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Original research article

Alterations of antioxidant defense in rat liver in methimazole-induced hypothyroidism

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Abstract

Background and purpose: *According to the well-established role of thyroid hormones in regulation of the metabolism, the changes in thyroid status affect intracellular redox state and antioxidant defense. However, there are inconsistencies in the literature regarding the pattern of changes in antioxidant defense of hypothyroid states, especially those induced by methimazole. Hence, we examined here the effect of this antithyroid drug on the organization of antioxidant defense in rat liver.*

Materials and methods: *To do this adult male Wistar rats were treated with 0.04% methimazole in tap water for different time periods (7, 15 and 21 days). Along with histopathological analysis, total glutathione (GSH) content and activity of glutathione peroxidase (GSH-Px), glutathione reductase (GR), copper, zinc superoxide dismutase (CuZnSOD), manganese superoxide dismutase (MnSOD), catalase, thioredoxin reductase (TR) and glutathione S-transferase (GST) were examined.*

Results: *We found that total GSH content and the activity of GSH-Px and GR were decreased compared to euthyroid control after 21 days of methimazole treatment (after 15 and 21 or 21 days, respectively), while SODs and catalase were not affected by the treatment of any duration. In contrast, the activity of TR was increased after 7- and 15-day treatment. After 21 days of methimazole treatment the activity of GST decreased in comparison with control.*

Conclusions: *The observed changes of hydrogen peroxide producing (SODs) and removing (GSH, GSH-Px and GR) systems, along with the reduced GST activity in the liver after 21 days of methimazole treatment suggest redox specific reorganization in this tissue.*

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INTRODUCTION

Antioxidant defense (AD) represents a complex network of enzymatic and nonenzymatic components important for maintaining of tissue redox homeostasis and protection against harmful effects of reactive oxygen species (ROS) in virtually all cells of aerobic organisms *(1).* Generally, the main components of AD are enzymes that catalyze the dismutation of superoxide anion to hydrogen peroxide: copper, zinc superoxide dismutase (CuZnSOD, EC 1.15.1.1) and manganese superoxide dismutase (MnSOD, EC 1.15.1.1) as well as enzymatic and nonenzymatic components that cooperate in regulation of peroxides level like catalase (EC 1.11.1.6), glutathione (GSH), glutathione peroxidase (GSH-Px, EC 1.11.1.9), glutathione reductase (GR, EC 1.6.4.2), thioredoxin (Trx) and thioredoxin reductase (TR, EC 1.8.1.9). Organization

of the AD is tissue-specific and susceptible to alterations in response to changes in oxidative pressure and the tissue metabolic activity *(2–8)*.

Thyroid hormones play an important role in the regulation of the metabolism in all cells and tissues *(9)*. There are plenty of literature data showing that the effects of thyroid hormones on cellular metabolism are closely related to the regulation of the production of ROS. Since the general metabolic effect of thyroid hormones is a relative acceleration of the basal metabolism, it has been expected that hyperthyroidism is coupled with the increase in oxidative pressure and cellular damage *(10)*, while hypothyroidism causes hypometabolic state associated with metabolic dysfunction *(11–13)* and decreases oxidative pressure *(14)*. However, the published data of the effects of hypo- and hyperthyroidism on the production of ROS and AD organization in many tissues are quite inconsistent. For example, hypothyroidism does not modify *(15)*, reduce *(16)* or even increase *(17, 18)* oxidative damage in metabolically active organs. It seems likely that several factors determine the outcomes of the hypothyroidism including the strategy for its induction (chemical or surgical thyroidectomy) and, in the case of chemical induction, the route of drug administration, the dose used and treatment duration.

The commonly used chemical approach for induction of hypothyroidism is administration of methimazole, widely accepted drug for treatment of hyperthyroidism *(19–21)*. Among its primary effects on inhibition of thyroid hormones synthesis in thyroid gland, methimazole itself and methimazole-induced hypothyroidism exert plenty systemic, extrathyroidal effects in many tissues including spleen, heart, kidney, lung, liver and pancreas *(22, 23)*.

Hypothyroidism is nowadays a metabolic disease on the rise across the world as a result both of impairment in thyroid hormone synthesis and complications during the treatment of hyperthyroidism with methimazole. However, obesity-related thyroid dysfunction ("silent" - subclinical hypothyroidism) is yet another important factor playing the role in development of this disease *(24)*.

In this work, we analyzed the earliest, time-correlated changes of AD in the rat liver in methimazole-induced hypothyroidism. We examined the activity of superoxide dismutases (CuZnSOD and MnSOD), peroxidative part of AD (catalase, GSH, GSH-Px, GR and TR) and the main antioxidant enzyme that mediates liver drug detoxifying function, glutathione S-transferase (GST, EC 2.5.1.18), in the rat liver after 0.04% methimazole treatment for different periods of time (7, 15 and 21 days). We believe our results may provide potential direction for the new therapeutic approach which would include antioxidants in hypothyroidism therapy.

MATERIALS AND METHODS

Experimental design

The experiments were approved by the Ethics Committee for the treatment of experimental animals of the Faculty of Biology at the University of Belgrade and by the Veterinary Directorate of the Ministry of Agriculture and Environmental Protection of the Republic of Serbia (323-07-07505/2015-05/4 and 323-07-06857/2011-05). Two-month-old Wistar rats (330 ± 30 g) were maintained under 12 h light/dark cycles at 22 ± 1 °C and fed with commercial rat food (Subotica, Serbia) ad libitum. The rats were divided into two groups: 1) the euthyroid, which received only tap water and served as euthyroid control and 2) methimazole-induced hypothyroidism, in which animals received this anti-thyroid drug daily, as 0.04% solution in drinking water (Methimazole crystalline M8506, Sigma-Aldrich Chemie GmbH, Munich, Germany). Duration of treatment in the methimazole-treated rats ranged from 7-21 days (7, 15 and 21 days), with six animals per group. The rats were sacrificed by decapitation at mentioned time points, the livers perfused and dissected out.

Histopathological analysis

Immediately after sacrifice, the part of liver was removed and rinsed with physiological saline. For microscopic evaluation liver was fixed in 10% neutral phosphate buffer formalin solution for 48 h. Following dehydration in ascending series of ethanol, tissue samples were routinely embedded in paraffin. Tissue sections of 5 μm (Reichert, Austria), were stained with Mayer's haematoxylin, subsequently dehydrated and mounted in DPX medium (Mounting medium for histology, Sigma). All samples were viewed and analyzed with a Leica DMLB light microscope (Leica Microsystems, Wetzlar, Germany).

Measuring of enzymes activity

The part of the liver was thoroughly rinsed with physiological saline to remove traces of blood, homogenized (a Janke and Kunkel Ka/Werke Ultra/Turrax homogenizer) at 0-4 °C in 0.25 M sucrose, 0.1 mM EDTA and 50 mM Tris buffer, pH 7.4 and the homogenates were sonicated. Homogenates were used for measuring of the parameters of AD. Protein content in the tissues homogenates was estimated by the method of Lowry *et al. (25)* using bovine serum albumin as a reference.

Total SOD activity was examined by a modified method of Misra and Fridovich *(26)*. For determination of MnSOD activity, the assay was performed after preincubation with 4 mM KCN. The CuZnSOD activity was calculated as the difference between total SOD and MnSOD activities. Enzymatic activity was expressed in

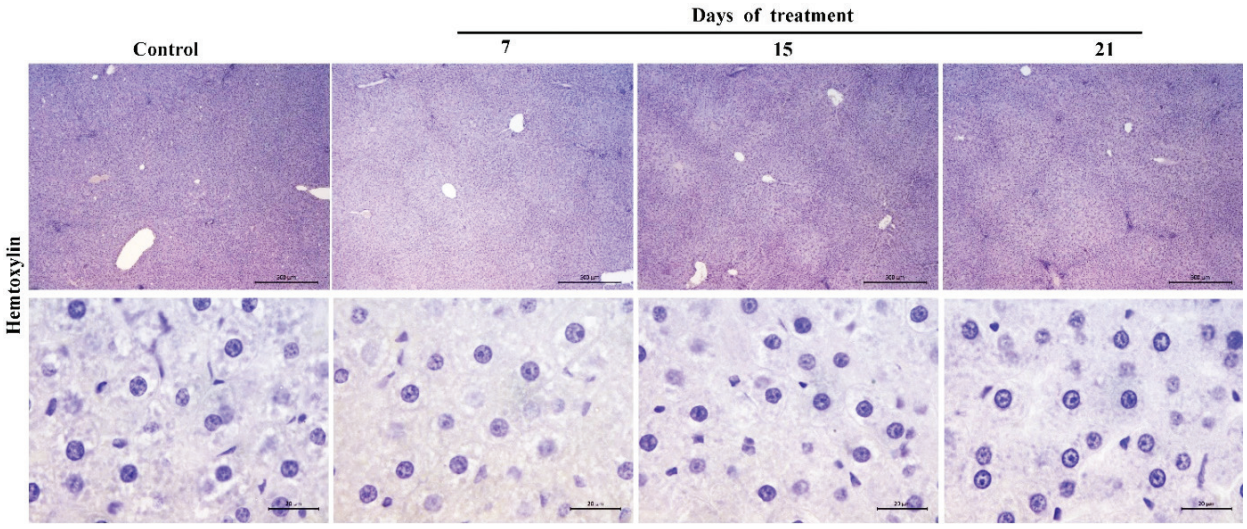

Figure 1. *Low (5x, upper panel) and high (100x, lower panel) magnification of rat liver sections stained with hematoxylin. Methimazole treatment during 7, 15 and 21 days did not cause noticeable histological and cytological changes. Magnification: 5x-upper panel, bar-500 μm; 100x-lower panel, bar-20 μm.*

U mg^{-1} protein. SOD units were defined as the amount of the enzyme inhibiting epinephrine autooxidation under the appropriate reaction conditions. Catalase was assayed as suggested by the supplier (Sigma-Aldrich, St. Louis, MO, USA) and the activity is expressed in μM H_2O_2 min^{-1} mg^{-1} protein. GSH-Px was determined with t-butylhydroperoxide as a substrate *(27)* and the activity is expressed in nM NADPH min^{-1} mg^{-1} protein. GR activity was assayed as suggested by Glatzle *et al. (28)* and expressed in nmol NADPH min^{-1} mg^{-1} protein. GST was measured by the method of Habig *et al. (29)* and the activity expressed in nmol GSH min^{-1} mg^{-1} protein. The content of GSH was examined in the tissue after deproteinization with sulfosalicylic acid. Total GSH was measured by enzyme-recycling assay after Griffith *(30)*, and expressed in nmol GSH g^{-1} tissue. TR was assayed according to Luthman and Holmgren *(31)*, and its specific activity was expressed in nM NADPH min^{-1} mg^{-1} protein.

Statistics

Analysis of variance (ANOVA) was applied for within-group comparison of the data from molecular analysis. If the F test showed an overall difference, Tukey's ***t***-test was used to evaluate significance of the differences. Statistical significance was accepted at $p < 0.05$ unless otherwise stated.

RESULTS

In the present study, we aimed to shed more light on the effect of methimazole-induced hypothyroidism on organization of AD in the rat liver. We analysed histology and AD in rat liver over 7, 15 and 21 days of methimazole-induced hypothyroidism.

Histopathological analysis

We first evaluated whether treatment with methimazole caused pathological changes in the liver on hematoxylin stained sections (Figure 1). The histological analysis of liver revealed normal histoarchitecture in both control (Figure 1, Control) and methimazole-treated rats (Figure 1, days 7, 15 and 21). In comparison to euthyroid control (Figure 1, Control), no signs of hepatic damage including hepatocyte's cytoplasmic vacuolization, necrosis and inflammatory cells infiltration, were observed at any of the examined methimazole treated groups (Figure 1, days 7, 15 and 21).

AD enzymes activity

As shown in Figure 2, methimazole treatment did not induce changes in the activity of MnSOD (B) and CuZn-SOD (C) in any examined time points.

However, total GSH content was decreased after 15- and 21-day of methimazole treatment in comparison to control (Figure 3A).

Also, the activity of GSH-Px was decreased after 15 days (Figure 3B), activities of GR (Figure 3C) and GST (Figure 3E) were decreased after 21 days, while catalase activity was not affected by the treatment at any time (Figure 3D). Contrary to the GSH-dependent part of AD, the activity of TR was increased compared to control after 7- and 15-day treatment (Figure 3F).

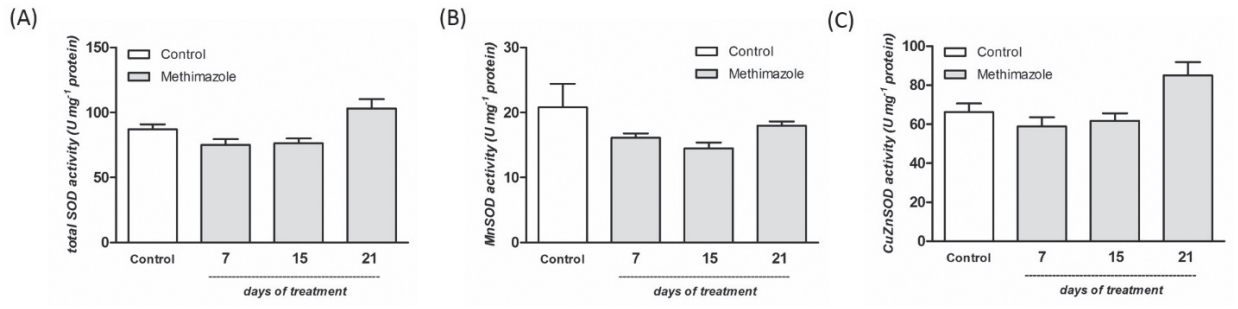

Figure 2. *The activity of total superoxide dismutase (total SOD, panel A), manganese SOD (MnSOD, panel B) and cooper-zinc SOD (CuZnSOD, panel C) in the liver of control and methimazole-treated groups. Bars represent the mean ± S.E.M of six animals per group.*

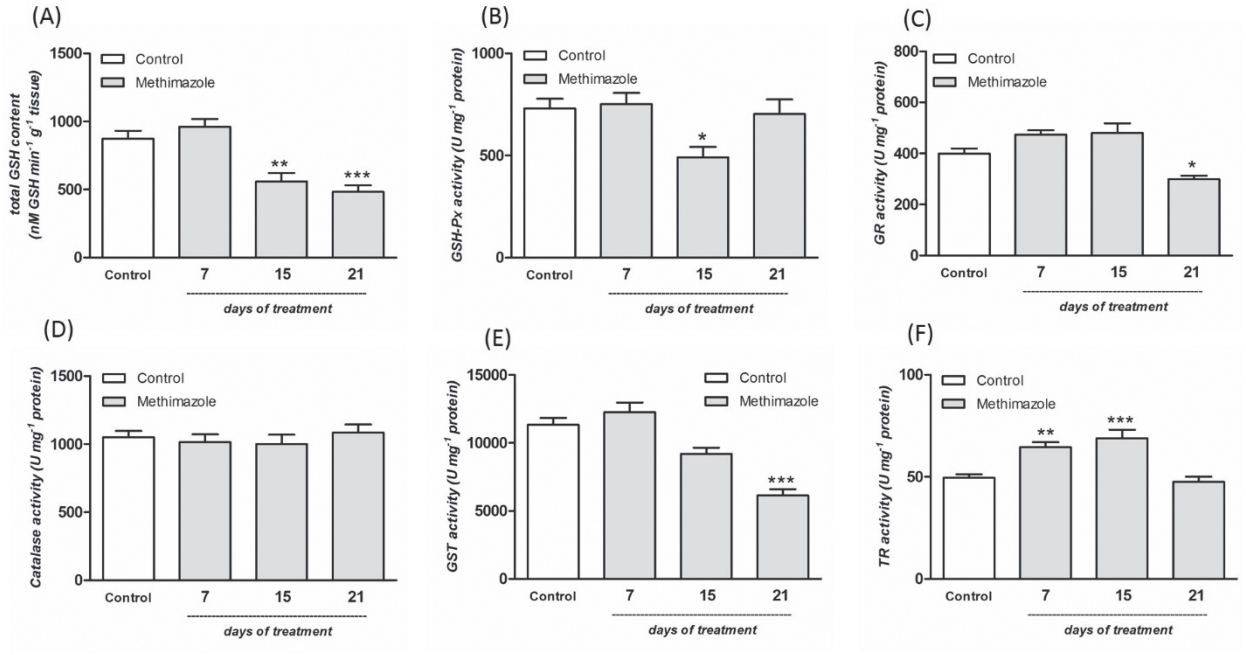

Figure 3. *Changes in total glutatione (GSH; panel A) and activities of GSH-Px (glutathione peroxidase; panel B), glutathione reductase (GR, panel C), catalase (D), glutathione S-transferase (GST, panel E), thioredoxin reductase (TR, panel F) in methimazole-treated groups. Bars represent the mean ± S.E.M of six animals per group. *Compared to control, *p < 0.05, **p < 0.01, ***p < 0.001.*

DISCUSSION

Thyroid hormones play an important role in regulation of whole-body metabolism *(32)*. However, the data of the effects of hypothyroidism, especially the effects of methimazole-induced hypothyroidism on intracellular redox and antioxidant state in the liver are not consistent. Herein we showed that methimazole-induced hypothyroidism drives reorganization in the AD in the rat liver in time-dependent manner: while there were no changes in the activity of superoxide dismutases (CuZnSOD and MnSOD), the activity of GSH-dependent part of AD including GSH-Px, GR and GST, along with the total GSH level, was decreased after 15- (total GSH, GSH-Px) and 21-day (GR and GST) treatment with methimazole. In contrast, the activity of TR was increased after 7 and 15 days of treatment. These changes in AD in the liver could reflect the effects of methimazole-induced hypothyroidism and/or methimazole itself on intracellular oxidant/antioxidant balance.

Bearing in mind the mode of action of thyroid hormones on tissue metabolism, the observed decrease in GSH-dependent part of AD after 15 and 21 days of methimazole treatment could be described as an adaptive response on suppression of metabolism due to prolonged methimazole treatment. Liver is continuously challenged with the high oxidative pressure as a result of the high metabolic activity, thus appropriate adaptive response of AD is crucial for maintaining the tissue redox homeostasis in the cases of metabolic disturbances. However, the existing literature data considering the effects of hypo- and hyperthyroidism on the production of ROS and AD

organization in many tissues are inconsistent, showing nonlinear ratio between respiration rate and ROS production. For example, hypothyroidism does not modify *(15)*, reduce *(16)* or even increase *(17, 18)* oxidative damage in metabolically active organs. Guerrero *et al. (33)* have found that hypothyroidism increases oxidative pressure in mouse liver, most likely the consequence of the effects of thyroid hormones on cellular metabolism. Production of ROS is complex and involve several aspects of THs action: a) regulation of mitochondrial respiratory state, synthesis of elements of respiratory chain *(34)*, mitochondrial proton leak *(35)* and mitochondrial biogenesis *(36)* and b) regulation of the expression of enzymes involved in ROS homeostasis, like NADPH oxidase and nitric oxide synthase *(37)*.

Considering the complexity of THs/ROS interplay, we should be careful when reaching conclusion that the decrease in GSH-related part of AD (GSH, GSH-Px and GR) is adaptive response on hypometabolism in methimazole-induced hypothyroidism; actually this could as well be the reason for increased oxidative pressure. Namely, the fact that the activity of SODs (which breaks down superoxide and thus contributes to the increase in hydrogen peroxide) does not decrease in parallel with hydrogen peroxide-scavenging AD components could increase peroxidative pressure. An increase in TR activity, as a part of peroxide-removing system complementary to GSH-dependent one supports this notion.

Decrease of the GST activity after 21 days of treatment also suggests that liver major detoxifying role in drug metabolism could be compromised after prolonged methimazole treatment. This is in line with the previously published data that methimazole itself may induce liver toxicity *(38, 23)*. The reduction of antioxidant defense and its relation with increased cellular damage in the liver in methimazole-induced hypothyroidism has also been reported *(39, 40)*. In contrast, we did not find any visible damage of hepatocytes using metimazole in concentration and administration route designed to examine early changes in AD *(19)*. Hence, our results demonstrate that methimazole treatment imposes the peroxidative pressure that could potentially be alleviated by antioxidants. Consequently, antioxidants may mitigate and prevent further ad alterations leading to hepatocyts damage and liver toxicity.

CONCLUSION

The results of the present study elucidate the effects of methimazole-induced hypothyroidism on antioxidative defense in the liver. It seems likely that methimazole treatment in a dose used therapeutically to reduce metabolic activity in hyperthyroidism leads to reorganization of antioxidative defense in the liver. Namely, the discrepancy in the changes in peroxide producing (SODs) and removing (GSH, GSH-Px and GR) systems represents specific response as a consequence of the newly established redox homeostasis. This indicates that specifically tailored antioxidant supplementation should be included to restore the redox environment to balance.

Our results highlight the importance of recognition of metabolic and oxidative tissue specific signature during methimazole administration and the significance of antioxidant intervention in order to mitigate liver-specific early changes in antioxidative defense.

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