ASSESSMENT OF THE POTENTIAL ROLE OF L- METHIONINE ON NICKEL SULFATE INDUCED RENAL INJURY AND OXIDATIVE STRESS IN RAT

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ABSTRACT

Objective: The study was designed to investigate the possible protective role of methionine (Met) in nickel sulfate induced oxidative stress in renal tissue.

Methods: Rats were divided into the following groups: Healthy control; L-methionine (Met, 100 mg/kg, orally); nickel sulfate (Ni, 20 mg/kg, intraperitoneally); and combination Ni+Met. The experiment lasted 21 days. Antioxidant and renal function parameters with histological study were performed.

Results: In the Ni group, marked renal damage was noticed with the significant elevation in the levels of creatinine, urea, and uric acid in serum. Animals also showed a significant rise in the lipid peroxidation level with a concomitant decrease in glutathione (GSH) and various antioxidant enzymes GSH peroxidase, catalase, and superoxide dismutase. Moreover, these changes in rats given the combined therapy nickel plus methionine were significantly less than those of group nickel, met prevented these alterations and maintained the antioxidant status. Histopathological examination of the kidney tissue proved the protective effect of Met against nickel toxicity.

Conclusions: These results demonstrated that methionine augments antioxidant defense against nickel-induced toxicity and provides evidence that it has therapeutic potential as a renoprotective agent.

Keywords: Nickel, Methionine, Nephrotoxicity, Oxidative stress.

INTRODUCTION

The toxicity of nickel (Ni) has become an object of great interest because of extensively distributed in environmental occurrence. Humans are exposed to nickel through food, water and air produced from wide different sources, including the production of stainless steel, alloys, electroplating, catalysts, foundries, batteries, welding rods, coinage, jewelry, paints, and dental and medical implants [1]. Several studies have reported that nickel can cause harmful effects to people and animal health; nickel provokes oxidative stress and induces cytotoxicity [2]. It may generate reactive oxygen species (ROS), which react with several cellular molecules, causing lipid peroxidation (LOP), protein oxidation, DNA damage, and results in cell apoptosis, and various cell injuries [3]. The oxidative damage may be related also to the destruction of thiol groups of amino acids and proteins [4]. Moreover, this metal decreases reduced glutathione (GSH) and a large number of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase, resulting a cell damage which has related to the accumulation of free-radicals in the cell [5]. A significant medical improvement has been shown to be associated with giving antioxidants as adjuvant therapy. The coadministration of sulfur-containing amino acids has been proved to be beneficial in the decline of oxidative stress and increase the tissue antioxidant status of rats. Methionine, in addition to its role as a methyl donor and as an essential amino acid to protein synthesis, serves as a precursor for GSH synthesis and has a crucial role in the detoxification of free radicals [6]. Since methionine can also help with chelation, the thiol group tightly binds with metals and thus serves as an important antioxidant [7,8]. The purpose of this study was to investigate the possible protective effect of methionine against nickel-induced renal oxidative stress in rats.

METHODS

Chemicals

Ni as nickel sulfate, (L-methionine) and all other chemicals used in the experiment were purchased from Sigma Chemical Co., St. Louis, France, all other chemicals used were of analytical grade.

Experimental procedure

Male Wistar rats weighing 180–220 g (provided by the Pasteur Institute of Algiers) were used in this study. Animals were housed in cages and maintained under standard conditions of temperature and humidity with 12 h light/dark cycle, with free access to the standard pellet diet and water for 2 weeks as an adaptation period. The experimental procedures were carried out according to the guidelines for the care and use of animals approved by the National Institute of Health and the Ethics Committee of our institution. The rats were divided into four groups (seven rats each): The first group served as a control? The second group treated with L-methionine (100 mg/kg bw. orally). The third Group administrated with nickel sulfate (20 mg/kg bw. i.p), and the fourth was given both nickel and L-methionien on alternate days for 3 weeks. At the end of the experimental period, animals were sacrificed by cervical decapitation after overnight fasting. Serum was separated by centrifugation (at 3000 g for 10 min) and the resultant supernatant was stored at −20°C for the biochemical analysis. The kidneys were removed, weighted, and rinsed with a physiological saline solution. A portion of the kidney was homogenized in 2 mL of buffer solution of Tris-buffered saline (TBS and pH 7.4). Homogenates were centrifuged at 10,000 g for 15 min at 4°C, and the resultant supernatant was used for the determination of LOP (MDA), reduced GSH levels, and the activity of GPx, CAT, and SOD. The kidney was dissected, fixed in 10% formalin solution and processed immediately for histological examination.

Determination of biochemical parameters

Creatinine, urea, and uric acid were measured as functional markers for nephrotoxicity. They were assessed using commercially available diagnostic kits (Spin react, Spain, ref: Creatinine - 1001111, urea - 1001329, and uric acid - 1001011), according to the enzymatic colorimetric method and using a spectrophotometer.

Protein quantification

The protein content of kidney homogenate was determined according to the method of Bradford [9] using bovine serum albumin as a standard.

Estimation of LPO levels

The kidney tissue malondialdehyde concentrations, an index of LOP, were determined spectrophotometrically according to Buege and Aust [10]. The process is determined in the supernatant of homogenate kidney tissue by the thiobarbituric acid (TBA) method. The absorbance of the resulting TBA-MDA complex was measured at 530 nm, and the level of hepatic MDA was expressed as nmol/mg protein.

Estimation of reduced GSH concentration

Kidney reduced GSH was estimated by the method of Jollow *et al.* [11] based on the reaction of 5,50- dithiobis-(2-nitrobenzoic acid) (DTNB) with compounds containing sulfhydryl groups and the development of yellow color. The maximum absorbance was recorded at 412 nm. Total GSH content was expressed as nmol/mg protein.

Estimation of antioxidant enzymes activities

GSH peroxidase activity (GPx) was assayed by the method based on the reaction between GSH remaining in the solution after enzyme-catalyzed reaction with DTNB acid to form a complex which is absorbed in a maximum wavelength of 412 nm [12]. CAT activity was measured spectrophotometrically according to Aebi [13], this assay is based on the ability of the enzyme to induce the decomposition of hydrogen peroxide. Superoxide dismutase (SOD) activity was determined by the nitroblue tetrazolium NBT test, the oxidation of the NBT is used to determine the production of superoxide anions O2- in such superoxide-generating systems as of riboflavin/methionine complex [14].

Histopathology examination

Small pieces of kidney tissues were collected in 10% buffered formalin for proper fixation. These tissues were processed and embedded in paraffin wax. Sections of 4 µm in thickness were made and stained with hematoxylin and eosin for histopathological examination [15].

Statistical analysis

All experimental expressed as means ± SEM. Data comparisons were analyzed by one-way analysis of variance, followed by student's t-test. The results were considered significant if $p<0.05$.

RESULTS

Evaluation of body and organ weights

No death was observed in any group during the experimental period. The (Ni) group showed a significant decrease in body weight ($p< 0.01$), kidney absolute weight ($p< 0.01$), and kidney relative weight ($p< 0.01$) compared to control group (Table 1). While the (Met) group along with Ni exposure (Nit+Met) observed significant restoration in the body weight, kidney both absolute, and relative weights as compared to (Ni) group.

Effect of treatments on functional kidney markers

Treatment of rats with 20 mg/kg bw. of nickel caused a significant increase ($p<0.01$) in the levels of serum nephritic markers (urea, creatinine, and uric acid) when compared with the control group. However, met in combination with nickel ameliorated significantly the elevation in the above-mentioned parameters (respectively, $p<0.05$; $p<0.01$; and $p<0.05$) when compared with those seen in Ni-treated group (Table 2).

Effects of treatments on renal oxidative stress parameters

Table 3 shows the effect of the Met and Ni on LOP in the control and experimental groups of rats. MDA levels in renal tissues were significantly higher ($p<0.01$) in Ni-treated rats compared to control rats. It caused also a significant reduction of the GSH level (Fig. 1), and in the activities of GPx ($p<0.001$), CAT ($p<0.01$), and SOD ($p<0.01$) (Table 3). However, the coadministration of Ni+Met led a recovery in the above-mentioned oxidative stress parameters as compared to Ni group.

Kidney histopathological changes

Next, to confirm the previous data, the histopathology of kidney was examined. Normal histology of the cortex and medulla was observed in the kidney of controls rats and the rats treated with methionine (Met) alone (Fig. 1a and b), while some nephrotoxic lesions, as indicated by glomerular and tubular degeneration and necrosis characterized by destruction of tubular epithelial cells, were noticed in rats treated with nickel (Fig. 1c). In contrast, the supplementation of the Met with Ni (Nit+Met) showed a remarkable improvement in the kidney histology (Fig.1d).

DISCUSSION

The biochemical mechanism of nickel-induced nephrotoxicity appears to trigger oxidative stress, by inducing overproduction of ROS by enhancing LOP and depleting the cellular antioxidant capacity. The increased level of Ni accumulation in the kidney could be discussed by his great affinity for SH-containing molecules such as GSH and metallothionein [16]. Hence, SH group is involved in the function of many enzymes; the Ni-SH complex possibly disturbs many functions of cell mainly mitochondrial dysfunction. The treatment of this toxicity can include chelation or antioxidant administration to remove nickel and scavenge generated ROS. There are many appreciated studies have demonstrated the potential use of methionine, as ROS scavenger, possesses potent antioxidant activity on the basis of its sulfhydryl group within its structure, has metal chelating property [17] and is currently being used clinically to diminish hepatic injuries after acetaminophen poisoning [18]. Therefore, this study aimed to assess and examine the possibility of methionine to prevent the alterations induced by nickel sulfate in kidney tissues of male albino Wistar rats.

The body weight change is used as a good indicator of the overall health status. In our study, changes in rats' body weight along with kidney weights can act as an essential indication of Ni toxicity. This is in agreement with earlier reports that nickel treatment leads to retarded
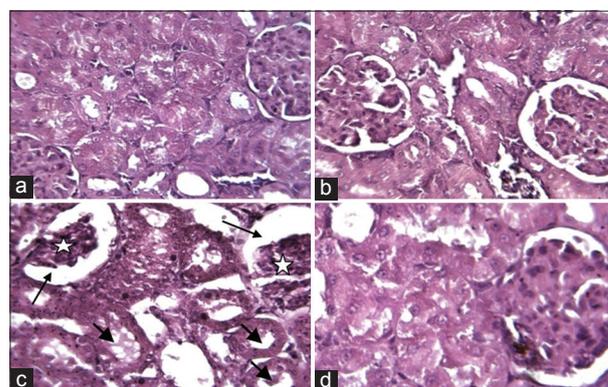

Fig. 1: Light photomicrograph of kidney sectional histology from control rats (a), L-methionine (c), nickel (d) and Ni+ Met (f) (H&E. X 400). (a and b) Kidney sections from control and methionine groups show the normal appearance of glomeruli and tubules.

(c) Kidney section from nickel treated rat showing a severe glomerular degeneration (star), wide Bowman's space (single arrow), vacuolar degeneration of tubular epithelial cells (dashed arrow), and tubular necrosis invaded by inflammatory cells. (d) Kidney section from a rat coadministrated methionine with nickel showing improvement in the kidney architecture shown by slight lesion of the tubules when compared with those receiving only Ni

Table 1: Body weight (g), absolute (g), and relative kidney weights (g/100 g bw) of rats in control and treatment groups

Parameters	Initial body weight (g)	Final body weight (g)	Absolute kidney weight (g)	Relative kidney weight (g/ 100 gbw)
Control	201.33±6.5	250.3±6.8	0.6±0.03	0.45±0.02
Met	201.2±5.15	239.3±4.9	0.58±0.04	0.48±0.03
Ni	202.33±6.9	181.7±11.3[a1]	0.8±0.03[a1]	0.92±0.1[a1]
Ni+Met	200±4.9	216.3±7.6[a]	0.63±0.03[b]	0.58±0.04[ab]

Values are given as mean±SEM of seven rats each group. Statistically differences from control: [a]$p<0.05$, [a1]$p<0.01$, [a2]$p<0.001$; from Ni: [b]$p<0.05$, [b1]$p<0.01$, [b2]$p<0.001$

Table 2: Serum biochemistry changes of control and rats treated with methionine (Met), nickel (Ni), or their combination (Nit+Met) after 3 weeks of treatment

Parameters	Urea	Creatinine	Uric acid
Control	37.32±2.28	5.68±0.34	2.5±0.17
Met	31.75±1.98	6.15±0.17	2.81±0.14
Ni	55.02±5.29[a1]	8.1±0.44[a1]	3.88±0.24[a1]
Ni+Met	38.3±1.93[b]	5.76±0.29[b1]	3.0±0.2[b]

Values are given as mean±SEM of seven rats each group. Statistically differences from control: [a]$p<0.05$, [a1]$p<0.01$, [a2]$p<0.001$; from Ni: [b]$p< .05$, [b1]$p<0.01$, [b2]$p<0.001$

animal growth and increase in organ-somatic index [19,20]. Our results were in accordance with those reported by Amudha and Pari [2], who mentioned a significant increase in the relative kidney weight in Ni-treated male rats. However, our results were opposing those reported by Dahmen-Ben Moussa *et al.* [21] and Adeyemi and Elebiy [20] who exhibited that Ni treatment resulted in a significant decrease in relative kidney weight. In the present work, coadministration of methionine prevented changes in relative kidney weight and body weights. Methionine is essential amino acids for the adequate growth and development of mammals, his ingestion in diet and supplements is required [22,23]. Tsiagbe *et al.* [24] reported that methionine directly influences broiler chicken's growth. Furthermore, excess usage of methionine can also have an adverse influence on growth. However, methionine deficiency diminishes the relative weight of the lymphoid organs, which can affect the growth [25]. In the study above, supplementation with 20 or 40 g/kg excessive methionine was found to diminish food intake and reduce weight gain [26].

Renal dysfunction is often manifested with elevation in serum levels of creatinine and urea. This elevation in the levels of renal functional markers is an indicator of impaired glomerular filtration rate and renal failure [27]. In this way, tissue damage occurs, and renal markers are released into the circulatory system. Rats given a nickel exhibited a marked elevation in serum urea, creatinine, and uric acid, ssuggesting the induction of nephrotoxicity in nickel treated rats. Likewise, Hfaïedh *et al.* [28] and Boulila *et al.* [5] as they noted increased creatinine and urea due to nickel and reflects its interaction with the cell membrane. Our results are also analogous to the findings of Chen *et al.* [29] and Adeyemi and Elebiyo [20].

The presence of notable histological damage in renal tissue following treatment with nickel strengthens the variation of kidney markers function. Nickel revealed severe glomerular degeneration and tubular necrosis invaded by inflammatory cells, signal the onset of chronic renal failure. According to Stengel *et al.* [30], the reduction in glomerular filtration is characterized by increased serum creatinine associated with a decrease in the number of functional nephrons. Hence, methionine might have performed an important role in maintaining the structural integrity of kidneys cells, which has resulted in reduced leakage of creatinine, urea, and uric acid, coadministration of methionine exhibited few changes after 3 weeks of treatment compared to nickel group. Methionine plays an important role as intermediary in the maintenance of cell membranes [31], and it has an important function for some reactions involved in protein and DNA synthesis [32].

These renal functional abnormalities were known to be accompanied by high renal oxidative stress. Lipid peroxidation is the main mechanism for oxidative stress induced by nickel [33], MDA is the major metabolite of LOP, and widely used as a biomarker for the assessment of LOP, its elevated levels could reflect the degrees of LOP injury in the rat kidney receiving Ni. Similar results were observed by Boulila *et al.* [5] and Hasanein and Felegari [34]. However, treatment with methionine significantly reversed these changes and reduced the levels of MDA in Ni-exposed rats suggesting its protective effects against oxidative damage. Hence, it may be plausible that the mechanism of renal protection of methionine is due to its antioxidant effect, methionine acts as a powerful free radical scavenger and confers some protection on the kidney tissue of Ni treated animals [22,35].

The antioxidant defense systems function relies on GSH and endogenous antioxidative enzymes, act cooperatively as free radical scavengers that protect and repair damage. Therefore they can protect the body from oxidative stress and degenerative diseases. GSH is an essential endogenous antioxidant, acts as a cofactor for antioxidant enzymes, directly scavenging ROS and protects cells against free radicals and toxic compounds [36]. The results of nickel exposure were coincide with the findings of Amudha and Pari [2] and Boulila *et al.* [5]. A significant increase in the renal GSH level was observed in the rats treated with nickel and methionine might be due to GSH regeneration. Methionine is readily adopted by the hepatocytes than cysteine for the direct synthesis of GSH [37]. In addition, GSH is influenced by dietary sulfur amino acid intake [38]. Reports have proved that supplementation of methionine can enhance the formation of GSH in human, rat, and broiler cells [39-41]. Antioxidant enzymes (GPx, CAT, and SOD) can protect against free radicals by converting them back to more stable molecules in the cell. The primary function of GPx is to lessen lipid hydroperoxides to their corresponding alcohols and assist to reduce free hydrogen peroxide to water and oxygen at the expense of the GSH. SOD and CAT are the enzymes, which act by converting superoxide $(O2^-)$ into H_2O_2 and then into H_2O and O_2. It has been reported that Ni itself may catalyze hydroxyl radical generation through the Haber-Wiess reaction [42]. Through the absence of enough GPx activity or GSH levels, LOP and hydrogen peroxide are not detoxified and perhaps converted by transition metals to hydroxyl radicals and lipid peroxyl radicals. The findings were similar to the results of Kubrak *et al.* [36] and Dahmen-Ben Moussa *et al.* [21] who found decreased GPx, CAT and SOD activities in the rat kidney by Ni cytotoxicty of antioxidant capacity may be coupled with the depletion of GSH and reduced total sulfhydryl contents or with their increased utilization for quenching free radicals and/or their inactivation by excessive Ni oxidation. Furthermore, Ni was reported to trigger nitric oxide (NO) creation [43], which may inhibit both CAT activities by binding to its heme prosthetic group [44] and GPx activity [45]. The coadministration of methionine showed marked elevation in the antioxidant activities in kidney tissue in comparison with the toxic group. Dietary methionine supplementation protects against renal injury induced by fluoride intoxication in rats and improved the activities of SOD and GSH-Px [46]. In addition to GSH synthesis and other metabolites, thiol groups in this amino acid might have helped in chelation of nickel from the tissue. Moreover, methionine can even directly scavenge the ROS including the hydroxyl radical and hydrogen peroxide, which can cause the oxidation of methionine as a free amino acid or protein residue [35].

Table 3. Lipid peroxidation levels and antioxidants parameters in kidney of control and rats treated with methionine (Met), nickel (Ni) or their combination (Nit+Met) after 3 weeks of treatment

Parameters	MDA (nmol/mg protein)	GSH (nmol/mg protein)	GPx (nmolGSH/mg prot)	CAT (μmol H_2O_2/min/mg protein)	SOD (U/mg protein)
Control	0.5±0.03	90±1.62	0.83±0.02	67.58±2.6	75.92±1.98
Met	0.46±0.01	88.8±2.36	0.72±0.01	58.88±2.87	67.58±2.6
Ni	0.75±0.05[a1]	70.83±2.67[a1]	0.66±0.02[a2]	53.17±1.96[a1]	52.2±2.28[a1]
Ni+Met	0.48±0.02[b]	86.55±2.9[b1]	0.83±0.03[b]	60.03±2.1[b1]	60.07±2.63[b]

Values are given as mean±SEM of seven rats each group. Statistically differences from control: [a]$p<0.05$, [a1]$p<0.01$, [a2]$p<0.001$; from Ni: [b]$p< .05$, [b1]$p<0.01$, [b2]$p<0.001$

CONCLUSION

The findings in our study clearly showed that methionine ameliorated the oxidative and histological damage caused by nickel. These results may indicate that methionine is beneficial as a protective agent in nickel-induced nephrotoxicity.

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AUTHOR'S CONTRIBUTION

Author Bouhalit S, data collection and analysis, interpretation of data, drafting article, writing manuscript, author Pr. Kechrid. Z critical revision of the article and validated the manuscript.

CONFLICT OF INTERESTS

The author(s) declared no potential conflicts of interest.

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