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Pathogenic Mechanisms of Heavy Metal Induced-Alzheimer's Disease

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Abstract

Alzheimer's disease is an increasing neurodegenerative disease in the aging population. The disease is associated with toxic chemicals of industrial origin. Industrial processes can result in airborne contamination such as fine dust, and water and soil contamination. In the processes, heavy metals are one of the major environmental pollutants. Also, heavy metals are widely used for many appliances. In particular, heavy metals are seriously toxic to the neural system. In several studies, researchers have emphasized the toxicity of heavy metals such as lead, mercury, and cadmium, as a cause of neurofibrillary tangles, aggregation amyloid beta peptides (AβPs) as well as neuronal cell loss. Based on neurotoxic studies showing that heavy metals induce Alzheimer's disease, this paper discusses molecular mechanisms by which exposure to heavy metals contributes to the pathogenesis of Alzheimer's disease. Also, we indicate pathway for heavy metal related Alzheimer's through integrated analysis based on molecular networks. We suggest that the study of signaling networks contributes to our ability to select significant factors for curing heavy metal induced Alzheimer's disease.

Keywords: Alzheimer's disease, Heavy metal, Lead, Mercury, Cadmium, Molecular mechanisms, Pathogenesis, Integrated analysis, Signaling networks

Introduction

As the aging population is increasing, pathogenesis of age-related disease in older adults becomes a serious public health issue. Alzheimer's is a major disease of ageing. It is caused by neurofibrillary tangles, aggregation of amyloid beta peptides (AβPs) which are a major component of amyloid plaques and loss of neuronal cells. Based on microscopy, brain shrinkage is observed as a result of progressive loss of neurons. Early symptoms include forgetting recent events. When the disease becomes worse, patients have problems with use of language and cognitive ability. In addition, patients with Alzheimer's show symptoms that include personality change, behavioral disorders and physical complications. There are several environmental risk factors for developing Alzheimer's disease. One of these is heavy metal exposure. In our surroundings, people can become exposed both through the heavy metal-polluted natural environment, in the home and from appliances.

Air, food, water and soil can all be contaminated. Heavy metals in the atmosphere mostly expose humans through fine dust pollutants generated due to industrial waste. Contamination in water and soil ultimately produce polluted-food and ingredients which we ingest. Heavy metals are widely used for products that make life more convenient. In addition, workers are repeatedly exposed in workplaces such as battery factories and this would count as professional exposure. Lead, mercury and cadmium are representative heavy metals and are frequently used in industrial applications. Lead is used for storage batteries, building construction, paint, soldering and as a gasoline additive[1]. Mercury is used for preservatives and in pesticides[2]. Cadmium is utilized for pigment resin color, corrosion inhibitor, vinyl manufacturing and nickel-cadmium batteries[3]. Because heavy metals are used extensively in numerous fields, exposure levels have been increasing.

Accumulated heavy metal in the human body has demonstrated toxic effects in various organs. Lead causes disorders including developmental defects, hypertension, hematopoietic problems, renal dysfunction and reproductive difficulties[4,5]. Exposure of mercury results in autoimmune disease and renal failure[6,7].

Also, cadmium cause arteriosclerosis, kidney failure[8] and itai-itai disease.

These heavy metals are commonly known to cause damage to the nervous system. Several studies especially have focused on neurological effects in the brain due to lead, mercury and cadmium. Researchers have investigated damage induced by heavy metals in several systems including neuroblastoma, astrocytes, glial cells etc[9-11]. *In vivo* studies have looked at cortical neurons and brain tissue from rats exposed to heavy metals[12-14]. Jian Huang *et al*. assessed neurotoxicity by detecting inhibition of marker proteins[9]. Also, it was shown that heavy metals induced cell death by confirming low cell viability[10] and it was demonstrated that oxidative stress as well as cell cytotoxicity are generated by heavy metals[11,14]. In addition, some studies have detected heavy metal-induced DNA damage[12,15].

Exposure to heavy metals induces neurological deficits including paralysis, memory loss, mental disorder and paresthesia. In fact, many recent studies have emphasized the severity of the neuronal disease burden due to heavy metals[16-18]. This neurotoxicity has been implicated not only in Alzheimer's, but also in Parkinson's disease. In particular, Alzheimer's disease is one of the major neurodegenerative disease that occurs by heavy metals. Previous studies have interested neurotoxicity of heavy metal inducing degenerative disease such as Alzheimer's disease[9-13]. Furthermore, pathogenic mechanism of neurodegenerative disease occurred by heavy metal have been actively studied in recent years to clearly identify correlation between heavy metal and neurodegenerative disease. It is important to understand the reason for pathogenesis. In this review paper, we describe molecular mechanisms of Alzheimer's disease induced by heavy metals. Understanding these molecular mechanisms will ultimately enable us to prevent and possibly cure Alzheimer's disease.

Epidemiological Study for Heavy Metal Induced-Alzheimer's Disease

Heavy metals induce neuronal damage in diverse ways, including through DNA damage, oxidative stress, activity of several brain enzymes, and amyloidogenesis. A lot of studies have focused on neuro disease caused by heavy metal[9-15]. Neuro disease such as degenerative disease especially has become a serious problem in society. In this regard, many reports have demonstrated that possible symptoms for Alzheimer's disease on the basis of epidemiologic study under heavy metal exposure (Figure 1). Hence, the pathogenic risk for Alzheimer's disease has been well established from multiple epidemiologic studies (Figure 1).

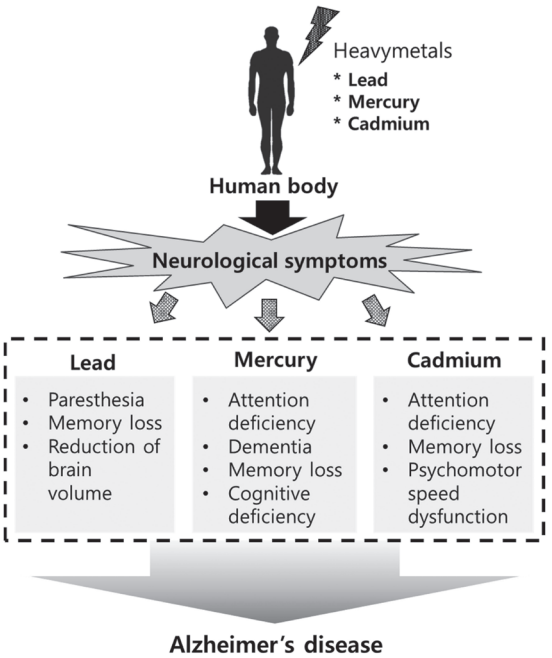

Figure 1. Symptoms for heavy metal induced-Alzheimer's disease in epidemiological studies. Heavy metals including lead, mercury and cadmium cause neurotoxicity in the human body. The neurotoxicity results in progressive neurodegenerative disease such as Alzheimer's disease. Several epidemiological studies demonstrated that heavy metals generate common symptoms in Alzheimer's disease.

Lead

Lead is well known to cause Alzheimer's disease[19]. Occupational exposure to lead is well known from studies of workers in the battery industry[20,21]. Workers in this industry are overexposed to lead compared to the average adult. They exhibit symptoms including psychological dysfunction including paresthesia, forgetfulness, vertigo and headaches[18]. In addition, lead is detected at high levels in the blood[18,20,21]. Sharma SV *et al*. demonstrated that the workers suffered from schizophrenia related differential structural problem of brain[20]. In this study, workers showed functional differences of brain activity in the hippocampus and frontal lobes[20]. In addition, there was a reduction in brain volume in the frontal cortex and temporal lobes[20]. These symptoms are commonly observed in Alzheimer's disease patients. They concluded that lead is able to induce neurodevelopmental diseases showing neurocognitive deficits such as schizophrenia as well as Alzheimer's disease[20].

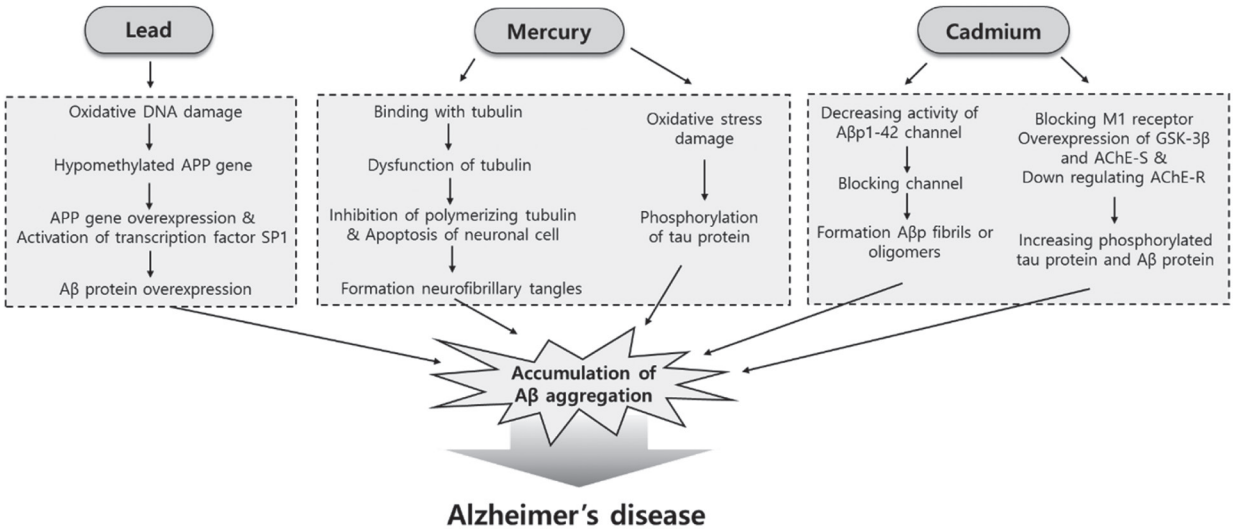

Figure 2. Pathogenic mechanisms of Alzheimer's disease caused by heavy metals in this molecular study. In mechanisms underlying Alzheimer's disease, the three heavy metals generate Alzheimer's disease due to individual pathogenic mechanisms. As heavy metal is exposed to brain system, details of a dotted line box are progressively generated. As a result, Alzheimer's disease occurs.

Mercury

Mercury has also been known to be a risk factor for Alzheimer's disease. In fact, high mercury levels have been detected in the blood of Alzheimer's patients and was also observed in brain tissue according to several studies[22-24]. Mercury concentrations have also been shown to be elevated in hair[25]. One group of subjects were degenerative brain disease patients and they compared mercury concentration in hair of the patient and control group[25]. Mercury concentrations were higher in these than in a control group[25]. In fact, mercury in the nervous system has been shown to cause memory loss, attention deficits and dementia a symptom of Alzheimer's disease[26,27]. Marc W. Haut *et al*. investigated workers exposed to mercury vapor[28]. These workers had high blood levels of mercury and suffered from cognitive deficits.

Cadmium

Cadmium may also cause Alzheimer's disease. The potential neurotoxicity of cadmium has been identified due to high concentrations detected in brain tissues[29], liver[30], and plasma[31] of Alzheimer's disease patient compared to healthy individuals[32]. In another study, high levels of cadmium were detected in blood and hair of Alzheimer's patients. Workers exposed to cadmium, have neurobehavioral problems in attention, psychomotor speed and memory[33]. Similar to humans, Li X *et al*. demonstrated that Amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mice show symptoms of ethological disorder such as learning and memory after cadmium exposure[34]. These symptoms are characteristic of Alzheimer's disease. Cadmium has been regarded as a probable contributory factor associated with Alzheimer's disease and appears to be related to formation of neurofibrillary tangles and aggregation of amyloid beta peptides (AβPs) which is major amino acids of amyloid plaques detected in brain of Alzheimer's patients[32].

Pathogenic Mechanism of Alzheimer's Disease Caused by Heavy Metals in Molecular Studies

Several studies have investigated the molecular basis underlying the development of Alzheimer's disease induced by heavy metals. This review describes the mechanisms and analyzes signaling pathways based on molecular networks associated with heavy metal (lead, mercury, cadmium) induced-Alzheimer's disease (Figures 2, 3). In addition, details of connectivity in signaling pathways were identified (Table 1).

Lead

Correlations between lead exposure and Alzheimer's disease have been well described through generation of oxidative DNA damage in molecular studies[35,36]. In particular, oxidative DNA damage has been detected in the brain during aging and is a primary factor for pathogenesis of Alzheimer's disease[35-39]. Oxidative stress following lead exposure may explain the increase of β-amyloid levels leading to oxidative damage of the neural system[36,40]. Oxidative stress related apoptosis (cell

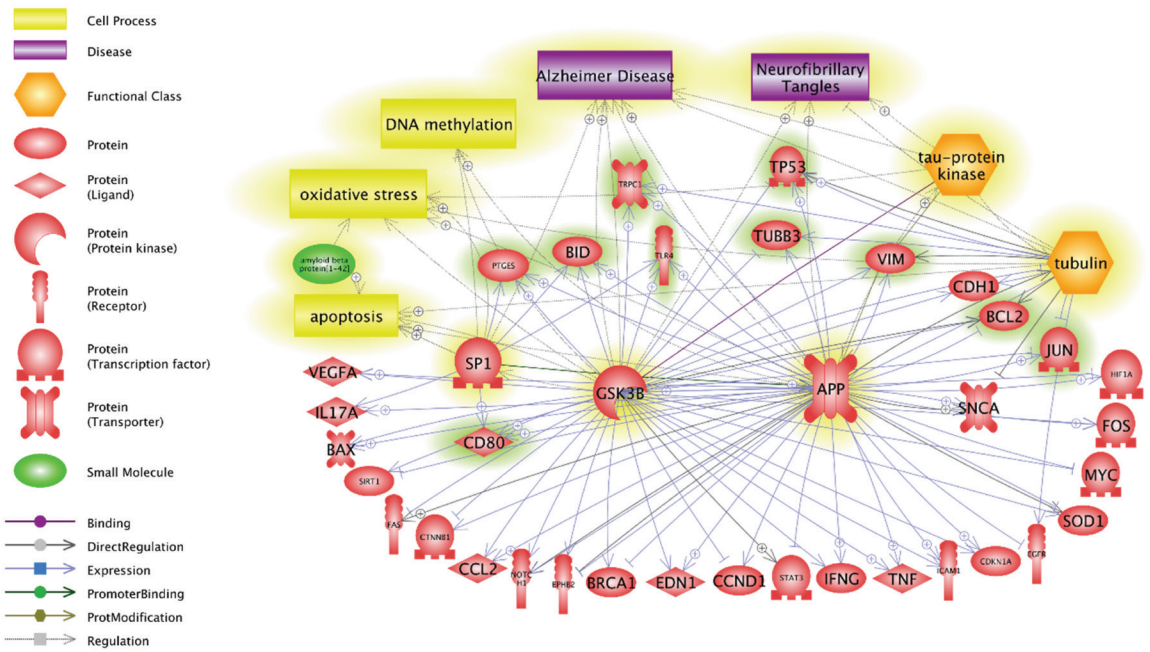

Figure 3. Signaling pathway analysis based on molecular networks associated with heavy metal (lead, mercury, cadmium) induced-Alzheimer's disease. This signaling pathway is based on direct molecular networks between individual heavy metals and Alzheimer's disease. In this review paper, the typical cell process, proteins and disease causing pathogenesis of Alzheimers are highlighted by yellow circles. The highlights in green circles have a comparatively high relation to direct pathways of Alzheimer's disease induced by heavy metals.

death) are implicated in amyloid beta protein accumulation which is a metabolic product of amyloid precursor protein (APP)[11,41,42]. In particular, oxidative DNA damage mechanism by lead toxicity may involve the fact that there is an imbalance between accumulation of 8-hydroxyguanosin (oxo8dG) and the activity of Ogg1 inducing oxidative DNA damage[36,40]. The formation of 8-hydroxyguanosin (oxo8dG) as a consequence of oxidative DNA damage is widely known as an oxidative DNA marker[36,40]. It has been suggested that the imbalance might be a pathogenetic mechanism for Alzheimer's disease[36]. Jinfang Wu *et al*. showed up-regulated Alzheimer's disease-related genes (APP, BACE1) in monkey's brain following lead exposure[43]. In particular, snippets of β-amyloid precursor protein (APP) result in aggregated β-amyloid (Aβ) peptides in Alzheimer's disease[44]. According to Celeste M. Bolin *et al*., exposure to lead early in life results in gene changes through hypomethylation of the APP gene which is a gene responsive to lead[40,45]. Hypomethylation consequently results in overexpression of the APP gene and increases APP production[40,45]. As the concentration of APP is high under lead exposure, activity of transcription factor Sp1 which regulates proteins associated with Alzheimer's disease is increased[40,44,45]. Consequently, Aβ aggregation was promoted and caused plaque formation in brain[40,44]. In fact, elevated APP expression was observed in a mouse hippocampal cell line under chronic low-dose lead exposure[46]. Also, Jinfang Wu *et al*. convincingly demonstrated that lead may drive Alzheimer's disease pathogenesis in study using monkey. They observed intracellular staining of total Aβ and dense-core plaques through immuno histochemical analysis in monkey's brain exposed to lead[43]. The results indicate accumulation of immune reactive Aβ aggregates inside neuronal cells and this suggested the possibility of Alzheimer's disease[43].

Mercury

Mercury inhibits the function of tubulin, which causes neuronal damage and ultimately Alzheimer's disease[47]. Tubulin has an extremely high affinity for mercury and upon binding this metal ligand the structural integrity of the protein is impaired resulting in an inhibition of polymerization of tubulin to micro-tubulin, causing formation of neurofibrillary tangles and senile plaques[47]. These neurofibrillary tangles and senile plaques are characteristic features in the brains of Alzheimer's patients[47]. The effects of mercury have been investigated in animal neuronal cell experiments and axon degeneration and formation of neurofibrillary tangles are detected in those studies as well[48]. In a stem

Table 1. Molecular objects in signaling pathway analysis associated with heavy metal (lead, mercury, cadmium) induced-Alzheimer's disease.

Name	Description	Object type	Connectivity	Local connectivity	Function	References
BCL2	B-cell CLL/lymphoma 2	Protein	5451	4	Anti-apoptosis	[75], [76], [77]
BID	BH3 interacting domain death agonist	Protein	999	3	Pro-apoptosis, regulator of cell death and mitochondrial damage	[78], [79], [80]
CD80	CD80 molecule	Protein	1138	3	Induce T-cell proliferation and cytokine production	[81], [82], [83]
JUN	Jun proto-oncogene	Protein	4340	3	Regulating gene expression for specific DNA sequence	[84], [85], [86]
PTGES	prostaglandin E synthase	Protein	746	3	Mediating acute pain in response of inflammation	[87], [88], [89]
TLR4	toll-like receptor 4	Protein	4450	3	Mediating production of cytokines for immunity	[90], [91], [92]
TP53	tumor protein p53	Protein	10162	4	Tumor suppressor	[93], [94], [95]
TRPC1	transient receptor potential cation channel, subfamily C, member 1	Protein	676	3	Forming non-selective channel	[96], [97], [98]
TUBB3	tubulin, beta 3 class III	Protein	616	3	Neurogenesis and axon guidance	[99], [100], [101]
VIM	vimentin	Protein	2538	3	Mediating immune system and making cytoskeleton	[102], [103], [104]

cell study, mercury contributed to apoptosis of neuronal cells as well as inhibiting the function of tubulin[48]. In addition, mercury hyperphosphorylates tau-protein which is a neuron-specific microtubule-associated protein, that regulates stabilization of microtubules in neuron[49,50]. In particular, oxidative stress induced by mercury influences the phosphorylation state of tau protein by increasing it[50,51]. Tau protein closely associates with Aβ exacerbates both pathology of Aβ and Tau-Aβ interactions in Alzheimer's disease[52]. It was suggested that accumulated Aβ initiates the hyperhposphorylation of tau in Alzheimers[52] and may indicate that accumulated Aβ induces signal transduction pathways for tau hyperphosphorylation[52-56]. The dysfunction of tau may result to pathogenesis of Alzheimer's disease[57]. Also, some studies have identified that mercury affect to the expression of APP gene[57-59]. Methylmercury causes astrogliosis which is also observed in Alzheimer's disease neuropathology, contributing to APP expression by activating glia[57,58,60-64].

Cadmium

Aggregation of amyloid beta peptides is significant proof of the pathogenesis of Alzheimer's disease[32]. The aggregation process of amyloid beta peptides (AβPs) is involved in cause of pathogenesis of Alzheimer's disease. Interactions between AβPs and cadmium implied that the risk of Alzheimer's disease may be increased[32]. Cadmium was implicated in the aggregation of amyloid beta peptides according to several studies[32,65,66]. It was suggested that certain metals are able to promote formation of AβP fibrils or oligomers[32]. In addition, Jiang *et al*. demonstrated that cadmium is associated with the formation of neurofibrillary tangles[32,67]. In fact it was recently shown that cadmium interacts with Amyloid beta-peptide1-42 (AβP1-42)[32]. AβP1-42 is known to be a prominent component of senile plaques a principal pathogenetic event in Alzheimer's disease[68-70]. Cadmium induced aggregation of amyloid beta peptides as it coordinates the Aβ peptide[32,65]. This state is based on histidine and tyrosine residues situated at the N-terminal part of peptide and binding results in blocking AβP1-42 ion channel[32,65]. Also, the risk of Alzheimer's disease is elevated by increased or decreased expression of particular proteins and these changes are promoted by cadmium exposure[71]. For example cadmium blocks M1 receptor, causes overexpression of AChE-S and downregulation of AChE-R[71]. They previously demonstrated that cadmium activates cell death of cholinergic neuronal cells in basal forebrain[71]. This is similar to the process of brain degeneration in Alzheimer's disease[71]. These symptoms are associated with increased GSK-3β, amyloid beta protein and tau filament formation[71]. GSK-3beta is a component of paired helical filament (PHF)-tau, which is found in the neurofibrillary tangle (NFT) deposits that disrupt neuronal function, and it is utilized as a marker of neurodegeneration in Alzheimer's[72].

Integrated Molecular Approach through Signaling Pathway Analysis

To analyze molecular networks for mechanisms of heavy metal related-Alzheimer's, we extracted protein, cell process, functional class, small molecule and disease in main Alzheimer's mechanism under heavy metal exposure. The main objects are APP, GSK3β, SP1, tau-protein kinase, tubulin, amyloid beta protein, DNA methylation, oxidative stress, apoptosis, Alzheimer's disease and neurofibrillary tangles. We obtained these main objects from previous mentioned papers and produced signaling pathways based on direct molecular networks for Alzheimer's disease related-objects affected by heavy metals (lead, mercury, cadmium). We utilized Pathway Studio ver. 11.2 (Elsevier, USA) to identify the signaling networks. In addition, we expanded the signaling networks as analyze common targets including cell process, disease, protein, direct regulation and expression in pathway tool (Figure 3). The integrated molecular approach through signaling pathway is contributed to investigating comparatively high relevant proteins. As a result, we extracted highly relevant proteins including BID, PTGES, TRPC1, TLR4, TP53, CD80, TUBB3, VIM, BCL2 and JUN (Table 1). Using this approach certain proteins are associated with major signaling networks in heavy metal induced-Alzheimer's disease and these proteins play important roles in apoptosis, regulator of cell death, immune system, neurogenesis and axon guidance.

These processes affect mechanisms underlying Alzheimer's disease. CD80 is positively expressed by SP1, APP, GSK3B. CD80 is implicated in T-cell proliferation and cytokine production[73]. TLR4 is positively expressed by GSK3B and APP, it regulates production of cytokines. VIM is implicated in regulating the immune system and it is expressed by APP, GSK3B and tubulin. In addition, PTGES mediates pain from inflammation and it is expressed by GSK3B and APP. In fact, inflammatory changes including increased T-cell, cytokine elevation and complement activation are observed in Alzheimer's disease patients[73]. The changes are thought to affect the early accumulation of amyloid beta protein 1-42 in the brain[73]. Also, apoptosis is activated as APP positively expresses BID which is pro-apoptotic. BCL2 which mediates anti-apoptosis is negatively expressed by APP. The relation promote activation of apoptosis. These networks indicate that apoptosis is implicated in neuronal cell death in the pathogenesis of Alzheimer's disease. JUN is expressed by APP, tubulin and GSK3B, it is anticipated to regulate Alzheimer's disease-related gene expression. GSK3B negatively expresses tumor suppressor proteins such as TP53. Tumor suppressors have an important role in regulating DNA repair, and cell death[74]. This negative regulation is thought to inhibit repair of Alzheimer's disease-related gene and activate neuronal cell death[74]. TRPC1 forms non-selective channels and is positively expressed by GSK3B, APP and tubulin. We speculate that reactive TRPC1 affects Alzheimer's disease related-channels. Also, TUBB3 is negatively expressed by GSK3B, which indicate that neurogenesis is inhibited and results in Alzheimer's disease. In summary, we suggest that molecular studies for comparatively specific proteins contributes to diagnosis in heavy metal induced-Alzheimer's disease.

Conclusion

As we use products that contain heavy metals, exposure to heavy metals is increasing. Several studies have demonstrated that heavy metal are a critical risk for the neural system. We recognized that the pathogenesis of Alzheimer's disease is linked to the toxicity of heavy metals. Each heavy metal is suggested to act through individual mechanisms that vary. To prevent neurodegenerative disease induced by heavy metals, studies of molecular mechanisms are important. In particular, this review paper suggests the importance of particular genes in signaling pathway as we have analyzed signaling pathways based on molecular networks associated with heavy metal (lead, mercury, cadmium) induced-Alzheimer's disease. Furthermore, identifying the relationship between particular heavy metals and specific genes it is possible to begin to provide solutions to this disease. The crucial genes related to Alzheimer's disease can be a target genes to cure the disease.

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Conflict of Interest

The authors declare that they have no conflicts of interest with the contents of this article.

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