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Iodine concentration and signs of apoptosis in the thyroid and pituitary of female rats after different single doses of potassium iodide

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Objective. The aim of this work was to study the content of iodine as well as the expression of caspase 8 and caspase 32 in the thyroid and anterior pituitary in rats after a single dose of iodide.

Methods. A total of 49 inbred rat females weighing 250-300 g at the stage of diestrus and/or metestrus were used. Pituitaries and thyroids were dissected from 15 control rats and from the groups of 8 rats each given potassium iodide by gavage in doses of 1, 4, 8 and 25 μg/100 g at 48 h before sacrifice. In two rats of each group the level of iodine in thyroids and pituitaries was estimated in terms of weight percent of iodide in dry tissue (wt % I^{-2}/dry tissue) using the wavelength dispersive spectrometry (WDS) quantitative analysis. The expression of caspase 8 and caspase 32 in thyroids and pituitaries in terms of the percentage of positive immunostained area (% PA) was measured by streptavidin-biotin method using specific polyclonal antibodies.

Results. In the thyroids, iodine concentration increased after 1 μg/100 g, but decreased after 8 and 25 μg/100 g, while that in the pituitaries significantly increased after all doses of iodide with the peak after 8 mg/100 g. After the same iodide dose also the peak of caspase 32 and caspase 8 appeared in the pituitary. However, in the thyroid only increased caspase 32 was found together with a decrease of iodine concentration.

Conclusion. Several interrelations between iodine in the thyroid and pituitary were found. In addition, the signs of apoptosis appeared directly related to the concentration of iodine in the pituitary, but inversely related to iodine concentration in the thyroid.

Key words: wavelength dispersive spectrometry, caspase 32, caspase 8, iodide, pituitary, thyroid, rats

In previous investigations with the use of wavelength dispersive spectrometry (WDS) quantitative analysis the level of iodine in the thyroid has been estimated and the accumulation of iodine in the pituitary has been demonstrated (Basalaeva et al. 2011a). It remained to be further studied if such phenomenon could be related to some functional purpose.

As based on previous findings, the oral dose of approximately 1 μg KI/100 g has been found out as that possibly resulting in certain quantity of iodine concentration in pituitary iodine-positive points, while that of 4 μg KI/100 g appeared, in this respect, about 5 times higher. In addition, however, the dose of 8 μg KI/100 g appeared about 10 times higher than the concentration of iodine in those pituitary

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iodine-positive points or about 1.5 times higher than the concentration of iodine in thyroid iodine-positive points. Finally, the oral dose of 25 μg KI/100 g resulted in about 5 times higher concentration of iodine-positive points in the thyroid. It was aimed to check the response of thyroid and pituitary iodine-positive points to increasing oral iodide doses within of above mentioned range.

A long time ago the fluctuation of thyroid function in rats for 72 hours after a single oral dose of various antithyroid drugs has been shown which was independent of chemical nature of the drug (Langer 1968). From our previous investigation it has been assumed that such phenomenon could be valid also for the effect of small doses of iodide (Basalaeva et al. 2011b). However, after using various small doses of KI the pituitary-thyroid interplay in our experiments was somewhat different from that observed after the administration of thiocyanate, mercaptoimidazole or perchlorate (Langer 1968). Actually, it was found that after 1 μg iodide/100g the level of TSH decreased and remained low after increasing iodide doses, while the response of thyroid hormones was different. Thus, after 1 μg iodide/100g the level of free thyroxine decreased together with TSH, but after 25 μg iodide/100g the decrease of free thyroxine was still more expressed, while the level of total triiodothyronine did not decrease none of doses (Basalaeva et al. 2011b).

The expression of NIS in the pituitary of rat females after the dose of 4 μg iodide/100g was increased, while that in the thyroids increased after 8 μg iodide/100g (Basalaeva et al. 2011a). Thus, it may be suggested that the pituitary appears more susceptible to the level of iodide in blood, but several questions still remain opened. Among them could be the interrelation between the activity of caspases and concentration iodine in the thyroid and pituitary after the administration of various doses of iodide which became the aim of this investigation.

Materials and Methods

Animals. A total of 49 inbred female rats of local laboratory strain weighing 250-300 g at the stage of diestrus and/or metestrus were used. They were kept in light (12:12 hr light: dark cycle; lights on at 7.00 a.m. local time) and temperature (24±1 °C) controlled animal room and fed standard commercial laboratory diet and tap water *ad libitum*. The experiment was conducted by observing humane principles as presented by European Community Directive 86/609/EC.

A total of 15 rats served as control and 34 rats were given various doses of potassium iodide per 100 g body weight in 0.5 ml distilled water by gavage (e.g. 8 rats - 1 μg; 10 rats - 4 μg; 8 rats - 8 μg; 8 rats - 25 μg). Immediately before sacrifice the blood sample was taken from jugular vein in ether anesthesia and then the animals were sacrificed under continuing ether anesthesia.

Wavelength dispersive spectrometry (WDS) quantitative analysis. From the thyroids and pituitaries of 6 control rats and of 2 rats from each other group the tissue fragments of no more than 2 mm thickness were obtained and subjected to the procedure of sample preparation. First, they were dried at 100 °C for 45 min (Basalaeva et al. 2009). After that they were coated with platinum by JFC-1600 Auto Fine Coater (JEOL, Tokyo, Japan) and examined in a JEOL JSM-6460 LV raster electron microscope (REM) (JEOL, Tokyo Japan) equipped with wave length dispersive X-ray analyzer Inca 500 (Oxford Instruments, High Wycombe, UK) at 20 kV and 2.5 nA (Fig 1A, Fig 1B). Silver iodide (AgI) and 20 % gelatine solution with known concentrations of thyroxine were used as standards. WDS counting times were 20 sec per analyzed point. Each sample was counted 5 times.

The analyses were carried out by elemental imaging using the multispectral analysis program Oxford Inca Energy Wave Crystal EWC453 (Oxford Instruments, High Wycombe, UK), 2003.

The results were expressed as wt % dry tissue (10^{-2} g/100 g) in each class and the averages were compared by one-way ANOVA followed the Duncan multiple range test at $p<0.05$.

Morphological evaluation. The samples of the pituitary with osseous tissues and the thyroids with the fragments of trachea were fixed by 10 % neutral formol and embedded in paraffin. Osseous and cartilage tissues were decalcified. Serial thin parallel slices were made, stained by hematoxyline-eosine and examined by light microscope.

Immunohistochemistry. The expression of apoptosis mediating enzymes – caspase 32 (CPP32) and caspase 8 (CPP8) in the pituitary and thyroid was determined by streptavidin-biotin method with the use of monoclonal antibodies to CPP32 (clone GHM62, 1:50 v/v), CPP8 (clone 11 B6, 1:30v/v) purchased from Novocastra (Newcastle upon Tyne, UK). Paraffin-embedded tissue sections were deparaffinized with xylene, rehydrated in sequential ethanol/water baths of descending ethanol concentrations, and subjected to microwave fixation for 15 min in 10 mM citrate buffer. Endogenous peroxidase was quenched with 0.3 % hydrogen peroxide in methanol for 10 min. Nonspecific binding was inhibited by 1 % (weight/

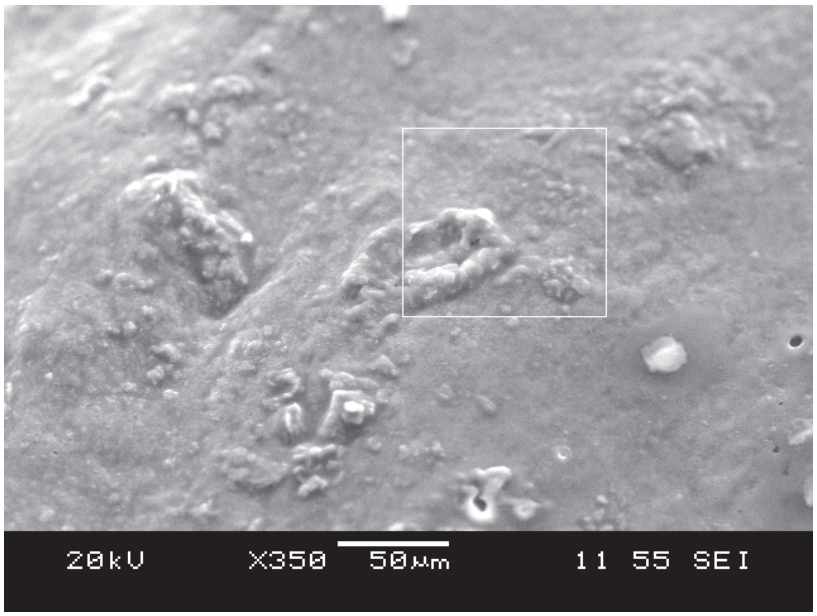

Fig. 1A. Representative scanning electron micrograph of the sample of rat thyroid dehydrated by drying at 100 °C for 45 min.

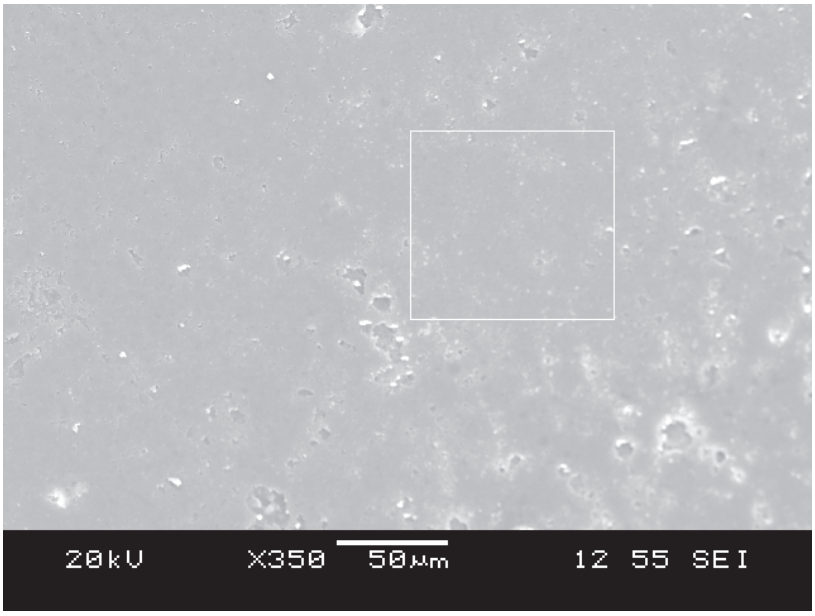

Fig. 1B. Representative scanning electron micrograph of the sample of rat pituitary dehydrated by drying at 100 °C for 45 min.

volume) horse serum albumin (HSA) for 30 min at room temperature. Primary antibodies were added to the slides in blocking 1 % (w/v) HSA solution and incubated for 30 min at room temperature. Tissue sections were incubated for 30 min at room temperature with a peroxidase-conjugated secondary antibody in blocking buffer. After washing, tissue sections were incubated for 5 min at room temperature with biotinyl tyramide (1:50 v/v) in 50 mM Tris HCl (0.01 % H_2O_2, pH 8.0) followed by 30 min incubation with alkaline phosphatase-conjugated streptavidin (1:100 v/v) in blocking buffer.

All sections were investigated by light microscope Axiostar plus (Carl Zeiss Jena, Germany) equipped by

the scanner with a 35 mm digital-camera (Cannon Power Shot A520), and afterwards saved and analysed with the BioVision Professional 3.0 (West Medica Handels GmbH, Vienna, Austria) for computerized image analysis and quantification of caspase 32 and caspase 8.

Mean values ± SD of specimen specific characteristics, such as percentage of positive stained area (% PA). In pituitaries percent of PIPP decreased from 65 % (control) to 28 % after 8 μg/100 g.

Statistical evaluation. For statistical evaluation Statistica for Windows 6.0 was used. The results were expressed as mean ± SEM for each group. The differences between groups were analyzed by one-way ANOVA followed by Duncan's multiple range test, the values of $p<0.05$ being considered as significant.

Results

Concentration of iodine (Fig. 2). A. Thyroid. As found by wavelength dispersive spectrometry the concentration of iodine in thyroid iodine positive points (TIPPs) increased significantly from 16.7±3.0 wt % I^{-2}/dry tissue in controls to 38.6±6.7 wt % I^{-2}/dry tissue after 1 μg/100 g ($p<0.05$), while it decreased to 11.9±2.4 wt % I^{-2}/dry tissue ($p<0.05$) after 8 μg/100 g ($p<0.05$) and to 12.8±1.8 wt % I^{-2}/dry tissue after 25 μg/100 g ($p>0.05$). In thyroids percent of TIPP decreased from 100 % (control) to 86.6 % after 25 μg/100 g.

B. Pituitary. However, in the pituitaries, iodine concentration in pituitary iodine positive points (PIPPs) showed a fluctuating and not significant slightly increasing trend after 1 μg (4.3±0.5 wt % I^{-2}/dry tissue), 4 μg (3.9±0.1 wt % I^{-2}/dry tissue) and 25 μg (5.1±1.1 wt % I^{-2}/dry tissue), while the only significant increase ($p<0.05$) was found after the iodide dose of 8 μg/100 g (7.2±1.2 wt % I^{-2}/dry tissue) as compared to control level (2.2±0.3 wt % I^{-2}/dry tissue). Thus, peak of iodine concentration in PIPPs appeared after the dose of 8 mg/100 g. In pituitaries percent of PIPP decreased from 65 % (control) to 28 % after 8 μg/100 g.

Histochemistry of caspase 32 (Fig. 3). In the thyroids, the concentration of caspase 32 significantly increased from 2.9±0.5 % PA in controls to 6.4±1.6 % PA after iodide dose of 8 μg/100 g ($p<0.05$), while the increase after the doses of 1, 4 and 25 μg/100 g was not significant. However, in the pituitaries the concentration of caspase 32 from the control level of 1.4±0.6 % PA significantly increased after all doses of iodide with the peak after 8 mg/100 g ($p<0.05$).

Histochemistry of caspase 8 (Fig. 4). In the thyroids the increase of caspase 8 concentration from the control level of 3.2±0.6 % PA after individual doses of iodide was not significant, although the average increase after the dose of 1 μg and 8 μg iodide was about twice as

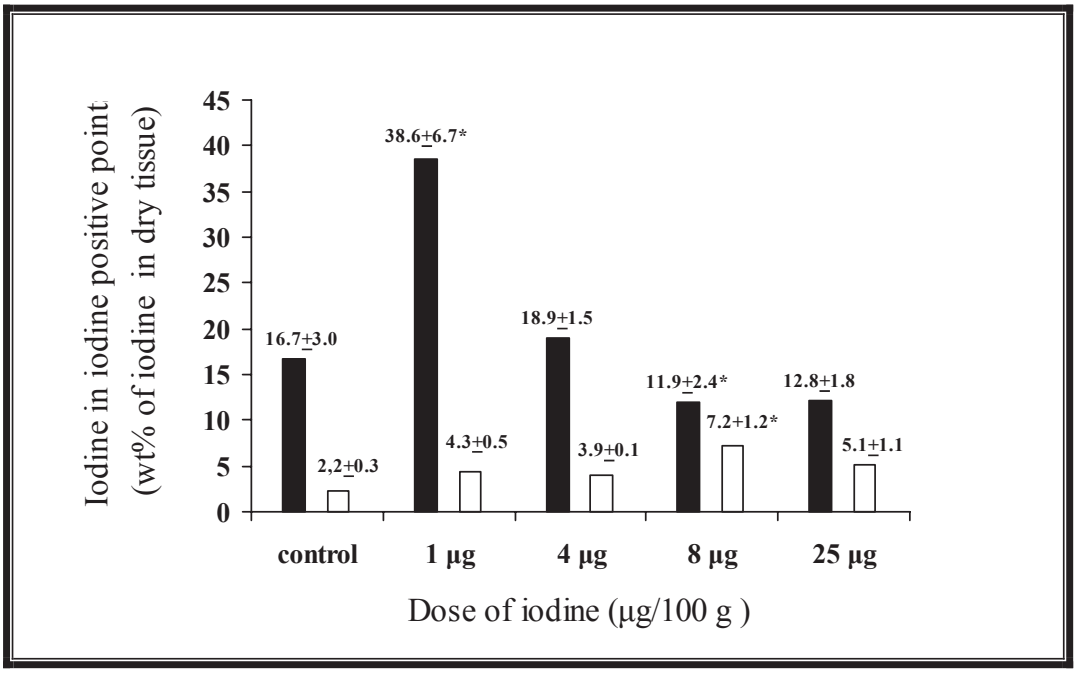

Fig. 2. Wavelength dispersive spectrometry (WDS) quantitative analysis of iodine concentration levels in thyroids (black columns) and pituitaries (white columns) of female rats at 48 hours after different single doses of KI (wt% I-2 dry tissue). * = p<0.05 vs. control group

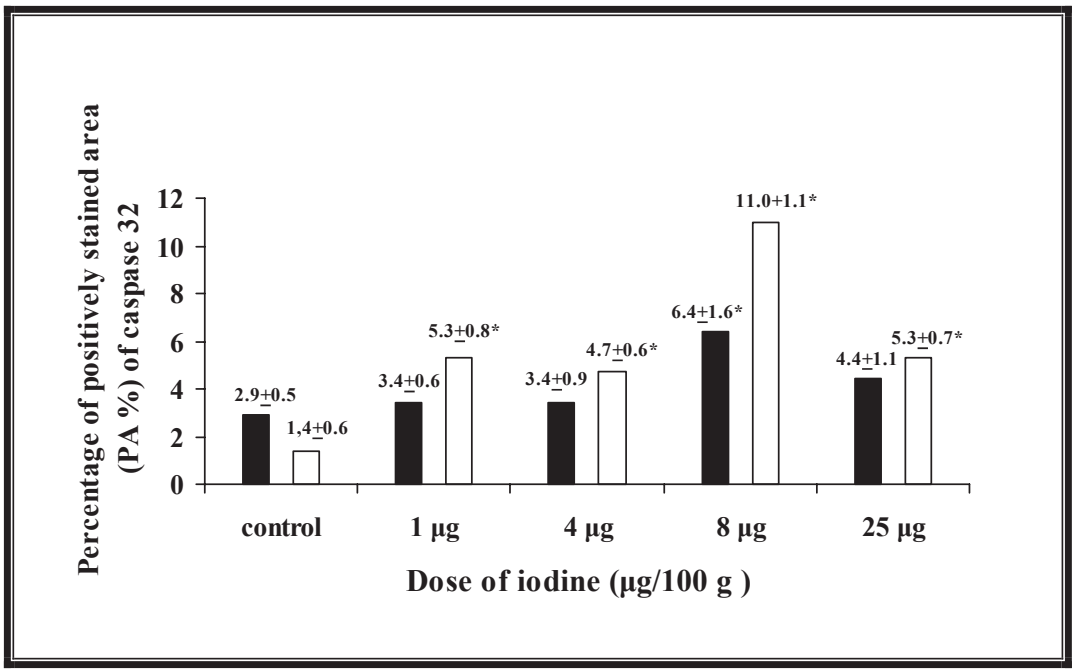

Fig. 3. Significant increase of CPP 32 in thyroids (black columns) and pituitaries (white columns) of female rats at 48 hours after the administration of different single doses of KI; in the pituitary the increase starts after 1 µg/100 g and shows maximum after 8 µg/100 g; in the thyroid significant increase appeared only after 8 µg/100 g. * = p<0.05 vs. control group

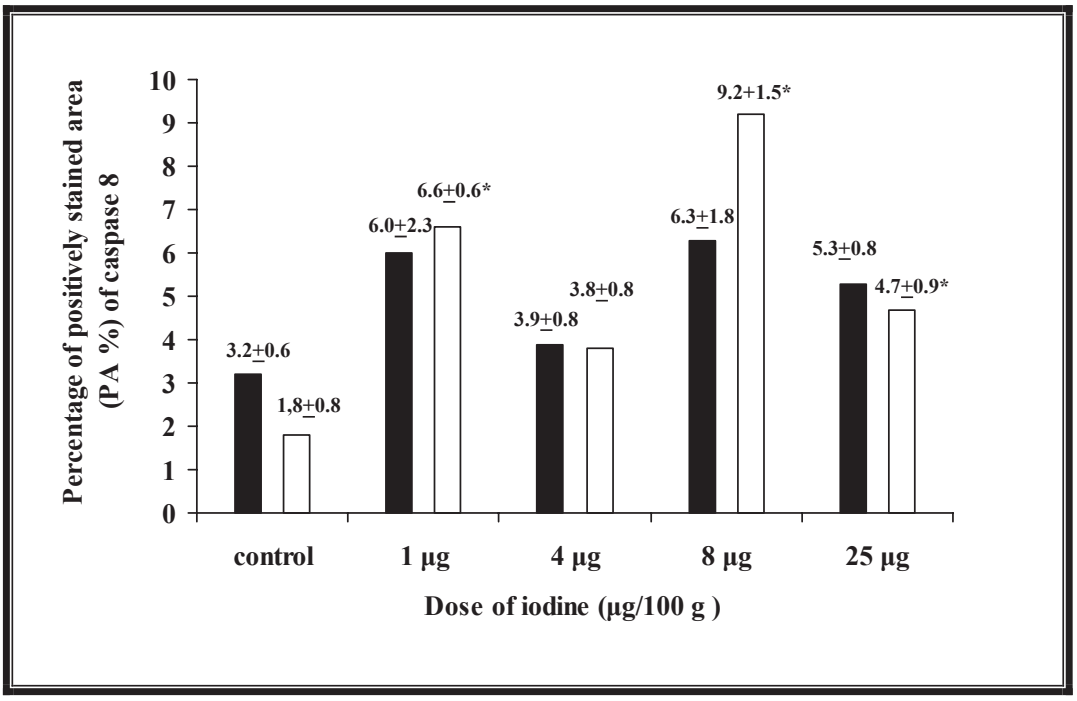

Fig. 4. Significant increase of CPP 8 in thyroids (black columns) and pituitaries (white columns) of female rats at 48 hours after administration different single doses of KI; in the pituitary the increase starts after 1 µg/100 g and shows the maximum after 8 µg/100 g, while in the thyroid in shows unsignificant increase.

high as the average value in controls. In contrast, in the pituitaries such increase of caspase 8 from the control level of 1.8±0.8 % PA was significant ($p<0.05$) after iodide doses of 1 μg (6.6±0.6 % PA), 8 μg (9.2±1.5 % PA) and 25 μg (4.7±0.9 % PA) with peak after dose of 8 mg/100 g too.

By such a way, increased iodine concentration in TIPPs was found after the dose of 1 μg/100g, thus corresponding to about 1/5 of iodine concentration in iodine positive points in the thyroid or to the level of iodine in iodine positive points of the pituitary.

Moreover, decreased iodine concentration in TIPPs was found after iodine dose of 8 μg/100g (which means at about 10 times higher iodine concentration in PIPPs in the pituitary) as well as after iodine dose of 25 μg/100g (which means about 5 times higher iodine level in the thyroid).

The changes of iodine level in the thyroid were accompanied by a significant increase of caspases only at a decrease of iodine dose to 8 μg/100g, though only caspase 32 one of them responded. Actually, increasing trend of caspase 8 appeared only during the period of indifferent fluctuation of iodine concentration – either decreasing or increasing.

Discussion

Concentration of iodine in the thyroid has been estimated by various methods, but their validity has been limited, since they were not sensitive enough for the estimation of minute amounts of iodine as low as 0.1 μg/g. In addition, a majority of those methods required the tissue destruction. In contrast, however, WDS method permitted to obtain the quantitative content of iodine in the tissue studied without any destruction and thus permitted to conclude that the response of thyroid tissue to potassium iodide does not consist only from the changes of iodine in the TIPP and possibly also from the level of NIS as we reported previously (Basalaeva et al. 2011), but also from the number of TIPP itself. Thus, it may be concluded that, during the Wolff-Chaikoff effect, also some components of thyroid tissue are participating which are escaping from the estimation by WDS.

WDS method permitted to establish that the decrease of iodine in the TIPP is starting already after 8 μg/100g, though in that case the decrease is lower than that after 25 μg/100g. From this follows that thyroid inhibition possibly starts at the same time as the dose of KI administered begins to increase over the level of KI in the TIPP. However, in contrast to Wolff-Chaikoff effect the thyroid blockade after 8 μg/100g is accompanied by a decrease of apoptosis activity in the thyroid (as supported by decrease caspase 32 expression in thyroids) and probably appears to be compensated by increased iodine level in the PIPP and by a simultaneous expression of caspase 32 in the pituitary.

In a case of Wolff-Chaikoff effect (after 25 μg/100g) any changes in the activity of caspase dependent apoptosis in the thyroid and of the increase of pituitary function did not appear.

According to the data by Vitale et al. (2000) the high doses of iodide are inducing caspase independent apoptosis in thyroids. In contrast, however, from our data it may be suggested that iodide is inducing caspase dependent apoptosis in thyroids which, however, appears rather dose dependent and occurs only in such a case, when the dose of iodine is corresponding to the level of iodine in TIPP (i.e. 8 μg/100g) and results only from the decreased level of iodine in the TIPP. In contrast, increased level of iodine in TIPP (after iodide dose of 1 μg/100g) is not accompanied by the changes in caspases expression.

The WDS method also showed that iodide in the pituitary is being concentrated in PIPP (Basalaeva et al. 2011a). It further appeared that the response of the pituitary after various doses of iodide, as well as that of the thyroid, is changing in three ways such as in the changes of iodine in the PIPP, in the number of PIPPs and in the level of NIS (Basalaeva et al. 2011).

As long as the iodide dose is within the limits of physiological iodine level in PIPP and TIPP, there exists a tendency to increase iodine level in the PIPP and to increase the expression of both caspase 8 and caspase 32 in the pituitary.

The critical dose of iodide effect on the pituitary – 8 μg/100g – appears about 10 times higher than the level of iodine in PIPP and about 1.5 times higher than the level of iodine in TIPP. Maximal (ten times) expression of caspase 32 and caspase 8 in the pituitary is associated with the maximal (three times) increase of iodide in PIPP and with decreased number of PIPP.

Simultaneous change of iodide level in the PIPP and of decreased PIPP number presumably appeared a compensatory mechanism to maintain a constant iodine amount in the pituitary which is contrasting to the thyroid in which, at the same time, the amount of iodine may increase. As already mentioned above, maximal increase of caspases in the pituitary after iodide dose of 8 μg/100 g was associated with the decrease of caspase 32 in the thyroid and with the decrease of iodine in TIPP.

However, after increasing iodide dose such effect does not appear any more since, probably, the pituitary is responding to iodide only within the range of 1 to 10 times higher iodine level in PIPP. This is a similar case as that one when, due to Wolff-Chaikoff effect, the level of iodine in PIPP after iodide dose of 25 μg/100g does not differ from the control and, at the same time, the expression of caspase 32 and caspase 8 does not differ from that obtained after iodide dose of 1 and 4 μg/100 g.

In the thyroid, after iodide dose of 25 μg/100g there possibly appear some negative, but less expressed trends to decrease iodine level in TIPP than after iodide dose of 8 μg/100g. Thus, the blockade of the thyroid at Wolff-Chaikoff effect possibly takes place even without any regulatory participation of the pituitary.

When comparing the process of TSH decrease in blood of those animals with that of iodine concentration changes in PIPP and TIPP as well as with the number of PIPP and TIPP, NIS and caspases concentration in thyroids and pituitaries, it may be hypothesized that TSH should decrease together with increased expression of caspase 32 and caspase 8 in the pituitaries.

Since the activity of caspases in the pituitary appears to be related with iodide level in PIPP, which is most clearly shown after the iodide dose of 8 μg/100g, it may be supposed that there possibly exists a direct effect of iodine on the pituitary function via the caspases related mechanism.

From this it should be noted that the tendency to increase iodine level in PIPP and increased expression of caspase 32 and caspase 8 in the pituitary could exist after all iodide doses. Apparently, this could possibly clarify the phenomenon described previously by Langer (1968) who observed that, after a single dose of antithyroid drugs, the duration of thyroid inhibition did not depend from the dose or chemical structure of the drug used. It may be suggested that the perturbation of the pituitary-thyroid axis depends on the fluctuation of iodide level in blood related to the diet or antithyroid drugs. The sensitivity of the pituitary to the fluctuation of iodine level is weakening the stereotype of the pituitary-thyroid response to different drugs and their doses, the main role being possibly played by iodide level in blood rather than that of chemical formula of the drug used.

Several investigations on the apoptosis in the pituitary were related to the pituitary adenoma (Nakabyashi et al. 2001). It was found that apoptosis can be triggered by many distinct and different stimuli including the exposure to physical and chemical agents such as inorganic materials like cadmium (Poliandri et al. 2003) or organic compounds like glutamate (Caruso et al. 2004), anacardic acid (Sukumari-Ramesh et al. 2011), curcumin (Schaaf et al. 2010), hormones like gonadal steroids (Zaldivar et al. 2011; Jaita et al. 2011), hormone analogs like dexamethasone (Nolan et al. 2002, 2004), bromocryptine (Drewett et al. 1993), somatostatin (Cerman et al. 2003) or gene (Tagliati et al. 2010). However, the attention has been also paid to some factors influencing the apoptosis in the pituitary adenoma tissue which do not influence the normal pituitary tissue such as proteosome inhibitors (Yu et al. 2002). It was also found that pituitary polypeptides are influencing the apoptosis in extrathyroidal tissues (Seaborn et al. 2011).

By such a way, however, the apoptosis in the pituitary has been evaluated predominantly from the pathological rather than from physiological viewpoint. From the results of above mentioned findings it may be supposed that the iodide-induced caspase dependent apoptosis in the pituitary appears one of the mechanisms influencing the pituitary functional activity.

Recently also a discussion has been opened about the role of iodine in extrathyroidal tissues (Cann et al. 2006). From our observations it may be possibly supposed that some direct effect of iodine on the functional activity of the pituitary may be mediated by PIPP via caspase dependent apoptosis, e.g. the higher the iodine the lower the activity of the pituitary.

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