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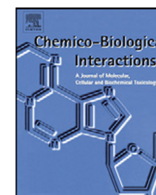

Mini review

Prion metal interaction: Is prion pathogenesis a cause or a consequence of metal imbalance?

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Functional role of cellular prion protein (PrPc) has been hypothesized to be in metal homeostasis and providing cells with a superoxide dismutase (SOD)-like activity to escape damage by reactive oxygen species (ROS). PrPc interacts with a range of divalent metal ions and undergoes Cu^{2+} as well as Zn^{2+}-associated endocytosis, thereby maintaining homeostasis of these and other metal ions. Conformational change to a β-sheet rich, protease resistant entity, reminiscent of the disease-associated scrapie form called PrPsc, has been found to be induced by interaction of PrPc with metal ions like Cu^{2+}, Zn^{2+}, Mn^{2+} and Fe^{2+}. This review compiles data from various experimental studies of the interaction of metals with PrPc. The effect of metal ions on the expression and conformation of the prion protein is described in detail with emphasis on their possible physiological and pathogenic role. Further, a hypothesis is presented where attainment of altered conformation by metal-bound PrPc has been viewed as a deleterious consequence of efforts made by cells to maintain metal homeostasis. Thus, PrPc presumably sacrifices itself by converting into PrPsc form in an attempt to protect cells from the toxicity of metal imbalance. Finally, possible reasons for contradictions reported in the literature on the subject are explored and experimental approaches to resolve the same are suggested.

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Contents

1. Introduction 283
 1.1. The structure of the prion protein 283
2. Evidence for interaction of metals with the prion protein 283
 2.1. Details of the binding of divalent metal ions to cellular prion protein and their physiological function 284
  2.1.1. Copper 284
  2.1.2. Zinc 285
  2.1.3. Manganese 286
  2.1.4. Iron 286
  2.1.5. Other metals 286
3. Role of divalent cations in the pathogenesis of prion diseases 286
 3.1. Copper 286
 3.2. Zinc 287
 3.3. Manganese 287
 3.4. Iron 287
4. Hypothesis 287
5. Conclusions 288
Conflict of interest statement 289
Acknowledgements 289
References 289

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1. Introduction

The study of the prion protein was initiated due to its involvement in a number of related neurodegenerative disorders seen in various species (bovine spongiform encephalopathy in cattle, scrapie in sheep and Creutzfeldt–Jakob disease in humans). The name PRION (for PRoteinaceous INfectious) emerged as the infectious agent of these diseases was found to be constituted significantly of protein [1]. A protein with identical sequence was found to be expressed in significant quantities in the brains of non-diseased animals. Hence, a consensus was reached that the protein existed in two distinct forms: the normal cellular form (PrPc) and the diseased or scrapie form (PrPsc). Presently, PrPsc is considered to be the major cause of the spongiform encephalopathies, although the possibility that a small ligand may contribute to the infectivity of the disease cannot be ruled out [2]. However, recent evidence suggests that the scrapie form of the protein may be sufficient by itself for transmission of the disease [3].

Transmissible spongiform encephalopathies (TSE) or prion diseases are characterized by the deposition of PrPc in the structurally altered PrPsc form. While PrPc is primarily α-helical and susceptible to proteolysis, PrPsc forms fibrillar aggregates containing high percentage of β-sheet and is rather resistant to proteolytic digestion [2]. TSE and related neurological disorders manifest physiological symptoms similar to aging which, in turn, have been shown to be affected by divalent metal ions. Over the past three decades the role of metal ions in TSE has attracted considerable attention particularly since 1970s, when Cu^{2+} chelator-induced histopathological changes were documented to be similar to scrapie [4]. Metal ions have been implicated as potential pathogenic candidates owing to their properties of being free-radical generators and their association with metalloenzymes such as superoxide dismutases (SODs) [5]. Pathological features of TSE resemble neuronal and brain tissue loss as is observed in the case of free-radical-mediated oxidative damage [6,7].

According to the "protein-only hypothesis" the conversion of PrPc to PrPsc which is a hallmark of prion diseases does not require any accessory molecule [2]. While this hypothesis stands perfectly for synthetic (in-vitro) conversion of purified PrPc to PrPsc, the mechanism of in-vivo conversion is still controversial, particularly in terms of the simplest infective entity produced during the conversion. The fibrils produced by in-vitro conversion achieved through various physicochemical modes (temperature, denaturant, pH, etc. either independently or in combination), have remarkable resemblance to the amyloids obtained from diseased brains in their morphological and tinctorial properties. However, most of them lack the capability to transmit disease [8–10]. Hence, the integrity of such amyloids formed in-vitro in terms of their infectivity is often questionable, with some notable exceptions [3]. Regardless of the debate on the character of the infective agent, the distinct properties and the mysterious conditions under which PrPsc fibrils emerge in diseased brains forces one to wonder about the natural role of PrPc in tissues where they are found in abundance.

Understanding the functions of cellular prion protein may have important implications in understanding the reason and the molecular mechanism behind the symptoms observed in the prion diseases. Three tentative functions related to metal homeostasis have been assigned to PrPc so far: protection from oxidative stress, transport of Cu^{2+} into the cell, and Cu^{2+} buffering [11,12]. Although there is still some dispute over the existence, and nature, of these functions, there is considerable evidence to suggest all or any of the three may represent the true function of the prion protein in-vivo. Other functions suggested for PrPc include roles in memory and inflammatory reactions, cell-proliferation and differentiation in the nervous and immune systems, signal transduction, etc. [13,14]. Apart from its GPI anchored membrane-bound form, soluble form of PrPc has been found to be secreted by resting as well as activated platelets [15]. A possible role of the released form of PrP has been suggested in the terminal stages of sperm maturation [16]. This review summarizes the current understanding of the role of metal ions in prion protein function and its conversion to the diseased PrPsc form.

1.1. The structure of the prion protein

An understanding of the interaction of metals with the prion protein can be sought from structural information. Prion protein is expressed constitutively in many cell-types and is the product of a single exon. It exists as a membrane-bound monomer of 231 amino acids. The N-terminal of the protein carries a signal sequence of 23 amino acids while the C-terminal contains a signal sequence for a glycosylphosphatidyl inositol (GPI) anchor (Fig. 1a). Glycosylation sites are also present near the C-terminal and the protein may exist in unglycosylated, mono-glycosylated and di-glycosylated form [17]. Structural and biochemical investigations have revealed the presence of high α-helical content (Fig. 1b) and high proteolytic susceptibility of the cellular form PrPc, whereas the scrapie form, PrPsc, shows high β-sheet content coupled with high protease resistance [18]. More precisely, PrPsc has a protease resistant core consisting of residues 90–231. NMR structure of full length prion protein (23–231) from human, hamster and sheep reveals a flexible N-terminus of residues 23–124, a globular central domain for residues 125–228 and a short flexible chain end at the C-terminus of residues 229–230 [19,20]. X-ray crystallographic structure of the prion protein from residue 90–231 is available at 2 Å resolution [21]. In contrast to the previously reported monomeric NMR structure, the crystallographic data revealed a C-terminal domain swapped dimeric form with an intermolecular disulphide bond. Further, from the finding of a conformational switch region at the dimer interface it was proposed that such 3D domain swapping may be an important mechanism for oligomerization. Some studies indicate that a metal-dependent dimerization of PrP may be important in both normal and aberrant functioning of PrP [22,23], and this may be evidence of the physiological importance of these dimeric structures. However, though these techniques have satisfactorily elucidated the structure of the globular domain, structural information for the N-terminal flexible domain is largely missing. The important role of the N-terminus in the PrPc → PrPsc conversion has been demonstrated both theoretically [24] and experimentally [25]. Primary-structure analysis shows several highly conserved octarepeat regions (OR) of sequence PHGGGWGQ in prion proteins of various animals at the N-terminus (Fig. 1a). Another highly conserved feature is the palindromic region from residues 113 to 120, which is a part of the hydrophobic core sequence.

2. Evidence for interaction of metals with the prion protein

The precise physiological function of the prion protein (PrP) is yet to be determined. PrP-knockout mice exhibit normal development and behavior as compared to wild type mice, perhaps pointing to a very subtle physiological role in natural circumstances. However, upon aging, these knockout mice show demyelination in the peripheral nervous system but lack any clinical symptoms. Behavioral studies show disturbed circadian rhythm and sleep pattern. There are also reports of some neurophysiological abnormalities, which can be rescued by the introduction of PrP transgene [26–29]. It has been the identification of PrPc as a Cu^{2+}-binding protein that led to the majority of hypotheses about its normal cellular function [30]. A major breakthrough was the discovery that Cu^{2+} and Zn^{2+} stimulate the endocytosis of PrPc, thus linking metal binding to a physiological response [31,32]. Accordingly, PrPc is thought

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