The results thus indicate that it is possible to modify the antitumor efficacy of FT in a particular direction by means of PFD, an inducer of the liver cytochrome P-450 system. A combination of FT with PFD potentiates the action of FT on tumors resistant to it (LLC, hepatoma H-2-73) on average by a factor of 2.5. The possibility of significantly reducing the dose of FT, which exhibits marked neurotoxicity, without any loss of antitumor efficacy is evidence that the use of such combinations in clinical practice is promising.

LITERATURE CITED


SOME MOLECULAR MECHANISMS OF THE ANTIOXIDATIVE ACTION OF DALARGIN ON THE LIVER IN EXPERIMENTAL CHOLESTASIS

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KEY WORDS: dalargin; antioxidative action; cholestasis; rat liver

Dalargin (Tyr-D-Ala-Gly-Phe-Leu-Arg), a synthetic analog of the opioid Leu-enkephalin, synthesized in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, by Professor M. I. Titov, and which possesses antistressor activity and exerts a protective effect on organs (including the liver), has begun to be used in recent years as a protective agent in anesthesiology. In such cases dalargin has been observed not to have a direct membrane-stabilizing effect on the myocardium [4], and the protective action of dalargin (in myocardial infarction, after wounding) has been shown to be realized in opioidergic receptor processes, for it is completely abolished by simultaneous administration of the structural morphine analog naloxone, a universal opioid antagonist [1, 7].

Meanwhile, the molecular mechanisms of the protective action of dalargin on the liver have not been adequately studied. There is no information in the literature on the action of the dalargin antagonist, naloxone, on liver function.
The aim of this investigation was to determine what changes in the hepatoprotective antioxidative action of dalargin may be observed as a result of simultaneous administration of naloxone.

EXPERIMENTAL METHOD

Experiments were carried out on 144 noninbred male albino rats weighing 200 g, with cholestasis, induced by ligation of the common bile duct. The rats were used in the experiments 24 h after the operation. The experiments took place in the following stages: 1) intraperitoneal injection of dalargin in a dose of 10 μg/kg body weight, 2) intraperitoneal injection of naloxone (Du Pont de Nemours, Germany) in a dose of 100 μg/kg body weight, and 3) injection of dalargin 10 min before naloxone in the above-mentioned doses (in this series naloxone was injected 10 min before dalargin). Animals with cholestasis, receiving 0.9% NaCl intraperitoneally, served as the control.

The rats were killed by decapitation 1, 3, and 5 h after injection of the preparations. Activity of xanthine oxidase [10], an enzyme catalyzing the formation of hydrogen peroxide and the superoxide-anion radical, activity of glutathione-S-transferase, an enzyme of antioxidative protection [13], and the level of lipid peroxidation [12], based on the degree of change of the malonic dialdehyde (MDA) level, were determined in liver tissue.

Activity of the hepatospecific enzymes histidase and urocaninase in the liver tissue and blood serum was determined.

The protein concentration in the liver tissue was determined by the method in [11]. In a separate series of experiments the effect of dalargin was studied on the Leu-enkephalin level in liver tissue. Leu-enkephalin was determined with the aid of RIA kits (Instar Corporation, USA). Radioactivity was counted on a gamma-counter (Tracor Analytic, USA). In this series dalargin was injected in a dose of 50 μg/kg and the rats were killed 1 h after injection of the preparation.

EXPERIMENTAL RESULTS

It follows from the data in Fig. 1a that in rats with cholestasis dalargin reduces xanthine oxidase activity in the liver tissue at all times of investigation (by 37.6, 34.8, and 32.5%, p < 0.01) after 1, 3, and 5 h respectively. Injection of naloxone led after 1 h to an increase in activity of the enzyme by 38% (p < 0.02). At the remaining times of investigation no significant changes in xanthine oxidase activity were found compared with the control data, although 5 h after injection a tendency for the activity of this enzyme to increase still remained.

In response to combined administration of dalargin and naloxone a slightly reduced level of xanthine oxidase activity was observed (although the decrease was less marked than after dalargin alone) 1 h after injection. At other times the parameters were virtually indistinguishable from the control.