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Epigenetics Involvement in Parkinson's Disease and Manganese-Induced Neurotoxicity

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Abstract

Parkinson's disease (PD) is a progressive neurological disorder of CNS and one of the most common neurodegenerative diseases. The exact mechanisms underlying PD has been unclear but it is believed that multiple factors are involved. Excessive exposure to manganese (Mn) can causes its accumulation in the human brain and subsequent neural damage and even development of PD-like movement disorder, referred to as manganism. Although recent studies indicated the pathologic and clinical distinction between PD and Mn-induced neurotoxicity, genetically they have been shown some common features and associations. In recent years, the role of epigenetic changes has been well studied in brain development as well as different brain diseases including PD. Meanwhile, environmental agents including Mn have been found to damage the developing and mature nervous system through altering epigenetic regulatory pathways such as DNA methylation. The aim of this contribution was to review the epigenetic involvement in the etiology of PD and Mn-induced neurotoxicity. Other aspects of these syndromes were also discussed. Several lines of evidence have indicated that epigenetic modulation of gene plays more important roles in PD processes. On the other hand, maternal Mn exposure has been found to be able to cause epigenetic changes in genes associated with neurodegeneration. The current data is very limited to show the association of Mn-induced epigenetic changes and PD etiology. Although conclusion about the relationship between PD and Mn exposure need more consolidated studies, studying the molecular mechanisms of the effect of Mn, genetically and epigenetically will be helpful to understand the etiology of PD which is essential for therapeutic strategies of this disease.

Keywords: Parkinson's disease; Epigenetics; Manganese; Environmental health; Neurotoxicity; Neurodegenerative disorders

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Manganese, Exposure and Health Effects

Manganese as a part of normal physiology: source in diet, role as a cofactor, deficiencies

Manganese (Mn) is a naturally occurring component in the environment and an essential trace element in for normal growth and development through maintaining of proper cellular functions and biochemical processes [1]. Manganese deficienciency would lead to some diseases and it may play a significant role in coronary spasm via reduction in SOD activity, resulting in increased superoxide levels which in turn inactivate NO, leading to coronary spasm [2]. In recent years it has been noted that there is more Mn content in infant formula than in human milk [3]. Although required by multiple physiological processes of the human body, elevated Mn in the body due to over exposure would elicit toxicological effects, particularly on the central nervous system (CNS).

Sources of toxicity and human exposure

Human exposure to Mn can occur through ingestions and inhalation. The general population can be exposed to Mn through the consumption of Mn-contaminated drinking water and food stuff [4]. However, Mn-induced toxicity mainly occurs in certain occupational settings through inhalation of Mn-containing dust [5]. With continuing improvement in production technology and prevention strategies, serious and acute poisoning of Mn have occurred rarely, but long-term and low dose exposure to Mn still exists which may impose health risks to factory workers and nearby residents. Besides, Mn is one of the constituents (24.4%) of in methylcyclopentadienyl manganese tricarbonyl (MMT) which has been used in leaded gasoline, unleaded gasoline, diesel fuel, fuel oil to improve combustion. The combustion of MMT in the combustion chamber leads to increased airborne Mn, including inorganic Mn particles such as manganese phosphate and manganese sulfate [6, 7]. Additionally, Mn is also found in some fungicides and pesticides, which could gradually lead to potential contamination of soil and waterways [8].

Manganese absorption, transport and excretion

Through inhalation and ingestion, Mn can be absorbed [9] into blood where it is mainly (>99%) in the 2+ oxidation state (Mn^{+2}) and bound to β-globulin and albumin with a small fraction with transferrin [10]. Facilitated by the divalent metal ion transporter 1 (DMT1), N-methyl-d-aspartate (NMDA) receptor channel and Zip8 [11], the Mn+2 transport across the blood–brain barrier and blood-cerebrospinal fluid barrier and accumulate in in center nerve system including the basal ganglia structures, specifically in the striatum, cerebellum and globus pallidus [12-16] where Mn cause pathologies of extrapyramidal system, referred to as manganism, or Parkinsin's disease (PD)-like syndrome [17]. Besides, Mn has also been contributed to the etiology of other neurodegenerative diseases, such as Huntington's disease and Alzheimer's disease [18, 19].

Absorption by astrocytes, levels in normal astrocytes vs. after exposure to Mn

Astrocytes the most abundant CNS cells (~ 50% by volume), can accumulate up to 50-fold higher Mn concentrations compared to neurons, thus serving as the main homeostatic and storage site for this metal [20]. At the subcellular level, the highest Mn concentration in astrocytes is noted within mitochondria [21]. In normal situation the intracellular concentration of Mn in astrocytes is 50-75 µM where it is an essential cofactor for the astrocyte-specific enzyme glutamine synthetase [22]. Astrocytes exposed to Mn (500 µM) had significantly reduced 3H-GABA uptake despite no change in membrane or cytosolic GAT3 protein levels. Mn accumulation in the membrane fraction of astrocytes was enhanced with fatty acid administration, and was negatively correlated with 3H-GABA uptake [23].

Manganese environmental epigenetics and neurotoxicity

Mn causes oxidative stress in primary cultures of astrocytes, leading to the mitochondrial dysfunction and energy insufficiency [24]. The main phenotypic characteristic of Mn intoxication is motor impairment due to the accumulation of Mn in the basal ganglia. The symptoms of manganism include rigidity, rapid postural tremor, bradykinesis, gait disturbance, memory and cognitive deficit, and mood disorder [25, 26]. While mechanisms of these extrapyramidal effects of Mn are unclear, results from in vitro and animal studies suggested that multiple pathways are involved. One of the main mechanistic pathways underlying the Mn-induced neurotoxicity is the effects on dopaminergic transmission and monoamine oxidase (MAO) [13, 27-30]. MAO is a flavo-enzyme involved in the oxidative deamination of amine neurotransmitters, including serotonin, dopamine and noradrenaline [31]. MAO can be oxidized into aldehyde amine, enough to degrade biogenic amines, including neurotransmitters such as norepinephrine, dopamine and serotonin (5–HT). It is the key enzyme of dopamine degradation, with detoxification function. In addition, Mn has been reported to disturb the dopamine metabolism via direct oxidation of dopamine, inhibition of its synthesis, and inhibition of monoamine oxidase activity in brain mitochondria [32]. In addition, MAO-A was found in catecholamine neurons with the highest expression [33]. Further, Mn can cause oxidative stress in mitochondrial [34-36] where MnSOD is the primary antioxidant [37]. Human and animal studies suggested the susceptibility to Mn-induced neurotoxicity [38] involves the Mn metabolism, distribution and ROS generation. Mn redox ability depends on the state of charge. Mn2+ in the body is more toxic when it is oxidized to Mn4+ and Mn3+ [39, 40] because the more Mn accumulation in the cells when Mn is oxidized [41]. In addition, Mn (III) was found to inhibit total cellular aconitase activity, reduce cellular serotonin more effectively and induced more oxidative stress compared to Mn (II) [42-44].

Glutamine can enhance the heat shock protein 70 (HSP70) [45], a protein playing an important role in preventing oxidative damage and protecting against neurodegeneration [46-49]. Mn are also important cofactors for various mitochondrial enzymes, as a result the high Mn levels in this organelle can directly interfere with oxidative phosphorylation leading to mitochondrial dysfunction [50-53]. Besides, Mn has been shown to trigger apoptosis in dopaminergic neurons in a caspase-3-dependent manner by activation of protein kinase C delta (PKC-δ) [54]. Futher more Mn can also induce oxidative stress [35, 55, 56]. Studies have shown that individual susceptibility exists and plays a role in metabolism and subsequent neurotoxic effects of Mn [38, 57]. The most of above effects are involved in the area of the basal ganglia and the dopaminergic system. Recent studies found that Mn can also interfere on cortical structures and cognitive functions involving in the cerebral cortex [58, 59] in which is chemic lesions are also found in pre-motor stages of Parkinson's disease (PD) [60, 61].

Parkinson's Disease (PD) and Etiology

Parkinson's disease (PD), also known as idiopathic or

primary parkinsonism, is a chronic, progressive neurological disorder of CNS and one of the most common neurodegenerative disorders and the second most prevalent after Alzheimer's disease comprising 1-2% of the population over 65 years of age [62]. The disease is more commonly found in people over 50 year old but it can also happen in younger patients. The exact mechanisms underlying PD has been unclear but it is believed that multiple factors are involved in case of sporadic PD which are the majority of PD cases [63]. About 15% of PD patients genetically inherited with gene mutations of *SNCA, LRRK2*, *Parkin*, *PINK1*, *DJ-1* and *ATP13A2* [64]. Clinically, PD is also characterized by a kind of active immune response [65]. The typical symptoms are movement-related including shaking, rigidity, slowness of movement and difficulty with walking and gait accompanied by thinking, sensory, sleep and emotional problems. Its pathogenesis is characterized by the loss of dopamine signaling due to the progressive degeneration or death of dopamine-generating neuron cells in the region of midbrain and accumulation of a protein termed as Lewy bodies in neurons. The main affected brain areas in PD include substantia nigra, basal ganglia and cerebral cortex [61, 66]. In addition to the aging and heritage, exposure to environmental factors such as pesticides has been identified to be a risk factor of PD [67, 68].

Association between excessive Mn exposure and PD

Resemblance in extrapyramidal symptoms between MN-induced neurotoxicity or manganese and Parkinson's disease has led to extensive study the possible relationship between these two syndromes. Eepidemiological studies suggested that pathologic and clinical difference between that chronic manganese (Mn) intoxication and PD. In addition, animal studies have shown that the therapy compound for PD is not effective for Mn-induced motor and non-motor deficits [59]. However, further evidences are required before the final conclusion can be made since genetically correlations between them have been keeping reported. Several genes have recently been identified to be genetic etiological factors of Parkinson's disease including alpha-synuclein (α-Syn), leucine-rich repeat kinase 2 (*LRRK2*) [69]. Functional or structural abnormality of α-Syn in the brain is a hallmark pathological feature of several neurodegenerative disorders [70]. In Parkinson's disease the accumulation of intraneuronal Lewy bodies/Lewy neurites containing misfolded fibrillar α-Syn are found [71]. A recent study using *Cynomolgus macaques* indicated that Mn exposure promotes α-Syn accumulation in neuronal and glial cells in the frontal cortex grey and white matter [72]. The induction of α-Syn aggregation by Mn may be due to defence mechanisms since an in vitro study showed that transgenic dopaminergic neuronal cells stably expressing human wild-type α-Syn hampered the Mn-induced toxicity during the early stages of exposure [73, 74]. The variation of *LRRK2* gene was found to be a risk factor for both familial and sporadic PD [69]. Down-regulation of this gene led in increased Mn-induced toxicity [75] suggesting the protective role of *LRRK2* gene in Mn toxicity. Additionally, the proteins encoded by parkin and ATP13A2 can protect cell from Mn-induced toxicity. [76, 77]. Over expression of parkin in cell by transient transfection has been found to attenuate the toxicity of Mn. Similarly, cells harboring wild type ATP13A2 showed more cell viability when compared with the cells with mutant ATP13A2 after exposure to Mn. These findings suggest that Mn-induced Parkinsonism and PD disease share at least partial common way of genetic initiation in disease onset.

Epigenetic involvement in of parkinson's disease and Mn-induced neurotoxicity

The normal physiological functions of cells are controlled by not only genetic mechanisms but also balanced epigenetic pattern. The epigenetic machinery plays an important role in the control of many cellular functions of the body. The epigenetic modifications include DNA methylation, histone modifications and non-coding RNAs (ncRNA) expression. Methylation of DNA, a process involving the addition of methyl groups to DNA typically at CpG dinucleotide context, can cause the conformational change of DNA structure and consequent alteration in gene expression [78, 79]. DNA methylation is import regulation mechanism for mammalian development [80]. However, abnormal DNA methylation patterns, hypermethylation or hypomethylation can lead to various pathogenesis or oncogenesis. Hypermethylations are generally associated with gene silencing or down regulation, whereas hypomethylation or unmethylated promoters are mostly linked to gene activation [81]. Epigenetic regulation gene expression can also be through modification of histone through post-translational modifications such as acetylation, phosphorylation, methylation and ubiquitination [82]. Histone modifications are important in genetic process including transcriptional regulation, DNA repair, DNA replication, alternative splicing and chromosome condensation [82-84]. Another important epigenetic modifier is ncRNA including microRNAs (miRs) and long non-coding RNAs (LncRNAs) [85].

In recent decades, the role of epigenetic changes in the development of diseases has drawn great attentions. Epigenetic changes are reversible and heritable modifications in phenotype without alteration of the primary nucleotide sequence [86]. Evidences have suggested that epigenetic mechanisms, including DNA methylation, histone modification and ncRNA DNA may regulate the expression of PD-related genes and provoke PD. It has been shown that methylation of the *α-Syn*, may in involved in PD through abnormal expression and accumulation of the protein [87, 88]. Hypomethylation of *α-Syn* was found in patients with sporadic Parkinson's disease which could lead to over-expression of *α-Syn* resulting in disease development [89]. Interestingly L-Dopa which has been used for years for treating Parkinson's disease can increase methylation of *α-Syn* [90]. Furthermore, *α-Syn* has been shown to sequester DNMT1 and consequently leading to epigenetic alterations of Lewy body [91]. Other epigenetic regulated genes involving in PD includes LRRK2, Parkin, PARK16/1q32, and GPNMB [92]. Histone modifications also play roles in PD disease and inhibitors for of histone acetyltransferases (HATs) and histone deacetylases (HDACs) showed effective in both in vitro and in vivo PD models [93]. Recent studies have shown that miRNAs are involved in PD [94-96].

Environmental factors, biological and chemical, have long-lasting

phenotypic effects without apparent underlying genetic change through above epigenetic modifications. In another words, environmental factors may change the gene expression directly or indirectly through epigenetic alterations such as DNA methylation or histone modifications. Heavy metalloid(s) such as arsenic, cadmium, chromium, lead, Mercury, coppers, nickel have been found to cause adverse effects through aberration of epigenetic patterns, which has been well reviewed [97-99]. These epigenetic changes in the developmental stages due to prenatal exposure to the environmental factors including Mn may contribute the abnormal phenotype including neurodegeneration. It has been reported that epigenetic gene regulation may contribute to Mn-induced neurogenesis in mouse offspring after maternal exposure to MN. Sustained promoter hypermethylation of Mid1, Atp1a3, and Nr2f1 and transient hypermethylation in Pvalb and consequent down regulation of these genes were found in mouse offspring after maternal exposure to Mn [100]. Epidemiological studies reported the epigenetic changes including DNA methylation, histone modifications and microRNA in subjects exposed to metal-rich air particles containing Mn [101-104]. Although Mn is one of the inhalable metal components in these studies, no significant association was found between Mn exposure and epigenetic changes.

Conclusion

While the role of Mn in the pathogenesis of PD remains controversial, the role of Mn as a modifier of PD warrants future study. Mn has been shown to induce mitochondrial dysfunction and oxidative stress, α-Syn aggregation and dopaminergic neurons which are pathological changes in PD. Recent work has shown the important role of epigenetic regulation as mediator between environmental factors and gene in PD onset and development. So far epigenetic studies on Mn-induced neurotoxicity have been sparsely reported. More and more epigenetic roles in PD have been reported while these genes with epigenetic changes in PD have been not reported in Mn-induced toxicity. To understand the epigenetic effects of Mn on these genes would be helpful to differentiate these two syndromes. This kind of work can improve our understanding of the role of Mn on early events as well as late life abnormalities of the nervous system. Although conclusion about the association between PD and Mn exposure need more consolidated studies, studying the genetic and epigenetic mechanisms of the effect of Mn will be helpful to understand the etiology of PD which is essential for therapeutic strategies of this disease. These studies will also helpful in finding suitable biomarkers not only for health risk assessment of Mn and other related environmental factors but also diagnosis and treatment of PD.

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