Effect of IL-1β Receptor Antagonist on Lipid Peroxidation in the Liver in Stress

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The content of molecular LPO products increased in the liver of rats exposed to daily 1-h immobilization. IL-1β receptor antagonist limited the stress-induced intensification of LPO.

Key Words: *stress; lipid peroxidation; interleukin-1β*

Stress exposure is often associated with accumulation of proinflammatory cytokines [1,4,8,9]. Previous study showed that 3 daily 1-h immobilizations (DIM) result in an increase of circulating IL-1β activity, paralleled by the development of proinflammatory changes in the liver and increase of the level of LPO molecular products in the organ [7]. Presumably, LPO intensification in the livers of stressed animals is related to increase in activity of this cytokine, because intracellular signal transduction for IL-1β is linked with sphingomyelinase stimulation and release of the acyl radical (peroxidation substratum) [4]. We verified this hypothesis experimentally.

MATERIALS AND METHODS

The study was carried out on 54 outbred male rats. The animals were divided into 3 groups. Group 1 comprised controls. Group 2 animals were exposed to 3 DIM episodes (immobilization by fixation in the supine position on a plywood sheet for 1 h with 24-h interval between the stress episodes.

Group 3 animals received IL-1β receptor antagonist (≥95%; Fluka) in a dose of 2 mg/kg 1 h before each immobilization stress episode. The dose of IL-1β receptor antagonist for adult outbred rats effectively preventing leukocytosis induced by recombinant IL-1β (Betaleukinum, hrIL-1β; Institute of Ultrapure Preparations) was determined in a special series of experiments. First, the drug was used in doses corresponding to single therapeutic doses in humans with consideration for differences in body surface areas [4]. The minimum dose of the studied range was $^1/_2$ of the estimated equivalent of the mean therapeutic dose. A 10-fold higher dose was the maximum dose in our experiments.

The content of primary (conjugated dienes) and secondary (ketodienes and conjugated trienes) molecular products of LPO were measured in liver homogenate in the isopropanolol phase (polar lipids, mainly phospholipids, were extracted in this phase) and in heptane phase (nonpolar lipids) [2]. LPO end-products (Schiff bases) were also measured [3].

The results were processed by methods of variation statistics and expressed as arithmetic mean±standard error of the mean. Statistical significance of λ test). The results were processed using Statistica 6.0 software.

RESULTS

LPO intensification in the liver was recorded 24 h after DIM. Liver content of heptane-soluble conjugated dienes increased by 13% in stressed animals. This was paralleled by a 29% elevation of heptanophilic ketodiene and conjugated triene levels. The content of isopropanolol-soluble molecular products of LPO virtually did not differ from the control (Table 1). However, the oxidation of isopropanolol-soluble li-

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TABLE 1. Effects of IL-1β Receptor Antagonist (IL-1β ra) on Liver Content of Molecular Products of Lipid Peroxidation in Rats Exposed to Stress ($M\pm m$; n=24)

Parameter	Group		
	1 (control)	2 (DIM)	3 (DIM+IL-1β ra)
Conjugated dienes (heptane phase)	0.621±0.006	0.704±0.021 $p_{1,2}$=0.003*U*	0.632±0.007 $p_{2,3}$=0.004*U*
Ketodienes and conjugated trienes (heptane phase)	0.145±0.007	0.187±0.014 $p_{1,2}$=0.021*U*	0.149±0.007 $p_{2,3}$=0.03*t*
Schiff bases (heptane phase)	0.024±0.004	0.023±0.004	0.021±0.004
Conjugated dienes (isopropanolol phase)	0.618±0.02	0.625±0.029	0.562±0.024
Ketodienes and conjugated trienes (isopropanolol phase)	0.274±0.008	0.281±0.019	0.239±0.010 $p_{2,3}$<0.025λ
Schiff bases (isopropanolol phase)	0.034±0.011	0.04±0.006	0.029±0.007
Conjugated dienes (isopropanolol phase), Fe^{2+}-ascorbate induction	1.034±0.018	1.051±0.049	0.963±0.055 $p_{2,3}$=0.02*WW*
Ketodienes and conjugated trienes (isopropanolol phase), Fe^{2+}-ascorbate induction	1.049±0.040	0.941±0.028 $p_{1,2}$=0.04*t*	0.992±0.054 $p_{2,3}$=0.01*WW*

Note. Level of LPO products is expressed in oxidation index arb. units (E_{232}/E_{220} for LPO primary products, E_{278}/E_{220} for LPO secondary products, and E_{400}/E_{220} for LPO final products). $p_{1,2}$: significant differences between groups 1 and 2; $p_{2,3}$: between groups 2 and 3.

pids decreased after DIM. It manifested in reduction of ketodiene and conjugated triene levels under conditions of ascorbate-induced PLO. This can be due to reduced content of unsaturated acyl radicals in the phospholipids and their subsequent translocation into cytoplasmic lipids. This is in good agreement with the above-mentioned increase in the level of LPO molecular products in the heptane phase.

Stress-associated intensification of LPO in the liver was completely prevented by preliminary injection of IL-1β receptor antagonist (IL-1β ra). The level of heptane-soluble conjugated dienes decreased by 10% in group 3 compared to group 2. This was paralleled by a 20% reduction of heptanophilic ketodienes and conjugated trienes. In addition, the levels of isopropanolol-soluble ketodienes and conjugated trienes dropped by 25%.

These results completely confirm the initial hypothesis on IL-1β-dependent intensification of LPO under conditions of DIM. Presumably, LPO activation is associated with transduction of the cytokine signal mediated by sphyngomyelinase.

Possible consequences of the post-stress increase in LPO molecular product levels in the liver are inhibition of microsomal oxidation by the free radical mechanism. It was shown that DIM is associated with inhibition of CYP1A1 and CYP2B1/2 isoforms in the presence of more intense leukocytic infiltration of the liver [6]. The capacity of some LPO products to act as chemoattractants [1] is worthy of note in this connection. Presumably, IL-1β-induced stimulation of LPO is involved in the realization of the proinflammatory effect of this cytokine.

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