Effect of propylthiouracil on the level of Schiff's bases in tissues of rats on diet with different doses of potassium iodide

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Submitted: August 6, 2006 *Accepted: August 18, 2006*

Key words: **propylthiouracil; Schiff's bases; potassium iodide; lung; liver; kidney**

Neuroendocrinol Lett 2006; **27**(5):595–599 **PMID:** 17159816 NEL270506A06

Abstract

OBJECTIVES: Iodide administration to animals, living in iodine-deficient areas, can induce oxidative processes in the thyroid gland and increase concentration of lipid peroxidation (LPO). Propylthiouracil (PTU) – a well-known antithyroid drug – may also act as an antioxidant. There are some reports, which consider the protective ability of this drug against LPO.
The goal of the study was to evaluate oxidative processes and the protective role of PTU in three rat organs during treatment with pharmacological doses of iodide.
MATERIAL AND METHODS: Schiff's bases (SB) concentrations (a parameter of oxidative stress) were measured in liver, lung and kidney homogenates of male Wistar rats. For 2 weeks the animals received iodides in their diet in the following concentrations: Group 1 – Controls (standard diet, approx. 0.7 mg of potassium iodide per kg; KI/kg); Group 2 – diet containing 0.25 mg KI/kg; Group 3 – diet with 4.0 mg KI/kg; Group 4 – diet with 8.0 mg KI/kg. Group 5 – standard diet with 0.1% of PTU in drinking water for two weeks. Subsequent tree groups (6–8) received KI in their diet in doses as above, respectively, together with PTU.
RESULTS: We noted increased SB levels in the lungs and in the liver, compared to those observed in the control group. We also found decreased SB concentrations in liver and lung homogenates after the administration of PTU but, unexpectedly, the level of SB increased in kidney homogenates of all the groups.
CONCLUSIONS: The results of this study indicate that iodine is involved in oxidative processes in different organs and PTU protects against iodine-induced oxidative stress.

ORIGINAL ARTICLE

Direct effects of iodine on the thyroid gland are well-known phenomena: small doses facilitate hormone synthesis, while large doses are inhibitory to the process. Besides this regulatory role, iodine demonstrates two other effects, exerted on the thyroid: toxicity, induced *in vivo* and *in vitro* in iodine-deficient glands, and facilitation of thyroid autoimmune disease development.

The toxic effects of iodine were, for the first time, shown in animals by Follis (1959) [7]. It has also been demonstrated that iodine excess in iodine-depleted thyroid glands can induce necrosis of thyroid follicular cells and produce changes, comparable to those, observed in oxidative stress and lipid peroxidation. Many et al. [14] found increased lipid peroxidation levels in mouse thyroids after high doses of iodine, as demonstrated by malondialdehyde concentrations and by partial protection by antioxidants. The free radical hypothesis, postulated by Denef et al. [5], confirms those changes. Free radicals are chemical constituents that have an unpaired electron in their outer orbital and are highly reactive, some of them being also toxic. Lipid peroxidation (LPO) is the most well known biological free-radical chain reaction.

Propylthiouracil (PTU) is a universally administered drug, used in hyperthyroidism [16]. However, PTU has also been reported to be a hydroxyl radical (•OH), hydrogen peroxide (H_2O_2) and superoxide anion radical ($O^{\bullet -}_2$) scavenger and an efficient inhibitor of lipid peroxidation [9]. Treatment with PTU has been shown to lower serum lipid hydroperoxide levels in hyperthyroid subjects [24]. It is successfully used in the therapy of alcoholic liver disease [15], in which chronic ethanol administration has been shown to induce hepatic hypermetabolic state with increased hepatic oxygen consumption and $O^{\bullet -}_2$ production [6].

Free-radical-mediated oxidative stress has been implicated in the development and exacerbation of several degenerative diseases. The involvement of free radicals in iodine toxicity mechanisms can be indirectly confirmed, i.e., via the demonstration of oxidative processes in animal organs during oxidative stress and lipid peroxidation.

The aim of the study was to examine the effects of PTU on oxidative processes, induced by different doses of iodide. Schiff's base (SB) concentrations (a parameter of oxidative stress) were measured in liver, kidney, and lung homogenates of male Wistar rats.

Materials and Methods

Male Wistar rats, weighing 200 ± 20g each at the beginning of the experiment, were used. The animals were kept in a room (21–23 °C) with stable temperature and controlled illumination (12 h light, 12 h darkness).

The animals (N=64) were divided into 8 groups, according to the contents of potassium iodide in food:

Group 1 – controls (standard normal-iodine diet – Motycz – containing aprox. 0.7 mg of potassium iodide (KI)/kg)
Group 2 – diet with 0.25 mg KI/kg
Group 3 – diet with 4.0 mg KI/kg
Group 4 – diet with 8.0 mg KI/kg
Group 5 – standard normal-iodine diet and 0.1% solution of PTU in drinking water
Group 6 – diet with 0.25 mg KI/kg and 0.1% solution of PTU in drinking water
Group 7 – diet with 4.0 mg KI/kg and 0.1% solution of PTU in drinking water
Group 8 – diet with 8.0 mg KI/kg and 0.1% solution of PTU in drinking water

The animals were decapitated after two weeks of the experiment, followed by collection of organs for studies. After weighing, the material was frozen in –80 °C till homogenisation and biochemical estimations were done.

SB concentrations – a connection of aldehydes with the amine group – were spectrofluorometrically estimated (the protocol, according to Buege and Aust – 1978) [3].

A statistical analysis of the obtained results was performed, using a one-way analysis of variance (ANOVA) and Newman-Keuls' test.

Results

We found increased SB levels in liver homogenates from the group of animals fed with 8.0 mg KI/kg in their diet and in lung homogenates from the group of rats fed with 4.0 mg KI/kg, compared to respective values in the control group and in the group of animals fed with 0.25 mg KI/kg in diet (Fig.1, 2). We did not find any statistical differences in SB levels of kidney homogenates. In liver homogenates, PTU decreased SB concentrations in the group of animals fed with 0.25 mg KI/kg and with 8.0 mg KI/kg in their diets, compared to those fed only with KI in the same concentrations (Fig. 3, 4). We also observed that PTU decreased SB concentrations in the group of rats on the 4.0 mg KI/kg diet, compared to those in lung homogenates from the group on the same diet (Fig. 5). Unexpectedly, PTU increased SB concentrations in kidney homogenates of Groups 5,6,7,8, compared to the values in the respective groups in which PTU was not administered (Groups 1,2,3,4) (Figures 6,7,8,9)

Discussion

The toxic effect of iodide, administered to iodine deficient animals, was described in rats, mice, chickens, and in isolated human follicles in culture [1,12,13]. The administration of large iodide doses to iodine-deficient animals induces necrosis of thyroid follicular cells. Morphological changes, induced by high doses of iodide, are consistent with the changes, observed during oxidative stress and lipid peroxidation.

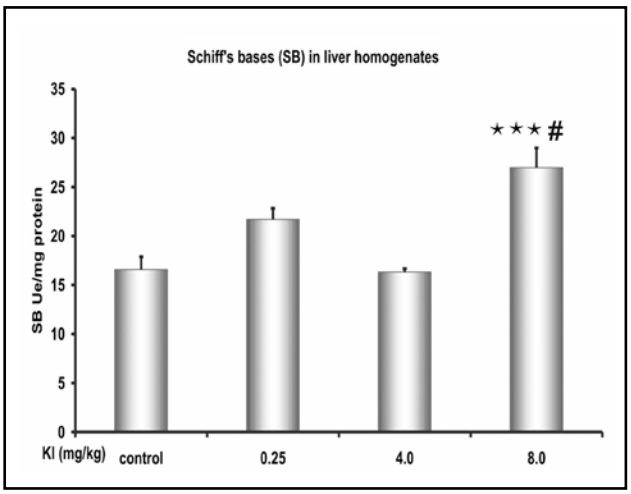

Fig. 1. Concentrations of Schiff's bases (SB) in liver homogenates. Mean values ± SEM. Statistical significance: ***p<0.05 vs. group of animals fed with 0,25 mg KI/kg in diet; # p<0.001 vs. Controls.

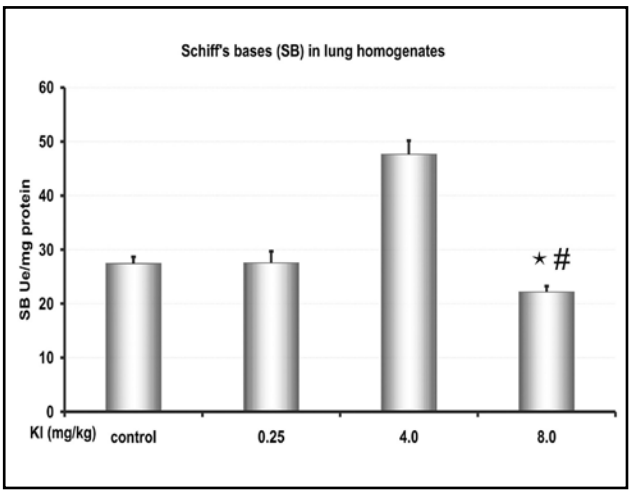

Fig. 2. Concentrations of Schiff's bases (SB) in lung homogenates. Mean values ± SEM. Statistical significance: * p<0.001 vs. group of animals fed with 0,25 mg KI/kg in diet;# p<0.001 vs. Controls.

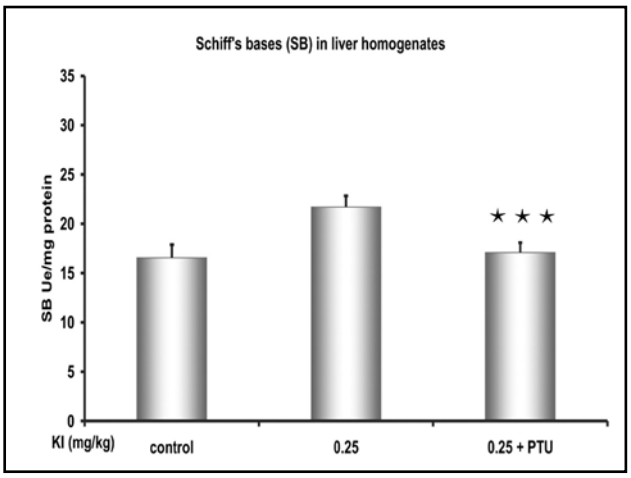

Fig. 3. Concentrations of Schiff's bases (SB) in liver homogenates after PTU administration. Mean values ± SEM. Statistical significance: *** p<0.05 vs. group of animals fed with 0,25 mg KI/kg in diet.

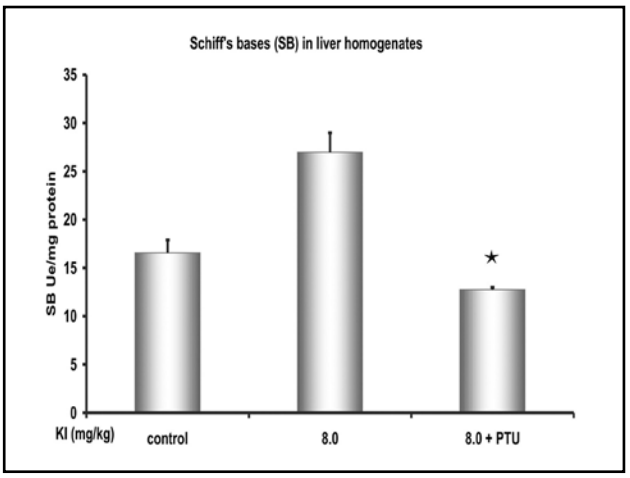

Fig.4. Concentrations of Schiff's bases (SB) in liver homogenates after PTU administration. Mean values ± SEM. Statistical significance: * p<0.001 vs. group of animals fed with 8,0 mg KI/kg in diet.

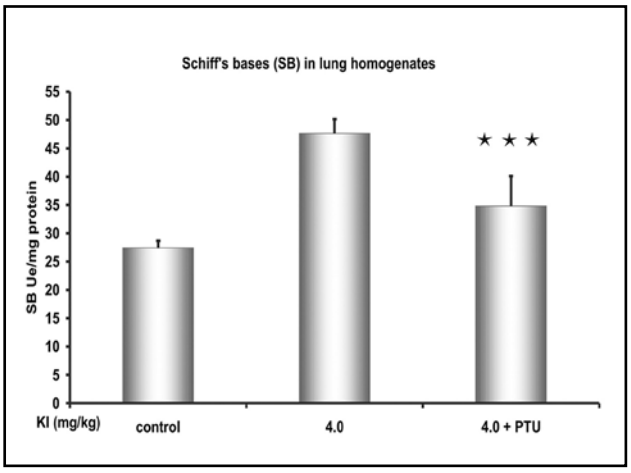

Fig.5. Concentrations of Schiff's bases (SB) in lung homogenates after PTU administration. Mean values ± SEM. Statistical significance: *** p<0.05 vs. group of animals fed with 4,0 mg KI/kg in diet.

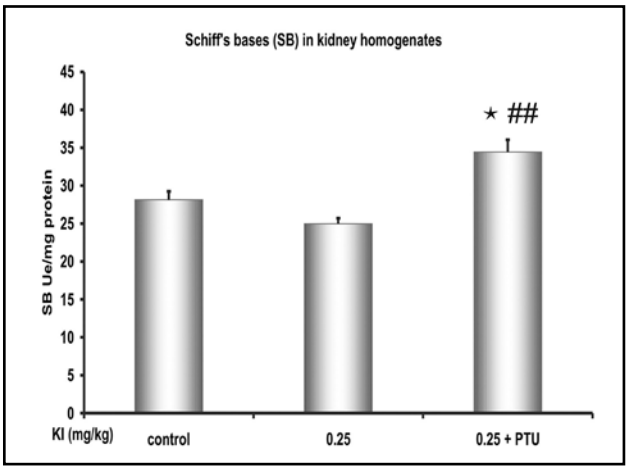

Fig.6. Concentrations of Schiff's bases (SB) in kidney homogenates after PTU administration. Mean values ± SEM. Statistical significance: * p<0.001 vs. group of animals fed with 0,25 mg KI/kg in diet; ## p<0.01 vs. Controls.

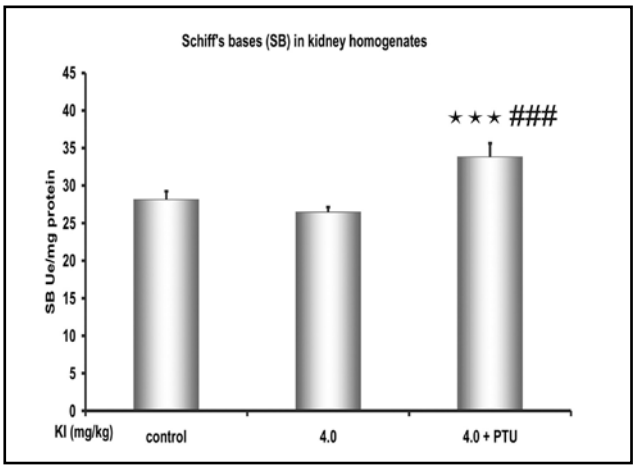

Fig.7. Concentrations of Schiff's bases (SB) in kidney homogenates after PTU administration. Mean values ± SEM. Statistical significance: *** p<0,05 vs. group of animals fed with 4,0 mg KI/kg in diet; ### p<0,05 vs. Controls.

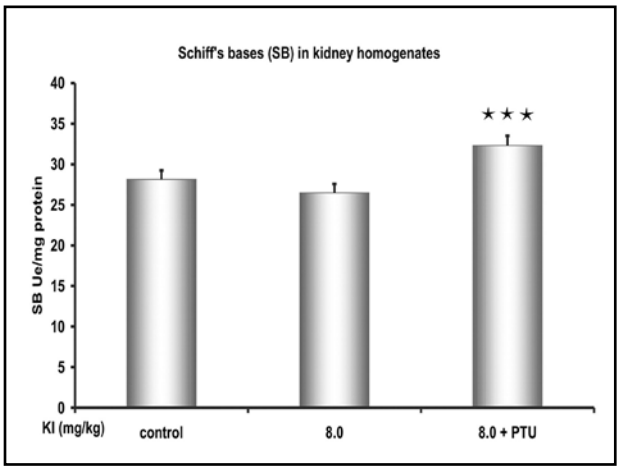

Fig.8. Concentrations of Schiff's bases (SB) in kidney homogenates after PTU administration. Mean values ± SEM. Statistical significance: ***p<0,05 vs. group of animals fed with 8,0 mg KI/kg in diet.

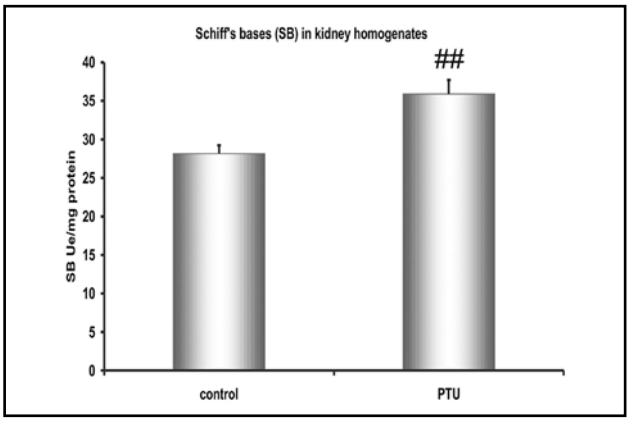

Fig.9. Concentrations of Schiff's bases (SB) in kidney homogenates after PTU administration. Mean values ± SEM. Statistical significance: ##p<0,01 vs. Controls.

The cellular response to free radicals is complex and depends on their concentration, on the molecular species, and on the type of cells and tissues.

The liver is an organ, which plays an important metabolic function in the organism, having a well-developed antioxidative defence system. Protective effects of PTU in the liver have been observed both in rats [8,10] and in humans [15]. PTU has also been demonstrated to reverse hypoxic liver damage, resulting from increased metabolic rate, associated with hyperthyroidism [24]. There are several studies, suggesting that PTU reduces alcohol-induced hepatocyte damage and severe alcoholic disease, due to scavenging reactions with hydroxyl radicals in particular and to its antioxidant potential in general [2,4,18].

In the present study, we observed increased SB levels in liver homogenates after the highest iodide dose. PTU decreased SB concentrations from the groups fed with 0.25 KI/kg and 8.0 KI/kg in their diet.

The lungs are organs, which have a close contact with the external environment. Because of that, the lungs have been equipped with a very effective system of endogenous antioxidants, activated after an excessive production of free radicals in this organ [11,17]. In our study, increased SB concentrations were demonstrated after high doses of iodine (4.0 mg KI/kg), compared to the values in the control group and those in the group with 0.25 mg KI/kg in diet. PTU decreased SB concentrations in the group of 4.0 KI/kg.

It has been shown in our previous paper that high doses of iodide induce lipid peroxidation in peripheral tissues [21], and melatonin, which is also well-known antioxidant, has protective effect [22]. Additionally, it has been shown, that Methimazole protects against oxidative stress induced by hyperthyroidism in Graves' disease [20], and PTU decrease LPO in basal condition and in L-thyroxine-induced hyperthyroidism in rats [23].

There has been no publications prepared by others, concerning the oxidative processes in the lung after high doses of iodine. There is a study which concludes that PTU treatment protects newborn rats against hyperoxia-induced lung injury and animals death. The protective

effect of PTU may be related to the inhibition of thyroid hormone production, the effects on oxygen metabolism, or its direct antioxidant properties [19].

In literature, we could not find any information, concerning the endogenous antioxidative system in the kidneys. In our experiment, in homogenates of this organ, PTU acted as a prooxidant, increasing SB levels in all the groups of rats. It is in agreement with the reports by Hick at al., suggesting that one of the radical forms of PTU, in concentrations above 50 μM, may intensify *in vitro* lipid peroxidation processes induced by linoleic acid [9].

Our results demonstrate that iodine is involved in oxidative processes in organs other than the thyroid gland as reported by other authors [14]. We cannot compare our results to those in other publications because of the lack of studies in general, which would deal with oxidative processes in peripheral tissues after an administration of high KI doses and with the protection by PTU. The results of this experiment confirm the differences in organ LPO production, which may be related to different sensitivity rates of tissues to oxidative processes and different amounts of endogenous antioxidants. We also proved the antioxidant role of PTU in the liver and in the lungs.

Acknowledgements

The study was financially supported by the Medical University of Łódź (Grant No. 502-11-805).

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