The Influence of Olmesartan on The Renin-Angiotensin-Aldosterone System of Rats with Thyroid Dysfunction

Kawa Dizaye* , Susan Abdulkadir Farhadi*
***College of Medicine , Hawler Medical University , Erbil, Iraq**
Correspondence: kawa.dizaye@hmu.edu.iq

(Ann Coll Med Mosul 2022; 44 (2):115-120).
Received: 25th Octo. 2022; Accepted: 19th Nove. 2022.

ABSTRACT

Background : The thyroid gland and its hormones participate and have a critical part in the development and function of different parts of the body like the kidney, which is the most important site of renin synthesis and release which is followed by angiotensin and aldosterone formation. As needs are; any abnormality in this gland's function can harm the Renin-Angiotensin -Aldosterone System.

We aimed to discover the effects of using an Angiotensin Receptor Blocker (Olmesartan) on the Renin-Angiotensin-Aldosterone System (RAAS) in rats with abnormal thyroid functions.

Methods : Thirty rats were used and three groups were formed. 6 rats (First group) were the control. 12 rats (Second group) was the hypothyroid group (6 rats control, 6 rats given Olmesartan). 12 rats (the Third group) was the hyperthyroid group (6 rats control, 6 rats given Olmesartan).

L-Thyroxine and Propylthiouracil (PTU) were given orally daily for induction of hyperthyroidism and hypothyroidism respectively.

Blood pressure measurement was done on days 1 and 40th day of the study. The rats were sacrificed on day 40th of the study.

Results : In hyperthyroid rats, T4 was raised and the use of Olmesartan on these rats caused a lowering of this parameter. Renin levels increased in hyperthyroid rats treated with Olmesartan. Angiotensin I increased in hyperthyroid rats. Systolic BP increased in hyperthyroid rats and the use of Olmesartan on these rats caused a lowering of this parameter. Diastolic BP and Mean BP both increased in the hyperthyroid rats.

T3 and T4 levels dropped and TSH increased in hypothyroid and hypothyroid treated with Olmesartan rats. The level of Renin decreased in hypothyroid rats and increased in Olmesartan-treated rats. Angiotensin I decreased in hypothyroid and Olmesartan-treated hypothyroid rats. Blood Pressure components decreased in both hypothyroid and hypothyroid treated with Olmesartan rats.

Conclusions : Olmesartan was able to decrease T4 level along with Systolic BP in hyperthyroid rats. It also decreased Angiotensin I and Blood Pressure components in hypothyroid rats.

Keywords : Thyroid dysfunction, Renin Angiotensin Aldosterone System, Olmesartan .

تأثير الاولميزرتان على نظام الرنيين – انجيوتنسين – الدوستيرون لدى الجرذان المصابة باختلال وظائف الغدة الدرقية

كاوه فاريق دزميي* ، سوزان عبدالقادر فه رهادى*
*كلية الطب ، جامعة هولير الطبية ، اربيل ، العراق

الخلاصة

الخلفية : تشارك الغدة الدرقية وهرموناتها ولها دور حاسم فى تطوير ووظيفة أجزاء مختلفة من الجسم مثل الكلى ، والتى تعد أهم موقع لتخليق وإطلاق الرينين والذى يليه تكوين الأنجيوتنسين والألدوستيرون. حسب الحاجة ؛ أى خلل فى وظيفة هذه الغدة يمكن أن يكون له تأثير سلبى على نظام الرينين - أنجيوتنسين - الألدوستيرون.

كان هدفنا هو اكتشاف آثار استخدام حاصرات مستقبلات الأنجيوتنسين (أولميسارتان) على نظام الرينين-أنجيوتنسين-الألدوستيرون (RAAS) فى الفئران التى تعانى من وظائف الغدة الدرقية غير الطبيعية.

الطرق والنتائج : تم استخدام ثلاثين فأرا وتشكلت ثلاث مجموعات. ٦ فئران (المجموعة الأولى) كانت السيطرة. ١٢ جرذًا (المجموعة الثانية) كانت مجموعة قصور الغدة الدرقية (٦ جرذان تحكم ، ٦ جرذان أعطيت أولميسارتان). ١٢ جرذ (المجموعة الثالثة) كانت مجموعة فرط نشاط الغدة الدرقية (٦ جرذان تحكم ، ٦ جرذان أعطيت أولميسارتان.(تم إعطاء L-Thyroxine و Propylthiouracil (PTU) عن طريق الفم على أساس يومى لتحريض فرط نشاط الغدة الدرقية وقصور الغدة الدرقية على التوالى.
تم قياس ضغط الدم فى اليوم الأول واليوم الأربعين من الدراسة. تم التضحية بالفئران فى اليوم الأربعين من الدراسة فى الفئران المصابة بفرط نشاط الغدة الدرقية ، تم رفع T4 وتسبب استخدام أولميسارتان على هذه الفئران فى خفض هذه المعلمة. زاد مستوى الرينين فى الفئران المصابة بفرط نشاط الغدة الدرقية التى عولجت بأولميسارتان. زاد الأنجيوتنسين I فى الفئران المصابة بفرط نشاط الغدة الدرقية. زاد ضغط الدم الانقباضى فى الجرذان المصابة بفرط نشاط الغدة الدرقية وتسبب استخدام أولميسارتان على هذه الفئران فى خفض هذه المعلمة. زاد كل من ضغط الدم الانبساطى ومتوسط BP فى الفئران المصابة بفرط نشاط الغدة الدرقية.
انخفضت مستويات T3 و T4 وزاد هرمون TSH فى قصور الغدة الدرقية والغدة الدرقية التى عولجت مع فئران أولميسارتان. انخفض مستوى الرينين فى الفئران التى تعانى من قصور الغدة الدرقية وزاد فى الفئران المعالجة بأولميسارتان. انخفض أنجيوتنسين I فى قصور الغدة الدرقية وعالج أولميسارتان فئران الغدة الدرقية. انخفضت مكونات ضغط الدم فى كل من الغدة الدرقية والغدة الدرقية التى عولجت بفئران أولميسارتان.
الاستنتاجات : كان Olmesartan قادرًا على خفض مستوى T4 جنبًا إلى جنب مع ضغط الدم الانقباضى فى الفئران المصابة بفرط نشاط الغدة الدرقية. كما أنه يقلل من مكونات أنجيوتنسين ١ وضغط الدم فى الفئران التى تعانى من قصور الغدة الدرقية.

الكلمات المفتاحية : ضعف الغدة الدرقية ، نظام رينين أنجيوتنسين الألدوستيرون ، أولميسارتان .

INTRODUCTION

Thyroid hormone (TH) which is produced by the thyroid gland, regulates the most important metabolic functions needed for normal growth and development [1].

There are two primary thyroid hormones that bind to and activate thyroid receptors (TRs): T3 and T4 (also known as thyroxine). T3 is the active form of TH, as T3 has a higher affinity to TRs than T4 [2]. T3 is mostly formed peripherally from 5 - monodeiodination of thyroxine (T4) [3].

The levels of circulating thyroid hormones are tightly regulated through a feedback mechanism in the neuroendocrine axis (i.e., the HPT axis). These hormones show tremendous effects on cardiac function, body weight, metabolism, metabolic rates, body temperature, bone, muscle, and behavior [4].

From a physiologic aspect, there seems to be a series of effects over the range of thyroid function, including within the known euthyroid range. These effects could be opposing and specific for different organs at both ends of the thyroid function range [5].

Thyroid function affects cardiac function, and abnormal thyroid function is regarded as a risk factor for developing cardiovascular disease [6].

The important signs and symptoms of hyperthyroidism are cardiac and hemodynamic manifestations including tachycardia, palpitations, exercise intolerance, dyspnea on exertion, and wide pulse pressure [7].

In thyroid gland overactivity, the preload, cardiac output and heart rate will increase; with a lowered peripheral vascular resistance and hyperdynamic circulation. The lowered systemic vascular resistance results in the lowering of renal perfusion pressure resulting in the activation of the Renin-Angiotensin-Aldosterone System (RAAS) and an increase in sodium absorption and blood volume [4].

The hemodynamic changes caused by hypothyroidism are opposite to those of hyperthyroidism [8].

The coaction between the thyroid gland and the kidney in their functions is a known fact. Abnormal thyroid function has effects on renal physiology and development, while kidney disease could result in abnormal thyroid function [9].

Other studies have shown that Renin-Angiotensin system (RAS) inhibitors such as angiotensin receptor blockers (ARBs) decrease the incidence of cardiovascular disease and end-stage renal disease [10].

We carried out this study to find out the outcomes of the angiotensin receptor blocker (Olmesartan) on the RAAS system in rats with abnormal function of the thyroid gland.

METHODS

Animals

Male albino lab rats were used in this study and were housed in the animal house of the College of Medicine (Hawler Medical University).

Materials

Olmesartan (Olmetec) 20 mg by Daiichi-Sankyo was purchased in Erbil. Levothyroxine (Eltroxin) 100 mcg by aspen. Propylthiouracil (Prouracil) 50 mg by Iran.

Study Design

We used thirty rats in this study. The rats were separated and divided into 3 groups. The 1st group of 6 rats was the control group. The 2nd group was of 12 hypothyroid rats, which were further divided into two smaller groups of 6 rats each. The 1st subgroup was a positive control. The 2nd subgroup was given Olmesartan daily [11].

The 3rd group of 12 hyperthyroid rats, was further divided into two smaller groups of 6 rats each. Again the1st subgroup was a positive control. The 2nd subgroup was given an Olmesartan daily [11].

Heart rate & blood pressure were recorded on day one of the study, and on the 40th day. Heart rate & blood pressure were taken using a non-invasive CODA monitor.

Hyperthyroidism was induced by giving (0.0012%w/v) L-Thyroxine in drinking water for 40 days and hypothyroidism through giving Propylthiouracil (PTU) (0.05%w/v) give the duration of treatment [12].

On day 40, the rats were given Xylazine 5mg/kg and Ketamine 35mg/kg intraperitoneally for anesthesia [11]. A cardiac puncture was done for blood withdrawal. After centrifuging the blood mention the speed and duration of centrifuging; levels of Renin, Angiotensin I & II, Aldosterone, T4, T3& TSH were estimated from the serum.

Statistical Analysis

Statistical data analysis was done using (SPSS) Version 25.0 for Windows. All the data were expressed as Mean ± SD and SE. Duncan test and student t-test for analyzing the data. A P-value of 0.05 or less was regarded as significant.

RESULTS

The results of this study showed that the T3 level was increased significantly in the hyperthyroid rats in comparison to the control group. Table 1 shows that the change in T3 level in the hyperthyroid + Olmesartan group was non-significant.

In table 1 it can be seen that the T4 level increased significantly in the hyperthyroid rats compared to the control rats. This parameter has fallen tremendously and significantly in the hyperthyroid + Olmesartan group.

On the other hand, serum THS showed a significant lowering in the hyperthyroid rats in comparison to the control group (table 1), but it has risen (non-significantly) again in the hyperthyroid + Olmesartan group of rats.

Renin in table 1 can be seen to have increased non-significantly in the hyperthyroid rats when compared to the control rats but the increase is significant in the hyperthyroid + Olmesartan group compared to the control.

Angiotensin I showed a significant rise in the hyperthyroid rats in comparison to the control group, while it was lowered non-significantly in the hyperthyroid + Olmesartan group of rats (table 1).

The changes in Angiotensin II and Aldosterone levels were non-significant in both hyperthyroid and hyperthyroid + Olmesartan groups once compared to the control group (table 1).

Table 1: Effects of hyperthyroidism and hyperthyroid treated with Olmesartan on different parameters

Parameters	Control	Hyperthyroid	Hyperthyroid+ Olmesartan
T3 nmol/L	1.77 ± .03 a	2.34 ± .27 b	1.43 ± . 04 A
T4 µg/dL	78.88 ± 16.55 b	295.62 ± 16.16 c	11.5 ± .7 A
TSH ng/L	6.08 ± .89 b	1.27 ± .29 a	5.15 ± .24 B
Renin pg/mL	274.58 ± 24.91 a	372.42 ± 42.02 ab	437.77 ± 56.86 B
Ang I pg/mL	216.23 ± 5.7 a	244.9 ± 9.3 b	198.77 ± 9.99 A
Ang II pg/mL	143.25 ± 9.59 a	166.25 ± 4.23 a	134.87 ± 15.24 A
Aldosterone pg/mL	353.86 ± 36.61 a	363.1 ± 27.24 a	306.88 ± 43.7 A

*** Different letters indicate significant differences at P<0.05

** Comparing to Control-P<0.001

* Comparing to Control-P<0.05

Table 2 shows the results of BP components and they are as follows:

Systolic BP was significantly increased in the hyperthyroid rats when compared to the control rats while the use of Olmesartan in the hyperthyroid rats caused a significant change when compared to the control rats.

Diastolic BP showed a significant increase in hyperthyroid rats and a non-significant change in the hyperthyroid + Olmesartan group of rats.

Regarding Mean BP, again the hyperthyroid group was the group with the significant change when compared to the control rats.

The changes in heart rate were non-significant in both groups in comparison to the control group.

Table 2: Effects of hyperthyroidism and hyperthyroid treated with Olmesartan on Blood Pressure components

arameters	Control	Hyperthyroid	Hyperthyroid+ Olmesartan
Systolic BP mmHg	119.38 ± 2.74 a	147.77 ± 3.8 c	129.54 ± 1.74 B
Diastolic BP mmHg	88.57 ± 1.77 a	107.33 ± 4.73 b	94.11 ± 3.75 A
Mean BP mmHg	98.46 ± 1.95 a	120.83 ± 4.19 b	105.677 ± 3.15 A
Heart rate Beat/Minute	382.53 ± 7.94 a	425.26 ± 19.1 a	412.74 ± 13.7 A

In table 3 it can be observed that T4 and T3 levels are significantly decreased in both hypothyroid and hypothyroid treated with Olmesartan rats in comparison to normal control rats while TSH is significantly increased in the hypothyroid and Olmesartan-treated hypothyroid rats compared to the control group.

On the other hand, Renin was significantly decreased in the hypothyroid and significantly increased in the Olmesartan group of hypothyroid rats in comparison to the control group (table 3).

Angiotensin I level was significantly decreased in both the hypothyroid and hypothyroid treated with the Olmesartan group of rats compared to the control rats (table 3).

No significant changes were observed in the levels of Aldosterone and Angiotensin II

Table 3: Effects of hypothyroidism and hypothyroid treated with Olmesartan on different parameters

Parameter	Control	Hypothyroid	Hypothyroid+ Olmesartan
T3 nmol/L	1.77 ± .027 a	1.07 ± .084 b	1.03 ± .012 b
T4 µg/dL	78.88 ± 16.55 A	17.52 ± 4.37 b	8.04 ± 1.67 b
TSH ng/L	6.08 ± .89 A	19.36 ± 4.39 b	9.81 ± 2.25 b
Renin pg/mL	274.58 ± 24.91 A	191.30 ± 19.83 b	829.66 ± 101.91 b
Ang I pg/mL	216.23 ± 5.7 A	181.02 ± 12.71 b	180.59 ± 9.72 b
Ang II pg/mL	143.25 ± 9.58 A	109.16 ± 9.04 a	121.53 ± 5.38 ab
Aldosterone pg/mL	353.86 ± 36.61 Ab	396.16 ± 49.76 ab	236.47 ± 17.52 a

In table 4 it can be seen that Systolic BP, Diastolic, Mean BP and Heart rate were significantly decreased in both the hypothyroid and hypothyroid treated with Olmesartan group of rats in comparison to the control rats.

Table 4: Effects of hypothyroidism and hypothyroidism treated with Olmesartan on Blood Pressure components.

Parameters	Control	Hypothyroid	Hypothyroid+ Olmesartan
Systolic BP mmHg	119.38 ± 2.74 B	107.07 ± 4.54 a	98.60 ± 2.07 a
Diastolic BP mmHg	88.57 ± 1.77 B	80.833 ± 4.6 ab	74.46 ± 2.54 a
Mean BP mmHg	98.46 ± 1.95 B	89.35 ± 4.62 ab	82.15 ± 2.3 a
Heart rate Beat/Minute	382.53 ± 7.94 b	301.93 ± 3.78 a	314.3 ± 14.49 a

DISCUSSION

It can be noticed from the results of this study that induction of hyperthyroidism significantly increased T4 level and lowered TSH in comparison to the euthyroid rats. Thyroxine is a synthetic T4 and its function is similar to the natural hormone which results in a raised level of T4 and T3 and a decrease in TSH level because of the hypothalamic-pituitary feedback. Likewise, hypothyroidism induction by administration of PTU resulted in a notable fall in levels of blood T4 and T3 with an increase in TSH level in comparison to the normal rats. PTU causes hypothyroidism through the inhibition of the iodination of tyrosyl residues in thyroglobulin in addition to the inhibition of the conversion of T4 to T3 peripherally. TSH increases as a result of the negative feedback mechanism [13].

Thyroid hormones regulate BP by two mechanisms. They either increase the response of cardiovascular system (CVS) to the effect of the sympathetic nervous system or/and through the direct activation of the RAAS [14].

In hyperthyroid-induced rats, there was a non-significant increase in Renin level.

Treatment of the hyperthyroid rats with Olmesartan resulted in an obvious yet non-significant rise in serum Renin level. ACEIs and ARBs are linked to a feedback loop that increases plasma renin activity, the removal of negative feedback leads to an increase in renin release [15]. A significant rise in the Angiotensin I was seen in the hyperthyroid group. Olmesartan reduced Angiotensin I non-significantly when compared to the hyperthyroid rats.

In hyperthyroidism, there is a state of sympathetic overactivity as it was referred to by Chen et al. (2010)[16]. The results that were obtained from this study on the effect of hyperthyroidism on blood pressure were a significant elevation in diastolic, systolic, and mean blood pressure when compared to the normal rats. The daily use of Olmesartan resulted in a significant lowering of the blood pressure parameters. Olmesartan is an antihypertensive agent that acts by blocking Angiotensin II receptors and disrupts the RAS activity involved in high blood pressure[17].

The outcomes of hypothyroidism are mostly opposite to that of hyperthyroidism. It was concluded by Kumar et al. (2013)[18] , T3 & T4 take part in the RAAS system maturation, that's why in hypothyroidism renin level is low most of the time.

Induction of hypothyroidism resulted in a non-significant decrease in Renin level in comparison to the normal rats. Treatment of the induced hypothyroidism in the rats with Olmesartan yielded a dramatic rise in Renin level in comparison to the hypothyroid rats. Following the use of Angiotensin receptor blockers and due to the activation of the feedback mechanism there will be an upsurge in Renin level [15].

Angiotensin I was notably decreased in the hypothyroid and the Olmesartan groups. This is attributed to the decreased sympathetic activity which is characteristic of hypothyroidism.

The impact of hypothyroidism on blood pressure components (systolic, diastolic, and mean BP) and Heart Rate was a significant reduction in both hypothyroid groups (positive control and Olmesartan) in comparison to the normal rats. Hypothyroidism is known to cause a downturn in sympathetic stimulation and dominance of parasympathetic (vagal) stimulation.

CONCLUSIONS

Olmesartan was able to decrease T4 level along with Systolic BP in hyperthyroid rats. It also decreased Angiotensin I and Blood Pressure components in hypothyroid rats. Olmesartan is a good antihypertensive in hypertensive patients with thyroid dysfunction.

Declarations

Ethics Approval

This work has been approved by the ethics committee in the College of Medicine /Hawler Medical University.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests

Funding

The authors received no funding for this work

REFERENCES

1. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiological reviews. 2014 Apr;94(2):355-82.
2. Schroeder AC, Privalsky ML. Thyroid hormones, t3 and t4, in the brain. Frontiers in endocrinology. 2014 Mar 31;5:40.
3. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH. Effects of thyroid hormones on the heart. Clínica e Investigación en Arteriosclerosis. 2014 Nov 1;26(6):296-309.
4. Heaton AL, Friedlander MK, Gay D, inventors; Quality IP Holdings LLC, assignee. Methods for improving thyroid function in a subject. United States patent US 8,815,311. 2014 Aug 26.

5. Cappola AR, Arnold AM, Wulczyn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. The Journal of Clinical Endocrinology & Metabolism. 2015 Mar 1;100(3):1088-96.
6. Chen S, Shauer A, Zwas DR, Lotan C, Keren A, Gotsman I. The effect of thyroid function on clinical outcome in patients with heart failure. European journal of heart failure. 2014 Feb;16(2):217-26.
7. Danzi S, Klein I. Thyroid disease and the cardiovascular system. Endocrinology and Metabolism Clinics. 2014 Jun 1;43(2):517-28.
8. Vlachopoulos C, Terentes-Printzios D. Thyroid, aldosterone and cardiovascular disease. Heart Metab. 2015;66:3-6.
9. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. Indian journal of endocrinology and metabolism. 2012 Mar;16(2):204
10. Miller AJ, Arnold AC. The renin–angiotensin system in cardiovascular autonomic control: recent developments and clinical implications. Clinical Autonomic Research. 2019 Apr 1;29(2):231-43.
11. Dizaye KF, Ahmed AA. Renoprotective evaluations of different angiotensin inhibitors on diabetic nephropathy in rats. Middle East Journal of Internal Medicine. 2016 Nov;63(4023):1-9.
12. Farhadi SA, Dizaye KF. Aliskiren, Fosinopril, and Their Outcome on Renin-Angiotensin-Aldosterone System (RAAS) in Rats with Thyroid Dysfunction. International journal of endocrinology. 2019 Jul 18;2019.
13. Rang HP, Ritter JM, Flower RJ, Henderson G. Rang & Dale's pharmacology. Elsevier Health Sciences; 2014 Dec 2.
14. Dousdampanis P, Trigka K, Vagenakis GA, Fourtounas C. The thyroid and the kidney: a complex interplay in health and disease. The International journal of artificial organs. 2014 Jan;37(1):1-2
15. Cagnoni F, Njwe CA, Zaninelli A, Ricci AR, Daffra D, D'Ospina A, Preti P, Destro M. Blocking the RAAS at different levels: an update on the use of the direct renin inhibitors alone and in combination. Vascular health and risk management. 2010;6:549.
16. Chen JL, Shiau YH, Tseng YJ, Chiu HW, Hsiao TC, Wessel N, Kurths J, Chu WC. Concurrent sympathetic activation and vagal withdrawal in hyperthyroidism: Evidence from detrended fluctuation analysis of heart rate variability. Physica A: Statistical Mechanics and its Applications. 2010 May 1;389(9):1861-8.
17. Medoxomil O, Standard T. PrACT OLMESARTAN.
18. Kumar A, Shanthi M, Parameswari R. The effect of L-thyroxine on metabolic parameters in newly diagnosed primary hypothyroidism. Clin Exp Pharmacol. 2013;3(3):1-4