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ORIGINAL ARTICLE

Indole-3-propionic acid reduces lipid peroxidation induced by potassium iodate in porcine thyroid

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ABSTRACT

Iodine is a trace element indispensable for thyroid hormone biosynthesis but its deficiency is a global problem. Programs of iodine prophylaxis are frequently based on salt iodization with the use of potassium iodate (KIO_3), which, however, reveals potential prooxidative properties. Indole-3-propionic acid (IPA), deamination product of tryptophan, is an effective antioxidant without prooxidative properties. We have shown in our previous study that melatonin is able to reduce lipid peroxidation caused by KIO_3. Taking into account the similarity between melatonin and IPA we decided to evaluate potential protective effects of this compound against KIO_3-induced lipid peroxidation in porcine thyroid homogenates. In the current study thyroid homogenates were incubated in the presence of different concentrations of KIO_3 without/with IPA. Six experiments were performed with different concentrations of IPA. Malondialdehyde+4-hydroxyalkenals (MDA+4-HDA) concentration (LPO index) was measured spectrophotometrically. IPA reduced in concentration-dependent manner (with statistical significance for concentrations of 10 mM, 7.5 mM, 5.0 mM) KIO_3-induced lipid peroxidation, but only when KIO_3 was used in concentrations of 10 mM and 7.5 mM, which are close to physiological iodine concentration in the thyroid (***i.e.*** ~10 mM). In conclusion, IPA might be considered as a pharmacological agent to be used for protection against prooxidative effects of iodates.

KEY WORDS: indole-3-propionic acid; potassium iodate; lipid peroxidation; thyroid, antioxidant

Introduction

Oxidative reactions are widely common in all tissues and organs. Reactive oxygen species (ROS) play an important role in physiological processes *e.g.*, in thyroid hormone biosynthesis (Brieger *et al*., 2012; Kehrer & Klotz, 2015). In the thyroid gland, ROS, such as hydrogen peroxide (H_2O_2), are produced in huge amounts. For this reason, the thyroid is regarded as an organ of "oxidative nature" (Karbownik-Lewinska & Kokoszko-Bilska, 2012). Under physiological conditions, there is a balance between prooxidants and antioxidative protective mechanisms in the thyroid (as in other tissues). However, any internal or external pathological factor may disrupt this balance leading to several thyroid diseases, such as Hashimoto thyroiditis or thyroid carcinoma (Ates *et al*., 2015; Tabur *et al.,* 2015).

Iodine is a fundamental trace element used for thyroid hormone synthesis. Iodine deficiency is a global problem. It can cause many adverse effects on growth and development *e.g.*, goiter, hypothyroidism, cretinism and impaired cognitive development (Niwattisaiwong *et al*., 2017). One of the safest and the most efficient methods of achieving iodine sufficiency is salt iodization. Furthermore, other exogenous iodine sources, such as iodine-containing multivitamins, may also be useful (Niwattisaiwong *et al*., 2017; Bouga *et al.,* 2018). Programs of iodine prophylaxis in different countries are based on the use of either potassium iodide (KI) or potassium iodate (KIO_3) (Wu *et al*., 2002). These two compounds have different properties, for example iodide (I^-) is rapidly absorbed in the upper gastrointestinal tract (in the stomach and duodenum), while iodate (IO_3^-) is reduced in the gut and absorbed as iodide (Nicola *et al*., 2015; Cao *et al*., 2015). KI and KIO_3 have also different pro- and antioxidative features. KIO_3 reveals stronger oxidizing properties than KI. This could

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be due to the fact that iodide is the reductant, whereas iodate is the oxidant and may react very easily with oxidisable substances (Cao *et al*., 2015). As mentioned above, to be effectively used in human body IO_3^- should be reduced to I^- (Cao *et al*., 2015). Furthermore, KI and KIO_3, when used in doses recommended in iodine prophylaxis (resulting in physiological iodine concentration in the thyroid (Taurog *et al.,* 1947; Taurog *et al*., 1951; Tiran *et al*., 1993)), revealed opposite effects on oxidative damage to membrane lipids; namely, KI was protective, whereas KIO_3 strongly increased lipid peroxidation (Milczarek *et al*., 2013). Additionally, the superiority of KI over KIO_3 relies on its stronger protective effects against oxidative damage to mtDNA (Karbownik-Lewinska *et al*., 2015).

Due to the potential prooxidative properties of KIO_3 confirmed also in our previous studies (Milczarek *et al*., 2013; Iwan *et al*., 2021) it is advisable to look for antioxidants, which can protect against damaging effects of this compound.

Indole-3-propionic acid (IPA), deamination product of tryptophan formed by symbiotic bacteria in the gastrointestinal tract of mammals and birds, is an effective antioxidant devoid of prooxidative properties (Poeggeler *et al*., 1999). Also, other potential favorable properties have been found recently. For example, IPA can probably improve glucose metabolism (Abildgaard *et al*., 2018) or reduce weight gain in rats (Konopelski *et al.,* 2019). Moreover, IPA may provide in the future a new therapeutic strategy for treating such diseases as nonalcoholic steatohepatitis (Zhao *et al*., 2019) or Alzheimer's disease (Bendheim *et al.,* 2002).

In our previous study, we showed that melatonin (N-acetyl-5-methoxytryptamine) is able to reduce lipid peroxidation caused by KIO_3 in thyroid homogenates (Iwan *et al*., 2021). Taking into account a similarity (structure, chemical properties) between melatonin and IPA we decided to evaluate potential protective effects of IPA against lipid peroxidation induced by KIO_3 in porcine thyroid homogenates.

Materials and methods

Ethical approval

The procedures used in the study were not required to be approved by the Ethics Committee of the Medical University of Lodz, Poland.

Chemicals

Potassium iodate (KIO_3) and indole-3-propionic acid (IPA) were purchased from Sigma (St. Louis, MO, USA). The ALDetect Lipid Peroxidation Assay Kit was obtained from Enzo Life Sciences, Inc. (Zandhoven, Belgium). All the used chemicals were of analytical grade and came from commercial sources.

Animals

Porcine thyroids were collected from twenty-one (21) animals at a slaughter-house, frozen on solid CO_2 and stored at –80 °C until assay. Each experiment was repeated three times. Therefore, three tissue pools were prepared, with six (6) thyroid glands used for each homogenate pool.

Assay of lipid peroxidation

Thyroid tissue was homogenized in ice cold 20 mM Tris-HCl buffer (pH 7.4) (10%, w/v) and then incubated for 30 min at 37 °C in the presence of KIO_3 (200, 100, 50, 25, 20, 15, 10, 7.5, 5, 2.5, 1.25 mM) without or with addition of IPA. Six experiments were performed with different concentrations of IPA, *i.e.*, 10, 7.5, 5.0, 2.5, 1.25, 0.625 mM.

The concentrations of KIO_3 and IPA were chosen on the basis of the results of our previous studies (Milczarek *et al*., 2013; Karbownik *et al*., 2005).

The reactions were stopped by cooling the samples on ice. Each assay was run in duplicate.

Measurement of lipid peroxidation products

The concentrations of malondialdehyde + 4-hydroxyalkenals (MDA+4-HDA), as an index of lipid peroxidation, were measured in thyroid homogenates with the ALDetect Lipid Peroxidation Assay Kit. The homogenates were centrifuged at 5,000 × *g* for 10 min at 4 °C. After obtaining supernatant, each experiment was carried out in duplicate. The supernatant (200 µl) was mixed with 650 µl of a methanol: acetonitrile (1:3, v/v) solution, containing a chromogenic reagent, N-methyl-2-phenylindole, and vortexed. Following the addition of 150 µl of methanesulfonic acid (15.4 M), the incubation was carried out at 45 °C for 40 min. The reaction between MDA+4-HDA and N-methyl-2-phenylindole yields a chromophore, which is spectrophotometrically measured at the absorbance of 586 nm, using a solution of 10 mM 4-hydroxynonenal as the standard. The level of lipid peroxidation is expressed as the amount of MDA+4-HDA (nmol) per mg protein. Protein was measured using Bradford's method (Bradford, 1976), with bovine albumin as the standard.

Statistical analyses

Results are expressed as means ± SE. The data were statistically analyzed, using a one-way analysis of variance (ANOVA) followed by The Neuman-Keuls' test or Student t-test. The level of $p<0.05$ was accepted as statistically significant.

Results

In the present study, we have chosen those concentrations of KIO_3 (200, 100, 50, 25, 20, 15, 10, 7.5, 5.0, 2.5, 1.25 mM), which revealed stimulatory effects on lipid peroxidation in thyroid homogenates in our previous studies (Milczarek *et al*., 2013; Iwan *et al*., 2021). Similarly to results of these studies (Milczarek *et al*., 2013; Iwan *et al*., 2021), KIO_3 did increase lipid peroxidation in all used concentrations and the strongest damaging effect to membrane lipids was observed for KIO_3 concentration of around 10–25 mM (Figures 1–6) with the highest LPO level induced by concentration of 15 mM (Figure 6).

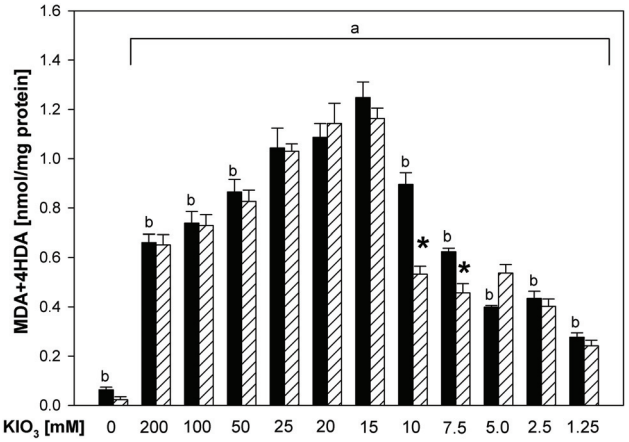

Figure 1. Lipid peroxidation, measured as MDA+4-HDA level, in porcine thyroid homogenates, incubated in the presence of KIO_3 (200; 100; 50; 25; 20; 15; 10; 7.5; 5.0; 2.5; 1.25 mM) with (striped bars) or without (black bars) IPA (10 mM). The experiment was repeated three times. Therefore, three tissue pools were prepared, with six (6) thyroid glands used for each homogenate pool. Data are expressed as nmol/mg protein. Values are expressed as mean ± SE (error bars).*p<0.05 vs. KIO_3 in the same concentration without IPA; $^a p$<0.05 vs. respective control; $^b p$<0.05 vs. KIO_3 at the concentration of 15 mM.

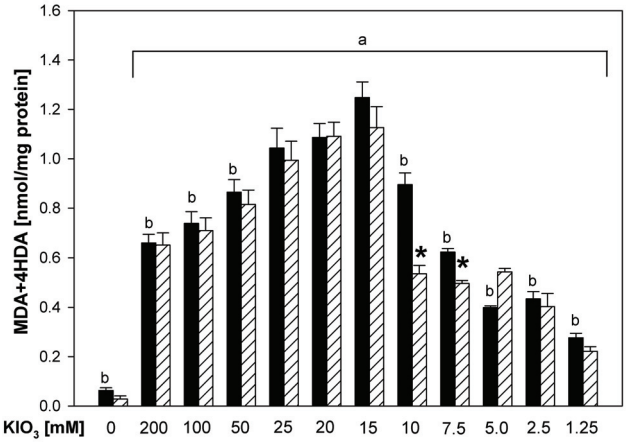

Figure 2. Lipid peroxidation, measured as MDA+4-HDA level, in porcine thyroid homogenates, incubated in the presence of KIO_3 (200; 100; 50; 25; 20; 15; 10; 7.5; 5.0; 2.5; 1.25 mM) with (striped bars) or without (black bars) IPA (7.5 mM). The experiment was repeated three times. Therefore, three tissue pools were prepared, with six (6) thyroid glands used for each homogenate pool. Data are expressed as nmol/mg protein. Values are expressed as mean ± SE (error bars). *p<0.05 vs. KIO_3 in the same concentration without IPA; $^a p$<0.05 vs. respective control; $^b p$<0.05 vs. KIO_3 at the concentration of 15 mM.

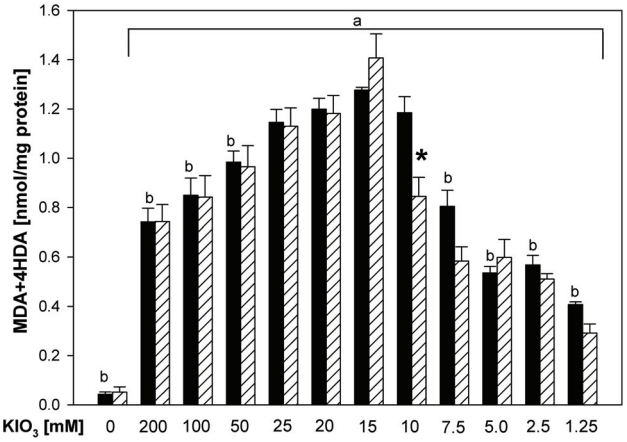

Figure 3. Lipid peroxidation, measured as MDA+4-HDA level, in porcine thyroid homogenates, incubated in the presence of KIO_3 (200; 100; 50; 25; 20; 15; 10; 7.5; 5.0; 2.5; 1.25 mM) with (striped bars) or without (black bars) IPA (5.0 mM). The experiment was repeated three times. Therefore, three tissue pools were prepared, with six (6) thyroid glands used for each homogenate pool. Data are expressed as nmol/mg protein. Values are expressed as mean ± SE (error bars). *p<0.05 vs. KIO_3 in the same concentration without IPA; $^a p$<0.05 vs. respective control; $^b p$<0.05 vs. KIO_3 at the concentration of 15 mM.

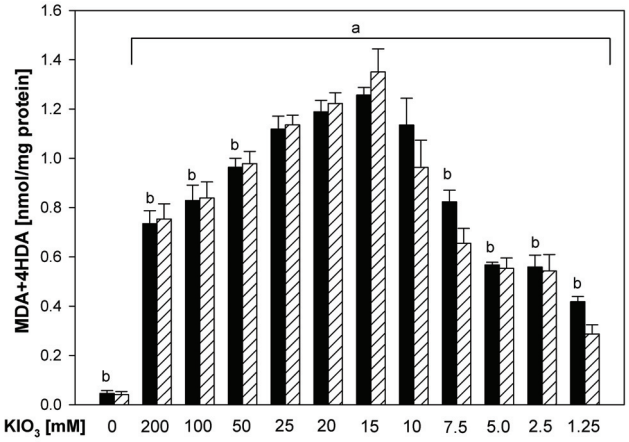

Figure 4. Lipid peroxidation, measured as MDA+4-HDA level, in porcine thyroid homogenates, incubated in the presence of KIO_3 (200; 100; 50; 25; 20; 15; 10; 7.5; 5.0; 2.5; 1.25 mM) with (striped bars) or without (black bars) IPA (2.5 mM). The experiment was repeated three times. Therefore, three tissue pools were prepared, with six (6) thyroid glands used for each homogenate pool. Data are expressed as nmol/mg protein. Values are expressed as mean ± SE (error bars). *p<0.05 vs. KIO_3 in the same concentration without IPA; $^a p$<0.05 vs. respective control; $^b p$<0.05 vs. KIO_3 at the concentration of 15 mM.

IPA, similarly to melatonin (Iwan *et al*., 2021), reduced in concentration-dependent manner KIO_3-induced lipid peroxidation, but only when this prooxidant was used at concentrations of 10 mM, 7.5 mM or 5.0 mM. More precisely, IPA – at concentrations of 10.0 mM and 7.5 mM – decreased lipid peroxidation, induced by KIO_3 in concentrations of either 10 mM or 7.5 mM (Figures 1–2). Lower concentration of IPA, *i.e.* 5.0 mM, decreased KIO_3-induced lipid peroxidation, but only when this prooxidant was used at the concentration of 10 mM (Figure 3). Lower concentrations of IPA used in our study, *i.e.* 2.5 mM, 1.25 mM and 0.625 mM, were not protective in our model (Figures 4–6).

The incubation of porcine thyroid homogenates in the presence of IPA only (in concentrations of 10, 7.5, 5.0, 2.5, 1.25, 0.625 mM) did not change the basal lipid peroxidation (Figures 1–6).

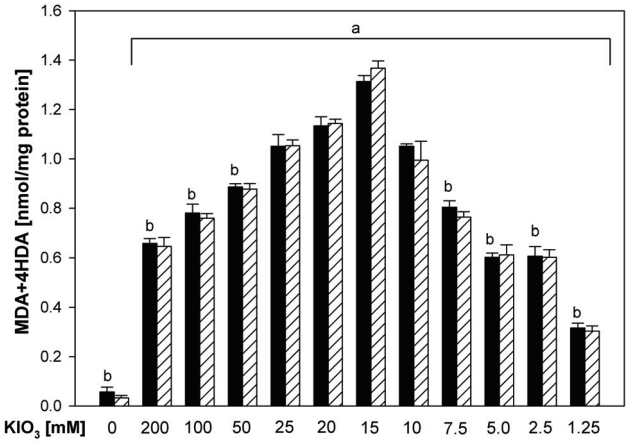

Figure 5. Lipid peroxidation, measured as MDA+4-HDA level, in porcine thyroid homogenates, incubated in the presence of KIO_3 (200; 100; 50; 25; 20; 15; 10; 7.5; 5.0; 2.5; 1.25 mM) with (striped bars) or without (black bars) IPA (1.25 mM). The experiment was repeated three times. Therefore, three tissue pools were prepared, with six (6) thyroid glands used for each homogenate pool. Data are expressed as nmol/mg protein. Values are expressed as mean ± SE (error bars). *p<0.05 vs. KIO_3 in the same concentration without IPA; $^a p$<0.05 vs. respective control; $^b p$<0.05 vs. KIO_3 at the concentration of 15 mM.

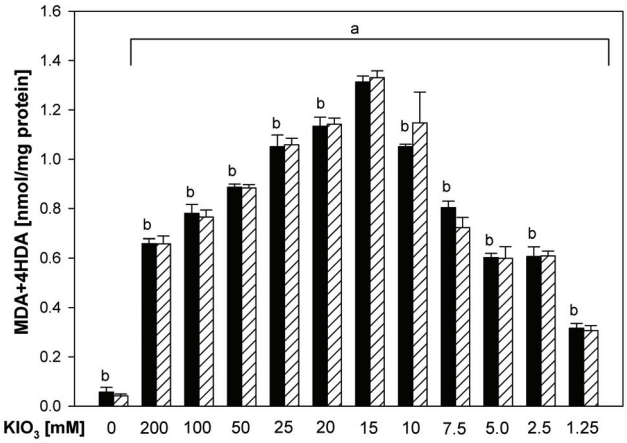

Figure 6. Lipid peroxidation, measured as MDA+4-HDA level, in porcine thyroid homogenates, incubated in the presence of KIO_3 (200; 100; 50; 25; 20; 15; 10; 7.5; 5.0; 2.5; 1.25 mM) with (striped bars) or without (black bars) IPA (0.625 mM). The experiment was repeated three times. Therefore, three tissue pools were prepared, with six (6) thyroid glands used for each homogenate pool. Data are expressed as nmol/mg protein. Values are expressed as mean ± SE (error bars). *p<0.05 vs. KIO_3 in the same concentration without IPA; $^a p$<0.05 vs. respective control; $^b p$<0.05 vs. KIO_3 at the concentration of 15 mM.

Discussion

Our study is the attempt to find another – besides melatonin (Iwan *et al*., 2021) – potential protective compound against prooxidative effects of KIO_3.

KIO_3 is the most commonly used iodine compound for salt iodization (Iodine Global Network, 2020) with the GRAS ("generally recognized as safe") status given by FDA (Trumbo, 2016), although there are available studies, which showed its potential toxicity (Iwan *et al*., 2021; Blankenship *et al*., 2018), but this observation was not confirmed in humans till now. KIO_3 belongs to halogenate salts together with chlorate and bromate. These salts are generally stable, but due to their oxidative properties they may react with oxidisable substances. Among these three halogenate salts, iodate is characterized by the lowest redox potential and it did not induce toxic effects under conditions that bromate did (Bürgi *et al*., 2001).

In our previous studies (Milczarek, *et al*., 2013; Iwan *et al*., 2021), the highest lipid peroxidation caused by KIO_3 was observed at the concentration around 15 mM, which corresponds to the physiological concentration of iodine in the thyroid (Taurog *et al*., 1947; Taurog *et al*., 1951; Tiran *et al*., 1993). In the present study, we have shown that IPA, used in high concentrations (*i.e.*, 10 mM, 7.5 mM and 5.0 mM), significantly reduced lipid peroxidation induced by KIO_3, when this prooxidant was used at doses close to physiological concentrations of iodine (*i.e.*, 10 mM and 7.5 mM).

As it was mentioned above, we chose IPA for our research because of its similarity to melatonin (Reiter *et al*., 2018). IPA is a very potent free radical scavenger, which inhibits hydroxyl radical-initiated lipid peroxidation in a dose-dependent manner, both *in vitro* and *in vivo* (Bendheim *et al*., 2002). The mechanisms of antioxidative effects of IPA are following: this compound has been shown to effectively scavenge the hydroxyl radical ($^{\bullet}OH$) (Poeggeler *et al*., 1999), to quench the superoxide anion radical ($O_2^{-\bullet}$) (Harderland *et al*., 1999) and to act synergistically with another intracellular antioxidant – glutathione (Poeggeler *et al*., 1999). It is worth mentioning that the capacity of IPA to scavenge ·OH may exceed that of melatonin, an indoleamine generally recognized as the most potent naturally occurring radical scavenger (Chyan *et al*., 1999). Moreover, in contrast with other antioxidants, IPA was not converted to reactive intermediates with prooxidant activity (Bendheim *et al*., 2002; Chyan *et al*., 1999) and it is recognized as safe.

In our previous study (Iwan *et al*., 2021), we observed that melatonin was effective only when KIO_3 was used at concentration close to physiological iodine concentration in the thyroid. The same effect we found in the present study – IPA reduced, in concentration-dependent manner, KIO_3-induced lipid peroxidation, when this prooxidant was used at concentrations of 10 mM and 7.5 mM. We hypothesize in our former paper (Iwan *et al*., 2021) that during phylogenetical development in mammals some protective mechanisms have been developed to protect against toxic agents, to which organisms are potentially exposed for a long time. That can be the reason, why not only melatonin but also IPA reduced LPO induced by KIO_3 in concentrations corresponding to physiological concentrations of iodine in the thyroid.

Conclusions

Protective antioxidative effects of IPA against oxidative damage caused by KIO_3 in porcine thyroid are similar to those caused by melatonin. This compound may be considered as pharmacological agent to be used for protection against prooxidative effects of iodates.

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