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Review

Cu and Zn coordination to amyloid peptides: From fascinating chemistry to debated pathological relevance ☆

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ABSTRACT

Several diseases share misfolding of different peptides and proteins as a key feature for their development. This is the case of important neurodegenerative diseases such as Alzheimer's and Parkinson's diseases and type II diabetes mellitus. Furthermore, metal ions such as copper and zinc might play an important role upon interaction with amyloidogenic peptides and proteins, which could impact their aggregation and toxicity abilities. In this review, the different coordination modes proposed for copper and zinc with amyloid-β, α-synuclein and IAPP will be reviewed as well as their impact on the aggregation, and ROS production in the case of copper. In addition, a special focus will be given to the mutations that affect metal binding and lead to familial cases of the diseases. Different modifications of the peptides that have been observed *in vivo* and could be relevant for the coordination of metal ions are also described.

Contents

Abbreviations: AD, Alzheimer's disease; AFM, atomic force microscopy; APP, amyloid precursor protein; Aβ, amyloid-β peptide; DHA, dihydro ascorbic acid; EPR, electron paramagnetic resonance; FAD, familial Alzheimer's disease; hAβ, hIAPP, human peptides; IAPP, islet amyloid polypeptide; mAβ, mIAPP, murine peptides; IDPs, intrinsically disordered peptides/proteins; MD, Molecular Dynamics; NAC, non-amyloid component; Nim, imidazole nitrogen; NMR, nuclear magnetic resonance; N-term, N-terminal; PB, phosphate buffer; PD, Parkinson's disease; rAβ, rIAPP, rat peptides; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; T2D, type II diabetes mellitus; ThT, Thioflavin T; WT, wild type (no mutated peptide); αSyn, alpha-synuclein; βSyn, beta-synuclein.

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1. Introduction

In the last decades, the discovery of a common characteristic to different diseases is leading the research on their development. Neurodegenerative diseases such as Alzheimer's (AD), Parkinson's (PD), Huntington's and prion diseases share with type II diabetes mellitus (T2D) the misfolding of specific proteins or peptides, which causes the deposition of amyloid fibrils and plaques in different tissues [1]. Furthermore, metal ions dyshomeostasis has been linked to AD, PD and T2D and could be a key factor in their development as they can greatly impact the aggregation and the redox activity of the implicated peptides and proteins [2–4]. Several studies have found a relatively high concentration of metal ions (Zn, Cu and Fe) in aggregates such as senile plaques (AD) formed by the amyloid-β (Aβ) peptide [5–9], and Lewy's bodies (PD) formed by α-synuclein (αSyn) protein [10]; and a probable correlation between amyloid deposits formation of islet amyloid polypeptide (IAPP, amylin), Zn deficiency and T2D [11]. Nevertheless, there is still no clear evidence of the *in vivo* metal-binding to Aβ, αSyn and IAPP upstream of the aggregates. One parameter to take into account is the relatively low binding constant for these peptides and protein, which makes metal-binding a low probability scenario in the cytosol [12]. However, interaction between Cu and Zn and intrinsically disordered peptides/proteins (IDPs) could be plausible in the extracellular space. In the case of AD, a "labile copper pool" was proposed [13]. Similarly, spots where high concentration of metal ions, especially loosely bound metals, would be present such as in β-cells in the pancreas could be key for the interaction of IDPs and these metal ions. Moreover, some deregulation of the metal ions' concentration might need to occur, which would increase the available metal ions, and hence permit metal binding to Aβ, αSyn and IAPP.

In this review, we will focus on Cu and Zn, due to their relatively high concentration in the synaptic cleft in the brain and β-cells of the pancreas. The coordination chemistry of Zn(II) and Cu(II/I) have been studied since more than two decades, at least for Aβ. Thus, we do not go into past controversies, which mainly concern the native structure of amyloid-β. We just report the most accepted structures (and refer to past reviews) and concentrate on the most recent advancements often obtained on mutations or modified forms of the peptides/proteins. A general perspective of the metal-induced aggregation and ROS production will be covered in Sections 3 and 4, aiming to compare the last data for the three peptides and protein. Surely this work will complete the reviews that aimed to cover the interaction of metal ions and amyloidogenic peptides individually. Moreover, we aim at outlining their coordination not only to Aβ, αSyn and IAPP, the main disordered peptides and proteins of the mentioned diseases; but also, to the mutated peptides which cause familial pathologies, and the murine peptides, which show different aggregating propensity features *in vivo* (Table 1). Studying how these mutations impact the coordination of metals ions, and consequently their aggregation and ROS production could be an important step to help elucidate this very interesting chemistry.

2. Coordination of Cu and Zn to amyloid-β, α-synuclein and IAPP and their mutants

The coordination of metal ions to the different amyloidogenic peptides and proteins has been thoroughly studied. There is still debate regarding some coordination modes. Nonetheless, in the next paragraphs the different coordination modes, including the most accepted and the new ones, proposed for Aβ, αSyn, IAPP and their mutated and murine homologues will be outlined (Table 1). In order to give a more global understanding of Cu and Zn binding to these peptides and protein, their association constants have been gathered in Table 2.

2.1. Coordination to Aβ, its FAD mutants and murine Aβ

The high affinity metal binding site of amyloid-β (Aβ) peptide is found at residues 1–16, which is proposed as an appropriate model of its coordination and redox properties of its Cu complex. The most accepted metal binding structures involving the native peptide will be described below. Meanwhile, the structures concerning mutated peptides will be discussed more profoundly. At physiological pH, two different binding modes can be found for Cu(II), known as component I (favored at lower pH) and II (at higher pH) [17–21]. They both present a distorted square-planar geometry and the coordination through the terminal amine of the Asp1 residue (Fig. 1A). In Component I, Cu(II) is also bound through the carbonyl from the Asp1-Ala2 amide bond, and the imidazole nitrogen atoms (Nim) from two histidine residues, His6 and His13 or His14 in equilibrium. In component II, the nitrogen atom from the Asp1-Ala2 amide bond is deprotonated and binds to Cu(II), together with the CO from the Ala2-Glu3 peptide bond and one imidazole nitrogen atom (N_{im}) with no preference. A different structure has been proposed for component II, involving the oxygen from the carbonyl group of the Ala2-Glu3 bond and the three N_{im} from His6, His13 and His14 [22]. Some authors have also proposed a carboxylate function being involved in the apical position [23,24]. A second site has been described for the $A\beta_{1-28}$ peptide but its low affinity would mean a lower biological relevance [25]. Cu(I) is bound in a linear fashion by the N_{im} of His6, His13 and His14 in an equilibrium, in which His13 and His14 seem to be the preferred ligands [26,27] (Fig. 1A). The amino acids involved in the coordination of Zn(II) are also found in the $A\beta_{1-16}$ sequence. First studies reported the involvement of the three histidine residues in the coordination site [28–34], being the fourth and, in some cases, fifth ligands the