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Original Research

Thyroid and Parathyroid Function and Structure in Male Rats Chronically Exposed to Cadmium

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Abstract

The effect of exposure to cadmium (Cd) on the function and structure of the thyroid with parathyroids and a relationship between Cd accumulation in these glands and their damage were studied on a male rat model corresponding to human exposure. For this purpose, male rats were treated with Cd in drinking water at concentration of 5 and 50 mg Cd/dm^3 for 12 and 24 weeks. The function of the thyroid was evaluated based on the measurement of serum concentrations of triiodothyronine (T_3) and tetraiodothyronine (T_4), and immunohistochemical identification of hormones such as calcitonin (CT), calcitonin-gene related peptide (CGRP) and somatostatin (ST). To assess the parathyroid function immunohistochemical reaction for parathyroid hormone-related peptide (PTHrP) was performed. Histological structure of the thyroid and parathyroid glands was evaluated in a light microscope.

Rats exposed to 5 and 50 mg Cd/dm^3 showed changes in the epithelium of follicular cells, intensified remodeling of the glandular structure of the thyroid, mononuclear cell infiltrations in connective tissue and pale staining of colloid. Hypertrophy and hyperplasia of endocrine parathyroid cells were evident. The intensity of reactions for CT, ST, CGRP and PTHrP was weakened. Exposure to Cd had no effect on the T_3 and T_4 serum concentrations, except for a marked increase in the concentrations of both hormones after 24 weeks of exposure to 50 mg Cd/dm^3. All the Cd-induced changes were much more advanced at exposure to 50 mg Cd/dm^3 than 5 mg Cd/dm^3.

The seriously disturbed structure and function of the thyroid and parathyroids at a low Cd concentration (0.087 ± 0.005 μg/g) in these glands suggests that the damaging Cd influence may be due to its indirect rather than direct action. Based on the results it can be hypothesized that a human body chronically exposed to moderate and relatively high Cd levels may be at risk of damage to the thyroid and parathyroid glands.

Keywords: cadmium, thyroid, parathyroids, structure, function, rat

Introduction

Cadmium (Cd) has been recognized as one of the most toxic environmental and occupational pollutants [1, 2]. The adverse effects of exposure to this metal in humans and experimental animals have been widely studied and reported, but in spite of many investigations not all effects and mechanisms of the action are completely understood and thus need further investigation.

Chronic, even relatively low, exposure to Cd poses a health threat. Cd damages various organs and systems, mainly the kidney and the skeleton [1-10]. The available literature data [5, 11-15] and our own findings [16-18] indicate that Cd may also damage the thyroid and parathyroids.

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Due to an important role of thyroid and parathyroids in the regulation of calcium and phosphate balance and bone metabolism, Cd influence on these glands has been taken into account as a possible mechanism of the damaging Cd action on bone [3, 4, 8, 13]. Thyroid parafollicular cells (C cells) via calcitonin (CT) secretion and parathyroid gland via parathormone (PTH) secretion are involved in the regulation of bone metabolism [19, 20]. Moreover, synthesis and secretion of regulatory thyroid hormones such as triiodothyronine (T_3) and tetraiodothyronine (T_4) take place in the C cells [21]. However, in spite of the important endocrine function of the thyroid and parathyroids, the effect of Cd on both glands has not been successfully studied. The available data are only fragmentary and often refer to relatively high Cd exposure [5, 11-15]. There are no comprehensive studies simultaneously evaluating the structure and function of both glands under the exposure corresponding to that observed in human life. The mechanisms of Cd impact on the thyroid and parathyroids and the risk of their damage at low and moderate chronic exposures as well as body burden of Cd at which the impact occurs are unknown. There is still too little knowledge on Cd accumulation in the thyroid and parathyroids and its relationship with damage to these glands.

Therefore, we have undertaken wide experimental studies on a male and female rat model of human exposure to assess the effect of Cd on the thyroid and parathyroid status [16-18]. In the current research, we evaluated the effect of repeated moderate and relatively high Cd exposures on the function and structure of the thyroid and parathyroids, and Cd accumulation in these glands in male rats. Our special attention was focused on the expansion of the damaging Cd influence with the duration and intensity of exposure. Moreover, we made an effort to estimate the critical Cd concentration in the thyroid with parathyroids and the relationship between Cd accumulation in these glands and their damage. According to our knowledge such a study has not been conducted until now.

Materials and Methods

Animals and Experimental Protocol

We used forty-two adult (2-month-old) male Wistar rats (180–200 g b.wt.) in our study. The animals were housed under controlled conditions (22 ± 1°C, relative humidity of 50 ± 10% and 12/12 h light/dark cycle). They were allowed free access to drinking water and a standard rat chow (LSM dry diet; Motycz, Poland). The rats were randomly allocated to three experimental groups of 14 animals each. Two groups received an aqueous solution of $CdCl_2$ (POCh, Gliwice, Poland) at a concentration of 5 or 50 mg Cd/dm^3 as the only drinking fluid. The third group drank water uncontaminated with Cd and served as control. The mean daily Cd intake during the experiment, calculated based on the 24-hour drinking water consumption, is presented in Fig. 1. The experimental model has been reported in details elsewhere [6]. The treatment with 5 mg Cd/dm^3 reflects exposure occurring in subjects inhabiting moderately polluted areas and cigarette smokers, whereas the administration of 50 mg Cd/dm^3 may be tantamount to environmental exposure in heavily contaminated areas or occupational exposure [6-8, 22]. There were no clinical symptoms of Cd toxicity at the used levels of exposure; however, biochemical and histopathological studies have revealed damage to the kidney and disorders in bioelement metabolism [6, 23].

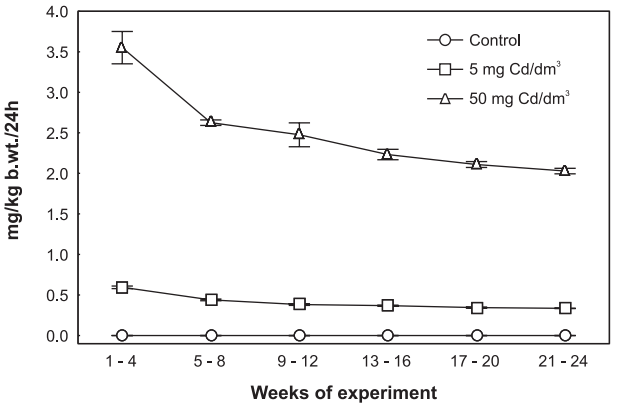

Fig. 1. Cadmium (Cd) intake in male rats. Each point represents mean ± SE Cd intake during four consecutive weeks of the experiment. The calculations were done for 14 animals during first 12 weeks, and for 7 animals from 13th to 24th week. Cd intake in drinking water of control rats was negligible and has been assumed to be 0. At each time point, Cd intake in the rats drinking water containing 5 mg Cd/dm^3 was statistically significantly ($P < 0.001$) lower than in those exposed to 50 mg Cd/dm^3.

Seven rats from each group, after overnight fasting, were sacrificed under intraperitoneal barbiturate anaesthesia (Vetbutal, 30 mg/kg b.wt.; Biowet, Puławy, Poland) after 12 weeks, while the remaining animals – after 24 weeks of the experiment. Blood from the heart (with and without anticoagulant) and thyroid with parathyroids were collected. In a rat, the parathyroids are situated inside the thyroid gland and they are always present, even though invisible, in the dissected thyroid (or one of its lobes). Thus, it is impossible to separate these glands without damage to their structure.

The whole blood and one thyroid lobe with parathyroids were assigned for Cd analysis, whereas T_3 and T_4 were determined in the serum. The second thyroid lobe with parathyroids was used for morphological and immunohistochemical examinations. The biological material not used immediately after sampling was frozen at -20 °C until further analysis.

The experiment was approved by the Local Ethics Committee for Animal Experiments in Białystok (Poland) for care and use of laboratory animals.

Analytical Procedures

The samples of whole blood collected in heparinized tubes were wet-digested with trace-pure concentrated nitric acid (69% HNO_3; Merck, Germany). One thyroid lobe with parathyroids from each rat, after weighing, was dry mineralized in an electric oven at 450°C and the ash was dissolved in 1 M HNO_3. Cd concentration in such preparations was determined by flameless atomic absorption spectrometry method (Z-5000, HITACHI, Japan) with electrothermal atomization in a graphite cuvette as reported elsewhere [6, 7]. Atomic absorption standard solution of Cd (Sigma, USA) and ultra pure water (Milli-Q water purification system; Millipore USA) were used in the analysis. Internal quality control was employed to keep the measurement process reliable.

Since the thyroid and parathyroids were weighed and mineralized together, the determined Cd level reflects its mean concentration in these glands.

T_3 and T_4 concentrations in the serum were determined radioimmunologically, using commercially available kits (POLATOM; Otwock-Świerk, Poland). A mini-gamma spectrophotometer (LKB WALLAC, Turku, Finland) was employed. All assays were performed in duplicate.

The thyroid lobes with parathyroids were fixed in Bouin's fluid at room temperature for 24 hours, embedded in paraffin, sectioned at 5 μm and routinely stained with hematoxylin and eosin (H+E). Such treatment is useful in distinguishing the thyroid and parathyroids, and allows evaluation of the histological structure of each of these glands individually. The structure of the thyroid and parathyroid glands was evaluated in a light microscope (NIKON ECLIPSE E 400, USA). The immunohistochemical reactions for hormones such as CT, calcitonin-gene related peptide (CGRP), somatostatin (ST) and parathyroid hormone-related peptide (PTHrP) were performed on paraffin slices using specific antibodies (human CT, Dako; rat CGRP, Sigma; human ST, Dako and mouse PTHrP, Calbiochem). The Labelled Streptavidin Biotin (LSAB) method was used to identify CT, ST and CGRP [24], whereas to determine PTHrP the Avidin-Biotin-Peroxidase Complex (ABC) technique was performed [25]. The intensity of the immunohistochemical reactions depends on the number of the secretory granules showing positive reaction for the identified hormone and it was estimated visually in the light microscope using the scale from + to +++.

Statistical Analysis

Statistical analysis was conducted by one-way analysis of variance (ANOVA) using the Kruskal-Wallis ranks test. Sperman correlation analysis was performed to investigate the relationship between some of the variables measured. P values < 0.05 were considered statistically significant.

Results

Thyroid with Parathyroids – Gross Findings and Weight

There were no changes in the gross findings in the thyroid with parathyroids in the rats exposed to 5 and 50 mg Cd/dm^3 for up to 24 weeks.

In the animals treated with 5 mg Cd/dm^3, the absolute weight and relative weight (weight expressed as a percentage of body weight) of the thyroid with parathyroids remained unchanged except for a clear increasing tendency of both variables after 12 weeks of the experiment; however, due to a wide range of values the differences did not reach statistical significance (Table 1). At higher

Table 1. Absolute and relative thyroid with parathyroids weight, and cadmium (Cd) concentration in the thyroid with parathyroids and blood of control and Cd-exposed male rats.

Group	Thyroid with parathyroids weight		Cd concentration	
	Absolute weight (mg)	Relative weight x10^{-6} (mg/100 g b.wt.)	Thyroid with parathyroids (μg/g)	Blood (μg/dm^3)
12 weeks				
Control	15.843 ± 0.967	3.789 ± 0.257	0.057 ± 0.007	0.767 ± 0.089
5 mg Cd/dm^3	20.086 ± 1.696	5.037 ± 0.429‡	0.087 ± 0.005***	2.370 ± 0.257**
50 mg Cd/dm^3	19.171 ± 1.059*	5.256 ± 0.225**	0.426 ± 0.044$^{***\,\dagger}$	16.27 ± 1.04$^{***\,\dagger}$
24 weeks				
Control	14.643 ± 2.089	2.964 ± 0.373	0.075 ± 0.010	0.626 ± 0.054
5 mg Cd/dm^3	15.229 ± 1.298	3.251 ± 0.278	0.192 ± 0.027***	1.970 ± 0.245***
50 mg Cd/dm^3	15.343 ± 1.608	3.263 ± 0.341	1.063 ± 0.141$^{***\,\dagger}$	13.59 ± 1.16$^{***\,\dagger}$

Data are mean ± SE of 7 animals in each group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$, $^{‡}P = 0.06$ vs. control, and $^{\dagger}P < 0.005$ vs. 5 mg Cd/dm^3 group.

exposure, an increase in both absolute and relative thyroid with parathyroids weight (by 21 and 39%, respectively) occurred after 12 weeks, but the effect was not further observed after 24 weeks of the experiment.

Cd Concentration in Blood and Thyroid with Parathyroids

The administration of Cd in drinking water resulted in an increase in the concentration of this heavy metal in the blood and its accumulation in the thyroid with parathyroids, depending on the time and level of exposure (Table 1). The blood Cd concentrations in the 5 and 50 mg Cd/dm^3 groups after 24 weeks of the experiment reached clearly lower numerical values of the mean than after 12 weeks; however, there were no statistically significant differences. There was a positive correlation between Cd concentration in the blood and its accumulation in the thyroid with parathyroids ($r = 0.7438$, $P < 0.0001$).

T_3 and T_4 Concentrations in Serum

The exposure to 5 mg Cd/dm^3 for 12 and 24 weeks had no effect on the serum concentrations of T_3 and T_4 (Fig. 2). The 12-week intoxication with 50 mg Cd/dm^3 had also no influence on the serum T_3 and T_4 concentrations; however, after 24 weeks of the exposure a marked increase in the serum T_3 and T_4 concentrations (by 30 and 48%, respectively) was noted (Fig. 2). The T_3/T_4 ratio in the serum remained unchanged by any treatment (Fig. 2).

Serum T_3 and T_4 concentrations correlated positively with Cd concentration in the thyroid with parathyroids ($r = 0.5652$, $P < 0.0001$ and $r = 0.6053$, $P < 0.0001$, respectively). There was also a positive correlation between the serum T_4 and the blood Cd concentration ($r = 0.4633$, $P < 0.005$) as well as between the serum concentrations of T_3 and T_4 ($r = 0.5582$, $P < 0.0005$).

Structure of the Thyroid and Parathyroid Glands

The proper structure of the thyroid and parathyroid glands was observed in all control male rats (Fig. 3). The morphological picture of these glands in the rats exposed to Cd differed compared to the control group (Table 2, Fig. 3).

In the thyroid of the rats exposed to 5 mg Cd/dm^3, follicles showed highly prismatic epithelium and light cytoplasm. Intensified remodeling of the glandular structure, mononuclear cell infiltrations in connective tissue and changes in the intensity of colloid staining (rarefied colloid and dense rift in places) were evident (Table 2, Fig. 3). In the rats exposed to 50 mg Cd/dm^3, the changes in the thyroid structure were of similar character as at the lower exposure, but they occurred in a greater number of thyroid fragments and were of higher intensity (Table 2, Fig. 3). At both levels of exposure to Cd all the changes observed in the morphological picture of the thyroid occurred already after 12 weeks of the experiment and most of them were found to progress with the duration of exposure (Table 2).

Hypertrophy and hyperplasia of the endocrine parathyroid cells in the rats exposed to 5 and 50 mg Cd/dm^3 were observed and the changes were more intensified at the higher dose (Table 2, Fig. 3). Hypertrophic endocrine parathyroid cells appeared in the whole peripheral zone, whereas hyperplasia was observed in some areas of the parathyroid gland (Fig. 3). In the rats exposed to 5 mg Cd/dm^3, the changes only slightly intensified with the exposure duration, whereas at the higher Cd treatment there was no difference in the escalation of the changes after 12 and 24 weeks of the experiment (Table 2, Fig. 3).

Immunohistochemical Reactions for CT, CGRP, ST and PTHrP

In the control rats, strong positive immunohistochemical reactions for CT and CGRP were noted in all thyroid

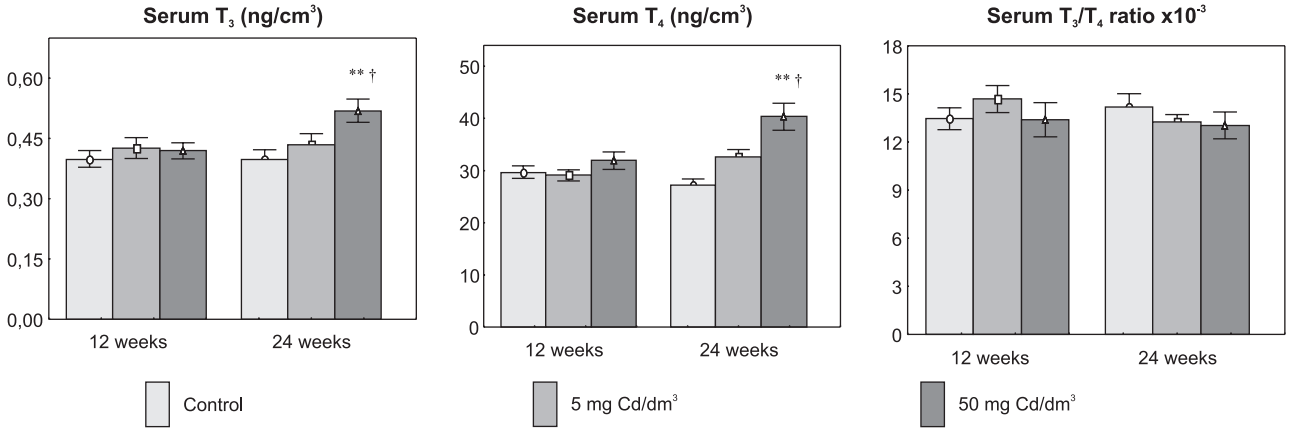

Fig. 2. Serum concentration of triiodothyronine (T_3) and tetraiodothyronine (T_4) and the ratio of T_3/T_4 in control and exposed to cadmium (Cd) male rats. Data are mean ± SE of 7 animals. $^{**}P < 0.01$ and $^{\dagger}P < 0.05$ vs. control and 5 mg Cd/dm^3 groups, respectively.

Table 2. Light microscopy findings in the structure of thyroid and parathyroid gland of male rats exposed to cadmium (Cd).

Findings	Weeks of exposure to Cd	Exposure to Cd							
		5 mg Cd/dm^3				50 mg Cd/dm^3			
		–	+–	+	++	–	+–	+	++
Thyroid gland[a]									
Follicles with highly prismatic epithelium; light cytoplasm in follicular cells	12	0[c]	0	0	7	0	0	0	7
	24	0	0	0	7	0	0	0	7
Remodeling of the thyroid glandular structure	12	0	5	2	0	0	2	5	0
	24	0	0	6	1	0	0	1	6
Mononuclear cell infiltrations in connective tissue	12	5	2	0	0	3	0	4	0
	24	4	3	0	0	4	0	0	3
Pale staining of colloid	12	0	5	2	0	0	0	5	2
	24	0	0	6	1	0	0	1	6
Parathyroids[b]									
Small, dark cells (hyperplasia)	12	5	2	0	0	0	2	5	0
	24	4	3	0	0	0	2	5	0
Enlarged, light endocrine cells (hypertrophy)	12	4	3	0	0	0	0	1	6
	24	3	4	0	0	0	0	1	6

[a] occurrence of the changes in the thyroid gland was marked as: – no lesion, +- sporadically, in some follicles, + in some fragments of the thyroid gland, ++ in many fragments of the gland; numerical values indicate the number of rats of each experimental group in which the change was observed

[b] occurrence of the changes in the parathyroid gland was marked as: – no lesion, +- sporadically observed on one of the poles of the gland, + in some fragments on the periphery of the gland, ++ on the whole periphery of the gland

[c] the number of rats with the findings

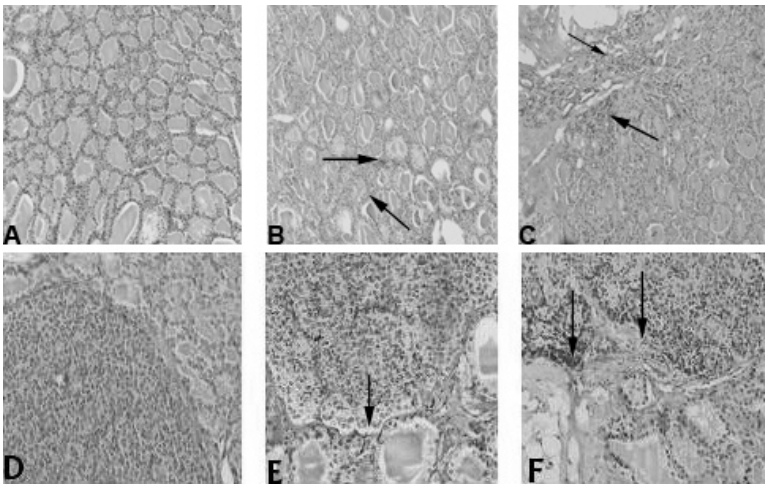

Fig. 3. Structure of the thyroid and parathyroid gland. A) The thyroid in the control group. Large follicles with dense colloid and cubic epithelium are evident. B) Group exposed to 5 mg Cd/dm^3 for 12 weeks. Remodeling of the thyroid glandular structure is sporadically found in some follicles. Rare mononuclear cell infiltrations, follicles with pale staining of colloid, dense rift colloid in some places are observed (*arrow*). C) Group exposed to 50 mg Cd/dm^3 for 24 weeks. Remodeling of the thyroid glandular structure and numerous mononuclear cell infiltrations are evident in some fragments of the thyroid gland (*barbed arrow*). H&E x 200. D) The parathyroid gland in the control group. Chief cells of the parathyroid gland with relatively dark acidophilic cytoplasm and small dark nuclei are observed. H&E x 200. E) Group exposed to 5 mg Cd/dm^3 for 12 weeks. Chief cells of the parathyroid gland with light cytoplasm and hypertrophic cells on the gland periphery are seen (*arrow*). F) Group exposed to 50 mg Cd/dm^3 for 24 weeks. The hypertrophic cells (*arrow*) and hyperplasia (*barbed arrow*) on the periphery of the gland are observed. H&E x 400.

Table 3. Immunohistochemical reactions in the thyroid C cells and chief cells of the parathyroid gland of control rats and those exposed to cadmium (Cd) for 12 and 24 weeks.

Group	Weeks of exposure to Cd	n	Thyroid C cells			Parathyroid
			CT	ST	CGRP	PTHrP
Control	12	7	+++a	+++b	+++b	+++c
	24	7	+++a	+++b	+++a	+++d
5 mg Cd/dm^3	12	7	++a	++b	++b	++c
	24	7	++a	++b	++a	++d
50 mg Cd/dm^3	12	7	+a	+b	+b	+c
	24	7	+a	+b	+a	+d

+++ – strong reaction (dark secretory granules in the cytoplasm), where +++a – in most C cells, +++b – in some C cells, and +++c – in one fragment of the parathyroid gland, +++d – in some fragments of the parathyroid gland; ++ – weaker reaction (light secretory granules in the cytoplasm) compared to the control, where ++a – weaker reaction in most C cells, ++b – weaker reaction in some C cells, ++c – weaker reaction in one fragment of the parathyroid gland, ++d – weaker reaction in some fragments of the parathyroid gland; + – markedly weaker reaction (very light secretory granules in the cytoplasm) compared to the control, where +a – weaker reaction in most C cells, +b – weaker reaction in some C cells, +c – weaker reaction in one fragment of the parathyroid gland, +d – weaker reaction in some fragments of the parathyroid gland; n – number of animals

C cells, whereas ST was identified only in some C cells (Table 3). In most of the parathyroid cells of the control rats strong positive reaction was noted for PTHrP. The exposure to 5 and 50 mg Cd/dm^3 for 12 and 24 weeks led to a weakening in the intensity of reactions for CT, ST, CGRP and PTHrP (Table 3). At the treatment with 50 mg Cd/dm^3, the reactions for CT, CGRP and PTHrP were more markedly weakened than at the 5 mg Cd/dm^3 (Table 3). The intensity of the reaction for ST in the Cd-exposed rats was attenuated only in some C cells. The analysis in light microscope revealed only a slight decrease in the intensity of the immunohistochemical reactions for CGRP and PTHrP with the duration of Cd exposure.

Discussion

Cd is a heavy metal characterized by strong cumulative properties in the living organisms [1, 2, 6, 23]. However, as it was noted in the present paper and in our previous study on female rats exposed to various Cd doses for 12 months [18], its accumulation in the thyroid with parathyroids is low. Since the Cd level determined in our study reflects its mean concentration in the thyroid with parathyroids it cannot be excluded that there exists a difference in the rate of Cd uptake and its retention between these two glands. However, the low mean Cd concentration in the thyroid with parathyroids seem to indicate that its accumulation in the thyroid as well as in parathyroids is low. The accumulation of Cd in these glands of male rats treated with 5 and 50 mg Cd/dm^3 was markedly lower than in their liver and kidney [6, 23], being the main sites of this metal storage in the organism [1, 2, 6, 23].

Despite low Cd accumulation in the thyroid with parathyroids, the exposure to both Cd levels resulted in numerous changes in the two endocrine glands, indicating their structural and functional damage. The effect of Cd on the thyroid with parathyroids was dose-dependent and intensified with the exposure duration. The positive correlations between T_3 and T_4 concentrations in the serum and Cd concentration in the thyroid with parathyroids as well as between Cd concentration in the endocrine glands and the blood confirm the relationship between the damaging Cd impact on the thyroid and parathyroids and the intensity of exposure and body burden of Cd.

Cd at both levels of exposure used in the current study had no influence on gross findings in the thyroid with parathyroids; however, after exposure to 50 mg Cd/dm^3 for 12 weeks an increase in their absolute and relative weight was noted. Hiratsuka et al. [13] also reported no changes in the macroscopic picture of the parathyroid in rats injected with 0.05 mg $CdCl_2$/kg body weight into the tail vein 5 days a week for 50 weeks, but they observed macroscopically enlarged parathyroid, and hypertrophy and hyperplasia of the chief cells of the parathyroid gland in the animals treated with 0.5 mg $CdCl_2$/kg body weight.

The enhanced remodeling of the glandular thyroid structure (follicular degradation and formation of new follicles) and mononuclear cell infiltrations indicate toxic Cd action in the thyroid follicular cells. The Cd-induced morphological changes in the thyroid may potentate with exposure duration leading to generalized damage to this gland and may contribute to disturbances in its function, including disorders in biosynthesis and secretion of hormones as well as hormone leakage through damaged cellular membranes.

In rats exposed to 5 mg Cd/dm^3, in which the prevalence and intensity of morphological changes were lower compared to rats exposed to 50 mg Cd/dm^3, there were no changes in the serum concentrations of T_3 and T_4. Comelekoglu et al. [5] also reported unchanged serum concentrations of T_3 and T_4, and free forms of these hormones (free T_3 and free T_4) in rats receiving intraperitoneal injections of 0.5 mg Cd/kg b.wt. three times a week for 18 weeks. In rats treated with 50 mg Cd/dm^3, having higher Cd accumulation in the thyroid with parathyroids and more marked morphological changes compared to lower Cd exposure, the serum concentrations of T_3 and T_4 increased. The highly prismatic epithelium, light cytoplasm and rarefied colloid in follicles indicate an enhanced secretory activity of the thyroid and this might be a cause of the increased serum T_4 concentration noted in rats exposed to 50 mg Cd/dm^3. The increase in serum T_3 concentration observed in those animals might be a consequence of the enhanced T_4 concentration which undergoes conversion into T_3 in peripheral tissues [11, 12]. The morphological picture of the thyroid follicles with a simultaneous increase in the serum concentrations of T_3 and T_4 at 50 mg Cd/dm^3 may suggest that relatively high chronic exposure to Cd leads to thyroid hyperactivity, i.e. to hyperthyroidism in male rats. However, further studies are needed to explain this action.

The morphological changes noted in male rats are comparable to those recently reported by us [18] in female rats chronically exposed to the same Cd concentrations. In both male and female rats treated with 5 mg Cd/dm^3 we observed morphological changes in the thyroid and parathyroids without any changes in the serum concentration of thyroid hormones. On the other hand, at 50 mg Cd/dm^3, structural changes in male and female rats were similar; however, in male rats the serum concentrations of T_3 and T_4 were enhanced, whereas in female rats [18] the concentration of T_4 decreased and that of T_3 was unchanged.

Weakening in the intensities of reactions for CT, CGRP and ST in the thyroid C cells and for PTHrP in the chief cells of the parathyroid of the Cd-exposed rats might result from enhanced secretion of these hormones and disorders in the regulatory action of the thyroid and parathyroid glands. The attenuated reaction for PTHrP together with increased serum PTH concentration in the male rats chronically exposed to 5 and 50 mg Cd/dm^3 (our previous finding) seems to indicate that Cd might stimulate this hormone secretion via the parathyroid gland.

The measurements performed in the current study have revealed that both the structure and function of the thyroid and parathyroids may be damaged at low Cd accumulation in these glands, reaching 0.087 ± 0.005 μg/g. Recently, we have reported that the threshold for Cd effects on the kidney may be close to 2.40 ± 0.15 μg/g [6]. These findings may suggest that the critical Cd concentration for thyroid with parathyroids may be lower than that for the kidney.

In conclusion, moderate (5 mg Cd/dm^3) and relatively high (50 mg Cd/dm^3) chronic exposure to Cd affects the structure and function of the thyroid and parathyroids in male rats. The effects occur at low Cd accumulation and potentate with the intensity and duration of exposure and body burden of Cd. Our observations on the male rat model seem to indicate that the critical Cd concentration for the thyroid with parathyroids may be lower that that for the kidney. Serious damage to the thyroid and parathyroids at low Cd concentration in these glands suggest that the damaging Cd influence may be caused by its indirect rather than direct action. The findings may have practical implications and thus need further investigation.

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