Methylmercury-induced pro-inflammatory cytokines activation and its preventive strategy using anti-inflammation N-acetyl-L-cysteine: a mini-review

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Mini Review

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Methylmercury-induced pro-inflammatory cytokines activation and its preventive strategy using anti-inflammation *N*-acetyl-L-cysteine: a mini-review

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Abstract: The exposure of methylmercury (MeHg) has become a public health concern because of its neurotoxic effect. Various neurological symptoms were detected in Minamata disease patients, who got intoxicated by MeHg, including paresthesia, ataxia, gait disturbance, sensory disturbances, tremors, visual, and hearing impairments, indicating that MeHg could pass the blood-brain barrier (BBB) and cause impairment of neurons and other brain cells. Previous studies have reported some expected mechanisms of MeHg-induced neurotoxicity including the neuroinflammation pathway. It was characterized by the up-regulation of numerous pro-inflammatory cytokines expression. Therefore, the use of anti-inflammatories such as *N*-acetyl-L-cysteine (NAC) may act as a preventive compound to protect the brain from MeHg harmful effects. This mini-review will explain detailed information on MeHg-induced pro-inflammatory cytokines activation as well as possible preventive strategies using anti-inflammation NAC to protect brain cells, particularly in *in vivo* and *in vitro* studies.

Keywords: methylmercury; NAC; neurotoxicity; pro-inflammatory cytokines.

Introduction

In recent years there has been increasing focus on the effects on human health of environmental pollution by numerous heavy metals. These heavy metals include arsenic (As), lead (Pb), cadmium (Cd), and mercury (Hg) [1]. Mercury is classified as elemental mercury (H^0), inorganic mercury (Hg^{2+}), and organic mercury [2]. Organic Hg is the compound formed from hydrogen and carbon combination and classified as allyl-mercury and alkyl-mercury [3]. Methylmercury (MeHg) belongs to the alkyl-mercury compound and is frequently found in ecological systems where it causes severe contamination of the aquatic environment [4]. It is formed by methylation of inorganic mercury by sediment bacteria in the aquatic environment [2].

Methylmercury

Methylmercury (MeHg) is known to be the most toxic type among the mercury compound [5]. The long half-life of Hg in human bodies is well known (about 74 days), therefore the exposure of contaminated fish and shellfish even though at a low level may cause Hg accumulation in the human bodies and affect human health [6, 7]. Recently, numerous studies on the dose-response assessment of MeHg have been performed to gather information related to mechanism and effect based on dose-response exposure.

The major human exposure source of MeHg is through the food chain via the consumption of contaminated fish and other aquatic species [8]. High concentrations of MeHg were reported in fish and shellfish (about 75–90%), and intake of fish and shellfish commonly caused high MeHg levels in the human body, particularly after 30 days [9]. The concentration of mercury in fish and shellfish is much higher compared with other seafood and about 90% of mercury exists in the MeHg form [3, 8, 10]. The concentration is in higher quantities in larger and longer-living fish species such as swordfish and shark [3, 10]. Since the exposure pathway in humans primarily from contaminated food, it becomes a high risk for those living nearby [2]. Approximately 99% of MeHg that is contained in the food will be

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easily absorbed in the intestinal tract and vascular distributed to all parts of the body, particularly the liver, kidney, and brain [11]. It can be transported by L-amino transported (LAT) to pass the blood-brain barrier (BBB) and accumulated in the brain [11, 12]. Previous studies reported that mercury-contaminated fish and shellfish intake were associated with hair mercury concentration in Minamata disease patients, as well as fishing communities in Brazil [3, 13].

Cytotoxicity of methylmercury

The cytotoxic effects of MeHg have been reported in both human and animal studies. Table 1 shows the MeHg cytotoxicity effect in *in vivo* studies using mice and rats. The exposure of MeHg caused cell damage and death commonly in the brain compared with other organs such as liver and kidney [14–19]. MeHg induced kidneys damage, as well as liver injury by hepatocyte swelling and inflammation [18, 19]. The exposure of 1 μM/L MeHg for 1 h in mouse pancreatic β-cell significantly induced reactive oxygen species (ROS) generation and reduced insulin secretion, indicating that MeHg caused pancreatic cell dysfunction [20]. Previous *in vivo* studies have reported some neurotoxic effects of MeHg in brain cells such as mitosis inhibition and apoptosis stimulation in rat hippocampus, as well as neuronal cell death and microglial activation [15, 16].

Neuronal cells are known as irreversible cells and the toxic effect of MeHg-induced brain cell damage was unrepairable [14]. Therefore, MeHg-induced neurotoxicity pathways are important to be understood to improve preventive strategies properly [21]. The exposure of MeHg has been reported to decrease cell viability in mice glial cells and the function of the sensorimotor and visual cortex of brain hemispheres, and at low concentration reduced intact Purkinje cell number in mice cerebellum that was associated with ataxia symptom [16, 22, 23]. The impairment of attention, fine-motor function, and verbal memory were associated with hair mercury concentration and fish consumption among the fishing population in the Pantanal region of Brazil, indicating that MeHg exposures could be a risk factor for deficits in neurocognitive functions [13].

Pro-inflammatory cytokines activation by methylmercury

The expected pathways of MeHg-induced neurotoxicity are inflammation mechanism by modifying the expression of pro-inflammatory cytokines [21, 24]. The activation of numerous pro-inflammatory cytokines expression has been reported by MeHg exposure in *in vivo* and *in vitro* studies. The previous study found that MeHg treatment at lower concentration (4 μM) could activate interleukin (IL)-6 and monocyte chemoattractant protein (MCP)-1 expression at both mRNA and protein levels in U-87MG human astrocytoma cell line [7], indicating that activated astrocytes which can be acted as macrophages in the brain could be induced by MeHg exposure. Other related studies supported this phenomenon of macrophage activation, where MeHg treatment at 2 and 10 μM has also activated other macrophages cell lines such as murine RAW264.7 and human U937 macrophages by up-regulating macrophage inflammatory protein (MIP)-2 (a murine homologue of human IL-8), IL-6 and IL-8 expressions [12, 25, 26]. Chang also reported that MeHg treatment at 10 μM significantly induced IL-6 expression in rat glioma cells [22]. Interestingly, the down-regulation of IL-6 expression was also reported in a culture of neonatal Balb/c mice glial cells that were treated with MeHg [27]. The recent study reported that MeHg could activate IL-6, MIP-2, and MCP-5 (a murine homologue of human MCP-1) pro-inflammatory cytokine expressions in brain tissues and blood serum of MeHg-exposed Balb/C mice [28].

Other pro-inflammatory cytokine expressions could be also stimulated by MeHg. Previous studies reported that MeHg administration in C57BL/6 mice at a single dose of 25 mg/kg body weight (BW) significantly increased IL-1β and IL-19 expressions in cerebrum and cerebellum, and at 10 mg/kg BW/day (subcutaneous injection) for 7 consecutive days stimulated CCL-2, CCL-4, CCL-7, CCL-9, and CCL-12 mRNA expression concentration in cerebellum [16, 17], as well as early growth response gene (Egr1), glutathione S-transferase (Gst-mu), chemokine (mKC), and macrophage inflammatory protein (MIP)-2 expression by oral administration with 3.1 mg/kg MeHg in adult male Kunming mice liver [19]. The activation of CCL-2 (also known as MCP-1) expression by MeHg treatment (10 μM) was also reported in *in-vitro* studies which were in human astrocytoma cell line 1321N1 [29]. Interestingly, Godefroy reported that the level of CCL-2 expression was reduced by MeHg administration at 5.4 ± 0.5 ng Hg/g of food pellet or 50nM–5μM in C57BL/6 mice brain cortex and pure rat cortical neurons culture, respectively [15] (See Table 2).

The stimulation of cytokine expression by MeHg exposure involved some pathways such as induction oxidative stress, cyclic adenosine monophosphate (cAMP), and cytosolic phospholipase A2 and C [30–32]. MeHg could

Table 1: Cytotoxicity effects of methylmercury in *in vivo* studies.

No	Reference	MeHg (dose, administration), Animals	MeHg effects
1	[14]	0.1 µmol/kg BW, intravenously Wistar rats	Produced irreversible brain damage
2	[15]	5 µg/g body weight [BW] in 100 µL intravenous 7-days old Sprague-Dawley rats	Decreased DNA synthesis in hippocampus, as well as induced caspase-3 immunoreactivity cells activation and hippocampal apoptosis
3	[16]	5.4 ± 0.5 ng Hg/g BW of a food pellet C57Bl/6 Jico inbred strain mice	Induced a decrease in CCL2 concentration (in the sensorimotor and visual cortex), neuronal cell death, and microglial activation
4	[17]	10 mg/kg BW/day (subcutaneous injection) 7 consecutive days Male C57BL/6 mice	Upregulated mRNA expression levels of CCL2, CCL4, CCL7, CCL9, and CCL12 in cerebellum
5	[28]	4 mg Hg/kg BW 17 days orally Male Balb/C mice	Activated pro-inflammatory cytokine expressions in serum (IL-6, MIP-2 and MCP-5), cerebrum (MIP-2 and MCP-5), and cerebellum (IL-6), as well as reduced intact cerebellum Purkinje cell number and caused ataxia symptom
6	[18]	25 mg/kg BW (subcutaneous injection) Single-dose C57BL/6 mice	Increased IL-1β expression in cerebellum and kidney (on day 1), and IL-19 expression in the cerebrum (on day 7), cerebellum (on day 5), and kidney with a lower degree than that in the brain
7	[19]	3.1 mg/kg BW 7 days orally Adult male Kunming mice	Produced spotted hepatocyte swelling and inflammation, increased the expression of liver injury biomarker genes such as metallothionein (MT)-1 and heme oxygenase (HO)-1, as well as inflammation biomarkers such as early growth response gene (Egr1), glutathione S-transferase (Gst-mu), chemokine (mKC) and macrophage inflammatory protein (MIP)-2, and Nrf2 pathway genes NAD(P)H, quinone oxidoreductase 1 (Nqo1) and glutamate-cysteine ligase catalytic subunit (Gclc)

stimulate the generation of ROS in astrocytes by increasing hydrogen peroxide (H_2O_2) and superoxide anion (O_2^-) concentration [12, 33]. The mechanisms related to transcription factors were also reported to be involved in MeHg-induced cytokine expressions such as nuclear factor kappa B (NF-$_K$B) and nuclear factor-erythroid 2-related factor (Nrf)-2 activation [19, 29, 32]. MeHg stimulated Nrf2 activation by altering the expression of quinone oxidoreductase (Nqo)-1, glutamate-cysteine ligase catalytic subunit (Gclc) [19].

Preventive strategy against methylmercury using *N*-acetyl-L-cysteine

As MeHg exposure could affect neurotoxicity by altering the pro-inflammatory cytokines expression and oxidative stress generation, the preventive strategy using anti-inflammation and antioxidant could be promising. *N*-acetyl-L-cysteine (NAC) is an anti-inflammatory compound that can act as an antioxidant as well [34]. Some studies concerning MeHg exposure effects both *in-vivo* and *in-vitro* have reported that NAC could be used as an alternative agent to protect cells from MeHg harmful effects, as shown in Table 3 [11, 12, 14, 15, 20, 28, 35, 36]. NAC inhibited MeHg's effects on decreasing plasma insulin levels, as well as raising blood glucose, glucose intolerance and plasma malondialdehyde [20]. It also suppressed MeHg-induced DNA synthesis reduction and caspase-3 immunoreactivity increase [15]. Ballatori reported the effect of administration of drinking water that contains NAC at 10 mg/mL was effective to increase the excretion of MeHg-contained urine and reduced MeHg levels in the tissue in C56BL/6 mice, indicating that NAC possibly worked as MeHg chelating agent [35]. The effect of NAC accelerated the urinary excretion of MeHg and MeHg concentration in the blood after being given orally or intravenously of 1 mmol/kg NAC in adult Wistar rats both pregnant and non-pregnant rats [11, 14]. The effect of NAC to stimulate urinary MeHg excretion decreased in multidrug resistance-associated protein (Mrp)-2 deficient (TR-) Wistar rats [11], suggesting that Mrp-2 has a role to play in urinary MeHg excretion after NAC treatment. Mrp2 that is also known as Abcc-2, is a subfamily C of the transporter ATP binding cassette (ABC) superfamily, works as an organic anion transport pump for GSH, glucuronide, and sulfate conjugates [37, 38]. NAC

Table 2: Cytotoxicity effect of methylmercury in *in vitro* studies.

No	Reference	MeHg (dose, administration), Cells	MeHg Effects
1	[27]	0–1.0 mM; Glial cells of neonatal Balb/c mice	Reduced the secretion of IL-6 in a dose-dependent manner but did not affect the secretion of TNF-α and IL-1β in microglia/astrocyte
2	[31]	a. 0–20 μM; 30 and 60 min; Rat C6 glioma cells b. 0–5 μM; 8 and 16 h; Rat C6 glioma cells c. 0–10 μM; 16 h; Human U251HF glioma cells d. 5 μM; 8, 12, 24 h; Human ARPE-19 retina pigment epithelial cells	Increased ROS generation from 0.625 μM or above after 30 min activated IL-6 expression started at 2.5 and 1.25 μM concentration for 8 and 16 h treatment, respectively stimulated IL-6 expression at 10 μM concentration Increased IL-6 expression and cell death (after 24 h treatment)
3	[22]	0–10 μM; overnight (>18 h); Cerebral glial C57BL/6 mice	Reduced cell viability and increased IL-6 expression from 5 μM concentration
4	[20]	a. 0.2–1 μM/L; 1 h b. 0.5–1 μM/L; 4 h Pancreatic β cell-derived HIT-T15 cells	Stimulated ROS generation at 0.5 μM/L Inhibited insulin secretion
5	[25]	0.5 and 2 μM; murine RAW264.7 macrophage cell line	Activated the MIP-2 and MCP-5 expressions at 2 μM for 3 h treatment
6	Garg TK and Chang JY 2006 [41]	0–20 μM; mouse N9 microglial cells	Reduced cell viability to ~50% at 9 μM and ~3% at 15 μM for 24 h treatment
7	[16]	50nM–5μM; 5 days; pure rat cortical neurons in culture	Blockade of the CCL2/CCR2 neurotransmission an increased neuronal cell death in response to MeHg neurotoxicity
8	[29]	10 μM MeHg; 0, 3, 6, 12, and 24 h; Human astrocytoma cell line 1321N1	Increased CCL2 expression in the cells, as well as the level of the NF-κB p65 subunit in the nuclei of 132N1 cells.
9	[12]	4 μM; U-87MG human astrocytoma cells	Induced MCP-1 and IL-6 expressions at both mRNA and protein levels.
10	[33]	10 μM MeHg; Astrocytic cultures from cerebral cortices of newborn Sprague–Dawley rats	Increased intracellular H_2O_2 and O_2^-
11	[26]	10 μM; 3, 6, 24 h; Human U-937 macrophage cell line 4 μM; 3, 6, 24 h; U-87 MG human astrocytoma cells	Up-regulated mRNA expression of IL-8 and IL-6 at 3 and 6 h treatment, respectively, as well as protein expressions for 12 h Increased IL-8 mRNA and protein expression at 6 and 12 h treatment, respectively

could suppress MeHg-induced pro-inflammatory cytokines of IL-6, MIP-2, and MCP-5 that also associated with reducing the Purkinje cell damage and ataxia symptom [28].

The suppressive effect of NAC in MeHg-induced IL-6 and MCP-1 pro-inflammatory cytokine expression has been reported at pre-, co- and post-treatment with 0.5 and 5 mM concentrations, and the mechanism involved stress oxidative pathway in U-87MG human astrocytoma cells [12]. It increased intracellular glutathione (GSH) to protect neurons and astrocytes from the MeHg effect, as well as decreased DNA synthesis inhibition and neuronal cytotoxicity [14, 39]. NAC could work as an antagonist of MeHg by suppressing ROS formation through Akt phosphorylation to counter MeHg-induced the inhibition of insulin secretion effect in mouse islets [20]. NAC that also acts as a GSH precursor, have been reported to suppress MeHg-induced toxicity and the astrocytes apoptotic ratio, suggesting that NAC could modulate the autophagy effect of astrocytes in MeHg existence [36].

To protect the brain damage from MeHg exposure, the preventive agent supposed to pass the BBC. NAC was reported effectively to reduce MeHg levels in the brain tissue, and placenta and fetus tissues as well in pregnant Wistar rats that received an intravenous injection of 0.1 μmol/kg MeHg, indicating that NAC against MeHg on body burden and transplacental transfer [14]. Its derivatives were also reported could enter mice brain, and its ability could be increased by LPS addition [34, 40].

Table 3: Suppressive effect of N-acetyl-L-cysteine in methylmercury-exposed animals/cells.

No	Reference	NAC/MeHg (dose, administration), Animals/Cells	Effect of NAC
a.	*in vivo*		
1	[14]	a. NAC 1 mmol/kg BW, intravenously injected 1 or 2 h after MeHg administration MeHg 0.1 µmol/kg, intravenous Adult Wistar rats	Effectively enhance MeHg excretion in urine
		b. NAC 10 mg/mL; oral (drinking water) after 24 h of MeHg administration; 2 days MeHg 0.1 µmol/kgBW; intravenous Pregnant rats	Protected fetuses by reducing MeHg concentrations in the placenta and the whole fetus, as well as in the brain, kidney, blood, and liver of maternal rats
2	[35]	NAC 10 mg/ml; oral (drinking water) for 5 days; 48 h before/after MeHg administration or together with MeHg MeHg 0.5 or 25 µmol/kg; intraperitoneal C56Bl/6 mice	Effectively enhanced methylmercury excretion by urine
3	[20]	NAC 150 mg/kg; oral; 2–4 weeks MeHg 20 µg/kg/day; oral; 7 days/week for 2–4 weeks ICR mice	Effectively suppressed mercury-induced down-regulation of plasma insulin levels, the elevation of blood glucose and glucose intolerance, as well as induced plasma malondialdehyde
4	[15]	NAC 10 ug/g BW intraperitoneal MeHg 5 ug/g BW in 100 uL intravenous 7-days old Sprague-Dawley rats	Prevented the reduction of DNA synthesis and the marked increase in caspase-3 immunoreactivity
5	[11]	NAC 0.42 or 0.84 mmol/kg, infused (intravenously) MeHg 2 mL/kg, intravenously Wistar rats	Accelerated urinary excretion of MeHg
6	[28]	NAC 150 mg/kg BW; orally; 17 days MeHg 4 mg Hg/kg BW; orally; 17 days Male Balb/C mice	Suppressed MeHg-induced IL-6 and MIP-2 in serum, and MCP-5 in the cerebrum, as well as prevented cerebellum Purkinje cells damage and ataxia symptom
b.	*in vitro*		
7	[12]	NAC 0.5 or 5 mM for pre-(0.5 and 1 h), co-, post-(1 and 3 h) treatment MeHg 4 µM U-87MG astrocytoma cell line	Suppressed MeHg-induced IL-6 and MCP-1 expression
8	[36]	NAC [illegible] mM for 4 h MeHg at 0, 1, 2, 5, or 10 µM for 6 h Astrocytes neonatal rats	Inhibited the activation of autophagy by MeHg

Conclusion

MeHg effect in neurotoxicity has involved pro-inflammatory cytokines activation, and the preventive strategy using anti-inflammation NAC is promising to protect the brain from MeHg harmful effect.

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