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Experimental Research Article

Serum levels of thyroid hormones change differently in the onset and progress phases of the experimental model of Parkinson's disease in rats

Shahram Darabi, Hashem Haghdoost-Yazdi*, Mohamad Sofiabadi, Mohamad Esmaeili, Mehrdad Delashoob

Non-communicable Diseases Research Center, Research Institute for prevention of Non- Communicable Disease, Qazvin University of Medical Sciences, Qazvin, Iran

ABSTRACT

Introduction: Changes in the levels of serum components can help in the early and differential diagnosis of Parkinson's disease (PD). The lesion in the dopaminergic (DAergic) system is the main pathophysiological mechanism underlying PD. This system is closely related to the hypothalamic-pituitary-thyroid axis. Here, we examined the impact of PD onset, progress, and severity in rats on the serum levels of thyroid hormones (THs).

Methods: The neurotoxin 6-OHDA was injected into the medial forebrain bundle. Behavioral tests were carried out for eight weeks after the toxin to assess the severity of PD and its progress. Blood was collected before the toxin and in the third and eighth weeks afterward. THs levels were determined using specific ELISA kits.

Results: Our findings show that the THs levels changed significantly after the toxin. The levels of T3 and T4 decreased slightly in the third week but remarkably increased in the eighth week. The decrease in the third week depended on the severity of the PD and was observed only in the rats with severe behavioral symptoms. On the other hand, the increase in the eighth week occurred in all 6-OHDA-received rats with severe or mild behavioral symptoms.

Conclusion: Our data indicate that serum levels of THs may decrease and increase in PD. At the onset of the disease, the levels may decrease if DAergic neuronal death is severe. In the progress phase of PD, THs levels may increase independent of the severity of the disease.

Keywords:
Parkinson's disease
Thyroid hormones
6-OHDA
Onset
Progress

Introduction

PD is a neurodegenerative, progressive, and age-related motor disorder essentially caused by the progressive death of DAergic neurons in one of the neural structures in the midbrain called the substantia nigra (SN) (Adani et al., 2020; Shulman et al., 2011). Patients with PD are characterized by several motor disorders, such as bradykinesia, rigidity, tremor at rest, and also non-motor symptoms, including olfactory and autonomic dysfunctions, sleep disturbances, and cognitive impairment

* Corresponding author: Hashem Haghdoost-Yazdi, hhaghdoost@qums.ac.ir
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(Chaudhuri and Schapira 2009; Reich and Savitt 2019). However, most of the time, the early and differential diagnosis of PD involves some difficulties. Many attempts have been made to identify effective biomarkers for the early detection of PD, especially those in the serum, which are easily accessible and may be effective in the early diagnosis of PD, its severity, and even its duration. However, these attempts, although they have made remarkable advances, could not remarkably reduce the diagnostic difficulties (Trupp et al., 2014).

THs, including T3 and T4, are essential for various physiological functions, including metabolism, growth, energy management, and CNS development. An imbalance in the secretion of THs has serious consequences and can lead to mood changes, cognitive decline, and even motor disorders (Oetting and Yen 2007). The secretion of THs is finely regulated by the hypothalamic-pituitary-thyroid (HPT) axis. In turn, the HPT axis is mutually adjusted by these hormones. Both human and animal studies indicate a close relationship between the DAergic system in the brain and the HPT axis (Krulich et al., 1977; Przegaliński et al., 1993; Scanlon et al., 1979). Through the activation of D2 receptors, dopamine (DA) stimulates the release of TRH at the hypothalamic level and inhibits pituitary thyroid-stimulating hormone (TSH) production (Duval et al., 2022). Clinical evidence confirms this relationship, and thyroid diseases are the most common endocrine disorders associated with PD (OCAK et al., 2022). However, both hypothyroidism and hyperthyroidism are reported to occur in patients with PD (Chen et al., 2020; Davies et al., 2001; Kim et al., 2005; Tandeter et al., 2001; Umehara et al., 2015). However, most studies have generally focused on the association between THs levels and common features or clinical symptoms of PD, and with little reported about the impact of the severity or progress of the disease on the serum levels of thyroid hormones.

6-OHDA is a hydroxylated analogue of dopamine that selectively destroys dopaminergic neurons (Hernandez-Baltazar et al., 2017). Within a few days after unilateral injection of 6-OHDA into the medial forebrain bundle or SN, a massive lesion is produced in the ipsilateral DAergic neurons, whichinduces asymmetrical behaviors in rats. The severity of this neuronal death increases as a function of time (Yuan et al., 2005), leading to a progressive increase in the intensity of the asymmetrical behaviors (Haghdoost-Yazdi et al., 2010; Minaei and Haghdoost-Yazdi 2019; Minaei et al., 2021). Based on this information, we hypothesized that 6-OHDA-induced PD may impact the HPT axis, and the progressive increase in behavioral symptoms can model PD progression in patients with this disease. Therefore, the present study was designed to examine the association between the serum levels of THs and the onset and progress of PD in rats.

Material and Methods

Animals and experimental groups

Adult male Wistar rats (Razi Institute, Karaj, Iran), weighing 250-300 g, were housed in large cages (38 - 59 - 20 cm) in a temperature-controlled colony room under a 12 h light/12 h dark cycle with free access to tap water and standard food. They were divided into three experimental groups according to the treatment protocol: the control group (n=10), which received no treatment; the sham group (n=9), which received 6-OHDA solution; and the 6-OHDA group (n=18), which received 6-OHDA. Behavioral tests and thyroid hormone assessments were conducted on all groups.

The Experimental schedule

Before the surgery and stereotaxic injection of 6-OHDA, the rats were evaluated by apomorphine-induced rotational and cylinder tests. Only rats that did not show significant circling behavior and asymmetric scores were selected and entered the study. Behavioral tests were repeated in the second, fourth, sixth, and eighth weeks after the surgery in all groups. Blood samples were collected before the surgery and in the third and eighth weeks afterwards (Fig. 1).

Stereotaxic surgery and 6-OHDA injection

Stereotaxic surgery was carried out on the sham and 6-OHDA groups. 6-OHDA was dissolved in isotonic saline (NaCl) containing 0.2% ascorbic acid. The rats were initially anesthetized with a solution containing both ketamine and xylazine (70 and 6 mg/kg, respectively, i.p.). Then, 4 µl of 6-OHDA (4 µg/µl), or its solution, was injected into the medial forebrain bundle (MFB) through two sites in the right hemisphere with the coordinates of anterior-posterior (AP): −4, lateral (L): −1.8, dorsoventral (DV): 9 and AP: −4.4, L: −2, DV: 8. The reference for AP and L was the bregma, and for DV, it was the surface of the skull.

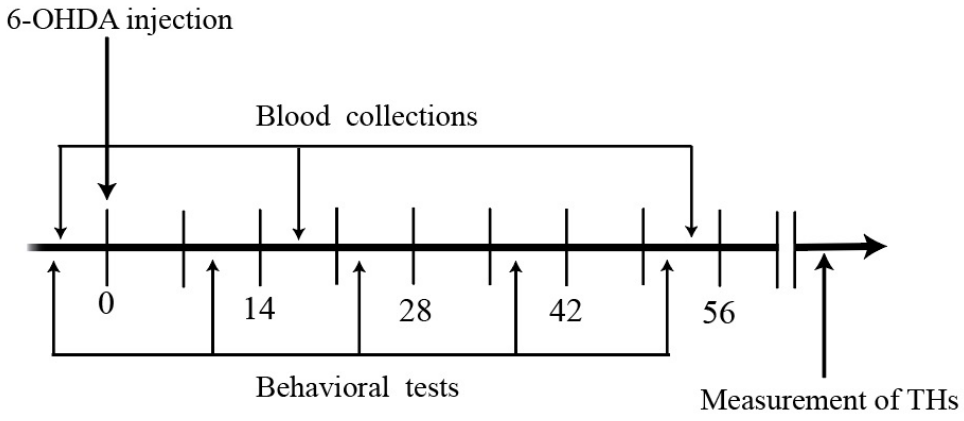

FIGURE 1. The schedule of the experiments. Numbers show the days after the toxin.

Behavioral test

Apomorphine-induced rotational test

The animals were allowed to acclimate to the test container for 5 minutes and then received an apomorphine hydrochloride injection (Sigma, 0.5 mg/kg, i.p). One minute after the injection, the number of full rotations was counted for 30 minutes in a cylindrical container (diameter, 28 cm; height, 38 cm). Contralateral and ipsilateral rotations were recorded as positive and negative scores, respectively, and the net number of rotations was calculated by subtracting the negative scores from the positive ones.

Cylinder test

The cylinder test is used to assess drug-free spontaneous forelimb use. The rats were placed individually in a cylindrical container (diameter, 28 cm; height, 38 cm) and allowed to move freely and explore the environment for 10 minutes. During the test, an observer directly counted the number of weight-bearing wall contacts made by both forelimbs, with one being unimpaired and the other impaired. An asymmetry score was then calculated using the equation: asymmetry score = I/I + C + B–C/I + C + B. Here, I and C represent the number of ipsilateral (unimpaired) and contralateral (impaired) forelimb contacts, respectively, and B indicates contacts made by both forelimbs. Asymmetry scores range from -1 to 1. Positive scores indicate the dominance of the unimpaired forelimb, while negative scores indicate the supremacy of the impaired forelimb in contacting the wall.

Blood sampling and THs measurement

Before the surgery and three weeks afterward, blood was collected from the rat's tail under conscious conditions. In the eighth week, animals were first anesthetized with ketamine and xylazine, and then blood was collected from the heart. The blood was allowed to coagulate, and then the serum was separated using a centrifuge and stored at -80°C until the measurement of THs. The ELISA method was used to measure thyroid hormones, following the instructions provided in the specific kit, with the typical detection range between 0.01 and 0.1 ng.

Statistical analyses

Analysis of the results by the Shapiro-Wilk test showed that the data were normally distributed. Therefore, repeated-measure analysis of variance (ANOVA) was used to analyze the effect of time and groups on the behavioral symptoms of 6-OHDA-induced PD. Other data were analyzed with one-way ANOVA followed by Bonferroni post hoc test for multiple-group comparisons. All statistical analyses were performed using SPSS version 20.0 (SPSS software, Inc., Chicago, IL, USA). Data are expressed as the mean ± standard error of the mean, and statistically significant differences were considered at a $P \leq 0.05$.

Results

Behavioral findings

Behavioral assessments of the 6-OHDA-induced PD were carried out before the toxin injection and in the second, fourth, sixth, and eighth weeks afterwards to

TABLE 1: Serum levels of T4 in experimental groups before the toxin and in the third and eighth weeks afterward.

T4	Control	Sham	6-OHDA
Before the toxin	58.7 ± 3.2 (nmol/L) 4.560 ± 0.248 (µg/dL)	54.1 ± 2.6 (nmol/L) 4.202 ± 0.201 (µg/dL)	55.8 ± 1.9 (nmol/L) 4.334 ± 0.147 (µg/dL)
Third week after the toxin	58 ± 2.9 (nmol/L) 4.505 ± 0.225 (µg/dL)	56.25 ± 2.3 (nmol/L) 4.370 ± 0.178 (µg/dL)	49.94 ± 2 (nmol/L) 3.88 ± 0.155 (µg/dL)
Eighth week after the toxin	54.46 ± 2.1 (nmol/L) 4.231 ± 0.163 (µg/dL)	53.66 ± 1.8 (nmol/L) 4.169 ± 0.139 (µg/dL)	61.17 ± 4.1 (nmol/L) 4.752 ± 0.320 (µg/dL)

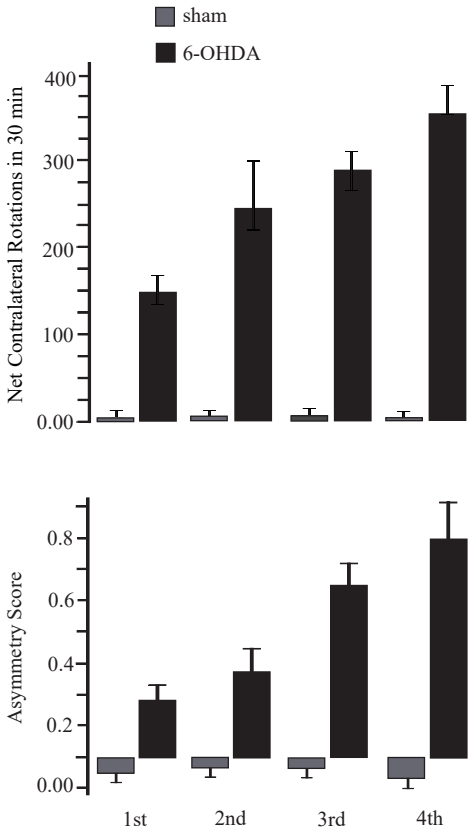

FIGURE 2. Plots show the findings of the behavioral tests in the sham and 6-OHDA-received groups in the second (1st), fourth (2nd), sixth (3rd), and eighth (4th) weeks after the toxin. While the rats in the sham and control groups did not show any behavioral symptoms, the 6-OHDA-received rats showed marked contralateral circling behavior and also a positive asymmetry score.

evaluate the induction or onset, severity, and progress of PD in rats.

Figure 2 shows the findings of the behavioral tests. Before the toxin, the rats in all groups showed no significant circling behavior in the apomorphine-induced rotational test. The circling behavior was not observed in the control and sham groups in the weeks after the toxin. On the other hand, the 6-OHDA-treated rats showed a significant number of net contralateral rotations, confirming that the model was well established. In addition, the number of rotations increased progressively (upper plot), demonstrating the progress of the PD.

The lower plot in Figure 2 shows the findings of the cylinder tests. Before the toxin, the asymmetry score in all groups was close to zero, indicating that the rats did not prefer using one hand to touch the wall of the test container. After the toxin, the control and sham groups did not show significant changes in the score. On the other hand, in the 6-OHDA-received rats, the asymmetry score increased remarkably and reached 0.17 ± 0.06,

TABLE 2: Serum levels of T3 in experimental groups before the toxin and in the third and eighth weeks afterward.

T3	Control	Sham	6-OHDA
Before the toxin	0.814 ± 0.06 (nmol/L) 0.052± 0,004 (µg/dL)	0.65 ± 0.09 (nmol/L) 0.042 ± 0,006 (µg/dL)	0.735 ± 0.04 (nmol/L) 0.047 ± 0,003 (µg/dL)
Third week after the toxin	0.735 ± 0.06 (nmol/L) 0.047 ± 0.004 (µg/dL)	0.70 ± 0.04 (nmol/L) 0.045 ± 0.003 (µg/dL)	0.58 ± 0.04 (nmol/L) 0.037 ± 0,003 (µg/dL)
Eighth week after the toxin	0.673 ± 0.03 (nmol/L) 0.043 ± 0.002 (µg/dL)	0.657 ± 0.03 (nmol/L) 0.042 ± 0.002 (µg/dL)	0.876 ± 0.03 (nmol/L) 0.056 ± 0.002 (µg/dL)

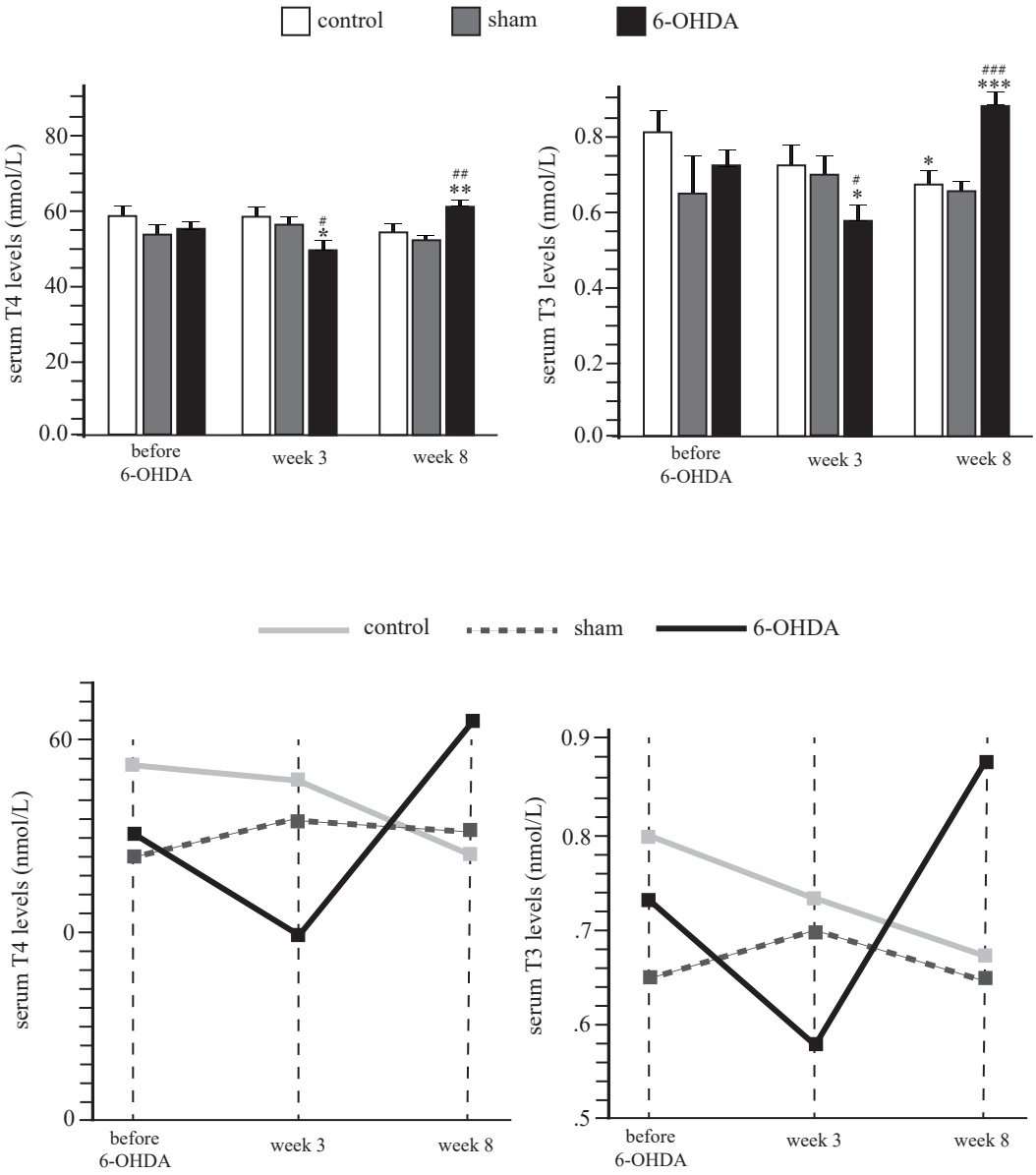

FIGURE 3. The serum levels of T3 and T4 in the different experimental groups before the toxin and in the third and eighth weeks after that. The lower graphs show the changes in serum levels of these hormones during the study. The statistical symbols are omitted from these graphs to clarify more of them.
*: P<0.05, **: P<0.01 and ***: P<0.001. In comparison to values before the toxin
#: P<0.05, ##: P<0.01 and ###: P<0.001: In comparison to values in the control and sham groups at the same week.

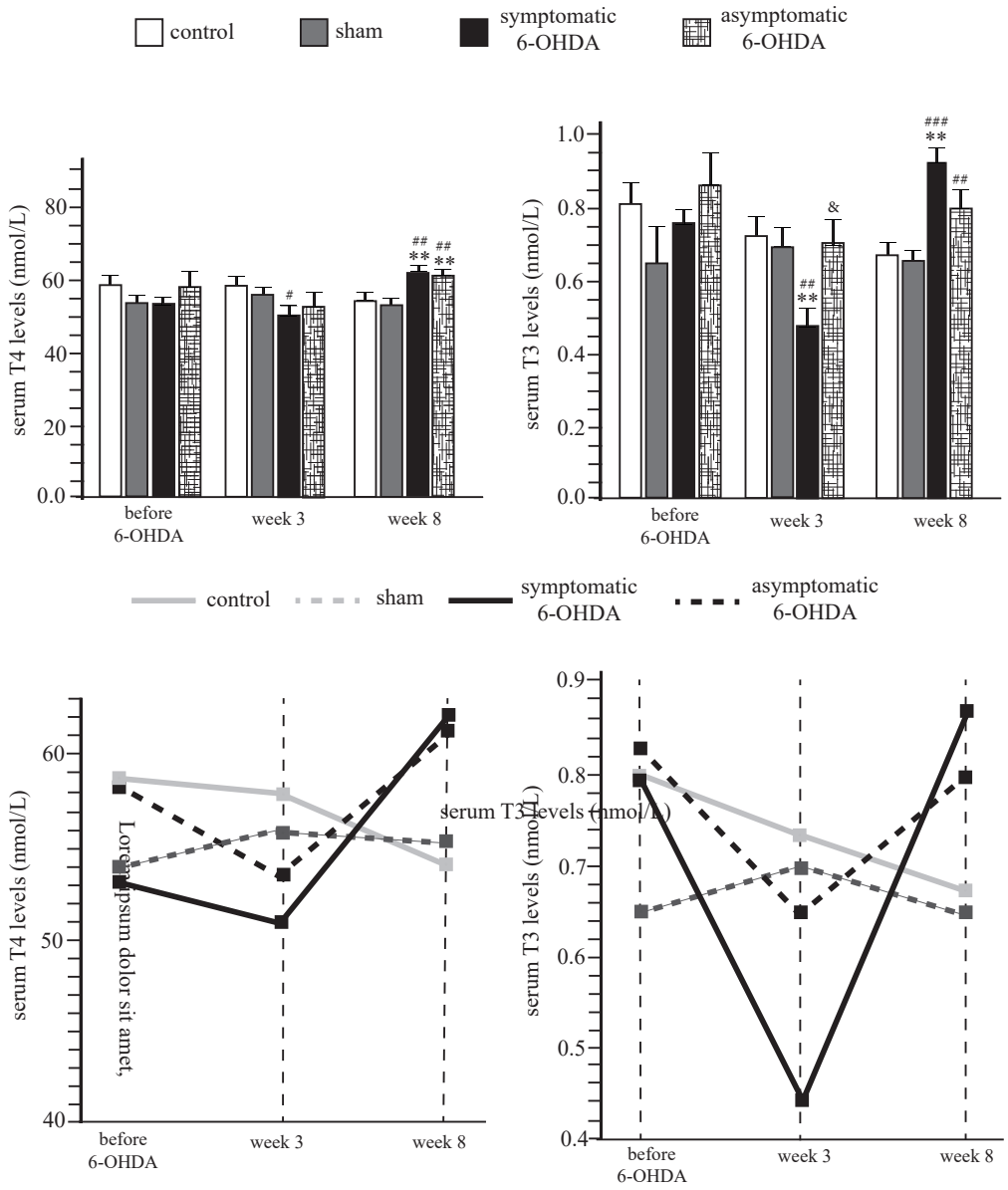

FIGURE 4. The upper plots show the serum levels of T3 and T4 in the control and sham groups, as well as symptomatic and asymptomatic subgroups of 6-OHDA-received rats. The lower graphs show the changes in these hormones during the study.
**: P<0.01. In comparison to values before the toxin
#: P<0.05, ##: P<0.01 and ###: P<0.001: In comparison to values in the control and sham groups at the same time
&: P<0.05. In comparison to values in the symptomatic subgroup at the same time

0.45 ± 0.08, 0.72 ± 0.08, and 0.85 ± 0.08 in the second, fourth, sixth, and eighth weeks, respectively. These values show that the 6-OHDA-received rats preferred to use their right hands to bear their weights.

Serum levels of Thyroid hormones

The serum level of T4 before the toxin was 56.16 ± 1.41 nmol/L (4.363 ± 0.2 mg/dl, n=37) .The maximum and minimum values were 75 and 44 nmol/L (5.827 and 3.418 mg/dl), respectively. The serum level of T3 was 0.730 ± 0.04 nmol/L (0.0475 ± 0.0026 mg/dl), and the maximum and minimum values were 1.3 and 0.3 nmol/L (0.0846 and 0.0195 mg/dl), respectively. Tables 1, 2, and Figure 3 show these levels in the different weeks of the study. As shown, in the weeks after the toxin, the T4 and T3 did not change significantly in the control and sham groups. However, in the eighth week, the T3 in the control group was significantly lower than before the toxin.

On the other hand, 6-OHDA-received rats showed

significant changes in both hormones. In the third week, the levels of both T4 and T3 decreased significantly and were lower than those in the control and sham groups. In contrast, in the eighth week, the levels of both hormones increased remarkably and were significantly higher than those in the control and sham groups.

Correlation between serum levels of thyroid hormones and severity of the 6-OHDA- induced PD

The severity of circling behavior varied among the rats that received 6-OHDA. For further study, we divided them into two subgroups based on the number of rotations in the apomorphine tests. The symptomatic subgroup exhibited a high number of rotations (more than 100, n=10), while the asymptomatic subgroup either did not show significant rotations or had fewer than 30 rotations in half an hour (n=8). Also, there was no progressive increase in the number of rotations in the asymptomatic subgroup.

Figure 4 displays the serum levels of thyroid hormones in these subgroups. In the third week, only the symptomatic subgroup showed a significant decrease in T4 and T3, with the decrease in T3 being much more pronounced. By the eighth week, T4 and T3 levels in both subgroups were much higher than those in the control and sham groups. Furthermore, T4 levels in both subgroups and T3 levels only in the symptomatic subgroup were higher than those before the toxin.

Discussion

It is well-known that the neurotransmitter dopamine has a regulatory impact on the HPT axis (Krulich et al., 1977; Przegaliński et al., 1993; Scanlon et al., 1979). On the other hand, animal studies suggest that THs have a regulatory impact on the metabolism of dopamine (Hassan et al., 2013; Menezes et al., 2019). The most important pathophysiological characteristic of PD is the degeneration of DAergic neurons in the SN, indicating that PD is possibly associated with changes in serum levels of THs. Confirming this, thyroid diseases are the most common endocrine disorders associated with PD, and patients suffering from this disease have THs disturbances (OCAK et al., 2022). On the other hand, it has been reported that both hyper- and hypothyroidism increase the risk of PD (Chen et al., 2020; Kim et al., 2005; Umehara et al., 2015). However, this association is unclear, and the effect of the severity and progress of PD on the THs levels is not well described. Therefore, in this study, we followed the changes in serum levels of THs in an experimental animal model of PD. In this model, the neurotoxin 6-OHDA is directly injected into the MFB region of the brain, where dopamine transporters at the DAergic terminals uptake the toxin and transfer it retrogradely to the neuronal cell body in the SN. Then, 6-OHDA causes inhibition of complex-1 of the mitochondrial electron transport chain, leading to the generation of oxidative stress, which damages the cytosolic targets. DAergic neurons have fewer defense mechanisms against oxidative stress and are therefore more susceptible to damage by it (Wei et al., 2018). Massive lesions in the SN lead to asymmetric behaviors in specific apomorphine-induced rotational and cylinder tests (Dauer and Przedborski 2003; Hernandez-Baltazar et al., 2017; Iancu et al., 2005). We performed these tests in the second, fourth, sixth, and eighth weeks after the toxin to evaluate the onset and progress of PD in the THs.

We used three groups of animals; control, sham, and 6-OHDA. With this design, we could evaluate the possible effects of the surgery and the lesion produced by the 6-OHDA-containing solution on the serum levels of thyroid hormones. While no significant differences were observed between the control and sham groups, the differences between these groups and the 6-OHDA-received group were significant. Also, the amount of 6-OHDA injected by stereotaxic surgery was too small to induce any systemic effect. These results clearly show that changes in THs in the 6-OHDA-received group were produced by the neurotoxic effects of 6-OHDA on the dopamine-secreting neurons in the SN.

Marked circling behavior and asymmetric scores were observed in the 6-OHDA-received rats two weeks after the toxin, confirming the induction of PD. In the subsequent weeks, the severity of behavioral symptoms progressed, representing the progression of PD. It has been evidenced that in 6-OHDA-induced Parkinsonism, the behavioral symptoms, especially asymmetrical circling, are the behavioral outcome of unilateral degeneration of DAergic neurons in the SN and striatal dopamine depletion (Dauer and Przedborski, 2003; Iancu et al., 2005; Yuan et al., 2005). Also, it has been reported that three weeks after the injection of 6-OHDA into MFB, about 80% of these neurons are degenerated. The neuronal death in the SN continues for several weeks afterward,

which, in turn, causes a progressive increase in the severity of behavioral symptoms (Haghdoost-Yazdi et al., 2010; Minaei and Haghdoost- Yazdi 2019; Minaei et al., 2021; Yuan et al., 2005). Therefore, the behavioral symptoms observed two weeks after the toxin indicate extensive neuronal death in the SN, and also, the progression of these symptoms reflects the ongoing neuronal death.

We measured THs levels in the third and eighth weeks after toxin administration to examine the association between the induction and progression of PD with THs levels. No significant changes were observed in T3 and T4 levels in the control and sham groups. In contrast, significant changes were observed in the rats that received 6-OHDA. They showed a significant decrease in T3 and T4 levels in the induction phase but a dramatic increase in the progression phase. Therefore, our data indicate that acute and massive DAergic neuronal death in the SN can be associated with a decrease in THs levels. On the other hand, prolonged and progressive neuronal death is associated with a remarkable increase in THs levels.

To examine the effect of the severity of PD on THs levels, we divided 6-OHDA-received rats into two subgroups: symptomatic and asymptomatic. The symptomatic rats showed clear and severe behavioral symptoms that progressively increased during the weeks after the toxin. On the other hand, asymptomatic rats neither showed clear circling behavior nor a progressive increase in its severity. Only the symptomatic rats showed a significant decrease in T3 and T4 at the onset of PD. However, both subgroups showed a remarkable increase in THs levels in the progression of PD. Our previous work showed that in symptomatic rats, DAergic neuronal loss in SN is extensive, and the number of these neurons was about 80% lower than that in controls. However, the neuronal death in the asymptomatic rats was also considerable, and they had 45% fewer neurons than the control group (Piri et al., 2022). Based on this, only acute and severe DAergic neuronal death lowers the levels of T3 and T4 in the induction phase of 6-OHDA-induced PD. On the other hand, both severe and moderate DAergic neuronal death can increase THs levels in the progression phase of PD.

Human and animal studies have shown that dopamine, through D2 receptors, stimulates the release of thyroid-releasing hormone (TRH) at the hypothalamic level (Krulich et al., 1977; Przegaliński et al., 1993; Scanlon et al., 1979). TRH regulates TSH synthesis by stimulating the transcription and translation of the TSH β-subunit gene. On the other hand, dopamine inhibits pituitary TSH production and the effect of TRH on the TSH β-subunit gene (Duval et al., 2022; Pereira et al., 2010). Confirming this, it has been reported that low TSH levels detected in some of the patients with PD can be secondary to levodopa treatment (Gupta et al., 2001). Dopamine also decreases prolactin secretion, which in turn causes changes in TSH secretion (Kimber et al., 1999). Nicola et al., 2000 reported that dopamine allows the gating of inputs via alteration of membrane properties and specific ion conductance. After that, Rye and Freeman 2008, explained that the physiological effects of the dopamine system are best characterized as "neuromodulatory," rather than eliciting excitatory or inhibitory postsynaptic potentials. One mechanism by which THs are modulated by dopamine is an enhancement of the biochemical functions of the complex family of cytochrome P450 enzymes. These enzymes are important for the biochemical degradation of THs (Pereira et al., 2010). We did not assess the effect of the DAergic system on the secretion of TRH or TSH. However, our data indicate that the effect of the lesion in the nigrostriatal dopaminergic pathway on THs levels depends on the time after the lesion. In a short time, THs levels decrease, but in prolonged time, their levels increase remarkably. Also, the severity of the lesion in this pathway is important. The decreasing effect in a short time occurs when the lesion is severe and extensive. However, the increasing effect might occur both in severe and moderate lesions.

Most of the human studies have reported a relationship between PD and THs levels. However, this relationship is not clear. It has been reported that both hypo- and hyperthyroid states occur in PD. Chen et al. 2020, conducted a large-population cohort study of around 5000 cases and showed that hypothyroidism nearly doubles the risk of PD. In another study conducted on 92 patients with PD and 225 healthy age-matched individuals, subclinical hyperthyroidism was more prevalent in the patients relative to healthy individuals (Tandeter et al., 2001). On the other hand, Oak et al., 2022 reported that there is no relationship between the severity of motor symptoms and THs in PD patients with normal thyroid functions. Other studies suggest that changes in THs

are underlying mechanisms in PD pathophysiology. For instance, maternal hypothyroidism has been shown to increase PD-like movements in rat offspring (Menezes et al., 2019). In contrast, Kim et al. 2005 reported that hyperthyroidism might exacerbate PD symptoms, and its treatment can attenuate the severity of PD. High THs levels can induce oxidative stress by increasing the basal metabolic rate, which increases oxygen consumption. Our data show that, depending on the severity and duration of the disease, both hypo- and hyperthyroid and even normothyroid states are expected.

In comparison to before the toxin was administered, rats in the control group showed a significant decrease in T3 levels in the eighth week. This difference might be due to variations in the site of blood collection (tail or heart) or the metabolic effect of ketamine/xylazine as reported previously for serum glucose and lipid levels (Chan et al. 2012; Wang et al. 2010; Rodrigues et al. 2006; Saha et al. 2005). However, such a difference was not observed in the sham and 6-OHDA groups. Additionally, considering this data can confirm our results, indicating that serum levels of THs increase in the progressive phase of PD.

In summary, our data show that following intracerebral injection of 6-OHDA into the MFB region and induction of PD in rats, there is a significant decrease in the serum levels of both T3 and T4. This decrease occurs when there is extensive DAergic neuronal loss in the SN, while mild or moderate neuronal loss has no significant effect. However, several weeks after the injection and during the progression of PD, the levels of these hormones increase dramatically. This increase is observed in rats with both extensive and moderate DAergic neuronal loss. These results clearly demonstrate that serum THs levels change differently in the onset and progression phases of PD, and accurate determination of THs levels may help evaluate the duration of the disease. However, the quality and quantity of these changes largely depend on the severity of the neuronal loss, especially in the onset phase. Because only extensive neuronal loss at the onset caused a decrease in THs levels, the determination of THs levels cannot help with the early diagnosis of PD.

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Ethics approval

All procedures of this study were performed based on the guidelines for animal experiments of the Research Council at Qazvin University of Medical Sciences. The ethical code of the study is IR.QUMS.AEC.1400.002.

Declarations of interest

none

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