Effect of Opioid Peptides on the Content of LPO Products and Antioxidant Enzyme Activity in the Liver of Rats after Restraint Stress

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Administration of opioid peptides dynorphin A (1-13) and DSLET was followed by a decrease in the stress-induced activation of LPO and increase in SOD activity in the liver tissue of rats. DAGO produced a similar, but less pronounced effect. The observed changes can be related to a specific distribution of opioid receptors in the liver tissue and stress-limiting influence of these peptides in the whole body.

Key Words: *opioid peptides; liver; stress; lipid peroxidation*

A large body of evidence indicates that stress exposure induces structural and functional changes in the liver [4]. The impairment of arterial blood flow under these conditions results in hepatocyte hypoxia and activation of LPO followed by mitochondrial damage and necrosis of liver cells [1,2,10]. The search for new drugs that can prevent stress-induced injury to hepatocytes is an urgent problem.

The endogenous opioid system is a major component of the antistress system in the body. There are at least three main types of opioid receptors (OR) that have selective agonists [6,11].

Here we compared the effects of selective agonists of different types of OR on LPO in the liver tissue during various periods after stress exposure.

MATERIALS AND METHODS

Experiments were performed on 104 male Wistar rats. The animals were divided into 13 groups of 8 specimens each; 8 rats were intact. Restraint stress was induced by 6-h immobilization of animals in the supine position on a special table. The rats were killed 39 h and 4 or 7 days after the end immobilization. These periods of the study were chosen from the data that the most severe damage to internal organs develops by the end of the alarm stage (39 h after stress). Compensatory processes in damaged organs were reported to occur at the beginning of the resistance stage (day 4) and 7 days after immobilization [2].

The content of LPO products (acyl hydroperoxides and MDA) and activity of antioxidant enzymes (SOD and catalase) in liver tissue were measured routinely [3,5,8].

We used the following selective agonists of OR in equimolar doses: μ-receptor agonist DAGO (Tyr-D-Ala-Gly-N-Methyl-Phen-Gly-ol, 6.3 μg/kg); δ-receptor agonist DSLET (Tyr-D-Ser-Gly-Phen-Leu-Trp, 10 μg/kg); and κ-receptor agonist dynorphin A (1-13) (20.1 μg/kg) [6]. These doses were chosen from the results of our studies and published data on high efficiency of peptides in specified doses [6,7]. The peptides (0.2 ml) were injected intraperitoneally once a day for 5 days after immobilization. Control animals received physiological saline.

The results were analyzed by Student's test and Fisher's test.

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RESULTS

Six-hour restraint stress was accompanied by activation of LPO. The concentration of intermediate and end products of LPO (acyl hydroperoxides and MDA) in the liver tissues was elevated in all periods of the study (Table 1). Catalase activity increased, while SOD activity decreased on day 7 after stress ($p<0.01$).

Administration of opioid peptides reduced LPO activation and increased activity of enzymes (primarily of SOD). κ-OR agonist dynorphin A (1-13) was most potent in this respect. This peptide had a normalizing effect on the content of acyl hydroperoxides and significantly decreased the concentration of MDA on day 4 of the study. Moreover, the increase in SOD activity was most pronounced after treatment with dynorphin A (1-13).

DSLET normalized the contents of acyl hydroperoxides and MDA on day 7 after restraint stress. Moreover, this peptide increased activities of catalase (day 4) and SOD (days 4 and 7). The influence of DAGO on study parameters was less pronounced. This peptide decreased the concentrations of acyl hydroperoxides and MDA in all periods of the study, but had little effect on enzyme activities.

Opioid peptides produced an antistress effect in the whole body. For example, they suppress the production of ACTH, glucocorticoids, and catecholamines under stress conditions. Opioid peptides reduce the severity of poststress changes in various organs and tissues [6,12].

Previous studies showed that agonists of various OR have the opposite effects on bile secretion in the isolated liver [9]. It should be emphasized that δ- and μ-receptor agonists produce the opposite effects under these conditions. δ-Receptor agonist stimulated, while μ-receptor agonist suppressed bile production. It was probably related to a specific distribution of various types of OR in the liver.

The observed effects of selective OR agonists on LPO and activity of the antioxidant system in the liver during restraint stress are probably associated with the distribution of receptors in the studied tissue and specific influence of these compounds in the whole body.

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TABLE 1. Effect of Opioid Peptides on the Content of MDA and Acyl Hydroperoxides and Activities of Antioxidant Enzymes in the Liver Tissue of Rats during Various Periods after Immobilization (*M*±*m*)

Group	Period after immobilization	MDA content, μmol/liter	Acyl hydroperoxide content, arb. units	Catalase activity, mcat/liter	SOD activity, arb. units/ml
Intact (non-stressed) group		17.4±0.4***	6.3±0.3***	21.1±0.9	23.1±1.0
Control group	39 h	51.3±1.2	16.2±0.7	23.3±1.2	23.7±0.8
	day 4	41.8±0.9	9.7±0.5	25.7±1.1	21.9±1.1
	day 7	32.8±0.7	10.6±0.4	25.4±0.8	17.8±0.7
DAGO, 6.3 μg/kg	39 h	43.2±0.5***	13.9±0.9	23.5±0.8	20.6±1.0
	day 4	37.8±0.5**	8.7±0.3	23.7±1.2	23.8±0.9
	day 7	25.6±0.4***	8.0±1.0*	24.5±0.6	24.3±1.2**
DSLET, 10 μg/kg	39 h	36.1±0.6***	10.1±0.7***	25.9±0.5	25.6±0.8
	day 4	27.5±0.5***	9.1±0.6	33.2±0.7***	38.4±1.2***
	day 7	15.9±0.6***	6.0±0.5***	20.4±1.4	35.8±1.1***
Dynorphin A (1-13), 20.1 μg/kg	39 h	27.6±0.4***	9.3±0.6***	19.7±2.4	35.4±1.2***
	day 4	25.4±0.4***	6.3±0.3***	33.5±0.8***	39.7±0.8***
	day 7	17.5±0.3***	6.1±0.3***	21.6±1.9	46.3±0.6***

Note. *$p<0.05$, **$p<0.01$, and ***$p<0.001$ in comparison with the control group.

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