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Effects of treatment with haloperidol and clozapine on the plasma concentrations of thyroid hormones in rats

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Objectives. Psychoactive drugs are group of compounds used to treat severe mental problems, including psychosis, as well as other conditions. This study assessed clinically relevant side effects of haloperidol and clozapine on the thyroid hormones.

Methods. Haloperidol (0.05 and 2 mg/kg) or clozapine (0.5 and 20 mg/kg) was intraperitoneally injected to male Wistar rats for 28 days. The control group received 2 ml of physiological saline. A chemiluminescent immunoassay was used to measure the plasma levels of thyroid hormones.

Results. Plasma concentrations of thyroxine (T4) in rats treated with high-dose (2 mg/kg) of haloperidol decreased significantly compared to the control group ($p=0.001$). However, both low (0.5 mg/kg) and high clozapine (20 mg/kg) doses did not have a significant effect on the plasma concentrations of T4 and triiodothyronine (T3) ($p>0.05$). Neither of the compound had a significant effect on T3 plasma concentration levels ($p>0.05$).

Conclusions. Haloperidol and clozapine act via different mechanisms and may have dissociable effects on thyroid hormones. Following treatment with haloperidol, significant changes in T4, but not in T3, serum levels were observed. Haloperidol and clozapine had different effects on the thyroid hormone levels. These results indicate that antipsychotic treatment can contribute to the thyroid dysfunction. Therefore, greater caution should be applied to the antipsychotics use. The thyroid function of the patients should be closely monitored, while using these drugs.

Key words: antipsychotics, chemiluminescent, thyroxine, triiodothyronine

The thyroidal hormone 3,3'-5-triiodo-l-thyronine (T3) and its prohormone, l-thyroxine (T4), play key roles in lipid, carbohydrate, and protein metabolism as well as physiological functions including heart rate, neural development, and cardiovascular functioning, and renal, brain, and cellular reactions (Jabbar et al. 2017; Khadem-Ansari et al. 2017). T4 plays a key role in the cellular differentiation and acts as an antiapoptosis factor. The 5'-deiodination of T4 produces the nuclear receptor binding hormone T3, which regulates several physiological and fundamental cellular processes in the body, including blood coagulation, inflammation, cellular differentiation, body temperature, cell growth and proliferation, dyslipidemia, sodium and water homeostasis, and blood pressure changes (Hercbergs et al. 2015; Gnocchi et al. 2016). The synthesis and storage of the thyroid hormones are tightly regulated by a feedback control system because of their complex of cellular and physiological roles. Two factors affect the synthesis of thyroid hormones:

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biological factors that affect gene expression, and protein kinases and/or ion channels (Chi et al. 2016; Gnocchi et al. 2016). The thyroid function and physiology can be altered by drugs indicated for a variety of uses in different clinical fields. These compounds may affect thyroid gland function by altering the synthesis and metabolism of thyroid hormones. Psychotropic drugs and antidepressants can interfere with the biosynthesis, function, and autoimmunity of thyroid hormones (Sauvage et al. 1998; Khalil and Richa 2011). Many patients with psychological illnesses take more than one antipsychotic drug that may affect the thyroid physiology. A thorough understanding of the effects of these drugs on thyroid metabolism is critical (Tandon and Halbreich 2003). The molecular mechanisms and potential toxic effects of long-term use of antipsychotics have been investigated and must be seriously considered (Chen et al. 2016). Clozapine and haloperidol are used to treat a variety of mental illnesses and psychotic disorders (Sauvage et al. 1998; Kudo and Ishizaki 1999). Clozapine is generally considered as one of the most effective antipsychotic drugs and has been used in the management of schizophrenia and bipolar disorder for many years (Chang et al. 2006; Lin et al. 2012). Haloperidol is a potent neuroleptic drug and tranquilizer, broadly used in the treatment of delirium, schizophrenia, and alcohol withdrawal. It is particularly effective in treating the symptoms of psychotic disorders (Muller et al. 2016; Zaprutko et al. 2016).

Long-term use of these drugs has an inhibitory effect on CYP 450 isoenzymes in patients with schizophrenia and depression (Micallef et al. 2005). Several psychoactive drugs have been shown to alter thyroid function and production as well as hormone transport mechanisms and metabolism (Barbesino 2010).

This study examined the effects of chronic clozapine and haloperidol treatment on T3 and T4 serum concentrations. Considerable endocrinological impacts of chronic haloperidol and clozapine treatment on thyroid hormones may occur. Understanding the effects of this drug class is critical to managing the thyroid abnormalities.

Materials and methods

Chemicals. Haloperidol and clozapine were obtained from Sigma Chemicals (St. Louis, MO, USA). Other agents used in this research were obtained from Merck (Germany).

Drug preparation. A 20 mg/ml stock solution of haloperidol was prepared by heating 200 mg of haloperidol in 10 ml lactic acid (1%) until dissolved. This solution was then diluted with distilled water to obtain the 0.5 and 2 mg/ml haloperidol solutions. NaOH (1N) was added to adjust the pH of the final solutions to 5.1. Clozapine was prepared every day by dissolving 140 mg of clozapine in 0.6 ml of HCl (1N) at a moderate heat, then diluting the solution with distilled water to obtain 0.5 mg/ml. These solutions were adjusted with NaOH (1N) to a pH of 5.1.

Animals and drug administration. All procedures and experimental protocols were approved by the Ethics Committee of Urmia University (Ir.umsu.rec.1390.115). Male Wistar rats (weight: 270±30 g; age: 14–15 weeks) were ordered from the Department of Physiology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran. Animals were allowed to acclimatize for 1 week before the commencement of the study. The rats were housed in ventilated soundproof boxes in filter-top standard cages, under a controlled environment with 50% humidity at 22 °C and a 12 h light-dark cycle (Khorrami et al. 2015). Rats (n=50) were housed two per cage with ad libitum access to water and food. After the habituation period, rats received daily intraperitoneal injections of either low-dose haloperidol (0.05 mg/kg, n=10), high-dose haloperidol (2 mg/kg, n=10), low-dose clozapine (0.5 mg/kg, n=10), high-dose clozapine (20 mg/kg, n=10). The control group was treated with 2 ml of physiological saline daily intraperitoneal injections of normal saline (n=10). This dose regimen was designed to imitate the therapeutic range of doses given to human patients and was shown to be effective in other biochemical and behavioral studies (Kapur et al. 2000; Lipska et al. 2001). All rats received daily injections for 28 days.

Determination of thyroid hormone (T3 and T4) levels. All experiments were started at the same time of the day (8.00 a.m.). After the experimental period, animals were anesthetized by ether and blood was collected by a direct cardiac puncture. Blood samples were centrifuged and the isolated serum measured and analyzed using the chemiluminescence immunoassay (CLIA) method (LIAISON Immunoassay; DiaSorin SpA, Saluggia, Italy) and its special kits for this set. All efforts were made to minimize animal suffering and reduce the number of animals used.

Statistical analysis. Descriptive statistics are presented as mean, standard deviation, minimum, and maximum values. The normality of T3 and T4 serum concentrations were evaluated using the Shapiro-Wilk test. The Kruskal-Wallis test was used to compare T4 and T3 serum levels among groups. Dunn's test was used for pairwise comparisons. A

p-value <0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics software (ver. 22.0; IBM Corp., Armonk, NY, USA).

Results

After 28 days of treatment with clozapine or haloperidol, there was a statistically significant difference in T4 serum levels seen between the control and at least one of the treatment groups (Table 1). No significant difference in T3 serum levels was observed between the treatment groups and the control group (p≥0.05). T4 concentrations decreased linearly with increased haloperidol dose but showed no change with increasing clozapine dose. The Kruskal-Wallis test, which is the nonparametric counterpart of ANOVA, was used to compare T3 and T4 concentrations among groups because the distribution in at least one subgroup was not normal (according to the Shapiro Wilk's test). The Kruskal-Wallis test indicated a significant difference among the groups for T4 (p<0.05). Dunn's test indicated that the T4 levels of rats treated with high-dose (2 mg/kg) haloperidol decreased significantly compared to controls (7.00±0.49 and 8.11±0.51, respectively; p=0.001). Additionally, the T4 serum concentration levels of rats treated with high-dose clozapine (20 mg/kg) were higher than low and high doses of haloperidol (8.32±0.10 vs. 7.67±0.32 and 7.00±0.49; p=0.006 and p<0.001, respectively).

Descriptive statistics and the results of pairwise comparisons of the five groups are shown in Table 1. The mean T3 levels of groups 1–5 were 149, 146.50, 149.80, 148, and 147.20 mg/kg, respectively. No significant difference was observed in terms of T3 serum concentration among the groups (p>0.05).

Low-dose clozapine decreased T4 serum levels, while high-dose clozapine elevated T4 levels. Pairwise comparisons indicated that these changes in T4 levels were not statistically significant compared to the control group (p=1.000 for both).

Figure 1 presents error bars summarizing changes in T3 (mg/kg) and T4 (mg/kg) serum levels by drug and dose. Both drugs do not have a significant effect on T3 while the high dose of haloperidol suppressed T4.

Discussion

Evaluating the thyroidal disorders in patients receiving antipsychotic medication presents a particular challenge. Many drugs have been prescribed for the treatment of non-thyroidal conditions and have shown efficacy for thyroid function (Baruah and Singh 2012). Patients treated with antipsychotic medications frequently present with thyroid abnormalities and thyroid function disorders (Sabeen et al. 2010; Kibirige et al. 2013). Studies have indicated that treatment with psychotropic drugs is associated with altered expression of the nuclear receptors and genes involved in thyroid hormone function (Langlois et al. 2001).

This study examined the subchronic effects of haloperidol and clozapine at two different dosages on thyroid hormone levels. Following treatment with

Table 1
Descriptive statistics of thyroxine (T4) and triiodothyronine (T3) plasma levels according to the treatment groups.

Variables	Median	Interquartile Range	Minimum	Maximum	p value
T4 (μg/dl)					
Control group	8.25[a]	0.73	7.10	8.80	<0.001
Haloperidol (0.05 mg/kg)	7.70[b]	0.40	7.00	8.10	
Haloperidol (2 mg/kg)	7.00[a,c]	0.65	6.20	8.00	
Clozapine (0.5 mg/kg)	7.83	0.16	7.64	8.20	
Clozapine (20 mg/kg)	8.32[b,c]	0.15	8.17	8.51	
T3 (ng/dl)					
Control group	148.00	9.50	139.00	158.00	0.727
Haloperidol (0.05 mg/kg)	147.50	9.50	139.00	153.00	
Haloperidol (2 mg/kg)	149.50	6.00	143.00	158.00	
Clozapine (0.5 mg/kg)	148.00	12.50	136.00	158.00	
Clozapine (20 mg/kg)	147.50	9.25	137.00	155.00	

Values with the same superscript letters differ significantly (p<0.05).

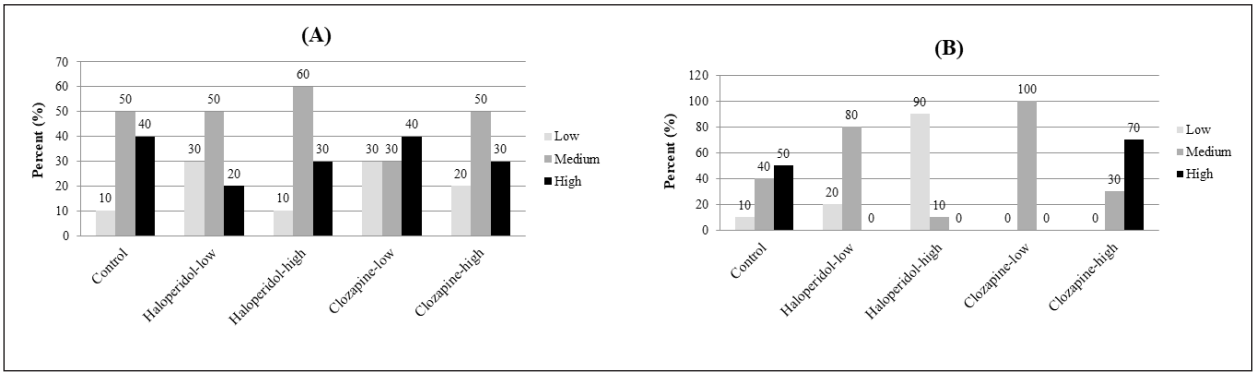

Figure 1. Summary of drug-dependent changes in the plasma levels of thyroxine (T4) (A) and triiodothyronine (T3) (B). Haloperidol-low and haloperidol-high indicate 0.05 mg/kg and 2 mg/kg, respectively, while clozapine-low and clozapine-high represent 0.5 mg/kg and 20 mg/kg, respectively.

haloperidol, significant changes in T4, but not in T3, serum concentration levels were observed. Haloperidol and clozapine have different effects on thyroid hormone levels. These results indicate that antipsychotic treatment can contribute to thyroid dysfunction, which is consistent with previous research of Radhakrishnan et al. (2013), who have observed abnormal thyroid hormonal status in a proportion of patients with schizophrenia-spectrum disorders. In this study, abnormal thyroid hormone status was frequently observed in animals treated with antipsychotic drugs. These results may not reflect the prevalence of thyroid dysfunction in psychiatric disorders in general. In the high-dose haloperidol group, we observed a decrease in T4 values. Decreases in T4 with fluvoxamine were also reported by Hoflich et al. (1992). Gitlin et al. (2004) have reported significant decreases in T4 values with selective serotonin reuptake inhibitor treatment. Lin et al. (2006) have demonstrated that chronic treatment with haloperidol for 28 days increased T4 and FT_4 levels in Sprague-Dawley rats.

In this study, high-dose clozapine increased the T4 serum concentration, similar to the increase in T4 values on treatment with reboxetine reported by Eker et al. (2008). Studies have reported a decrease in T4 values, and no significant changes in free T4, values after treatment with sertraline (Eker et al. 2008). We observed no significant changes in T3 concentrations after treatment with haloperidol or clozapine.

Changes in thyroglobulin (Tg) concentration, an essential factor for the synthesis of thyroid hormones, were observed after treatment with haloperidol and alprazolam, in association with alterations in thyroid hormones (Samadi et al. 2017). Antidepressants and typical and atypical antipsychotic drugs can alter thyroid function (Sauvage et al. 1998; Khalil and Richa 2011). Elevated serum concentrations of T4 and T3 in acute-phase antipsychotic-medicated patients has been observed (Bunevicius et al. 2014). In our previous study, we observed a decrease in antithyroglobulin (aTg) concentrations in rats treated with haloperidol and alprazolam (Samadi et al. 2017). No significant changes in Tg levels in the haloperidol treatment group were observed. Tg levels were reduced significantly in rats treated with alprazolam. No statistically significant differences in anti-thyroid peroxidase (aTPO) antibodie levels between haloperidol- and alprazolam-treated rats were observed (Samadi et al. 2017). Major changes in thyroid hormone concentrations after treatment with haloperidol and clozapine were observed.

The results of this study indicate that haloperidol interferes with thyroid function. It can, therefore, be concluded that there is an association between the use of antipsychotic drugs and thyroid function (Samadi et al. 2017). Intraperitoneal administration of the tricyclic antidepressant desipramine, twice a day for 14 days, did not alter T3 and T4 levels in rats (Atterwill et al. 1989). An assessment of thyroid function in schizophrenic patients revealed a slight change in thyroid axis function, with a major decrease in T4 serum concentrations in patients taking quetiapine (Kelly and Conley 2005).

Baumgartner et al. (2000) have observed significant changes in the T4 serum levels of schizophrenic patients after 4 weeks of treatment with the phenothiazine derivative perazine. They concluded that increased T4 serum levels may be associated with acute schizophrenia and that neuroleptic medication may affect thyroid hormone metabolism. Ottenweller et al. (1989) have determined that the serum

hormone levels of hamsters treated with alprazolam were similar to those of uninjected healthy and cardiomyopathic hamsters. Additionally, T4 levels were not affected by alprazolam, while T3 levels increased. No significant effects of haloperidol or alprazolam treatment on serum TSH levels were observed. A significant decrease in antithyroglobulin levels in the control group compared to drug-treated rats was identified (Samadi et al. 2017). An earlier study (Gittoes and Franklyn 1995) has reported high serum thyroxine T4 concentrations, with or without a decrease in triiodothyronine T3 concentrations, similar to the findings of this study.

A variety of therapeutic drugs and compounds can affect the concentration of thyroid hormones in the blood, which may not be accompanied by clear clinical signs, dysfunction or pathology of the thyroid gland. Drugs can affect thyroid function by altering mechanisms of metabolism, transport, action, and excretion. They may also modulate the regulation of the hypothalamic-pituitary-thyroid (HPT) axis and cause various abnormalities. Despite useful therapeutic applications of antipsychotic drugs, adverse effects associated with the dosage and duration of use may affect thyroid function. It is critical for clinicians to recognize the effects of drugs in laboratory tests, to avoid misdiagnosis and unnecessary treatment. Patients receiving antipsychotic medications should be screened for thyroid function abnormalities regularly after initiating drug treatment.

The mechanisms underlying alterations in thyroid hormones in patients treated with antipsychotic medications remain unclear. Basal thyroid hormone levels may affect response to treatment, and antipsychotics may affect thyroid hormone levels that in turn affect mood. Haloperidol and clozapine act via different mechanisms and may have dissociable effects on thyroid hormones. This indicates for a existance of a complex relationships between neurotransmitter systems and the HPT axis. Further studies utilizing larger samples are required to investigate the effects of antipsychotics on thyroid hormones, to clarify these relationships.

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