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# The effect of capsaicin on TBARS and TAS levels in rats with hypothyroidism

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**ABSTRACT**

In this study, capsaicin was administered to rats with experimental hypothyroidism. İt was aimed to determine the changes in plasma levels of thiobarbituric acid reactive substances (TBARS), which are indicators of oxidative stress, and total antioxidant capacity (TAS), which is one of the components of antioxidant defence mechanisms. A total of 32 healthy male Wistar Albino rats weighing 300-350 g, approximately 12 weeks old, were used as animal material in the study. Rats were divided into four equal groups control (K), Capsaicin (C), Hypothyroid (H) and capsaicin + Hypothyroid (CH). During the 30-day trial period, (10mg / kg / day) capsaicin was administered to the rats in group C by oral gavage per animal. In group H, 6-n-propyl-2-thiouracil (PTU) was added daily to their drinking water at 0.05% weight/volume (W/V). In the CH group, 10 mg/kg/day of capsaicin was administered by oral gavage method and 0.05% weight / volume (W / V) of PTU was added to drinking water. At the end of the application, we obtained plasma and serum samples from the subjects in the groups under general anaesthesia (thiopental anaesthesia, 40 mg/kg) and by taking sufficient amount of blood from the heart by cardiac puncture. We determined thyroid-stimulating hormone (TSH), total triiodothyronine (TT3), free T3 (fT3), total thyroxine (TT4) and free T4 (fT4) levels from serum samples, and TBARS and TAS levels from plasma samples. In conclusion, in the light of the data obtained in this study, we determined that lipid peroxidation and oxidative stress occur in hypothyroidism. However, we concluded that the application of capsaicin is partially sufficient to maintain the oxidant/antioxidant balance.

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## Introduction

Thyroid hormone secreted by the thyroid gland regulates the metabolic rate necessary for the normal function of tissues. Although thyroid hormone is not absolutely necessary for life, physical and mental regression is observed in its absence (Noyan, 2011).

Hypothyroidism is a term used to describe physiological disorders caused by suboptimal circulating levels of thyroid hormones. Hypothyroidism is associated with hypometabolism characterized by decreased blood thyroid hormone levels, decreased resting energy expenditure, weight gain, increased blood cholesterol levels, decreased lipolysis, and decreased gluconeogenesis (Brent 2012).

Oxidative stress parameters have been examined in different studies in patients with high (hyperthyroidism) and low (hypothyroidism) thyroid hormone levels in the blood, and it has been reported that there are changes in the body's oxidant and antioxidant systems in both hyperthyroidism and hypothyroidism (Torun et al., 2009; Santi et al., 2010).

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In hypothyroidism, a decrease in free radical production is expected due to metabolic suppression brought about by the decrease in thyroid hormone levels (Pereira et al., 1994). The effect of hypothyroidism on antioxidant enzymes has been investigated in several tissues, but the results are highly controversial. In some cases, the change in antioxidant enzyme activity appears to be tissue-specific (Venditti et al., 1997). On the other hand, within a single tissue, the response of antioxidant enzymes to hypothyroidism is not always similar (Das and Chainy 2001). Conversely, Duntas (2005) reported that hypothyroidism is associated with increased ROS production.

The hot component of cayenne pepper is capsaicin, and its active derivatives are called capsaicinoids. Capsaicinoids have been found to exert multiple pharmacological and physiological effects, including analgesia, anticancer, anti-inflammatory, antioxidant, and anti-obesity activities (Luo et al., 2011). Therefore, capsaicinoids may have potential clinical value for pain relief, cancer prevention and weight loss (Sun et al., 2016). In addition, capsaicinoids show benefits on the cardiovascular and gastrointestinal systems. The beneficial effects of capsaicin on cardiovascular function and metabolic regulation have been confirmed in experimental and population studies (Li et al., 2019).

Reactive free radicals produced during oxidative attacks lead to architectural changes in the cellular dimension, resulting in abnormal changes in macromolecules. These toxic changes are responsible for the pathogenesis of various diseases. The studies show that capsaicin as a dietary supplement may be beneficial in combating oxidative stress (Chaudhary et al., 2019).

Capsaicin, the main component of red pepper, has attracted increasing attention due to its multiple biological activities. Therefore it has been the subject of many studies in recent years (Antonious, 2018). On the other hand, it has been one of the most studied subjects hypothyroidism, especially in our country and in the world, because of the endemic regions in terms of iodine deficiency (Gluvic et al., 2020). However, we concluded that studies on the effects of capsaicin on thyroid hormones and metabolisms in humans and animals, and thus examine the protective effects of capsaicin in hypothyroidism, are quite insufficient. Therefore, this study planned to examine whether capsaicin affects TBARS and TAS in mice with experimental hypothyroidism, with the thought that it would contribute significantly to the knowledge on the subject.

In this study, it was aimed to determine the protective effect of capsaicin, whose antioxidant properties are well known, to reduce the amount of ROS increased Because of oxidative stress in experimentally induced hypothyroidism, to increase the amount of decreased antioxidants and to keep the inflammatory response in balance.

## Material and Methods

In the research, S.U. Obtained from the Experimental Medicine Research and Application Center, 32 healthy male Wistar Albino rats, approximately 12 weeks old, weighing 300-350 g, were used. In the trial covering a 10-day adaptation period and a 30-day main research period; Appropriate living conditions were provided for the rats in the form of 22 ± 2 °C room temperature, 50 ± 10 % relative humidity and 12/12 day and night light periods. In the study, the average amount of water that the rats could drink daily was determined (average 50 ml/day/rat), and their water was refreshed daily. Animals were fed with standard rat chow (Bil-Yem) ad libitum. Chemically, PTU (Trademark; Sigma P3755) and capsaicin (Trademark; Tokyo Chemical Industry TCI M1149) were used.

During the trial, in the control group; standard rat feed and drinking water were given ad libitum and no application was made. To the capsaicin group; Standard rat food and drinking water were given ad libitum. Capsaicin was administered orally at a daily amount of 10 mg/kg/day (Joo et al., 2010). To the hypothyroidism group; Standard rat food and drinking water were given ad libitum. During the adaptation period, the daily average amount of water consumed by the rats was determined and 0.05 % PTU (Moulakasis et al., 2008; Tousson et al., 2012; Kandır, 2015) was added to the drinking water daily throughout the experiment in order to create hypothyroidism. Capsaicin+Hypothyroidism group; Standard rat food and drinking water were given *ad libitum*. A daily amount of 10 mg/kg/day capsaicin and 0.05 % PTU were added to drinking water.

**Blood analysis:** At the end of the experiment, animals were decapitated after taking sufficient amount of blood (approximately 10-12 ml) from the heart under general anesthesia (thiopental anesthesia, 40 mg/kg) and cardiac puncture at the end of the experiment. Collected blood was put into tubes with or without ethylene diamine tetra acetic acid (EDTA) to obtain plasma and serum. Plasma samples were obtained by centrifuging the blood at 3500 rpm at +4°C (HettichRotina 35 R). Plasma and serum samples were stored at -80 °C until analysis.

**Determination of hormone levels in serum samples:** TT3, TT4, fT3, fT4 and TSH hormone levels in serum

samples were determined by the chemiluminescence method using the immunoassay system on Abbottarchitech i2000 analyzer and commercial kits (Abbott) as specified in their package inserts (Sarandol et al., 2005; Kandır, 2015).

**Determination of oxidative stress and antioxidant levels in plasma samples:** Plasma TBARS and TAS levels were determined by colourimetric method by reading the absorbance values with the Biotek brand ELX800 model ELISA device such as by the package inserts of the commercial kits (Messarah et al., 2010; Kandır, 2015).

**Statistical analysis:** SPSS 25 statistical package program was used to evaluate the data. Variables mean ± standard error values were used. Kruskal Wallis test was used to analyze the statistical difference between the groups. P<0.05 value was accepted for the significance level of the tests.

## Results

**Thyroid Hormone Levels:** In the research, considering TSH, TT4, TT3, Free T3 and Free T4 values, it can be said that PTU administration causes hypothyroidism in hypothyroid (H) and capsaicin+hypothyroid (HC) groups. As a matter of fact, the serum TSH level in the H and CH groups was higher (p<0.05) than in control (K) and capsaicin (C) groups, on the other hand, serum TT4 and TT3 values, which are the main thyroid hormones effective on tissues, and serum-free thyroxine and triiodothyronine levels were both The fact that it was found in lower amounts in rats in both H and CH groups compared to the same values in other groups confirms this (Table 1).

**Antioxidant and free radical parameters:** It was determined that plasma TBARS level in the hypothyroidism+capsaicin (CH) group was higher than the TBARS levels in the other 3 groups (K, C and H) (p<0.05). It was noted that there was no significant difference (p>0.05) between the same parameter levels among the K, C and H groups (Table 2).

When the plasma TAS variable of the groups was examined, a significantly higher value was determined only in the hypothyroidism group (H) compared to the other groups (F, C, CH) (p<0.05), and there were a significant difference between the TAS levels of the K, C and CH groups. İt is seen that there is no difference (p>0.05) (Table 2).

**Table 1.** Blood serum mean TSH (thyroid stimulating hormone), TT4 (total thyroxine), TT3 (total triiodothyronine), fT3 (free T3) and fT4 (free T4) levels of the groups used in the study, given capsaicin and/or hypothyroidism (x ± standard error).

| Group | Control (n = 8) | Capsaicin (n = 8) | Hypothyroidism (n = 8) | Capsaicin + Hypothyroidism (n = 8) |
|---|---|---|---|---|
| TSH (mIU/L) | 1.51 ± 0.74 [a] | 4.64 ± 1.76 [a] | 43.24 ± 16.04 [b] | 49.36 ± 12.4 [b] |
| $TT_3$ (ng/mL) | 1.21 ± 0.13[a] | 1.19 ± 0.12[a] | 0.51 ± 0.03[b] | 0,51 ± 0.03[b] |
| $TT_4$ (ug/dL) | 7.46 ± 1.51 [a] | 8.39 ± 0.93 [a] | 0.53 ± 0.09 [b] | 0.63 ± 0.1 [b] |
| $fT_3$ (ng/L) | 3.12 ± 0.6 [a] | 2.62 ± 1.23 [a] | 0.02 ± 0.02 [b] | 0.05 ± 0.05 [b] |
| $fT_4$ (ng/dL) | 2.88 ± 0.19 [a] | 3.15 ± 0.31 [a] | 0.21 ± 0.22 [b] | 0.19 ± 0.05 [b] |

a, b; The difference between the mean values of the same parameter displayed with different letters on the same line is important (p<0.05). There was no significant difference between groups containing the same letter ($P > 0.05$).

**Table 2.** TBARS and TAS levels measured from the blood plasma of the groups used in the study, given capsaicin and/or hypothyroidism (x ± standard error).

| Group | Control (n = 8) | Capsaicin (n = 8) | Hypothyroidism (n = 8) | Capsaicin + Hypothyroidism (n = 8) |
|---|---|---|---|---|
| Tbars (nmol/mL) | 4.63 ± 2 [a] | 3.38 ± 0.94 [a] | 4.46 ± 1.83 [a] | 6.01 ± 0.73[b] |
| TAS (mmol/L) | 9.31 ± 2.16 [a] | 11.01 ± 2.5 [a] | 14.09 ± 1.72 [b] | 11.59 ± 1.84 [a] |

a, b; The difference between the mean values of the same parameter displayed with different letters on the same line is important ($P < 0.05$). There was no significant difference between groups containing the same letter ($P < 0.05$). TBARS = Thiobarbituric acid reactive substances, TAS = Total antioxidant status

## Discussion and Conclusion

In the study, when the obtained findings were compared, the increase in serum TSH level ($p<0.05$), the decrease in TT4, TT3, fT4 and fT3 levels ($p<0.05$) in the H and CH groups, which were applied PTU, were experimentally determined when compared to the K and C groups shows that hypothyroidism is formed (Table 1). Rondeel et al. (1992), Kandır (2015) and Yazıcı (2019) also reported that hypothyroidism was induced by adding PTU to the drinking water of rats.

Thiobarbituric acid reactive substances (TBARS) is a lipid peroxidation index and is one of the important indicators of oxygen reactive species (ROS) activities and is associated with membrane lipid degradation (Ottaviano et al., 2008). Messarah et al. (2007) and Coria et al. (2009) report that lipid peroxidation products such as malondialdehyde and hydroperoxide concentrations do not change in clinical hypothyroidism and subclinical hypothyroidism compared to euthyroidism. However, some researchers have observed that the level of TBARS in the blood is increased in clinical hypothyroidism compared to euthyroidism (Nanda et al., 2007; Erdamar et al., 2008; Santi et al., 2010). Reports also state that oxidative stress is reduced in experimental hypothyroid animal models (Brzezińska-Slebodzińska, 2003; Mogulkoc et al., 2005; Tenorio-Velázquez et al., 2005). The results obtained from this study, in accordance with the studies of Messarah et al(2007) and Coria et al (2009), show that the TBARS concentration did not change in rats in the hypothyroidism group compared to the rats in the control group ($p>0.05$). In the case of hypothyroidism, the reasons for opposing views in the literature can be attributed to tissue and organ sensitivity, lipid peroxidation measurement methods, animal species, and application method differences (Messarah et al., 2011; Cano-Europa et al., 2012).

Although the antioxidant property of capsaicin is well known (Chaudhary et al., 2019), it is reported that it can increase oxidative stress in some cases (Abdel-Salam, 2006; Baek et al., 2008; Schwartz et al., 2008), as observed in this study. It has been stated that when capsaicin is injected intradermally, the central transmission of nociceptive impulses induced by capsaicin may increase spinal reactive oxygen species due to increased mitochondrial superoxide production in dorsal horn neurons (Schwartz et al., 2008). It has been reported that capsaicin induces a complex expression pattern of both oxidative stress genes and antioxidant defence genes, and during apoptosis in response to capsaicin, reactive oxygen species levels increase or decrease depending on the cancerous cell type (Baek et al., 2008). Another study reported that oxidative stress created by endotoxin lipopolysaccharide application, liver MDA increased significantly after capsaicin application (Abdel-Salam et al., 2012). In this study, although the plasma TBARS level decreased in the capsaicin-administered group compared to the control group, this decrease was not statistically significant ($p>0.05$). When capsaicin was applied to the hypothyroidism group, the TBARS level increased ($p<0.05$), and its results are similar to the last reports mentioned above (Baek et al., 2008; Schwartz et al., 2008).

The mechanism of increased oxidative stress in hypothyroidism is controversial. It can be thought that An insufficient antioxidant defence system in hypothyroidism may be one of the factors (Torun et al., 2009). Venditti and Di Meo (2006) showed that antioxidants were not affected in the same way in different tissues of hypothyroid rats; They reported that they increased in some tissues, decreased in others or remained unchanged. Konukoglu et al. (2002) found that antioxidant plasma protein thiol levels decreased in patients with hypothyroidism and returned to normal with thyroxin treatment. This suggests that the deficiency of the antioxidant defence system may be a leading factor in the increase of oxidative stress in hypothyroidism (Santi et al., 2010). In another study, the antioxidant ceruloplasmin was decreased in hypothyroid patients compared to normal controls. While most of these studies evaluate different and only one or a few antioxidants, it may also be important to measure total antioxidant capacity, which may be more informative about overall antioxidant defences. Total antioxidant capacity (TAS) gives information about all antioxidants in the organism (Torun et al., 2009). In the study of Salama et al. (2013), in which they experimentally induced hypothyroidism in rats with PTU, it was reported that rats with hypothyroidism had higher plasma and tissue MDA, plasma NO2, NO3 and tissue total antioxidant levels compared to the control group rats. Cebeci et al. (2012) also recorded that they found the plasma total antioxidant capacity to be significantly higher in patients with hypothyroidism in their measurements, while Torun et al. (2009) found that the total antioxidant levels of SH and OH patients were lower than the control group. Similarly, Mancini et al. (2010), Gomathi et al. (2012), Deraz et al. (2016), and also report that plasma TAS levels are significantly lower in patients with hypothyroidism compared to healthy subjects. In their study, Kumari et al. (2011) reported that hypothyroidism did not cause a change in NO, SOD and total antioxidant levels compared NO, SOD

and total antioxidant values in hyperthyroid and hypothyroid patients. The data obtained in this study, in line with the findings of Cebeci et al. (2012) and Salama et al. (2013), were found to have a higher plasma TAS level in the hypothyroidism group than in the other groups ($p < 0.05$) (Table 2). In our study, the fact that plasma TAS levels were found to be higher in rats in the H group with hypothyroidism than in the rats in the K, C and CH groups ($p<0.05$) may indicate that the total antioxidant capacity of the body may have increased due to the increased oxidative stress in hypothyroidism (Table 2). Different findings among some studies: it may be caused by differences in tissue and organ sensitivity, measurement methods, animal species and application method (Messarah et al., 2010; Cana-Europa et al., 2012).

Capsaicin has potent antioxidative effects in vivo through a non-receptor-mediated mechanism. As a matter of fact, Chaudhary et al. (2019), in their study on erythrocytes without TRPV1 channels, reported that the plasma antioxidant capacity increased significantly ($p<0.05$) in capsaicin supplemented rats. This observation shows that capsaicin administration can protect cells from oxidative damage (Chaudhary et al., 2019). In a study examining the hypolipidemic and antioxidant effects of dietary capsaicin in hypercholesterolemic rats, it was found that while the levels of ascorbic acid and α-tocopherol, which are antioxidant molecules in the serum, did not change in the capsaicin diet compared to the control group, the total amount of thiol decreased (Manjunatha and Srinivasan, 2007). On the other hand, it was reported that the total thiol, α-tocopherol and intracellular total thiol levels in the basement membrane of erythrocytes in rats fed a high-fat diet did not change with the application of capsaicin, and in the same study, it was reported that the total thiol amount in the cell decreased with capsaicin in hypercholesterolemic animals (Kempaiah and Srinivasan, 2004b). The data obtained in this study show parallelism with the work of Manjunatha and Srinivasan (2007). TAS levels, which increased significantly ($p<0.05$) due to oxidative stress in the hypothyroidism group, decreased with capsaicin administration (Table 2). This may show that the use of antioxidants is increased to reduce oxidative stress.

In conclusion, the data obtained in this study suggest that lipid peroxidation and oxidative stress occur in hypothyroidism, but capsaicin administration is partially sufficient to provide oxidant/antioxidant balance. On the other hand, it has been concluded that the study's findings can contribute to the information that can be considered insufficient on the subject and can be a source for other research that can be done in this direction.

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**Ethical Statement**

This study was approved by Selcuk University Animal Experiments Ethics Committee with the decision dated 29.04.2019 and numbered 2019-20.

**Conflict of Interest**

The authors declared that there is no conflict of interest.

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