Effect Of Cadmium Chloride On Function Of Thyroid Gland In Rats.

By

Zienab, Y. Mohamed and Heba, H. El-Gharieb

Pathology Dept, Animal Health Research Institute, Dokki, Giza, Egypt.

- Accepted in 1/11/2008

SUMMARY

This study was carried out on forty five male albino rats, divided into three equal groups each contain 15 rats, the first group kept as control. The 2nd and 3rd groups (G2 and G3) were administrated cadmium chloride (Cd Cl₂) in drinking water at doses of 0.55 and 2.19mg/L (1/160 and 1/40 LD₅₀), respectively for 12 weeks followed by another 6 weeks as withdrawal period. The present results recorded a significant increase in cadmium residues and cholesterol levels in the serum of G2 and G3. While body weight, and serum levels of TSH, T3, T4, albumin, calcium and phosphorous revealed a significant decrease. Concerning to withdrawal period The previous parameters showed the same results going to slight modulation. This study concluded that cadmium has a toxic effect on thyroid gland leads to dispersed its function.

INTRODUCTION

Environmental pollution is considered as one of man's greatest crimes against himself. Pollution of the ecosystem with industrial, agricultural and sewage effluents results in contamination of air, food and water with some toxic agents such as heavy metals which constitute a major public hazards. Heavy metals are metallic element their density at least five times more than that of water. Pouls (2005) stated that not only high concentration of heavy metals produced a state of toxicity but also the low doses which accumulated in body tissues by time can reach the toxic concentration. Among the various heavy metals, cadmium is unique metal because of its low dosage toxicity, long biological half life and low rate of excretion from the body and its ability to be stored in tissues (Barbier et al., 2005).

Cadmium can accumulate in the body over many years because
the body hasn't a homeostatic mechanism to keep cadmium at constant level (Nasri, 2006).

There are many sources of cadmium pollution to aquatic compartment of the environment including mining companies which release their effluents into rivers, sewage, sludge applied to land and phosphate fertilizers (Masson et al., 1994 and Nogawa et al., 2004).

Cadmium is well known to damage various organs and tissues, specially liver, kidneys, lungs, testis and bone in human and animals (WHO, 1992 and Broska et al., 2003). Some studies were recorded the effect of cadmium on thyroid gland (Gupta and Kar 1999; Pilet et al., 2002 and Pilet et al., 2004).

Thyroid gland is an endocrine gland, its follicular and parafollicular cell synthesize and secret important regulatory hormones such as thyroxine (T4) and triiodothyronine (T3) which are synthe-sized in the follicular cells, theses hormones are necessary to increase the metabolism of most cell, (stimulating growth via induction of DNA transplant, which results in greater activity in cell synthesize, oxidative phosphorylation and membrane transport of electrolyte) (Dieter and Joann, 1998). Also, parafollicular cells secrete calcitonine through connective tissues that plays an important role in regulation of calcium and phosphorous metabolism (Swoucki, 1995 and Sakare et al., 2000).

Cadmium accumulated in the mitochondria of thyroid follicular epithelial cells and inhibited the synthesis and release of thyroid hormones (Yoshizuka et al., 1996). Moreover, Cadmium appears to be the large single contributar to auto-immune thyroid disease (Gupta and Kar 1999).

The present study aimed to evaluate the effect of chronic cadmium exposure and withdrawal period on the function of thyroid gland.

MATERIALS AND METHODS

Cadmium chloride: Cadmium chloride (CdCl₂ 2.5 H₂O) was obtained from Winlab, England.

Animals: Forty five adult male albino rats with an average body weight 170-200 g. were used in this study. They were kept for two weeks for accommodation and observation before starting the experiment. The experimental animals were kept under hygienic conditions ( temperature 25 C , day light 12 hr.) and fed on a well balanced ration.

The experimental Design: The animals were divided into
three equal groups. The first group (G1) was kept without any treatment and served as a control. The second and third groups were given cadmium chloride daily doses of 0.55 (G2), 2.19 (G3) mg/L in drinking water representative 1/160 and 1/40 LD_{50} of cadmium chloride, respectively according to Mahmoud (1999). For three months. All groups were left without treatment for 6 weeks as withdrawal period.

*Samples:

Samples were collected after 6, 12 and 18 weeks from the beginning of the experiment. Five animals were weighted (5 from each group) and blood samples were collected via retro-orbital venous plexus in dry clean test tube to separate serum for cadmium residue assay, biochemical and hormonal analysis, Then sacrificed rats.

*Serum analysis:

The serum was used for measuring the levels of cadmium residue according to Meret and Henkin (1971) by using Atomic Absorption (Unicom 969)

Serum thyroxine, triiodothyronin and thyroid stimulating hormone were carried out by radioimmunoassay method according to Britton et al. (1975).

Estimation of serum albumin was done according to Drupt (1974), cholesterol was estimated according to Henry et al., (1974) calcium was determined according to Qundler and Kin (1972) and inorganic phosphorous was determined according to Goldenberg (1966).

*Statistical analysis:

The obtained data was statistically analyzed by student t-test according to Snedecor (1993).

RESULTS

Table (1) showed the body weight (g) of rats after administration of (0.55 and 2.19 mg/L.) cadmium chloride in drinking water. The results revealed a significant decrease in all animals weight throughout the experiment in comparison with the control group.

The residue of cadmium chloride (Table, 2) in serum of group two and three were significantly increased when compared to control group.

Table (3) showed a marked increase in the levels of TSH, T3 and T4 hormones of both treated groups all over the experimental period with slight modulation after the withdrawal period in rats of both treated groups.

Table (4) showed a significant decrease in all animals weight, calcium and inorganic phosphorus, while total cholesterol
showed a significant increase in treated group after 6 and 12 weeks of treatment. The previous results persist the same with slight modulation after the withdrawal period in groups (G2 & G3) if compared with control one.

Table (1): Effect of cadmium chloride on average body weight of rats (g.) during the experimental period. (Mean and ± S.E)

<table>
<thead>
<tr>
<th>Time Groups</th>
<th>0 ± S.E</th>
<th>6 ± S.E</th>
<th>12 ± S.E</th>
<th>6 weeks (withdrawal period) ± S.E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (G1)</td>
<td>180.17 ± 13.82</td>
<td>260 ± 10</td>
<td>320 ± 7.07</td>
<td>390 ± 3.71</td>
</tr>
<tr>
<td>0.55 mg/L cadmium chloride (G2)</td>
<td>183 ± 11.50</td>
<td>230 ± 11.83</td>
<td>260* ± 7.07</td>
<td>320* ± 8.60</td>
</tr>
<tr>
<td>2.19 mg/L cadmium chloride (G3)</td>
<td>185.42 ± 12.10</td>
<td>210* ± 10.95</td>
<td>230* ± 12.24</td>
<td>310* ± 6.32</td>
</tr>
</tbody>
</table>

Table (2): Serum cadmium residues (µg/L) of control and treated rats during the experimental period (Mean and ± S.E)

<table>
<thead>
<tr>
<th>Time Groups</th>
<th>6 weeks of treatment</th>
<th>12 weeks of treatment</th>
<th>6 weeks (withdrawal period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (G1)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>0.55 mg/L cadmium chloride (G2)</td>
<td>1.38* ± 0.06</td>
<td>1.85* ± 0.05</td>
<td>1.21* ± 0.07</td>
</tr>
<tr>
<td>2.19 mg/L cadmium chloride (G3)</td>
<td>1.81* ± 0.02</td>
<td>2.54* ± 0.09</td>
<td>1.82* ± 0.03</td>
</tr>
</tbody>
</table>

* Significant at P ≤ 0.05.
DISCUSSION

Metals are a ubiquitous class of agents both in the natural environment and in workplace. There are numerous natural and artificial forms of metals. The common occurrence of metals in the human environment is dictated by both their wide natural distribution and their intensive use in ever growing numbers of industrial processes (Friberg and Nordberg, 1986).

Cadmium is one of many metals that are not physiologically or biochemically essential to organisms. This element is extremely dangerous as it is easily absorbed and remains in tissues for a long time. Long exposure to high or low doses of cadmium may cause biochemical and functional changes in some critical organs (Grosicki and Kowalski, 2002).

Cadmium appears to be the largest single contributor to autoimmune thyroid disease. It is very powerful and toxic metal which seems to be placed at the thyroid target, not only does cadmium appear to play a very pivotal role in thyroid disease, but also it is the very unique mineral, it is extremely toxic and has toxic biological effects at concentrations smaller than almost any commonly found mineral (Goyer et al., 1995).

Cadmium atoms combined with selenium atoms and are excreted out of the body via bile when selenium depleted by cadmium cause reduction in 5-deiodinase enzymes in liver and kidneys which convert thyroxin (T4) to triiodothyronin (T3) resulting hypothyroidism, also the decrease in selenium leads to reduction in glutathione peroxidase which is one of the body antioxidants, that leads to increase level of reactive oxygen and hydrogen peroxide, which damage thyroid gland (Ghosh and Bhattacharya, 1992). The present studies approach from effect of cadmium chloride on function of thyroid gland of rats. Rats received cadmium chloride (0.55 mg/ L G2, 2.19 mg/L G3) for 6-12 weeks showed significant decrease in their body weight, this findings are in accordance with that recorded by Massanyi and Uhrin (1996), Grosicki and Kowalski (2002) and Randa (2006).

Concerning to level of cadmium residues in the serum of all animals after 6-12 weeks from exposure to cadmium chloride revealed highly significant increase, this results are parallel to those obtained by Lansdown and Sampson (1996) who explained the fact that cadmium chloride has an accumulative effect (Pouls, 2005).
This work was conducted to assess the influence of chronic intoxication of cadmium on the function of thyroid gland. It was evaluated by measuring the serum thyroid hormones such as triiodothyronin (T₃), thyroxine (T₄) and the pituitary hormone (TSH). Our studies revealed significant decrease in (T₃), (T₄) and (TSH) in both groups of rats exposed to cadmium chloride for 6-12 weeks, this observation draw a convincing support from the work of Yoshida et al., (1987); Tanaka et al. (1991) and Marcikiewicz et al. (2003). Paier et al. (1993) suggested that cadmium (Cd) interferes with thyroid function at the glandular level as well as at the peripheral level by inhibiting conversion of T₄ to T₃. Gupta et al. (1997) recorded that cadmium prevents the elevation of TSH to correct the decrease of T₄ and T₃ levels. Pavia et al. (1997) reported that lack of significant response of TSH to decreased serum T₃ and T₄ may be due to Cd interference with pituitary regulation of thyroid hormones production and secretion, also the accumulation of cadmium in the mitochondria of thyroid follicular epithelial cells might be disturb the oxidative phosphorylation of this organelle and loss its energy supply caused inhibition of synthesis and release of thyroid hormones. Kelly (2000) recorded that changes in serum concentration of thyroid hormones can reflect disturbance in their glandular synthesis by lowering secretion as well as disorder in their extrathyroidal peripheral metabolism in the peripheral tissues by (deiodination, conjugation, deamination and decarboxylation) which was affected by cadmium exposure due to its cell injury effect. Moreover, Yousif and Asma (2009) recorded inhibition in the production of thyroid hormones in the presence of Cd. This indicate that animals exposed to cadmium may be at risk of thyroid damage (primary and secondary hypothyroidism).

Concerning to biochemical analysis albumin level showed significant decrease in all rats received Cd for 6-12 weeks, this result similar to those obtained by Zeinab (2004) and Randa (2006). Henery (2001) recorded hypothyroidism associated with low serum albumin. Cadmium induces increased excretion of both low and high molecular weight proteins by increases the urinary concentrations of low molecular weight proteins (B₂ microglobulin) and induced defect in reabsorption by proximal tubules, while the high molecular weight proteins may be filtered at the glomerulus and then incompletely reabsorbed in proximal tubules (Jarupt et al., 1993).

Regarding to level of cholesterol was recorded a significant in-
crease in rats treated with cadmium chloride in drinking water. The same results were previously reported by Coles (1986). The level of serum cholesterol is affected by thyroid activity and varies inversely with the degree of its activity. Moreover, Kaneko (1989) recorded definitive laboratory findings in hypothyroidism animals that revealed low T₄ and/or T₃ levels with little or no response of the TSH test. In initial screen, an increased in cholesterol is often the first clue to hypothyroidism. Also, Mary (2003) mentioned that hypothyroidism is the most common secondary cause of high cholesterol level in blood.

In this study, serum calcium levels showed a significant decrease in treated groups of rats G2 & G3 after 6-12 weeks of exposure to cadmium chloride, nearly the same results were obtained by Marcinkiewicz et al. (2003). This result may be attributed to calcium bound with plasma protein mainly albumin, therefore calcium is in a direct proportion with albumin, this confirmed in our results, the fine control of calcium depend on thyroid and parathyroid hormones which mainly affected by exposure of cadmium. Also cadmium induced renal tubular dysfunction leads to increased urinary excretion of calcium and phosphorous, Fledman et al. (1973) added to inhibition of activation of vitamin D in kidney leads to decreased synthesis of calcium binding protein in the intestinal mucosa and decreased intestinal absorption of calcium. The previous results disagree with that of Mahmoud et al. (2007) who recorded an increase in serum calcium level of rats received cadmium chloride, Marcinkiewicz et al. (2003) reported the degree of hypocalcemia was proportional to the dose of cadmium used and duration of exposure. Concerning to serum phosphorus levels in G2 & G3 after 6–12 weeks from exposure to cadmium revealed a significant decrease. This results anaemia harmony with the results obtained by Pavia et al. (1997) recorded hypophosphatemia in animals received cadmium, this hypophosphatemia may be due to action of parathyroid hormones which is phosphorus diuresis or due to renal tubular dysfunction.

Regarding to withdrawal period the weight, hormonal and biochemical analysis revealed slight modulation or no improvement in the affected parameters in comparison to control group.

In conclusion, exposure to cadmium has been shown to have a toxic effects on the function of thyroid gland and on some metabolic disorders parameters. Thus, it is recommended that industries
producing cadmium must be associated with appropriate methods of waste disposal to minimize the hazardous effects of heavy metals generally and cadmium specially.

REFERENCES


Massanyi, P. and Uhrin, V. (1996): "Growth of rabbits after a per oral administration of cadmium and its distribu-


97-104.
تأثير الكادميوم كلوريد على وظيفة الغدة الدرقية في الفنران

زينب يوسف محمد ، هبة الغريب حمزة
قسم الباثولوجيا – معهد بحوث صحة الحيوان - الدقى

- مقبول للنشر بتاريخ 11/11/2008

الملخص العربي

اجنحت هذه الدراسة على خمس وأربعون فئران (ذكور بالغين) وذلك لدراسة التأثير السمي للكادميوم على وظائف الغدة الدرقية، وقد قسمت إلى ثلاثة مجموعات متساوية الأولى استخدمت كمجموعة ضابطة والثانية والثالثة جرعت كلوريد الكادميوم لمدة 12 أسبوع بجرعات 1/255، 1/219، 1/275 ملجرام/كجم /لتر على التوالي في مياه الشرب وهي تتعادل 1/160، 1/400 من الجرعة النصف مميتة، وقد تركت الحيوانات لمدة 6 أسابيع دون تجريب (فترة سحب الجرعة).

وقد أخذت العينات بعد 6، 12، 18 أسبوع من بداية التجربة، وقد استمرت النتائج بعد تحليلها إحصائيا على حدوث نقص معنوي في الوزن في كلا المجموعتين المعالجين، بينما حدثت زيادة معنوية في مستويات الكادميوم في سيرم الدم لكلا المجموعتين المعالجين و استمرت حتى بعد فترة سحب الجرعة مع حدوث تحسن طفيف.

وقد وجد نقص معنوي في هرمونات الغدة الدرقية (TSH، T3، T4) طوال التجربة في المجموعتين الثانية والثالثة مع تحسن بسيط خلال فترة سحب الجرعة. وكذلك وجد نقص معنوي في كل من الألوستيرون وال كالستيرون والفسفور، بينما وجد زيادة معنوية في الكولسترول طوال التربة في كلا المجموعتين المعالجين.

وقد أوضحت الدراسة مدى التأثير السمي للكادميوم على وظائف الغدة الدرقية مع استمرارها حتى بعد توقف التعرض للكادميوم.

المحاكم:

استاذ الفسيولوجيا – كلية الطب البطري – جامعة القاهرة
أ.د. هدى حاتم

استاذ الكيمياء – معهد بحوث صحة الحيوان - الدقى
أ.د. هاني حلمي حليم