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Review Article

Impact of Heavy Metal Exposure on the Nervous System and Endocrine-Mediated Processes in Crustaceans

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ABSTRACT

Milton Fingerman, Manjula Devi, Palla S. Reddy and Rajesh Katyayani (1996) Impact of heavy metal exposure on the nervous system and endocrine-mediated processes in crustaceans. *Zoological Studies* **35**(1): 1-8. Contamination of the aquatic environment by heavy metals and their toxicological impact on flora and fauna have been of increasing concern in recent years. This review deals with the effects of heavy metals on the nervous system and endocrine-mediated processes in crustaceans. The possible use of hormonally regulated processes, such as molting, color changes, and blood glucose level, as biomarkers of heavy metal stress is discussed.

Key words: Hormones, Neuroendocrine system, Neurohormones, Pollutants.

INTRODUCTION

The term heavy metals is often used without strict definition, as discussed by Nieboer and Richardson (1980). Some metals, such as sodium, potassium, calcium, and magnesium, are essential for life, and are generally not thought of as heavy metals. The metals generally referred to as heavy metals include mainly lead, mercury, copper, cadmium, nickel, cobalt, chromium, manganese, zinc, and selenium. Lead, mercury, and cadmium are the most dangerous. Heavy metals are toxic at higher concentrations to flora and fauna, but interestingly some of them, such as zinc and selenium, at trace metal concentrations are essential for normal body functions.

The anthropogenic sources of heavy metals in the environment include fossil fuel burning, waste incineration, mining, processing of ores, production of chemicals, and industrial waste discharges. In recent years major attention has been paid to the toxic effects of the heavy metals that have accumulated in aquatic ecosystems.

There are several parameters that can be

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measured to assess the effects of exposure to toxic metals (Furness and Rainbow 1990). More recently, Peakall (1992) described the biomarkers in animals that have been used for biomonitoring. In this review our main focus is on the impact of heavy metals on the nervous system and on endocrine-mediated processes in crustaceans.

EFFECTS OF HEAVY METALS ON THE CRUSTACEAN NERVOUS SYSTEM

The basic plan of the crustacean nervous system is that this system consists of dorsal cerebral ganglia (brain), a circumenteric ring, and a double ventral nerve cord that has segmental ganglia connected by commissures. In long-bodied crustaceans, such as crayfishes, the ventral ganglia are discrete; but in short-bodied forms, such as crabs, fusion of ventral ganglia has occurred, resulting in a more centralized or compact nervous system.

Serfozo et al. (1990 1991 1992) published a series of articles on accumulation of heavy metals from the polluted water of the Berettyo River in Eastern Hungary in the central nervous system of the crayfish, *Astacus leptodactylus*. The amount of cadmium accumulated in the nervous system showed no seasonal variation. More recently Serfozo (1993) described the necrotic effects of cadmium, lead, and mercury that had accumulated in the central nervous system of this crayfish. The main pathological changes were nuclear pycnosis, mitochondrial disorganisation, abnormal development and collapse of Golgi vesicles, and fragmentation of the endoplasmic reticulum.

Amaldoss and Mary (1992) studied the effect of chromium on the neurosecretory cells in the brain and thoracic ganglia of the shrimp, *Penaeus monodon*. Acute exposure produced an increase in the amount of stored neurosecretory material and shrinkage of the neurosecretory cells. However, with chronic exposure peripheral vacuolization and depletion of neurosecretory material occurred.

An increase in the acetylcholinesterase activity in the thoracic ganglia of the freshwater field crab, *Barytelphusa guerini*, was noticed after four days of exposure to cadmium chloride, but after 15 days of exposure this enzyme was inhibited (Reddy and Venugopal 1993). Most recently, Devi and Fingerman (1995) found that acetylcholinesterase activity in the brain and ventral nerve cord of the red swamp crayfish, *Procambarus clarkii*, decreased significantly after 24 and 48 hours of exposure to lead, mercury, or cadmium. Cadmium has been shown to damage the central nervous system and sensory ganglia in mammals (Gabbiani et al. 1967a,b). Cadmium, mercury and lead accumulate in the brain and inhibit sulfhydryl group-containing enzymes (Valle and Ulmer 1972, Jacobson and Turner 1980). Later, however, Donaldson et al. (1981) suggested inhibition of acetylcholine binding to its receptors is the primary mechanism of cadmium neurotoxicity. Methyl mercury seems to owe its high toxicity to the fact that this compound readily passes across cell membranes by passive diffusion, and once inside the cell exerts its toxic action (Christie and Costa 1984). In contrast, there is evidence that inorganic mercury interacts with phospholipids in cell membranes to form stable complexes (Christie and Costa 1984, Miura and Imura 1987). These complexes may damage or otherwise change the physical properties of the cell membrane and lead to cell dysfunction. Toxic effects on cell membranes have been demonstrated with lead, copper, and cadmium also. Once inside the cell such heavy metals, in addition to inhibiting enzymes, are known to alter mitochondrial function and delay mitosis (Chin et al. 1978). This effect on mitosis is due to disruption of the mitotic spindles (Meyer et al. 1991). With respect to the cell membrane itself, heavy metals are thought to inhibit membrane bound enzymes such as Na^+/K^+ ATPase and to cause oxidative destruction of polyunsaturated lipids present in the membrane, leading to the production of superoxide anion radicals. These superoxides are probably then converted to hydroxyl radicals, substances known to be toxic to cells. With specific reference to neurons, heavy metals have been implicated as affecting such membrane functions as the electrical properties of axons and release and uptake of neurotransmitters (Miura and Imura 1987).

Recent studies from our laboratory showed that exposure to 10 ppm cadmium for 10 days caused damage to neurosecretory cells in the brain and eyestalk ganglia of the fiddler crab, *Uca pugilator* (Reddy and Fingerman 1995). Rupturing of the cell membrane, loss of cytoplasm from the cells and depletion of neurosecretory material were evident. Previously, Deecaraman and Fingerman (1985) reported that exposure to the water soluble fraction of South Louisiana crude oil or the aromatic hydrocarbon naphthalene resulted in the accumulation of neurosecretory material in the brain of *U. pugilator*. Reddy and Fingerman (1995) hypothesized that with chronic exposure hydrocarbons

inhibit release, but not the synthesis of neurosecretory material, which contains neurohormones, whereas with chronic exposure heavy metals inhibit the synthesis but not the release of the neurohormones, thereby accounting for the different amounts of neurosecretory material that have been observed following such exposures. The different effects produced by cadmium and the organic pollutants in the neurosecretory cells require further study if the modes of action of these pollutants are to be fully understood.

EFFECTS OF HEAVY METALS ON ENDOCRINE-MEDIATED PROCESSES IN CRUSTACEANS

In many instances toxicity induced by a pollutant is the result of interference by the compound, or one of its metabolites, with the biochemical events involved in the homeostatic control of a physiological process (Brouwer et al. 1990). Physiological processes are often coordinated by hormones. Dramatic changes in hormone levels can upset the normal balance of physiological events. Changes in hormone levels would be expected to occur soon after exposure to a pollutant. Therefore, it follows that biosentinal parameters of toxicity can be identified by looking for alterations in endocrine patterns. The crustacean endocrine system has been well studied. Both classical epithelial endocrine glands and neuroendocrine structures, such as the sinus gland that is a neurohemal organ in the eyestalks of higher crustaceans, are present. Here our emphasis will be on metal induced changes in endocrine regulated physiological processes of crustaceans, such as molting, limb regeneration, blood glucose level, color changes, and reproduction.

Molting and limb regeneration

The phenomena of limb regeneration and molting are closely related to each other in crustaceans. After a crab loses a limb by autotomy, the regenerating limb develops folded within a layer of cuticle and unfolds at ecdysis when it becomes functional. Clare et al. (1992) and Weis et al. (1992) proposed the use of molting and limb regeneration to analyze the developmental, physiological, morphological, and endocrinological effects of pollutants on crustaceans.

Cadmium, mercury, and lead retard limb regeneration and molting of *U. pugilator* (Weis 1976). Furthermore, the number of tubercles on regenerated limbs of fiddler crabs exposed to cadmium or mercury is reduced (Weis et al. 1986). Inhibition of limb regeneration and ecdysis of three species of fiddler crabs, *U. pugilator*, *U. pugnax*, and *U. minax*, is greatly intensified when the fiddler crabs are exposed to the combination of methylmercury and cadmium at 30 ppt salinity compared to the effects of exposure to each metal separately (Weis 1978). However, at a reduced salinity (15 ppt) the combination of cadmium and methylmercury produces less inhibition of limb regeneration and molting than does each metal separately. Zinc is less inhibitory to regeneration of limbs of *U. pugilator* than is methylmercury or cadmium (Weis 1980). Interestingly, the combination of zinc and methylmercury is more inhibitory to limb regeneration than is either metal alone, but the combination of zinc and cadmium is less inhibitory to this process than is either metal alone (Weis 1980).

Short term physiological acclimation of *U. pugilator* to polluted water resulted in resistance to cadmium stress (Weis 1985). After pre-exposure to 0.5 ppm cadmium for one week, limbs regenerated more rapidly upon subsequent cadmium exposure, particularly in the early stages, than those that had not been pre-exposed (Weis 1985). However, she noticed that molting was not similarly accelerated, which suggests that the protective effect of the pre-exposure is on the growth process alone, and not on the neuroendocrine system which controls the molt cycle.

Selenium delays the onset of proecdysis in *Daphnia magna* (Schultz et al. 1980). Bodar et al. (1990) found that cadmium-exposed *D. magna* contains up to 3.5X as much ecdysteroids as do control individuals. This high concentration may be inhibitory to the growth process, inhibiting exuviation, thereby accounting for the smaller body weights of cadmium-exposed individuals.

The organometallic compound, tributyltin (TBT), was extensively used in antifouling paints in the U.S.A. until recent legislation restricted its use. TBT retards limb regeneration and molting in fiddler crabs and produces anatomical abnormalities in the regenerates (Weis et al. 1987). There is curving in the wrong direction of the regenerated dactyl of the major chela of the males. The impact of TBT on limb regeneration by the freshwater prawn, *Caridina rajadhari*, was studied by Reddy et al. (1991). They reported a significant retardation of regenerative limb growth when prawns were exposed immediately after amputation of limbs as well as when exposure began 4 days after amputa-

tion. But TBT had no effect on limb regeneration of prawns when the exposure began either 2 or 6 days after limb removal, implying that the middle part of the regenerative process is more sensitive to TBT toxicity than the initial and later stages. Reddy et al. (1992) also reported a TBT dose dependent retardation of molting of *C. rajadhari*. The lowest dose (0.015 ppm) had no effect on the first two molts, but at the third molt after the exposure began, a significant increase in the length of the intermolt cycle was noticed.

Cyclic cuticle deposition and resorption of calcium from the old cuticle are part of the molt cycle of crustaceans. TBT inhibits calcium resorption from the exoskeleton of *C. rajadhari* (Nagabhushanam et al. 1990). Significant increases in weight and calcium content of cast exuviae occurred when prawns were exposed to TBT. These increases became progressively larger when the prawns were kept in TBT containing water continuously for three molts.

Blood glucose

Hyperglycemia, anemia, and depletion of plasma ions typically occur in fishes during sublethal exposure to metals (Haux and Larsson 1984, Haux et al. 1986, Tort and Torres 1988, McDonald et al. 1991). With respect to crustaceans, Nagabushanam and Kulkarni (1981) and Machale et al. (1989) reported respectively that cadmium exposure, as in fishes, induces hyperglycemia in the freshwater prawn, *Macrobrachium kistnensis*, and the crab, *Barytelphusa cunicularis*. The medulla terminalis X-organ-sinus gland complex in the eyestalk is the source of the crustacean hyperglycemic hormone (CHH), which regulates the blood glucose levels. Recent studies from our laboratory provided evidence for the involvement of CHH in cadmium-induced hyperglycemia in *P. clarkii* (Reddy et al. 1994). The CHH activity in eyestalks of cadmium exposed crayfish was less than in control crayfish kept in clean water. These results suggest that cadmium not only induces hyperglycemia in the crayfish, presumably by causing CHH release, but also inhibits CHH synthesis. The ongoing research in our laboratory resulted in another interesting as yet unpublished observation, namely that naphthalene and cadmium induce hyperglycemia in the fiddler crab, but the CHH activity in the eyestalks of naphthalene-exposed crabs was much more, and that in eyestalks of cadmium-exposed crabs much less than in eyestalks of crabs kept in clean water. Santos and Keller (1993) reviewed the role of CHH in the regulation of carbohydrate metabolism and noted that in crustaceans the metabolic pathways are quite well established but very little is known about their operation under different physiological and environmental conditions. How pollutants affect carbohydrate metabolism certainly fits this statement of Santos and Keller (1993).

In our laboratory we also investigated with *P. clarkii* the effect of cadmium on still another CHH regulated physiological process, amylase activity in the gastric juice. Sedlmeier (1988) reported release of amylase from the hepatopancreas is one of the actions of CHH. With cadmium exposure a significant increase in the pH of the gastric juice and a concomitant decrease in the amylase activity in *P. clarkii* occur (Reddy and Fingerman 1994). As a result of the experiments from our laboratory we hypothesized that cadmium exposure simultaneously stimulates the release of CHH from the sinus gland, inhibits the synthesis of CHH and induces degenerative changes in the hepatopancreas that result in reduced digestive enzyme synthesis. Sarojini et al. (1992) earlier reported that amylase, lipase, and protease activities in the stomach, midgut and hindgut of *C. rajadhari* exposed to TBT were reduced.

Color changes

Integumentary pigments serve useful biological functions such as camouflage, thermoregulation, and protection against deleterious radiation (Fingerman 1970). Color changes in crustaceans are regulated by pigment-dispersing and pigment-concentrating neurohormones that affect the distribution of the pigment within the chromatophores (Carlson 1935, Sandeen 1950, Fingerman 1956). Past studies from this laboratory revealed that the polychlorinated biphenyl, Aroclor 1242, and also naphthalene affect the coloration of *U. pugilator* (Fingerman and Fingerman 1978, Hanumante et al. 1981, Staub and Fingerman 1984a,b). These organic compounds inhibit release of the black pigment-dispersing hormone (BPDH), with the result that the integument of the crabs exposed to these compounds does not become as dark as that of unexposed individuals. Weis (1977) noticed a reduced number of melanophores in regenerated limbs of *U. pugilator* after exposure to methyl mercury. Recent studies revealed that exposure to cadmium, like to these organic compounds, results in a diminished ability of *U. pugilator* to disperse its black pigment (Reddy and Fingerman 1995).

This effect of cadmium is not directly on the chromatophores but is on the neuroendocrine system which regulates these pigment cells. The eyestalks of crabs kept in clean water contained 3.27 times as much BPDH as did the eyestalks of cadmium exposed crabs. It was, therefore, hypothesized that cadmium inhibits BPDH synthesis in the neurosecretory cells. In contrast, exposure to Aroclor 1242 or naphthalene resulted, in both instances, is four times more BPDH activity in the eyestalks of *U. pugilator* (Fingerman and Fingerman 1978, Staub and Fingerman 1984b), which is consistent with an inhibitory mode of action of these hydrocarbons on BPDH release. The histological studies of eyestalks and brains of *U. pugilator* exposed to napthalene or cadmium (Deecaraman and Fingerman 1985, Reddy and Fingerman 1995) that were described above also support this hypothesis.

Reproduction

In decapod crustaceans two antagonistically acting neurohormones have key roles in the regulation of gonadal maturation. One is the gonad-inhibiting hormone (GIH) from the sinus gland and the other is the gonad-stimulating hormone (GSH) found in the brain and thoracic ganglia. The effects of heavy metals on reproduction of crustaceans have so far received very little attention.

Winner and Farrell (1976) observed an increase in female mortality and reduction of brood size in *D. ambigua*, *D. pulex*, and *D. parvujla* exposed to copper. A decrease in the number of hatchlings per brood in *D. magna* exposed to nickel was reported by Lazareva (1985). *D. magna* exposed to 3 ppb cadmium showed a higher mortality when deprived of selenium in their diet (Winner and Whitford 1987). Exposure to more than 150 ppb nickel decreased the percentages of female cladocerans, *D. magna* and *Simocephalus vetulus*, carrying eggs (Ravera and Gatti 1988). Ravera and Gatti also noticed that exposure to 50-100 ppb nickel resulted in a significant decrease in the percentage of viable hatchlings with another cladoceran, *Pleuroxus truncatus*. Bodar et al. (1988b) found that cadmium exposure leads to a decrease in the amount of food consumed by *D. magna*. McCahon and Pascoe (1988) determined the toxicity of cadmium to sexually mature males, and also to females carrying eggs. The 48 h LC_{50} value for sexually mature males was 1.9 times greater than for females carrying eggs of stages 2-6 or embryos, and was 12.8 times greater than for females not carrying eggs. Chandini (1989) reported that at the food level of 5×10^5 cells ml^{-1} *Chlorella*, 27-162 ppb cadmium reduced the life-history parameters of *D. carniata*, such as survivorship, longevity, life expectancy, fecundity, age at first reproduction, and growth rate, but at higher food levels (4.5×10^6 cells ml^{-1} *Chlorella*), the toxic effects of cadmium were greatly reduced.

Some investigators have reported beneficial effects in cladocerans of exposure to low concentrations of heavy metals. Marshall (1978) reported that exposure to low concentrations of cadmium (1-20 ppb) for 22 weeks reduced the population size and biomass of *D. galeata*, whereas the proportion of ovigerous females increased. Elnabarawy et al. (1986) confirmed this report that daphnid reproduction is stimulated by low concentrations of cadmium. Similarly, Bodar et al. (1988a) found with *D. magna* that cadmium concentrations as low as 0.5-5.0 ppb cause an increase of both the number of broods and hatchlings per brood compared with the control group in clean water. Lazavera (1985) observed that nickel stimulates fertility of *D. magna* in the first generation that is exposed, but fertility is depressed in the next three generations while in the nickel contaminated water.

Exposure of adult *D. magna* to cadmium results in lengthening of the intermolt cycle, reduction in the number of successful ecdyses, and reduction in body weight, and in addition the size of the neonates is reduced (Bodar et al. 1988a,b). Bodar et al. (1990) investigated the effects of exogenous ecdysteroids on molting and reproduction of *D. magna* exposed to cadmium in order to determine whether the cadmium effects described by Bodar et al. (1988a,b) might have been due to changes in ecdysteroid titers. Cadmium produced significant increases in the ecdysteriod level in this daphnid, up to 3X as much as in the controls with 20 ppb cadmium. Exogenous ecdysteroid reduced both the number of successful exuviations and the number of progeny per female, but the size of the neonates was unaffected. Consequently, Bodar et al. (1990) hypothesized that the increased ecdysteroid level in *Daphnia* exposed to cadmium was responsible for the reduction in successful ecdyses reported by Bodar et al. (1988a,b), but that the cadmium induced reduction in neonate size did not appear to be due to the increased ecdysteriod level. In this laboratory Sarojini et al. (1994) reported a possible neurotransmitter-neuroendocrine mechanism in napthalene-induced atresia of the ovary of *P. clarkii*. Naphthalene

appears to inhibit GSH release from the neuroendocrine centers, resulting in atresia of the ovaries. Injection of 5-hydroxytryptamine, which is known to stimulate GSH release (Richardson et al. 1991), reversed the naphthalene induced changes. Comparison of the effects of cadmium and naphthalene on crustacean ovaries and testes should prove interesting.

PERSPECTIVES

Although attention has increasingly been given in recent years to studies of the accumulation of heavy metals in invertebrates, little attention has been given to the effects of heavy metals on the nervous and endocrine systems. Interactions of combinations of metals and hydrocarbons need to be addressed. The apparent different modes of action of cadmium and naphthalene on CHH and BPDH release identified in this laboratory with crustaceans illustrate the type of study needed for endocrine-mediated processes with mammalian systems also. The crustacean neuroendocrine system can serve as a model for such studies with higher animals. Furthermore, we suggest that several of the parameters discussed herein, such as acetylcholinesterase activity and blood glucose concentration, can serve as useful biomarkers of pollution.

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重金屬對甲殼類動物神經及內分泌體系之影響

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由重金屬所引起的水生動植物所棲息之生態環境的污染及對動植物之毒理影響，近年來日趨嚴重。本文論述了重金屬污染對甲殼類動物之神經及內分泌體系的影響，並將激素所調控的生理過程如蛻皮、體表顏色變化及血中葡萄糖濃度高低等，作爲重金屬污染之生物指標做了可能性的研究與解說。

關鍵詞：激素, 神經內分泌系統, 神經內分泌激素, 污染物。

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