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Protein fibrillation and the olfactory system: speculations on their linkage

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Protein fibrillation refers to the formation of large linear agglomerates of protein fibrils possibly by misfolding of amyloidic proteins (i.e., toxic folding) [1]. In the body, this can result from long-term age damage or overexpression of proteins, resulting in crowding, denaturation, and precipitation. Until recently, the two more widely acknowledged molecular hypotheses suggested to explain the pathology of Alzheimer's disease (AD) include (i) misfolding of some brain proteins or peptides (e.g., amyloid β, Aβ) and (ii) the effects of multivalent cations (e.g., Zn^{2+}, Cu^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, and Al^{3+}) as modulating events in the formation of plaques and tangles in the brain [2].

The major challenge in AD and other amyloidogenic diseases is their early diagnosis before progression to major neuropathology. Significant efforts have been focused on determining specific biomarkers associated with severe loss of cognitive function. Detection of amyloid fibrils in neuron tissue in the early stages of disease has not been possible because of the low sensitivity to early fibril or precursor precipitation of current imaging methods (e.g., magnetic resonance imaging). Hopes for early diagnosis of AD have been considerably increased with the introduction of nanotechnology to medicine, specifically as contrast agents. Because of the low targeting capability of nanoparticles (which are limited by their inherent formation of protein coronas), however, the contrasts achieved are not yet sufficient for early diagnosis [3].

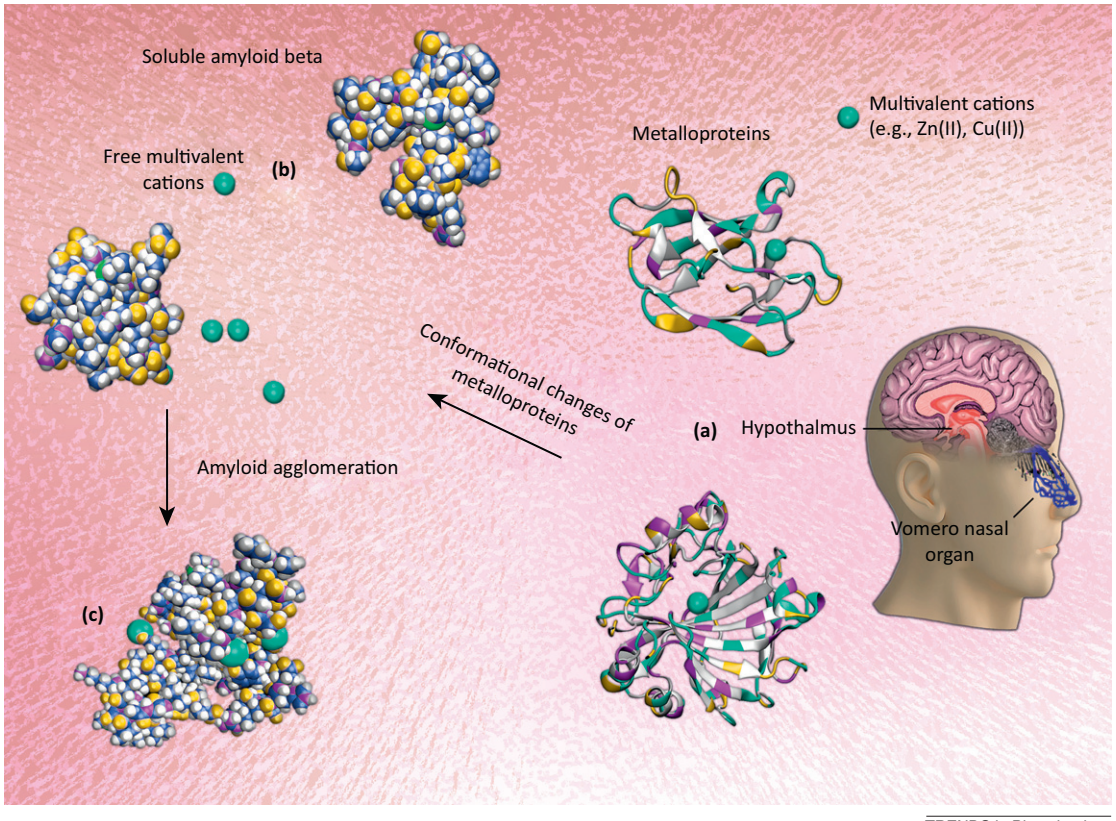

Figure 1. Scheme showing the crucial effects of metal ions and metalloproteins on amyloidic protein agglomeration. **(a)** Conformational changes in metalloproteins or in malfunction of metal ion transport can release multivalent metal cations. **(b)** These free cations may link soluble amyloid monomers together and **(c)** induce the first seeding of the fibrillation process.

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Perceptual symptoms (e.g., losses in memory, language, visual, olfactory, and auditory processing) are recognized as promising indicators for early detection of AD [4,5]. In fact, olfactory dysfunction may be the most promising hallmark for early detection of AD [6]. Olfactory disorders in AD-induced mice are due to the initial deposition of Aβ agglomerates in the olfactory bulbs, followed by subsequent deposition in the olfactory cortex and hippocampus [6]. It is noteworthy that olfactory disorders have also been reported in all other amyloidogenic disorders, such as Parkinson's disease, Lewy body disorder, and frontotemporal dementia [4,7]. We might therefore expect that these olfactory deficits can be recognized as a specific biomarker for amyloidogenic disorders.

Various crucial intracellular biochemical and homeostatic sensing reactions are modulated by transition metals, typically in the form of metalloproteins. Interestingly, polycationic metal ions [e.g., Cu(II) and Zn(II)] play a crucial role in odor recognition and the structure and function of olfactory receptors [8]. Polycationic metal ions can also significantly induce or accelerate the amyloidic protein fibrillation process [3]. We therefore speculate that a reduced olfactory response and the formation of amyloid fibrils may be causally linked: fibrillation may start from molecular malfunction of metalloproteins or of transport and incorporation of metal ions into metalloproteins, including those responsible for olfactory systems. More specifically, irreversible conformational changes in metalloproteins, as one example, can release polycationic metal ions to soluble amyloids. There, the cations can create stable binding between amyloids, which may initiate the fibrillation process, either kinetically or thermodynamically.

Bioinorganic chemistry has made substantial advances in probing the functions, mechanisms, and structures of metalloproteins [9,10]. The nature of metal ion interactions with proteins is diverse and the strength of interactions covers the full range from strong covalent bonding between metal ions and functional groups of proteins (e.g., the imidazole of histidine and thiolate of cysteine) to weak electrostatic or outer-sphere interactions with coordinated water molecules [9]. As a consequence, metal ion–protein associations can range from essentially irreversible to rapidly exchanging [9–11]. A scheme of our hypothesis is presented in Figure 1.

In summary, molecular aspects of olfactory dysfunction can be recognized as a hallmark of amyloidogenesis-related diseases and there may even be a causal link through the disruption of multivalent metal ion transport and storage. We therefore suggest that it may prove fruitful to examine the relationships among amyloidogenic diseases, metal ion transport, and metalloprotein function.

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Bacillus spore display

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Molecular display, a technique that presents proteins or peptides on the surface of microorganisms, enables high-throughput screening and has become an essential tool in bimolecular engineering. To display properly, the proteins should be fused to a display motif, translocated through the membrane, and anchored at the cell surface. Many surface proteins, for example, Lpp-ompA, InaK and AIDA-I from *Escherichia coli*, have been used for displaying target proteins, such as antigens, enzymes, and bioadsorbents [1]. Here, we discuss the unique molecular display system of *Bacillus* spores: (i) the spore is the most resilient life form; (ii) no secretion is required for the display; and (iii) the foreign proteins can be displayed in their native forms, thus obviating the need to produce fusion proteins.

Formed in response to nutrient starvation, *Bacillus* spores are robust and can withstand extremes of heat, desiccation, and chemicals. The spores of *Bacillus subtilis* are encased in a protective coat consisting of an inner and an

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