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SYNTHESIS AND INVESTIGATION OF THE VASOACTIVE PROPERTIES OF FRAGMENTS OF THE CALCITONIN GENE-RELATED PEPTIDE

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Calcitonin gene-related peptide (CGRP), consisting of 37 amino acid residues, is synthesized as the result of alternative processing of the RNA formed on the transcription of the calcitonin gene [1]. The physiological role of CGRP consists in the regulation of the cardiovascular function and the local blood flow, while the peptide exerts an action on the gastrointestinal and nervous systems and is one of the most powerful drugs possessing vasodilator activity.

The synthesis of analogs of the hormone has been described in the literature [2, 3], and the biological activities of individual fragments of the natural molecule have been investigated. The majority of such investigations have been devoted to the structure-activity relationship in the N-terminal part of the CGRP molecule [4, 5]. Together with this, it has been shown that the peptide sequence 8-37 possess antagonistic activity, while peptide 12-37 is a weaker antagonist [6]. At the same time, the biological activities of fragments of the central and C-terminal parts of the CGRP molecule have been investigated to a considerably smaller degree.

With the aim of a more detailed study of the roles of individual sections of the molecule in the manifestation of vasoactive properties, we have performed the synthesis of fragments 1-9, 10-20, 15-24, 21-29, 21-31, and 30-37 of the sequence of human α-CGRP. Peptides 15-24, 21-29, and 30-37 were obtained by the methods of classical peptide chemistry. Fragments 1-9, 10-20, and 21-31 were obtained by the solid-phase method using Pam (fragment 10-20) and the MBHA polymer. The final products were purified by HPLC. In the case of the peptide with the 1-9 sequence, in the performance of the cyclization reaction we used both oxidation with atmospheric oxygen and the action of potassium ferricyanide, the best results being obtained in the first case.

The study of the vasoactive properties of the fragments was carried out in the Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, on male rats of the Wistar line. The arterial pressure was recorded (gauge connected to the femoral artery) and the frequency of cardiac contractions was determined. The direct action of the CGRP fragments on the microvessels of the rat mesentery was also investigated by intravital television microscopy. The investigations performed showed that fragments 1-9 and 30-37 possssed no vasoactive properties. The administration of the peptides with the sequences 10-20 and 15-24 led to a brief rise and fall, respectively, in the arterial pressure, but only in a dose of 3 mg per animal. Fragments 21-29 in a dose of 2 mg per animal caused a prolonged fall in the arterial pressure by 30-40 mm Hg and exerted a vasodilatory effect in experiments on the microvessels. An analogous, but somewhat weaker, action was exterted by the peptide of the sequence 21-31.

Thus, among the compounds investigated vasoactive properties were found only in fragments of the central part of the CGRP molecule, and this in doses considerably exceeding the physiological level.

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