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The Effect of an Angiotensin II Antagonist on Hormones of Pituitary-Gonad Axis in Adult Male Rats

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Abstract

***Background*:** The aim of this study was to investigate the effect of valsartan, an angiotensin II antagonist, on the function of the pituitary- gonad axis.
***Materials and Methods*:** Adult male Wistar rats (200 to 220 g) were used as experimental and control groups. The 3 experimental groups received either 100, 200, or 400 mg/kg/day valsartan in 1 ml water orally for 28 days, while a set of control group received 1 ml distilled water for the same period of time and another set received no treatment. At the end of the experimental period, blood was collected and serum was analyzed for FSH, LH, testosterone and dihydrotestosterone levels by RIA methods.
***Results*:** There were no significant differences among FSH levels at all doses of valsartan used, while the serum LH level was decreased significantly at the maximum dose of the drug used. Serum testosterone level decreased at both the 200 and 400 mg/kg dose compared to the control, while the dihydrotestosterone level was reduced significantly at all the three dosages used.
***Conclusion*:** According to our founding, suggested that the effects of valsartan on serum LH, testosterone and dihydrotestosterone may be mediated through angiotensin II receptor.

Introduction

In order to decrease blood pressure, renin is secreted into blood from kidneys to convert angiotensinogen to angiotensin I. Renin-Angiotensin System (RAS) is an enzyme basket which plays several important roles in adjusting cardiovascular function and is involved in vasoconstriction, liquid and electrolyte balance and the function of sympathetic nervous system [1]. Angiotensin I is converted to angiotensin II (Ang II) by angiotensin converting enzyme (ACE). At present, two receptors are identified for Ang II, namely AT1, and AT2. In humans, only one subgroup of AT1 receptor is present, while in rats, we have two subgroups of AT1A and AT1B [2]. AT1 receptors are mostly present in smooth muscle cells of blood vessel walls and also in the cells of the glomerulosa layer of adrenal cortex, while AT2 receptors are found in adrenal gland, heart, brain, embryo, reproductive system and injured tissues [3]. AT2 receptors are present at a higher level in immature rats and function in the growth and differentiation of the reproductive system [4, 5]. AT1 receptor in the tail and the lower part of the head of spermatozoa is affected by angiotensin II of adrenal gland and induces sperm movement [6].

Transfer of Ang II from ovary to fallopian tubes increases fecundation and the presence of more AT1 receptors in the oviduct ampoules is effective in fecundation [5].

Valsartan which was approved by the American Food and Drug Administration in 1996 is a non-peptide drug with the general chemical formula of $C_{24}H_{29}N_9O_3$ [7]. It blocks Ang II receptor by binding to AT1 receptors in smooth muscle cells of the vascular wall to prevent the vasoconstriction effect of Ang II and to decrease the blood pressure upon increasing vessel diameter [8, 9].

Valsartan binds to the AT1 receptors in the glomerulosa cells of adrenal cortex leading to a decreased production and secretion of aldosterone, thus causing a reduction in the reabsorption of sodium and water from the nephrons, thereby decreasing blood pressure [8, 9]. Endoplasmic reticulum 5-alpha reductase and aromatase enzyme system convert testosterone to dihydrotestosterone and estradiol, respectively [10].

Millions of people in the world suffer from high blood pressure. Valsartan has a direct effect on the AT1 receptors and has no effect on bradykinin. Since its side effects are less than other blood pressure medications and its performance is better than ACE inhibitors, therefore it is used to a higher extent in blood pressure treatment [11]. Therefore, it is necessary to study the effect of this drug on the physiologic functions of various organs. The aim of this study is to investigate the effects of this drug on the functions of the pituitary-gonad axis.

Materials and Methods

The present study is empirical research. In this study, a total of fifty 90-day-old adult male Wistar rats weighing from 220 to 250 g obtained from Razi Vaccine and Serum

Table 1. Serum concentration of FSH and LH hormones in control and various experimental groups

Groups	Serum LH (Mean±SD) mU/ml	Serum FSH (Mean±SD) mU/ml
Control	5.7±0.19	10.01±0.42
Sham (1 ml saline)	6.13±0.31	10.13±0.30
Experiment 1 (100 mg/kg valsartan)	5.9±0.19	10.17±0.36
Experiment 2 (200 mg/kg valsartan)	5.46±0.18	9.78±0.39
Experiment 3 (400 mg/kg valsartan)	5.10±0.23*	10.06±0.25

*: Indicate a significant difference in the level ($p \leq 0.01$) with control and sham groups

Table 2. Serum concentrations of testosterone and dihydrotestosterone hormones in control and various experimental groups

Groups	Serum testosterone (Mean±SD) ng/ml	Serum dihydrotestosterone (Mean±SD) pg/ml
Control	10.54±0.32	663.4±18.5
Sham (1 ml saline)	10.51±0.32	637.1±20.5
Experiment 1 (100 mg/kg valsartan)	9.95±0.18	572.1±18.1*
Experiment 2 (200 mg/kg valsartan)	9.29±0.28*	525.7±16.2*
Experiment 3 (400 mg/kg valsartan)	8.66±0.28*	465.8±27.9*

*: Indicate a significant difference in the level ($p \leq 0.05$) compared with the control and sham groups

Institute (Karaj, Iran) were used. The animals were divided into 5 groups of 10 animals each including the control, the sham and 3 experimental groups. Separate cages were used for each group and a ten day period was allowed for the animals to adjust to the laboratory conditions.

During the experimental period, all animals were given food and water ad libitum. The rat room temperature was 22±2ºC with 12 h of darkness and 12 h of light. The research protocol was approved by the ethics committee of the university based on international protocols. In this research, the control group received no treatment and the sham group received 0.9% NaCl orally for 28 days. The 3 experimental groups received orally 100, 200 or 400 mg/kg body weight of valsartan for the same time period. At the end of the experimental period, the animals were mildly anesthetized with ether between 10-11 am, and blood was collected from the heart using a 5 ml syringe. After incubating the blood samples at 37ºC for 15 min, serum was prepared upon centrifuging the samples at 5000 RPM for 15 min. The serum samples were kept at -20ºC until analyzed for FSH, LH, testosterone and dihydrotestosterone hormones using radioimmunoassay kits and a gamma counter. The data were statistically analyzed by one-way analysis of variance (ANOVA) and Tukey's HSD test using SPSS-18.

Results

The results demonstrate that valsartan has no statistically significant effect on the level of serum FSH, and its effect on serum LH level becomes statistically significant at the maximum dose of 400 mg/kg body weight, resulting in a decrease of this hormone in the serum (Table 1).

All the 3 doses of valsartan significantly reduced serum dihydrotestosterone level, while only the 200 and the 400 mg/kg valsartan produced a significant reduction in the level of serum testosterone (Table 2).

Discussion

As the results shows that valsartan has no statistically significant effect on the serum level of FSH and produces a significant decrease in LH only at the maximum dose, while the two higher dosages of the drug resulted in a significant reduction in serum testosterone and all dosages decreased serum dihydrotestosterone concentration dose dependently.

Studies have shown that this drug produces a significant reduction in serum level of testosterone in subjects with high blood pressure compared with the normal healthy individuals [12]. Previous investigations demonstrate that Ang II binds to its receptor in the interstitial cell membrane of the testis and through regulation of adenylate cyclase enzyme, decreases the amount of testosterone produced by these cells [2]. It has been demonstrated that testosterone reduction in men leads to an increase in abdominal triglyceride deposition and an increase in blood pressure resulting in obesity [12]. Additionally, leptin which is produced by the fat cells decreases the production and secretion of testosterone hormone from interstitial cells of obese individuals upon reducing LH secretion [2]. It has been reported that valsartan is diabetogenic and increases blood sugar and insulin and upon insulin increase in the plasma, leptin also increases [13]. Leptin causes a reduction in LH hormone's pulse which is secreted from the anterior pituitary [12]. LH reduction diminishes the conversion of non-differentiated cells into interstitial cells and also results in a decreased production and secretion of testosterone hormone [2].

Some workers show that Ang II increases the level of prolactin and since this hormone decreased the secretion of GnRH from hypothalamus, it will lead to a decrease in LH and through its effect on the interstitial cells, LH diminishes the testosterone hormone, thus causing hypogonadism [14].

Prolactin also affects the production of steroid hormones in the interstitial cells of the testis and decreases the activity of enzymes involved in steroidogenesis and the production of testosterone through regulation of cAMP production [15].

Studies reveal that FSH concentration changes much slower than LH hormone and the FSH hormone secretion related to the Sawyer secretion of GnRH is less than that

of LH, and changes at a slow rate in response to long-term changes in GnRH [10]. Therefore the metabolic clearance of FSH being less than LH, results in its higher half life [16]. After the synthesis of testosterone in the interstitial cells of the testis, 5-alpha reductase enzyme converts it to dihydrotestosterone which is more potent than testosterone and has a higher affinity for testosterone receptor [10, 17]. Therefore, it is clear that a reduction of testosterone results in a diminution of dihydrotestosterone synthesis. On the other hand since valsartan increases prolactin secretion through elevation of Ang II and the increased prolactin decreases the enzyme activities of 3-beta hydroxyl steroid dehydrogenase (3B-HSD), 17-ketosteroid dehydrogenase (17-KSD) and especially 5-alpha reductase and aromatase involved in steroidogenesis, reduction of dihydrotestosterone levels due to valsartan treatment may be a result of elevated prolactin. Some investigators argue that the increase of Ang II upon valsartan consumption and the regulatory effect of Ang II on the reproductive system and the pituitary-gonad axis, predicts clearly the reduction in the levels of LH, testosterone and dihydrotestosterone [12].

Some studies showed that valsartan blocks Ang II receptor, and therefore prevents the effect of Ang II on water reabsorption and a decrease in urine output, resulting in an increase in vasopressin secretion. Another study suggests that the blocking of Ang II receptor by drugs such as valsartan does not increase blood pressure and mainly results in the secretion of more renin by the neighboring glomerula cells of the kidney, leading to an augmented level of Ang II [18].

It has been demonstrated that there is a high level of T1A receptors in the middle ventrolateral preoptic nucleus, paraventricular, supra optic, and lateral abdominal medulla [3]. Researches show that the production of nitric oxide (NO) decreases in the brain upon an increase in the level of Ang II in the central nervous system, thereby increasing the sympathetic activity [19].

Since valsartan consumption leads to an increase in Ang II in the body, NO production which is one of the major factors in GnRH secretion will diminish resulting in a significant reduction in the synthesis and secretion of LH from anterior pituitary. The stimulatory effect of Ang II on the paraventricular nucleus that leads to an increase in CRH, POME production and secretion and ultimately to endorphin increase in the pituitary, will regulate the GnRH secretion and thus may lead to a decreased pituitary-gonadal function. Also the regulation of prostaglandin synthesis will result in an increased NO production [10]. NO regulates P450scc enzyme production that is involved in the control of the steroid synthesis in the interstitial cells of testis [20]. Researches demonstrate that Ang II stimulates vasopressin secretion leading to a decrease in testosterone production through its appropriative receptor in the testis [14].

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Authors' Contributions

Author had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The author declares no conflict of interest.

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