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Review Article

The Role of Zinc in Alzheimer's Disease

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Zinc, the most abundant trace metal in the brain, has numerous functions, both in health and in disease. Zinc is released into the synaptic cleft of glutamatergic neurons alongside glutamate from where it interacts and modulates NMDA and AMPA receptors. In addition, zinc has multifactorial functions in Alzheimer's disease (AD). Zinc is critical in the enzymatic nonamyloidogenic processing of the amyloid precursor protein (APP) and in the enzymatic degradation of the amyloid-β (Aβ) peptide. Zinc binds to Aβ promoting its aggregation into neurotoxic species, and disruption of zinc homeostasis in the brain results in synaptic and memory deficits. Thus, zinc dyshomeostasis may have a critical role to play in the pathogenesis of AD, and the chelation of zinc is a potential therapeutic approach.

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia, which affects more than 37 million people worldwide, with an estimated cost of $422 billion in 2009 [1, 2]. Moreover, the incidence of the illness and the prospect of an aging population will result in rising social and economic demands. AD is characterised by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles within the afflicted brain, which cause neuronal loss in the neocortex, hippocampus, and basal forebrain, leading to progressive cognitive and behavioural decline [3]. Zinc, in addition to copper and iron, has been shown to be involved in AD. Here, we review the current literature relating to neuronal zinc metabolism and the way in which zinc can modulate normal brain activity. We discuss also the contribution of zinc to the formation, aggregation, and degradation of the amyloid-β (Aβ) peptide and the contribution of zinc to the pathogenesis of AD.

2. Physiological Role of Zinc in the Brain

As the most abundant trace metal in the brain, zinc is found tightly associated with numerous proteins conferring either structural or catalytic properties upon them [4]. However, a significant amount of loosely bound, chelatable zinc can be found sequestered in presynaptic vesicles forming a subpopulation of "zinc enriched" (ZEN) neurones [5, 6], which co-release zinc with the neurotransmitter glutamate upon excitation. The majority of these "gluzincergic" neurones [7] have their cell bodies located in either the cerebral cortex or the limbic structures of the forebrain [8], and so an extensive network uniting limbic and cerebrocortical functions is created [9]. This connection between zinc and glutamatergic neurotransmission allows the ion to modulate the overall excitability of the brain and also influence synaptic plasticity [10].

The identification of synaptic zinc was first made by McLardy over fifty years ago who identified that a band of zinc dithizonate staining correlated with hippocampal mossy fibre axons [7]. Since then, many more cerebrocortical pathways have been identified which contain zinc-rich synaptic vesicles; indeed nearly 50% of the glutamatergic synapses are actually "gluzincergic" in some parts of the cerebral cortex. Significantly, only small amounts of chelatable zinc can be determined in glutamatergic pathways which originate outside the cerebral cortex or limbic systems.

Despite this extensive network of zinc-containing neurons, little is known about how zinc homeostasis is maintained within the neuron. There are two families of zinc transporters: the ZnT family, which act to decrease intracellular zinc concentrations by exporting zinc from the cytoplasm to the lumen of organelles or the extracellular

space, and the ZIP family, which import the metal from the extracellular space or organellar lumen into the cytoplasm [11]. Whilst many of the transporters have particular distribution patterns, only ZnT3 expression is restricted to the brain and the testis [12]. It is located in the vesicular membrane [13] and is necessary to transport zinc from the cytoplasm into the synaptic vesicle of the neuron. The vesicular concentration of zinc correlates with the amount of ZnT3 present [14]. Targeted disruption of ZnT3 in a mouse model resulted in a complete lack of chelatable zinc [15].

A number of approaches have been taken to confirm that zinc is coreleased with glutamate from the presynaptic bouton during neuronal excitation: imaging of zinc in boutons before and after stimulation [16], analytical detection of zinc released into perfusates [17], and direct imaging of released zinc using fluorescent extracellular probes [18, 19]. This latter approach has provided the most definitive results. An early study employed a reporter construct whose fluorescence properties changed upon zinc binding. Stimulation of organotypic cultures from rat hippocampus produced a cloud of green fluorescence as the released zinc bound an apometalloenzyme confirming the release of zinc from the culture [17]. A later study by Quinta-Ferreira and colleagues [20] demonstrated a release of zinc with each pulse of an action potential. Whilst there is now no doubt that zinc is released during synaptic activity, there is little consensus on the amount or duration of its existence in the synaptic cleft [21].

Following an intense burst of neuronal activity, the release of glutamate and postsynaptic membrane depolarisation open a variety of zinc-permeable ion channels which contribute to removing the ion from the extracellular fluid. These include N-methyl-D-aspartate (NMDA) channels and calcium permeable α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate channels. The consequences of zinc acting on these receptors are diverse and demonstrate the significance zinc has in modulating fast excitatory glutamatergic transmission. Zinc can act to either enhance or depress synaptic activity with varying degrees of potency [21].

The most studied interaction is zinc with NMDA receptors (NMDAR). Initially, zinc was thought to selectively inhibit NMDAR-mediated neuronal activity by inducing a voltage-independent noncompetitive inhibition that decreased the probability of the channel being open [22–24]. A voltage-dependent inhibition of NMDAR could be observed at higher concentrations of zinc (>20 μM) and was believed to be due to binding of the cation within the channel pore [25]. With the cloning of NMDAR subunits, it was confirmed that zinc could cause both voltage-independent and voltage-dependent inhibition [26]. The exceptional sensitivity of the GluN2A subunit towards zinc suggests that even contaminating ions found in routine laboratory solutions are sufficient to cause inhibition [27]. Significantly, despite being responsible for inhibitory effects at NMDAR, it has also been shown that NMDAR activation may provide a route of influx for zinc contributing to toxic effects of exposure [28] (Figure 1).

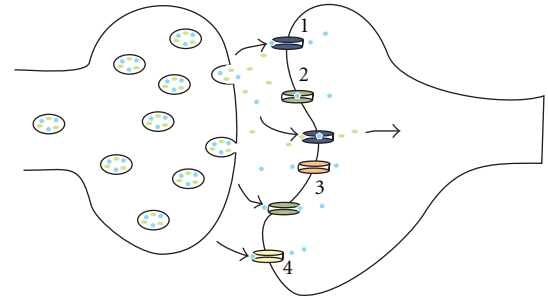

Figure 1: Multiple mechanisms for zinc uptake following synaptic release. Zinc and glutamate are released from a "gluzincergic" synapse during neurotransmission. The actions of glutamate, alongside membrane depolarisation, open a number of zinc-permeable channels on the postsynaptic membrane which clear the ion from the extracellular fluid. (1) AMPA receptors; (2) NMDA receptors; (3) voltage-gated calcium channels; (4) TRPM7. (blue pentagons) zinc ion and (green ellipses) glutamate molecule. For simplicity, zinc-permeable channels are only shown on the postsynaptic membrane.

Whilst it is thought that zinc exposure generally attenuates NMDAR-mediated neurotoxicity, zinc has been shown to potentiate AMPAR-mediated toxicity at suggested physiological concentrations (50 μM). Originally, it was proposed that the toxic effect was due to zinc influx via voltage-gated calcium channels [29], with Lin et al. [30] showing that desensitisation of AMPAR would explain such an enhancement. Subsequently, it has been demonstrated that zinc can carry currents directly via AMPAR, mostly via the calcium-permeable subtype [31] (Figure 1). At high supraphysiological doses (1 mM), zinc has been shown to inhibit AMPAR [21, 32]. A few studies have also looked directly at zinc-mediated inhibition of voltage-gated calcium channels, as their proximity to vesicular release sites on the presynaptic membrane suggests they could interact [33, 34]. Most recently, neurotoxicity has been attributed to transient receptor potential metastatin 7 (TRPM7) channel activation resulting in increased intracellular zinc [35] (Figure 1).

The significance of synaptically released zinc centres on the amount that is released into the synaptic cleft upon excitation. Some authors argue that the amount of zinc (10–100 μM) released following an action potential arriving at the glutamatergic bouton is high enough to bring about the voltage-dependent inhibition of NMDAR and that there would be no spillover onto neighbouring cells [36, 37]. Other authors disagree, suggesting that the zinc concentration would be sufficient to affect nearby cells [38]. It has also been demonstrated that the zinc level (low nM) is only sufficient to block the voltage-independent component of NMDAR activity [39]. Alternatively, it could be that there is little or no diffusible zinc released, supporting the notion that zinc behaves in a "tonic" mode. Kay and Tóth [40] proposed that zinc is exocytosed from the presynaptic membrane and that instead of diffusing into the extracellular space it remains tightly bound to an as-yet unidentified presynaptic component. This would create a "veneer" [41] of zinc ions

which would build up with synaptic activity or erode with quiescence to modulate plasticity.

Thus, the implication is that there are three different groups of zinc signals. First, "synaptic zinc" acts as a conventional neurotransmitter, is contained within presynaptic vesicles, and is released upon excitation and binds to a variety of receptors on the postsynaptic membrane. The downstream consequence of receptor binding is one of tonic modulation of glutamatergic excitatory synapses. The second type is similar to calcium signalling and occurs in conjunction with synaptic zinc signalling. A transmembrane flux of "synaptic zinc" from the extracellular space passes through post-synaptic zinc-permeable ion channels. The third is "intracellular zinc signalling" whereby existing intracellular stores are released [7]. This class is difficult to define and as yet has not been identified in neurons but has been demonstrated in mast cells [42].

Therefore, zinc can be classified as an endogenous modulator of synaptic transmission. It is found in synaptic vesicles, released upon excitation, and has multiple synaptic targets. The significant inhibitory effect of zinc on NMDAR, alongside the crucial function of NMDAR in both neurophysiology and pathophysiology, advocates a vital role for zinc in both healthy and diseased brains [21].

3. Role of Zinc in APP Processing

The most prominent lesions in the brain of AD sufferers are the amyloid or "senile" plaques, which predominantly consist of Aβ peptides derived from the proteolytic processing of the amyloid precursor protein (APP). APP is an ubiquitously expressed glycosylated transmembrane protein with a large N-terminal extracellular domain, a single hydrophobic transmembrane domain, and a small C-terminal cytoplasmic domain. A specific and saturable binding site for zinc (K_D = 750 nM) has been reported in the cysteine-rich region on the ectodomain of APP [44, 45]. It is hypothesised that zinc could have a role in sustaining the adhesiveness of APP during cell-cell and cell-matrix interactions [46, 47]. APP can be processed by one of two pathways: the amyloidogenic pathway, leading to the production of Aβ, and the non-amyloidogenic pathway (Figure 2(a)), reviewed in [48].

In the amyloidogenic pathway, APP is sequentially cleaved by the aspartyl protease, β-site APP-cleaving enzyme 1 (BACE1) forming the secreted APPβ (sAPPβ) fragment and a membrane bound C-terminal fragment of 99 amino acids (C99). The C99 fragment is then further processed by the γ-secretase complex into APP intracellular domain (AICD) and Aβ peptides, predominantly 40 and 42 amino acids in length. It is these aggregation-prone Aβ peptides which form oligomeric and fibrillar structures which deposit in the brain and over time cause AD. The γ-secretase complex comprises four components: presenilin (PS) 1 or 2, nicastrin (Nct), presenilin enhancer 2 (PEN-2), and anterior pharynx defective-1 (Aph-1) [49]. sAPPβ is involved in the pruning of synapses during the development of central and peripheral neurons [50] and AICD is known to be a transcription factor for several genes, including the upregulation of the Aβ-degrading enzyme, neprilysin (NEP) [51].

The predominant APP-processing pathway in healthy brain is the nonamyloidogenic pathway where APP is cleaved by the α-secretase within the Aβ region forming the secreted APPα (sAPPα) fragment and the membrane-bound C-terminal fragment of 83 amino acids (C83) (Figure 2(a)). C83 is subsequently cleaved by the γ-secretase complex generating AICD and p3 (Figure 2(a)). α-secretase activity is attributed to the disintegrin and metalloprotease (ADAM) family of zinc metalloproteases (reviewed in [48, 52]). The ADAMs, along with the matrix metalloproteases (MMPs), are members of the metzincin clan of metalloproteases as they have a long zinc-binding consensus sequence *H*EBX*H*XBGBX*H* (*H*, histidine, zinc ligand; E, catalytic glutamate; G, glycine; B, bulky apolar residue; X, any amino acid) which contains three zinc ligands [53]. Structurally, the catalytic domain is globular and divided into two subdomains, with the active site cleft running between the two [54]. The defining feature of the metzincins is the conserved methionine residue which creates a 1,4-β-turn (Met-turn), creating the catalytic cleft [53]. The catalytic zinc atom sits at the bottom of the groove between the subdomains, with the subsites in the groove determining specificity for particular amino acid sequences in the substrate (reviewed in [52]). A number of enzymes in this family, namely, ADAM9, 10, 17 (also known as TNF-α converting enzyme, TACE) and 19, are known to exert α-secretase activity, but it is unclear which enzyme or enzymes are responsible for the α-cleavage of APP *in vivo* [55–58]. ADAM10 appears to be the predominant enzyme as overexpression of functional ADAM10 in AD transgenic mice led to an increase in sAPPα and reduced Aβ production, plaque deposition, and cognitive deficits [59]. Although fibroblasts from ADAM10$^{-/-}$ mice showed no deficiency in α-secretase activity, probably due to compensation by ADAM17 [60], a recent detailed study has provided strong evidence that ADAM10 is the physiologically relevant constitutive α-secretase in primary neurons [61].

4. Role of Zinc in Aβ Degradation

In a healthy brain, the relatively small amount of Aβ-constitutively being produced is rendered safe by Aβ degrading enzymes. The steady state levels of Aβ synthesis and clearance in cerebrospinal fluid (CSF) are 7.6% and 8.3% per hour, respectively [62]. A large number of candidate Aβ-degrading enzymes have been identified, with the majority being zinc metalloproteases. These include NEP, insulin-degrading enzyme (IDE), endothelin-converting enzyme (ECE) 1 and 2, MMP2, 3, and 9, and PreP (reviewed in [43]). NEP, ECE1 and 2, and MMPs have the conserved zinc-binding motif *H*EXX*H* (*H*, histidine, zinc ligand; E, catalytic glutamate; X, any amino acid), and IDE and its homolog PreP are both inverzincins, as they contain the inverted zinc-binding motif *H*XXE*H*.

NEP appears to be the dominant Aβ protease [63–66], and is capable of degrading monomeric and oligomeric Aβ [63, 67] (Figure 2(b)). NEP knockout mice have significantly

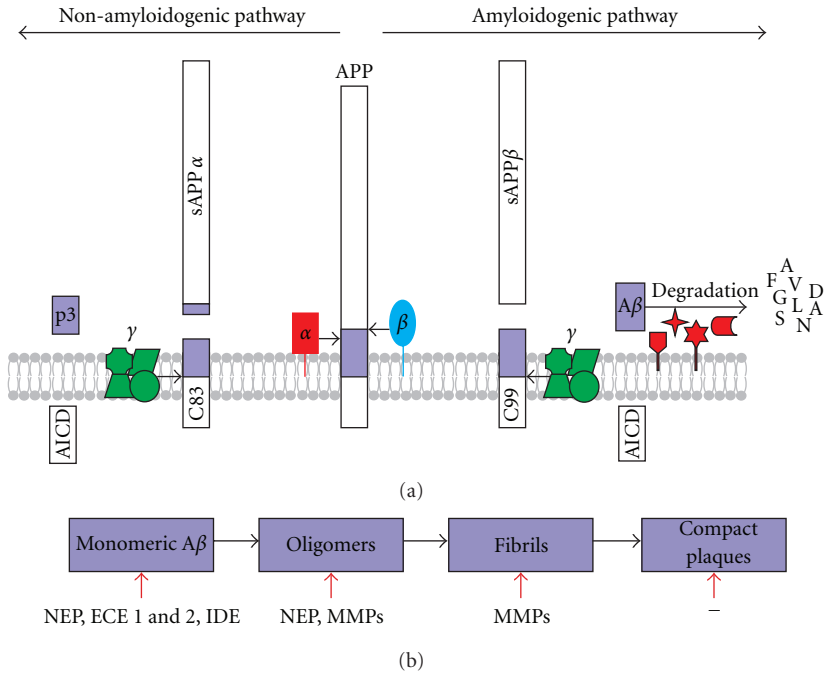

Figure 2: Zinc metalloprotease activity in APP processing. (a) In the amyloidogenic pathway, the transmembrane APP is cleaved first by β-secretase (β) to form the soluble sAPPβ and the membrane-bound C99, which in turn is cleaved by γ-secretase (γ) to form AICD and the amyloidogenic Aβ peptides. The Aβ peptides are degraded by a number of zinc metalloproteases including NEP and IDE. In the nonamyloidogenic pathway, APP is cleaved first by the α-secretase (α) (zinc metalloprotease) to form the soluble sAPPα and the membrane bound C83, which is then cleaved by γ-secretase (γ) to form p3 and AICD. Zinc metalloproteases depicted in red. Representative amino acids from the degradation of Aβ are shown in single letter code. (b) Action of zinc metalloproteases on monomeric and aggregated forms of Aβ (modified from [43]). Aβ: Amyloid β; AICD: APP intracellular domain; APP: Amyloid precursor protein; ECE: Endothelin-converting enzyme; IDE: Insulin degrading enzyme; MMP: Matrix metalloprotease; NEP: Neprilysin.

elevated Aβ levels [68, 69] and more importantly, human postmortem tissue analysis suggests that NEP expression is inversely related to the extent of AD pathology [70–72]. IDE is predominantly a cytosolic enzyme but has been found extracellularly [73] and can only degrade monomeric Aβ and not oligomers (Figure 2(b)), although it did lower the net production of oligomers by cultured cells [74]. Even though there are conflicting data regarding IDE and AD [75], IDE knockout mice have elevated levels of endogenous Aβ [76, 77]. There are two isoforms of ECE, 1 and 2, both of which have similar catalytic activity, with ECE 1 being the predominant isoform within the brain [65, 78]. However, both ECEs are primarily localised to endothelial cells but have been detected in neurons and glial [78]. The MMPs, specifically MMP2 and MMP9, degrade fibrillar Aβ [79], whereas PreP degrades monomeric Aβ. However, PreP is confined to mitochondria, so it would therefore have limited action on the majority of Aβ which is extracellular [80].

5. Zinc Binding to Aβ

High concentrations of zinc (up to 1 mM) have also been found within amyloid plaques [81], which is thought to have been released from glutamatergic synapses [82]. Aggregation of the Aβ peptides can be rapidly induced in the presence of zinc ions under physiological conditions *in vitro* [83, 84]

Figure 3: Aβ peptide sequence with potential zinc binding sites highlighted. Histidine residues are shown in blue and other potential zinc-binding sites are shown in pink.

and studies on AD tissues show that zinc colocalised with Aβ deposits [85]. The metal binding site for zinc on Aβ is the same as the copper binding site and lies within the N-terminal hydrophilic region, the first 16 residues [86] (Figure 3). The majority of studies on zinc binding to Aβ have utilised truncated peptides of 16 (Aβ1–16) and 28 (Aβ1–28) amino acids, as the binding region is situated within these sequences [86]. Aβ1–16 does not aggregate under moderate conditions [87–90], making it an ideal model system, and Aβ1–28 can undergo aggregation and fibril formation, but at significantly reduced rates, to the full-length peptides [91]. Zinc binds to Aβ in a 1 : 1 stoichiometry with a mononuclear binding site [84, 86–90, 92–94]. NMR studies have shown that all three histidine residues (residues 6, 13 and 14; see Figure 3) are involved in zinc binding [87, 88, 90, 93, 95], with confirmation from mutational studies [96, 97]. Other possible ligands have also been reported as zinc coordination classically involves four to six ligands [91]. The candidate ligands are Asp1 [91, 93], Arg5 [94],

Ser 8 [93], Glu11 [90], and Tyr10 [95] (Figure 3) however, Tyr10 has been ruled out [89] and Arg5 has been deemed highly unlikely [91]. The carboxyl side chain of Glu11 is a zinc ligand [88, 90] however, Asp1 is considered the most attractive zinc ligand, either through its N-terminal amino group and/or its side-chain carboxylate group [87, 88, 91, 93]. Raman spectroscopy has shown zinc binding to the Nτ site of histidine side chains in senile plaques taken from AD brains [98], but it is unclear if zinc only binds to free Aβ peptides that subsequently aggregate or whether zinc binds to Aβ in preformed plaques.

The reported apparent binding constants (^{a}Kd) of zinc to Aβ peptides vary from 1 to 300 μM (reviewed in [91]). The published ^{a}Kd values vary greatly due to the *in vitro* conditions (e.g., buffer composition, pH), Aβ fragment, and experimental method. The high ^{a}Kd (20–300 μM) values come from tyrosine fluorescence experiments however, even these are contentious and hard to reproduce [99–101], and any change in tyrosine fluorescence could be due to Aβ aggregation rather than zinc binding [101]. Discounting the tyrosine fluorescence measurements, the most likely apparent ^{a}Kd value for zinc binding to Aβ peptides is a range of 1–20 μM [91]. The binding affinity of zinc for preformed Aβ fibrils is approximately the same as of the peptides with a ^{a}Kd of 1–20 μM [89, 101].

6. Role of Zinc in Alzheimer's Disease

Numerous studies have looked to address whether zinc levels change with AD progression. It has been shown that there is a significant increase in serum [102] and hippocampal [5] zinc in AD patients compared to age-matched controls. Jiménez-Jiménez et al. [103] demonstrated a significant decrease in CSF zinc but could find no difference in serum zinc levels between AD and age-matched controls. A decrease in serum zinc has also been reported, though it is possible that some of the AD patients included in one study were malnourished [104, 105]. Overall, there is currently no consensus on what happens to zinc concentrations in AD subjects though much of the discrepancy could be put down to differences in patient allocation, sample type, postmortem interval, or type of analysis used.

Alternatively, a redistribution of zinc could be sufficient to promote disease progression. Lovell and coworkers [106, 107] have mapped the expression levels of a number of the ZnT zinc transporters in AD. ZnT-1, 4, and 6 were all found to show increased expression in early stages of disease, though ZnT-1 expression was decreased during mild cognitive impairment [106, 107]. Although it is unknown whether increased expression necessarily correlates with increased activity, these changes in transporter level could result in modified subcellular zinc concentrations. An increase in ZnT6 would lead to an increase in zinc in the TGN [108] which could reduce α-secretase activity [83].

It is well established that amyloid plaques contain increased concentrations of copper, iron, and zinc [98, 109]. Whilst copper and iron appear to be primarily responsible for the toxicity of Aβ via oxidative-stress-type mechanisms [109, 110], zinc has a crucial role in Aβ aggregation which is the most well-established contribution that zinc may have in AD pathogenesis. Whilst the concentration of zinc required for fibrillisation to occur is contentious, with concentrations differing by 100-fold being suggested, zinc is an unequivocal partner in the process [83, 111, 112]. In 2006, Dong and co-workers were able to show that zinc could control the rate of self-assembly of the Aβ peptides and go on to regulate the amyloid morphology via specific coordination sites [113]. Furthermore, it has been demonstrated that zinc can spontaneously coordinate both intra-and intermolecular bridging between two peptides to promote Aβ aggregation [114] and that synaptic zinc promotes Aβ oligomer formation and their accumulation at excitatory synapses [115].

Studies with synthetic Aβ showed that chelation chemistry could help solubilise amyloid plaques, with depletion of zinc having a more marked effect on extracting Aβ than depletion of copper [116]. Oral treatment with 5-chloro-7-iodo-8-hydroxyquinoline (Clioquinol CQ) in Tg2576 mice resulted in a 49% reduction in cortical amyloid deposition [117]. Although CQ has a fairly low affinity (nM) for both copper and zinc, it was still able to release the ions from the Aβ binding site [118]. A pilot phase II trial in humans showed a decrease in cognitive decline and a reduction in plasma $A\beta_{1-42}$ in moderately severe AD compared with placebo control [119]. It has been suggested that although CQ may chelate copper and zinc from metallated Aβ and promote disaggregation, it may not completely holt the aggregation process [120]. A second generation chelator (PBT-2), with improved blood brain barrier penetration, has just completed a phase II clinical trial in early AD with promising results showing good tolerance, a reduction in CSF Aβ and neuropsychological testing [121].

Recently, it has been shown that zinc can also accelerate the aggregation of a Tau peptide under reducing conditions [122]. Zinc inhibited the formation of intramolecular disulphide bonds but promoted intermolecular bonds between key cysteine residues. Furthermore, zinc exposure has been shown to increase the phosphorylation of PI3K and MAPK-dependent pathways which are key players in Tau modifications [123].

The essential requirement for ZnT3 in loading zinc into synaptic vesicles would suggest that this transporter could have a major impact on zinc signalling in the neuron, even regulating cognitive function. Whilst a lack of zinc signalling in brain slices from $ZnT3^{-/-}$ mice confirmed the vesicular origin of the released zinc, the mice failed to express a cognitive phenotype. Initial studies detailed a 20% reduction in total zinc level and a loss of histochemically reactive zinc in the synaptic vesicle; however, there was no impairment of spatial learning, memory, or sensorimotor function [124]. The implication being that the vesicular zinc is not required for cognitive function or that compensatory mechanisms made up for the deficits. However, a follow-up study demonstrated marked differences in learning and memory when an older (6 month) cohort of mice was used [125], suggesting that the lack of effect in the previous study was due to the young age (6–10 weeks) of the mice and highlights the importance of aging (the most significant risk

factor) when modelling AD pathology. The results obtained from the older ZnT3$^{-/-}$ cohort established a requirement for zinc in memory function and the maintenance of synaptic health upon aging. Adlard and colleagues proposed that β-amyloid pathology could cause cognitive impairment by trapping zinc within plaques rather than via a directly toxic mechanism [125]. The zinc immobilisation by amyloid would then have similar consequences as a loss of ZnT3 activity with a loss of zinc-dependent synaptic modulation promoting cognitive decline

An alternative approach to minimising the consequences of released zinc could be to promote mechanisms which enhance reuptake. Recently, it has been shown that the cellular form of the prion protein (PrP^C) is an evolutionary descendent of the ZIP family of divalent metal transporters. In particular, ZIPs 5, 6, and 10 were found to have a "prion-like" domain with significant structural similarity. As both PrP^C and the ZIPs bind divalent metal ions via histidine-rich motifs contained with N-terminal repeating sequences, this could suggest that PrP^C is involved in zinc sensing, scavenging, or transport [126]. In agreement with that possibility, we have shown that PrP^C promotes zinc uptake (Watt et al., unpublished). Ensuring efficient clearance of extracellular zinc from the synaptic cleft via PrP^C would exploit an existing physiological process. Furthermore, enhancing zinc uptake would help prevent its ability to contribute to the synaptic targeting of Aβ oligomers, thus preserving synaptic function [115] and maintaining the proposed ferroxidase activity of APP [127]. As PrP^C levels decrease with age and in sporadic AD [128], it is possible that zinc is cleared less efficiently from the synaptic cleft enhancing aggregation of Aβ and inhibiting APP ferroxidase activity to promote a pro-oxidative environment. This would suggest that preserving PrP^C function during AD could provide multifactorial benefits, an inhibition of BACE1 which would reduce Aβ formation [129] and ensure efficient clearance of zinc from the synaptic cleft to prevent aggregation of Aβ peptides, as well as provide protection against oxidative stress [130, 131].

7. Conclusions

It is clear that zinc not only plays critical roles in the structural and functional integrity of many proteins, but that it also modulates the activity of glutamatergic synapses and indeed may act as a neurotransmitter in its own right. Several of the enzymes involved in processing APP and Aβ are zinc metalloproteases, with an essential requirement for zinc in their catalytic activity. Zinc binds to Aβ, promoting its aggregation and thereby modulating its neurotoxicity. Although zinc dyshomeostasis may contribute to the development of AD, further work is required to clarify the molecular and cellular mechanisms affected by zinc under both normal and disease situations.

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