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Original Article

MITIGATING ROLE OF ZINC AND IRON AGAINST CADMIUM INDUCED TOXICITY IN LIVER AND KIDNEY OF MALE ALBINO RAT: A STUDY WITH REFERENCE TO METALLOTHIONEIN QUANTIFICATION

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ABSTRACT

Objective: The present study is carried out to know the mitigating role of zinc (Zn) and / or iron (Fe) supplementation on cadmium (Cd) induced toxicity in rats with special reference to metallothionein (MT) protein.

Methods: Wistar strain male albino rats were treated orally with Cd at a dose of $1/10^{th}$ of LD_{50} / 48h (i. e. 22.5 mg/kg) for 7, 15 and 30 days (d) long sojourn. 15d Cd treated rats were then subjected to trace element supplementations of Zn (12mg/kg) and Fe (40mg/kg) individually and in combination for another 7, 15 and 30d time intervals. After specific time intervals, rats were decapitated and tissues like liver and kidney were isolated. The vital oxidative stress enzymes such as GST and GPx were assayed by using the standard methods in the test tissues. LPO levels were also measured by using the standard protocol. MTs, the metal binding proteins which are the first line of defense against Cd toxicity were quantified by using the standard methods in the test tissues.

Results: A significant ($P < 0.05$ level) elevation in LPO levels with decreased activity levels of GST and GPx were observed during Cd intoxication. With Zn and Fe supplementation, a significant reversal in the above said parameters were observed. MT protein levels were significantly elevated in the test tissues during Cd treatment and also after supplementation with Zn and / or Fe. Maximum MT protein synthesis was observed in 30d rat kidney under combined supplementation of both Zn and Fe.

Conclusion: The present study focuses on the mitigating role of trace elements Zn and Fe in reducing the Cd body burden from the selected tissues of rat. Supplementation with Zn and / or Fe envisages the therapeutic role of trace elements in combating the heavy metal, Cd insult.

Keywords: Cadmium, Oxidative stress enzymes, Zinc and iron supplementation, Metallothionein, Liver, Kidney, Rat.

INTRODUCTION

Environmental pollution is a global problem and is common to both developed as well as developing countries. This pollution was caused by numerous chemicals, xenobiotics, heavy metals etc. Among the heavy metals, Cadmium (Cd) is one of the most toxic, non- essential heavy metal with many industrial uses that can contribute to a well-defined spectrum of diseases in animal models as well as in humans [1, 2].

Over the past two centuries, anthropogenic and industrial activities have led to high emissions of Cd into the environment at concentrations significantly exceeding those originating from natural sources [3]. Cd has an estimated elimination half-life period of 20-30 years in the human body [4] and is highly cumulative, especially in the liver and kidney [5 - 8]. The main sources of Cd are storage batteries, electroplating, pigments, plastics, fertilizer industries and cigarette smoking.

It is an ubiquitous toxic metal and induces oxidative damage by disturbing the prooxidant – antioxidant balance in the tissues [9]. Cd is readily distributed in tissues after exposure and interferes with intracellular signaling network and gene regulation at multiple levels and induces lipid peroxidation (LPO). Lipid peroxides that accumulate due to LPO are known to be harmful to cells and tissues and inhibit the antioxidant system of the cells [10, 11]. As a result of this inhibition, the electron transport chain becomes highly reduced, electrons are transferred directly to available oxygen and lead to enhanced formation of reactive oxygen species (ROS) [12]. ROS may lead to increase oxidative stress in tissues, cellular damage, peroxidation of membrane lipids and loss of membrane bound enzymes [13, 14], which might result in histological changes and physiological damage to different organs [15, 8, 16, 3]. Intake of Cd results in consumption of glutathione (GSH) and protein binding sulfhydral groups and subsequently the levels of free radicals such as hydrogen peroxide, hydroxide and superoxide are increased [17].

Sulfhydral – rich, metal binding protein, Metallothionein (MT) may function in a manner similar to GSH. Wherein MT provides an intracellular 'nucleophilic sink' to trap free radicals, electrophiles and alkylating agents. MT's is a class of low molecular weight (6-7kDa), cysteine rich and transition metal binding proteins. MT's occur throughout the animal kingdom and are also found in higher plants, eukaryotic microorganisms and in some prokaryotes [18 - 21]. MT's have the capacity to bind heavy metals through the thiol group of its cysteine residues. A large amount of subsequent work has shown MT to serve in many cell types in the management of essential divalent metal cations, to interfere with the toxic effects of xenobiotics, heavy metals, free radicals and to serve as a regulator of specific transcription factors. Cells that contain an excess amount of MT are resistant to Cd toxicity [22, 23].

The complex inter-relationships between Cd and some essential trace elements have not been elucidated. Several essential trace elements like zinc (Zn), iron (Fe), selenium (Se) and copper (Cu) participate in controlling various metabolic and signaling pathways. Among the trace elements Zn and Fe are essential for maintenance of life and health. Zn is an essential trace metal with numerous functions in biological systems. Zn controls several enzymes of intermediary metabolism, DNA and RNA synthesis, gene expression, immunocompetence and plays a significant role in homeostasis of hormones. Zn also takes part in the defense against excessive amounts and following damage of certain metals, and it does so through the interaction with metallothionein. It has been noted that Zn has a relationship with many enzymes in the body and can prevent cell damage through activation of the antioxidant defense system [24, 25]. Fe plays an essential role in many biological processes and it is important to maintain iron concentration within its narrow normal range. Fe supplementation reduces Cd retention and Cd induced anemia during fast growth in young rats [26]. *In vitro* studies suggests that there is a competition for transport mechanism between Cd and some essential trace elements like Zn