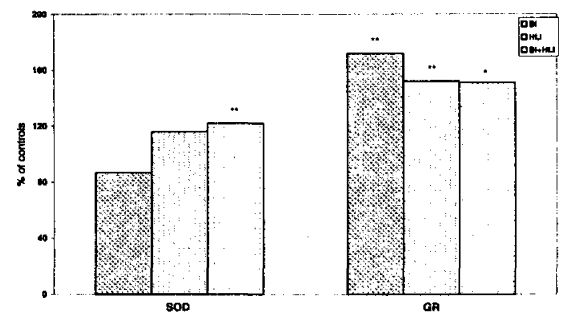

Fig. 4 – Activity of SOD and GR in the brain cortex of Mongolian gerbils 1 hour after brain ischemia (BI), hind limb ischemia (HLI), and combined injury (BI + HLI). Presented values are significant, compared to control values (Student's t-test; * $p< 0.05$, ** $p< 0.01$).

Discussion

Intact functional and morphological integrity of CNS is the clue for maintenance of homeostasis and regulation of general response to trauma (3). It is assumed that changes in brain functions, without regard to be the sequelae of direct CNS injury, or they occurred indirectly, as the result of peripheral tissue injury, basically modify complex interaction (homeostasis) in the response of each organ and organic system to injury (27).

Presented results indicate that CNS injury, as a part of combined injury, substantially aggravates the course and final outcome in comparison to peripheral tissue injury of similar severity. Simultaneous application of injuries with low lethality of peripheral tissue (LD_{20}) and CNS (LD_5), resulted in high mortality of experimental animals (LD_{80}), which could be the consequence of modified general response to trauma by CNS (Fig. 1). Inadequate regulatory and integrative function of CNS could occur as a result of disbalanced central regulatory mechanisms by afferent nerve impulses and mediators/modulators transmitted from

the damaged peripheral tissue, as well as locally released mediators in the CNS.

The main acute effect of extremity ischemia according to Rosenthal is the loss of volume from the circulation to the injured tissue with consequent development of edema (10, 28). Hypovolemia of different degree is the result of these mechanisms, that is followed by hemoconcentration, manifested by fast and significant hematocrit increase, the most pronounced in combined injury (Fig. 2).

One of the protective reactions of an organism, which compensates posttraumatic hypovolemia, is the increase of glycemia after the injury. There has been shown a correlation between posttraumatic hyperglycemia and severity of trauma, which well reflects the degree of the response to trauma (10). In our investigations we have also found the increased glycemia 1 hour after the trauma, with the maximum in the group with combined injury (Fig. 2).

Early posttraumatic period is characterized by endogenous hypothermia. Our results showed that 1 hour after the peripheral injury body temperature was 93%, and 86% of controls in combined injury (Fig. 2).

The degree of body temperature decrease depends on the trauma severity. Besides, there is a significant correlation between posttraumatic hypovolemia and decrease of body temperature (10). Decreased body temperature in the early posttraumatic period could be the result of diminished heat generation, which is a consequence of changes in central thermoregulatory mechanisms of hypothalamus (29).

It could be concluded that protective character of the acute phase of general response to the injury includes the adequate supply of energy substrate with easily utilization (glucose), and by the decrease of metabolism to the basic level an organism stores energy for the later demands in hypermetabolic phase. It is obvious that the acute posttraumatic period is the best defined by posttraumatic hyperglycemia, hypothermia and hemoconcentration on represented models of peripheral tissue injury, as well as combined peripheral and central injury on Mongolian gerbil.

Reduced cerebral blood flow, caused by posttraumatic hypotensia, hemoconcentration and diffuse afferent nerve stimulations, leads to the decreased supply of CNS with oxygen and consequent ischemic damage of neurons. One of the hypotheses in this investigation was that oxidative stress initiated by ischemia could lead to biochemical changes in neuronal cells, followed by changes in biomolecules, as well as in adaptive response to ischemia. We measured the production of active oxygen metabolites and activity of antioxidative enzymes, as the indicators of oxidative stress. Index of lipid peroxidation was followed as a measure of oxidative stress severity, since this process of cell membrane damage represented the final phase (manifestation) of oxidative stress.

Damage of tissue macromolecules, mediated by free radicals, has started with superoxide anion generation (30). There was the increase of superoxide anion production in each model of injury 1 hour after the trauma. Significant correlation ($p<0.01$) was found between index of lipid peroxidation and generation of superoxide anion in the brain cortex of Mongolian gerbil after the both, isolated central and peripheral trauma ($r=0.82$), and combined trauma ($r=0.98$).

SOD neutralizes superoxide anion by catalysis reaction of its dismutation in which oxygen and hydrogen peroxide are generated. Activity of SOD was significantly increased in brain cortex of animals subjected to combined injury. Relative values of ratio between superoxide anion production and SOD activity 1 hour after injury were increased ($p<0.05$) compared to control value (1), and were $r=2.34$ in brain ischemia, $r=1.34$ in hind limb ischemia, and $r=1.62$ in combined injury. Disturbed homeostasis between the increased production of superoxide anion and ability of SOD to neutralize it is manifested by the increase in values of their ratio. It is obvious that neutralization of superoxide anion was insufficient even if SOD activity was increased. Increase of superoxide anion/SOD activity could be the result of its inadequate function or reached saturation, and could be an indicator of oxidative stress intensity (15, 31–39).

Oxidative brain damage includes the generation of some other reactive oxygen species. Hydrogen peroxide, in reaction with superoxide anion, is converted in more reactive hydroxyl radical (32). Scavenging of hydrogen peroxide in brain is mediated by glutathione peroxidase, which catalyses its reduction by reduced glutathione (GSH), producing the oxidized form of this tripeptide (GSSG) and water. For continuous catalytic enzyme activity, permanent reduction of GSSG to GSH is necessary that is catalyzed by NADPH-dependent glutathione reductase (GR) (32–41).

Activity of GR in brain cortex 1 hour after the injury was increased in each examined group. The lower activity of GR in combined injury, compared to the other two models of trauma, in conditions of intensive production of reductive equivalents, indicates that free radicals could induce changes in enzyme molecules by decreasing its activity. The other possibility is that free radicals could reversibly inactivate molecules of GR, since enzymes (including antioxidative enzymes) are susceptible to oxidative damage mediated by free radicals (34–50).

The main consequence of decreased GR activity is mainly related to the function of glutathione-dependent system of peroxidases. Hydrogen peroxide and other peroxides, generated in reaction of lipid peroxidation and cascade of arachidonic acid, are almost exclusively scavenged by this system. Insufficient activity of GR leads to intracellular accumulation of oxidized glutathione with consequent inadequate peroxide scavenging, maintaining the conditions for reinitiation and propagation of lipid peroxidation reactions.

It could be concluded that biochemical changes in the brain, caused by the injury, are represented by complex of closely connected reactions, which induce each other with reciprocal modulation, leading to cell damage and death by

this metabolic cascade. The disruption of central regulatory mechanisms is the consequence of these processes, including the disturbances in CNS-peripheral organs regulatory axis, which causes the aggravation of general response to trauma in combined injury of peripheral tissue and CNS (30–48).

Conclusion

Based on the results obtained in this investigation, it could be concluded that:

1. Worsening of general response to trauma (extensive hypothermia, hemoconcentration and hyperglycemia) is the sequela of CNS and peripheral tissue injury combination, followed by high lethality of experimental animals.

2. Such outcome of combined trauma is mediated by disturbances of central regulatory mechanisms caused by the developed oxidative stress in brain, a physiopathological event, which biological consequences (lipid peroxidation, disruption of antioxidative defense) are significantly connected and potentated with free radical reactions.

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ОКСИДОРЕДУКТИВНИ СТРЕС МОЗГА КОД СИНДРОМА УЗАЈАМНОГ ПОГОРШАЊА НА МОДЕЛУ КОМБИНОВАНЕ ПОВРЕДЕ КОД ПУСТИЊСКОГ МИША

Општа реакција организма (преживљавање, телесна температура, хематокрит, концентрација глукозе у крви) праћена је код пустињских мишева подвргнутих изолованој повреди главе (исхемија мозга-LD_5), периферној повреди (обострана исхемија задњих екстремитета-LD_{20}) и комбинованој повреди (повреда главе+периферна повреда). У раном периоду (1 час) после повреде праћени су показатељи оксидоредуктивног стреса у кори мозга (супер-

оксидни радикал, индекс липидне пероксидације, активност супероксид дисмутазе и глутатион редуктазе). Добијени резултати показују да удруживање повреде периферних ткива и главе ниске смртности доводи до погоршања опште реакције организма на повреду и до високе смртности експерименттних животиња (LD_{80}). Такође, добијени пораст стварања супероксидног радикала и индекса липидне пероксидације, као и поремећај активности ензима антиоксидативне одбране у кори мозга указују на значајну улогу оксидоредуктивног стреса мозга у настанку синдрома узајамног погоршања код животиња изложених комбинованој повреди.

Кључне речи: **povrede kombinovane; mozak, ishemija; udovi; ishemija; stres, oksidativni; superoksid dizmutaza; glutation, peroksidaza; lipidi, peroksidacija.**