New insights into morphological, stereological and functional studies of the adrenal gland under exposure to the potent goitrogen thiourea

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ABSTRACT
Thiourea (thiophen-3-yl-acetic acid) is a well established antithyroid drug used for treating hyperactivity of the thyroid gland as it blocks the conversion of thyroxine (T4) to triiodothyronine (T3) in peripheral tissues. Human exposures to thiourea include contaminated drinking water and vegetables for its extensive use in fertilizers. Chronic thiourea exposure can cause thyroid dysfunction leading to redox imbalance. However, such effects on morphological, quantitative, functional and hypothalamo-pituitary-adrenocortical axis (HPA) analysis of the adrenal gland are yet to be explored. The aim was to explore the effect of thiourea on structural and functional status of the adrenocortical region with special reference to the HPA axis. Control rats were fed a normal laboratory standardized diet whereas to experimental rats, thiourea at a dose of 0.3 mg/day/Kg body weight was administered orally, once every day for consecutive 28 days. Histology and histometry, including morphometry of the adrenal, adrenal ∆5 3β HSD and 17β HSD activity, LPO level and serum corticosterone profile were assessed. Statistical significance was studied by ‘Mann-Whitney U’ test at $p<0.05$. Hypertrophy and hyperplasia of the adrenocortical cells was found especially in the layer zona fasciculata ($p=0.0027$) and enhanced adrenal ∆5 3β HSD activity ($p=0.0067$) in comparison to that of the control. Increased lipid peroxidation ($p=0.0054$) and up-regulated corticosterone release ($p=0.0064$) through adrenocortical stress signalling pathway were also noted. Stereological analysis of the left adrenal gland showed significant increase in volume ($p=0.0025$) and mass of cells ($p=0.0031$) in adrenocortical region in comparison to that of control animals. This study concludes that thiourea, in addition to its antithyroidal activity, develops stress in the adrenal as evident by enhanced lipid peroxidation in the gland that in turn through the HPA axis causes hypertrophy and hyperplasia of adrenocortical cells to enhance synthesis and release of corticosterone secretion to counteract the stress developed under the influence of this potent chemical agent.

KEY WORDS: adrenal gland; oxidative stress; thiourea; thyroid hormones; corticosterone

Introduction
Thiourea is a potent antithyroidal drug and in pharmacological doses it is used in management of hyperthyroidism and/or Grave’s Disease. Altered thyroid function is reported to be closely associated with both hypothalamo-hypophyseal-gonadal and hypothalamo-hypophyseal-adrenal axis which may lead to the generation of oxidative stress in the long run (Weng et al., 2007; Poncin et al., 2010). The important neuroendocrine mechanism in a stress reaction is the activation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in a rapid increase in circulating corticotrophin (ACTH) and subsequent rise in glucocorticoids, which are critical for successful adaptation (Miller et al., 2007). Thus, plasma levels of ACTH and glucocorticoids are a good indicator of stress response intensity, particularly in its acute phase (Otis et al., 2007). Incidentally, thiourea is added to fertilizers to inhibit the nitrification process (Wang et al., 2017) and under conditions not favoring biotic or abiotic removal; thiourea may be present in surface waters and sediments over longer periods (Mutic et al., 2017). Therefore thiourea contaminated drinking water and food are a potent route of exposure to humans in relation to the harmful side effects of this chemical.
Oxidative stress generation is a resultant of increased production of reactive oxygen species (ROS) and there are reports which suggest that in various organs, including the adrenal gland, lipid peroxidation is increased in conditions of oxidative stress (Chakraborty et al., 2014). ROS are chemically reactive molecules containing oxygen which form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signalling and homeostasis. Examples include oxygen ions and peroxides. Cumulative effects of ROS may result in significant damage to cell structures and have been implicated as an underlying agent in various pathological conditions (Chakraborty et al., 2016).

Thiourea, due to its antithyroidal properties, might alter adreno-cortical physiology in the long run as adrenal and thyroid are functionally interrelated. However the effect of sub-chronic exposure to thiourea in adrenal gland function is yet to be clearly elucidated experimentally. No conclusive experimental or clinical data are available about its effects on adrenergic stress signalling pathway on regular ingestion. Taking all this into consideration, as well as the fact that there are very few reports on morphological, quantitative and functional analysis of adrenal glands after thiourea exposure, the present study has been undertaken to determine its effects on adrenal gland morphology and functions in adult rats.

Material and methods

Animal maintenance and grouping for the study

For the investigation, twelve adult female virgin albino rats of 110±10g were used. They were housed in two cages with six rats each in an air-conditioned room and 12 hrs light/12 hrs dark cycles were maintained. The rats were acclimatized to housing conditions for at least one week prior to experiment. All animal experiments were performed in accordance to the ethical guidelines approved by the Institutional Animal Ethics Committee, Department of Physiology, University of Calcutta [Approval no. IAEC/Project Proposal (PG)/ENDO-(SP)/2013–2014]. The rats were allowed free access to drinking water and basal diet made of locally available wheat flour, Bengal gram powder, milk powder, vegetable oil and recommended amount of vitamins. Approximately 10g of food was fed per 100 g of body weight (Vento et al., 2008). The rats were divided into two groups of six animals each. The experimental group was orally administered thiourea for 28 days and was paired with a control group.

Control rats were fed normal laboratory standardized diet, whereas the experimental rats received thiourea at a dose of 0.3 mg/day/Kg body weight fed to treated rats orally, according to body weight once every day for 28 days (Hamden et al., 2008). Simultaneously, animals of the control group were provided equal quantity of sterile water by the same route and for the same duration. The animals were housed in hygienic polypropylene cages and maintained in a controlled environment at a temperature of 22±2°C and relative humidity (40–60%) in an animal house with a constant 12 hrs light/12 hrs dark schedule. The animals were fed a standardized diet, which consisted of 70% wheat, 20% Bengal gram, 5% fish meal powder, 4% dry yeast powder, 0.75% refined sesame oil, 0.25% shark liver oil, and water ad libitum (Chakraborty et al., 2014).

Sacrifice of the animals

The animals were sacrificed at the end of the experimental period of 28 days, following institutional ethical procedure. Anesthesia was given using ether prior to sacrificing the animals. Blood was collected separately from each animal of both groups from the hepatic portal vein and the serum was separated by centrifugation. Then the adrenal gland was collected from each animal and was stored separately. Before sacrifice the body weight of each rat were recorded.

Histological study

On the day of the sacrifice of the animals, the adrenal gland of both the groups of animals were removed and weighed and fixed in Bouin's solution. For dehydration, the tissues were kept in various ascending gradations of alcohols followed by absolute alcohol for an hour each. The tissues were then transferred to xyloil for 15 mins (two times) and then to paraffin (56–58°C), which contained 50% melted paraffin and 50% xylol. Finally the tissue was kept in melted paraffin and blocks were prepared. The tissue sections were cut using microtome and the sections were taken on a slide. These sections were stained in hematoxylin and eosin and each slide was examined under a light microscope (Model – CH20i Olympus; serial no. 8A06177) at ×400 magnification for histopathological examination. The photomicrographs of the sections were taken using the Nikon Cool Pix P1500 digital camera (Chakraborty et al., 2014).

Morphometric analysis of adrenal gland

A single paraffin section containing both the cortical and medullary area was chosen for adrenal gland morphometry. In this section 50 test areas of the outer zona fasciculata (ZF) were counted (Sarwar et al., 2008). Since the adrenocortical cells of rats are mononucleated, the numerical density of the nuclei corresponds to the number of cell per mm² (Bozzo et al., 2006). The test area was measured with a 10X objective using the Image-Pro Plus software (Rockville, USA). To measure these areas, a circular area was selected with the aid of the software, in which the nuclei were counted. After this procedure, the area of the ZF adrenocortical cells of the adrenal gland was calculated by dividing the number of nuclei counted by the circular area measured.

Assay of Δ5 3β hydroxysteroid dehydrogenase (HSD) and 17β HSD activity

For measurement of adrenal steroidogenic enzymes Δ5 3β-HSD and 17β-HSD, the adrenals were collected and homogenized in homogenizing fluid (20% spectroscopic grade glycerol, 5 mM potassium phosphate and 1 mM ethylenediaminetetraacetic acid (EDTA) at a tissue concentration of 0.1 M). A single paraffin section containing both the cortical and medullary area was chosen for adrenal gland histomorphometry. In this section 50 test areas of the outer zona fasciculata (ZF) were counted (Sarwar et al., 2008). Since the adrenocortical cells of rats are mononucleated, the numerical density of the nuclei corresponds to the number of cell per mm² (Bozzo et al., 2006). The test area was measured with a 10X objective using the Image-Pro Plus software (Rockville, USA). To measure these areas, a circular area was selected with the aid of the software, in which the nuclei were counted. After this procedure, the area of the ZF adrenocortical cells of the adrenal gland was calculated by dividing the number of nuclei counted by the circular area measured.

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concentration of 100 mg/mL homogenizing mixture). The homogenized sample was then centrifuged at 10,000 rpm at a constant temperature of 4°C. Then the supernatant was used for the assay. The activity of adrenal steroidogenic enzymes ∆5 3β HSD was determined by optical measurement of the rate of reduction of nicotinamide adenine dinucleotide (NAD). The final volume of reaction system was 3.0 mL which contained 1 mL of 100 M of sodium pyrophosphate (pH8.9), 20 L of 30 g of substrate (17-estradiol) of 3 each in 0.02 mL of purified doxin and a suitable quantity of enzyme (100–500 mL). The reaction was initiated by adding 1 mL of 0.5 mM of NAD (Chandra et al., 2011). The activity of adrenal 17 HSD was determined by using the same supernatant fluid as described earlier. The reaction system contained 1.5 mL of 440 M of sodium pyrophosphate (pH8.9), 0.5 mL of 5% BSA (bovine serum albumin), 40 L of 0.3 M of substrate (17-estradiol) of 17 each in 0.02 mL of purified doxin and a suitable quantity of enzyme (100–500 L) to initiate the reaction finally by adding 1 mL of 1.35 M of NAD (Mondal et al., 2013). Both the reactions were carried out in the silica cuvettes having 1.0 cm light path, in a spectrophotometer at 340 nm absorbance, as mentioned in the preceding paragraph. The activities were measured at 15 s intervals against a blank (containing all components except the tissue homogenate).

### Measurement of lipid peroxidation (LPO) activity

Two (2) mL of thiobarbituric acid-trichloroacetic acid-hydrochloric acid (TBA-TCA-HCl) reagents was added to 2 mL of tissue extract and mixed thoroughly. The solution was heated for 15 min in boiling water bath. After cooling, the flocculent precipitate was removed by centrifugation at 10,000 rpm for 10 min. Malonaldehyde (MDA) forms adducts with thiobarbituric acid (TBA), which was measured spectrophotometrically in a spectrophotometer (UV-1240 Shimadzu, Japan) at 532 nm against a blank containing 50 mM phosphate buffer (pH7.4) instead of biological sample. MDA, a product of LPO, was measured as a standard. An extinction coefficient of 156,000 M–1cm–1 was applied for calculation (Chandra et al., 2010).

### Assay of serum corticosterone

Serum corticosterone was assayed using ELISA kit developed by National Institute for Health and Family Welfare (NIHFW), Govt. of India, New Delhi, India. Briefly, the solid phase enzyme immunoassay for corticosterone is a competitive type immunoassay wherein horseradish peroxidase labelled corticosterone (HRP-corticosterone) competes with corticosterone present in the sample for a fixed and limited number of antibody sites immobilized on the wells and washed. The HRP-corticosterone fraction bound to the antibody in the solid phase is measured by adding a chromogen/substrate solution which is converted to a blue compound. After 15 min incubation, the enzymatic reaction is stopped with 1 M sulphuric acid which changes the solution to yellow color. The absorbance of the solution photometrically measured at 450 nm is inversely related to the concentration of corticosterone present in the sample.

### Statistical analysis

Results were expressed as mean ± standard error of mean (SEM). Differences between-group were established using Mann-Whitney U test. A value of p<0.05 was interpreted as statistically significant. Statistical analyses were performed using Origin 8.1 (Northampton, MA, USA) and MS-Office Excel 2007 software packages.

### Results

#### Body weight

The body weight of the control animals increased progressively throughout the period of investigation, with a net body weight gain of +42.49% (Table 1). However, the net body weight gain of the animals of thiourea-treated group was only +29.80% at the end of the total experimental period.

### Adrenal gland weight and morphometry

There was a significant increase in relative adrenal weight in thiourea-treated group of rats followed by morphometric alterations in all the three cortical layers as well as in the medulla compared to control group of rats (p=0.0028) (Table 2).

### Adrenal Δ5 3β hydroxysteroid dehydrogenase (HSD) and 17β HSD activity

The activity of the adrenal Δ5 3β HSD enzyme was significantly increased (p=0.0067) and the activity of the adrenal 17β HSD enzyme was also increased, however not significantly in the thiourea-treated group in contrast to control (p=0.8745) (Table 3).

#### Serum corticosterone and lipid peroxidation (LPO) assay

Serum corticosterone level was increased in thiourea-treated group as compared with control (p=0.0064). Similarly in the thiourea treated groups there was an elevation of LPO in comparison to the control (p=0.0054), indicating generation of oxidative stress on its exposure (Table 4).

### Histological changes of adrenal gland

In all examined sections, the adrenal gland consisted of three cortical zones clearly identifiable by arrangement and stainability of cells: zona glomerulosa (ZG), zona

### Table 1. Thiourea induced alteration in body weight in female rats.

| Groups          | Initial body weight (g) | Final body weight (g) | Gain in body weight percent |
|-----------------|-------------------------|-----------------------|----------------------------|
| Control         | 95.52±1.79              | 136.11±2.31           | 42.49                      |
| Thiourea-treated| 97.19±2.09              | 126.16±2.49           | 29.80*                     |

*p-value 0.872 0.003

| (Values are Mean ± SEM; n=6) | Comparison between control and thiourea-treated groups was done following two tail Mann-Whitney U test and significant difference was found between the two groups (p<0.05).
fasciculata (ZF) and zona reticularis (ZR) (Figure 1). The thickness of the overall cortex and the respective zones remained fairly hypertrophied in adrenals after thiourea administration in comparison to normal. Just under the ZG, oval or cuboidal epithelial cell lining was also noticed. ZF, covering almost 2/3rd volume of the cortical cross-sections, possessed long cords, mainly with cuboidal cells of light fronton cytoplasm and round nucleus. ZR was formed by epithelial cells lying long ways of thinly wall blood vessels (Figure 2).

**Discussion**

In the study, the effect of a potent synthetic antithyroidal drug, thiourea, was evaluated on the morphological and functional status of the adrenal gland in rats. The investigated parameters were detailed morphology and morphometry of the gland along with evaluation of adrenocortical steroidogenic enzyme activities and with lipid peroxidation level, as well as serum corticosterone profile in both control and thiourea exposed groups of animals.

Exposure to thiourea markedly reduced the net body weight gain of the experimental animals as compared to the control animals. Similar observations have been reported earlier on the potentiality of thiourea as an inhibitor of morphometric growth and body weight in other species; which may be due to its positive association with hypothyroid condition, in which both syntheses of proteins and growth rate is retarded resulting in weight loss despite a normal appetite (Gupta et al., 2013). In another study, the decrease in body weight has been suggested to be positively associated with plasma glucose-lowering activity in vivo by thiourea derived compounds (Zhang et al., 2009), which may be also related with the decreased in body weight of experimental animals, corroborating the observations as found in this study.

The thiourea treated group of animals showed an increase in relative adrenal gland weight compared to the control group of animals. Detailed morphometry of the adrenal revealed that the volume of all three respective areas, i.e. zona glomerulosa (ZG), zona fasciculata (ZF) and zona reticularis (ZR) were increased in the treated group of rats in comparison to their control counterparts. Cells of the zona glomerulosa have little cytoplasm containing only a small amount of lipid. The ZF is the broadest of all the three zones of the adrenal, which makes up about 75% of the total cortex. Its cells are polyhedral and have many intracytoplasmic lipid droplets (Ulrich-Lai et al., 2006). These lipids, mostly cholesterol and cholesterol esters, are used as substrates for steroidogenesis (Miller and Bose, 2011). These lipid droplets are mobilized from the stores to mitochondria for the synthesis of steroids. In this study, marked histological involvement was found in each of the zona layers of the adrenal cortex; particularly the zona fasciculata was disorganized under the effect of thiourea administration. This adrenocortical layer produces corticosterone (in rodents) under the influence of adreno-corticotropic hormone (ACTH). The cells of this

### Table 2. Detailed morphometric alterations of the cortex and medulla of left adrenal gland of control and thiourea-treated rats.

| Parameters                             | Control       | Thiourea treated | p-value |
|----------------------------------------|---------------|------------------|---------|
| Adrenal gland weight (mg)              | 25.69 ±0.58   | 29.84±0.38*      | 0.0028  |
| Volume (mm³) the entire gland          | 159.7±0.64    | 181.9±0.96*      | 0.0025  |
| Zona glomerulosa                       | 12.22±0.42    | 14.7±0.30        | 0.0041  |
| Zona fasciculata                       | 90.5±0.56     | 101.23±0.29*     | 0.0027  |
| Zona reticularis                       | 25.13±0.68    | 46.43±0.19*      | 0.0026  |
| Medulla                                | 22.41±0.38    | 18.64±0.14*      | 0.0037  |

### Table 3. Thiourea induced alteration in adrenal Δ⁵ 3β and 17β HSD activity in female rats.

**Groups** | **Δ⁵ 3β HSD activity (Δ OD/min/mg protein)** | **17β HSD activity (Δ OD/min/mg protein)** |
|-----------|---------------------------------------------|-------------------------------------------|
| Control   | 0.13 ±0.008                                  | 0.18 ±0.004                               |
| Thiourea-treated | 0.17 ±0.020*                                | 0.21 ±0.007                               |
| p-value   | 0.0067                                      | 0.8745                                    |

(Values are Mean ± SEM; n=6; The comparison between control and thiourea-treated group was done following two tail Mann-Whitney U test and significant difference was found between the two groups (p<0.05).

### Table 4. Thiourea induced alteration in serum corticosterone level and adrenal lipid peroxidation level.

**Groups** | **Serum corticosterone level (µg/dl)** | **Lipid peroxidation level (nmole TBARS/mg protein)** |
|-----------|----------------------------------------|--------------------------------------------------------|
| Control   | 23.1±1.71                               | 4.16±0.93                                              |
| Thiourea-treated | 45.4±2.38*                             | 9.51±0.49*                                             |
| p-value   | 0.0064                                  | 0.0054                                                 |

(Values are Mean ± SEM; n=6; The comparison between control and thiourea-treated groups was done following two-tail Mann-Whitney U test and significant difference was found between the two groups (p<0.05).
Figure 1. Photomicrographs of adrenal gland sections are shown at 40× after H&E staining (A) Control. Scale bar = 18.13 µm (approx). Distinctive features of ZG and ZF (B) and ZR (C) of control adrenal gland after H/E stain at 400×. c=cortex, m&M=medulla; ZG=zona glomerulosa, ZF=zona fasciculata and ZR=zona reticularis.

Figure 2. Photomicrographs of adrenal gland sections are shown at 40X after H/E staining (A) Thiourea treated. Scale bar = 18.13 µm (approx). Distinctive features of ZG and ZF (B) and ZR (C) of thiourea treated adrenal gland stained with H/E stain at 400×. ZG in thiourea rats, showing hypertrophic and hyperplastic appearance of adrenocortical cells. In ZF cells are cuboidal with round nucleus; in ZR cells are distorted having irregular arrangement. Scale bar 15 µm. c=cortex, m&M=medulla; ZG=zona glomerulosa, ZF=zona fasciculata and ZR=zona reticularis.
layer remain arranged in cords in control, but are anarchically arranged after thiourea exposure. All these indicate that prolonged exposure to thiourea caused structural and functional (Kapoor et al., 2006) modifications in the adrenal gland. A similar finding has been reported in rats exposed to different stressful external stimuli. The average size along with the distribution and number of the cells especially in ZF and ZR were significantly increased in the adrenal of thiourea treated groups, indicating their hypertrophy and hyperplasia. Thus thiourea administration over a period of time has significant impact on adrenal gland morphology and morphometry, with possible occurrence of endocrine dysfunction in the long run.

There is a direct functional relationship between adrenal gland activity and increased gland weight (Hui et al., 2009). Hypertrophy and macroscopic hyperemia (increase of blood flow) have been previously described in response to administration of ACTH or following prolonged exposure to stress (Hui et al., 2009). In this investigation the adrenal gland weight was increased following thiourea administration. It was reported previously that such a condition can arise as a result of the stress response, yet it may also occur due to deficient glucocorticoid feedback regulation of ACTH due to toxicity to the adrenal cortex (Chakraborty et al., 2016). Thus excess thiourea as used in this study might be responsible for producing oxidative stress in the adrenal resulting in the cellular and subcellular alterations. There was a significant elevation of adrenal lipid peroxidation (LPO) level when compared to the control group of rats. As widely known, LPO refers to oxidative degradation of lipids. It is a gradual process in which free radicals steal electrons from the lipid in the cell membrane. Malonaldehyde (MDA) levels thus formed indicate the intoxication and generation of oxidative stress in this organ, considered an endpoint of oxidative stress formation (Chakraborty et al., 2016). This clearly suggests that thiourea exposure caused elevation of LPO level or in other words generation of oxidative stress resulting in adrenal gland weight and subsequent changes in the activity of the gland by feedback mechanism to ACTH.

In parallel to adrenal weight elevation there was also subsequent increase in adrenal $\Delta^3\beta$ hydroxydehydrogenase (HSD). It is one of the important regulatory enzymes of the adrenal steroidogenic pathway. Thiourea at the dose used in this study caused significant increase in adrenal weight followed by hyperactivity of adrenal $\Delta^3\beta$-HSD activity with concomitant rise in corticosterone level, possibly an ameliorative effect to the developed stress under the influence of thiourea. Recent reports suggest an important endocrinological concept from the above, most relevant to the pathological manifestations of toxicity or stress in the adrenal cortex, the feedback regulation of the hypothalamic–pituitary axis by glucocorticoids. This reflects the possible involvement of hypothalamic-pituitary-adrenal axis following thiourea administration in experimental animals. Similarly, adrenal $17\beta$ HSD was concomitantly elevated, though not significantly, following thiourea exposure, also indicating its hyperactivity when compared to control animals. These reports of an increase in adrenal $17\beta$ HSD positively correlating with adrenal adenoma, an adrenal tumor in humans (Gangkak et al., 2015) suggesting additional evidence for hyperplasia and weight gain in the gland after thiourea administration.

A major neuroendocrine mechanism in a stress reaction is the activation of the hypothalamic-pituitary-adrenal axis (HPA), resulting in a rapid increase in circulating corticotropin (ACTH) and subsequent rise in glucocorticoids, which are critical for successful adaptation (Miller et al., 2007). Thus, plasma levels of ACTH and glucocorticoids are good indicators of stress response intensity, particularly in its acute phase (Otis et al., 2007). Acute as well as chronic stress excites the HPA axis to stimulate the release of corticotrophin releasing hormone (CRH) from the hypothalamus that triggers the release of ACTH from the pituitary, resulting in enhanced corticosteroid synthesis and release from the adrenal cortex (Rodríguez-Gutiérrez et al., 2014). Increased activity of adrenal $\Delta^3\beta$-HSD was found in parallel with the rise in the level of ACTH in serum (Markov et al., 2009). This study demonstrates an increase in adrenal $3\beta$-HSD parallel with the rise in serum corticosterone, confirming that thiourea in the doses as used in this study elevates the adrenal stress signaling pathway leading to oxidative stress in the gland, which was further confirmed by increase in adrenal LPO level.

The overall results revealed that the chronic thiourea exposed group of animals develop morphological and functional changes of the adrenal gland (especially in the area of zona fasciculata) with increased level of lipid peroxidation, enhanced adrenal $\Delta^3\beta$ HSD activity followed by elevated serum corticosterone level. Thus thiourea in pharmacological doses as in this study, does not only suppress thyroid gland function but also modulates the activity of the adrenal cortex, which is a major concern in health and disease.

It would have been better if the investigation had been carried out in patients using thiourea as a drug, followed by evaluation of the activity status of the adrenal. Further for the non-availability of rat ELISA kits, one of the most important parameters, ACTH, was not assayed. However these studies are likely to be helpful to understand the functional status of the adrenal gland in hypothyroid conditions, as in the patients who are consuming anti-thyroid drugs.

**Conclusion**

Based on the observation of the study it may be concluded that though thiourea has antithyroidal activity yet simultaneously develops stress in the adrenal, as evident by enhanced lipid peroxidation in the gland, that in turn through the hypothalamo-pituitary-adrenal axis it causes hypertrophy and hyperplasia of adrenocortical cells to stimulate the synthesis and release of corticosterone to counteract the generated stress under the influence of this chemical agent. This study provides novel insights...
and raises new concerns about the hyperactivation of the adreno-cortical functional status linked with oxidative stress in populations exposed to excess thiourea for considerable long periods.

Several studies found it necessary to understand the structural and functional status of the adrenal under the influence of other antithyroidal drugs like propyl thiouracil, marcapto imidazole, etc.

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