Research Article

Effects of alprazolam and haloperidol on thyroglobulin, antithyroglobulin, anti thyroid peroxidase and TSH in Rat

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Alprazolam ve haloperidolün sıçan tiroglobulin antitiroglobulin, anti tiroid peroksidaz ve TSH üzerine etkileri

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Abstract

Background: A large number of psychotropic drugs can interfere with the thyroid physiology, function and autoimmunity.

Objective: The aim of the present study was to investigate the effects of alprazolam and haloperidol on thyroglobulin, antityrogblobulin (aTg), antithyroid peroxidase, and thyroid stimulating hormone levels on rats.

Materials and Methods: First group of adult male Wistar rats was the control, second group received 0.5 mg kg⁻¹ haloperidol in physiological saline and the third group received 0.5 mg kg⁻¹ alprazolam, via gastric gavage once daily for 28 days. Plasma levels of all thyroid function tests were measured with chemiluminescent assay.

Results: We have investigated a decrease in aTg amounts of control group (5.461 ± 0.718) compared with drug treated rats with alprazolam (1.433 ± 0.225) and haloperidol (1.21 ± 0.228). (PaTg = 0.00[ALP], PaTg = 0.01[HAL]). Although there were not any change in thyroglobulin levels in the haloperidol treated groups (0.9583 ± 0.014) relative to control group (0.975 ± 0.015); but in opposition Tg levels decreased significantly in response to alprazolam (0.36 ± 0.16) compared with the control group (0.975 ± 0.015), p-values are (PTg = 0. 001[ALP]), (PTg = 0. 021[HAL]).

Conclusion: We found that these two drugs may interfere with the thyroid physiology and metabolism.

Keywords: Alprazolam; Haloperidol; Thyroglobulin; Antithyroglobulin; Antithyroidperoxidase; Thyroid stimulating hormone; Antipsychotic drugs.

Özet

Amaç: Psikotropik ilaçların büyük bir kısmi tiroit fizyolojisi, fonksiyonu ve otoimmünitesi üzerine etki edebilir. Alprazolam ve haloperidol’un sıçan tiroglobulin (Tg), antitiroid peroksidad (TPO), ve tiroid stimülasyon hormon (TSH) üzerine etkilerinin araştırılması bu çalışmanın amacıdır.

Materyal ve Metot: Hayvanlar üç gruba ayrıldı: birinci gruba kontrol grubu olarak fizyolojik salin, ikinci gruba fizyolojik salin içinde 0,5 mg kg⁻¹ haloperidol, üçüncü gruba ise 0,5 mg kg⁻¹ alprazolam 28 gün süre ile günde bir kez gastrik gavage yoluyla ilaç verildi. Plazmada tiroglobulin antitiroglobulin, antitiroid peroksidaz ve tiroid uyarıcı hormon düzeyleri kemiluminesant yöntemi ile ölçüldü.

Bulgular: Haloperidol (1,21 ± 0,228) ve alprazolam (1,433 ± 0,225) ile tedavi edilen sıçanların aTg düzeyleri kontrol grubu (5,461 ± 0,718) ile karşılaştırıldığında, önemli bir ölçüde azalma olduğu gözlandi. (PaTg = 0,00[ALP], P_{aTg} = 0,01[HAL]). Haloperidol ile tedavi edilen grubun Tg düzeyi (0,9583 ± 0,014) kontrol grubu ile karşılaştırıldığında (0,975 ± 0,015) önemli bir değişiklik gözlenmekten, alprazolam ile tedavi edilen grupta (0,36 ± 0,16), önemli

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ölçüde azalma saptandi P değerleri, (P₁₀ =0,001 [ALP]), (P₁₀ = 0,021 [HAL]).

Sonuç: Bizim bulgularımızda göre bu iki psikotrop ilaç tiroid fizyoloji ve metabolizmasını etkileyebilir.

Anahtar Kelimeler: Alprazolam; Haloperidol; Tiroglobulin; Antitiroidperoxidase; Tiroid uyarıcı hormon; psikotrop ilaçlar.

Introduction

Antipsychotic drugs have been used for the treatment of psychiatric disorders and agitated mental disorders since the mid-1950s [1]. A large number of psychotropic drugs, anticonvulsants, non-steroidal anti-inflammatory drugs, beta-adrenoceptor antagonists and antiepileptic drugs can increase of thyroid-stimulating hormone (TSH) and decrease of free triiodothyronine thyroid hormone (TH) secretion and may cause induction of autoimmune hypothyroidism or hyperthyroidism. These drugs affect the transport, metabolism, action and excretion of T₄ or inhibit thyroid peroxidase activity, enhance deiodination of T₄ to T₃ or affect iodine capture by thyroid cells [2–8]. As antipsychotics and tranquilizer drugs are administered over long periods, clinicians need to be aware of possible outcomes, adverse effects in various diseases [9, 10]. Thyroid abnormalities occur frequently in patients with psychotic syndromes thus, patients should be regularly tested in clinical or subclinical thyroid abnormalities on all drug therapies to prevent adverse effects [11].

Alprazolam; 8-chloro-1-methyl-6-phenyl-4H-[1, 2, 4] triazolo [4,3-a] benzodiazepine is a widely prescribed short-acting benzodiazepine which is used in the management of anxiety disorders especially used in panic disorder. This drug belongs to the class of anxiolytic, sedative and hypnotic anticonvulsant which is one of the most commonly used antidepressant [1, 3, 12]. Alprazolam rapidly reduces the symptoms of anxiety, however, the overuse of benzodiazepines was shown to have adverse effects [3]. Compared with other benzodiazepines, alprazolam has short half-life, and high binding affinity to the GABA receptor, and a rapid onset of action [12–14]. In a previous study, researchers evaluated effects of alprazolam on hamsters and found out that there are important effects of this drug on thyroid function [15]. Haloperidol is a butyrophenone and dopamine antagonist typical neuroleptic agent characterized as a high effective antipsychotic used in the treatment of schizophrenia and its' used to alleviate care of many syndromes, such as nausea, vomiting and delirium [16, 17]. This drug is often associated with various metabolic side effects [18]. In a previous study which was done on male schizophrenic patients, haloperidol had some effects on TSH responses. The researchers pointed out that TSH releasing actions of TRH are not mediated via receptors that are effectively blocked by haloperidol [19]. Haloperidol has roles in free radical involvement, thus leading to neurodegeneration and these side effects appointed during and after administration of the drug. The neurotoxic metabolites of this drug may have an obscure role in the neurodegenerative diseases [10, 16]. The thyroid plays a significant role in cognition. Disorders of the thyroid have been investigated in Alzheimer’s disease and neuropsychiatric behaviors [20, 21]. Hypothyroidism and subclinical hyperthyroidism have both been associated with cognitive impairment and dementia and elderly patients with cognitive impairment should always be assessed for hypothyroidism [22].

Studies in the field of molecular mechanisms and role of enzymes help us to provide a better understanding of the both cascade of biochemical events that occurs with the effects of the mentioned drugs on thyroglobulin, antithyroglobulin, antithyroid peroxidase and TSH [23]. Thyroidal disorder evaluation in antipsychotic medicated patients presents a particular challenge [10]. These findings made us promptly to explore the effect of alprazolam and haloperidol on some thyroidal factors. We examined the effects of alprazolam and haloperidol treatment on thyroglobulin, antithyroglobulin, thyroid peroxidase, anti-thyroid peroxidase and TSH in rats. Thyroidal disorder assessment in antipsychotic medicated patients presents a particular challenge. This made us promptly to investigate the effect of alprazolam and haloperidol on some thyroidal factors.

Materials and methods

Male Wistar rats, body weight 250–300 g were fed a standard rat chow diet with ad libitum access to food and water. They were housed individually in filter-top standard cages and they were situated in ventilated soundproof boxes. They were kept in a temperature and humidity controlled (22–24°C) animal room, with an alternating light-dark cycle with the lights going on at 7:00 a.m. (12 h light: 12 h dark schedule). A stock solution of haloperidol (Sigma Chemicals, St Louis, MO, USA) was prepared by heating haloperidol in 10 mL 1% lactic acid until dissolved. To obtain solutions of 0.5 mg/mL haloperidol, the stock solution was diluted with distilled water.
Alprazolam (Sigma Chemicals) was prepared daily by dissolving 140 mg of alprazolam in 0.5 mL of 1 N HCl with gentle heating, then diluting the solution with distilled water to 0.5 mg/mL. After an adaptation period of 1 h and examination of the rats we started to give the drugs by means of oral gavage. All experiments were started at the same time of the day (8.00 a.m.). The animals received drugs orally daily with gastric gavage during 28 days. Bloods were collected by a direct cardiac puncture. After centrifugation of the blood samples, the isolated plasma analyzed and measured automatically by the chemiluminescence Immuno Assay (CLIA) method, (LIAISON Immunoassay, DIA Sorin S.P.A Italy) and its special kits for this set.

This study was performed in Urmia University, Faculty of Medicine, department of medical Biochemistry.

All research and animal care procedures were conducted in conformity with international laws and policies. All the animals used for in our experiments were carried out in compliance with EU legislation. (EEC Council Directive 86/609, OJ L 358, I, Dec.12, 1987; Guide for the Care and Use of Laboratory Animals, US National Research Council, 1996). The rats anesthetized by ether. Bloods were collected by direct cardiac puncture. All efforts were made to minimize animal suffering and reduce the number of animals used.

Statistical evaluation

Statistical evaluation was performed using ANOVA followed by the Tukey HSD and Dunnett T3 for our data. A p-value less than $p < 0.05$ was defined to be statistically significant. The data are expressed as mean ± standard deviation (SD).

Results

Effects of alprazolam (Figure 1A) [24] and haloperidol [25] (Figure 1B) on thyroglobulin, antithyroglobulin, antithyroid peroxidase and TSH levels were studied. Six male rats were in each group. The animals were assigned randomly into three main experimental groups. According to the treatments they were divided into three groups; group 1 or control group, no drug or placebo, received control serum normal saline 0.9% 2 mL per rat; the second group received serum normal saline 0.9% 2 mL per rat +0.5 mg kg⁻¹ haloperidol; the third group, received serum normal saline 0.9%, 2 mL per rat +0.5 mg kg⁻¹ alprazolam. This dose regimen was chosen to emulate the therapeutic range of doses given to patients and was shown to be effective in other behavioral and biochemical studies. There are a few animal models studies have been done in understanding the mechanism of action of antipsychotic drugs and the doses have been often chosen for haloperidol 0.5 mg/kg, 1 mg/kg and 2 mg/kg, respectively [26–28], and for alprazolam were 0.3 mg/kg 2 and 4 mg/kg [29, 30].
The results of the control group in comparison with treated groups showed that these drugs have not any significant change and effect on TSH. According to p < 0.05, the amounts of these drugs in relation with this hormone is (p TSH = 0.99 [ALP], p TSH = 1.00 [HAL]) (Figure 2). Accordingly, there were not any significant change in the haloperidol treated group; however, Tg levels decreased significantly in response to alprazolam (Figure 3). Under treatment with haloperidol, p = 0.21 gained for Tg thus there is not any significant change, but there are significant changes in Tg amounts under treatment with alprazolam (p = 0.001).

We found that antithyroglobulin levels decreased significantly in drug treated rats compared with control group (Figure 4). P aTg = 0.00 gained for aTg after treatment with these drugs showed significant changes (p < 0.05). According to these amounts (p aTPO = 0.73 [ALP], p aTPO = 0.94 [HAL]), there were not any statistically significant differences in aTPO levels in response to treatment with alprazolam and haloperidol (Figure 5). Thyroglobulin levels, did not change significantly in haloperidol treatment group; however, Tg levels decreased significantly in response to alprazolam (Figure 2). We have also shown the results of the control group in comparison with drug treated groups (Table 1).

Discussion

As antipsychotics and tranquilizer drugs are administered over long periods in humans, their possible endocrine toxic effects and adverse outcomes must be taken into consideration [9]. According to our study there are some changes in the amount of Tg after treating with alprazolam and haloperidol. Increased levels of serum Tg and aTg is associated with thyroid disorders such as Graves’ disease, toxic adenoma, nontoxic goiter and subacute thyroiditis. We observed, decreasing amount of Tg after treatment with alprazolam and haloperidol. Accordingly, these drugs may be an alternative use for treatment of some thyroid diseases as well as we saw increasing levels of serum Tg and aTg [31]. According to studies antipsychotic medicated patients, frequently present thyroid function disorders such as hypothyroidism and thyroid abnormalities [32–36]. It has been suggested that the most consistent findings derive from antipsychotic medicated patients, in whom serum levels of TSH seem to be reduced, although still within the
normal ranges [37]. Furthermore, it has been also demonstrated by various researchers that antidepressant treatment results in thyroid hormones without a significant reduction in TSH [19, 38]. Our study results are consistent with these studies. In another study Robertas and Prange confirmed significant changes on thyroid after psychotropic therapy [7]. It is important to keep in mind that a few drugs, are associated with the development of clinically significant thyroid disease [39]. These psychotropic medications are frequently administered especially for adults. Consumption of these drugs is associated with potentially serious side effects [40]. Thyroid disorder evaluation in antipsychotic medicated patients presents a particular challenge. Many psychotropic compounds interfere with the thyroid physiology as a result of their action on many levels [41, 42]. Animal studies have shown that treatment with antipsychotics, like haloperidol is associated with changes in the expression of nuclear receptors and genes involved in thyroid hormone function [43]. For management of any thyroid disorders that can happen for patients medicated with these drugs, understanding the effects of every class of drugs is very important.

Psychotic drugs may affect thyroid function in various aspects and this problem may be more serious in elderly patients. They showed that treatment with alprazolam decreased the T3 concentration in serum, but it was not any significant change on T4 [15]. We demonstrate that treatment with alprazolam decreased the amount of Tg. According to these results, alprazolam changed the amount of Tg and T3, but did not have any effects on T4. Because Tg is the main and essential factor for the synthesis of thyroid hormones and it is their precursor, so any changes in Tg amount, might cause some changes in the thyroid gland. A similar conclusion was reached by Baumgartner et al. [44] that thyroid function may be altered as a direct consequence of antipsychotic drug treatment. On the other hand, psychotic drugs such as haloperidol associated with diagnoses of thyrotoxicosis [45].

Therefore, consumption of these drugs might cause some disease and disorders of the thyroid gland and this hypothesis require more researches.

Conclusion

Over the years, several drugs used in the treatment of non-thyroidal conditions have been shown to affect thyroid function and metabolism. Some of the interactions of antipsychotic drugs with thyroid function have already been explained but mechanisms remains to be demonstrated. Psychotic drugs may affect thyroid function in numerous ways and they can cause different abnormalities. In addition to common side effects, many drugs cause dangerous side effects and patients receiving these drugs should be screened for thyroid function abnormalities regularly after drug initiation. Above all, the relationship between the thyroid and some psychoactive drugs is generally unknown. Taken together, these data demonstrate the relationship between thyroid function and taking these drugs. Future studies and investigations can be conducted on various animal models. Knowledge of the site of drug interaction and the physiologic features of the thyroid should enable the clinician to anticipate changes that may occur in thyroid homeostasis. Being aware of drugs that raise the risk of thyroid abnormalities would help in monitoring those patients at high risk and would lead to early diagnosis and treatment. Potential effects of these drugs on the results of thyroid function must always be considered in decisions regarding patient care. Much further work will be required to confirm these theories. The relationship between the thyroid and some psychoactive drugs is generally unknown, further studies are required in this field. A better understanding of the influence of thyroid status on antidepressant treatments could help to improve their efficacy.

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<table>
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<th>Variables</th>
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<td>aTg (IU/mL)</td>
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<td>1.433±0.225*</td>
<td>1.210±0.228*</td>
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<td>aTPO (IU/mL)</td>
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<td>Tg (ng/mL)</td>
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<td>0.360±0.160a*</td>
<td>0.958±0.014</td>
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*Denotes statistical significance of control subjects (p<0.05). Variables showed Mean±SD.
Conflict of Interest statement: The authors have no conflict of interest.

References