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Review Article

Metallic Mysteries: Deciphering Their Contribution to Alzheimer's Pathogenesis

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ABSTRACT

Alzheimer's disorder is the most prevalent type of insanity. It can start with a slight loss of memory and progress to a loss of response to stimuli and interaction. Deregulation of the antioxidant response and neurotransmission has been linked to neuro-decadence illnesses, likely Alzheimer's disorder. Metals, along with microelements, support the proper operation of the nervous system. Heavy and essential metals both increase tau protein hyperphosphorylation and Aβ assemblage. The root of Alzheimer's disorder is summarized in this article, along with the roles played by daily exposure to substances like pesticides and some macro and microelements. So, by knowing them, we can limit their exposure of them in day-to-day life. Gaining insight into these functions in brain health and illness could lead to discovering new curative targets for neuro-decadence diseases. Since metal ions are implicated in most degenerative diseases, future treatments may target them. One method is to limit the ions' ability to obstruct oxidative processes or disturb protein folding by chelating and sequestering them.

Introduction

The human body needs metals to maintain cell structure, control gene expression, trigger antioxidant reciprocation, and enhance neurotransmission. Elevated absorption of metals inside the brain system is detrimental as it can lead to oxidative damage, block the actions of mitochondria, and hinder the work of numerous enzymes. A person's quality of life might be significantly reduced and serious neurological issues can result from metal overload. Unintentional metal exposure has been linked to several neuro-decadence illnesses, including Alzheimer's disorder (AD), an almost prevalent kind of insanity that causes age-related deterioration.[1]

Progressive cognitive impairment is an assay mark of Alzheimer's disorder, the neuro-decadence condition that affects the elderly the most and is the lead cause of insanity. Among the most important health problems of the 21st century, AD is becoming more and more commonplace globally. With almost 110 years having passed since the discovery of AD, numerous connected pathogenic pathways have been hypothesized; the most well-known of these are the tau and amyloid theories.[2]

Indian Scenario

Based on the Global Burden of Disease Study (GBDS) 2019, there will be an alarming 166% rise in insanity diagnoses between 2019 and 2050, impacting the lives of almost 152.8 million individuals.[3,4] These forecasts are consistent with the World Health Organization's (WHO). Furthermore, the largest increase in the incidence of insanity is expected to happen (up to 330%) in countries with low sociodemographic index scores (like India). In terms of insanity cases, India was in fourth place globally in 2019, but by 2050, it is expected to surpass both the US and Japan to occupy the top spot. The prevalence of AD varies significantly throughout the states in the country; the top 5 states contributing to the overall number of AD

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cases in the country are Kerala, Goa, Andhra Pradesh, Tamil Nadu, and Himachal Pradesh.[5]

In India, 7.4% of people 60 years of age and older are thought to have insanity. Insanity affects 8.8 million Indian adults over the age of 60. In both rural and urban areas, insanity is more prevalent in women than in males.[6]

Amyloid Hypothesis

The amyloid hypothesis states that diseased conditions or aging decrease the amount of β- and γ-secretase, which breaks down amyloid-beta (Aβ) produced from the amyloid precursor protein. As a result, Aβ, particularly amyloid-beta Aβ40 and amyloid-beta Aβ42, accumulate. Raising the ratio of amyloid-beta 42/Aβ40 results in the creation of amyloid-beta-amyloid fibrils, which subsequently lead to tau pathology and neurotoxicity, neurodegeneration, and death of neuronal cells.[7]

Tau Hypothesis

The protein linked with microtubules In contrast, tau is essentially unearthed in the axons of normal neurons. Here, tau is an essential controller of microtubule dynamics, affecting the processes of maturation, extension, and assembly. Tau protein helps keep microtubules stable and coincide, which is obligatory for brain tasks as well as the transportation of crucial chemicals and organelles.[5] Through the Interlinking of alpha and beta tubulin monomers, tau controls the length, stability, and thickness of axonal microtubules.[8] Many physiological functions in the human body depend on bimetals, or metals having biological activity, and important trace metals. Some of them may be involved in cellular signaling pathways when they are free, and when they are attached to proteins, they might have structural or regulatory effects on how proteins fold and function. Because of their interdependence, it is more difficult to achieve a balance between various metals. The complex interactions betwixt trace metal ions and their ligands control the amount of trace metal ions present.[9]

The Biological Mechanism by which Metals bring on Alzheimer's Disorder

Higher metal levels inside the brain may have an impact on several AD-related pathological processes, such as tau polypeptide hyperphosphorylation, neuroinflammation, oxidative damage, disruption of the blood-brain barrier, neuronal programmed cell death and necrosis, autophagy, also inflammation.[10-12] Investigational evidence suggests that heavy and crucial metals both promote tau protein hyperphosphorylation and aggregation, as well as Aβ aggregation.[13-15] Oxidative damage can be brought on by a few important metals, such as iron[16-18], copper, zinc, and calcium.[19,20] Reactive oxygen species may be formed as an outcome of Fenton reactions, in which Fe takes part.[21] According to experimental evidence, oxidative damage may occur before the documented disruption of the blood-brain barrier[23,24] besides the neuronal apoptosis and necrosis that occurs when exposed to heavy metals.[24] Neurons are very susceptible to oxidative damage. Wang *et al.*[24] state that oxidative damage can result from an imbalance in metal ions and that this stress may subsequently have the following negative effects:

- Tau protein would become more phosphorylated if there was an imbalance between protein kinases and phosphatases.
- An imbalance in secretases, which would lead to a rise in Aβ production.

Arsenic

- *Sources of arsenic exposure in the environment*

While arsenic trioxide (As_2O_3) is the most common conformation of inorganic arsenic in the air, aspartic acid (AsO_3) and arsenites (AsO_2) are two forms of arsenic that are frequently found in food, water, and soil.[24,25] Because of its widespread application in microelectronics, gallium arsenide also referred to as GaAs, is an inorganic arsenic compound that poses an earnest risk to human well-being.

- *Dietary sources*

Grains, mushrooms, poultry, and shellfish are the principal foods that expose humans to arsenic. The most frequent sources of arsenic poisoning include deliberate delivery, work-related exposure, and tainted wine or moonshine. Pigments that make eye shadows and cosmetic colors are often contaminated with toxic substances like arsenic. Makeup for the eyes might cause eczema. Wet skin can absorb arsenic particles that have been dissolved in water. Carcinogenesis may occur when considerable concentrations of arsenic are absorbed through the skin and enter the bloodstream.

Poor memory and cognitive function were indicative of early Alzheimer's disorder symptoms, even after adjusting for potential confounders such as ApoEε4.[25] Low levels of arsenic (3–15 µg/L, as in water) exposed over an extended period are linked to several symptoms. Human cognitive decline and memory loss have been linked to workplace arsenic susceptibility.[26] The chronic susceptibility of children and adolescents to arsenic inside air else palatable water in the Kingdom of Thailand, Bharat, Bangladesh, Mexico, Taiwan, and mainland China has been frequently associated with cognitive loss.

- *The molecular underpinnings of arsenic poisoning and the consequences for AD*

Reactive free radicals are generated, which induce oxidative damage and eventual cell damage by oxidizing proteins, lipids, and DNA in cells. Arsenic-induced DNA oxidation reduces ATP-synthase and promotes lipid peroxidation in rat brains *via* lowering the antioxidant capacity of rodent brains and polypeptide thiols inside the cortex, striatum, also hippocampus.[26] Arsenic toxicity

is mostly shown as oxidative damage, inflammation, ER damage, mitochondrial debilitation, apoptosis, also altered protein homeostasis.[27]

Pesticides

Pesticides are environmental chemicals that are widely utilized worldwide, particularly in India. Less than 0.1% of the 2.5 million tonnes of insecticides used each year in the world completely remove pests. As a result, the vast majority (99%) of pesticides now in use are released into the environment at random. Studies on pesticide effects on the nervous system have shown that various pesticide families, such as carbamates, organophosphates, organochlorines, and bipyridyles, can cause considerable neurological harm.[28]

- *The way that pesticides cause neurotoxicity is as follows*

Neurotoxic mechanisms are the cause of many pesticides' deadly adverse effects. Neurological consequences encompass a range of outcomes such as impaired neurobehavioral performance, dysfunction of the senses, motor, and nerves, memory, attention, visual-spatial processing, pattern memory, and others.[29] About 40% of insecticides used in India are organochlorines. Dieldrin, hexachlorocyclohexane (HCH), dichlorodiphenyltrichloroethane (DDT), and endosulfan are examples of OCPs that are persistent environmental contaminants.[30] When an impulse is carried along nerve fibers and across synapses, either from one nerve to another or from a nerve to a muscle fiber, the majority of organochlorine pesticides (OCPs) work by altering this process. OCPs are very lipophilic, chemically stable, and have a slow breakdown rate.[31] These substances are concentrated high up the food chain and can be found in food, as well as drinking water. OCPs can produce free radicals that harm the mitochondrial machinery and cause oxidative damage. They can also have neurotoxic effects.[32]

Cadmium

- *Sources*

Cadmium is a prominent environmental contaminant that is discovered in a broad span of foods but is mostly present in vegetables, seafood, cereals, root crops, and leftover meat. However, the primary source of cadmium is tobacco smoke. It should be mentioned that inhaling tobacco smoke or ingesting tobacco products increases the risk of CD-related morbidities.[33]

- *Mechanism of inducing neurotoxicity*

Cadmium can penetrate the blood-brain barrier, build up inside brain tissue, and have a major detrimental effect on neurons. Exposure to lead (Cd) results in inflammation, oxidative damage, and neuronal demise inside the brain. Reactive oxygen species also oxidative damage are strongly induced by Cd, according to a number of studies.[34,35] These processes then modulate several signaling pathways and cellular homeostasis, ultimately resulting in neurodegeneration.

Lead

- *Sources of lead*

- Paint (old homes, toys, furniture, crafts)
- Dust
- Soil
- Stay hydrated
- Air
- Ayurvedic, folk, and cosmetic remedies
- Jewelry and toys for children
- In the workplace
- Lead can be found in various products, including sweets, wrappers, pottery, and ethnic meals, imported foods in cans.[36]

- *How lead contributes to the etiology of AD*

Lead inhibits the release of neurotransmitters that are dependent on calcium ions by increasing the activity of protein kinase C and inhibiting NMDA-ion channels. By keeping calcium from exiting mitochondria, it also interferes with energy metabolism by producing reactive oxygen species, causing mitochondria to "self-destruct," and ultimately leading to neuronal death.[37, 38]

Mercury

- *Sources of mercury*

Most commonly found in plant, animal, and earth tissues. Humans can be exposed to mercury through the use of dental amalgams, seafood eating, thimerosal, and certain occupational contexts. Mercury is classified into three conformations: elemental mercury (Hg0), inorganic mercury (Hg^{2+}), and organic mercury (Hg^{2+}). Elementary mercury has been utilized in dental fillings and, more recently, commercial thermometers.[39] Mercury salts, skin-lightening beauty creams, homeopathic treatments, and batteries are a few naturally occurring forms of inorganic mercury found in the environment. The two forms of organic mercury are methyl and ethyl mercury. Apart from its usage as a thimerosal preservative in vaccines, ethyl mercury has also been utilized as an antibiotic and fungicidal. Methyl mercury is highly soluble in water, making it a ubiquitous element in the environment that accumulates in greater quantities within the aquatic food cycle.

- *Mechanism of action*

Mercury interacts rapidly with intracellular molecules or structures, interrupting normal cellular function. The significant affinity of mercury for the sulfhydryl groups present in antioxidants reduces their ability to help the body recover from oxidative damage. For example, When mercury interacts with glutathione (GSH), it loses its

antioxidant properties. This has an immediate impact on the phase II detoxification pathway.[40] Mercury also reduces the passive ion permeability of the cell membrane transport system and carrier-mediated ion transporter. Microtubules shape the cytoskeletal system and neurotransmitter transport in brain tissue. Long-term mercury exposure disrupts neuronal function by preventing brain tubulin from polymerizing, an essential process for microtubule formation.

Aluminum

- *Sources*

Although Aluminum (Al), is the most common metal in the Continental crust and is not cardinal for existence, compounds containing Al in unconstrained, combined, and its chemical valence of three forms have been employed for centuries to make products such as alum, clays, and glasses. Aluminum is occasionally found in common products like cookware, food packaging, some medications, and deodorants or antiperspirants.[41,42] The daily allowance of Al is consumed in drinking water to the extent of about 5%. Consequently, it's possible that certain of the components in drinking water impede or speed up the absorption of aluminum. It has been shown that the interaction of silicate with aluminum in the water lowers the toxicity of fish. Because of this, drinking water's silicate content could potentially be high.

- *Mechanism of action*

Al^{3+} builds up inside the central nervous system (CNS) and also results in physiological reactivity.[41] The entorhinal portion of the cortex, the hippocampus, and the amygdaloid nucleus are some of the brain regions affected by AD that have greater concentrations of aluminum. Al was found to be co-deposited with fibrillar amyloid β in amyloid plaques in a study of brain tissue samples from altruists with familial Alzheimer's disorder as well as the PSEN1-E280A (Glu280Ala) alteration.[40] This alteration raises cortical Aβ levels in donors and is linked to an accelerated development of Alzheimer's.[42] Due to its unique correlation with Aβ and its increased concentration in particular brain regions, aluminum may have contributed to the neuropathology linked to Alzheimer's syndrome.

Al can bind to several proteins and initiate the process of oligomerization, which modifies the structure of the protein and renders it resistant to degradation by proteases. More specifically, large phosphorylated cytoskeleton polypeptide clumps also concentrate as an outcome of Al^{3+} binding to phosphorylated amino acids.[43] After being exposed to Al, glial cells and neurons undergo apoptosis. That aluminum-beta-amyloid co-deposition in FAD correlates with intraneuronal NFTs is unsupported by data.[45] Although an interaction amidst tau may happen later in the illness, Al is predicted to bind to amyloid-beta in amyloid plaques in the preliminary stages.[46]

The connection between oral aluminum intake in drinking water and Alzheimer's disorder has been the subject of many studies.[47] Alzheimer's is much more prevailing in regions with elevated aluminum concentrations in the potable water. A huge body of investigation has been completed to examine the relationship between oral aluminum exposure from potable water and Alzheimer's; nevertheless, additional investigation is needed to completely comprehend the roles that lifestyle, hereditary, and environmental components act in the progression of AD.

Crucial Metals for Alzheimer's Disorder

Essential metal equilibrium has been disturbed in Alzheimer's disorder patients.[43] This word describes the range of naturally occurring metals found in the body that function as different polypeptides and or as secondary messengers. The most frequently needed metals in the human body are sodium, calcium, and magnesium, with trace amounts of iron (Fe), zinc, molybdenum, cobalt, manganese, and chromium also there. Several earlier investigations have also discovered a connection between important metals, specifically iron, copper, and zinc, and clinical alterations in Alzheimer's.

Iron

Lots of bodily functions, including those in the brain region, are regulated by ferrous ions. Among the many processes that iron is needed for are the synthesis of proteins, the division and proliferation of cells, the transfer of oxygen, the electron chain in oxidation-reduction reactions, and gene regulation. In addition, development, neurotransmitter system function, and myelination all depend on iron. In[44] beta-amyloid plaques and neurofibrillary tangles have been shown to have greater ferrous contents. Alzheimer's disorder patients' brains produce reactive oxygen species (ROS) and oxidative damage, which are linked to iron across the Fenton reaction. The phosphorylation of tau protein, amyloid beta aggregation, also tau aggregate formation *in-vitro*

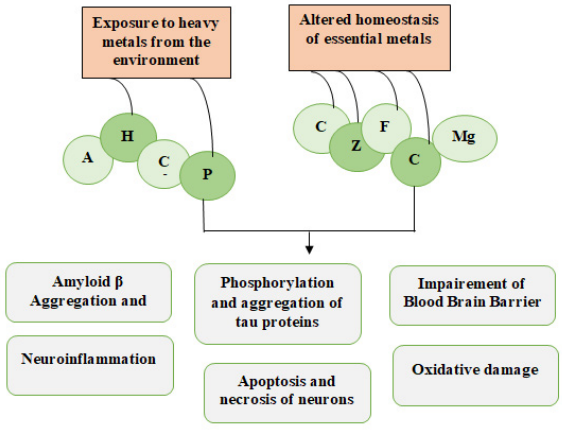

Fig. 1: Metal-enhanced pathological process[4]

are all facilitated by iron. Interestingly, APP causes Fe release by keeping the iron-exporter ferroprotein on the cell surface.[45]

The cerebrospinal fluid (CSF) of Alzheimer patients did not significantly alter, even though their plasma and serum[44,45] had far lower Fe levels than their CSF. This is according to meta-analyses. On the other hand, several investigations discovered a link between CSF Fe concentrations also several CSF Alzheimer biomarkers (Fig. 1). Other observational studies, however, did not discover any variations in Iron levels within Alzheimer's patients and controls.

Zinc

Compared to other organs, the brain possesses higher zinc (Zn).[46] Zinc protects neurons from glutamate-induced excitotoxicity by acting as an antagonist to glutamate N-methyl-D-aspartate (NMDA) receptors. This clarifies the necessity of zinc for neurotransmission.[46, 47] Zinc, which binds to amyloid-beta and promotes its accumulation to form plaques, is present in amyloid plaques.

Furthermore, tau protein phosphorylation, translation, and aggregation are all increased by zinc. Meta-analyses, however, revealed that zinc levels in AD patients' serum, plasma, and hair had dramatically dropped.[48] whereas levels in their brain and CSF had not changed much. MR studies have not yet found a connection between zinc and an increased risk of AD.

An *in-vivo* study employing Zn supplementation was found to have good effects on AD-prone mice, while a small double-blind clinical trial demonstrated that AD patients' cognitive capacities stabilized after six months. Although Loef *et al*. discovered no proof of a significant improvement in Alzheimer's, Zn supplementation has been proposed as a means of improving the cognitive abilities of people with AD. *In-vivo*, studies have revealed that Zn supplementation increases Ayloid beta deposition and neurofibrillary tangle genesis.[49]

Copper

The disruption of brain metabolism suggests that proper Cu levels are required for brain function to function normally. Menkes syndrome sufferers, for example, are affected by neurodegeneration and intellectual disability. This illness is typified by reduced intestinal absorption of copper, which lowers the amount of copper present in the cytosol of all bodily cells saving the kidneys and intestines.[49] The X chromosome's ATP7A gene, which codes for a polypeptide participating in the cytoplasmic transport of Cu ions, has a sex-linked mutation that is the cause of it. Insanity, Parkinsonism, and psychosis are associated with excessive copper accumulation in the body in Wilson's sickness. Alzheimer's disorder also compromises copper homeostasis. Cu ties up to amyloid-beta and promotes oligomer formation and aggregation. Cu chelation can help reduce the cytotoxic effects of the Cu-amyloid β combo. Cu assembles in plaques. There is evidence of an association between Cu and APP. Cu can cause tau phosphorylation and aggregation, and it has a function in the pathological processes of Alzheimer's disorder by interacting with apolipoprotein E. ApoE2 has the greatest rapport for divalent copper, zinc, also iron ions, while ApoE4 has the smallest. According to meta-analyses, AD patients' serum Cu levels increased significantly, whereas their brain Cu levels declined.[50] Unexpectedly, the latest research has found that elevated Cu lessens the occurrence of Alzheimer's disorder.

Calcium

Calcium (Ca) is an important secondary messenger that controls hundreds of signaling tracks required for remembrance and perception-related cells and systems to function properly. Cellular Ca signaling dysfunction is a frequent assay mark of several neuro-decadence disorders, including Alzheimer's.[51] Excessive calcium ion entry using ionotropic glutamate receptors is a major cause of excitotoxic cell demise. Calcium homeostasis disturbance encourages the pathogenesis of tau protein and Aβ proteins. Human research, on the other hand, has yielded inconsistent results, with both high and low Ca levels identified as determinant factors. In the latest MR investigations, higher calcium was found to lessen the incidence of Alzheimer's disorder, but no association was found between the two.[51,52]

Manganese

Magnesium is required for polypeptide formation, glucose and lipid catabolism, also resistance to oxidative damage. Nevertheless, it is also a toxicant found in the environment, and high concentrations have been linked to impaired cognitive function. Patients with Alzheimer's disorder have also been observed to have upraised Mn levels, but Du *et al*.'s meta-analysis discovered a notable fall in manganese levels mediating the AD and control groups.[53]

Magnesium

Magnesium shortage has been shown in human studies to impair memory[54], but magnesium supplementation improves cognitive performance in insanity patients. Furthermore, Alzheimer's patients' tissues contain lower quantities of magnesium. Nonetheless, in several of the trials analyzed, the magnesium levels in the brains of Alzheimer's patients remained constant.[55] Magnesium levels affect APP refining and conveying, with small levels promoting the beta-secretase trackway and elevated levels favoring the alpha-secretase trackway. In experimental animals, magnesium sulfate injection reduces tau phosphorylation and has an impact on both cognitive ability and synaptic plasticity. CSF magnesium concentrations did not differ across groups, although AD patients had lower serum and plasma magnesium levels than controls. According to Thomassen *et al*.[55], there is no

link between plasma magnesium levels and the prevalence of Alzheimer's disorder in a study encompassing over 100,000 people. Kieboom *et al*. found a link between high and low magnesium levels and an augmented risk of insanity. They concluded that there was a U-shaped rather than a linear connection between magnesium and the risk of insanity.[56]

Another Crucial Metal

Alzheimer's also disrupts the sodium, potassium, and cobalt equilibrium. Earlier research has linked high sodium levels to Alzheimer's disorder. Both went up and down.[57] Although AD has been linked to elevated K levels, several investigations have shown no indication of elevated K levels in AD. Cobalt, in addition to being harmful to the environment, is a crucial constituent of vitamin B12. Zheng et colleagues. discovered that mice tend to Co-develop neurodegeneration as they age.[58]

Metal chelators for alzheimer's disorder therapy

Since the definite step underlying progressive Alzheimer's disorder remains unknown, it's challenging to pinpoint potential therapeutic targets for drug development. Nonetheless, there is growing interest in a range of pharmaceutical treatments that can help maintain a good quality of life while slowing the rate of aging-related cognitive and operative impairments. According to the widely accepted metal hypothesis of Alzheimer's disorder, aberrant metal ion homeostasis and collaboration mediate metal ions and amyloid-beta are associated with the disease's neuropathology.[62,64] This notion has resulted in the development of metal chelation treatment as a method of lowering metal-amyloid beta neurotoxicity also restoring metal ion balance inside the brain.[65] Nevertheless, chelators must possess specific features to be evaluated as prospective medications for the therapy of neuro-decadence disorders. To penetrate the blood-brain barrier (BBB), chemicals must be stable, have a lesser molecular weight, and be weakly or never charged. Huge non-distinct chelation would result in the widespread exhaustion of metal ions, involving those of metalloenzymes, which are critical, thus they must target specific metal ions. For the surplus metal ions in the clumped polypeptides to be dissolved as well as eliminated, the chelator must be able to complex them within the brain. In conclusion, the effectiveness of a chelator is contingent upon its low toxicity and minimal side effects. Treatments for Alzheimer's disorder using metal ion chelation have included a variety of metal chelators. The first drug developed to break up amyloid aggregates and treat metal overburdened in the central nervous system was called desferrioxamine B. This drug dramatically improved the behavioral and cognitive abnormalities seen in Alzheimer's patients.[66] Unfortunately, applying this siderophore has several disadvantages:

- Its hydrophilic and charged nature prevents the blood-brain barrier from crossing;
- It breaks down rapidly in the living system, and
- It originates major adverse impacts like forgetfulness as a result of its intense attraction for Ferrous(III) plus alternative bivalent cations.

Drugs that chelate substances have been studied for their latent to manage neurodecadence.[67–71] When treated with the hydrophobic metal complexing agent DP-109, the brains of genetically engineered mice demonstrating human being amyloid b progenitor polypeptide exhibited less amyloid pathology[71] With binding units for 4-benzothiazole-2-yl-phenylamine and DTPA, compound XH1 is a bifunctional metal chelator. Its foundation is the brand-new idea of "pharmacophore conjugation". It has been demonstrated to selectively reduce the expression of the amyloid precursor protein in human SH-SY5Y neuroblastoma cells, moreover diminishing cortical Aβ amyloid disease state in PS1/APP genetically engineered mice, all lacking visibly detrimental side effects or behavioral problems.[69] It has also received a lot of attention to study the byproduct of a 14-membered saturated tetraamine. The bicyclam analog JKL169 (1,1'-xylyl bis-1,4,8,11 tetraazacyclotetradecane) reduced the amounts of copper in the rats' brain cortical layer, but Cu stages in their blood, cerebrospinal fluid, as well as corpus callosum did not change.[60]

A trial phase II clinical study is presently being conducted on cloquinol, one of the substances that has shown the greatest potential for treating a variety of neuro-decadence illnesses. According to the trial's findings, clioquinol (CQ) may help certain patients' discernment purpose and lessen the extent of Ab42 plasma. HLA-20, MA-30, and VK-28 are the other chemicals in this series. Cloioquinol, also known as 5-chloro-7-iodo-8-hydroxyquinoline, or CQ is a tiny, hydrophobic, bio-usable metal complexant that has been shown to effectively intersect the blood-brain barrier and

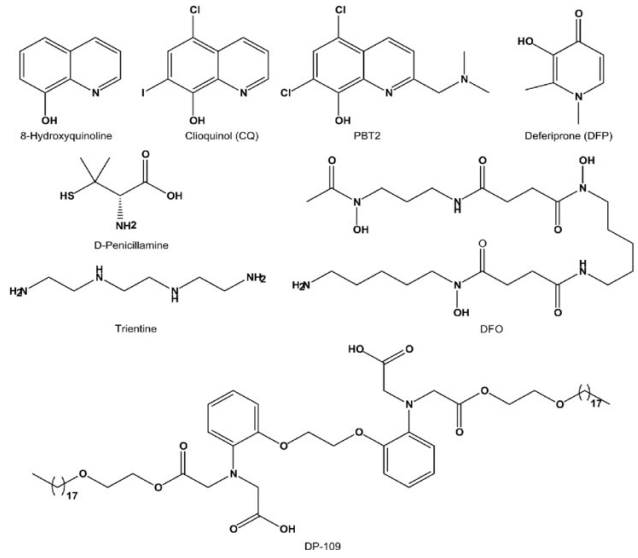

Fig. 2: Metal chelators for Alzheimer's disorder[77]

also dissolve amyloid plaques in the brain. This is likely due to the metallic ions being removed from the framework, which may permit their reallocation.[76, 74]

The drug ciprofloxacin, created by Ciba-Geigy, was broadly utilized as a secure intestinal antiseptic upto it was banned from oral application in 1970s [75] because it was linked to a neurotoxicity outbreak in Japan that was called sub-acute myelo-opticoneuropathy. We still don't fully understand this poisoning mechanism. The prevailing basic idea states that in the presence of clioquinol, cobalamin (vitamin B12) is less bioavailable, resulting in a deficit and a state resembling sub-acute combined degeneration.[76] On the other hand, it has been observed that sub-acute myelo-opticoneuropathy episodes can be prevented by vitamin supplementation and cautious, controlled dosage delivery.[74] CQ adheres Cu^{2+} and Zn^{2+} (2:1 ratio) in a quadrilateral, planar structure with an intermediate affection.[75,76] CQ disperses artificial Amyloid β-Cu^{2+}/Zn^{2+} complexes also, amyloid β accumulates found in the autopsy of Alzheimers brains (Fig. 2), according to research done in 1999 by Ashley I. Bush and colleagues.[72] In APP2576 genetically engineered mice, an in-living model of Alzheimer's disorder, they uncovered that oral therapy alongside clioquinol significantly decreased amyloid-beta accumulates (49% decline) without obviously inducing neurotoxicity. The body weight and overall health indicators of the test animals also showed a marked increase in consistency.[73] These results have been confirmed by C. Grossi *et al*. A step II clinical study adds to the evidence supporting the benefits of clioquinol for Alzheimer's endures. In this experiment, clioquinol was adequately tolerated; patients who received clioquinol showed much less cognitive decline and lower levels of plasma Ab than those who received a placebo.[76] Regarding CQ's potential mode of action and capacity to disrupt brain metal metabolism, competing theories are presently in circulation. When used therapeutically, clioquinol does not cause metal excretion, in contrast to high-affinity chelators. The concept that CQ functions as an ion carrier, aiding metal assimilation in brain tissue, is supported by C. Grossi *et al*.'s discovery[74] of a minor but significant rise in Zn^{2+} and $Fe^{2+}/^{3+}$ steps in the neocortex and Cu^{2+} stages in the hippocampus of TgCRND8 mice managed with CQ (Fig. 3).[75,76]

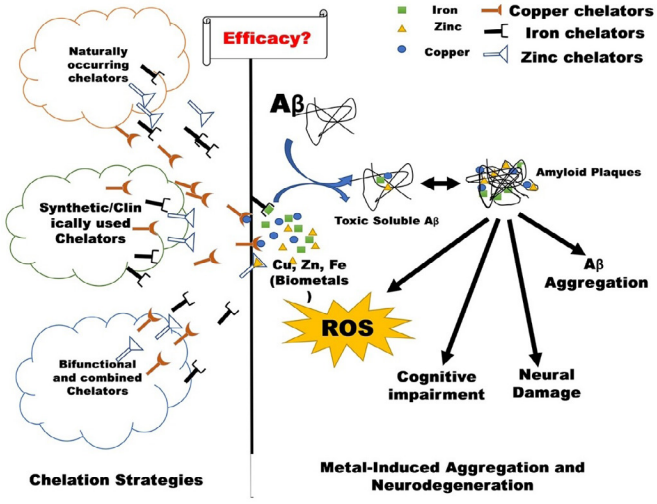

Fig. 3: Chelation of metal ions using metal ion chelators for treating Alzheimer's[78]

Conclusion

The upkeep of metallic ion equilibrium is vital for brain physiological processes. Neuro-decadence illnesses caused by oxidative damage, polypeptide misfolding and accumulation, mitochondrial malfunction, and energy exhaustion can all be attributed to an imbalance of metal ions. These processes all eventually lead to neural network failure. Aggregation, tau hyperphosphorylation, and excessive synthesis of Aβ can all be caused by imbalanced or elevated metal ions. Future developments in neuro-decadence research will result from a multisystem integrative approach that is necessary to comprehend these pathways. While metal ion concentrations have been reported to both rise and fall in AD, increasing ion overload/accumulation is more common.

As a result, a lot of research has been done on using metallic ion complexants to manage diseases also enhance intellectual function in Alzheimer's patients. The following characteristics are necessary for a good metal chelator:

- Capable of overcoming the blood-brain barrier.
- Aims for a particular metallic ion, also

Does not obstruct the regular metabolism of metal ions. To bind and sequester ions in order to limit their ability to obstruct oxidative processes or disturb protein folding. Utilizing contemporary techniques to redistribute metal ions has therapeutic advantages. A number of neuro-decadence illnesses, including Alzheimer's disorder, may benefit from the use of iron-chelating medications, such as hydroxypyridones, which activate transferrin to facilitate iron redistribution. Drugs have been created to lower metal ion levels that cause Aβ aggregation and to create reactive oxygen species by chelation. Developing medications that target several targets may be the subsequent stage in the management of neuro-decadence illnesses like Alzheimer's.

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