conclude that in certain doses BP can produce positive anxiolytic neurotropic effects that are probably related to the previously discovered stress-mitigating properties of this penicillin.

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Effects of Enkephalins on Bile-Secreting Function

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Various doses of leu- and met-enkephalins injected into the portal vein of rats inhibited predominantly the secretory function of the liver. In most instances, the changes in bile secretion were observed to coincide in direction, time of occurrence, and magnitude with those in the secretion of bile acids.

Key Words: *enkephalins; liver; bile secretion*

The endogenous opioid peptides enkephalins play an important part in regulating the functional state not only of the central nervous system but also of many visceral organs and systems, including the cardiovascular, digestive, and excretory systems [3,7,8]. There are reasons to believe that the functional state of the liver is also regulated to some extent by enkephalins, as is indicated by their liver-protecting action [4], their influence on metabolic processes in liver cells [2], and the presence of opiate receptors on the plasma membrane of these cells [1]. However, there is no direct experimental evidence that enkephalins are involved in the regulation of a major liver function, namely bile secretion. The purpose of the present work was to examine how enkephalins might influence the bile-secreting function of the liver.

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MATERIALS AND METHODS

The study was conducted on male white rats with a cannulated common bile duct and involved acute tests. The intensity of bile and bile acid secretions was measured as described earlier [6]. Leu-(LE) and met-(ME) enkephalins, received from the Institute of Organic Synthesis of the Latvian Academy of Sciences, were infused via the portal vein in doses of 0.1, 1, and 10 μg per 100 g body weight. The infusion rate was 50 μl/min and the infusion time, 30 min.

RESULTS

The intensity of bile secretion during and after the intraportal infusion of LE and ME varied depending on the type and dose of the peptide. When LE was infused in the dose of 0.1 μg, bile secretion decreased throughout the test period, whereas the dose

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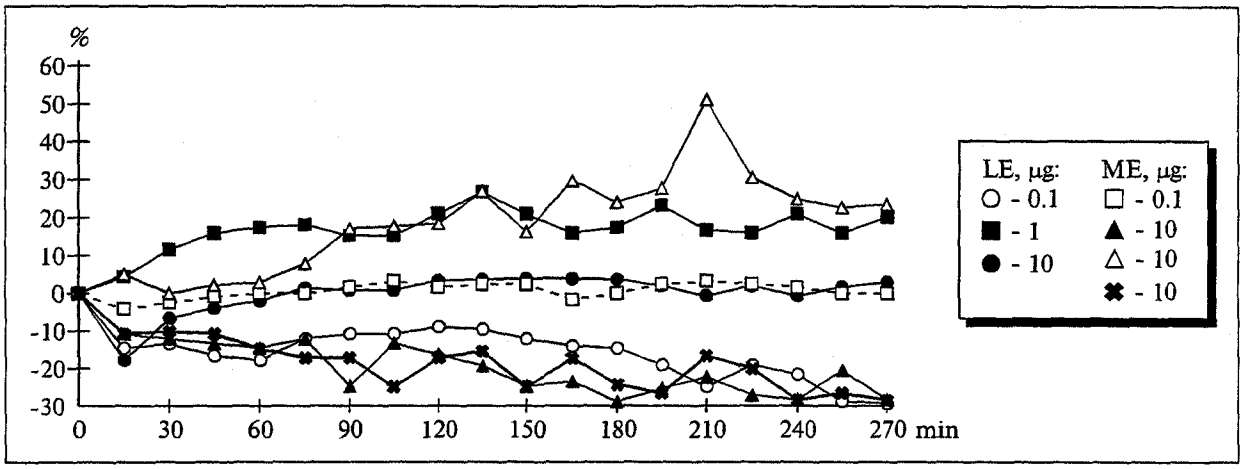

Fig. 1. Variations in bile secretion intensity under the action of LE and ME in different doses.

of 10 μg decreased bile secretion only during the infusion period. During infusion, LE inhibited bile secretion by 17.8% in both doses ($p<0.05$). The maximal inhibition of bile secretion by LE was 29.3%. In the dose of 1 μg LE, on the contrary, increased bile secretion by 26.8% ($p<0.05$; Fig. 1).

ME did not influence bile secretion in the 0.1 μg dose, but inhibited it throughout the test period in the 1 μg dose. In this case, the pattern of change in bile secretion intensity was the same as with the 0.1 μg dose of LE. Maximal bile secretion amounted to 28.9% ($p<0.02$). In the 10 μg dose, ME either inhibited (by 28.4%; $p<0.02$) or enhanced (by 51.1%; $p<0.01$) bile secretion (Fig. 1).

Thus, the same LE and ME doses had differential effects on the bile-secreting function. Since ME in the lowest dose (0.1 μg) did not affect bile secretion intensity while reducing it in the 1 μg dose to the same extent as did LE in the 0.1 μg dose, the liver appears to be more sensitive to LE.

It is commonly believed [5,9] that the rate of bile secretion is determined by osmotic properties of organic and inorganic bile components, including bile acids, inorganic ions, and proteins. Bile acids are responsible for the formation of the acid-dependent fraction of bile and inorganic ions and proteins, for the formation of its acid-independent fraction.

Measurement of bile acid secretion in the presence of enkephalins showed that the regulation of bile-secreting function by these peptides occurs in part at the level of the acid-dependent bile fraction. Thus, when LE was used in the 0.1 μg dose, the time course of bile secretion coincided with the reduction in the secretion of conjugated and free bile acids (Figs. 2 and 3). With the LE dose of 1 μg, bile acid secretion remained unchanged, although bile secretion was stepped up, whereas, conversely, the secretion of bile acids intensified while bile secretion remained unchanged with the 10 μg dose of this enkephalin. ME did not influence either bile acid or bile secretion in the 0.1 μg dose, but reduced both in the 1 μg dose. With the 10 μg dose of this enkephalin, variations in the secretion of bile acids and bile were similar.

Thus, the secretory function of the liver, as well as that of other organs such as the stomach and

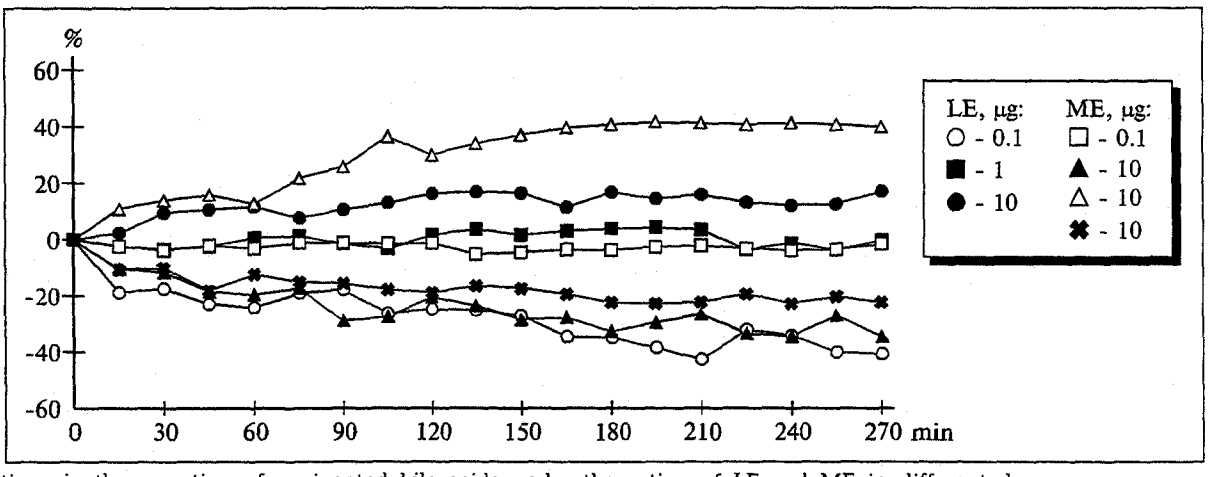

Fig. 2. Variations in the secretion of conjugated bile acids under the action of LE and ME in different doses.

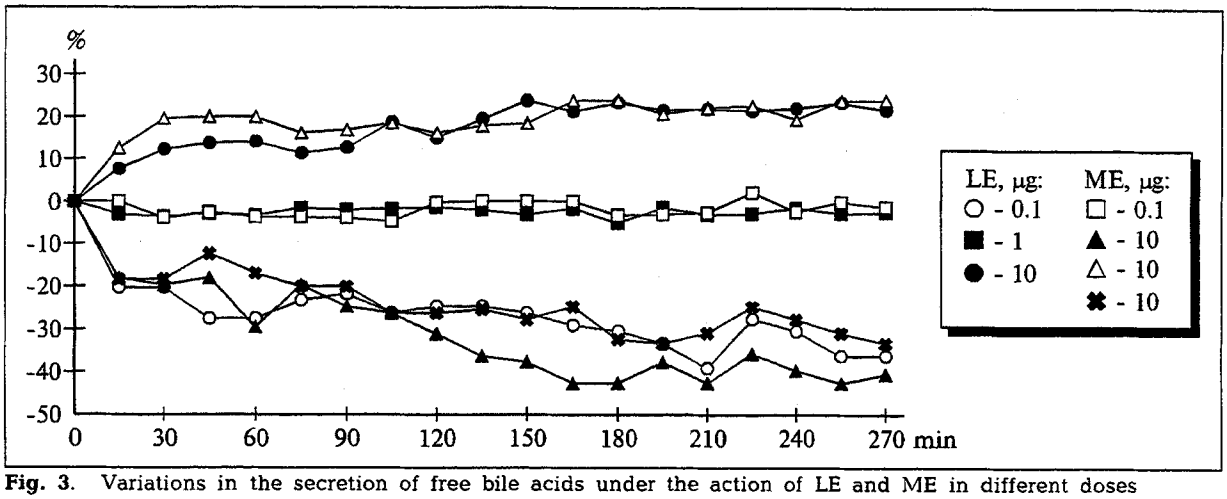

Fig. 3. Variations in the secretion of free bile acids under the action of LE and ME in different doses

pancreas [3,7,8], is regulated by enkephalins. Since enkephalins tend to depress the secretory function of the liver, stomach, and pancreas [3,7,8], the physiological regulatory role of these peptides appears to be inhibition of the secretory activity of the organs concerned.

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