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Mini Review

Research Progress of Autophagy and Heavy Metal (Cd, Pb, MeHg) Induced Neurotoxicity

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Abstract

Autophagy is a fundamental catabolic process crucial for neuronal removal of denatured proteins and senescent organelles. Indeed, autophagy dysfunction is closely associated with the onset of several neurodegenerative disorders. Overexposure to heavy metals can cause extensive lesions in the central nervous system. However, the precise role of autophagy in heavy metal-induced neurological diseases, whether protective or detrimental, remains a subject of active investigation. In this review, we consolidate current knowledge on the involvement of autophagy in the progression of neurotoxicity induced by Cadmium (Cd), Lead (Pb), and Methylmercury (MeHg) exposure, integrating recent mechanistic insights and highlighting future research directions.

Keywords: Autophagy, Heavy metal, Neurotoxicity, Cadmium, Lead, Methylmercury

Introduction

Heavy metals are pervasive environmental pollutants posing significant hazards to human health. Excessive intake of heavy metals adversely affects various tissues and organs, with the Central Nervous System (CNS) being particularly vulnerable. Heavy metal exposure can impair fetal neuronal development, disrupt synaptic function and neurotransmitter homeostasis, and lead to learning and memory deficits [1]. Autophagy is a critical catabolic process for removing damaged proteins and organelles, serving as a key cellular defense mechanism against toxic injury. Dysfunctional autophagy not only contributes to the pathogenesis of multiple neurodegenerative diseases but also modulates heavy metal-induced neurotoxicity. This review provides an updated overview of the relationship between autophagy and the neurotoxic effects induced by Cadmium (Cd), Lead (Pb), and Methylmercury (MeHg), integrating recent molecular findings to guide future research.

Overview of Autophagy

Autophagy is a cellular process where damaged or misfolded proteins and organelles are sequestered within double-membrane structures called autophagosomes, which subsequently fuse with lysosomes to form autophagic lysosomes. The contents are then degraded by lysosomal hydrolases, enabling metabolic recycling and organelle renewal. Based on the delivery pathway to the lysosomal lumen, autophagy is categorized into three types: macroautophagy, microautophagy, and Chaperone-Mediated Autophagy (CMA) [2,3]. Macroautophagy, commonly referred to as autophagy, is a process in which cells respond to adverse external stimuli. In this process, cytoplasmic misfolded proteins and damaged organelles are sequestered by cup-shaped membranes to form autophagosomes, which subsequently fuse with lysosomes to generate autolysosomes, where hydrolytic enzymes degrade the sequestered contents. This pathway primarily mediates the bulk degradation of long-lived proteins or organelles in the cytoplasm [2,3]. In contrast to macroautophagy, microautophagy involves the direct engulfment and degradation of cellular components by lysosomes without the intermediate involvement of transport vesicles. It is mainly responsible for the selective degradation of unneeded organelles. CMA exhibits high substrate selectivity by recognizing cytosolic proteins containing a specific pentapeptide motif. With the help of

chaperones, substrate proteins are bound by lysosomal membrane receptors and directly translocated into lysosomes for degradation. Unlike the other two pathways, CMA acts only on soluble proteins with strict selectivity [2,3].

Autophagy and Heavy Metal-Induced Neurotoxicity

Cadmium (Cd)

Cadmium is a globally prevalent pollutant derived from both industrial sources and environmental exposure. It can disrupt the blood-brain barrier, enter the CNS, and cause neurological disorders, including Parkinsonian-like symptoms, cognitive deficits, and learning/memory impairment [4,5]. Epidemiological and experimental evidence suggest Cd as a risk factor for neurodegenerative diseases. For instance, Cd exposure in Alzheimer's Disease (AD) model mice increases β-amyloid (Aβ) deposition and exacerbates memory deficits [6]. Studies on the neurotoxic mechanism of cadmium revealed that it can increase intracellular Ca^{2+} concentration, activate apoptosis-related proteins, and ultimately lead to cell apoptosis. Disruption of intracellular calcium homeostasis is considered one of the mechanisms underlying Cd toxicity [5]. In addition, lipid peroxidation damage may be another important pathway for cadmium's neurotoxic effects. Cadmium can also reduce the synthesis and release of monoamine neurotransmitters, such as dopamine and serotonin [3].

Mounting evidence has proved that Cd can induce autophagy in different cell and animal models. However, whether Cd-induced autophagy exerts a protective or detrimental effect on the nervous system remains controversial. *Xu, et al.,* (2021) showed that Cd impairs autophagy and triggers apoptosis in neuronal cells via Ca^{2+}-dependent JNK activation, and that chelating intracellular Ca^{2+} or inhibiting the activation of JNK suppressed Cd-induced autophagosome expansion, which led to the consequent apoptosis [5]. These results suggest that enhanced autophagy could be a promising approach to alleviate cadmium-induced neurotoxicity and neurodegeneration. On the other hand, autophagy can also promote cell death under specific conditions. For example, puerarin, a natural compound, has been shown to alleviate Cd-induced neuronal injury by inhibiting PINK1/Parkin-mediated mitophagy and the mitochondrial apoptosis pathway in rat cerebral cortex [7]. It can be concluded that Cd-induced mitophagy acts as a mediator of neuronal injury. Based on current findings, a comprehensive review highlights that Cd-induced autophagy can be either protective or adverse depending on the exposure dose, duration, and cell type or animal model [8].

Lead (Pb)

Pb is a pervasive environmental toxicant that poses a worldwide threat to public health. For the general population, the main routes of lead exposure are the ingestion of food and drinking water contaminated with Pb. Pb can damage various organs and systems in the human body, with the central nervous system being the most sensitive and primary target. Pb exposure is linked to intellectual disability, learning and memory deficits, and increased risk for neurodegenerative diseases like Parkinson's Disease (PD) and AD [9,10]. The neurotoxicity of Pb involves interference with neurotransmitter systems (dopaminergic, cholinergic, glutamatergic), particularly as a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors (it plays vital physiological roles in neuronal development and synaptic plasticity), disruption of Ca^{2+} homeostasis, and induction of autophagy [11,12].

Pb can induce cellular autophagy, which has been reported to be associated with neurotoxicity in some studies, while others suggest that it serves as a protective mechanism against lead-induced CNS damage. The molecular mechanisms of autophagy-mediated Pb neurotoxicity are now better understood. For example, *Huang, et al.,* (2020) showed that Pb exposure induces autophagy by blocking the Akt/mTOR signaling pathway, thereby accelerating inflammatory and oxidative damage in rat astrocytes [13]. In pubertal rats, *Zhang, et al.,* (2023) further demonstrated that Pb exposure impairs learning and memory by activating hippocampal autophagy through the inhibition of the IGF-1/PI3K/Akt/mTOR signaling pathway [3]. In contrast, *Ji, et al.,* (2021) found that chlorogenic acid and its analogues can protect against Pb-induced developmental neurotoxicity in zebrafish by modulating autophagy, reducing dopaminergic neuron loss and locomotor impairment [14]. Beyond kinase signaling, Pb disrupts intracellular Ca^{2+} homeostasis by damaging mitochondria and by inducing endoplasmic reticulum stress, leading to Ca^{2+} release and subsequent autophagic activation [12,15]. The overall effect is context-dependent, as moderate lead exposure may induce protective autophagy, whereas excessive or sustained exposure drives overactivation of autophagy and potentially contributes to neurological disease.

Methylmercury (MeHg)

Mercury is a metallic element that is liquid at room temperature. In aquatic environments, mercury is converted by microbial biomethylation into methylmercury (MeHg), a more toxic substance [12,16]. MeHg has strong lipophilicity, easily crosses the blood-brain barrier, and exerts potent neurotoxicity, with the developing nervous system being particularly sensitive. Researchers have found that exposure to MeHg during pregnancy, even in the absence of maternal symptoms, can cause intellectual disability, fine motor deficits, and neurodevelopmental delay in infants [16]. Studies on the neurotoxic mechanisms of MeHg have revealed that it can interfere with protein synthesis in the nervous system, affect the expression of NMDA receptors and intracellular Ca^{2+} homeostasis, alter the expression levels of nerve growth factors in the brain, and impact the release of neurotransmitters. These neurotransmitters are involved in various brain functions such as learning, memory, cognition, movement, and language [4].

Recent studies have dissected the complex role of autophagy in MeHg neurotoxicity. As demonstrated by *Lin, et al.,* (2019), MeHg promotes autophagy independent of the mTOR pathway by acti-

vating the JNK/Vps34 complex cascade, thereby inducing autophagosome aggregation and neuronal death [17]. Moreover, *Wei, et al.,* (2021) and *Ni, et al.,* (2022) found that MeHg promotes oxidative stress, which in turn regulates autophagy through the PI3K/AKT/mTOR or AMPK/TSC2/mTOR pathways, confirming that oxidative stress-induced autophagy is an important mechanism of MeHg-induced neurotoxicity [18,19]. Besides, a study by *Zhu, et al.,* (2020) using zebrafish revealed that low-dose MeHg exposure impairs locomotor activity by disrupting intestinal inositol metabolism via gut microbiota alterations. Supplementation with myo-inositol restored autophagy and apoptosis-related gene expression and ameliorated neurotoxicity, highlighting a novel gut-brain axis mechanism[20]. Additionally, *Li, et al.,* (2024) showed that MeHg induces inflammatory responses and autophagy in microglia via ROS-mediated activation of the NLRP3 inflammasome, suggesting a link between neuroinflammation and autophagic dysfunction [21].

Conclusions and Future Outlook

Conclusions

Current research indicates that autophagy plays a dual role in heavy metal-induced neurotoxicity. Moderate or protective autophagy helps cells withstand toxic insults, whereas excessive or dysfunctional autophagy contributes to cell death and neurodegeneration. The transition between these opposing roles depends on the heavy metal species, exposure dose, duration, and the specific cellular context. Significant progress has been made in understanding key molecular pathways, such as Ca^{2+}/JNK signaling, Akt/mTOR and IGF-1/PI3K/Akt/mTOR signaling, the JNK/Vps34 pathway, the oxidative stress-AMPK/mTOR cascade, and the NLRP3 inflammasome pathway. Furthermore, emerging evidence highlights the importance of the gut-brain axis (MeHg) and the therapeutic potential of natural compounds (puerarin, chlorogenic acid, myo-inositol) in modulating autophagy to counteract heavy metal-induced neurotoxicity.

Future Outlook

Future research should focus on: 1) identifying the precise molecular thresholds that determine whether autophagy is protective or detrimental; 2) further elucidating the interplay between autophagy, apoptosis, neuroinflammation, and the gut microbiome in heavy metal toxicity; 3) developing targeted therapeutic strategies that modulate specific autophagic pathways to alleviate heavy metal-induced neurological damage.

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Conflict of Interest

The author declares no conflicts of interest.

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