

The complex-formation behaviour of His residues in the fifth Cu²⁺ binding site of human prion protein: a close look.

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Streszczenie

Human Prion Protein (hPrP^C) is able to bind up to six Cu²⁺ ions. Four of them can be allocated in the “octarepeat domain”, a region of the unstructured *N*-terminal domain containing four tandem-repetitions of the sequence PHGGGWGQ. It is widely accepted that the additional binding sites correspond to His-96 and His-111 residues. However, recent literature does not agree on the role and the behavior of these sites in Cu²⁺ complexation to hPrP^C. In order to shed more light on this topic, some peptidic analogues of the PrP_{92–113} fragment were synthesized: (H96A)PrP_{92–113}, (H111A)PrP_{92–113}, (H96N^τ-Me-His)PrP_{92–113}, (H111N^τ-Me-His)PrP_{92–113}, (H96N^τ-Me-His)PrP_{92–100}, (H111N^τ-Me-His)PrP_{106–113}, where an alanine or a histidine methylated at the τ nitrogen atom of its imidazole ring have been substituted to His-96 or His-111. The first two ligands allowed to confirm that His-111 binding site is stronger than His-96 one: they act as independent sites even at Cu²⁺-ion substoichiometric levels. Neither multi-histidine binding nor bis-complex formation has been detected at neutral pH. N^τ methylation gave evidence that τ nitrogens of imidazole residues can participate in complex-formation only at acidic pH, where displacement of amidic protons by Cu²⁺ ions is not allowed. Finally, the length of the fragment does not appear to have any significant influence on the behavior of the two His-96 and His-111 binding sites, from the point of view of either the coordination geometry or their relative strength.

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