DIFFERENTIAL APPROACH TO TREATMENT OF THE STRESS SYNDROME DEPENDING ON STAGES OF THE PROCESS

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The response of the body to stress is realized as the general adaptation syndrome, which includes four main stages: emergency adaptation, the change from emergency to long-term adaptation, long-term adaptation, and exhaustion [2]. The process of formation of the general adaptation synchrome is accompanied by disturbance of brain bioenergetics, destabilization of permeability of neuron membranes, and disturbance of their functions [4]. The aim of this investigation was to study the possibility of a differential approach to the pharmacological correction of stress, taking account of the biochemical mechanisms of formation of its different stages. Taking into consideration data on the key role of destabilization of membrane permeability in the development of the stress syndrome, most attention was concentrated on the study of the dynamics of parameters of free-radical oxidation of lipids of biological membranes and the antioxidative defense system controlling this process.

EXPERIMENTAL METHOD

Experiments were carried out on 125 Wistar albino rats weighing 160-180 g. Chronic stress was induced by the usual method [10] by deprivation of the paradoxical phase of sleep. The biochemical tests were conducted on whole blood and on packed erythrocytes from intact and stressed animals on the 1st, 2nd, 3rd, and 4th days of stress. The total antioxidative activity (AOA) of the blood [6], concentrations of pyridine nucleotides (PN) [8], total and reduced glutathione [1], superoxide dismutase (SOD) [11], catalase [3], and glutathione reductase (GRD) activities, and also the intensity of free-radical lipid oxidation, based on the concentration of diene conjugates (DC) of unsaturated fatty acids, and the end product of free-radical oxidation (malonic dialdehyde – MDA) [7], were determined.

EXPERIMENTAL RESULTS

The first day of stress was characterized by a significant decrease in concentrations of PN and total and reduced glutathione, and also of total AOA of the blood (Fig. 1). The other parameters studied did not differ from their initial values.

The second and third days of sleep derivation were accompanied by more marked changes in the component of the antioxidative defense system. SOD activity on the 2nd day of stress was only 37% of its initial level, falling to 27% on the 3rd day ($p < 0.001$). Similar changes were observed in catalase activity. Meanwhile GRD activity rose on average by 32% compared with the first day of stress, but it was still only half as high as the initial level ($p < 0.02$). The DC level rose under these conditions on averge by 2.3 times and MDA by 60% ($p < 0.05$).

Thus formation of the stress reaction significantly modified lipid peroxidation and antiradical defense of the membranes. However, the greatest changes in the parameters studied were observed on the 4th day of sleep deprivation and were characterized by the following changes. A sharp decrease in the concentration of PN, a key component of the antioxiative defense system, was observed. Whereas in intact animals the value of this parameter was 0.51 ± 0.03, on the 4th day it was down to 0.22 ± 0.02 g/liter ($p < 0.001$). Under these circumstances the reduced glutathione concentration fell from 0.6 ± 0.002 to 0.3 ± 0.001 g/liter ($p < 0.001$) and the total glutathione concentration rose by 38% ($p < 0.02$). By this

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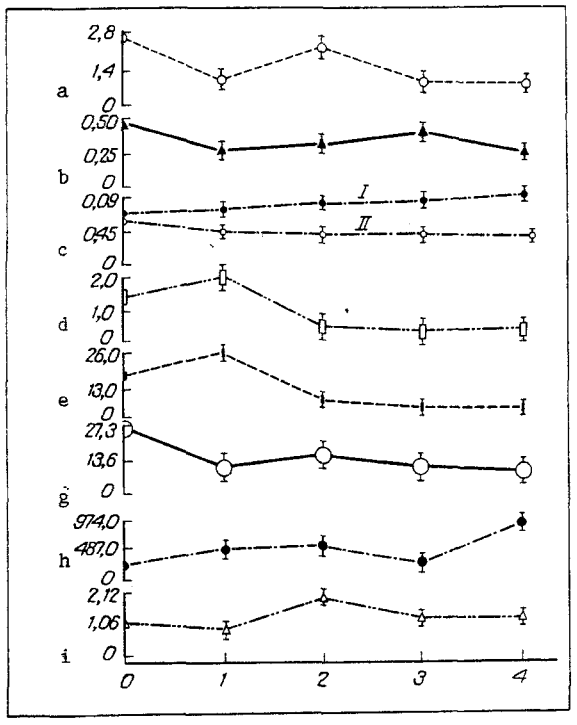

Fig. 1. Dynamics of activity of antioxidative defense system and intensity of free-radical lipid oxidation during formation of stress syndrome induced by sleep derivation. a) Total blood AOA (in meq·min^{-1}·ml^{-1}); b) total PN (in g/liter); c) total (I) and reduced (II) glutathione (in g/liter); d) SOD activity (in U·mg^{-1} protein); e) catalase activity (in mmoles·g^{-1} protein·min^{-1}); g) GRD activity (in nmoles·mg^{-1} protein·min^{-1}); h) DC concentration (in mmoles·mg^{-1} protein); i) MDA concentration (in mmoles/liter). Abscissa, days of stress; ordinate, values of biochemical parameters.

time SOD activity had fallen by 68% and catalase and GRD activity by 65% ($p < 0.01$). One result of the changes described was a significant fall of the integral parameter of function of the antioxidative defense system (the total blood AOA) to 0.75 ± 0.07 on the 4th day compared with 2.80 ± 0.56 meq·min^{-1}·ml^{-1} packed erythrocytes in the intact animals. One result of the changes described above was a marked increase in the intensity of pre-radical oxidation. The DC level was 4.7 times, and the MDA level 39% higher than initially. Continued exposure to stress led to massive mortality among the experimental animals.

The following conclusions were drawn from these investigations.

Stage I (the emergency stage of adaptation), and stage II (the transition from emergency to long-term adaptation), developed during the first hours from the beginning of exposure to stress and continued for 24 h. Intensification of free-radical oxidation is not accompanied by loss of control of the antioxidative defense system. The changes discovered are compensated and reversible in character. The most sensitive step in the "breakdown" of the antioxidative defense system is lowering of the PN concentration. Normalization of the level of this parameter ought evidently to be the most important aim of pharmacological correction undertaken at this stage.

Stage III (long-term adaptation) takes place on the second day of stress and continues for 48 h. The trend of changes in total blood AOA, PN level, and SOD, catalase, and GRD activity is evidence of the uncompensated character of function of the antioxidative defense system, and the probability of its impending exhaustion and possible collapse.

It can be concluded from these results that total loss of control of free-radical oxidation by the antioxidative defense takes place on the 4th day, i.e., in the period of development of stage IV of stress – the stage of exhaustion and a change from stress to distress.

Pharmacological correction, undertaken in stage III and, in particular, in stage IV of stress, is a difficult and complex task. It requires medication to act on the different steps of the antioxidative defense system. Abolition of stress in stage III and IV must include not only psychotropic agents, but also other groups of drugs. For instance, inhibition of lipid peroxidation can be achieved by strengthening the antioxidative action of tocopherol by combining it with ascorbic acid, flakumin, and membranotropic drugs. The concentration of reduced glutathione can be increased by administration of lipoic acid. The blood AOA is effectively increased by lipocerebrin. These groups may evidently be used in the combined treatment of the stress syndrome.

The results of these investigations indicate that pharmacological correction of the stress syndrome must take place mainly in the stage of emergency adaptation and its transition to long-term adaptation, i.e., stages I and II of stress. Drugs affecting the levels of the

biochemical parameters which are changed during the stages of stress may prove to be the most promising stress protectors. These compounds, in particular, include derivatives of nicotinic acid, lithium nicotinate, picamilon (sodium N-nicotinoyl-aminobutyrate), and other preparations capable of raising the PN level during biotransformation in the stressed organism [5]. It can be concluded from these results that one way of making pharmacological correction of the stress syndrome more effective is by the differential use of different groups of stress protectors, depending on the stage of chronic stress.

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PHARMACOKINETICS OF KEMANTANE IN RATS

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The pharmacokinetics of the new Soviet immunostimulator kemantane was studied by gas–liquid chromatography in experiments on noninbred rats. It was shown that after internal administration kemantane is quickly metabolized, with the formation of an active metabolite. Both kemantane and its metabolite are distributed rapidly from the blood into the internal organs. The preparation is excreted mainly in the form of the metabolite from rats.

Kemantane (1-hydroxyadamantan-4-one) is an original nitrogen-free oxygen-containing derivative of adamantane, with no substituent groups in position 2 of the adamantyl radical, which was synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR. The theoretical basis for its development was data in the literature indicating that adamantane-containing compounds possess a range of pharmacological, including anticataleptic, activity for which reason kemantane was initially suggested as a remedy for the treatment of patients with parkinsonism. Clinical trials of kemantane, on too small a scale, have failed to reveal any advantages over midantan [5], currently used in medical practice. Subsequent experimental studies have shown that kemantane possesses immunomodulating properties in animals with depressed immunity, and it also has an inducing effect on the cytochrome P-450 system [3], which provided a basis for its clinical study as a nonspecific immunomodulator. Clinical trials of kemantane have now been successfully concluded and the preparation has been recommended by the Pharmacopoeial Committee of the Ministry of Health of the USSR for

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