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Effects of Epithalon on Activities Gastrointestinal Enzymes in Young and Old Rats

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Peroral administration of Epithalon (Ala-Glu-Asp-Gly) to male and female Wistar rats aging 3 and 11 months changed activity of enzymes hydrolyzing carbohydrates, proteins, and phosphoric acid esters in various portions of the gastrointestinal tract. The most pronounced activation of enzymes was observed in 11-month-old animals. This effect diminished the differences in enzyme activities between young and old rats (compared to untreated animals). Our results indicate that Epithalon modulates activity of gastrointestinal enzymes during aging.

Key Words: *Epithalon; peptides; digestive enzymes; gastrointestinal tract; aging*

Aging is accompanied by involutive changes in the mucosa in various portions of the gastrointestinal tract (GIT), which leads to digestive disorders and various diseases [2,3,8]. Recently, in the development of new approaches to prolonging the life span particular attention was given to physiologically active peptides modulating functional activity of various organs and systems [4,5,9,12,13]. Geroprotective properties of short synthetic peptides are of considerable interest in this respect. Previous studies demonstrated that synthetic peptides carnosine (β-Ala-His) [1], thymogen (Glu-Trp), Vilon (Lys-Glu), and Epithalon (Ala-Glu-Asp-Gly) [7,9] prolong animal life span.

Our experiments showed that Vilon normalizes activity of digestive enzymes in old male and female Wistar rats [11]. Here we studied the effects of Epithalon on activity of digestive enzyme in various portions of GIT in rats of different ages.

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MATERIALS AND METHODS

Experiments were performed on 40 Wistar rats aging 3 and 11 months, kept under standard conditions with free access to food and water. Male and female animals were divided into control and experimental groups. Experimental rats received 100 mg Epithalon for 2 weeks (in addition to the standard food). Epithalon was synthesized by E. I. Grigor'ev at the St. Petersburg Institute of Bioregulation and Gerontology. Body weights were measured before and after the experiment.

Tissue specimens were isolated as described elsewhere [6]. Activities of membrane-bound enzymes invertase (EC 3.2.1.48), maltase (EC 3.2.1.20), alkaline phosphatase (EC 3.1.3.1), and aminopeptidase M (EC 3.4.11.2) and intracellular glycyl-L-leucine dipeptidase (EC 3.4.13.2) were measured in mucosal homogenates from the stomach, duodenum, jejunum, ileum, and large intestine.

Enzyme activities were measured in the linear range by routine techniques [4] and expressed in mmol hydrolysis products/g wet tissue/min. The results were analyzed by Student's t test.

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RESULTS

Peroral administration of Epithalon to 11-month-old females increased their body weight by 30% ($p<0.05$). In other experimental groups this parameter did not differ from the control.

In 3-month-old male rats receiving Epithalon maltase activity in the jejunum, ileum, and large intestine and glycyl-L-leucine dipeptidase activity in various portions of the small intestine decreased 2-fold compared to the control ($p<0.05$).

In 3-month-old males Epithalon treatment reduced invertase activity in the small and large intestine and alkaline phosphatase activity in the stomach. Aminopeptidase M activity increased in the duodenum (by 30%), stomach, and large intestine (by 2 times, $p<0.05$). Glycyl-L-leucine dipeptidase activity in the ileum and large intestine increased by 2 and 3 times, respectively, compared to the control ($p<0.05$).

Epithalon induced more pronounced changes in digestive enzyme activities in 11-month-old rats compared to 3-month-old animals. It should be emphasized that in young rats receiving Epithalon we observed both activation and inactivation of digestive enzymes, while in old animals Epithalon increased enzyme activities in various portions of GIT. The only exception was invertase activity in the large intestine (activity of this enzyme in this GIT portion was low in both control and experiment). In 11-month-old rats Epithalon increased invertase activity in the duodenum and ileum (by 2 times), maltase and aminopeptidase M activities in the duodenum (by 1.8 times, $p<0.05$), and glycyl-L-leucine dipeptidase activity in various portions of the small and large intestine (Fig. 1).

In 11-month-old females receiving Epithalon maltase activity in the duodenum, jejunum, and ileum increased by 1.5, 1.9, and 1.6 times, respectively; glycyl-L-leucine dipeptidase activity increased in all portions of GIT (Fig. 1).

Thus, peroral administration of Epithalon for 2 weeks increased activities of digestive enzyme, especially, in old rats. We previously hypothesized the existence of a functional relationship between the pineal gland and GIT realized via pineal gland peptides

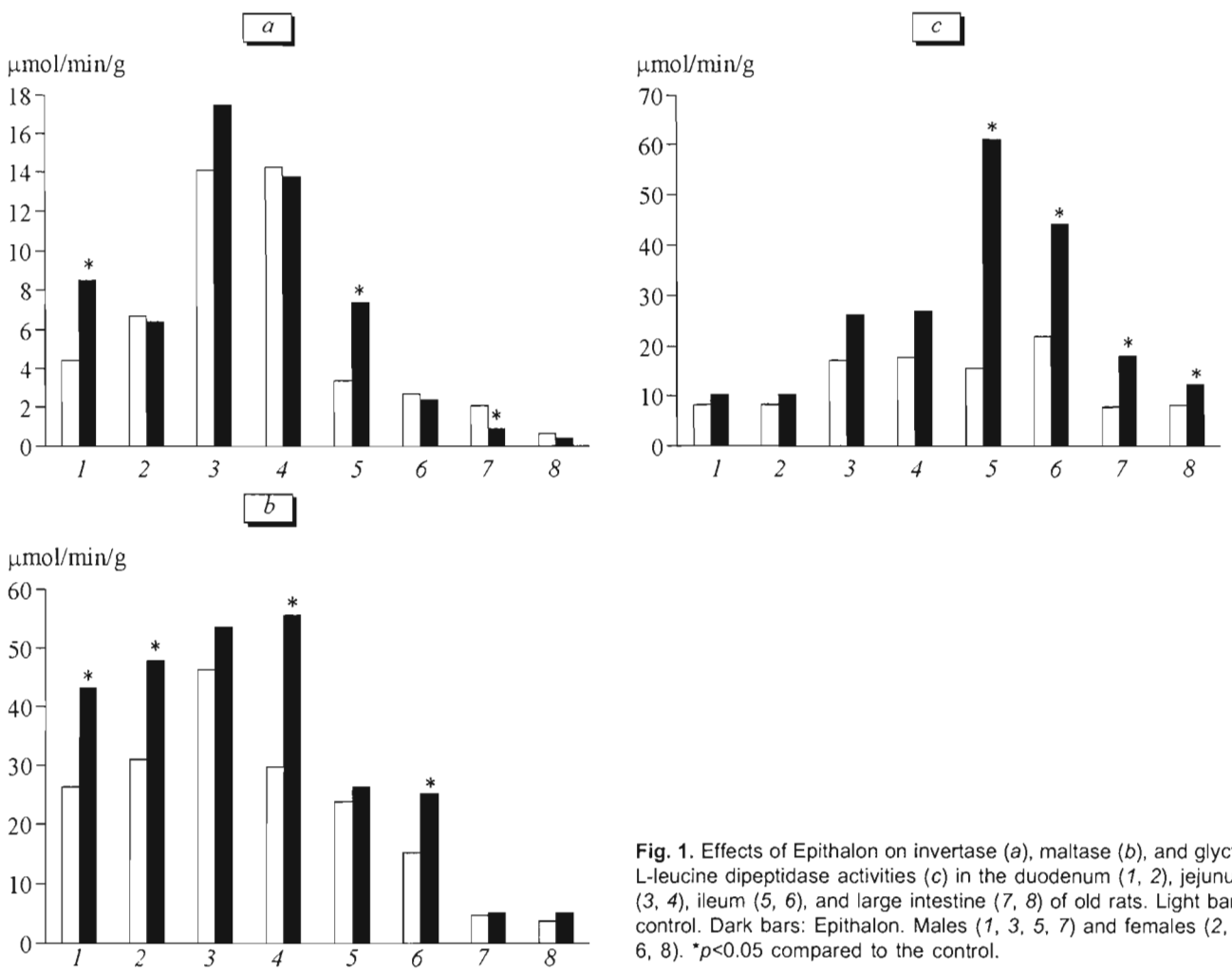

Fig. 1. Effects of Epithalon on invertase (*a*), maltase (*b*), and glycyl-L-leucine dipeptidase activities (*c*) in the duodenum (*1*, *2*), jejunum (*3*, *4*), ileum (*5*, *6*), and large intestine (*7*, *8*) of old rats. Light bars: control. Dark bars: Epithalon. Males (*1*, *3*, *5*, *7*) and females (*2*, *4*, *6*, *8*). *$p<0.05$ compared to the control.

[11]. Our results indicate that Epithalon synthesized on the basis of amino acid sequence of Epithalamin, a polypeptide preparation from the pineal gland, produces a pronounced homeostatic effect on digestion in the small intestine, especially, in old animals.

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