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Fenvalerate Exposure Alters Thyroid Hormone Status in Selenium- and/or Iodine-Deficient Rats

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Abstract Considering the potential adverse effects of selenium and iodine deficiencies, and taking into account the widespread but often careless use of pyrethroid insecticides and their possible endocrine-disrupting effects, this study was undertaken to investigate the effects of fenvalerate on thyroid hormone parameters in both healthy and selenium- and/or iodine-deficient rats. Fenvalerate exposure had no effect on the TT4 levels of healthy controls but caused significant increases both in iodine deficiency (ID) and selenium plus iodine deficiency (ISeD), and a significant decrease in selenium deficiency (SeD). Dramatic increases in TT3 of all groups were observed by fenvalerate. Moreover, it caused insignificant decrease of thyroid stimulating hormone in healthy controls, no effect in SeD, and significant elevation in ID and ISeD. These results, thus, showed that the widely used pyrethroid insecticide fenvalerate has the potential to change significantly thyroid hormone parameters both in normal and deficiency states, and consequences of its thyroid status modifying effect might be of critical importance particularly in sensitive individuals and patients with thyroid dysfunction.

Keywords Fenvalerate · Pyrethroid · Thyroid hormones · Selenium deficiency · Iodine deficiency · T_4 · T_3 · TSH

Introduction

The thyroid is one of the largest endocrine gland in the body, and its importance in maintaining human health is well recognized [1]. Thyroid hormones, principally thyroxine (T_4) and triiodothyronine (T_3), have diverse actions, control the rate of the metabolism, and virtually act on every cell of the body to alter gene transcription. T_3 and T_4 are extremely

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essential for normal growth, development, and function of several organs including brain and central nervous system.

There has been detailed research concerning thyroid gland biochemistry and control mechanisms of the secretion of thyroid hormones [1–4]. Synthesis, metabolism, and action of thyroid hormones require availability of the essential trace elements, selenium, and iodine. Adequate levels of these elements affect the homeostasis of thyroid hormone-dependent metabolic pathways [2, 5]. Hyperthyroidism (overactive thyroid) and hypothyroidism (underactive thyroid) are the most common problems of the thyroid gland, and under- and over-production of thyroid hormones have potent effects on human health. Iodine deficiency is a recognized nutritional risk factor for thyroid dysfunction (hypothyroidism) and impaired mental and physical development. Severe iodine deficiency is the main cause of endemic goiter and cretinism in several geographic parts of the world [2, 6].

Although thyroid gland secretes T_4 mainly, it also secretes T_3 at relatively very low levels. T_4 in the circulation enters all tissues of the body, where it may be converted to the metabolically active hormone T_3 by isozymes of iodothyronine 5′-deiodinase [7, 8]. Selenium has fundamental importance in thyroid hormone synthesis and metabolism, because the iodothyronine 5′-deiodinases are selenoproteins. Selenium deficiency impairs T_4 conversion to T_3, and selenium supplementation decreases plasma T_4 levels, increases deiodinase activity, and improves the conversion of T_4 to T_3 [9]. The severity of goiter caused by iodine deficiency may be increased in selenium deficiency, and combined iodine and selenium deficiency may exacerbate hypothyroidism and myxoedematous cretinism [10, 11].

Pyrethroid insecticides have been used in the control of a variety of insects in agriculture, as well as in domestic environments for more than 30 years and account for approximately one fourth of the worldwide insecticide market [12, 13]. Synthetic pyrethroids are generally viewed as safe insecticides available due to their low acute toxicity to mammals [14]. The other main advantages of their use are the photostability, high efficacy at low concentrations, easy disintegration, and their limited soil persistence [13, 15, 16].

Fenvalerate belongs to type II pyrethroids; is commonly used for destroying a variety of insects damaging several vegetable, fruit, and cotton crops; as well as to mitigate household insects like flies, cockroaches, and mosquitoes (Fig. 1). Exposure of the general population to fenvalerate is mainly via dietary residues. Human beings are also exposed to formulated fenvalerate preparations mostly by inhalation during spraying in fields for crop protection and also during handling and packaging at manufacturing plants [17]. Fenvalerate has moderate toxicity in mammals [18, 19] and is rapidly hydrolyzed in experimental animals to yield fenvaleric acid as a major metabolite [20]. Several studies demonstrated that pyrethroids including fenvalerate are particularly toxic to neurons, acting directly on the

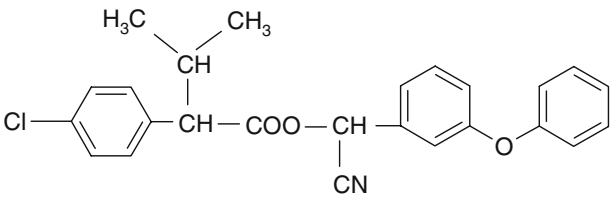

Fig. 1 Chemical structure of fenvalerate

axon by interference with the sodium channel [21, 22]. Recently, the effects of fenvalerate as an endocrine disruptor have been reported [17, 23–26]. The process of endocrine disruption is disturbing normal endocrine function through agonistic or antagonistic actions, as well as interfering with cell signaling or receptor expression. Endocrine-disrupting chemicals have been defined as exogenous agents that interfere with the synthesis, secretion, binding, action, or elimination of the hormones in the body [27]. Fenvalerate has been suggested as inducing significant decrease in testis weight, epididymal sperm production and storage, sperm counts, sperm motility, and marker testicular enzymes for testosterone biosynthesis [17, 28]. Available studies indicate that fenvalerate also causes alterations on thyroid hormone status. However, the results of these limited studies are controversial [29–32].

This study was carried out to evaluate the effects of fenvalerate on thyroid hormone parameters in both healthy and selenium- and/or iodine-deficient rats.

Materials and Methods

Materials

Technical grade fenvalerate was from Koruma Tarım (İzmit, Turkey) and had a purity of 92%. Radioimmunoassay (RIA) commercial kits for total T_4 (TT_4) and T_3 (TT_3) were purchased from Biocode (Liège, Belgium) and for thyroid stimulating hormone (TSH) from Abbott Laboratories (Waukegan, IL, USA). Selenium-deficient diet (<0.005 mg selenium/kg) was supplied by SAFE (Augy, France).

Animals, Diet, and Treatment

Three-week-old male Wistar rats were obtained from Hacettepe University Experimental Animal Laboratory. The animals were divided randomly in eight groups of eight of each, and each group was housed in plastic cages with stainless-steel grid tops. The cages were maintained in a room with controlled temperature (23°C), humidity (50%), and a 12-h light–dark cycle. Feeding period was 7 weeks, and animals were allowed free access to diet and water. Body weights (bw) were monitored weekly.

In the experimental groups, (1) control group (C) was fed with regular diet and drinking water. (2) Control-fenvalerate group (CF) was fed with regular diet and drinking water and received 100 mg/kg/day, i.p., fenvalerate (1/3 LD_{50}) during the last week of feeding period. (3) Iodine-deficient and selenium normal group (ID) was fed with the same regular diet and received 1% sodium perchlorate containing drinking water as described by Giray et al. [33]. (4) Iodine-deficient and fenvalerate group (IDF) was fed with regular diet, received 1% sodium perchlorate containing drinking water, and received 100 mg/kg/day, i.p., fenvalerate during the last week of feeding period. (5) Iodine normal and selenium-deficient group (SeD) was fed with selenium-deficient diet and received normal drinking water. (6) Selenium-deficient and fenvalerate group (SeDF) was fed with selenium-deficient diet and received normal drinking water and received 100 mg/kg/day, i.p., fenvalerate during the last week of feeding period. (7) Iodine and selenium-deficient group (ISeD) received both selenium-deficient diet and 1% sodium perchlorate containing drinking water. (8) Selenium plus iodine-deficient-fenvalerate group (ISeDF) was fed with selenium-deficient diet and 1% sodium perchlorate containing drinking water and received 100 mg/kg/day, i.p., fenvalerate during the last week of feeding period. The animals were treated humanely and

with regard for alleviation of suffering, and all studies have been approved by the local University Ethical Committee.

Twenty-four hours after the last dose, animals were weighed and sacrificed by decapitation under thiopental anesthesia. Thyroid glands were removed, and venous blood samples were collected into heparinized tubes. Plasma samples were separated after centrifugation at 800 g for 15 min. All samples were immediately aliquoted and kept at −80°C until analysis.

Measured Parameters and Methods

Thyroid hormone status was determined by measuring the plasma TSH, TT_4, and TT_3 concentrations by RIA.

Statistical Analysis

Experimental data were analyzed with one-way analysis of variance followed by the Student's *t* test using a Statistical Package for Social Sciences program (SPSS) for windows packed program. The p values <0.05 were considered significant. Values are given as mean ±SEM.

Results

Body and Organ Weights

Iodine deficiency and combined deficiency produced significant increases in thyroid size and relative thyroid weight (mg thyroid/100 g bw), whereas they did not change in selenium-deficient rats. Fenvalerate treatment did not cause any significant changes in control rats, but induced significant enhancements in IDF (approximately 40%) and SeDF (approximately 80%; Fig. 2).

Thyroid Hormone Levels

Iodine deficiency and resulting hypothyroidism was evidenced by higher TSH and lower plasma TT_4 and TT_3 levels along with increased thyroid weights in rats exposed to sodium perchlorate (1%) in drinking water for 7 weeks (Fig. 3). TT_4 levels in selenium deficiency

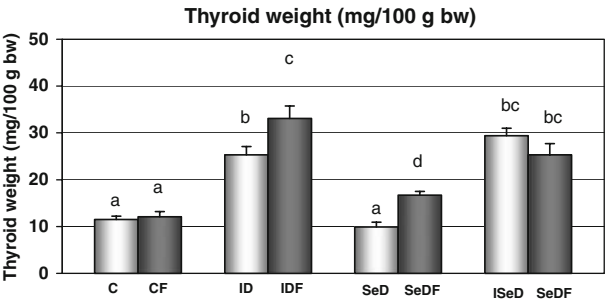

Fig. 2 Relative thyroid weights in experimental groups. [a,b,c,d] Superscripts of different letters differ significantly $p<0.05$ from each other

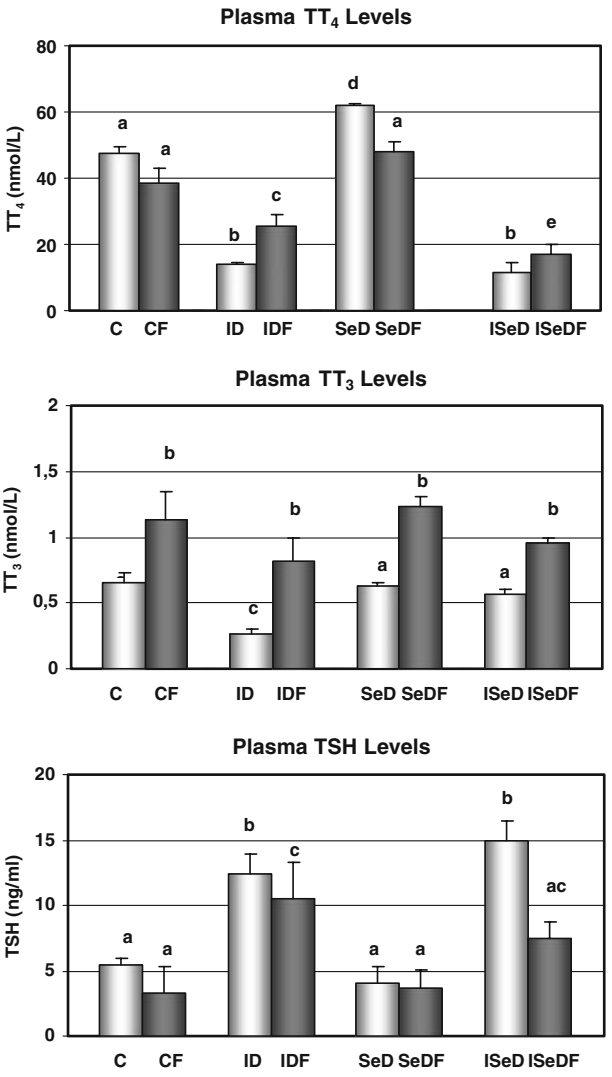

Fig. 3 Plasma TT_4, TT_3, and thyroid stimulating hormone levels in experimental groups. [a,b,c,d,e] Superscripts of different letters differ significantly $p<0.05$ from each other

were higher significantly compared to control group, but TT_3 and TSH levels did not change. The highest TSH elevation was observed in ISeD (approximately threefold), TT_4 levels of which were lower than those of control rats, while TT_3 levels did not differ from the values of neither control group nor SeD. These results were in agreement with the observations of our previous study, which was carried out with the same conditions except for a feeding period of 5-weeks [33].

Except for the insignificant reduction in TSH and TT_4 in control rats and no alteration of TSH in selenium deficiency, fenvalerate treatment induced significant changes in all three parameters of thyroid in the study groups. While TT_3 was elevated significantly (approximately 70% to approximately 200%) in all groups, significant elevation in TT_4 and decrease in TSH was observed both in iodine and combined deficiencies. The effect of fenvalerate on TT_4 in selenium-deficient rats was a significant reduction to the level of control values.

Discussion

Thyroid hormones regulate and promote cellular growth and development, and normal thyroid hormone levels are essential for the maintenance of normal metabolic functions in living organisms. The prohormone T_4 is produced exclusively in the thyroid gland, and the T_4 in the circulation enters all tissues of the body, where it may be converted to the metabolically active hormone T_3 by the isozymes of deiodinases, which are characterized by their tissue distribution, structure, and biochemical properties [7, 8]. The homeostatic control of thyroid hormone synthesis and secretion in the thyroid gland is carried out by a sensitive feedback mechanism that involves hypothalamus-pituitary-thyroid (HPT) axis. The hypothalamus senses low levels of circulating thyroid hormones (T_3 and T_4) and responds by releasing the thyrotropin-releasing hormone (TRH). The TRH stimulates the pituitary to produce TSH, which in turn stimulates the thyroid gland to produce thyroid hormones until their levels in blood return to normal.

Over several decades, endocrine-disrupting chemicals became the focus of public and scientific interest [34], and available data strongly indicate that in addition to the reproductive system, HPT axis may be a target of endocrine disruption. It has been shown that there may be multiple targets for various endocrine-disrupting chemicals to interfere with the complex regulatory network of thyroid hormone, including their synthesis, metabolism, distribution, and action on the various levels of endocrine regulation and feedback control [35–39].

Pesticides have been suggested as the endocrine-disrupting chemicals, and there are various studies on their adverse effects particularly on male fertility and reproductive systems [40–42]. However, studies on the alterations of thyroidal system by exposure to pyrethroid insecticides including fenvalerate are limited, and the results are controversial. Maiti and Kar [31, 32] reported that fenvalerate treatment (40, 80, and 120 mg/kg, orally) of female mice for 7 days caused significant decrease in serum T_4 levels, and serum T_3 levels and the activity of the type I iodothyronine 5′-monodeiodinase were found to be significantly lower in the higher dose group following 7 or 15 days of treatment. The conclusion of the authors was that the effect of fenvalerate was through the inhibition of monodeiodination of T_4, the principal pathway of T_3 generation. On the contrary, Kaul et al. [29] observed significant increases in plasma T_4 and T_3 by treatment of fenvalerate (100 mg/kg, i.p., 45 days) in male Wistar rats. Wang et al. [43] observed a dose-dependent decrease in T_4 and T_3 and elevation in TSH in permethrin-treated rats; however, with deltamethrin, the only alteration was the decrease of T_4 levels. Similar results were observed with bifenthrin and Lambda-cyhalothrin [44], and recently, Liu et al. [45] observed the same trend in Wistar rats treated with cypermethrin plus methyl parathion. These diverse results might be stemmed from the different study designs with respect to the dose, route, and length of insecticide treatment, as well as the sex, species, and strain differences of used animals. However, it is obvious that pyrethroid insecticides, including fenvalerate, have actions affecting the HPT axis.

In the presented study, observation of TT_3 elevation and although insignificant, decreases in TT_4 and TSH with fenvalerate treatment in control rats, might be due to an inducing effect of the insecticide on monodeiodination pathway of TT_4. This might also be true for the SeDF group where TT_4 was lowered and TT_3 was increased despite the selenium dependency of TT_3 generation pathway of TT_4. However, the same argument cannot be applied for the IDF and ISeDF where alterations were more pronounced and both TT_3 and TT_4 levels increased and TSH decreased accordingly. It is certain that the endpoints measured in our study are limited; and further studies with other thyroid-relevant

parameters such as morphology of thyroid gland, iodide uptake, and thyroid peroxidase activity would be needed for better understanding of the mechanism of interference of fenvalerate on HTP axis. However, in a comprehensive study where several in vivo and in vitro assays were conducted with a wide range of endocrine-disrupting compounds, although interference on several levels of HTP axis were determined (multi-target and multimodal action), the effects of the agents did not reflect classical mechanism of hormone-dependent regulation and feedback. For instance, lower TT4 was not always accompanied by high TSH; thyroid histology did not necessarily reflect hormone levels.

On the other hand, our study is the first to evaluate the effects of pyrethroid insecticides on thyroid hormone parameters in selenium and/or iodine deficiency. Although the thyroid has a high capacity to adapt to adverse effects of chemicals, this study showed that in case of iodine and/or selenium deficiency, modification of thyroid hormone status by fenvalerate was pronounced. Iodine deficiency is still prevailing in many parts of the world, and deficiency or at least insufficiency of selenium is not rare. Thus, compounds like fenvalerate, in addition to their own effects, may unmask or aggravate effects elicited by deficiency states. Changes in thyroid hormone levels can adversely affect fertility, pregnancy outcome, and postnatal development in humans and animals [46]. An insufficient supply of thyroid hormones to the developing brain may result in mental retardation. Consequences of thyroid status modifying effect of fenvalerate might thus be critical importance particularly in sensitive individuals and patients with thyroid dysfunction.

Acknowledgements

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