ANALOGS OF THE TETRAPEPTIDE GASTRIN WITH A MODIFIED TRYPTOPHAN RESIDUE

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A study of the biological activity of analogs of the COOH-terminal tetrapeptide of the hormone gastrin (I) has permitted the conclusion that the tryptophan and methionine residues in the peptide are mainly responsible for the addition of the hormone to the receptor, and the functional groups of the aspartic acid and the phenylalanine amide [1], or even the aspartic acid alone [2], are the direct initiators of the corresponding physiological reaction

$$H-Trp-Met-Asp-PheNH_2 \quad (I)$$
$$H-Phe-Met-Asp-PheNH_2 \quad (II)$$
$$H-His-Met-Asp-PheNH_2 \quad (III)$$

To investigate the hormone-receptor interaction further, the modification of the tryptophan residue presents definite interest. It is known from the literature [1,2] that substitution in the benzene ring of the tryptophan residue has little effect on the biological activity of the product, while changes in the heterocyclic part of the molecule lead to compounds with little or no activity. The analog of the tetrapeptide with phenylalanine (II) shows a considerable activity, while the analog with histidine (III) has a low activity. The elimination of the α-amino group of tryptophan has no effect on the activity.

In view of what has been said above, to investigate the topography of the receptor and the forces acting between the tetrapeptide and the receptor, we have synthesized analogs of the tetrapeptide I with naphthylpropionic, naphthylacrylic, and methylindolylaminopropionic acids in place of tryptophan. The syntheses were carried out by the addition of the corresponding acids (by means of dicyclohexylcarbodiimide) or their activated esters to the tripeptide obtained by the method described previously [3].

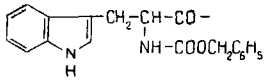
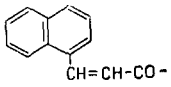
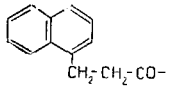
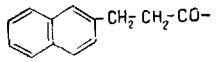
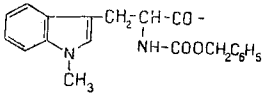
The influence of these analogs of gastrin on the secretory function of the stomach (the amount, acidity, and enzymatic activity of the gastric juice) was studied on experiments on cats (table). With the exception of the 2-naphthyl derivatives of the tripeptide (VI and VII), all the analogs had an activity of the same order as that of the tetrapeptide of natural gastrin (IV).

The present level of ideas on intermolecular interactions and the existing theory of these interactions do not make it possible to give a quantitative evaluation of the intermolecular forces and to give an exhaustive description of them. However, the results of the biological tests permit a qualitative evaluation of the role and importance of the aromatic system, of the imidazole nitrogen, and of the hydrogen attached to it in the binding of the hormone to the receptor and enable some considerations to be put forward.

The interaction of the hormone with the receptor, like any other intermolecular interaction, is determined by electrostatic, induced, and electrokinetic forces. When the indole nitrogen is blocked by a methyl group (compound VIII), the possibility of the following types of interaction disappears: ion with ion, ion with dipole, and interaction through a hydrogen bond. When the indole ring is replaced by a naphthalene ring, the interaction of a dipole with a dipole or an induced dipole also becomes impossible, and London dispersion forces remain as the main force of the interaction.

The molecules of aromatic compounds are readily polarized and frequently take part in strong interactions with cyclic systems similar to them or with other polarizable groups, especially if their mutual orientation permits a close juxtaposition of the corresponding parts of the surface of the molecule. Molecules with a high degree of conjugation containing several aromatic rings with a high electron mobility are capable of forming complexes with the parallel orientation corresponding to the maximum dispersion interaction. According to de Boer, the dispersion energy of interaction of two benzene rings arranged in parallel at a distance of 3.5 A is 24.6 kcal/mole [4]. For naphthalene it is undoubtedly greater (for comparison, we may recall that the energy of a hydrogen bond is 4–8 kcal/mole and that of a covalent bond 50–100 kcal/mole).

Influence of Analogs of the COOH-terminal Tetrapeptide of Gastrin R-Met-Asp-PheNH_2 on the Secretory Function of the Cat Stomach in vivo

Compound	Radical R	Structure	Mol. wt. of the peptide	MR^*_{50}, μg/kg	Relative activity**	Maximum response reaction at doses of μg/kg***	Amount of HCl secreted****, meq	Activity of the proteolytic enzymes	
								dose μg/kg	increase in activity
IV	α-(benzyloxycarbonylamino)-β-(indol-3-yl)propionyl		730.8	11.0	16.9	15— 25	1.18	15	2-fold
V	β-(1-naphthyl)acrylyl		590.7	Inactive	—	—	—	—	—
VI	β-(1-naphthyl)propionyl		592.7	Inactive	—	—	—	—	—
VII	β-(2-naphthyl)propionyl		592.7	69.5	2.6	60— 90	0.92	30—80	1.5-fold
VIII	α-(benzoyloxylcarbonylamino)-β-(1-methylindol-3-yl)propionyl		744.8	23.5	8.0	30— 60	0.50	40—60	1.5-fold
	Histamine	—	—	186.0	1.0	100—400	0.67	200	1.7-fold

*Dose of peptide in μg/kg body weight the administration of which caused the secretion of 50% of the maximum secretion of HCl.
**Activity of histamine taken as unity.
***Results from five cats.
****In 1 hr after the administration of the substance.

CONCLUSIONS

On the basis of results of the biological study of the analogs synthesized, it has been established that the interaction of the tryptophanyl residue of the tetrapeptide of gastrin with the receptor is performed mainly through London electrokinetic forces.

REFERENCES

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