Opioid Peptides Modulate Secretion of the Basic Determinants of Bile Secretion

I. V. Rudin and M. A. Medvedev

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The effects of the synthetic opioid peptide dalargin and the antagonist of opiate receptors naloxone hydrochloride on the rate of bile secretion and concentration of bile acids and sodium ions is studied in rats. It is shown that the substances with opioid activity insignificantly raise the rate of bile secretion and concentration of the studied compounds. It is suggested that the secretion of the carbonate ion and glutathione increase under these conditions.

Key Words: *bile secretion, opioid peptides, dalargin, naloxone*

The role of endogenous opioid peptides (endorphins and enkephalins) in the regulation of physiological reactions and in modulation of pathological processes has been extensively investigated. It was demonstrated that opioid peptides (OP) modify stress reaction [5], acting as a stress-limiting system factor. They produce a protective effect in myocardial ischemia [7]. These peptides modulate the release of neurotransmitters and conductivity of neuronal membrane [12]. They also produce a wide range of biological effects on the digestive system. For instance, μ- and δ-agonists modify the amount and composition of pancreatic juice and limit pathological process in acute pancreatitis [1]. Synthetic OP analogs exhibit antiulcer [6] and hepatoprotective [2] activities. However, there is no data on the effect of OP and their synthetic analogs on secretory function of the liver. A close anatomic and functional relationship between the organs of the proximal alimentary canal and detection of binding sites for the substances with opioid activity in the liver [4] strongly suggests that OP play a role in the regulation of secretory function of the liver. Based on the finding that dalargin stimulates bile secretion, we decided to examine the effect of dalargin on the major determinants of bile secretion [10].

Department of Normal Physiology, Siberian Medical University, Tomsk

MATERIALS AND METHODS

Experiments were performed on male Wistar rats (n=50, body weight 160-250 g). The animals were deprived of food for 12 h and had free access to water. The dynamics of bile secretion and bile composition were studied in acute experiment under Nembutal anesthesia (50 mg/kg). The synthetic OP analog dalargin (10 mg/kg, Vektor-Bioprodukt, Novosibirsk) and the antagonist of opiate receptors naloxone hydrochloride (1 mg/kg, Solyaris, Moscow) were injected intraperitoneally in normal saline (0.3 ml/200 g body weight). When administered together, the preparations were given in the same doses, naloxone being injected 5 min before dalargin. Bile was collected 1, 2, and 3 h after the injection from a cannula inserted in the common bile duct. Bile secretion rate, the total content of bile acids (modified Zlatkis—Zak reaction [3]), and Na^+ concentration (flame photometry) were determined. The rate of bile secretion was calculated per 100 g body weight. The dose of dalargin was chosen based on the literatures data on its hepatoprotective effect. Control animals were given normal saline. Four series of experiments were carried out: control (I), administration of dalargin (II), administration of naloxone (III), and simultaneous administration of dalargin and naloxone (IV). The results were analyzed by Student's t test (p<0.05).

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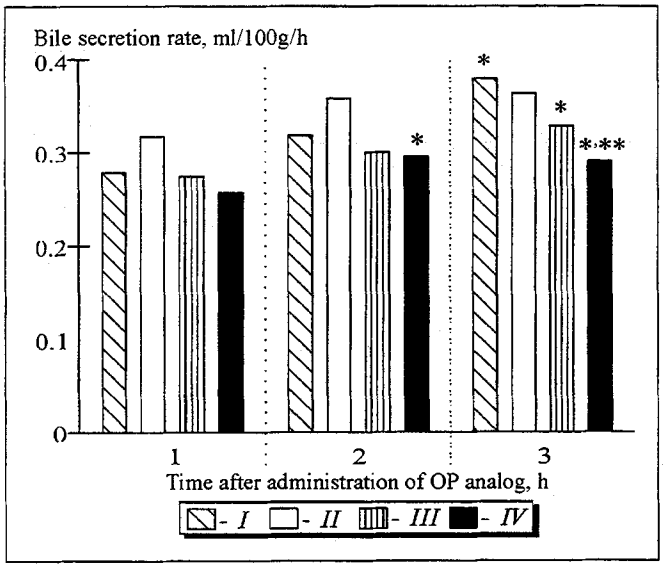

Fig. 1. Effects of synthetic opioid peptide analogs on the rate of bile secretion in albino rats. Here and in a Figs. 2 and 3: *I*) control (normal saline); *II*) dalargin, 10 μg/kg; *III*) naloxone, 1 mg/kg; *IV*) naloxone, 1 mg/kg+dalargin, 10 μg/kg. The differences are significant: *compared with the value after 1 h in the respective series; **compared with the respective hour in the control series.

RESULTS

A tendency towards an increase in the rate of bile secretion was observed both in control and experimental series (Fig. 1); the increase became statistically significant by the second hour in series VI and by the third hour in series I and III. However, the rate of bile secretion was higher than in the control series, although statistically insignificant, only in series II (dalargin): by 12.4% after 1 h and by 11.8% after 2 h. In control series, the Na^+ concentration increased throughout the entire observation period (Fig. 2). In series II and III, it decreased by the 2nd and 3rd hour, remaining higher than in the control. Higher Na^+ concentration and bile secretion rate reflect an increase in the absolute secretion of sodium relative to the control (except series IV by the 3rd hour) and during the experiment irrespective of administered preparations or their combination.

Most pronounced changes were observed in the bile acids (BA) content (Fig. 3). A common tendency towards a decrease in the BA concentration, which was observed in all series, may result from an impaired liver-intestine circulation of BA [11]. Synthetic analogs of OP increase BA concentration by the 1st hour by 28.72% ($p<0.005$), 34.56% ($p<0.001$), and 20.93% ($p<0.05$) in series II, III, and IV, respectively. After 3 h, this parameter decreased only in series II ($p<0.05$), while in series III and IV the BA concentration did not decrease, remaining at the control level.

The dynamics of absolute BA secretion was similar to that of bile secretion. By the end of the first hour after dalargin administration, the amount of secreted BA was 33.52% higher ($p<0.001$) than in the control, while by the 3rd hour it decreased by 34.75% compared with the control ($p<0.05$), which may result from reduced reabsorption, secretion, and synthesis. After 3 h, absolute secretion of BA in series II and III slightly differed from the control: 5.24 and 5.66 *vs.* 5.074 mg/100 g body weight, which may be due to the chosen model and short period after administration of OP.

Thus, OP analogs modify both determinants of bile secretion. It remains unclear which fraction

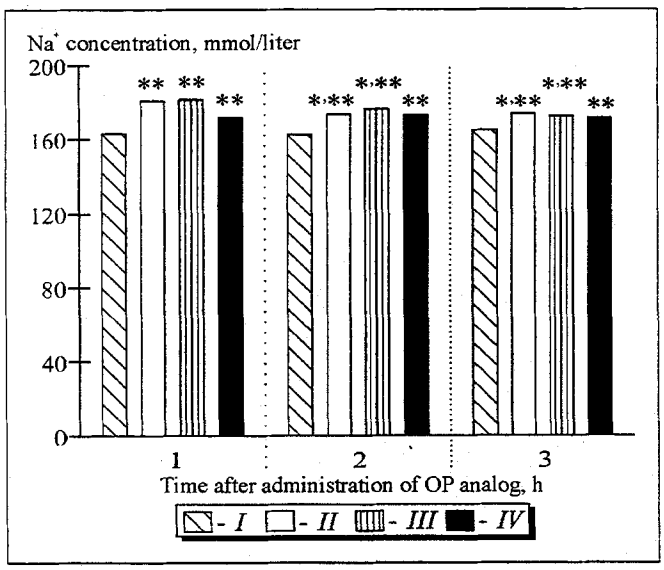

Fig. 2. Effect of synthetic OP analogs on bile concentration of sodium ions.

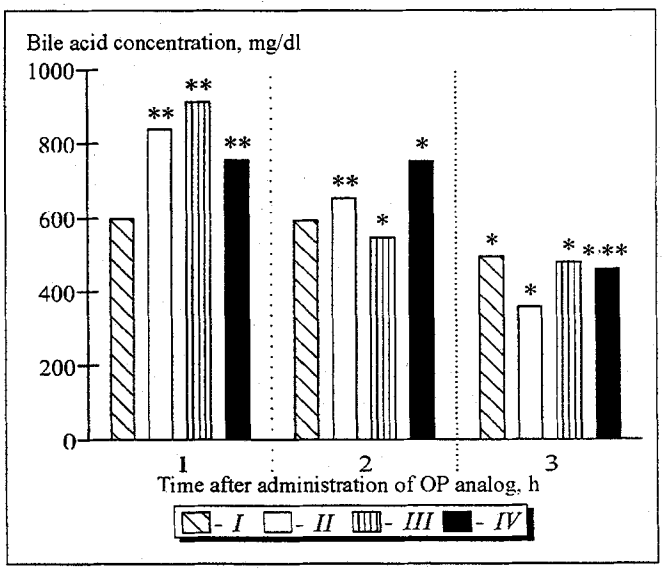

Fig. 3. Effect of synthetic OP analogs on the total content of bile acids.

(cholate-dependent or cholate-independent) prevails in determining the rate of bile secretion after administration of substances with opioid activity, owing to ambiguous effect of changes in BA concentration on the rate of choleresis [8,9]. Since the concentration of BA in all series, as well as concentration of sodium ions in series II and III, significantly decreases by the 3rd hour, while the rate of bile secretion tends to increase, an increased secretion of other osmotically active bile components (carbonate anion and glutathione), which markedly contribute to formation of cholate-independent fraction [13], is plausible.

It should be noted that sodium and BA concentrations increased in response to both agonists and antagonists of opiate receptors, which does not agree with the current concept on the physiological effects of OP. In the available literature we did not find any data on such effects produced by exogenous substances with opioid activity. Further research with the use of selective analogs and opiate receptor blockers are necessary to elucidate the mechanisms underlying these effects.

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