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LPO and Antiradical Defense Processes in the Liquor of Patients with Severe Craniocerebral Injury

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Acute posttraumatic period of severe craniocerebral trauma is associated with sharp activation of LPO processes and rapid exhaustion of antioxidant enzymes and especially low-molecular-weight antioxidant system in the liquor. This leads to the development of severe oxidative stress and failure of adaptation processes during the early posttraumatic period.

Key Words: *craniocerebral injury; liquor; lipid peroxidation; antioxidant system; oxidative stress*

Recent studies demonstrated the key role of free-radical reactions in the pathogenesis of various injuries to cell structures in the CNS. The interest to the analysis of the liquor in various CNS pathologies, *e. g.* in traumatic brain injury (TBI), is determined by several factors. Changes in the blood detected in TBI depend on concomitant somatic diseases in patients, which can lead to erroneous interpretation of laboratory findings. The liquor is an "internal" medium washing the brain and closely involved in all processes in cells and intercellular structures of the brain in health and disease. Hence, the liquor sooner and more accurately than the blood reflects all changes in the CNS, which is important for the prediction of the disease course and planning the treatment and diagnostic strategy for each patient. Lipids constitute 40-70% of the CNS tissues, and therefore changes in LPO intensity and activity of the antioxidant system (AOS) are more intense in the liquor and can be detected earlier than in the blood.

The aim of our study was to evaluate the time course of LPO and AOS processes in the liquor of patients with severe TBI during specific neuroprotective drug therapy.

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MATERIALS AND METHODS

Fifteen patients with TBI (11 of these men), mean age 38.7±1.1 years, were examined. Specific neuroprotective therapy included antioxidants (tocopherol, 300 mg/day, and ascorbic acid, 250 mg/day), nootrops (encephabol, 1 g/day), calcium channel antagonists (nimotop, 1 g/day, and magnesium sulfate, 12 g/day), metabolic (actovegin, 2-4 g/day) and vascular drugs (instenone, 2-4 ml/day). Only patients requiring no forced ventilation were selected for the analysis of the clinical laboratory findings. The data of laboratory tests of 15 age- and sex-matched donors served as the normal. The group of donors was similar to the group of patients by age and sex. The severity of patient status was evaluated using classification proposed by Konovalov *et al.*[4]. The level of awakening was quantitatively evaluated as described previously [14]. We measured the concentration of MDA [8], dienic conjugates (DC) [7], and Schiff bases (SB) [9]. Superoxide generating activity was evaluated using a modified method [1], superoxide eliminating activity as described previously [13]. Imbalance coefficients (K_I) in the LPO—AOS system were estimated using our formula as the ratio of superoxide-generating to superoxide-eliminating activities. The concentration of α-tocopherol was measured as described previously [3]. The content of ceruloplasmin was evaluated by a previously described method [3].

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RESULTS

Significant activation of LPO processes was noted starting from the first days of the posttraumatic period (Table 1).

Pronounced activation of LPO processes was detected in the liquor: by the end of the first 24 h of the posttraumatic period the concentration of DC (primary LPO product) 7.8-fold surpassed the normal, the concentrations of MDA and SB surpassed the normal by 6.5 and 8.2 times, respectively ($p<0.001$). LPO activity tended to increase and by day 7 of the posttraumatic period the content of LPO products significantly surpassed the normal (9.3, 7.8, and 12.6 times for DC, MDA, and SB, respectively, $p<0.001$). The concentration of MDA correlated with the permeability of the blood-brain barrier; accumulation of MDA in biological fluids, particularly in the liquor, attests to increased permeability of this barrier (Fig. 1).

In parallel with these changes in the plasma prooxidant pool, superoxide-generating activity (an integral parameter reflecting, apart from prooxidant activity, stability of cell membranes, in our case neurocyte membranes [6]) significantly increased at all terms of the study (8.5, 11.4, 12.1 times, respectively, $p<0.001$) compared to the normal (Fig. 2).

Accumulation of prooxidants in the liquor was paralleled by an increase in SOD activity (the key enzyme of antiradical protection). During the first 24 h of the posttraumatic period its activity 3.9-fold surpassed the normal ($p<0.001$). Later SOD activity tended to decrease, but remained above the normal (by 2.4 times, $p<0.001$). SOD is an intracellular enzyme, and its drastic activation in the liquor seems to be due to its release from cells because of neurocyte membrane damage. The life-span of intracellular SOD forms outside the cell is very short, the enzymes are rapidly inactivated and cannot effectively function [2].

After a transient and sharp increase in ceruloplasmin activity during the first 24 h ($p<0.001$) this parameter dropped on days 3-7 of the posttraumatic period. This sharp increase in ceruloplasmin activity can indicate failure of adaptation mechanisms [5,11].

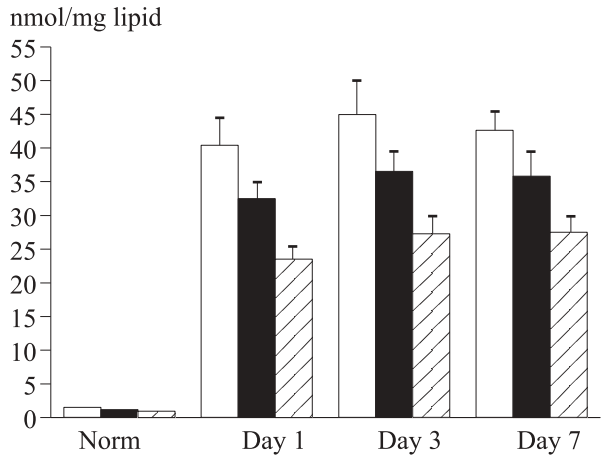

Fig. 1. Dynamics of LPO activity in the liquor of patients with severe traumatic brain injury (TBI). Light bars: dienic conjugates; dark bars: MDA; cross-hatched bars: Schiff bases.

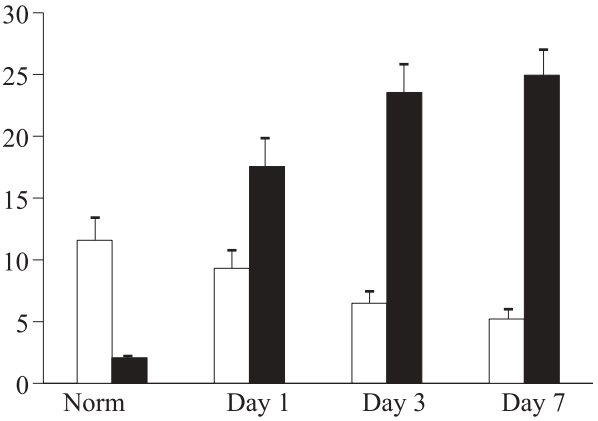

Fig. 2. Superoxide-eliminating (light bars) and superoxide-generating (dark bars) activities of the liquor in patients with severe TBI.

The content of low-molecular-weight antioxidant α-tocopherol in the liquor of patients decreased by 3.3 times in comparison with its normal level as early as by the end of the first 24 h of the posttraumatic period, while by day 7 its content dropped to 5.5% of normal ($p<0.001$). This attests to exhaustion of endogenous and late involvement of exogenous α-tocopherol in antiradical defense processes [10].

Superoxide-eliminating activity (an integral parameter reflecting activity of processes of superoxide

TABLE 1. Dynamics of AOS Parameters in the Liquor of Patients with Severe TBI ($M\pm m$; $n=15$)

Parameter	Normal	Day of analysis		
		1st	3rd	7th
Ceruloplasmin, μmol/liter	1.07±0.05	3.21±0.34*	1.87±0.18	0.64±0.07
SOD, μmol/liter	0.52±0.08	1.89±0.15*	2.40±0.31*	2.94±0.56*
α-Tocopherol, μg/liter	0.191±0.022	0.103±0.018*	0.043±0.008*	0.031±0.006*

Note. *$p<0.001$ compared to normal.

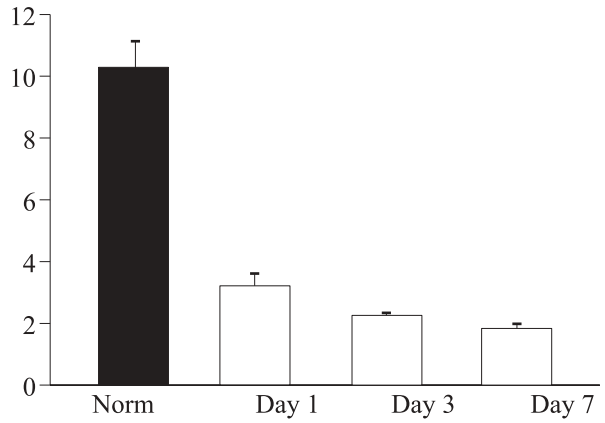

Fig. 3. Time course of imbalance coefficient in the liquor of patients with severe TBI.

anion radical elimination) increased by 78.6% compared to the normal on day 1 of the posttraumatic period ($p<0.01$), while later it progressively decreased and by day 7 its content was 2.2 times below the normal ($p<0.01$; Fig. 2).

The K_I coefficient, an integral parameter of the imbalance in the LPO—AOS system, which can be regarded as an indicator of the severity of oxidative stress, was markedly lowered during all periods of the study (31.2, 22.0, 17.8% of normal level on days 1, 3, 7, respectively, $p<0.001$), which attests to extreme severity of the oxidative stress (Fig. 3).

Hence, acute posttraumatic period of TBI is characterized by appreciable activation of LPO processes in the liquor (starting from day 1), which is associated with rapid exhaustion of enzymatic and low-molecular-weight AOS in the liquor (despite treatment with antioxidants, *e. g.* α-tocopherol acetate). Inadequate function of the antioxidant defense system in the presence of the outburst of free-radical activity can be regarded as failure of adaptation reaction resulting in aggravation of the posttraumatic period of severe TBI and its outcome, in general.

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