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THE CUPRIC INTERACTION WITH OPIOID PEPTIDES

The role of peptides as classical hormones has long been known. More recently it has been appreciated a different role of some peptides acting in the central nervous system (*e.g.* thyroliberin, somatostatin, opiate related peptides, etc.). It is thought that they act as local tissue regulators and in some instances also as neurotransmitters [1]. Control of sleep, memory, perception are possible functions for these peptides.

All these peptides may serve as special chelate agents for trace elements, widely distributed in the body, especially for copper present in brain. It has been proved that some of the neuropeptides retain their biological activity in the form complexed by transition metal ions [2].

Since a few years we have been interested in metal (especially Cu(II)) interaction with some neuropeptides [3,4] and their chemical analogs [5]. All these peptides proved to be very specific ligands for metal ions.

Recently we have been studying the cupric complexation by some opiate related peptides *i.e.* β -casomorphin-5 and its di-, tri- and tetra-peptide fragments and enkephalin analogs.

β -casomorphin-5 is the opioid isolated from β -casein with the following sequence: Tyr-Pro-Phe-Pro-Gly. For our studies besides the β -casomorphin-5 itself, we have used a series of peptides: Tyr-Pro-Phe-Pro, Tyr-Pro-Phe, Tyr-Pro, Pro-Phe-Pro-Gly, Pro-Phe-Pro. Spectroscopic

(CD, EPR) and potentiometric studies have shown that the Cu(II) interaction with the β -casomorphin fragments depends strongly on the *N*-terminal amino acid. With Pro in this position typical peptide complexes containing the Cu-N⁽⁻⁾ bond are formed. With Tyr in this position a dimeric species, Cu₂L₂, becomes a major complex at physiological pH values, with the copper(II) bound to the -NH₂, CO groups of one ligand and to the phenolic oxygen of a second ligand.

The proline residue in the second and fourth positions in β -casomorphin-5 acts as a «break-point» to Cu(II) coordination and destroys completely the coordination ability of amino acid residues after the first Pro. In other systems with a proline residue inside the peptide chain the *N* and *C* terminals either interact separately [6] or form a macro-chelate with the peptide bent in a β -conformation [7].

Similar to the β -casomorphin, the enkephalin peptides with opiate activity contain the L-tyrosine residue on the *N*-terminus. This position of Tyr residue is a common feature to most endorphins and it is an important factor for their biological activity. Only the 2nd and 5th positions of enkephalin analogs can be safely manipulated to give a peptide with potent activity. Enkephalins and their structural analogs are of great interest to physicians and pharmacologists, because their properties might give the information on the mechanism of the development of drug addiction. Besides the pharmacologists are looking for enkephalin analogs which elicit analgesia but are less addicting with the hope to find the addiction-free pain relievers.

The following peptides have been studied: Tyr-Gly-Gly-Phe-Met (Met-enkephalin), Tyr-D-Ala-Gly-Phe-Met-NH-CH₂-CH₂-NH₂, Tyr-D-Ala-Gly-Phe-Met-N-(CH₃)₂, Tyr-D-Ala-Gly-Phe-Leu-ol. Spectroscopic and potentiometric data have indicated that all peptides mentioned above form similar four nitrogen complexes with cupric ions. Only in some cases a weak interaction of the phenolic oxygen with Cu(II) has been observed.

It is interesting to compare the role of a Tyr residue placed in a different position of a peptide chain. In β -casomorphin-5 the Tyr residue plays an important role in the formation of a major dimeric complex, while in enkephalin analogs the

N-terminal tyrosine interacts with cupric ion only through the amino and carbonyl groups. In earlier studies a Tyr residue plays a critical role in the formation of a dimeric cupric complex of Gly-Pro-Tyr-Gly [6], while a similar dimeric complex is only a minor species in the Tyr-Pro-Gly-Gly system and it is undetectable in the Gly-Pro-Gly-Tyr case [6].

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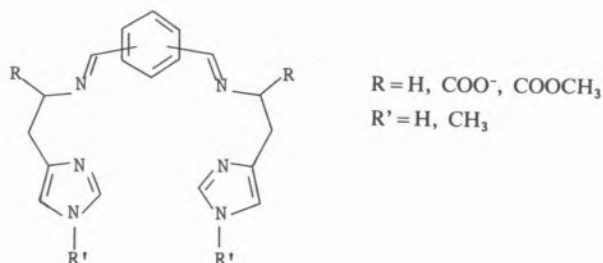
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MONONUCLEAR AND BINUCLEAR COPPER(I) AND COPPER(II) COMPLEXES DERIVED FROM L-HISTIDINE AND L-*N*⁷-METHYLHISTIDINE

The imidazole groups of histidine residues appear systematically involved in metal binding at the active site of copper proteins and enzymes, parti-

cularly those that function as oxygen carriers or promote some kind of oxygen activation [1]. Recently some copper(I) complexes containing the imidazole groups of histamine or histidine residues have been reported, also by us, to exhibit an apparent partially reversible oxygenation behavior in solution [2,3]. Though, in general, the oxygenated species in these or other systems [4] do not mimic the spectral features of the corresponding protein derivatives.

We have synthesized a series of mononuclear and binuclear copper(I) and copper(II) complexes of the ligands derived from the condensation of phthalic dicarboxaldehydes and two molecules of histamine, L-histidine, or their *N*⁷-methylated derivatives:



The binuclear copper(I) complexes are formally two-coordinate, while additional ligand molecules are required to obtain the corresponding copper(II) complexes. By changing the type of substitution of the xylil residues and the nature of the additional ligands we expect to vary the distance between the metal ions in the binuclear complexes, while the substituents R and R' affect the donor properties and charge of the ligands. The characterization of the complexes and the reactivity to dioxygen and other molecules of the copper(I) systems will be discussed.

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