EFFECT OF DALARGIN ON SOME PARAMETERS OF LIPID PEROXIDATION IN THE LIVER: AN EXPERIMENTAL STUDY

R. M. Shloznikov, R. N. Korotkina, N. V. Babkina, A. A. Karelin, and E. P. Fomchenkov

UDC 615.31:547.95:547.943.015.4:616.36-008.939.15-39].076.9

KEY WORDS: pathology of the liver, hepatoprotective effect, synthetic opioid hexapeptide, general anesthesia with dalargin

During a study of the effect of some components of general anesthesia on the liver the writers found previously that mobilization of endogenous opioids under conditions of transcranial percutaneous electrical stimulation (TPES), and also administration of the Soviet synthetic hexapeptide dalargin, a Leu-enkephal in analog (synthesized in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, by Professor M. I. Titov), have a hepatoprotective action in an experimental model of acute cholestasis and pancreatitis [4, 5].

The aim of the present investigation was to study the mechanism of the hepatoprotective effect of dalargin in the early period of its administration.

An important role in the development of the pathological process in the organs and tissues is played by disturbance of the integrity of cell membranes, due in particular to intensification of lipid peroxidation (LPO) [3, 9]. One of the enzymes catalyzing the formation of hydrogen peroxide and of the superoxide anion-radical is xanthine oxidase. Determination of xanthine oxidase activity combined with investigation of the LPO level in the liver tissue during administration of dalargin under the conditions of a model of acute cholestasis and pancreatitis may prove to be an important metabolic criterion for evaluating the action of dalargin.

As an additional metabolic test we also used determination of activity of the hepatospecific enzymes histidase and urocanase.*

EXPERIMENTAL METHOD

Experiments were carried out on 144 noninbred male rats with an average weight of 200 g, with a model of acute cholestasis and pancreatitis [6]. The common bile duct was ligated in the experimental animals, and 24 h later they were given an intraperitoneal injection of dalargin solution in a dose of 10 μmoles/100 g body weight. The tissues were studied 1, 3, and 5 h after injection of the preparation. Animals receiving an intraperitoneal injection of 0.9% NaCl solution at the same times and in the same volume served as the control.

Xanthine oxidase activity in liver tissue was determined by the method in [7] and expressed in nmoles reduced ferricytochrome/mg protein; the LPO level was determined as in [8] and expressed in nmoles of malonic dialdehyde (MDA)/mg protein.

Activity of the hepatospecific enzymes [1, 2] was expressed in pmoles urocanase of urocanic acid formed (histidase) or decomposed (urocanase) during 1 sec per milligram protein (liver) or per milliliter serum (blood serum).

EXPERIMENTAL RESULTS

The experiments showed that at all stages of the investigation dalargin depressed xanthine oxidase activity in the liver tissue by 37.6% ($p < 0.02$), 34.8% ($p < 0.01$), and 32.5% ($p < 0.02$) after 1, 3, and 5 h respectively (Fig. 1). Meanwhile the

*Urocanate hydratase (EC 4.2.1.49).

A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 110, No. 12, pp. 609-610, December, 1990. Original article submitted November 30, 1989.

 0007-4888/90/0012-1658$12.50

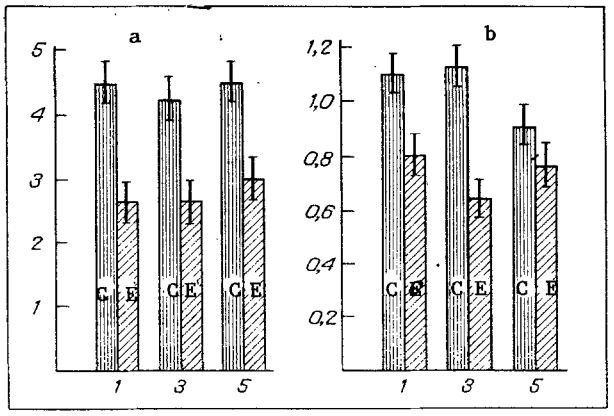

Fig. 1. Effect of dalargin on xanthine oxidase activity (a) and LPO (b) in rat liver. Abscissa, time after injection of dalargin (in h); ordinate: a) xanthine oxidase activity (in nmoles reduced ferricytochrome/mg protein), b) MDA level (in pmoles/mg); C) control, E) injection of dalargin.

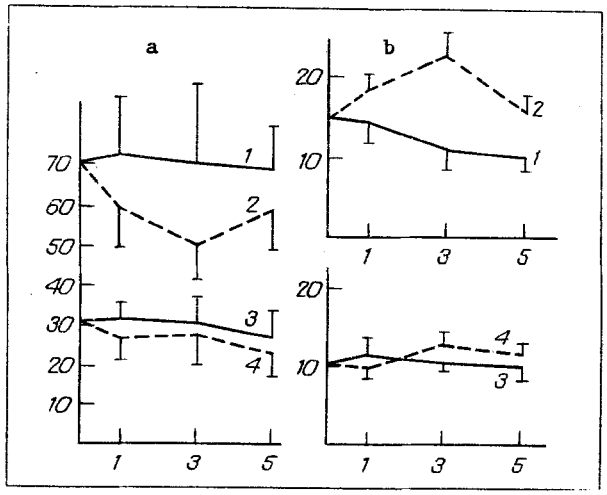

Fig. 2. Dynamics of histidase and urocanase activity in rat blood serum (a) and liver (b) after injection of dalargin. Abscissa, time after injection of dalargin (in h); ordinate: a) enzyme activity in blood (in pmoles urocanase urocanic acid/ml/sec); 1, 2) histidase; 3, 4) urocanase; 1, 3) control; 2, 4) dalargin. b) Enzyme activity in liver (in pmoles urocanic acid/mg protein/sec).

MDA level was observed to fall, and this effect was most marked 3 h after injection of dalargin (by 43.8%, $p < 0.01$). The results are evidence that injection of dalargin into the animals with experimental cholestasis and pancreatitis led to reduction of LPO activity in the liver cell membranes and, as a result, to stabilization of the membranes and to a decrease in the elution of hepatospecific enzymes from the liver into the blood stream. It was shown (Fig. 2b) that injection of dalargin significantly increased histidase activity in the liver tissue, more especially after 3 h (by 104.3%, $p < 0.01$) and 5 h (by 56.3%, $p < 0.05$). Meanwhile a tendency was observed for histidase activity in the blood serum urocanase to fall (Fig. 2a). Admittedly, no appreciable changes were found in urocanase activity in the liver and blood serum.

It can be concluded from these results that in the early stages after injection of dalargin it exhibited hepatoprotective properties. The most important of these properties of dalargin is its ability to inhibit LPO, which may be manifested at not only the organ level (liver), but also at systemic levels. This fact may be of great importance during anesthesiologic protection with the use of dalargin instead of narcotic analgesics.

LITERATURE CITED

1. V. A. Burobin, Methods of Investigation of Activity of Some Enzymes in Clinical Medicine [in Russian], No. 6, Moscow (1967), p. 28.
2. V. A. Burobin, Methods of Investigation of Activity of Some Enzymes in Clinical Medicine [in Russian], No. 6, Moscow (1967), p. 33.
3. V. P. Grigorevskii, Abstracts of Proceedings of the 6th Congress of Surgeons of Moldavia [in Russian], Kishinev (1986), p. 106.
4. M. I. Kuzin, M. Ya. Avrutskii, et al., Byull. Éksp. Biol. Med., No. 8, 176 (1987).
5. M. I. Kuzin, A. A. Karelin, R. N. Korotkina, et al., Byull. Éksp. Biol. Med., No. 9, 266 (1988).
6. Y. Docter-Hünicke and T. Goetze, Acta Biol. Med. Germ., **21**, 495 (1968).
7. B. L. Herecker and L. Q. Heppel, in: Methods in Enzymology, ed. by S. P. Colowick and N. O. Kaplan, Vol. 11, New York (1955), pp. 482-485.
8. I. Ohkawa, N. Ohishi, and Y. Kanio, Analyt. Biochem., **95**, 351 (1979).
9. D. A. Parks and G. B. Bulkley, Surgery, **94**, 415 (1984).

EFFECT OF RECENT ALCOHOL INTAKE ON ACCEPTOR PROPERTIES OF HIGH-DENSITY LIPOPROTEINS AND THEIR INTERACTION WITH LIVER CELLS

S. A. Kurilovich, E. V. Pozdeeva, A. P. Serdyuk, I. O. Svetlova, and Yu. A. Shakhov

UDC 616.36-018.1-008.939.639.15-02:547.262]-07

KEY WORDS: alcohol intake, hyperalphacholesterolemia, high-density lipoproteins, subfractional composition, cholesterol acceptance, interaction with liver cells

Alcohol is one of the factors that raises the blood serum high-density lipoprotein (HDL) level. Epidemiological studies conducted in various countries have demonstrated positive correlation between alcohol consumption and the cholesterol (ChS) and HDL levels [11]. The causes of the rise of the HDL level after alcohol intake (alcohol hyperalphacholesterolemia — hyper-AChS) have not been finally elucidated, although they clearly depend on the dose of alcohol taken and the duration of its administration [14]. One of the most probable mechanisms is an inducing effect of alcohol on synthesis of the principal apoproteins of HDL and, correspondingly, of nascent HDL, in the liver [6]. Another pathway of HDL accumulation is increased synthesis of very low-density lipoproteins (VLDL) and an increase in the rate of their catabolism, leading to the formation of mature HDL [14]. A third possibility is slowing of catabolism of HDL as a result of disturbance of their interaction with liver cells, but this has received the least study. Another point for discussion is the problem of the validity of alcohol hyper-AChS from the point of view of the ability of HDL to accept ChS from cells of peripheral tissues and, in particular, blood vessel walls.

We know that small and ChS-deprived particles of the HDL_3 subclass (acceptance of ChS) interact with peripheral cells, and large and ChS-rich particles of HDL_2 (transfer of ChS into the liver) with liver cells [5]. The writers previously demonstrated that hepatoma HepG2 cells and ChS-loaded fibroblasts can be used as models of liver cells and peripheral cells, respectively,

Institute of Therapy, Siberian Branch, Academy of Medical Sciences of the USSR, Novosibirsk. All-Union Preventive Medicine Research Center, Ministry of Health of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR Yu. P. Nikitin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 110, No. 12, pp. 611-613, December, 1990. Original article submitted March 22, 1990.

 0007-4888/90/0012-1660$12.50