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Mini Review Article

TOXIC EFFECTS OF LEAD ON FISH AND HUMAN

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Abstract: *Bioaccumulation is a characteristic aspect in toxicity caused by Pb exposure. Toxic effects are induced in fish due to Pb exposure effecting its biochemical and physiological functions. Exposure pathway (dietary and waterborne), environmental factors (salt-water or fresh water) and Pb binding capacity with protein, SH and sulfur group decide accumulation pattern of Pb exposure. Activation of antioxidant responses like TBARS, GSH, GST, CAT and SOD occurs in fish for its protection in response to the oxidative stresses induced in fish due to Pb accumulation. Disruption of neurotransmitter function also occurs due to Pb accumulation which causes neurotoxicity in fish. Pb interaction also disturbs immune system responses. In fish, various systems are affected due to Pb toxic exposure which can be used as an indicator of toxicity in aquatic environment.*

Keywords: Lead, heavy metal, toxicity, antioxidant, biochemical, physiological

Lead

Earth crust contains lead in trace amount that is generally found in plant, rocks, air, water and soil (Cheng and Hu, 2010). Although aquatic habitats are omnipresent with lead but anthropogenic activities that include smelting, mining, manufacturing of paints, cement and batteries raise its level (Chain, 2010; Flegal, 1986; Kim and Kang, 2016b). Lead combines (naturally) with other elements to form lead compounds and in environment it occurs predominantly in inorganic form (Pb II, TEL, trimethyl lead), however organic states found which was reported record toxic in the form of TtEL (Chang et al., 2007; Chen et al., 2014; Flegal, 1986; Lee and Jiang, 2005). Pb bio- magnification does not occur in food chain. Accumulation of pb in older organisms causes the increase in body burden as they are stored on bony tissues.

Lead toxicity in human

Lead compound mainly target reproductive (Apostoli et al., 1998; Assennato et al., 1987; Braunstein et al., 1978; Lerda, 1992; Telisman et al., 2000), digestive (Sakai, 2000), skeletal (Oflaherty, 1995), peripheral and central NS (Campara et al., 1984; Hogstedt et al., 1983; Lead, 1995; Mantere et al., 1984), immunological system (Coscia et al., 1987; Ewers et al., 1982; Gidlow, 2015) and kidney (Ehrlich et al., 1998; Gerhardsson et al., 1992; Goyer, 1989; Lead, 1995; Loghman-Adham, 1997). While chronic Pb exposure leads cardiotoxicity (Evis et al., 1987; Lai et al., 1991), neurotoxicity, nephrotoxicity (Khalil-Manesh et al., 1993), carcinogenicity (IARC, 2006) and genotoxicity (IARC, 2006) in humans. Ingesting Pb contaminated sea food causes acute toxicity in kidney and brain. Pb gastrointestinal absorption is dependent on iron, calcium status of the human body as well on the age that is kids are more vulnerable as they absorb more lead. Lead is accumulated in bones, blood and soft tissue after its absorbance into the blood steam. Lead has high affinity with protein due to its stable complex formation with sulfur and oxygen atom of protein structure (Verstraeten et al., 2008). Ferrochelatase (involve in the catalyzation of porphyrin ring by iron), delta-aminolevulinic acid synthase (synthesize porphobilinogen (PBG) which is important for biosynthesis of hemeproteins) and delta-aminolevulinic acid dehydratase are three vital human heme enzymes which are inhibited due to Pb accumulation. This inhibition causes hemoglobin level to drop and inhibit the metabolism of cytochrome P450- dependent phase (Alvares et al., 1976; Bernard and Lauwerys, 1984; Goering, 1993; Jaishankar et al., 2014; Philip and Gerson, 1994; Ponka, 1999).

Lead toxicity in fish

Inhibition of inocytes basolateral transport mechanism in the epithelium of gills causes

hypocalcemia in fish due to lead accumulation. It is because of lead high affinity with Ca^{2+} ATPase, $Na^{2+}K^{+}$ ATPase and $Na^{+}Ca^{2+}$ exchanger which disturb ion regulation and electrochemical gradient in cells (Verstraeten et al., 2008). Hence, bioaccumulation even at small concentration due to Pb exposure can prove fatal to aquatic animals (Kim and Kang, 2015b). Lead poisoning and oxidative stress can be caused by the imbalance between antioxidants and pro oxidants (Kim and Kang, 2017b). In fish, persuaded intensified antioxidant response due to lead exposure can produce ROS (reactive oxygen species). Pb has high affinity for RBCs which result in toxic effects on function and structure of cellular membranes and cause high oxidative stress in fish (Gurer and Ercal, 2000). Immunological parameter including piscine immune system is being affected due to the lead stress (Kim and Kang, 2016c). In animals, Pb acts as a critical immune toxicant (Paul et al., 2014). Lead has diverse stroke exposure and toxic effects; thus, an inclusive research is needed to define the Pb exposure in fish.

Bioaccumulation

Metals show its toxic effects in fish when they are taken up by the body and is bioaccumulated followed by the detoxification mechanism, metabolic and excretory process (Eroglu et al., 2015). In fish metal contamination occur either through gastrointestinal track when they intake contaminated food or through gill if metal ions are present in water. Liver as metal excretory system play its role in binding of Pb to steroid in bile and then out of the body through feces (Sures et al., 2003; Zhai et al., 2017). Circulatory system is responsible for circulating the ingested metal to rest of body (Zhai et al., 2017), where metals either stored in tissues, or is lethal to target organ or is excreted outside the body via gills and kidney (Kim and Kang, 2014, 2015a, 2016a). Dietary exposure of Pb to juvenile rockfish, *Sebastes schlegelii*, show accumulation of Pb in its various tissue include gills, intestine, liver and spleen. Hwang et al. (2016) also testified the similar trend of Pb accumulation in *Platichthys stellatus* who was experienced to dietary Pb.

Ca^{2+}, Na^{+} and K^{+} ionic homeostasis is disturbed when body have chronic exposure against lead (Grosell et al., 2006). Antagonistic actions of Ca^{2+} and Pb^{2+} lessen Pb toxicity in fish body because Ca2+ stick to dissolved ambient Pb and help to lower Pb accumulation in body (Alves et al., 2006; Audesirk, 1993; Rogers et al., 2003). There are two pathways by which metal can accumulate in the body i.e. dietary or waterborne metal exposure. Water borne exposure result in the accumulation of metal in gills because during osmoregulation and respiration, gills come in direct contact with metal (Alves et al., 2006; Rogers et al., 2003). While dietary exposure accumulates high metal concentration in intestinal tissues (Alves et al., 2006; Castro-González and Méndez-Armenta, 2008). Water borne exposure has high risk of Pb accumulation in the gills as compared to the dietary intake (Dural et al., 2007; Farkas et al., 2003; Grosell et al., 2006; Kalay et al., 1999; Souid et al., 2015). Metals bound to the subcellular fractions of prey when the gut is exposed to dietary metal pathway makes the microbiota to reduce however when exposed to water the bioavailability is 20-60 times more (Alsop et al., 2016). Environmental differences also play its role in the bioaccumulation of the metal i.e. sea water and fresh water. To avoid from dehydration under high osmotic pressure condition, marine fish drink a lot of water that cause prominent metal accumulation in the intestinal tissue. While in the case of fresh water specie, gills are at high risk of metal accumulation because fish under low osmotic pressure environment actively transport ions outside the body through inocytes in the gill (Kim and Kang, 2014). Metabolic active organs have been reported to be on a high risk for metal accumulation. Acute or chronic Pb effects the target organs liver and kidney, due to their role in detoxification and elimination of toxic element outside the body (Javed, 2012; Patra et al., 2001; Vinodhini and Narayanan, 2008; Zhai et al., 2017). Spleen is also accumulated with Pb because it functions in the removal of xenobiotic from blood (Kim and Kang, 2015b; Somero et al., 1977). Gills and intestine accumulate Pb directly from water or food (Kim and Kang, 2017a). Pb accumulation has been reported lowest in the fish muscles and it is important indicator of food safety because fish muscles are directly accumulated by the humans (Al-Balawi et al., 2013; Dural et al., 2007; Farkas et al., 2003; Sures and Siddall, 1999; Zhai et al., 2017).

Neurotoxicity

Pb is neuro toxicant whose exposure directly affect CNS of fish that results in the neurotoxicity, cognitive and behavioral dysfunction (Hsu and Guo, 2002; Zhu et al., 2016). Pb neurotoxicity causes neurogenerative disorder, neurotransmission impairment and cell signaling deregulation and change in brain morphology because Pb disturb Ca^{2+} flux that result in disrupting calcium regulatory functions, thus cell necrosis and oxidative stress occurs (Marchetti, 2003; Verstraeten et al., 2008). Calcium is an important ion for the regulation and release of neurotransmitters. Pb makes its way into the transport system of calcium by mimicking it, and ultimately enters the nervous system. Calcium homeostasis is disturbed due to pb accumulation and

it effects the mechanisms of neurotransmission (Westerink and Vijverberg, 2002). Brain transcription factors are regulated by zinc finger proteins. When the body is exposed to pb, it replaces zinc ions, which result in neurological injuries tracked by hyperactive movement that cause hyperventilation in fish (Zizza et al., 2013). Cholinesterase is an enzyme responsible for functioning of NS by catabolizing acetylcholine. Pb inhibits cholinesterase activity by occupying its position that result in the accumulation of Ach which lead to severe neurotoxicity that can be life threatening (Nunes et al., 2014). In fish, lead exposure leads to neurotransmitter changes and synaptic damage which leads to behavioral and neurological problems and it was observed that changes in neurotransmitter systems were directly related to ATP (Senger et al., 2006). Pb toxicity also damage structural and functional conformation of protein, that alter gene expression and disturb DNA repairing process (Richetti et al., 2011). To assess the toxicity caused by Pb in fish, neurotoxicity can be used as a biomarker for indicating the Pb interaction to that fish.

Immune response

In fish Pb exposure cause alteration in immune response that effect immune functions and cause neurological disorder, physiological and biochemical disturbance (Paul et al., 2014; Small, 2004). Environmental immune toxicant Pb also disrupt antibody production, hematopoietic and phagocytic activity also reduced (Dunier, 1996). It has been reported by (Adeyemo et al., 2010) that Pb exposure cause tissue injury in fish, that cause change in the lymphocytes count, Witeska (2005) reported that this decrease is due to stress reaction which induces cortisol secretion that promote apoptosis (Witeska, 2005). Pb activity also disturbs cytokines expression which is responsible for regulating immune response. In crucian carp (Dai et al., 2018) observed that Pb cause serious damage to immune system of fish as amplification in mRNA expression of TNF and IL10 was spotted, however both factors are responsible for inflammatory immune action and apoptosis (Dai et al., 2018; Savan and Sakai, 2006). Pb has a toxic effect on fish immune system as it disturbs immune responses i.e. inflammation or apoptosis of leukocytes and lymphocytes, disrupt intracellular transduction signals by inhibiting biomolecules activity. Thus, to determine toxicity in fish disturbed immune response is giving the signal of Pb exposure in the environment.

Oxidative stress

Reactive oxygen species (ROS) like superoxide radicals, hydroxyl radicals and hydrogen peroxides are produced in fish due to the induction of oxidative stress when metal gets accumulated in its tissues (Eroglu et al., 2015; Kim and Kang, 2016d; Kim et al., 2017a). A Fenton reaction also occurs due to oxidative stress which converts hydrogen peroxide to hydroxyl radicals which causes nucleic acid and protein damage and lipid peroxidation in fish body (Kim and Kang,2015b, c; Kim et al., 2017a). An imbalance between biological detoxification systems (e.g., antioxidant responses like GST, GSH, CAT and SOD) and free radicals generated causes oxidative stress in fish (Kim and Kang, 2015c; Kim et al., 2017b). Therefore, oxidative stress in metal-exposed-fish can be evaluated by checking for their antioxidant responses. Superoxide dismutase (SOD) activity is directly related to the exposure concentration of Pb i.e. SOD activity decreases as antioxidants production decreases and SOD activity increases as ROS production as a defensive mechanism increases (Alsop et al., 2016; Chen et al., 2014; Kim et al., 2017a). After Pb exposure, Atli and Canli (2007) observed amplified CAT activity in *Oreochromis niloticu* as a measure to shield the tissue and cell against injury caused by ROS generation.

Conflict of interest

The authors declared absence of conflict of interest.

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