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Review

An inorganic overview of natural Aβ fragments: Copper(II) and zinc(II)-mediated pathways

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ABSTRACT

Unravelling the molecular basis for Alzheimer's disease (AD) represents one of the main scientific challenges we face when it comes to treating and – most importantly – preventing the onset of this devastating condition. The amyloid-beta peptide (Aβ) is a key element around which the metabolic pathways linked to sporadic AD forms have been investigated. The right balance between production and degradation of Aβ is fundamental to the physiological activity of the peptide and to preventing the formation of toxic aggregated species. Whilst the metabolic pathways for the formation of Aβ from the amyloid precursor protein (APP) have been unveiled, the mechanism involved in the control of Aβ levels through enzymatic systems (UPS, lysosomes and Aβ-degrading enzymes), both *in vitro* and *in vivo*, is underexplored.

Overwhelming evidence clearly indicates that the abnormal aggregation of Aβ is not the main – or even the only – biochemical event that characterizes the onset and progression of AD, which can be also driven by the alteration of metallostasis (metal homeostasis) of d-block metal ions, such as copper(II) and zinc (II). The "Metal Hypothesis" in AD also concerns the effects of these metal ions on the formation and activity of Aβ fragments. Once Aβ is processed by the Aβ-degrading systems, the amyloid fragments can lose, maintain or modify the metal binding properties, unlike the full-length peptide. In addition, the physiological and/or pathological functions of the peptide fragments and their metal complexes can be different from those exerted by Aβ and its metal complex systems.

We will outline the Aβ fragments detected in human fluids and tissues from both healthy and AD patients, as well as the structural and biochemical features of copper(II) and zinc(II) complexes with the naturally-occurring Aβ fragments. Then we will delve into the essential features and functionalities of the enzymatic systems involved in the clearance and degradation of Aβ and the effects of Cu^{2+} and Zn^{2+} in their activity. Finally, we will explain how we to match the cleavage sites of the Aβ-degrading enzymes to the natural-occurring cleavage sites of Aβ.

Contents

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1. Introduction

Alzheimer's disease (AD) is an increasingly widespread condition affecting several million people worldwide [1]. Given these alarming numbers, unravelling the molecular basis for this neurodegenerative disorder remains a priority when it comes to preventing the onset of such a devastating disease. Among the various endogenous factors involved in the progression of AD, the amyloid-beta peptide (Aβ) is a key element around which most of the metabolic pathways linked to the sporadic AD forms has been investigated [2]. Aβ is the product of a multistep pathway in which the amyloid precursor protein (APP) represents the origin.

Aβ, as a multifunctional – as well as a puzzling – peptide, has a propensity for conformational transitions ranging from a random-coil-structured species to β-sheet rich forms. For reasons that are not quite clear yet, such conformational transition turns out to be accelerated in pathological conditions, resulting in the formation of soluble and toxic oligomers; these species, much more than larger aggregates and amyloid fibrils, have a driving role in the amyloid cascade hypothesis [3].

The right balance between production and degradation of Aβ is crucial to the physiological activity of the peptide and to avoiding the formation of toxic aggregated species. Therefore, the modulation (inhibition or activation) of the proteases involved in Aβ degradation becomes a potential pathway to control Aβ metabolism. Even if the numerous studies on the non- and pro-amyloidogenic pathways that process APP have exhaustively clarified the mechanisms involved in the formation of both soluble non-toxic APP fragments and Aβ, little we do know about how several proteases hydrolyze Aβ *in vitro* and *in vivo*. This class of proteases includes Insulin Degrading Enzyme (IDE), Neprilysin (NEP), Matrix Metallo-Proteases (MMPs), Endothelin and Angiotensin Converting Enzymes (ECE and ACE) [4].

The deposition of Aβ in the cerebral plaques as the driver of AD pathogenesis is the core of the amyloid cascade hypothesis [2].

Therapeutic strategies, consequently, have focused on lowering Aβ levels and decreasing levels of toxic Aβ aggregates through (1) inhibition of the transformation of APP into Aβ, (2) inhibition, reversal or clearance of Aβ aggregation, and (3) Aβ immunization.

The outcomes of recent clinical trials based on anti-Aβ therapies, centered both on BACE1 inhibitors [5] and anti-amyloid antibody [6], failed to meet the expectations generated by results in animal models, [7] being this an outright challenge to the amyloid hypothesis [8]. Notwithstanding, these results should rather encourage the unveiling of other targets. Control of Aβ production or the aggregation process remains the main goal when it comes to testing new therapeutics for AD [2].

Both APP and Aβ play a key role in the homeostasis of copper and zinc [9,10]. The effect of these metal ions on human health, and neurodegeneration in particular, is still widely debated. The toxic effects of abnormal levels of copper(II) in the diet has been pointed out as one of the main causes of AD, whereas zinc is considered the 'buffer' agent against the deleterious action of copper (II) in AD [11]. Counterintuitively, severe copper deficiency is a hallmark showing in several brain regions of patients affected by AD [12,13]. The balance between the intra- and extra-cellular content of copper and zinc should represent the main issue to be addressed in order to fully understand how the dys-homeostasis of d block metal ions affects AD. As a matter of fact, a series of metal binding molecules that are able to deliver copper and zinc towards the intracellular compartment (copper and zinc ionophores) give rise to unquestionable outcomes both *in vitro* and *in vivo*: Aβ coming from the APP-processing pathway is rapidly decreased, thus preventing the amyloid aggregation [14]. Even if copper and zinc have not deemed to be antagonistic in AD, their mutual influence [15] is further indication that any therapeutic approach should consider the co-presence of both Cu^{2+} and Zn^{2+}.

The altered metallostasis (metal homeostasis) [16] found in AD patients [17] prompted the study of the relationship between metal ions and Aβ aggregation. Proteins localized in different compartments (i.e., plasma membrane, organelles, and cytoplasm) ensure the regulation of metal homeostasis and prevent both the accumulation of extracellular metal ions and the depletion of intracellular metal stores [18]. Under this scenario, the blocking of metal signaling [19] represents the final frontier of research that connects the metal ions trafficking to the proteins involved in the metal homeostasis, including Aβ.

All this experimental evidence led to the proposal of the "Metal Hypothesis" of AD [20], i.e. pathogenic effects of Aβ in AD are dependent on metal ion dyshomeostasis that, in turn, affects the metal-Aβ interactions and, as a final step, the aggregation process. For this reason, the structural features of the metal-Aβ complex systems have properly been investigated under several experimental conditions. Once Aβ is processed by the physiological Aβ degrading enzymes, the peptide fragments can lose, maintain or modify the metal binding properties with respect to the full-length peptide. Moreover, the physiological and/or pathological functions of the peptide fragments and their metal complexes can be different from those exerted by Aβ and its metal complex systems.

Therefore, the aim of this review is to report on:

- the Aβ fragments detected in human fluids and tissues of both healthy and AD patients;
- the structural and biochemical features of copper and zinc complexes with naturally-occurring Aβ fragments;
- the essential features and functionalities of the protein systems involved in the clearance and degradation of Aβ and the effects of copper and zinc on their activity;
- the *in vitro* cleavage sites of the Aβ-degrading enzymes in comparison to those involved in the formation of the natural Aβ fragments.

The importance of the natural Aβ fragments and their metal complexes seems to be rather underestimated. A deeper investigation of these fragments and their metal complexes *in vivo* could address many issues regarding the onset and/or the propagation of AD, as summarized in the Perspectives section.