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Review Article

Alzheimer's Disease and Metals: A Review of the Involvement of Cellular Membrane Receptors in Metallosignalling

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Alzheimer's disease (AD) is a debilitating form of dementia. The hallmark protein associated with the disease is the amyloid beta (Aβ) peptide. Aggregation of Aβ has been shown to depend on interactions with metals. The recent studies now demonstrate that metals also play additional important roles in the disease process. Consequently, there may be benefit from modulating metal homeostasis. However, the role and subcellular location of metals within neurons is not well understood. There is growing evidence to suggest that metals can act at the site of cellular membrane receptors and affect cellular signaling by modulating the signal transduction of those receptors. The glutamatergic and cholinergic receptor systems, both well-known neurotransmitter systems affected in AD, have well-documented metal interactions, as do the tropomyosin-receptor kinase (Trk) family of receptors and the epidermal growth factor (EGF) receptor. In this paper, the metal interactions with these membrane receptor systems will be explored and thus the potential for membrane receptors as an intervention point in AD will be assessed.

1. Introduction

Alzheimer's disease (AD) is the most common form of age-related dementia [1, 2]. The key neuropathological features include extracellular amyloid beta (senile) plaques (Aβ), intracellular neurofibrillary tangles, chronic oxidative stress, and disease progression leading to cognitive decline and eventually neuronal cell loss [1, 2]. The cognitive decline observed in AD has its roots at the synapse, the space between neurons, through which they communicate. The synapse is also the site at which the Aβ peptide, the characteristic amyloid protein associated with AD, is believed to first deposit [2]. It is also the site where Aβ may interact with metals released as a consequence of glutamatergic transmission. In the recent years, growing evidence points to soluble Aβ oligomers being the toxic species [3] and whose appearance correlates with disease progression [4, 5]. It has also been hypothesized that small oligomers as opposed to Aβ fibrils induce synaptic failure [6, 7], after experiments showed Aβ oligomers to inhibit long-term potentiation (LTP) [8–10], a biochemical model of synaptic strength [11]. Furthermore, early memory loss associated with the disease has been attributed to synapse loss occurring prior to neuronal cell death [6, 7], and there are reports of a decrease in synaptic protein levels in AD [12].

2. Metals, Aging, and Alzheimer's Disease

The ability of life to utilize oxygen is dependent on the chemistry of transition metal ions. Metal ions are able to coordinate O_2 enabling transport, and the ability of transition metal ions to move between various oxidation states allows the activation and ultimately utilization of oxygen. If not properly regulated the same chemistry that allows the transport and utilization of oxygen can have the potential to generate reactive oxygen species (ROS). Metals are integral for the function of enzymes and numerous intracellular signaling proteins, and in a healthy individual, the levels of these metals are highly regulated. With normal

aging and more so in a neurodegenerative disease state, such homeostatic mechanisms are postulated to become perturbed, leading to aberrant metal-dependant enzyme function, mitochondrial dysfunction, and the production of ROS, all of which are well-known aetiologies associated with AD.

The transition metals implicated in AD include copper (Cu), zinc (Zn), and iron (Fe) [13]. These metals are generally found ligand-bound, and not as free ions. Although there do exist pools of metal that are coordinated to lower affinity ligands and as such are readily exchangeable. There is increasing evidence to suggest that Cu and Zn may exist as free ions when released into the synapse as part of the synaptic transmission process (reviewed in [1]). These metals can reach up to micromolar levels in the synaptic cleft [1], with Cu reaching 15 μM but Zn reaching up to 300 μM in the mossy fibres of the hippocampus postaction potential input [1, 14].

Aging is the main risk factor associated with all neurodegenerative diseases. Metal dyshomeostasis is an important feature of AD and this may be related to aging. There is an apparent state of intracellular Cu deficiency and an extracellular increase in Cu and Zn, possibly due to the metals binding to Aβ (reviewed in [1]). Binding of metals to Aβ can promote aggregation of the peptide with pathological consequences [15].

In the case of AD, the most common form of age-related dementia [16, 17], a state of Cu imbalance, can also lead to a dysfunction of vital cuproenzymes such as cytochrome c oxidase (COX) of the electron transport chain, as well as antioxidants such as superoxide dismutase (SOD1), resulting in oxidative stress via the generation of reactive oxygen species (ROS). Fe levels are also increased in the neuropil of the AD brain [13] and can contribute to the production of ROS and oxidative stress. Oxidative stress can ultimately result in neuronal cell dysfunction, which can lead to a lack of synaptic transmission.

There is growing evidence that suggests metals are able to act on receptors at the cell membrane with the hypothesis being that altered metal homeostasis affects cell signaling due to outside-in signal transduction. In this paper, known metal interactions with relevant membrane receptors will be discussed and potential therapeutic implications to AD will be assessed.

3. The Glutamatergic System and AD

The major neurotransmitter at excitatory synapses in the brain is glutamate. The glutamatergic system of synaptic transmission contains ionotropic and metabotropic glutamate receptors, with the latter lacking a channel for ion flux but instead glutamate binding induces a change in the intracellular domain of the receptor, allowing for intracellular signaling. Failure in glutamatergic transmission is common in most neurodegenerative diseases, including AD [18].

The ionotropic glutamate receptors are divided into N-methyl-D-aspartate (NMDA) and non-NMDA receptors with both receptor classes allowing the flux of ions whereby an electrical signal is translated into a chemical signal. The non-NMDA receptors (non-NMDARs) are α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kainate receptors, with AMPA receptors (AMPARs) being responsible for fast and transient synaptic transmission. The role of the kainate family of ionotropic receptors is less well understood however they are present pre- and post-synaptically and maybe involved in neuron-glia signaling [19], as well as being involved in the modulation of synaptic transmission and plasticity [20]. Activation of NMDARs by presynaptically released glutamate causes calcium (Ca^{2+}) entry which activates the Ca^{2+} dependant kinase, Ca^{2+}/calmodulin dependent-protein kinase II (CaMKII) [21]. The activated CaMKII associates with the NMDAR, leading to AMPAR phosphorylation [21–23]. This event encourages greater channel conductance of the AMPAR, and more importantly AMPAR insertion upon an LTP-inducing stimulus [21, 24, 25]. Soluble Aβ oligomers bind to NMDAR in AD [26] and induce NMDAR internalization [27]. There is further work indicating that binding of CaMKII to the NMDAR channel is required for LTP induction [28].

NMDARs are reported to interact directly with a suite of intracellular proteins, adhesion and signaling molecules, such as CaMKII, neuronal nitric oxide synthase (nNOS), and F-actin (see [29]) and indirectly influence the activation of cAMP response element-binding (CREB) and brain-derived neurotrophic factor (BDNF) (see [30]) as well as intracellular kinases such as extracellular signal regulated kinase (ERK), glycogen synthase kinase 3 (GSK3), and Akt.

There is evidence to suggest that the NMDAR interacts with amyloid peptides and their precursor proteins. For example, patch clamp recordings of primary hippocampal cultures from APP KO mice showed increased NMDAR-mediated EPSCs [31]. Aβ has both direct and indirect interactions with the receptor. It is postulated, as described earlier, that small oligomeric species are the key toxic elements in numerous amyloid diseases, such as AD [3]. These species have been shown to colocalize with the NR2B NMDAR subunit in rat hippocampal slices [32]. These species, as well as the Aβ peptide itself, interact with the NMDAR and can induce an increase in intracellular Ca^{2+}. This in turn leads to membrane permeabilisation, a common phenomena when amyloid proteins interact with the cell membrane [33–36]. Aβ can also propagate the loss of NMDARs from the cell surface [37]. A loss of NMDARs from the synapse has been found in AD brains [38, 39]. Hoey et al. also recently reported that activation of synaptic NMDARs promoted α-secretase mediated APP processing and inhibited Aβ production in mouse primary cortical neurons [40].

It has been shown that different Aβ oligomers can exert different affects. In *in vitro* studies looking at the dentate gyrus, Aβ1–40 was found to selectively increase NMDAR-mediated transmission, whereas Aβ1–42 has been shown to reduce NMDAR-mediated synaptic currents in the dentate gyrus [41, 42]. Thus it is apparent that Aβ is able to influence glutamatergic transmission via the NMDAR.

Due to the implication of NMDARs in neurodegenerative diseases, and especially AD, drugs that exploit the properties of the receptor have been developed as potential therapeutics for the disease. Excitotoxicity, caused by overstimulation of NMDARs due to excessive glutamate release, is a common cause of neuronal loss in most neurological insults including stroke as well as neurodegenerative diseases, such as AD [43]. As a result, NMDAR antagonists have become attractive therapeutics for the potential treatment of these diseases with memantine being utilized clinically, to treat AD patients.

4. The Glutamatergic System and Metals

The most extensive work done examining the glutamatergic system and transition metals is via study of the NMDAR and its metal interactions. Metals, especially Cu and Zn, have been shown to have a modulatory effect on NMDAR function within the glutamatergic system.

Zn is coreleased along with glutamate into the glutamatergic synapse [44–46], thus its role in signaling within the brain may best be assessed in its role as a neurotransmitter. It is well documented that the NMDAR possesses an inhibitory Zn binding site on the NR2 subunit [47–50]. The equilibrium dissociation constant (K_d) of Zn for the NMDAR was reported to be 13 μM [51] but almost a decade later extracellular Zn concentrations as low as 3 nM were shown to be inhibitory of NR1-NR2A containing receptors [50]. Zn inhibits the NMDAR in both a voltage-dependent and -independent manner with the affinity being higher in the latter, inferring that Zn binds at a different site on the receptor to the voltage-dependent magnesium (Mg) channel blocking site. Also, the IC_{50} of the voltage-independent Zn inhibition is 50-fold lower in NR1-NR2A containing receptors than NR1-NR2B containing receptors [50]. Zn released from excitatory synapses in the hippocampus inhibits NMDARs [52, 53]. Furthermore, synaptic Zn entry via glutamate receptors into neurons in the CA3 region of the hippocampus evokes LTP [54]. Interestingly, in the CA1 region of the rat hippocampus, synapses containing presynaptic vesicular Zn showed a decrease in postsynaptic AMPAR subunit levels whilst NMDAR levels were unchanged [55]. This implies that vesicular Zn could confer the behavior of a synapse during synaptic transmission, further cementing the modulatory role that Zn plays at the glutamatergic synapse.

A known interaction of the NMDAR with metals, is the role it plays in Cu homeostasis within the cell. Schlief and Gitlin have developed a model based on experiments in mouse hippocampal neurons [56]. Upon NMDAR activation by glutamate, Ca^{2+} enters into the cell, as previously discussed. This increase in Ca^{2+} within the cell having activated an intracellular signaling cascade induces the Menkes ATPase protein to translocate to a membrane bound compartment to generate and replenish a readily releasable pool of Cu. An increase in Ca^{2+} as a result of NMDAR activation can act upon this novel pool and cause the extracellular release of Cu. This released free Cu can then act back upon the NMDAR in a functionally negative feedback fashion, to inhibit Ca^{2+} flux and inhibit further Cu release. The Menkes ATPase protein is required for Cu efflux [56], and translocation of the protein as a result of NMDAR activation creates a link between NMDAR activation and Cu homeostasis.

Further work from Schlief et al. demonstrated that Cu treatment of hippocampal neurons showed a decrease in the elevation of intracellular Ca^{2+}, without affecting the localization or distribution of NMDARs, suggesting that Cu has a direct effect on NMDAR function [57]. As Cu^{2+} is a potent electron acceptor, it can potentially catalyze S-nitrosylation of NMDARs, resulting in a loss of secretable Cu as in the case of Menkes Disease. This then leaves the cell deficient in controlling NMDAR activation which may lead to an increase in Ca^{2+} [56]. LTP studies on the CA1 region of rat hippocampus showed reduced EPSCs by low micromolar Cu concentrations [56].

Cu is released post-synaptically [58, 59] where as Zn is believed to be co-released with glutamate, presynaptically, into the synaptic cleft [60]. Cu and Zn can reach micromolar concentrations within the synaptic cleft (see above) as compared to glutamate which can reach low millimolar concentrations after excitatory synaptic transmission [56].

These data taken together suggest that metals play an important role in modulating NMDAR function.

5. The Cholinergic System and AD

Acetylcholine (ACh) is a neurotransmitter, which is important in learning and memory networks [61, 62]. Cholinergic receptors are receptors that respond to ACh. Cholinergic receptors are divided into two categories, depending on their exogenous agonists. This includes nicotinic receptors (nAChR) whose exogenous agonist is nicotine, and muscarinic receptors (mAChR) whose exogenous agonist is muscarine. Both nAChRs and mAChRs are found in the central nervous system and in the periphery; however the neuronal subclasses of each receptor type will be discussed in this paper.

Along with hallmark pathologies associated with AD for example, presence of high levels of Aβ, there are also known deficits in the cholinergic system in the AD brain [63–65]. Brain regions highly affected in AD, as the neocortex and the hippocampus have significant changes to their cholinergic innervation [64]. There are several reports of a loss of cholinergic fibers and terminals in AD, as well as reductions in cholinergic receptors [64, 66, 67]. The activities of the two major cholinergic enzymes, choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), are reported to be decreased in AD [68–70]. Reductions in ChAT activity are the greatest [71, 72] and correlate with disease severity [68, 73].

The basal forebrain is where the origins of the cholinergic neurons innervating the cortex lie. It is widely reported that there is a loss of these cholinergic basal forebrain neurons in the AD brain [69, 74, 75]. There is uncertainty however, if this neuron loss occurs as result of Aβ toxicity on the cortical cholinergic terminals causing retrograde degeneration, or if the loss of cholinergic basal forebrain neurons is a primary consequence of Aβ toxicity, with the loss of cortical cholinergic innervation being a secondary

consequence. Numerous transgenic mouse models and cell lines have been used to attempt to delineate this. In aged APP23 mice, there was a significant decrease in cortical cholinergic fiber length but no loss of cholinergic basal forebrain neurons when compared with aged-matched wild-type neurons suggesting that deficit of cortical cholinergic innervation in these mice is a local effect of Aβ which is not caused by deficit of cholinergic basal forebrain neurons [72]. A significant decrease in ChAT activity in the tissue of APP23 mice with no significant effect on AChE levels, when compared with aged-matched wild-type mice was shown. Similar results were reported by Pedersen et al. where a decrease in the activity of ChAT was observed with no effect on AChE activity in SN56 cells, a mouse cell line derived from basal forebrain cholinergic neurons [71]. They also showed Aβ1–42 suppressed the synthesis of ACh in a nontoxic manner with this reduction being prevented by cotreatment with all-*trans*-retinoic acid, a compound formerly shown to increase mRNA expression of ChAT in these cells [71], indicating that Aβ can have non toxic effects on the basal forebrain cholinergic neurons.

Aβ has also been shown to bind to neuronal α7 nicotinic ACh (α7nACh) receptors with high affinity [76, 77] which can cause a suite of toxic consequences. As previously discussed Aβ binding to the NMDAR can cause internalization of the NMDAR and inhibit LTP. Snyder et al. reported α-bungarotoxin, a specific α7nACh antagonist, to reduce Aβ-induced NMDAR internalization, suggesting that NMDAR function may be negatively affected by an Aβ-α7nACh interaction [27]. Wang et al. recently showed in synaptosomes prepared from both AD postmortem tissue as well as frontal cortex slices from postmortem tissue exposed to Aβ1–42 that S 24795, a partial α7nACh agonist, can release Aβ from the Aβ-α7nACh complex allowing for partial recovery of function of the α7nACh and the NMDAR [78]. This demonstrated that disruption of the Aβ-α7nACh interaction may be a mean of reducing pathophysiological features of AD.

6. The Cholinergic System and Metals

There are a few reports of lead (Pb), aluminium (Al), and cadmium (Cd) having an effect on the cholinergic system *in vitro* and *in vivo* [79–81].

As Pb exposure can produce poor learning and deficits in intelligence tests [82], the interaction of Pb with the cholinergic system has been studied extensively as a mean of discovering the mechanism of toxicity of Pb in the brain which causes these neurological effects.

There are conflicting reports, however, on the affect of Pb on the cholinergic system. Moingeon et al. reported that an acute *in vivo* treatment of rats with the metal inhibits ACh turnover, decreases ACh content in certain brain regions, and induces a reversible increase in mAChRs in the striatum and cortex [83]. However, this latter finding is refuted by Schulte et al., where they had found there to be no major effect of Pb on mAChRs in the frontal cortex of mouse brain [84]. This finding was supported by Gotti et al., using an *in vitro* model of both differentiated and undifferentiated cholinergic neurons [85]. They also found that Pb increased the number of nAChR binding sites, although Costa and Fox had reported that chronic Pb exposure to decrease mAChRs in the visual cortex alone of neonatal rats [79]. It is apparent that the effect that Pb has on the cholinergic system is very much dependant on the type of cholinergic receptor studied.

Al increased the number of mAChRs in cholinergically differentiated IMR32 cells, a human neuroblastoma cell line, whereas it had no effect on nAChRs, as measured by α-bungarotoxin binding sites [85]. However Johnson and Jope reported Al reduced the effects of an *in vitro* ACh agonist, carbachol [80]. In the same paper, Cd increased both the mAChR and nAChR expressions in cholinergically differentiated and undifferentiated IMR32 cells.

As discussed, there are few studies investigating the role of cholinergic receptors and metals, and of those that do, few give conclusive outcomes and did not investigate other metals associated with AD pathology such as Cu and Zn. As a result, more work is required to determine if metals could play a role in mediating the cholinergic deficits associated with AD.

7. TrkB Receptors and AD

Tropomyosin-receptor kinase (Trk) receptors are necessary for the survival, differentiation, and maturation of the developing brain [86]. Trk receptors have been shown to play a role in synaptic plasticity as well as in modulating synaptic transmission [87, 88]. Furthermore a Trk receptor family variant, the TrkB receptor, has been reported to be important for LTP in CA1 neurons [89, 90]. The endogenous agonists for TrkB receptors are brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 (NT-4/5), with BDNF being specific for TrkB receptors [91].

TrkB activation was traditionally believed to be via neurotrophin binding, inducing TrkB receptor dimerisation leading to phosphorylation of the cytoplasmic tyrosine kinase tails. This mediates an elaborate signaling cascade ultimately resulting in antiapoptotic outcomes [91, 92]. However Lee et al., showed that TrkB signaling can occur independently of neurotrophin binding, through what is known as "transactivation" by G protein-coupled receptor (GPCR) ligands for example, adenosine and PACAP. Follow-up studies revealed the role of Src kinase-tyrosine phosphorylation in intracellularly activating cell membrane and intracellular TrkB receptors [93, 94].

There are reports of the TrkB receptor-BDNF pathway being compromised in AD. In the hippocampus of AD patients, a decrease in BDNF protein levels [95] as well as a reduction in BDNF mRNA levels [96, 97] has been reported. A decrease in BDNF protein levels in the entorhinal and temporal cortex of AD suffers has also been described [98]. Abnormal TrkB expression of full length and truncated forms and altered distribution has been found in AD brains [95, 99]. Ferrer et al. reported various changes in BDNF, including truncated TrkB and full length TrkB in glial cells, in neurons with hyperphosphorylated tau tangles and

dystrophic neurons surrounding Aβ plaques from brains of individuals with severe AD [100].

Although the most widely studied Trk receptor is the TrkB receptor, recently Capsoni et al. (2010) reported that TrkA beneficially activates Aβ accumulation in a transgenic mouse model and discusses the role of proNGF, NGF, and TrkA versus p75 neurotrophin receptor (p75NTR) in AD neurodegeneration [101].

8. TrkB Receptors and Metals

There have been few studies looking into a possible role for metals in TrkB signaling. Jung et al. reported that treatment of cortical neuron cultures with micromolar Zn concentrations can robustly activate TrkB as well as kinases downstream of the receptor, such as Src, ERK, and Akt [102]. The mechanism of Zn activating TrkB was found to be an extracellular one, mediated by activation of matrix metalloproteinases (MMPs) causing release of pro-BDNF by the cells, which then gets converted to mature BDNF by extracellular MMPs [93, 102]. In support of this, recently Corona [103] reported the protective role of dietary Zn supplementation in a transgenic mouse model of AD, where Zn appeared to increase BDNF signaling by MMP activation. *In vitro*, in PC12 cells, Zn has been shown to inhibit neurite outgrowth by BDNF [104] but in cortical cultures, this inhibition was only slight, revealing that the activation by Zn overrides the potential BDNF/TrkB inhibitory effect [102]. Thus, Zn release from the glutamatergic synapse could play an important role in activity-dependant activation of TrkB.

The same group later reported that Cu too was able to activate TrkB in cortical neuron cultures in an MMP dependent fashion [105]. Cu, like Zn, was able to activate Src kinase, ERK, and Akt and increased the activity of MMP2 and MMP9, thereby catalyzing the conversion of pro BDNF to mature BDNF [105]. They proposed that if Cu is released at the synapse post-depolarisation as postulated by Hartter and Barnea then as with Zn, there maybe physiologically beneficial effects that could be mediated by both metals, such as activation of TrkB signaling [58].

Huang et al. reported for the first time the ability of Zn released by stimulated CA3 hippocampal neurons to transactivate TrkB *in vivo* via Src kinase [106]. The activated TrkB receptors then play an important role in LTP at the mossy fiber-CA synapse. As previously discussed, TrkB receptor signaling has been reported to be important in hippocampal CA1 LTP, but this study puts forward a link between Zn, TrkB, and hippocampal CA3 LTP. With LTP known to be inhibited in AD, in an Aβ-NMDAR associated manner, assessing the Zn, TrkB, and LTP link may provide an interesting opportunity for therapeutic intervention in AD.

9. Membrane Receptors, Metals, and Implications for AD

The membrane receptor systems described so far have proposed roles in AD, and therefore metal interactions with these membrane receptor families could provide beneficial modulatory and intervention points, in the pursuit of the amelioration of AD pathology. Work done within our group has shown that Cu and Zn, delivered into the cell by the metal chaperones CQ, PBT2, and CuGTSM, can cause activation of phosphatidylinositol 3-kinase (PI3K) and the consequent phosphorylation of Akt and GSK3 and the subsequent activation of MAPK (ERK), all kinases previously discussed as having antiapoptotic effects. This caused activation of MMP2 leading to extracellular Aβ degradation [107–109].

CQ and PBT2 are 8-hydroxyquinoline metal ligands. CuGTSM belongs to the metal bisthiosemicarbazone (M-BTSC) family of metal-based drugs. They are stable, of a low molecular weight, neutral and most importantly capable of crossing cell membranes [108]. Due to their versatility *in vitro*, their use has been widely adopted within our group. CuGTSM has demonstrated therapeutic effects in an AD mouse model and was found to affect cellular signalling pathways central to AD as well as the amyloid proteins, Aβ and tau [109].

Price et al. reported CQ coordinated to Cu activated epidermal growth factor receptor (EGFR) in epithelial cells and neurons [110]. This activation, by phosphorylation of EGFR, did not require EGF or TGF-α making it ligand independent. The phosphorylation was mediated by Src kinase and was specific for Cu. Interestingly however, activation of EGFR by CQ coordinated to Cu resulted in the activation of ERK only, with no effects on PI3K-Akt or JNK but still resulted in Aβ degradation by MMP activation. This would infer that activation of ERK by intracellular bioavailable metals is a necessary step in Aβ degradation, mediated by upregulation of MMP.

We later reported the EGFR activation by CuGTSM and ZnBTSCs in a glial cell line as well, but CuGTSM, in contrast to CQ coordinated to Cu, did not phosphorylate EGFR in a Src kinase-mediated manner, rather CuGTSM inhibited the activity of protein tyrosine phosphatase (PTP). CuGTSM, as with CQ coordinated to Cu, did however induce activation of PI3K-Akt-GSK3, ERK, and JNK [111].

Whilst EGFR has not directly been linked to AD, the pathway downstream of the receptor being activated by an increase in intracellular Cu and Zn involves kinases associated with AD and appears to be rather similar to TrkB signalling. Thus EGFR and its metal interactions could be an interesting area to investigate and provide clues on other possible membrane receptors affected in AD.

10. Conclusion

In conclusion, an imbalance of transition metal levels in the AD brain plays a neurotoxic role, but how and where this imbalance affects signaling are not known. However, their interactions with membrane receptors in the glutamatergic system, TrkB and EGF signaling system, and to a lesser extent in the cholinergic system infer a potentially important effect on AD through these membrane receptor systems. This may involve a combination of effects including inhibitory, modulatory or activation of membrane receptor-mediated functions that have an important role in AD. Therefore it is

likely that the link between metals and membrane receptors may offer a unique point of intervention in AD.

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