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Current Trends in Clinical Toxicology

Toualbia N, et al. Curr Trends Clin Toxicol: CTT-102.

Research Article

DOI: 10.29011/ CTT-102.100002

Role of Hepatic Oxidative Stress of Nickel Toxicity in Rabbits (*Oryctolagus cuniculus*)

Nadjiba Toualbia*, Rachid Rouabhi, Aya Salmi, Samira Boussekine, Amani Yousfi, Hadjer Chenikher, Chahinez Taib

Department of Applied Biology, University of Tebessa, Algeria

***Corresponding author:** Nadjiba Toualbia, Department of Applied Biology, University of Tebessa, Algeria. Tel: + 213662225982; Email: nanatoualbia@yahoo.com

Citation: Toualbia N, Rouabhi R, Salmi A, Boussekine S, Yousfi A, et al. (2018) Role of Hepatic Oxidative Stress of Nickel Toxicity in Rabbits (*Oryctolagus cuniculus*). Curr Trends Clin Toxicol: CTT-102. DOI: 10.29011/ CTT-102.100002

Received Date: 27 June, 2018; **Accepted Date:** 12 July, 2018; **Published Date:** 23 July, 2018

Abstract

The Nickel is a toxic metal involved in several human diseases related to oxidative stress, in this experimental study we were interested in the toxicity of nickel, which is a heavy metal frequently encountered in ecosystems and has intracellular damage to all types of biomolecules. Oxidative activity (GST, CAT) and lipid peroxidation is evaluated by the measurement of MDA. The results on bio markers measured high light in rabbits has two concentration 250ppm and 500 ppm Ni Cl 2 for a period of 3 months compared to witnesses a decrease the rate of GSH in liver and increase of GST, GPx, CAT Finally, we can confirm that nickel has hepatotoxic effects due to their effects on the metabolic function of the liver biochemical and enzymatic parameters.

Keywords: Enzymatic; Metal; Metabolic; Nickel; Rabbits

Introduction

Heavy metals are pollutants generated by human activity and have a high toxicological impact. Toxic metals are numerous but most notably arsenic, cadmium, lead and mercury. They have impacts on plants, consumer products and on humans [1]. The metallic elements are in various forms always present in the environment. In the state of traces, they are necessary even essential to the living being [2]. Heavy metals do not all present the same risk due to their effects on the organisms, their chemical, physiochemical and biological properties. their toxicity is very variable and their impact on the environment is very different [3]. The metals transferred to humans can be the cause of an oxidative stress which represents one of the factors potentiating the genesis of plurifactorialy diseases such as cardiovascular diseases, diabetes, rheumatism asthma, cancer and diseases neurodegenerations diseases [4].In fact, the risk on human health is to abort associated with properties of heavy metals has pollute water, the atmosphere food and soil and dependent also the state chemical their chemical form, of their concentration the environmental context, the possibility of passage in the chain living [5].

Toxicology, they can be defined as metals cumulative nature (often in tissues fat) having essentially effects very adverse living organism. Nutrition and agronomy, they can even be assimilated to trace elements essential for organizations especially by their catalytic action at the metabolism [6,7]. Nickel (atomic number 28, the atomic weight 58.69) is a metal which belongs to the group VIIIB of periodic table. The oxidation states the largest nickel is 2, while the oxidation states +3 and +4 are also known [8]. The nickel compounds are important in modern industry and are used in electroplating and for the production of battery nickel cadmium and electronic equipment. The nickel alloys, as stainless steel, are used in the production of tools, machinery arms and devises, they are also used to flow coins and produce jewel and prostheses medical [9]. The pure nickel can be polished, forged, welded, rolled and inert corrosion by the air, water, acids, alkalis and many organic solvents non-oxidizing [10]. Salts of nickel are used in electroplating, ceramics, pigments and feedstock (e.g.: catalysts, the formation of other nickel compounds) [11]. Nickel is commonly used in many industrial processes and implications Eco toxicological important [12]. Rabbits of different varieties have been used to establish experimental models that are very useful in various spheres of biomedical research (embryology, toxicology, virology) and they are frequently used routinely in serology because

the readily produce antibodies against a multitude of antigens [13]. In our work, we tried to demonstrate the effect of nickel chloride at two concentrations 250and 500 ppm on rabbits.

Material and Methods

Animals

For our experiments, we chose to work on rabbits *Oryctolagus cuniculus*. All rabbits were males weighing between 1,5 - 1,8Kg. Animals were kept under constant conditions of temperature environ 25 ± 3°C and humidity 35 ± 5%. The total body weight was daily recorded before and during the experiments. There was a gain in body weight and increase of food consumption indicating the good conditions of laboratory.

Experimental Design

We have handled 15 rabbits. These rabbits were divided on 2 lots of 5 rabbits and we kept five rabbits as control. The treatments began 15th day (adaptation period of rabbits) all treatments are per os (p.o) as follows:

Lot1: controls no treatments

Lot2: treated with $NiCl_2$ at 250ppm for 90 days of treatment

Lot3: treated with $NiCl_2$ at 500ppm for 90 days of treatment

After 90 days of treatment, the rabbits were sacrificed. The liver was recovered, collected, weighed and stored for the determination of certain biochemical metabolites and certain oxidative stress parameters (GSH, GPx, CAT, MDA, GST).

Dosing Methods

Extraction and dosage of proteins

The method used for protein assay is Bradford (1976) [14], using BSA (Bovine Albumin Serum) as the standard.

Determination of glutathione GSH

The determination of glutathione realized by Weckbeker and Cory (1988) [15]. the principle of this determination is based on measuring the absorbance of 2nitro-5-mercapturique.

Determination of Glutathione Peroxidase (GPx)

The enzymatic activity of GPx was measured by the method of Flohe and Gunzler (1984) [16], using H2O2 as substrate.

Determination of Glutathione S-Transferase Activity (GST)

The measuring of glutathione s transferase activity was determinate by the method of Habit et al. (1974) [17]. It is based on the conjugation reaction between GST and a substrate.

Determination of activity Catalase (CAT)

The spectrophotometric determination of catalase (CAT) activity is carried out according to the method of Chakma and Horst (1991) [18].

Statistical Analysis

The significant differences between the control and the treated groups were determined by the Student's t test. Statistical calculations were carried out using Minitab 17.1 statistical package and the Excel 16.0 (Microsoft, Inc.).

Results and Discussion

The results are expressed by the mean ± (standard deviation) of n experiments. The differences are considered: significant when $P \leq 0.05$, very highly significant when $P \leq 0.001$, highly significant when $P \leq 0.01$. The purpose of this study was to demonstrate the potential toxicity of $NiCl_2$ to certain biochemical, enzymatic and non-enzymatic parameters of *Oryctolagus cuniculus* rabbits as a biological model. The Oxidative stress is typically defined as an imbalance in the balance between antioxidant defense systems and the production of ROS in favor of these systems [19]. In our work, we have shown an increase in the level of liver proteins. This result confirms the study of the exposure of rabbits to environmental stress (Cadmium, Copper and Zinc) can modify the metabolism of proteins and their syntheses at the level liver [20]. These results are confirmed by [21,22] which showed a correlation between the disruption of the total protein level and the xenobiotic toxicity. This effect is explained on the one hand by the induction of protein synthesis Stress related to the phenomenon of bio activation / biotransformation and on the other hand by the lipid peroxidation generated by the ROS. Metallothioneins (MTs) are proteins capable of trapping free radicals and chelating metals, which is confirmed by the work of [23,24] who found a significant increase in metallothionein levels in the liver of rabbits treated with cadmium. The Exposure of rats to environmental stress (Ni) can alter the metabolism of amino acid proteins and their synthesis in the liver [25].

The Phagocyte nickel by the cell increases the activity of oxygen radicals, catalyzes the transformation of DNA and can cause cancer, the intervention of endogenous and exogenous antioxidants stops these reactions [26-29]. The organism can defend and adapt these stresses by its endogenous antioxidants and its stress proteins such as metallic thiamine's encountered in humans and many animals [30]. In our study, the administration of nickel chloride in rabbits caused oxidative damage. Nickel with cadmium and chlorine, are considered as oxidative stresses [31]. The Oxidative stress in the cell can be induced either by increased production of

ROS or inhibition of the antioxidant defense system. This balance between the production and catabolism of oxidants is essential for the maintenance of the biological integrity of the tissues [32].

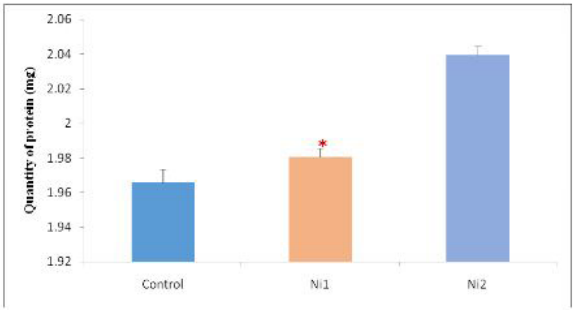

Figure 1: Variation of protein (mg) in the control and treated rabbits after 90 days of treatment.

MDA is a secondary product generated during the oxidation of polyunsaturated fatty acids [33]. Our results show an increase in the level of hepatic MDA in rabbits treated with a high dose of $NiCl_2$ (150 mg / kg / day) compared to control rabbits, which is a marker of lipid peroxidation. Our results confirm those of [34], who found an alteration in antioxidant status in nickel-treated rats. This alteration is accompanied by an increase in lipid peroxidation and a decrease in cellular GSH level. MDA is also a by-product of prostaglandin biosynthesis [35]. Our results are in agreement with those of Viareggio et al. Which studied the toxic effects of heavy metals on lipid peroxidation in Mytillusgalloprovinciallis. They had demonstrated a significant level of MDA after exposure to copper [36].

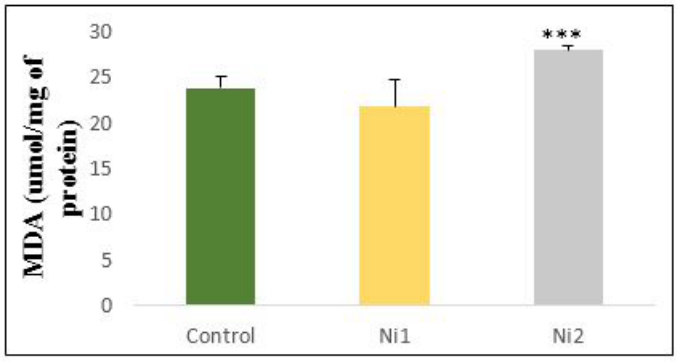

Figure 2: Variation of MDA (µM/mg pot) in the control and treated rabbits after 90 days of treatment.

For Glutathione S-Transferase (GST), this enzyme plays an important role in the detoxification of xenobiotic and / or in protecting against harmful metabolites generated after degradation of macromolecules following exposure to oxidative stress [37]. According to our results, an increase in GST in the liver [38]. Report an increase in hepatic and cerebral GST activity following an injection of cadmium to guinea pigs. The results obtained confirm the ability of the metal to generate cellular radical effects at various metabolic levels. Glutathione also intervenes at a second level in anti-radical defense by its involvement in detoxification reactions catalyzed by Glutathione-S-transferase [39]. The response of GST activity depends on several factors such as xenobiotic type, concentration, exposure time and species [40].

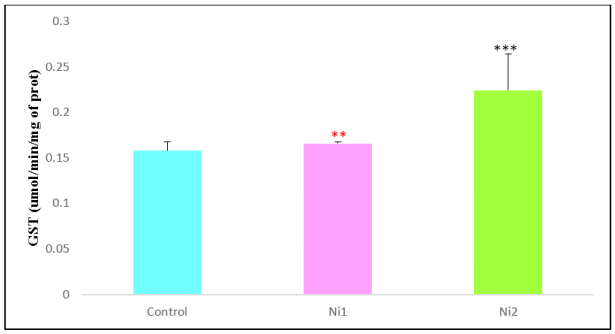

Figure 3: Effect of $NiCl_2$ on the activity of GST (µM/min/mg) after 90 days of Treatment.

GSH is a crucial element of the antioxidant defense mechanism, functions as a direct reactive free radical sensor. In our experimental conditions [41], we notice a statistically significant decrease in GSH levels, which can be explained by an adaptive response to oxidative stress. The decrease in GSH can be explained by several assumptions: First, GSH plays a key role in the detoxification of free radicals and heavy metals [42] and in the case of nickel, the latter interacts directly with high affinity to the GSH thiol (-SH) groups, second, glutathione Can also interact with the free radicals generated by this metalloid [43-46], third, nickel inhibits glutathione synthetize, and glutathione reductase [47], so little GSH is produced. The effect of nickel chloride on the concentration of the hepatic GSH and the activities of the antioxidant enzymes (GPx, GST) is accompanied by an increase in the free radical's ROS. The latter initiated the lipid peroxidation [48].

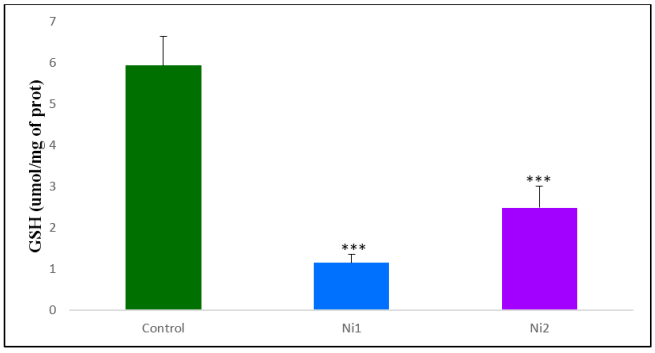

Figure 4: Variation of GSH (µM/mg prot.) in the control and treated rabbits after 90 days of treatment.

Glutathione peroxidase, superoxydedismutase and catalase are mutually supportive defense against ROS [49,50]. Our results showed an increase in GPx, CAT and hepatic GST activity in rabbits treated nickel. GPx is a key antioxidant enzyme that regulates the level of ROS (GPx is able not only to reduce hydrogen peroxide to water, but also hydro peroxides resulting from the oxidation of unsaturated fatty acids) and thus protects the cells Against the damage caused by nickel [51]. The antioxidant enzymes (SOD, GPx and CAT) limit the effects of oxidizing molecules in tissues and play a role in defense against cellular oxidative damage being free radical scavengers [52].

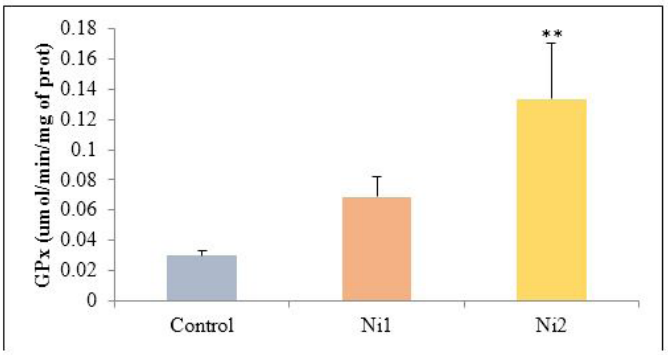

Figure 5: Effect of $NiCl_2$ on the activity of GPx (µM/min/mg) after 90 days of Treatment.

Catalase plays an important role in protecting the body against oxidative stress damage [53]. Zikic et al report an increase in the activity of both enzymes (SOD and CAT) in erythrocytes and tissue Pisces.

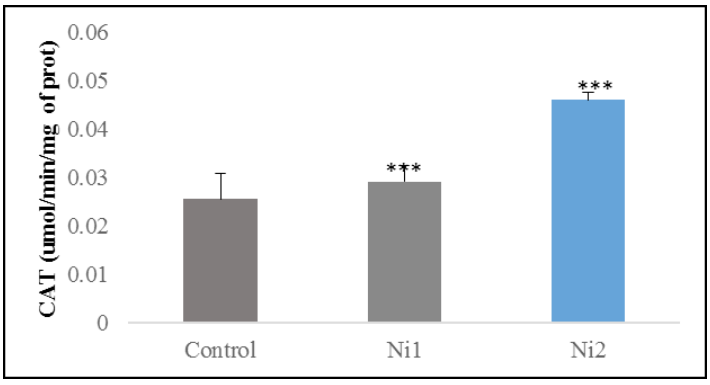

Figure 6: Effect of $NiCl_2$ on the activity of Catalase (µ M/min/mg) after 90 days of treatment.

Conclusion

In this study, we investigated the effect of nickels on the oxidative stress biomarkers of the liver of rabbits *Oryctolagus cuniculus*. We can conclude that this species is sensitive to the presence of metals, this sensitivity was manifested by the effects of induced oxidative stress and the enzymatic mechanisms involved.

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