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Effects of pesticides and metals on the oxidative stress of fish – a need for Consideration

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Abstract

Since long time fish are used as the food especially for the people living near the sea shores and other water bodies all over the world. They serve as a good source of proteins, calcium, phosphorus, essential amino acids etc. Fishes are aquatic in nature occupying all the levels of water column and face varied number of challenges in the aquatic world. They use their gills to take up the oxygen dissolved in water, an adaptation that allows them to live in water. Oxygen is very useful for the existence of aerobic species. However, the metabolism of oxygen results in the production of oxygen species as by products, which are reactive in nature (reactive oxygen species, ROS). These ROS species cause the damage to the cellular components of the organisms- lipids, proteins and DNA. Nevertheless, an organism possesses a variety of strategies to remove these ROS and maintain a balance between the production of reactive species of oxygen and antioxidant defenses. However, many external and internal factors have been reported to act as inducers/stressors that evoke either more production of ROS or disruption of the antioxidant strategies of the organism. Among these factors, metals and pesticides are becoming a major cause for inducing oxidative stress in fish. Although oxidative stress has been studied in many species of vertebrates, less attention has been paid to fish in this regard. Eating exposed fish may have a harmful impact on human health but not all species of fish are edible. Thus, this paper summarizes the effects of some pesticides and metals to highlight their toxic effects and suggests that the concerned knowledge should be shared with the industrialists and common man also so that we can move towards a safer environment.

Keywords: oxidative stress, pesticides, metals and Fish

Introduction

Fishes are among the vertebrates that fascinate scientists as well as common man. They serve as ornamental species and are widely kept in aquarium for the same purpose. They are extensively used as food all over the world as they provide many nutrients especially proteins and are delicious in taste. Being aquatic, they have to defend themselves from predators and must overcome the changes in the temperature, oxygen availability, pH, environmental pollutants etc in order to survive. Few fishes are migratory in nature that migrates for low salinity water bodies to high salinity water bodies and vice-versa. Being aerobic species they utilize oxygen for their life activities. Apart from the beneficial effects of oxygen, oxygen metabolism results in the formation of by products which are very reactive in nature, reactive oxygen species (ROS). Thus, oxygen is both essential as well as toxic in nature. The generation of ROS seems to be prevalent in the aquatic world where oxidative stress is an important component of the stress response. They are also referred to as free radicals and are known to damage the integrity of lipids (Yla-Herttuala, 1999), proteins (Stadtman and Levine, 2000) and DNA (Marnett, 2000), often leading to cumulative injury. Intracellular production of ROS reacts with proteins, lipids and DNA and destroys their functions resulting in oxidative stress.

Fish tissues contain high level of polyunsaturated fatty acids. Thus, they are considered to be the easy targets for the free radical oxidation due to the presence of many double bonds. Study of oxidative stress in fish is important because of the properties of the water environment and its relationship with organisms (Winston and Di Giulio, 1991; Kelly et al., 1991;, Nikinmaa and Rees, 2005). Like other vertebrates, fish possess an antioxidant defense system (Wilhelm, 1996; Aksnes and Njaa, 1981) and low molecular weight antioxidants. In most fish, liver, kidney and gills are more important than red muscle in contributing towards the generation of ROS (Jos et al., 2005). Fish also possess metallothioneins, low molecular proteins rich in cysteine residues that provide protection to fish by binding to metals, including copper, cadmium mercury, silver, lead etc (Hamer, 1986).

Reactive Oxygen Species (ROS)

ROS include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical ($^{\cdot}$ OH) and others that are reported to have deleterious effects on living organisms (Halliwell and Gutteridge, 1984). **Superoxide anion** itself is harmful to cellular structure and function and also generates other oxygen reactive species. Its activity is known to depend on the environment and pH (Kohen and Nyska, 2002). Dismutation of the super oxide anion results in the production of another reactive oxygen species, H_2O_2. Though not free radical by definition $\mathbf{H_2O_2}$, it can cause damage to the cell at a relatively low concentration. They can freely dissolve in aqueous solution and can easily penetrate biological membranes affecting the cell either directly or indirectly (Kohen and Nyska, 2002). Indirectly, they serve as a source for more deleterious species such as OH and HCLO. Directly, H_2O_2 is capable of oxidation of DNA and lipids, inactivation of enzymes and degrading haem proteins. The **hydroxyl radical** is supposed to be the most important ROS detected in natural waters and is highly reactive. The reactive oxygen species can be generated from both exogenous and endogenous sources. Exogenous sources for the generation/production of ROS include ionizing and non- ionizing radiations, food, drugs, pollutants, xenobiotics and others. The invasion of bacteria and virus might also result in the production of reactive species of oxygen. A large number of variety of xenobiotics including pesticides produce ROS as a by-product of their metabolism *in vivo.* Endogenously, ROS are mainly produced by metabolism (mitochondria) and under diseased condition e.g. metal disorders, cancers etc. Mitochondrial respiration is the main endogenous source of ROS.

Pesticides and Oxidative stress in Fish

Fish are bound to get exposed to pesticides as they are released in the aquatic environment due to the activities of humans. Studies have reported that several pesticides besides other stressors may induce oxidative stress in fish. However, the mechanism by which a pesticide poses its effect may be different and may affect the fish differently. Pyrethroid pesticides that include deltamethrin, cypermethrin and lambda-cyhalothrin mainly cause pathological effects in the gills, liver and muscles in fish (Yang et al., 2020). They are strictly banned in most countries but still are in use. They are reported to be highly toxic in nature and alter the activities of antioxidant enzymes making the fish more sensitive to oxidative effects of other environmental pollutants. As fish lack pyrethroids-metaboling enzyme, carboxylesterase, its toxicity persists for longer time when they are exposed to pyrethroids. Oxidative stress plays an important role in the neurological, reproductive and development toxicity caused by pyrethroids (Yang et al., 2020).

DDT is reported to mainly affect livers of fish and cause increase in the lipid peroxidation products or protein carbonyl derivatives with a decrease in GSH concentration. Exposure to low concentration of both methylmercury and DDT in *Hoplias malabaricus* produced greater effect than isolated exposure. Hexachlorobenzene (HCB) was introduced for its use as pesticide in 1945. It is reported to get accumulated in the tissues which are rich in lipids, mainly affecting liver (Marc et al., 2017). Though it is less toxic, it has cancer causing capacity (carcinogen) in humans. Exposure to HCB causes the release of ROS, responsible for inducing oxidative stress. A severe oxidative stress was observed after 5 days of exposure (Song et al., 2006). Many pesticides can cause oxidative stress besides inducing teratogenicity and embryotoxicity in fish species. Effect of endosulfan-induced oxidative stress has been studied in many fish species. In *Oreochromis niloticus,* endosulfan decreased the levels of antioxidant enzymes catalase, SOD, glutathione peroxidase and glutathione. Similar results were obtained in all the organs studied in fresh water fish, *Channa punctatus*. However, pre-acclimatization of these fishes to copper before the exposure to endosulfan resulted in the protection of liver only (Pandey et al., 2001). Levels of antioxidant enzymes were also modulated in accordance with the oxidative damage. Fish *Channa striatus* etc. Majority of the pesticides cause oxidative stress in fish liver, gill and fish muscle, liver being the most affected organ. Oxidative stress induced by other pesticides have also been studied, namely trichlorfon, fenthion, chloropyriphos, Cypermethrin, rotenone etc. Most of the pesticides have been reported to induce oxidative stress the liver of fish. However, Fenthion and Azinphosmethyl caused oxidative stress in the fish brain besides affecting gills and kidney.

Metals and Oxidative stress in Fish

Metals are one of the important stressors that induce oxidative stress in organisms. Aquatic organisms are also exposed to the stress imposed by these metals, especially heavy metals as they exist as contaminants of the aquatic environments worldwide. Industrial waste, motor traffic, advanced agriculture, mining are the main sources of metal disposal to the environment. Metals disposed off in the water bodies result in their accumulation in the tissues of aquatic organisms, including fish. Fish can get contaminated by metals through body surface, the gills and digestive tract (Tao et al., 2001; Kamunde et al., 2002). It is the need of the hour to have cumulative knowledge about the oxidative stress in fish as they inhabit all the levels of water bodies and forms top part of aquatic food chain and also serve as food source for humans all over the world. Eating of contaminated fish will be harmful for the human health. The most common mechanism for the formation of hydroxyl ion is the metal catalyzed reaction (Halliwell and Gutteridge, 1984). Sea water is known to contain metals, thus this reaction can take place in sea water generating hydroxyl ions (Kim et al., 1999). The amount of dissolved metal strongly depends on the pH of water. Out of variety of metals involved in inducing the oxidative stress in fish, the most important ones are copper (Cu), mercury (Hg), lead (Pb), iron (Fe), chromium (Cr) and cadmium (Cd^{2+}).

Copper

Copper (Cu) is found to occur naturally in soil and water. Besides being essential, it is also toxic to fish and its toxicity varies with the physic-chemical properties of water such as suspended particles, pH, alkalinity, hardness and organic compound content. Copper appears to have greatest toxicity in fresh water and lowest being at iso-osmotic salinities. Exposure to copper causes oxidative damage in the gill, liver and intestine of many fish species, characterized by protein carbonyls; lipid peroxidation and DNA damage products in the affected organ (Ransberry et al., 2015). In Zebra fish exposure to sub lethal dose of copper resulted in the elevated levels of protein carbonyls in the gills and liver. An increase in super oxide dismutase (SOD) and a reduction in catalase (CAT) activity were also obtained (Criag et al., 2007). Exposure to copper for the forty eight hours in *Piarctus mesopotamicus* showed similar results. Copper is also reported to increase the levels of ROS, resulting in DNA damage. Copper induces the oxidative stress in the fish brain also resulting in the increase in brain ROS production, lipid peroxidation and protein oxidation (Jiang et al., 2014). It has the capability to bind thiol- containing molecules such as glutathione. Depletion of total GSH was observed in the livers of *Gasteroteus aculeatus* exposed to copper sulphate with the concomitant increase in the activities of enzymes, glutathione peroxidase, SOD, and CAT within the first week of exposure to copper sulphalte. This was associated with the accumulation of copper in the liver. Besides fish liver, the depletion of GSH has also been reported in the fish muscle. Copper is thus, can be interpreted as an inducer of oxidative stress in fish by catalyzing the formation of ROS, causing lipid peroxidation and DNA damage.

Mercury

Mercury is released from the natural and anthropogenic sources to the environment (Clarkson and Magos, 2006). Like copper, mercury also reacts with the thiol groups of GSH and induces its depletion resulting in the oxidative stress in tissues (Stohs and Bagchi, 1995). Mercury has been reported to interfere with the antioxidant protection of gills of fish, depleting glutathione peroxidase and superoxide dismutase activities in mercury contaminated area. Mercury exists in two forms, organic (methylmercury) and inorganic forms (mercurous, mercuric) in nature. Several field studies reported that methylmercury induced oxidative stress. Both the forms of mercury are able to generate ROS (Larose et al., 2008; Mieiro et al., 2010). Oxidative stress induced by inorganic mercury is characterized by increased lipd peroxidation and protein carbonyl content and its accumulation in all the fish tissues studied (gills, liver, heart and white muscle), gills being the most affected tissue (Monteiro et al., 2010).

Lead and Arsenic

Water borne Lead is harmful metal for aquatic animals. It has the ability to accumulate in the tissues of fish viz. gills, intestine, liver and muscle depending on the type of water (fresh or marine and the nature of exposure (water borne or dietary borne). Exposure to the high concentrations of lead results in the significant decrease of antioxidant enzymes. Lead can induce its effects directly or indirectly through the formation of complexes with selenium to decrease GPx activity (Eract et al., 2001). Intraperitoneal administration of lead in fish *Halobatractus didactylus* resulted in the increased levels of metallothionein (MT) but decreased lipid peroxidation in the liver after 10 days of injection of lead (Campana et al., 2003). Arsenic exists in three major forms inorganic, organic and arsine gas. Inorganic arsenic is considered to be more toxic than the organic form. It is one of the components of many pesticides. Continuous exposure to low concentrations of arsenic results in its accumulation mainly in the liver, kidney and intestine of fish. It is absorbed through gills and is reported to induce oxidative stress via the generation of both ROS and RNS (reactive nitrogen species). Besides the generation of reactive species, arsenic disrupts the antioxidant system. Exposure to arsenic for 10 days in Indian catfish, *Clarias batrachus* resulted in the increased lipid peroxidation levels and excessive production of hydrogen peroxide (Bhattacharya and Bhattacharya, 2007).

Iron, Chromium, Selenium and other metals

Iron is essential trace element and performs many biological functions. However, excess Iron (> 1ppm in water and 100 ppm in fish tissue) is reported to induce oxidative stress. Excessive uptake of iron can cause the formation of ROS via Fenton reaction and result in DNA damage, lipid peroxidation and oxidation of proteins (Valko et al., 2005). Xenobiotics are known to release bound iron, enabling it to produce free radicals (Stohs and Bagchi, 1995). Interestingly, nano iron is known to cause increased levels lipid peroxidation and changes in oxidant enzyme activity in embryonic and adult *Oryzas latipes* (Li et al., 2009). Chromium gains entry into water bodies through effluents discharged from industries such as textiles, ore mining, dyeing, medical industries, metallurgy, electroplating etc. It is found mainly three oxidation states- Cr (II), Cr (III) and Cr (VI) (Bakshi and Panigrahi, 2018). Out of these, Cr (VI), hexavalent chromium is the most toxic as it can readily pass through the membranes and get reduced to trivalent state inside the cell. Exposure to low concentrations of hexavalent chromium induces excess production of ROS and affected the activities of antioxidant enzymes. Both the hexavalent and trivalent ions were found to induce oxidative stress in goldfish (Kubrak et al., 2010). DNA damage has been reported in the tissues of salmon *Onchorhyncus tshawytscha* after the chronic exposure to hexavalent chromium. Similar results were observed in the erythrocytes of *Micropterus salmoides* upon exposure to hexavalent chromium in water and diet (Kuykendall et al., 2006). Major source of selenium is coal mining. Selenium is toxic to fish at high doses and is known for the generation of ROS.

Conclusions

Oxidative stress is induced by pesticides and metals because of their ability to get accumulated in the tissues/ organs of fish, liver being the most affected organ.Other organs affected are gills, kidney, intestine, heart and brain. Only few studies reported oxidative stress in the fish brain. Fish like other organisms have antioxidant mechanisms to overcome the harmful impact of oxidative stress. Pesticides and metals may either generate ROS (directly or indirectly) and act as pro- oxidants or attack the antioxidant mechanisms of exposed fish. Study of oxidative stress in fish provides information about the pollution status/environment of the concerned area. Few studies reported that the pretreatment with a metal provides the protection against oxidative stress induced by a pesticide. Moreover, existence of co-pollutants may cause excessive oxidative stress in fish. Thus, this paper suggests the need of combination studies as they will be closer to the conditions prevailing in natural environment and emphasizes on the strict implementation of proper disposal protocol for various industries so that contamination of the environment can be reduced.

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