NEW INFORMATION ON THE MECHANISMS UNDERLYING THE NEUROTOXICITY CAUSED BY METHYLMERCURY AND MANGANESE

Waqar Ahmad Khan

Department of Chemistry Sarhad University of Science and Information Technology Hayatabad Peshawar, Pakistan

ABSTRACT

Toxic elements are extensively distributed in the Earth's crust and individuals may be exposed to several of them. Indeed, exposure to toxic elements such as mercury (Hg) can be a potential health risk factor of health, mainly by ingestion of fish containing methylmercury (MeHg). On the other hand, essential elements such as manganese (Mn) play an important role in physiological process in human body. In this regard, it is well known that MeHg and Manganese have neurotoxic effects on the developing brain. Therefore, we discuss the effects of Methylmercury and Manganese on cell signaling pathways in this review, as these effects may contribute to the molecular mechanisms underlying Methylmercury and Manganese -induced neurotoxicity.

KEYWORDS

Hg, MeHg, Mn, Heavy metal, Neurotoxicology, pathways signaling.

1. INTRODUCTION

Diseases can arise as a result of exposure to heavy metals and metalloids such Ar, Pb, Cd, and (Hg) (Kaur *et al.,* 2021; Martins *et al.,* 2020). Others, however, are regarded as "vital ingredients." These substances, including copper, selenium, and manganese (Mn), play crucial roles in the control of key systems enzyme and are necessary for a number of physiological activities (Gerardo*et al.*, 2020; Méplan *et al*., 2020) However, necessary components may disturb typical biological processes and trigger cellular stress responses when present in larger amounts, which can lead to the onset of diseases (Ajsuvakova *et al.*, 2020; Martins *et al.*, 2019).

Mercury is ranked third among hazardous elements. There are several chemical forms of this dangerous contaminant, including elemental mercury, inorganic compounds mercury (Hg2), and organic compounds mercury (MeHg). Aquatic sulfate-reducing bacteria can bio methylate Hg2 in an aquatic environment, producing Methylmercury, which has a significant bio-magnification potential and accumulates along the food chain. As a result, eating fish is the main way that humans are exposed to methylmercury (da Cunha Martins *et al.*, 2018; Antunes dos *et al.,* 2018). According to several studies, exposure to methylmercury may cause neurological changes such as cognitive and motor impairment as well as reductions in memory and learning (Fujimura *et al.,* 2020; Martins *et al.,* 2020). The essential element Manganese is necessary for a number of biological functions, such as immune response, skeletal development, brain etc (Horning *et al*., 2015; Miah *et al.,* 2020). it serves as an essential co-factor for many enzymes, taking part in the synthesis and metabolism of amino acids, lipids, proteins, and enzymes that protect organisms from oxidative stress. Diet is the main way that Manganese is exposed to people (Horning *et al*.,

2015). In addition, exposure to high concentrations of airborne Manganese aerosols during job activities is a significant source of exposure for employees. It is widely known that excessive Manganese deposition in the (CNS) from Manganese exposure can cause manganism (Martins *et al.*, 2020). Moreover, alterations of chronic Manganese levels in the brain may trigger the development of neurodegenerative diseases, such as PD and AD Balachandran *et al.*, 2020; Schetinger *et al.*, 2019).

Currently, mounting data points to Manganese and methylmercury's role in harmful effects on the nervous system. It's interesting to note that combined exposure to methylmercury and Manganese has more dramatic toxic effects than exposure to either metal alone. In Caenorhabditis elegans (C. elegans), co-exposure to these metals has been linked to developmental delays in worms, an increase in antioxidant system-related enzymes, and cholinergic degeneration (Ke *et al.*, 2019). As a result, both metals may contribute to the emergence of neurotoxicity. However, a single process is unable to adequately explain the molecular mechanisms underlying Heavy metal-induced neurotoxicity. Instead, a number of modifications to pathways the cell signaling that are difficult in the control of brain cell regulation are what cause those effects

2. METHYLMERCURY INDUCED NEUROTOXICITY

Methylmercury is a naturally occurring, very toxic neurotoxin that is created when inorganic mercury is transformed by microbes in water sediments. Methylmercury exposure in humans is primarily caused by eating fish that have bio-accumulated the toxin from aquatic lower tropical species. People who regularly consume marine food as their main source of protein, particularly growing women and children who are nursing and pregnant may be at risk for health problems because to the comparatively high levels of Hg in top tropical fish. Chronic methylmercury exposure throughout the developing stage has long-term effects on neuro-behavioral processes, whereas acute Methylmercury exposure at high levels permanently damages neuronal function.(Fujimura *et al.*, 2020).

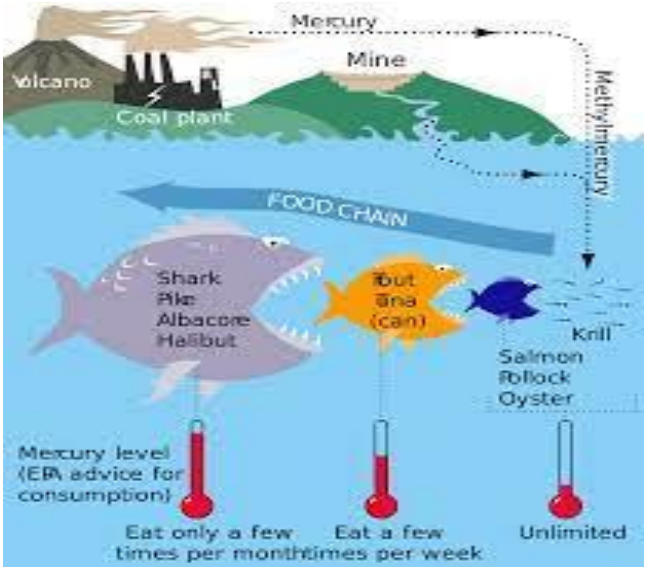

Figure 1. Methyl mercury in Fish

Evidence is mounting suggesting these systems play a role in various critical cellular processes and activities, ultimately leading to damage neuronal (Lin *et al*., 2020).

At a crucial embryonic stage, low-level methylmercury exposure has a significant impact on neuronal cell integrity and behaviour (Freire *et al.,* 2020). New research using highly tractable animal models shows that low doses of methylmercury altered cellular morphology and organismal behavioral patterns (Zhu *et al*., 2019; Ke *et al.,* 2020). A chronic Methylmercury exposure model using C. elegans has recently been developed for the evaluation of dopaminergic neurodegeneration. This model was developed by comparing the neuronal morphology of worms exposed to various long-term Methylmercury exposure regimes (Melentijevic *et al.,* 2017). The removal of spatially structured proteins and organelles destined for breakdown by neural cells was shown to be accelerated by proteotoxic stress in a unique type of neuronal homeostasis in C. elegans (Ke *et al.,* 2020). Methylmercury inhibited the removal process, according to studies using the C. elegans model (Kendricks *et al*., 2020).

Methylmercury has long been known to mess with the oxidative balance and protein homeostasis. One of the underlying causes for neurobehavioral impairment is altered membrane transporter and receptor functioning as a result of methylmercury exposure. methylmercury's disruption of dopamine neurotransmission is a factor in d-ability amphetamine's to inhibit behavior on a baseline basis (Colón-Rodríguez *et al.,* 2020). Studies demonstrating that the cytotoxic effects of methylmercury in motor neurons were mediated by the stimulation of 2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid receptors were also used to draw novel mechanistic insights (Sceniak *et al.,* 2020).

Recent research suggests that the antioxidant signaling network also affects a number of significant cellular domains, such as protein breakdown and differentiation, in addition to the traditional functions that antioxidant pathways play in methylmercury-induced cytotoxicity (Akiyama *et al.,* 2020)

The morphology of nicotinamide adenine dinucleotide phosphate) neurons appeared to be immune to the toxic effects of methylmercury, nevertheless. According to a tenable theory, the decline in astrocytic NADPHd reactivity is caused by chronic methylmercury poisoning's detrimental effects on NADPH-d synthesis and transport in afferent pathways to the visual cortex (Lin *et al.,* 2020).hypoxia-inducible factor-1a over expression reduced the cytotoxicity caused by methylmercury (Akiyama *et al.,* 2020).

Mobilized Sulphur found in reactive Sulphur species (RSS) rapidly binds to xenobiotic electrophiles to produce Sulphur adducts. Methylmercury-induced motor impairment is prevented by cystathionine glyase (CSE), an enzyme required for RSS production. CSE-deficient animals were more vulnerable to the harmful effects of Methylmercury, which can be prevented by restoring RSS with sodium tetra sulfide supplementation (Ke *et al.,* 2019).

Additionally, it has recently come to light that microorganisms can affect methylmercury's toxicity (Zhu *et al.,* 2020). It has been demonstrated that Methylmercury-induced decrease of locomotor activity was significantly influenced by the gut flora (Ijomone *et al.,* 2019).. A possible connection between the gut microbiota and methylmercury-induced neurotoxicity has been suggested by metabolomics profiling, which also revealed that methylmercury promotes changes in intestinal microbial composition and Brain-derived neurotrophic factor level (Ke *et al*., 2020).

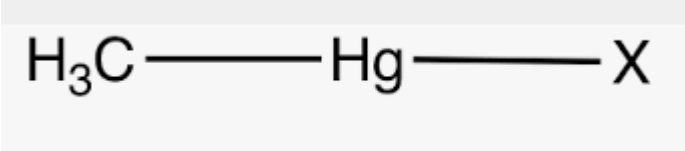

Figure 2. Chemical Formula of Methyl Mercury

3. MN-INDUCED NEUROTOXICITY

The exposure chronic to Manganese can disturb important pathways cell signaling that regulate cell survival, differentiation, and apoptosis. Indeed, several factors interplay to form the cascade of events involved in Manganese Mn neurotoxicity's, neuro-inflammation, transporter dysregulation, mitochondrial such as oxidative stress.

Figure:1 dysfunction, and protein misfolding (Harischandr *et al.*, 2019; Wang *et al.*, 2020). Moreover, Manganese -induced neurotoxicity shares pathways associated with the development of neurodegenerative diseases (Balachandran *et al.*, 2020).

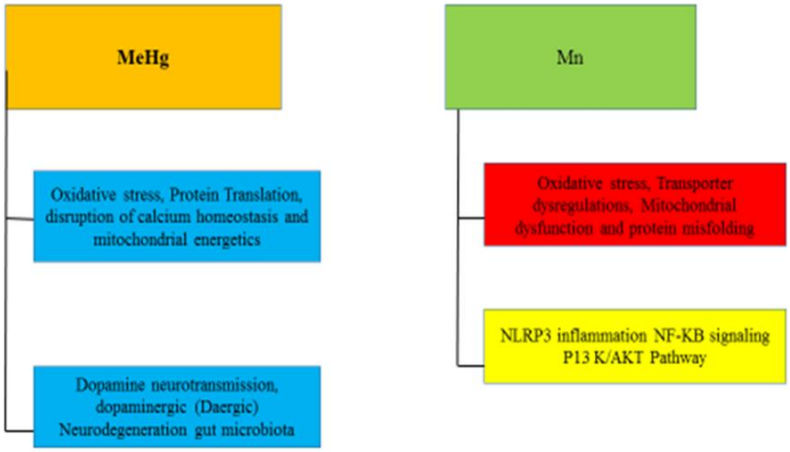

Figure 3: A new mechanisms Methylmercury-induced and Manganese -induced toxicity.

Overexposure to manganese may be linked to alterations in the aggregation of Ab and Tau proteins, which are hallmarks of Alzheimer Disease. Wang et al. recently discovered that after Mn exposure, rats' brains produced more Tau and Ab1-40. The authors also noted that NLRP3 (nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3) inflammatory mediators and inflammasome like IL-1b and IL-18 were found in higher concentrations in manganese-exposed rats' brains than in control rats, indicating that manganese promoted the activation of NLRP3 inflammasome and that the expression of inflammatory mediators was up-regulated in cerebral tissues (Sarkar et al., 2019; Peng et al., 2020).

There seems to be a connection between mitochondrial malfunction and the effects of manganese exposure on the NLRP3 inflammasome and neuroinflammation. Inflammatory processes benefit greatly from the NF-kB signaling pathway. Under normal circumstances, IkB-a, NF-inhibitory kB's protein, is linked to nuclear factor kappa-light-chain-enhancer of activated B cells in the cytoplasm. When IkB-a is activated, IkB-a is phosphorylated and degraded, which causes NF-kB to be phosphorylated, moved from the cytosol to the nucleus, and then activate target genes like IL-1b, Tamour necrosis factor and IL-6 (Popichak et al., 2018; Nkpaa *et al.*, 2019). In fact, earlier

research found that manganese increased NF-kB signaling, altering the expression of inflammatory genes (Li *et al*., 2021). According to reports, manganese increased levels of the proinflammatory cytokines Tamour necrosis, IL-1b, and IL-6 in the rat hippocampus and striatum through stimulating NF-kB signaling pathways (Vanhaesebroeck *et al*., 2016). According to an in vitro study, manganese stimulated the NF-kB pathway in BV2 microglia, causing them to produce more inflammatory cytokines and phosphorylate the P65 protein and express more mRNA (Bryan *et al*., 2018). Collectively, these findings provide evidence that the neuroinflammatory process caused by manganese is activated NF-kB signaling.

A phosphatidylinositol kinase called phosphatidylinositol 3 kinase (PI3K) controls cell proliferation, differentiation, and apoptosis as well as oxidative stress (Cheng *et al.,* 2018). Peres *et al.* (2018) demonstrated using the C. elegans model that worms lacking Akt (akt-1 and akt-2) have stronger resistance to Mn than wild-type worms, indicating that Akt may be a potential therapeutic target for Mn neurotoxicity (Peres *et al.*, 2018;Waqar Ahmad Khan et al.,2022).

4. PARKINSON'S DISEASE

PD is a late-onset neurodegenerative condition marked by a progressive and severe loss of dopaminergic neurons in the SNpc and the appearance of Lewy bodies, which are clumped intracellular inclusions that contain a-synuclein. Parkinson's disease patients' postmortem brain samples show lysosomal depletion and a buildup of autophagosomes, which may indicate impaired autophagic clearance (Martinez-Vicente *et al*., 2015). The proteasome, CMA, and macroautophagy are all capable of destroying a-synuclein (Vogiatzi *et al*., 2008; Webb *et al.,* 2003). Numerous investigations have demonstrated that pharmacological and genetic stimulation of autophagy lowers a-synuclein aggregation and disease pathology, which is consistent with the critical role of autophagy in the clearance of a-synuclein (Nah *et al.,* 2020; Spencer et al., 2009; Ghavami *et al.,* 2014). Although the pathogenic a-synuclein mutations (A53T and A30P) bind more strongly to the lysosomal membrane receptor, they are not transported across the membrane and are hence poorly digested by CMA (Cuervo *et al.,* 2004). The mutations function as receptor inhibitors, slowing down the breakdown of other CMA substrates, increasing cytotoxicity. A-synuclein with a specific post-translational modification, such as (DA)-modified a-synuclein, has been shown to have compromised CMA (Martinez-Vicente *et al*., 2004). Aberrant a-inhibition synuclein's of CMA results in an increase in macroautophagy as a form of compensation, but it can also result in autophagic cell death under stressful circumstances (Cuervo *et al.,* 2004; Shen *et al.,* 2013;Lynch-Day *et al.,* 2012).Additionally, the mislocalization of Atg9, a protein crucial for the production of autophagosomes, brought on by overexpression of a-synuclein can have an impact on the macroautophagy pathway Winslow *et al.,* 2010 Other PD-related proteins, in addition to a-synuclein, are directly involved in autophagy pathways. The lysosomal transmembrane ATPase ATP13A2 is a protein that is encoded by the ATP13A2 gene (Dagan *et al.,* 2016). Due to abnormalities in lysosomal acidification caused by Parkinson's disease-related mutations in ATP13A2, autophagosome clearance is decreased and a-synuclein accumulates Ramirez *et al.,* 2006; Dehay *et al.,* 2012).It has been demonstrated that the proteins (UCHL1) and (LRRK2) linked to PD influence CMA activity. Leucine-rich repeat kinase 2 pathogenic mutations impair CMA substrate degradation by preventing the translocation CMA complex from assembling at the lysosomal membrane (Orenstein *et al.,* 2013). Numerous investigations have suggested that the mutants of ubiquitin carboxy terminal hydrolase L1 interact with (LAMP)-2A and remain stacked in the lysosomal membrane, inhibiting the CMA machinery (Kabuta *et al.,* 2008).Parkinson's disease is known to have an autosomal-recessive type that is caused by loss-of-function mutations in PARK2 and PINK1 Lesage *et al.,* 2009; Kitada *et al.,* 1998; Valente *et al.,* 2004; Vives-Bauza `*et al.,* 2010). An E3 ubiquitin ligase and Parkin is encoded by PARK2, while PINK1 encodes a threonine/serine protein kinase that is expressed in the outer membrane

mitochondrial (Narendra *et al.*, 2008). These proteins control mitophagy, the breakdown of damaged mitochondria (Matsuda *et al.*, 2010). (Fig. 1a).

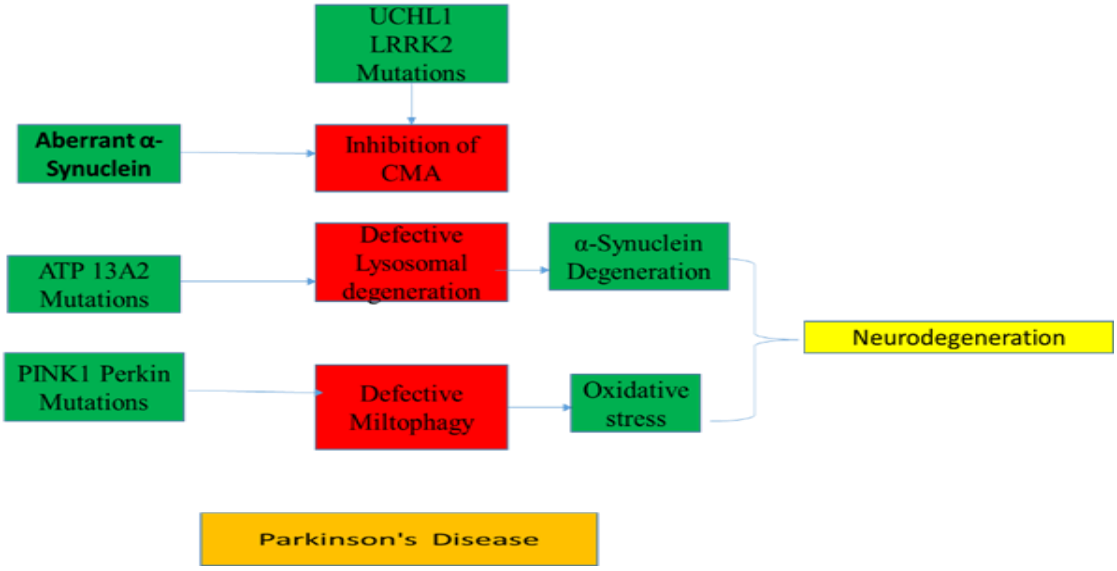

Fig 4a. Autophagy in PD: Aberrant a-synuclein suppresses the CMA. Moreover, Parkinson disease-linked gene mutations result in chaperone mediated autophagy failure, impaired mitophagy and defective degradation lysosomal

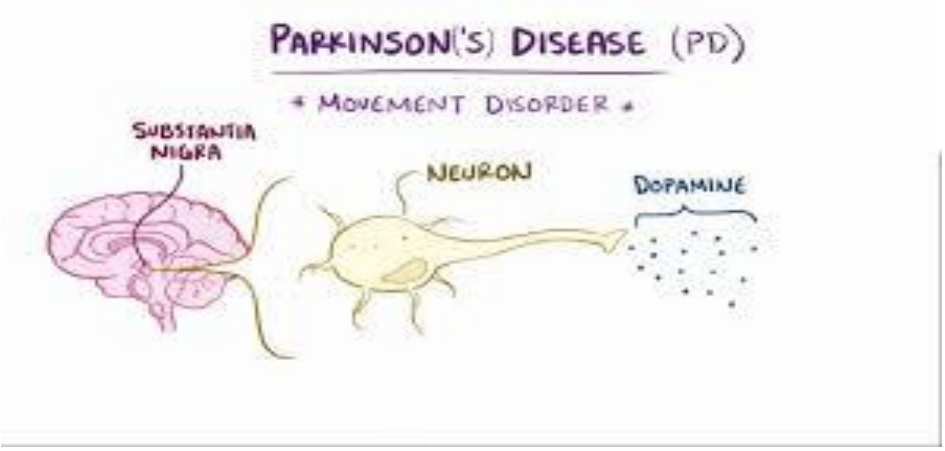

Figure 5. PD

5. LITERATURE REVIEW

Karki *et al.*, 2015 one of the information that The majority of non-neuronal glial cells in the brain are called astrocytes. Contemporary dogmas attribute many active activities for neurons, once consigned to a merely supportive function in the (CNS), including maintenance of appropriate glutamate levels in synapses. We will talk about manganese-induced neurotoxicity and the function of astrocytic glutamate transporters in neurodegenerative disorders in this review.

Wang *et al.*, 2022 stated that exposure to (MeHg) has drawn attention on a global scale. Methylmercury's effects on the nervous system have received the most attention in studies of its developmental toxicity to date. It has been demonstrated that the neuroprotective compound

resveratrol (RSV) may increase hippocampus plasticity. These findings imply that impairment to synaptogenesis is a component of methylmercury's developmental neurotoxicity, and that RSV intervention can repair this damage.

Liu *et al.,* 2014 reported that the common environmental pollutant called (MeHg) has the potential to cause oxidative stress and indirectly glutamate-mediated excitotoxicity. The precise mechanisms by which Methylmercury affects the CNS are still not well understood, and little is known about how oxidative stress and Glu dyshomeostasis interact to cause Methylmercury neurotoxicity. The findings concluded that oxidative stress brought on by increased ROS production is a key factor in the neurotoxicity of methylmercury. Through its antioxidative capabilities, TP has the capacity to reduce the neurotoxic effects of methylmercury.

Adedara *et al.,* 2016 studied looked into how DPDS protected Drosophila melanogaster against manganese-induced toxicity. The combined data show that DPDS may be a good chemo preventive medication candidate mitigates neurotoxicity brought on by acute Mn exposure.

Milatovic *et al.,* 2011 they suggested that a multi-pronged therapeutic approach for protecting dysfunctional dopaminergic transmission and slowing the progression of manganese-induced neurodegenerative processes may involve controlling oxidative stress/mitochondrial dysfunction, changes in biomarkers of oxidative injury, synaptodendritic degeneration and neuroinflammation.

Ibrahim *et al.,* 2020 objective was to assess the neurotoxic effects of manganese and any potential protective properties of ALA and Spirulina platensis (SP), both separately and together. Co-treatment with Alpha Lipoic Acid and SP demonstrated their capacity to guard mitigates oxidative harm, neurobehavioral abnormalities, and metabolic alterations brought on by Manganese.

Fujimura *et al.,* 2022 Environmental contaminant (MeHg) is well-known for its severe neurotoxicity. Methylmercury exposure age (foetal, childhood, or maturity), exposure amounts, and changes in the properties of tissues and cells are all factors that might cause neurotoxicity. In this section, we go through the mechanisms underlying redox abilities, neuronal expansion and synapse development, cellular signaling pathways, epigenetics, and the inflammatory circumstances that microglia experience.

Hernández *et al.,* 2021 Finally, we found that 84% of the pathways involved in neurodegenerative disorders were shared by manganese (II)-induced cytotoxicity in RA-SH-SY5Y cells.

6. RESULT AND DISCUSSION

When two toxic chemicals substances methyl mercury and manganese are transferred into the human body but the neurodegeneration disease produced. Methylmercury damage of the brain, neurological disorder, wild life and gastrointestinal tract, cardiovascular disease and effect of the human health and fish, hearing impairment and blindness of visual and slowness of the speech.

Kerper, *et al*., 1992 studied that methylmercury that has been consumed is quickly and completely absorbed by the digestive system. The majority of the time, it is present in complexes with free cysteine and with proteins and peptides that also include that amino acid. Methionine, another essential amino acid, is recognized as and/or by amino acids proteins transporting in the body as the methylmercuric-cysteinyl complex.

Choi *et al.,* 2009 investigated that adult exposure to methylmercury has also been associated with a higher risk of cardiovascular disorders, including heart attacks.

Scheuhammer *et al.,* 2007 indicated that methylmercury impairs the health of wildlife and fish in both severely polluted ecosystems and ecosystems with low levels of Megh. Numerous studies have shown that methylmercury contamination in aquatic ecosystems reduces the reproductive success of fish, mammals, fish-eating birds according to two reviews.

Seki *et al*., 2021 supported that the gut microbiota is involved in reducing MeHg toxicity by capturing and inactivating the hydrogen sulphide and hydrogen per sulfide produced by intestinal microbes.

7. CONCLUSIONS

A growing body of research indicates that excessive exposure to manganese and methylmercury might have harmful effects, mostly in the brain, which can contribute to neurodegenerative disorders. The public health issue of exposure to metals heavy like manganese and methylmercury is significant. Whole, the discoveries concise in this evaluation (Figure 3) imply that a strategy to treat or prevent the neurotoxic effects caused by these metals may be based on an understanding of how toxic and sub-toxic levels of methylmercury and manganese may stimulate several crucial pathways cells signaling that are difficult in a variety of biological processes and disease states. Furthermore, research utilizing "omics" tools like proteomic, transcriptomic, and bioinformatics studies is essential and opens up new avenues for toxicological investigation.

ACKNOWLEDGEMENT

I would like to express my very great gratitude to Professor Dr.E.M Forster for his appreciated and suggestions constructive during the planning and development of this research work. His willingness to give his time so kindly has been very much appreciated. I would like thanks to my elder brother Dr. Shaukat Ali and my father Mr. Haji Ahmad Jan who have a lot of supported me to completed my research work on time. This research paper is dedicated to my wife Salma Waqar Ahmad khan she has motivated me to accomplished my research work.

DECLARATION OF INTEREST

The author declares there is no financial interest in this research paper review.

REFERENCES

[1] Akiyama, M., Unoki, T., Yoshida, E., Ding, Y., Yamakawa, H., Shinkai, Y., ... & Kumagai, Y. (2020). Repression of mercury accumulation and adverse effects of methylmercury exposure is mediated by cystathionine γ-lyase to produce reactive sulfur species in mouse brain. Toxicology Letters, 330, 128-133

[2] Antunes dos Santos, A., Ferrer, B., Marques Gonçalves, F., Tsatsakis, A. M., Renieri, E. A., Skalny, A. V., ... & Aschner, M. (2018). Oxidative stress in methylmercury-induced cell toxicity. Toxics, 6(3), 47.

[3] Ajsuvakova, O. P., Tinkov, A. A., Willkommen, D., Skalnaya, A. A., Danilov, A. B., Pilipovich, A. A., ... & Skalnaya, M. G. (2020). Assessment of copper, iron, zinc and manganese status and speciation in patients with Parkinson's disease: A pilot study. Journal of Trace Elements in Medicine and Biology, 59, 126423.

[4] Adedara, I. A., Abolaji, A. O., Rocha, J. B., & Farombi, E. O. (2016). Diphenyl diselenide protects against mortality, locomotor deficits and oxidative stress in Drosophila melanogaster model of manganese-induced neurotoxicity. Neurochemical research, 41(6), 1430-1438.

[5] Bryan, M. R., Uhouse, M. A., Nordham, K. D., Joshi, P., Rose, D. I., O'Brien, M. T., ... & Bowman, A. B. (2018). Phosphatidylinositol 3 kinase (PI3K) modulates manganese homeostasis and manganese-induced cell signaling in a murine striatal cell line. Neurotoxicology, 64, 185-194.

[6] Balachandran, R. C., Mukhopadhyay, S., McBride, D., Veevers, J., Harrison, F. E., Aschner, M., ... & Bowman, A. B. (2020). Brain manganese and the balance between essential roles and neurotoxicity. Journal of Biological Chemistry, 295(19), 6312-6329.

[7] Cuervo, A. M., Stefanis, L., Fredenburg, R., Lansbury, P. T., & Sulzer, D. (2004). Impaired degradation of mutant α-synuclein by chaperone-mediated autophagy. Science, 305(5688), 1292-1295.

[8] Cheng, H., Xia, B., Su, C., Chen, K., Chen, X., Chen, P., ... & Yang, X. (2018). PI3K/Akt signaling pathway and Hsp70 activate in hippocampus of rats with chronic manganese sulfate exposure. Journal of Trace Elements in Medicine and Biology, 50, 332-338.

[9] Choi, A. L., Weihe, P., Budtz-Jørgensen, E., Jørgensen, P. J., Salonen, J. T., Tuomainen, T. P., ... &Grandjean, P. (2009). Methylmercury exposure and adverse cardiovascular effects in Faroese whaling men. *Environmental health perspectives*, *117*(3), 367-372.

[10] Cheng, H., Xia, B., Su, C., Chen, K., Chen, X., Chen, P., ... & Yang, X. (2018). PI3K/Akt signaling pathway and Hsp70 activate in hippocampus of rats with chronic manganese sulfate exposure. Journal of Trace Elements in Medicine and Biology, 50, 332-338.

[11] Chang, J., Yang, B., Zhou, Y., Yin, C., Liu, T., Qian, H., ... & Wang, S. Acute Methylmercury Exposure and the Hypoxia-Inducible Factor-1a Signaling Pathway under Normoxic Conditions in the Rat Brain and Astrocytes in Vitro. Environmental Health Perspectives, 127006, 1.

[12] Colón-Rodríguez, A., Colón-Carrión, N. M., & Atchison, W. D. (2020). AMPA receptor contribution to methylmercury-mediated alteration of intracellular Ca2+ concentration in human induced pluripotent stem cell motor neurons. Neurotoxicology, 81, 116-126.

[13] Dehay, B., Ramirez, A., Martinez-Vicente, M., Perier, C., Canron, M. H., Doudnikoff, E., ... & Bezard, E. (2012). Loss of P-type ATPase ATP13A2/PARK9 function induces general lysosomal deficiency and leads to Parkinson disease neurodegeneration. Proceedings of the National Academy of Sciences, 109(24), 96119616.

[14] Dagan, E., Schlesinger, I., Kurolap, A., Ayoub, M., Nassar, M., Peretz-Aharon, J., & Gershoni-Baruch, R. (2016). LRRK2, GBA and SMPD1 founder mutations and Parkinson's disease in Ashkenazi jews. Dementia and Geriatric Cognitive Disorders, 42(12), 1-6.

[15] Da Cunha Martins Jr A, Carneiro MFH, Grotto D, Adeyemi JA, Barbosa Jr F: Arsenic, cadmium, and mercury-induced hypertension: mechanisms and epidemiological findings. J Toxicol Environ Health B Crit Rev 2018, 21:61–82.

[16] Fujimura, M., Usuki, F., & Unoki, T. (2020). Decreased plasma thiol antioxidant capacity precedes neurological signs in a rat methylmercury intoxication model. Food and Chemical Toxicology, 146, 111810.

[17] Freire, M. A. M., Lima, R. R., Nascimento, P. C., Gomes-Leal, W., & Pereira Jr, A. (2020). Effects of methylmercury on the pattern of NADPH diaphorase expression and astrocytic activation in the rat. Ecotoxicology and environmental safety, 201, 110799.

[18] Fujimura, M., & Usuki, F. (2022). Cellular Conditions Responsible for MethylmercuryMediated Neurotoxicity. International Journal of Molecular Sciences, 23(13), 7218.

[19] Gerardo, B., Cabral Pinto, M., Nogueira, J., Pinto, P., Almeida, A., Pinto, E., ... & Freitas, S. (2020). Associations between trace elements and cognitive decline: an exploratory 5Year follow-up study of an elderly cohort. International journal of environmental research and public health, 17(17), 6051.

[20] Gunderson, J. T., Peppriell, A. E., Vorojeikina, D., & Rand, M. D. (2020). Tissue-specific Nrf2 signaling protects against methylmercury toxicity in Drosophila neuromuscular development. Archives of toxicology, 94 (12), 4007-4022.

[21] Ghavami, S., Shojaei, S., Yeganeh, B., Ande, S. R., Jangamreddy, J. R., Mehrpour, M., ... & Łos, M. J. (2014). Autophagy and apoptosis dysfunction in neurodegenerative disorders. Progress in neurobiology, 112, 24-49.

[22] Horning, K. J., Caito, S. W., Tipps, K. G., Bowman, A. B., & Aschner, M. (2015). Manganese is essential for neuronal health. Annual review of nutrition, 35, 71.

[23] Harischandra, D. S., Ghaisas, S., Zenitsky, G., Jin, H., Kanthasamy, A., Anantharam, V., & Kanthasamy, A. G. (2019). Manganese-induced neurotoxicity: new insights into the triad of protein misfolding, mitochondrial impairment, and neuroinflammation. Frontiers in Neuroscience, 13, 654.

[24] Hernández, R. B., de Souza-Pinto, N. C., Kleinjans, J., van Herwijnen, M., Piepers, J., Moteshareie, H., ... & Golshani, A. (2021). Manganese-induced neurotoxicity through impairment of cross-talk pathways in human neuroblastoma cell line SH-SY5Y differentiated with retinoic acid. Toxics, 9(12), 348.

[25] Ibrahim, F., Nomier, M. A., Sabik, L. M., & Shaheen, M. A. (2020). Manganese-induced neurotoxicity and the potential protective effects of lipoic acid and Spirulina platensis. Toxicology Mechanisms and Methods, 30(7), 497-507.

[26] Ijomone, O. M., Aluko, O. M., Okoh, C. O., Martins Jr, A. C., & Aschner, M. (2019). Role for calcium signaling in manganese neurotoxicity. Journal of Trace Elements in Medicine and Biology, 56, 146-155.

[27] Ke, T., Santamaria, A., Rocha, J. B., Tinkov, A., Bornhorst, J., Bowman, A. B., & Aschner, M. (2020). Cephalic neuronal vesicle formation is developmentally dependent and modified by methylmercury and sti-1 in Caenorhabditis elegans. Neurochemical Research, 45(12), 2939-2948.

[28] Ke, T., Gonçalves, F. M., Gonçalves, C. L., Dos Santos, A. A., Rocha, J. B., Farina, M., ... & Aschner, M. (2019). Post-translational modifications in MeHg-induced neurotoxicity. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1865(8), 2068-2081.

[29] Kaur, I., Behl, T., Aleya, L., Rahman, M. D., Kumar, A., Arora, S., & Akter, R. (2021). Role of metallic pollutants in neurodegeneration: effects of aluminum, lead, mercury, and arsenic in mediating brain impairment events and autism spectrum disorder. Environmental Science and Pollution Research, 28(8), 8989-9001.

[30] Karki, P., Smith, K., Johnson Jr, J., Aschner, M., & Lee, E. (2015). Role of transcription factor yin yang 1 in manganese-induced reduction of astrocytic glutamate transporters: Putative mechanism for manganese-induced neurotoxicity. Neurochemistry international, 88, 53-59.

[31] Koentjoro, B., Park, J. S., & Sue, C. M. (2017). Nix restores mitophagy and mitochondrial function to protect against PINK1/Parkin-related Parkinson's disease. Scientific reports, 7(1), 1-11.

[32] Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., ... & Shimizu, N. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. nature, 392(6676), 605-608.

[33] Ke, T., & Aschner, M. (2019). Bacteria affect Caenorhabditis elegans responses to MeHg toxicity. Neurotoxicology, 75, 129-135.

[34] Kerper, L. E., Ballatori, N. A. Z. Z. A. R. E. N. O., & Clarkson, T. W. (1992). Methylmercury transport across the blood-brain barrier by an amino acid carrier. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *262*(5), R761-R765.

[35] Kendricks, D. R., Boomhower, S. R., & Newland, M. C. (2020). Methylmercury, attention, and memory: baseline-dependent effects of adult d-amphetamine and marginal effects of adolescent methylmercury. Neurotoxicology, 80, 130-139.

[36] Kabuta, T., Furuta, A., Aoki, S., Furuta, K., & Wada, K. (2008). Aberrant interaction between Parkinson disease-associated mutant UCH-L1 and the lysosomal receptor for chaperone-mediated autophagy. Journal of Biological Chemistry, 283(35), 23731-23738.

[37] Ke, T., Tsatsakis, A., Santamaría, A., Soare, F. A. A., Tinkov, A. A., Docea, A. O., ... & Aschner, M. (2020). Chronic exposure to methylmercury induces puncta formation in cephalic dopaminergic neurons in Caenorhabditis elegans. Neurotoxicology, 77, 105-113.

[38] Lin, X., Zhao, J., Zhang, W., He, L., Wang, L., Chang, D., ... & Li, Y. F. (2020). Acute oral methylmercury exposure perturbs the gut microbiome and alters gut-brain axis related metabolites in rats. Ecotoxicology and environmental safety, 190, 110130.

[39] Liu, W., Xu, Z., Yang, T., Deng, Y., Xu, B., Feng, S., & Li, Y. (2014). The protective role of tea polyphenols against methylmercury-induced neurotoxic effects in rat cerebral cortex via inhibition of oxidative stress. Free radical research, 48(8), 849-863.

[40] Lesage, S., & Brice, A. (2009). Parkinson's disease: from monogenic forms to genetic susceptibility factors. Human molecular genetics, 18(R1), R48-R59.

[41] Li, J., Deng, Y., Peng, D., Zhao, L., Fang, Y., Zhu, X., ... & Jiang, Y. (2021). Sodium Paminosalicylic acid attenuates manganese-induced neuroinflammation in BV2 microglia by modulating NF-κB pathway. Biological Trace Element Research, 199(12), 4688-4699.

[42] Lynch-Day, M. A., Mao, K., Wang, K., Zhao, M., & Klionsky, D. J. (2012). The role of autophagy in Parkinson's disease. Cold Spring Harbor perspectives in medicine, 2(4), a009357.
[43] Martins, A. C., Urbano, M. R., Lopes, A. C. B. A., Maria de Fatima, H. C., Buzzo, M. L., Docea, A. O., ... & Paoliello, M. M. (2020). Blood cadmium levels and sources of exposure in an adult urban population in southern Brazil. Environmental research, 187, 109618.
[44] Méplan, C., & Hughes, D. J. (2020). The role of selenium in health and disease: emerging and recurring trends. Nutrients, 12(4), 1049.
[45] Martins Jr, A. C., Morcillo, P., Ijomone, O. M., Venkataramani, V., Harrison, F. E., Lee, E., ... &Aschner, M. (2019). New insights on the role of manganese in Alzheimer's disease and Parkinson's disease. International journal of environmental research and public health, 16(19), 3546.
[46] Martins, A. C., Krum, B. N., Queirós, L., Tinkov, A. A., Skalny, A. V., Bowman, A. B., & Aschner, M. (2020). Manganese in the diet: bioaccessibility, adequate intake, and neurotoxicological effects. Journal of agricultural and food chemistry, 68(46), 1289312903.
[47] Miah, M. R., Ijomone, O. M., Okoh, C. O., Ijomone, O. K., Akingbade, G. T., Ke, T., ... &Aschner, M. (2020). The effects of manganese overexposure on brain health. Neurochemistry international, 135, 104688.
[48] Martins Jr, A. C., Gubert, P., Villas Boas, G. R., Meirelles Paes, M., Santamaría, A., Lee, E., ... & Aschner, M. (2020). Manganese-induced neurodegenerative diseases and possible therapeutic approaches. Expert review of neurotherapeutics, 20(11), 1109-1121.
[49] Melentijevic, I., Toth, M. L., Arnold, M. L., Guasp, R. J., Harinath, G., Nguyen, K. C., ... & Driscoll, M. (2017). C. elegans neurons jettison protein aggregates and mitochondria under neurotoxic stress. Nature, 542(7641), 367-371.
[50] Martinez-Vicente, M. (2015, April). Autophagy in neurodegenerative diseases: from pathogenic dysfunction to therapeutic modulation. In Seminars in cell & developmental biology (Vol. 40, pp. 115-126). Academic Press.
[51] Mizuno, Y., Hattori, N., Kubo, S. I., Sato, S., Nishioka, K., Hatano, T., ... & Mochizuki, H. (2008). Progress in the pathogenesis and genetics of Parkinson's disease. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1500), 2215-2227.
[52] Martinez-Vicente, M., Talloczy, Z., Kaushik, S., Massey, A. C., Mazzulli, J., Mosharov, E. V., ... & Cuervo, A. M. (2008). Dopamine-modified α-synuclein blocks chaperonemediated autophagy. The Journal of clinical investigation, 118(2), 777-788.
[53] Matsuda, N., Sato, S., Shiba, K., Okatsu, K., Saisho, K., Gautier, C. A., ... & Sato, F. (2010). 748 Kimura M, Komatsu M, Hattori N, and Tanaka K. PINK1 stabilized by mitochondrial depolarization 749 recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. The Journal of cell 750 biology 189: 211-221, 751.
[54] Milatovic, D., Gupta, R. C., Yu, Y., Zaja-Milatovic, S., & Aschner, M. (2011). Protective effects of antioxidants and anti-inflammatory agents against manganese-induced oxidative damage and neuronal injury. Toxicology and applied pharmacology, 256(3), 219-226.
[55] Nah, J., Yuan, J., & Jung, Y. K. (2015). Autophagy in neurodegenerative diseases: from mechanism to therapeutic approach. Molecules and cells, 38(5), 381.
[56] Narendra, D., Tanaka, A., Suen, D. F., & Youle, R. J. (2008). Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. The Journal of cell biology, 183(5), 795-803.
[57] Orenstein, S. J., Kuo, S. H., Tasset, I., Arias, E., Koga, H., Fernandez-Carasa, I., ... & Cuervo, A. M. (2013). Interplay of LRRK2 with chaperone-mediated autophagy. Nature neuroscience, 16(4), 394-406.
[58] Peres, T. V., Arantes, L. P., Miah, M. R., Bornhorst, J., Schwerdtle, T., Bowman, A. B., ... &Aschner, M. (2018). Role of Caenorhabditis elegans AKT-1/2 and SGK-1 in Manganese Toxicity. Neurotoxicity research, 34(3), 584-596.
[59] Popichak, K. A., Afzali, M. F., Kirkley, K. S., & Tjalkens, R. B. (2018). Glial-neuronal signaling mechanisms underlying the neuroinflammatory effects of manganese. Journal of Neuroinflammation, 15(1), 1-15.
[60] Peng, D., Li, J., Deng, Y., Zhu, X., Zhao, L., Zhang, Y., ... & Jiang, Y. (2020). Sodium para-aminosalicylic acid inhibits manganese-induced NLRP3 inflammasome-dependent pyroptosis by inhibiting NF-κB pathway activation and oxidative stress. Journal of neuroinflammation, 17(1), 1-15.
[61] Ramirez, A., Heimbach, A., Gründemann, J., Stiller, B., Hampshire, D., Cid, L. P., ... & Kubisch, C. (2006). Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nature genetics, 38(10), 11841191.

[62] Schetinger, M. R. C., Peres, T. V., Arantes, L. P., Carvalho, F., Dressler, V., Heidrich, G., ... & Aschner, M. (2019). Combined exposure to methylmercury and manganese during L1 larval stage causes motor dysfunction, cholinergic and monoaminergic up-regulation and oxidative stress in L4 Caenorhabditis elegans. Toxicology, 411, 154-162.

[63] Sceniak, M. P., Spitsbergen, J. B., Sabo, S. L., Yuan, Y., & Atchison, W. D. (2020). Acute neurotoxicant exposure induces hyperexcitability in mouse lumbar spinal motor neurons. Journal of Neurophysiology, 123(4), 1448-1459.

[64] Sarkar, S., Rokad, D., Malovic, E., Luo, J., Harischandra, D. S., Jin, H., ... & Kanthasamy, A. G. (2019). Manganese activates NLRP3 inflammasome signaling and propagates exosomal release of ASC in microglial cells. Science signaling, 12(563), eaat9900.

[65] Scheuhammer, A. M., Meyer, M. W., Sandheinrich, M. B., & Murray, M. W. (2007). Effects of environmental methylmercury on the health of wild birds, mammals, and fish. *AMBIO: a Journal of the Human Environment*, *36*(1), 12-19.

[66] Thomas, B. (2009). Parkinson's disease: from molecular pathways in disease to therapeutic approaches. Antioxidants & redox signaling, 11(9), 2077-2082.

[67] Spencer, B., Potkar, R., Trejo, M., Rockenstein, E., Patrick, C., Gindi, R., ... & Masliah, E. (2009). Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in α-synuclein models of Parkinson's and Lewy body diseases. Journal of Neuroscience, 29(43), 13578-13588.

[68] Seki, N., Akiyama, M., Yamakawa, H., Hase, K., Kumagai, Y., & Kim, Y. G. (2021). Adverse effects of methylmercury on gut bacteria and accelerated accumulation of mercury in organs due to disruption of gut microbiota. *The Journal of Toxicological Sciences*, *46*(2), 91-97.

[69] Shen, Y. F., Tang, Y., Zhang, X. J., HuANG, K. X., & Le, W. D. (2013). Adaptive changes in autophagy after UPS impairment in Parkinson's disease. Acta Pharmacologica Sinica, 34(5), 667-673.

[70] Vives-Bauza, C., Zhou, C., Huang, Y., Cui, M., De Vries, R. L., Kim, J., ... & Przedborski, S. (2010). PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. Proceedings of the National Academy of Sciences, 107(1), 378-383.

[71] Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M., Harvey, K., Gispert, S., ... & Wood, N. W. (2004). Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science, 304(5674), 1158-1160.

[72] Vanhaesebroeck, B., Whitehead, M. A., & Piñeiro, R. (2016). Molecules in medicine minireview: isoforms of PI3K in biology and disease. Journal of molecular medicine, 94(1), 511.

[73] Vogiatzi, T., Xilouri, M., Vekrellis, K., & Stefanis, L. (2008). Wild type α-synuclein is degraded by chaperone-mediated autophagy and macroautophagy in neuronal cells. Journal of Biological Chemistry, 283(35), 23542-23556.

[74] Wang, W., Deng, C., Chen, F., Zhang, L., Hu, Y., Lu, Q., & Zhang, A. (2022). Resveratrol attenuates methylmercury-induced neurotoxicity by modulating synaptic homeostasis. Toxicology and Applied Pharmacology, 440, 115952.

[75] Winslow, A. R., Chen, C. W., Corrochano, S., Acevedo-Arozena, A., Gordon, D. E., Peden, A. A., ... & Rubinsztein, D. C. (2010). α-Synuclein impairs macroautophagy: implications for Parkinson's disease. Journal of Cell Biology, 190(6), 1023-1037.

[76] Webb, J. L., Ravikumar, B., Atkins, J., Skepper, J. N., & Rubinsztein, D. C. (2003). αSynuclein is degraded by both autophagy and the proteasome. Journal of Biological Chemistry, 278(27), 25009-25013.

[77] Waqar Ahmad Khan. (2022). Preventive Agent of Vitamin c Against Pb-induced Toxicity: a review: International Journal of Advances in Biology (IJAB) 1/2/3August Volume 9, Number 10.5121/ijab.2022.9301

[78] Wang, H., Yang, F., Xin, R., Cui, D., He, J., Zhang, S., & Sun, Y. (2020). The gut microbiota attenuate neuroinflammation in manganese exposure by inhibiting cerebral NLRP3 inflammasome. Biomedicine & Pharmacotherapy, 129, 110449.

[79] Zhu, J., Tang, L., Qiao, S., Wang, L., Feng, Y., Wang, L., ... & Li, L. (2020). Low-dose methylmercury exposure impairs the locomotor activity of zebrafish: Role of intestinal inositol metabolism. Environmental Research, 190, 110020.

[80] Zhu, J., Wang, C., Gao, X., Zhu, J., Wang, L., Cao, S., ... & Li, L. (2019). Comparative effects of mercury chloride and methylmercury exposure on early neurodevelopment in zebrafish larvae. RSC advances, 9(19), 10766-10775.