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Interactive effects of chronic dietary selenomethionine and cadmium exposure in rainbow trout (*Oncorhynchus mykiss*): A preliminary study

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HIGHLIGHTS

- Interaction between dietary Cd and Se was studied in *Oncorhynchus mykiss.*
- Co-exposure to dietary Se can prevent Cd-toxicity in fish.
- Moderate level of Se reduced Cd-induced hepatic oxidative stress.
- High dose of dietary Se does not prevent Cd-induced toxicity.
- Dietary Se mobilized Cd from liver and kidney to muscle.

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ABSTRACT

The present study investigated the interactive effects of dietary cadmium (Cd) and selenium (Se) on the tissue-specific (liver, kidney, and muscle) accumulation of these two elements, hepatic oxidative stress response, and morphometrics in rainbow trout (*Oncorhynchus mykiss*) during chronic exposure. Fish were exposed to elevated dietary Cd (45 $\mu g\, g^{-1}$ dry wt.), and medium (10 $\mu g\, g^{-1}$ dry wt.) or high (45 $\mu g\, g^{-1}$ dry wt.) dietary selenium (added as selenomethionine), both alone and in combination, for 30 days. Exposure to dietary Cd alone caused oxidative stress in fish as reflected by reduced thiol redox (GSH:GSSG), increased lipid peroxidation, and induction of anti-oxidative enzymes (catalase, superoxide dismutase, and glutathione peroxidase) in the liver. Also, an increase in tissue-specific Cd burden and impaired morphometrics (hepato-somatic index and condition factor) were also recorded in fish following exposure to dietary Cd. In contrast, the dietary co-exposure to Cd and Se (at both medium and high doses) resulted in a decrease in Cd burden in the liver and kidney of fish. However, co-exposure to medium, but not high, dose of dietary Se completely alleviated Cd-induced oxidative stress and impaired morphometrics in fish, indicating that the reduced Cd tissue burden might not have been the primary factor behind the amelioration of Cd toxicity by Se. Overall, our study demonstrated that the protective effect of Se against the chronic Cd toxicity in fish is mainly mediated by the anti-oxidative properties of Se, but this protective effect is dose-specific and occurs only at a moderate exposure dose.

1. Introduction

Cadmium (Cd) is a non-essential element and known to induce toxic effects in all biological forms at relatively low exposure levels (Benavides et al., 2005; Trevors et al., 1986). Although it is a rare and a naturally occurring element, the anthropogenic activities have dominated the Cd biogeochemical cycle, which has elevated its concentrations in many aquatic ecosystems (Cullen and Maldonado, 2013). In natural waters, Cd is highly persistent and can biomagnify along the food chain (Croteau et al., 2005). Thus, diet is an important source of Cd in aquatic organisms in addition to the water, and several studies have suggested that dietary Cd is more bioaccumulative than waterborne Cd in fish (Guo et al., 2017; Harrison and Klaverkamp, 1989; Maunder et al., 2011; Ranaldi and Gagnon, 2009). Therefore, the carnivorous fish, such as rainbow trout (*Oncorhynchus mykiss*), that occupy higher trophic levels in

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the food chain can be more susceptible than the herbivorous fish to Cd toxicity through diet in metal contaminated aquatic habitats (Croteau et al., 2005).

The toxicity of chronic Cd exposure in fish is often associated with the disruption of cellular redox balance due to the increased production and accumulation of reactive oxygen species (ROS) (Baldisserotto et al., 2005; Cuypers et al., 2010; Verbost et al., 1989; Wood et al., 2006). Cadmium has very low standard reduction potential and cannot generate ROS *via* direct redox reactions under normal physiological conditions (Cuypers et al., 2010). However, Cd can increase the cytoplasmic concentration of free redox-reactive metals, such as iron, by replacing them in various metalloproteins. The free redox-reactive metals in the cytoplasm can generate ROS *via* Fenton reaction (Cuypers et al., 2010). Cadmium can also cause leaks in the mitochondrial membrane, and induce NADPH-oxidases that generate superoxide anions ($O_2^{\bullet-}$) (Cuypers et al., 2010; Onukwufor et al., 2017). In addition, Cd can also induce oxidative stress by disrupting the activities of enzymatic antioxidants (e.g., catalase, superoxide dismutase) and/or depleting the non-enzymatic antioxidant pool (e.g., glutathione), which can ultimately lead to the accumulation of intracellular ROS (Bertin and Averbeck, 2006; Cuypers et al., 2010; Waisberg et al., 2003).

In natural water bodies, such as rivers and lakes, that receive effluents from mining and smelting industries, Cd often co-exists with other metals and metalloids (Barwick and Maher, 2003; Ponton et al., 2016; Yuan, 2017). These elements, depending on their concentration and chemical speciation, can interact with each other, and antagonize or exacerbate their toxicity in exposed organisms. Selenium (Se) is one such element that has been reported to have an antagonistic relationship with Cd (Messaoudi et al., 2010; Zwolak and Zaporowska, 2012; Jamwal et al., 2016). Selenium is essential for the synthesis of various selenoproteins that have vital adaptive and housekeeping functions, including the maintenance of cellular redox homeostasis (Reich and Hondal, 2016). On the other hand, Se can also be extremely toxic to fish, when its concentration in the body exceeds the physiological threshold (Janz, 2012). Recent studies have indicated that exposure to elevated Se causes toxicity in fish by inducing ROS production and oxidative stress (Kim and Kang, 2015; Kupsco and Schlenk, 2014; Thomas and Janz, 2016). Although fish can accumulate Se *via* both water and diet, the predominant route of Se exposure to fish is the diet, especially in its organic form (selenomethionine) (Janz, 2012).

The ameliorative effects of low or moderate doses of Se against chronic Cd toxicity in fish have been reported in a few studies previously (Banni et al., 2011; Talas et al., 2008; Xie et al., 2016). Talas et al. (2008) and Banni et al. (2011) suggested that Se (as selenite), *via* water and diet, respectively, alleviates oxidative stress in fish during chronic exposure to waterborne Cd. More recently, Xie et al. (2016) also demonstrated that pre-exposure to Se-supplemented diet (both in the form of selenite and selenomethionine) led to lower oxidative stress and whole body Cd burden in fish during short-term exposure to waterborne Cd. Although these studies provided useful insights into the interaction of Cd and Se in fish, their environmental implications are limited. This is mainly because all of these studies were carried out using physiologically optimum or non-toxic exposure levels of Se, and also at waterborne Cd concentrations (0.4–2.0 mg L^{-1}) that were well above the range of environmentally relevant Cd exposure levels. To date, it is not understood how the interactions of Se and Cd are influenced by different Se exposure levels, particularly at levels that exceed the physiological threshold and may cause toxicity to fish by itself. Moreover, no previous studies have investigated how the interaction of Cd and Se modulates the accumulation pattern of both elements in critical body organs (e.g., liver, kidney, muscle) in fish. Interestingly, it has been reported in a recent field study that higher Se levels in the liver were correlated with lower hepatic oxidative stress in fish naturally exposed to metals including Cd (Ponton et al., 2016). This indicates that the physiological response in fish during chronic exposure to Cd and Se may be directly linked with the tissue-specific burden of each element, and thus worthy of further investigation.

The present study was designed to conduct an in-depth investigation of the interactive effects of dietary Cd and Se exposure in fish, and also to elucidate how these effects are influenced by Se exposure levels. Juvenile rainbow trout were chronically exposed to an environmentally relevant dietary Cd concentration (40 μg g^{-1} feed dry wt.), concurrently with different doses of dietary Se [low (1.2 μg g^{-1} feed dry wt.), moderate (10 μg g^{-1} feed dry wt.) and high (40 μg g^{-1} feed dry wt.); as selenomethionine]. The specific objectives of this study were to examine: (i) how Se affects Cd-induced alteration in morphophysiological indices (condition factor, hepato-somatic index) of fish, (ii) how Cd-induced changes in hepatic anti-oxidative responses and oxidative stress markers are modulated by Se exposure, and also (iii) how the interaction of Cd and Se alters the tissue-specific burden of each element in fish. We hypothesized that Se would ameliorate Cd toxicity by augmenting the cellular redox potential as well as by reducing Cd accumulation in critically important tissues such as liver and kidney, but these protective effects would be evident only at the moderate Se exposure level, with no protection or potential exacerbation of toxicity at the high Se exposure level.

2. Materials and methods

2.1. Chemicals

L (+)-Selenomethionine (>99% purity; CAS number: 3211-76-5) was procured from Fisher Scientific, Canada. High purity Cadmium chloride (>99.99% trace metal basis; CAS number: 10,108-64-2) was purchased from Sigma Aldrich, USA. Aquacalm™ (Metomidate hydrochloride; CAS number: 36,557-22-9) was purchased from Syndel Laboratories Ltd., Canada. The reference standards and reagents for graphite-furnace atomic absorption spectroscopy were purchased from PerkinElmer, Canada. All other chemicals and reagents were procured from VWR, Canada unless stated otherwise.

2.2. Experimental fish

Fertilized triploid eggs were sourced from an adult rainbow trout female and hatched in the Aquatic Toxicology Research Facility (ATRF) at the University of Saskatchewan, Canada. Hatched fish were raised on commercial dried pellet feed, fed at 2% body weight (wet wt.) ratio throughout the husbandry period. Fish were reared in dechlorinated, aerated water [hardness 159 ± 2.36 mg L^{-1}, alkalinity 105 ± 1.36 mg L^{-1} (both as $CaCO_3$), dissolved organic carbon (DOC) 2.1 ± 0.06 mg L^{-1}, pH 7.5–7.8, Se 5.2 ± 1.72 μg L^{-1}, Cd < 0.1 μg L^{-1}] in a flow-through system (1 L min^{-1}). The photoperiod was set at 14:10 h light to dark cycle and the water temperature was maintained at 12 ± 2 °C.

2.3. Diet preparation

Brine shrimp (*Artemia franciscana*) containing 5.8% crude protein, 0.6% crude fat, 0.25% crude fiber, and 90% moisture (all on a wet wt. basis) was used to prepare the experimental diets. First, the shrimps were rinsed several times with deionized water and then ground in a commercial blender. A known amount of selenomethionine and/or cadmium (as $CdCl_2$) that would result in the desired concentration of Se or Cd in the dry feed was dissolved in