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ORIGINAL ARTICLE

Anti-Thyroid Effect of High Aluminum Intake in Rats

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Patients with chronic renal failure have abnormal thyroid function and higher levels of serum aluminum. In recent years, the toxicity of Al in human and animals has been a matter of concern. In this study the effect of high aluminum intake in the diet has been investigated in rats.

Materials and Methods: Aluminum (1620 mg/kg of the diet as aluminum chloride) was added to the diet of Wistar rats for 40 days. At the end of this period serum aluminum, T_4 and TSH concentrations were measured. Aluminum was determined by atomic absorption spectrometry and the hormones were assayed using commercially available kits.

Results: Serum aluminum concentration of the test rats (6.3±.1 µg/L) was not significantly different from controls (6.6±.4 µg/L). Serum T_3 concentration in animals consuming a diet with high aluminum content (138±8 ng/dL) was not significantly different from the control animals (146±7 ng/dL). Serum T_3, T_4 concentration of the test animals (3.0±0.3 µg/dL) was significantly lower than control animals (4.7±0.5 µg/dL, $p<0.05$). Thyrotropin concentrations were not significantly different.

Conclusion: The results of this study indicate that high aluminum intake in rats can disturb thyroid function and possible adverse effect(s) of the element need to be considered and fully investigated in subjects in close contact with high amounts

Key Words: Aluminum, Thyroid, Calcium Channel Blocker, Rat

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Introduction

Aluminum (Al) is the most abundant element in the earth's crust, comprising about 8% of it.[1] Aluminum enters the body through different routes[2] and its concentration in the serum of healthy subjects is very low.[3] It is poorly absorbed through the gastrointestinal tract[4] and the physiological role of the element has not yet been established.[5] In recent years toxicity of aluminum has been a matter of concern. Serum aluminum concentration in patients with chronic renal failure is high[6] and some of the impairments in these patients such as dementia,[6] anemia,[7,8] osteoporosis,[9] and abnormalities of thyroid function[10] have been related to high concentrations of the element.

Thyrotropin releasing hormone release,[11] its effect[12,13] and effects of thyroid stimulating hormone on thyroid cells[14] are dependent on extracellular calcium concentration. On

the other hand, the calcium channel blocking effect of aluminum has been well established.[15-17] In this study the effect of chronic orally administered aluminum on thyroid function has been tested on rats.

Materials and Methods

The study was carried out on male N-MRI rats weighing 180-250 gr. The animals, obtained from the Razi institute, were kept under standard conditions (12:12 hours cycle, Tem. 24±2 °C with free access to food and tap water). Animals in the control group (n = 12) consumed ordinary diets (purchased from a local producer, Shoshtar animal food production Co.), while animals in the test group (n =13) received similar food containing 1620 mg/kg of aluminum as aluminum chloride for 40 days.[18] At the end of this period, animals were anesthetized with 50 mg/kg of sodium thiopental (Pharmacia, Sweden) and the abdomen was opened. Two 2.5 ml samples of blood were obtained through abdominal aorta and centrifuged; sera were separated and kept at -20°c until the time of the assay. Aluminum concentration of the serum samples was determined using flameless atomic absorption spectrometry (AAS, 5EA, Carl Zaiss, Germany) with a recovery value of 93±8% and intra-assay coefficient variation of 9±2%. Detection limit for aluminum assay was 1 μg/L. Serum total thyroxin (TT_4), total tri-iodothyronin (TT_3) and thyroid stimulating hormone (TSH) concentrations were assayed with radioimmunoassay kits purchased from local supplier (Kavoshiar Co.-Iran) each in a single batch assay. Sensitivities of the assays for TT_4, TT_3 and TSH (IRMA) were 0.4 ug/dL, 5ng/dL and 0.02 mIU/L, respectively. Mean±SE of the data were compared using student t-test and P values less than 0.05 were considered significant.

Results

Mean the serum aluminum concentration of the test rats (6.3±0.1μg/L) was not significantly different from that of the control animals (6.6±0.4 μg/L) (Fig. 1). In animals consuming diets with high aluminum content, serum TT_3 concentration (138±8 ng/dL) was not significantly lower than that of control animals (146±7 ng/dL).

Mean serum TT_4 concentrations of the test animals (3.0±0.3 μg/dL) was significantly lower than that of control animals (4.7±0.5

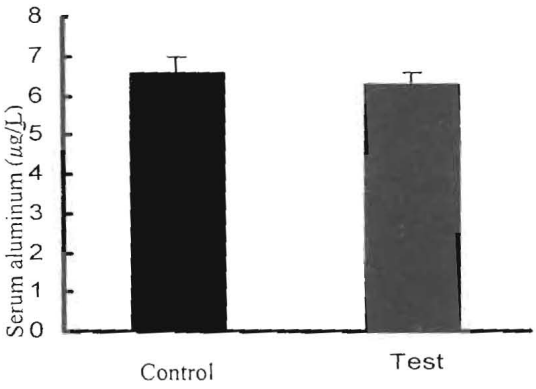

Fig. 1. Serum aluminum concentration in controls (n= 12) and rats with high aluminum intake (n=13)

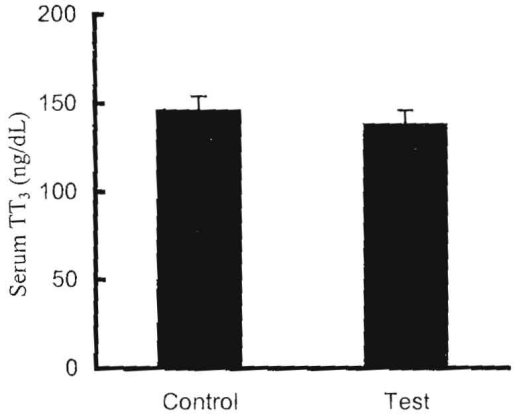

Fig. 2. Serum T_3 concentration in controls (n=12) and rats with high aluminuim intake (n=13)

μg/dL) (Fig. 3). Thyrotropin concentrations were not statistically different (Fig. 4).

The weights of the animals in the groups were not significantly different at the beginning of the study and did not change insignificant until the end (225±5 for the controls versus 234±7 gr for the test animals).

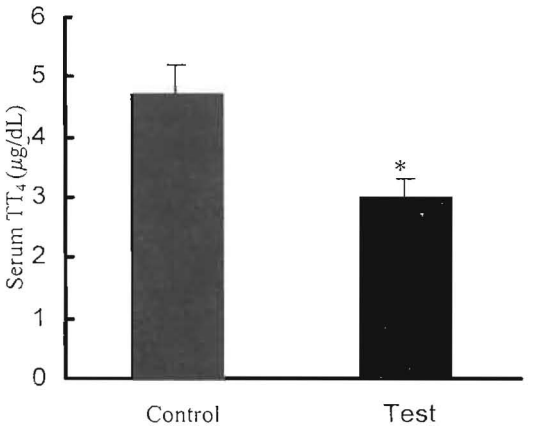

Fig. 3. Serum T_4 concentration in controls (n=12) and rats with high aluminum intake (n=13) * P<0.05

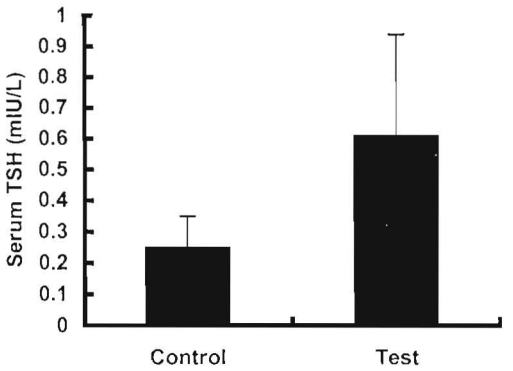

Fig. 4. Serum TSH concentration in controls and rats with high aluminum intake

Discussion

The results of this study show that high oral aluminum intake induces hypothyroidism in rats. Lack of similar studies on the effect of aluminum on thyroid makes it difficult to compare the results. However, the effects of calcium channel blockers have been investigated in vitro and in vivo. In a study on healthy human subjects, orally administered nifedipine did not alter thyroid function.[19] It should be noted that in the study mentioned, the blocker was administered only for one week and this period may not be sufficient to alter plasma TT_3 and T_4 concentration, In another study, it has been shown that TRH under normal physiological conditions, appears to cause mobilization of intracellular calcium and induces influx of extracellular Ca^{2+} on thyrotrope cells. Presence of the calcium channel blocker verapamil could reduce calcium influx in vitro.[20] It has been suggested that TRH uses both intracellular calcium stores and extra cellular calcium through voltage-dependent calcium channels to increase intracellular calcium concentration causing TSH secretion.[21] Release of TRH as a neurohormone, too, depends on extracellular calcium.[22] Aluminum is a potent calcium channel blocker[15-17] and therefore it is expected to inhibit both TRH and TSH release. In fact, this effect has been reflected in this study as a low T_4 concentration (Fig. 1) and not increased TSH concentration (Fig. 2). This inhibitory effect of aluminum also shown in the rat, may explain at least in part the thyroid dysfunction seen in patients with chronic renal failure.[23] These patients have high aluminum concentrations in their serum.[24]

Although TSH concentrations of the test animals did not change significantly, there was a general increase in the test animals (Fig. 4). Thyrotropin concentration in this study should be considered carefully because of the high variation of the hormone between individual samples. Also, it must be mentioned that the kit which was used in this study was for human TSH assay and the exact cross-reactivity of the kit was not determined. Comparing, however, the results of the assay for the control animals with those

of another study,[25] it appears that the antibody of the kit has been able to recognize the hormone to a certain extent.

Plasma aluminum concentration did not increase in the test group despite high aluminum intake in the diet. This might be due to the fact that the element was added to the diet and naturally would be consumed gradually. The absorption of the element through gastrointestinal tract is poor[3] and the changes of the serum aluminum concentration after oral administration of the element have been a matter of controversy. Some reports indicate that after oral administration, aluminum concentration in the serum increases significantly.[22,23] However, it also has been suggested that when the renal function is normal, the element may not accumulate in the serum even when administered orally.[24] A report states that the plasma concentrations of the aluminum-exposed workers hardly differ from those of the control group and they have concluded that aluminum in plasma could not be used as an indicator of daily exposure.[26] The effect might be exerted through accumulation of the element in the thyroid and pituitary glands. Although there is evidence of different levels of uptake by different tissues,[27,28] in this study aluminum contents of the tissues from control and test animals were not compared.

Some studies have shown that in those patients who receive aluminum hydroxide as antiacid and levothyroxine simultaneously, levothyroxine absorption is significantly decreased while serum TSH concentration increases significantly.[29-30] Although similar studies have not been carried out in rats, one can assume that high aluminum in the diet may interfere with the enterohepatic cycle of the thyroid hormones. This possible effect remains to be clarified.

The present results cannot be explained with general toxic effect of aluminum because firstly, the administered amount is far less than the toxic level,[28] and secondly, the weight of the animals demonstrate their well being during the test period.

From the results of this study it is possible to conclude that exposure to aluminum can disturb pituitary-thyroid function in rats. Possible adverse effects of the element on neuroendocrine systems need further investigation and studies.

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