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# Acute Effects of Potassium Iodide after Propylthiouracil Administration: Contents of Iodine and Selenium in the Thyroid, Pituitary, Adrenal Glands and Ovaries of Female Rats

## Level of Iodine and Selenium in Rat Endocrines

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***Abstract***

The purpose of this study was to determine the contents of iodine and selenium in the thyroid, pituitary, adrenal glands and ovaries of female rats under the influence of propylthiouracil (PTU) and the effects of a single dose of potassium iodide (KI) administered two days after the administration of PTU. For the analyses, electron probe microanalysis (EPMA), wavelength-dispersive spectrometry (WDs) and point analysis were used in this study. Ninety-six hours after the first PTU administration the thyroid gland iodine level decreased three-fold in iodide positive points (I-PPs) and the percentage of positive points (%I-PPs) fell by one half. Administration of a single dose of potassium iodide slightly increased the iodine level in I-PPs and restored %I-PPs to the control level. After PTU administration the selenium positive points (Se-PPs) in the thyroid gland decreased by one half, but KI did not help to level these changes. In ovaries, pituitary and adrenal glands PTU administration did not significantly alter the average levels of iodine and selenium, but the Se-PPs and % I-PPs varied over a wide range. Administration of KI restored the levels of iodine and selenium in the pituitary and adrenal glands, but worsened the changes of iodine in ovaries.

***Keywords***

*Wavelength Dispersive Spectrometry; Iodide; Selenium; Thyroid; Pituitary; Adrenal Gland; Ovaries; Rats*

## Introduction

The hyperactivity of the thyroid gland during the first week of administration of anti-thyroid agents such as propylthiouracyl (PTU) is not yet fully understood [10]. In general, it is considered that the thyroid gland saturates with iodine within one week and then saturation blocks further absorption of iodine. M. Sue confirmed this premise [15], by determining that PTU causes the expression of the sodium iodide symporter (NIS) to increase in thyrocytes in absence of the thyroid-stimulating hormone (TSH). In a previous study using EPMA under iodine-induced thyroid blockade, we found that the expression of NIS in the thyroid gland increased during the first 5 days of the blockade, along with a decrease of intrathyroidal iodine [2]. One of the objectives of this study was to again use EMPA for the speciation of intrathyroidal iodine under the influence of PTU.

Other reports have proven that PTU-induced thyroid blockade is leveled by KI [1], but the underlying mechanisms of this effect are not yet well established [17]. It is possible that determination of intrathyroidal iodine under acute effect of iodide after PTU administration by means of EPMA would help to better understand these mechanisms.

Administration of PTU suppresses the synthesis of thyroid gland hormones, blocking the thyreoperoxidase activity inhibiting the transformation of thyroxine into triiodothyronine [16]. It is uncertain if this process affects the functional activity of other endocrine organs, interrelated or associated to the thyroid gland. According to some investigators, PTU suppresses the functional activity of the adrenal [12] and gonadal systems [9, 11]. However, the question of the reversibility of this influence by iodides, similar to the thyroid gland, was not actively investigated.

In a previous study [8], the pituitary-gonadal system functional activity was suppressed in female rats 96 hours after the administration PTU. Posterior effects of acute iodide from KI intensified this effect. Along with this, there was no influence of PTU on the function of adrenal glands and there was no cortisol level increase after a single dose administration of KI [7]. These changes of the gonad and adrenal glands functions were followed by the pituitary thyroid system reaction: PTU suppressed the thyroid gland function and KI restored its activity, as reported in previous investigations [13]. Investigating the iodine levels of ovaries, thyroid, pituitary and adrenal glands under acute effects of iodide given two days after PTU administration would help understanding the underlying mechanisms. In addition, using the selenium level as indicator of the tissues selenoprotein content is also an interesting research objective, as PTU is known to affect the selenoprotein-thyroid peroxidase system.

Thus, the purpose of this study was to use EPMA to determine the content of iodine and selenium in ovaries, thyroid, pituitary and adrenal glands of female rats under PTU-induced rebound effect and the effects of a single dose iodide to PTU-administered female rats.

## Materials and Methods

### *Animals*

The experiments were conducted according to the guidelines for animal experimentation stated by the European Community Directive 86/609/EC.

A total of 14 inbred female rats in the diestrus and metaestrus stages weiging 250- 300 g were obtained from a local laboratory were used in the study. They were kept in a temperature-controlled animal room (24±1°C) on a 12/12h light/dark cycle (lights on at 7.00 a.m. local time) and fed a standard commercial laboratory diet. Tap water was provided ad libitum. After the experimental period the rats were sacrificed under ether anesthesia, in the 11 AM – 1 PM time interval to obtain the necessary samples.

The thyroid blockade was accomplished by administration of 300μg PTU per 100g body weight. Six rats were given PTU for two days, after which three of the rats were given a single dose of 8 μg/100 KI. The dose was chosen based on previous studies [3]. Both KI and PTU were diluted in 0.5 ml of distilled water and administered once by gavage. A second set of 3 rats were administered PTU during two days (Group PTU-2), and then treated with a single dose of KI (Group PTU-2, KI-1). Eight rats did not receive any treatment to be used as controls. All animals were killed 96 hours after first administration of PTU.

### *Electron-Probe Microanalysis*

The experiments were carried out at the Department of Physical Chemistry, South Ural State University, Chelyabinsk, Russia. Specimens of thyroid glands, anterior pituitary glands, adrenal glands and ovaries were surgically extracted and then dried at 100°C, for 45 min. The samples were weighted at each stage. The dry to wet matter ratios (D/W) were determined for each sample, averaging 0.30±0.06 g. The results for all of the elements studied are given in reference to the dry weight of samples (d.w.).

After thermal dehumidification the samples were coated with platinum using a JFC-1600 Auto Fine Coater (JEOL, Tokyo, Japan) at 3 Pa and examined by means of a JSM-6460 LV scanning electron microscope (SEM), also from JEOL, Tokyo Japan. The SEM was equipped with an energy dispersive x-ray analyzer (EDS) and a wavelength

dispersive x-ray analyzer (WDS), both from Inca 7574 (Oxford Instruments, High Wycombe, UK). The WDS operated at high vacuum with an accelerating voltage of 20kV at a 2.5 nA tube current. A thin layer of silver iodide and 1.5% Se-Sn bearing alloy were used as standards. The WDS counting times were 20 sec per analyzed point at the peak and background position.

The points that had measurable levels of iodine or selenium were defined as I- or Se- positive points (IPP or Se-PPs). The percentage of iodine-positive points related to all analyzed points were defined as the percentage of positive points (% PP).

Iodine was determined in 8 thyroid glands, 12 pituitary glands, 8 adrenal glands and 10 ovaries. Selenium was determined in 8 thyroid glands, 8 pituitary glands, 6 adrenal glands and 6 ovaries. The iodine and selenium levels in three thyroid-, anterior pituitary- and adrenal glands and in three ovaries of rats were determined after the 2-fold PTU administration; another set of three of each of the glands and ovaries were studied after 2-fold PTU administration plus a single dose of KI. From the controls, 2 thyroid glands, 6 anterior pituitary glands, 2 adrenal glands and 6 ovaries were analyzed. On average, the number of trials for I was 5.2 and 5.1 for Se, measuring in different points of the organs studied.

The elemental imaging was conducted using a multispectral analysis program from Oxford Inca Energy Wave Crystal EWC453 (Oxford Instruments, High Wycombe, UK). The results were expressed as wt % (g/100 g) x $10^{-2}$ dry weight [14] in each group and the means were compared by one-way ANOVA followed the Duncan multiple range test setting the significance level at $p < 0.05$.

## Results and Discussion

A total of 342 points (95 in thyroid, 99 in pituitaries, 65 in adrenal glands and 83in ovaries) were analyzed at random. 198 points were analyzed for iodine (49 in thyroid, 62 in pituitaries, 34 in adrenal glands and 53 in ovaries) and 144 points were analyzed for Se (46 in thyroid, 37 in pituitaries, 31 in adrenal glands and 30 in ovaries).

The results of point analysis for iodine and selenium in the thyroid gland are shown in Table 1. A three-fold decrease of the iodine level in the I-PPs occurred after PTU administration the %I-PPs decreased by half. Administration of KI did not increase in I-PPs, but % of I-PPs was restored to the control level. The changes of Se were not as definite, but it should be noted that Se-PPs decreased to one-half after administration of PTU, and KI did not restore their normal level.

TABLE 1 IODINE AND SELENIUM IN THYROID WITHIN DIFFERENT THYROID BLOCKING AGENTS

| Groups | Thyroid | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I-PPs (wt% x $10^{-2}$ d.w.) | | | | Se-PPs (wt% x $10^{-2}$ d.w.) | | | |
| | Mean ± SD | Min | Max | % PP | Mean ± SD | Min | Max | % PP |
| Control | 16.7±3.0 | 2.6 | 59.0 | 100 | 2.2±0.3 | 0.4 | 0 | 42.8 |
| PTU-2 | 5.9±1.1 [a] | 0 | 11.5 | 53.3 | 2.4±0.7 | 0.5 | 0 | 40 |
| PTU-2, KI-1 | 8.4±1.3 [a] | 0 | 17.5 | 93.3 | 2.6±0.7 | 0.5 | 0 | 46.6 |

[a] Significant differences with respect to controls.

The results of the point analysis of iodine and selenium in the pituitary gland are shown in Table 2. In all of the study groups the average values of iodine and selenium levels did not show significant changes in comparison controls. Administration of PTU did not change the level of I in the pituitary gland but administering KI after PTU increased the I-PPs by 30%. After PTU administration the Se-PPs doubled and %Se-PPs decreased by half. Administering KI after PTU normalized the Se-PPs, but did not restore the number of points of tissue containing selenium.

The results of the point analysis of iodine and selenium in the adrenal gland are shown in Table 3. The average values of iodine and selenium in the study groups did not show appreciable changes in comparison to controls. After PTU administration the I-PPs decreased by 30%, the %I-PPs by 36% while the Se-PPs decreased by 30% and the %Se-PPs by 50%. After administration of KI the I-PPs and %Se-PPs returned to normal, but the %I-PPs and Se-

PPs did not.

TABLE 2 IODINE AND SELENIUM IN ANTERIOR PITUITARY WITHIN DIFFERENT THYROID BLOCKING AGENTS

| Groups | Pituitary | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I-PPs (wt% x $10^{-2}$ d.w.) | | | | Se-PPs (wt% x $10^{-2}$ d.w.) | | | |
| | Mean ± SD | Min | Max | % PP | Mean ± SD | Min | Max | % PP |
| Control | 2.2±0.3 | 0 | 6.3 | 65 | 1.8±0.8 | 0 | 3.5 | 57.1 |
| PTU-2 | 2.9±0.6 | 0 | 5.5 | 53 | 2.8±0.1 | 0 | 7.5 | 40 |
| PTU-2, KI-1 | 2.7±0.9 | 0 | 9.5 | 60 | 2.1±0.6 | 0 | 4.0 | 40 |

[a] Significant differences with respect to controls.

TABLE 3 IODINE AND SELENIUM IN ADRENAL GLAND WITHIN DIFFERENT THYROID BLOCKING AGENTS

| Groups | Adrenal gland | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I-PPs (wt% x $10^{-2}$ d.w.) | | | | Se-PPs (wt% x $10^{-2}$ d.w.) | | | |
| | Mean ± SD | Min | Max | % PP | Mean ± SD | Min | Max | % PP |
| Control | 3.3±0.9 | 0 | 6.8 | 54.5 | 3.4±0.1 | 0 | 6.3 | 44.4 |
| PTU-2 | 3.4±0.6 | 0 | 4.4 | 40 | 2.5±1.8 | 0 | 4.2 | 20 |
| PTU-2, KI-1 | 3.4±0.9 | 0 | 6.8 | 38.4 | 2.1±0.6 | 0 | 4.5 | 50 |

[a] Significant differences with respect to controls.

The results of the point analysis of iodine and selenium in ovaries are shown in Table 4. There were no significant differences among the study and control groups. Administration of PTU resulted in a 50% decrease of I-PPs but had no effect on the %I-PPs The Se-PPs decreased by one half and the %Se-PPs had a 40% decrease. Administration of KI normalized the selenium level, but resulted in a 70% decrease of I-PPs and caused a threefold decrease of %I-PPs relative to controls.

TABLE 4 IODINE AND SELENIUM IN OVARIES WITHIN DIFFERENT THYROID BLOCKING AGENTS

| Groups | Ovaries | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I-PPs (wt% x $10^{-2}$ d.w.) | | | | Se-PPs (wt% x $10^{-2}$ d.w.) | | | |
| | Mean ± SD | Min | Max | % PP | Mean ± SD | Min | Max | % PP |
| Control | 3.1±0.5 | 0 | 9.7 | 54.5 | 1.9±0.9 | 0 | 5.6 | 50 |
| PTU-2 | 2.8±0.7 | 0 | 4.8 | 50 | 1.5±0.7 | 0 | 2.8 | 30 |
| PTU-2, KI-1 | 2.4±0.4 | 0 | 2.8 | 17 | 2.2±0.5 | 0 | 3.9 | 50 |

[a] Significant differences with respect to controls.

Thus, 96 hours after the first PTU administration, the iodine level in the thyroid gland decreased in I-PPs and %I-PPs followed by a rebound period as previously described by Langer [10] and in previous unpublished results by the author. It should be noted that changes during the PTU-induced thyroid blockade differed from changes during the iodine-induced thyroid blockade from a previous study [2]: for the 4th day of iodine-induced thyroid blockade the average iodine level in I-PPs decreased, but %I-PPs was unchanged while during PTU-induced thyroid blockade the quantity of IPPs decreased by 50%.

Thus, as described in other studies [10,13], it is possible to assume that the thyroid gland hyperactivity during the initial days of PTU- and KI administration lowers the average iodine level in the thyroid gland, and the thyroid blockade occurs right after administration of these agents. In 1998, J.Wolff [18] stated: "An interesting phenomenon seen upon iodide withdrawal: that is rebound "hyperactivity" of the thyroid gland. This may last for weeks. It is seen in nearly all the cases in which it is looked for, as characterized by high 131I uptake values. Whether this represents true rebound hyperactivity due to increased TSH stimulation following hypothyroidism or persistence of preexisting stimulation that can now be fully expressed because carrier iodide is withdrawn and because organic iodine formation is possible"

As described before [10], the absorption of 131I absorption by the thyroid gland increases during the rebound effect and is probably connected to the NIS expression increase after administration of KI [2] and PTU [15]. This phenomenon is a reaction to the thyroid gland blockade and the change of iodine content in the thyroid gland. However the manifestations differ: PTU decreases the iodine level in I-PPs and the number of I-containing tissue

points while KI decreases the iodine level in I-PPs but does not reduce the number of I-points [2].

After a single KI administration, the PTU-treated rats had a slight increase of the average iodine level in I-PPs and a posterior restoration of the number of the iodine points to the control level. Thus, restoration of the thyroid gland functional activity during the PTU-induced thyroid blockade differs to the iodine-induced thyroid blockade.

The EPMA point analysis changes of selenium in the thyroid gland were non-specific: the Se-PPs decreased after PTU administration, but KI did not result in any changes. The decrease of Se-PPs max was followed by an increase of tT3 after PTU administration, but it was not affected by KI [8].

The average values of iodine and selenium levels in other organs were not affected by PTU, or by KI after PTU administration. However, the PPs and %PPs did change. Treatment with PTU resulted in a decrease in I-PPs and of %I-PPs with various degrees of intensity in the pituitary, the adrenal gland and the ovary. In the adrenal gland there was a decrease of Se-PPs of %Se-PPs, but in the pituitary Se-PPs increased and %Se-PPs decreased. Active changes of the selenium level probably were related to the inhibitory influence of PTU on the transformation of thyroxine into triiodothyronine that were followed by the change of functional activity confirmed by the 10–fold decrease of the TSH level and the 5–fold decrease in progesterone in blood as compared to controls. Changes of the follicle-stimulating hormone (FSH), luteinizing hormone (LH) and cortisol were not detected [8].

During PTU treatment, KI did level the iodine and selenium changes in the pituitary and adrenal glands, but some changes were still observed in the pituitary gland, namely the increase in I-PPs was greater than controls, but the quantity of Se- containing tissue points was not restored. The normalization of TSH and threefold increase of FSH and LH from normal to a level of constant estrous occurred in parallel to these trace elements changes [8].

After PTU treatment, KI administration resulted in a decrease of I-PPs and %I-PPs, (3x and 2x, respectively). These changes were concurrent with a 10-x decrease of the progesterone level in blood [8].

Previous studies on the functional activity of the reproductive system of female rats concluded that KI at a dose of 4 and 8 μg/100 g body weight causes continual estrous increasing the expression of FSH and LH in the pituitary gland and a decrease of blood progesterone followed by an increase of the NIS expression in the pituitary gland on the second- and fifth days of the blockade, and in the ovaries on the third- and sixth days of blockade [5,6]. The EPMA point analysis indicated that the pituitary gland experienced some significant changes of the iodine level: the average iodine level in I-PPs increased, %I-PPs decreased, together with some insignificant changes in ovaries: only a 2-fold decrease in %I-PPs [5].

Thus, when comparing the influence of two thyroid-blocking agents on the pituitary-gonadal system, PTU influenced the ovary function without changing that of the pituitary gland and without actively changing the average iodine level. In contrast, KI did influence the average iodine level and expression the FSH and LH in tissues of the pituitary gland and increasing the blood levels of pituitary gonadotropins [4]. Administering KI after PTU resulted in continuous estrous with the increase of the FSH and LH levels as in the KI-only treatment, but without its characteristic iodine level changes in the above-mentioned organs. It should be noted that in the EPMA point analysis the expressed hormonal changes originated by KI were followed by changes of the average iodine and selenium levels in both thyroid and pituitary glands, while PTU treatment resulted only in changes of thyroid gland average iodine level followed by the less pronounced hormonal changes.

The changes of trace elements in tissue of adrenal glands were not associated to changes in cortisol level. However, in a previous study on iodine-induced thyroid blockade, the cortisol level increased 2-fold from the second to the fifth day of the blockade and spontaneously stopped on the sixth day of the blockade [7]. Administering KI after PTU did not cause an increase of cortisol, suggesting that PTU possibly changed the reaction of the adrenal gland to those of the acute effects of iodide.

In conclusion, the reaction of the endocrine organs of female rats to PTU and KI share similar features and differences. Using EPMA to follow the iodine and selenium changes in the endocrine status of the ovaries, thyroid, pituitary and adrenal glands allowed us not only to compare some features of the K- and PTU-thyroid blockade, but also to compare the changes of these microelements in specific tissues of these organs.

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