Effects of certain antioxidants on lipid peroxidation process in lung homogenates of L-thyroxine-receiving rats

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Abstract

OBJECTIVE: A possible role of antioxidants in thyreotoxicosis was investigated. We examined the parameters of lipid peroxidation (LPO): conjugated dienes (CD), malondialdehyde (MDA), Schiff bases (SB) in lung homogenates of male Wistar rats.

METHODS: Two control groups were created: Group 1 – intact animals and Group 2 – animals injected with 0,9% NaCl. In Experiment I, the animals received L-thyroxin (LT4) i.p. (Groups 3–7). After one week the rats received additionally: Group 4 – melatonin (MEL); Group 5 – propylthiouracil (PTU); Group 6 – Ambroxol (AMB); Group 7 – N-acetylcysteine (NAC). In Experiment II, the animals received only antioxidants.

RESULTS: In Experiment I, we noticed a significantly higher MDA and SB level in Group 2, compared to that in Group 1. Moreover, we observed a significantly higher MDA and SB level in Group 3, vs. that in Group 1, but SB level was lower in Group 3 than in Group 2. Melatonin, PTU and NAC reduced CD; PTU, AMB diminished MDA and MEL, AMB lowered SB levels as compared to Group 3. In Experiment II, we observed significantly higher MDA and SB level in Group 2, vs. that in Group 1. Melatonin, AMB and NAC decreased MDA and SB level, when compared to Group 2 but PTU elevated MDA and SB level vs. that in Group 1.

CONCLUSIONS: 1) L-T4 suppresses LPO, 2) MEL, AMB and NAC protect against LPO, 3) PTU is an antioxidant in thyreotoxicosis, however, when administered alone, it enhances LPO, 4) stress accelerate LPO.
INTRODUCTION

Free radicals (FR) occur as by-products of mitochondrial metabolism in the mechanism of electron leak from the respiratory chain. Lipid peroxidation (LPO) is the best-known chain free radical process. The following products result, among others, from subsequent stages of this process: conjugated dienes (CD), aldehydes, such as: malondialdehyde (MDA) and Schiff bases (SB) (Asayama et al. 1987).

An excess of thyroid hormones accelerates the basic metabolism, especially aerobic metabolism in mitochondria (Fernandez et al. 2006; Harper and Seifert 2008). Triiodothyronine (T₃) - induced enhanced oxygen use leads to excessive production of aerobic free radicals and - subsequently - to an increased use of intracellular antioxidants, as well as to inactivation of antioxidative enzymes, inducing, in this way, oxidative stress in tissues, both in thyroid hormone receiving animals and in people with hyperthyroidism (Fernandez et al. 2006). Excessive LPO in hyperthyreosis results from enhanced cellular respiration; euthyreosis restoration normalises the process (Bianchi et al. 1999).

The cells are equipped with an antioxidative protection system, which is responsible for systemic protection against detrimental effects of free radicals (Sewerynek and Wiktorska 1997). However, the efficiency of this system fails in cases of an excessive severity of oxidative stress (Bartosz 2003). Studies of many authors concentrate on searching for substances which, when, administered, could suppress the production of free radicals and reduce the degree of FR-induced damage. Examples of such compounds include drugs, such as prophylthiouracil (PTU), ambroxol (AMB), N-acetylcysteine (NAC) or certain hormones, such as melatonin (MEL).

Prophylthiouracil is well known anti-thyroid drug. It has also got antioxidative properties (Hicks et al. 1992; Wiktorska et al. 2002). A number of authors claim that a therapy with PTU application reduces LPO severity in patients with hyperthyroidism (Bianchi et al. 1999). It is not clear, however, if PTU directly “sweeps” FR and LPO products (Hicks et al. 1992) or if this activity results from regained euthyreosis (Bianchi et al. 1999).

Melatonin (5-metoxy-N-acetyltryptamine) is a hormone, synthesised in the pineal gland. During recent years, much attention has been paid to its antioxidative and anti-neoplastic potential (Karbownik et al. 2001). Many authors highlight the fact that MEL effectively reduces the degree of LPO in lung homogenates (Sewerynek et al. 1993, 1995). It should be stressed that this agent reveals affinity to pulmonary tissue, where its concentrations are much higher than in blood. There are also many reports on anti-oxidative effects of NAC (Nowak et al. 1993; 1995). The most significant NAC activity is associated with increasing the resources of intracellular GSH (Gillissen and Nowak 1998). It should be stressed that the lungs, as an organ, directly exposed to contacts with the outer environment, are at the highest risk of being the target for many harmful biological and chemical agents, contained in the air. Smaller basic intensification of LPO (López-Torres et al. 1993) and smaller – than in remaining studied rats’ organs – activity of cytochrome oxidase (Pérez-Campo et al. 1993) evidence about efficiency of antioxidant defense mechanisms in lung.

The goal of this study was an evaluation of LPO severity in the lung of rats, administered with levothyroxin (L-T₄) injections. Either the levels or the concentrations of LPO – CD, MDA and SB products in lung homogenates were measured, as well as the antioxidative effects of PTU, MEL, AMB and NAC were determined in suppressing the process. The study aimed also at an analysis of the antioxidative effects of PTU, MEL, AMB and NAC on the basic level of LPO products.

MATERIAL AND METHODS

The experiments were performed on male Wistar rats with initial body weight of 220 ± 20 g. The animals were kept at a room with constant temperature (21–23°C) and controlled light conditions (12 h light/12 h darkness, the light phase beginning at 6:00 a.m.). The rats had constant access to standard feed (LSM-Agropol, Motycz) and tap water.

All the injections were done intraperitoneally (i.p.) between 4:00–4:15 p.m. The active substances were administered, following their prior solution in 0.9% sodium chloride (NaCl) (the volume of injected solutions – 0.8 ml). Melatonin was, at first, solved in a small ethanol (absolute alcohol) volume and then in 0.9% solution of NaCl (ethanol concentration in the final solution was not above 1%). The solutions of used agents were prepared every day, ex tempore.

After experiment time period, planned for each study group, the animals were anaesthetised, weighed and decapitated. Immediately before decapitation, blood was aspirated by heart apex puncture. Then, lungs were collected from all the animals, which were stored in –80°C until homogenised and biochemically assayed. The homogenates were prepared in 1:10 dilution (1 weighed part of defrozen tissue: 10 volumetric parts of homogenate), using redistilled water of temperature close to 0°C. In blood plasma, thyroid hormone concentrations – free thyroxin (FT₃) and free triiodothyronine (FT₁) – were measured by the immonochromolinescent method. The following LPO products were measured in tissue homogenates: MDA (acc. to Rice and Evans (1991)) and CD (acc. to Buege and Aust
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Two experiments were performed. Because of different ways of antioxidant administration, two control groups were introduced in both experiments (Group 1 and 2). The animals of Group 1, not receiving any injections (intact animals), were in the control group for the rats, which received PTU in their drinking water. Additionally, Group 1 was regarded as the control for the effects of other substances (NaCl, L-T₄, MEL, AMB and NAC). The rats, receiving injections of 0.9% NaCl solution (Group 2), were regarded to be the control for the animals, receiving L-T₄, MEL, AMB and NAC also by injections. In Experiment I, the animals received L-T₄ in dose of 100 µg/kg b.w. per day, i.p., for 14 days (Group 3–6) and, additionally, antioxidants for a 7-day, decapitation preceding period: PTU in drinking water – 0.1% solution (Group 4), MEL in dose of 5 mg/kg b.w. per day, i.p. (Group 5), AMB in dose of 0.169 mmol/kg b.w. per day, i.p. (Group 6) or NAC in dose of 0.169 mmol/kg b.w. per day, i.p. (Group 7). In Experiment II, the animals received L-T₄ in dose of 100 µg/kg b.w. per day, i.p. (Group 4), AMB in dose of 0.169 mmol/kg b.w. per day, i.p. (Group 5) or NAC on dose of 16.9 mmol/kg b.w. per day, i.p. (Group 6).

The results, obtained in both experiments, were submitted to statistical analysis by means of the one-way ANOVA test (a one-way analysis of variance). Newman-Keuls's test was applied in order to identify statistically different groups and to determine statistical significance. The calculations were performed by the “STATISTICA” computer program. The results have been presented as figures, on which the levels of statistical significance (p) are indicated.

RESULTS

Experiment I

After the experiment, a lower body mass was found in the rats of the group administered with L-T₄ and PTU (Group 4), if compared with either the group, receiving L-T₄ (Group 3) or both control groups (Group 1 and 2) (Figure 1).

In all the studied groups of animals, which were injected L-T₄ (Groups 3–7), an increase of FT₄ concentration was indicated with reference to both control groups (Group 1 and 2). In the rats, submitted to the activity of L-T₄ and PTU (Group 4), L-T₄ and AMB (Group 6), L-T₄ and NAC (Group 7), the concentration of FT₄ was higher in comparison with the animals, which received L-T₄ (Group 3) (Figure 2). Higher FT₃ concentration was observed in the rats, receiving L-T₄ (Group 4) in comparison with Groups 1 and 2. FT₃ concentration was lower in the rats, exposed to the activity of L-T₄ and PTU (Group 4) and L-T₄ and MEL (Group 5), when referred to the rats, injected with L-T₄ (Group 3) and was not statistically different from the concentrations, observed in Groups 1 and 2. FT₃ concentration in the animals, receiving L-T₄ and NAC (Group 7) was higher in comparison with the rats, receiving L-T₄ (Group 3). In the animals, injected with L-T₄ and AMB (Group 6) or L-T₄ and NAC (Group 7), higher concentrations of FT₃ were obtained than in Groups 1 and 2 (Figure 3).

It was also found that PTU (Group 4), MEL (Group 5) and NAC (Group 7) decreased CD level with regards to the rats, receiving L-T₄ (Group 3) (Figure 4).

A difference of MDA and SB concentrations was obtained between the control groups – the parameters reached higher values in the animals, injected with 0.9% NaCl solution (Group 2), when compared with intact animals (Group 1) (Figures 5 and 6).
**Fig. 2.** Concentrations of FT$_4$ in the serum of rats. Data represent means ± SEM. Level of significance:
- ▲▲▲ - vs. untreated controls, p<0.0005
- ■■■ - vs. saline treated group, p<0.0005
- *** - vs. L-T$_4$ - treated group, p<0.0005
- ** - vs. L-T$_4$ - treated group, p<0.005
- * - vs. L-T$_4$ - treated group, p<0.05

**Fig. 3.** Concentrations of FT$_3$ in the serum of rats. Data represent means ± SEM. Level of significance:
- ▲▲▲ - vs. untreated controls, p<0.0005
- ■■ - vs. untreated controls, p<0.005
- ■■■ - vs. saline treated group, p<0.0005
- ■■ - vs. saline treated group, p<0.005
- *** - vs. L-T$_4$ - treated group, p<0.0005

**Fig. 4.** Levels of CD in the lungs of rats. Data represent means ± SEM. Level of significance:
- * - vs. L-T$_4$ - treated group, p<0.05
Malondialdehyde concentration was higher in the rats, which had been administered L-T₄ (Group 3) than in Group 1. Prophylthiouracil (Group 4) and AMB (Group 6) decreased MDA concentration in comparison to both the group, receiving L-T₄ (Group 3) and Group 2, down to a value not significantly differing from that, observed in Group 1. In the animals, submitted to the joint activity of L-T₄ and MEL (Group 5) or of L-T₄ and NAC (Group 7), the value of that parameter was higher with regards to Group 1 (Figure 5).

Shiff bases level had the lowest values in the rats, which had been injected L-T₄ (Group 3), when referred to Group 2, while it demonstrated a higher value from that, obtained in Group 1. In the animals, submitted to the joint activity of L-T₄ and MEL (Group 5) or of L-T₄ and NAC (Group 7), the value of that parameter was higher with regards to Group 1 (Figure 5).

Experiment II
After the experiment, a lower body mass was found in the rats of the PTU administered group (Group 3) in comparison to both control groups (Groups 1 and 2) (Figure 7).

Lower concentration of FT₄ was obtained in the PTU receiving animals (Group 3) than in both control groups (Groups 1 and 2). NAC (Group 6) decreased the value of that parameter, with reference to the rats, injected with 0.9% NaCl solution (Group 2) (Figure 8). Also, a decrease in FT₃ concentration was observed in
the animals, exposed to PTU activity, when compared with that in Group 2. The studied parameter reached a higher values in the MEL administered rats (Group 4), when compared to intact animals (Group 1) (Figure 9).

No statistically significant differences were noted in CD level (Figure 10).

It was found, however, that MDA concentration and SB level were higher in Group 2 than in Group 1 (Figures 11 and 12).

The administration of MEL (Group 4), AMB (Group 5), NAC (Group 6) decreased MDA concentration in comparison with Group 2, however, that parameter had a higher value from that, observed in Group 1. Prophylthiouracil (Group 3) increased MDA concentration in comparison with the respective control group (Group 1); however, that parameter demonstrated a lower value, when compared to the one in Group 2 (Figure 11).

Melatonin (Group 4) and NAC (Group 6) decreased the value of that parameter with regards to Group 2, down to a value not significantly different from that, obtained in Group 1. In turn, AMB (Group 5) decreased SB level, when compared to that in Group 2; that parameter reached a higher value from that in Group 1. It was demonstrated that PTU administration (Group 3) increased SB level in comparison to the respective control group (Group 1), although that parameter had a lower value from that, observed in Group 2 (Figure 12).
DISCUSSION

In the present paper, body mass decrease was demonstrated in the rats, administered either PTU alone or PTU together with L-T₄, when compared with the animals of the other groups. Similar observations were made by other authors (Asayama et al. 1987; Kariya et al. 1983, Sahoo et al. 2008). The suppression of body mass growth in the animals after PTU may be explained by the toxic effects of anti-thyroid drugs (Kariya et al. 1983). However, no statistically significant difference was observed in body mass of the rats, receiving L-T₄. It is conformable with reports of other authors (Asayama et al. 1987).

It is worth noting that the identification of clinical symptoms of thyreotoxicosis in rats is rather difficult. As it has already been mentioned, neither in this paper nor in reports of other authors, no body mass decrease – a phenomenon, typical for hyperthyroidism in humans – was demonstrated. A proof for the efficacy of L-T₄ administration was the statistically significant increase of FT₄ and FT₃ in blood serum, also observed by other authors (Asayama et al. 1987; Baydas and Meral 2005; Mano et al. 1995; Sewerynek et al. 1999).

In the present study, MEL, administered together with L-T₄, decreased FT₃ concentration in blood of the animals, while, when given separately, it demonstrated an opposite activity – increasing the level of FT₃. There are numerous reports, indicating the suppressive effect of MEL on growth processes and synthesis of the thyroid hormones (Karbownik and Lewinski 2003).

In the performed experiments, similarly as in the earlier publication (Wiktorska et al. 2005), a difference was observed between the two control groups in the content of LPO products. The levels of oxidative stress parameters were significantly higher in the animals, receiving injections of 0.9% NaCl solution, when compared with intact animals. Those results suggest a stimulatory effect of stress on LPO. The stress may probably have been induced by manual handling of the animals and by the accompanying laboratory procedures. Smith-Kielland (Smith-Kielland and Morland 1981) claims that the enhanced synthesis of proteins in the livers of rats, receiving intraperitoneal injections of 1 ml of 0.9% NaCl solution resulted from stress and suggests that catecholamines and some steroid hormones mediate these changes.

Surgical stress is a known factor, enhancing LPO in pulmonary tissue (Jablonka et al. 1992). Other authors observed amplified oxidative stress in rats, resulting from opening the abdominal cavity and touching the intestine (Thomas et al. 2003). Other stressors, intensifying LPO process, include noise (Manikandan et al. 2006), sleep deprivation (Singh et al. 2008), long-term isolation (Huong et al. 2005) and immobilisation and cold (Bozhko and Gorodetskaya 1991).

In the available literature, numerous reports can be found on oxidative stress intensification in the course of hyperthyroidism in humans (Wiktorska et al. 2006a). Many of these reports indicate LPO enhancement in hyperthyreosis and normalisation of these parameters under PTU (Bianchi et al. 1999; Erdamar et al. 2008; Yavuz et al. 2004), or tiamazol therapy (Bozhko and Gorodetskaya 1991; Sewerynek et al. 2000). It should be noted that some authors have observed enhanced LPO in the course of both hyper- and hypothyroidism in

![Fig. 11. Concentrations of MDA in the lungs of rats. Data represent means ± SEM. Level of significance:

- vs. untreated controls, p<0.0005
- vs. saline treated group, p<0.0005
- vs. saline treated group, p<0.005](image1)

![Fig. 12. Levels of SB in the lungs of rats. Data represent means ± SEM. Level of significance:

- vs. untreated controls, p<0.0005
- vs. saline treated group, p<0.005](image2)
humans (Dumitriu et al. 1988; Erdamar et al. 2008; Oge et al. 2004). There are also numerous papers, reporting that L-T₄ administration to rats enhances LPO in blood (Baydas and Meral 2005), in the brain (Wiktorska et al. 2005; Mogulkoc et al. 2005c), in the heart (Asayama et al. 1987; Mogulkoc et al. 2005c), in the liver (Mogulkoc et al. 2005c) and in kidneys and testes of rats (Mogulkoc et al. 2005a).

Unexpectedly, in this study, no LPO induction was demonstrated in lung homogenates of the rats injected with L-T₄ on the contrary, the level of SB in those animals was lower, when compared with the control group, receiving 0.9% NaCl solution. LPO decrease in thyrotoxicosis is in conformity with reports of other authors. According to Bozhko and Gorodestkaia (1991), an administration of pharmacological doses of iodide (Sewerynek et al. 1995) of rats.

It was observed in the present study that PTU had decreased CD level and MDA concentration in lung homogenates from the L-T₄ administered animals. Similar observations were made in brain homogenates (Wiktorska et al. 2005). In another study PTU decreased SB concentrations in liver and lung homogenates after the administration of pharmacological doses of iodide (Sewerynek et al. 2006). According to Rodriguez-Pierce et al. (1994), PTU, when administered to pregnant rats, reduced the formation of MDA and of pathological changes in the lungs and increased the survival of new-borns, submitted to hyperoxia. There are also studies, confirming the inhibitory effect of this drug on oxidative processes in the course of hyperthyreosis in humans (Bianchi et al. 1999; Erdamar et al. 2008; Yavuz et al. 2004).

However, PTU, administered to animals, which did not receive L-T₄ before, induced hypothyreosis and increased the levels of MDA and SB in lung homogenates. It is known that hypothyreosis causes profound changes in oxidative processes of organisms (Wiktorska et al. 2006b). Intensification of oxidative stress was observed in studies on hypothyroidism in humans (Dumitriu et al. 1988; Erdamar et al. 2008; Nanda et al. 2008; Oge et al. 2004). The authors assume that that the excessive LPO results from slower metabolic changes (Dumitriu et al. 1988). Also in the studies, performed on animals, PTU enhanced LPO in internal organs: the brain (Rahaman et al. 2001), the liver (Yilmaz et al. 2003), the testis (Sahoo et al. 2008) and in the heart (Chattopadhyay et al. 2003). Supposedly, PTU has also got prooxidative properties per se (Hicks et al. 1992; Wiktorska et al. 2002).

There are also papers, reporting that hypothyreosis caused LPO suppression in the brain (Mogulkoc et al. 2005b; Wiktorska et al. 2005), in the liver (Mogulkoc et al. 2005b), in the heart (Mogulkoc et al. 2005b; Yilmaz et al. 2003), in the testis (Mogulkoc et al. 2005d; Sahoo et al. 2008), in the kidney (Mogulkoc et al. 2005d) and in the thyroid (Yilmaz et al. 2003). Moreover, hypothyreosis in experimental animals minimises oxidative pulmonary damage, associated with the application of ionising radiation (Sener et al. 2006) and hyperoxia (Rodriguez-Pierce et al. 1994). Probably, PTU administration is advantageous only in thyreotoxicosis and in such cases which, in a certain degree, simulate the condition, leading to increased metabolism (Wiktorska et al. 2006b). Furthermore, Sahoo et al. (2008) has claim that transient hypothyroidism induced by PTU treatment for 30 days decreased LPO in rat testis, but LPO were elevated during persistent hypothyroidism (90 days treatment).

In the present study, MEL decreased CD and SB levels in lung homogenates of the animals, receiving injections of L-T₄. Also in other experiments, suppression of excessive LPO was observed in the brains (Mogulkoc et al. 2006; Wiktorska et al. 2006b), in kidneys (Mogulkoc et al. 2005a; Sewerynek et al. 1999), in the testes (Mogulkoc et al. 2005a) in the heart and in the liver (Mogulkoc et al. 2006; Popov et al. 2008), as well as in the blood (Baydas and Meral 2005; Popov et al. 2008) of rats in experimentally induced hyperthyreosis. Moreover in our laboratory, noticed that MEL decreased SB concentrations in liver and lung of rats after the treatment with different doses of iodide, but – unexpectedly – the level of SB increased in lung in the group with the highest dose of iodine in diet (Świerczyńska-Machura et al. 2004).

In the present study, MEL decreased the basic levels of MDA and SB in lung homogenates. It appears from earlier reports that this hormone reduced the basic LPO in the brain (Wiktorska et al. 2005) and in kidneys (Sewerynek et al. 1999).

It was observed in the performed studies that AMB had decreased MDA and SB levels in lung homogenates of rats after L-T₄ injections. Similar observations were made in brain homogenates of the rats, receiving L-T₄ (Wiktorska et al. 2005). It appears from the studies, performed by Nowak et al. (1993) that AMB reduced CD formation in the lungs and in the heart of mice, induced by administration of endotoxins. In another experiment, those authors demonstrated that a single AMB administration had brought back CD and MDA levels to their normal values in the cardiac muscle, however, it failed to protect against dexorubicine-induced LPO in the lungs and the livers of mice (Nowak et al. 1995). Moreover, this drug, when intraperitoneally injected to mice, reduced LPO in lung homogenates, submitted to the temperature of 50°C and to H₂O₂ (Nowak et al. 1994).

It should be noted that in Experiment II, AMB decreased the basic concentration of MDA, as well as SB levels in lung homogenates. In other experiments, a decrease of the basic level of CD and SB was obtained in the brains of rats (Wiktorska et al. 2005) and of CD
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in homogenates of the lungs, the heart and the liver in mice, following the administration of this medication (Nowak et al. 1994).

In our present study, NAC reduced CD level in lung homogenates of the L-T4 receiving animals. It remains in conformity with other reports, demonstrating that this drug used to suppress LPO in the brains of L-T4 receiving rats (Wiktorska et al. 2005), as well as in the hearts of rats after T3 (Venditti et al. 1998). In earlier experiments, protective activity of NAC was observed in the organ in question, suppressing endotoxin (Nowak et al. 1993), 50°C temperature (Nowak et al. 1994) and nicotine (Sudheer et al. 2008) induced LPO.

In the present study, NAC, administered separately, decreased values of the majority of studied LPO parameters in lung homogenates. A decrease of basic CD level in homogenates of the lungs, the heart and the liver, following the administration of this drug, was also noted by Nowak et al. (Nowak et al. 1994).

The results of the performed studies indicate that:
1) the administration of L-T4 suppresses LPO in the lungs of rats, 2) MEL, AMB and NAC effectively protect against LPO, 3) PTU is an effective antioxidant in thyreotoxicosis, however, when administered alone, it induces hypothyreosis and enhances LPO, 4) the differences in LPO, observed between the two applied control groups, suggest a stimulatory effect of stress on oxidative processes in the lungs.

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