



The protective impact of vitamin E against atenolol effect on Ca^{+2} , Testosterone and FSH in male rats Safa M. Abbas and Luma W.Khalil

Abstract

Background and objective: Atenolol is β_1 -selective antagonist nonetheless this selectivity is not absolute and at higher dosages atenolol represses β_2 Adrenoceptors mainly located in bronchial and vascular musculature, also β -blocker atenolol effects on testosterone and FSH production. Therefore, this study was designed to investigate the possible protective effect of vitamin E on reproductive efficiency in male rats exposed to atenolol.

Materials and methods: Thirty-two healthy adult males Wistar rats at random divided into four equal groups and treatment for 56 days as follows: -First group (control): Animals in this group received tap water and served as control. Second group (group T₁): Animal in this group will be receive atenolol orally at dose (100mg/kg/day). Third group (group T₂): Animal in this group will be receive Vit.E (800IU /B.W.) orally and Fourth group (group T₃): Animal in this group will be receive Vit.E (800IU/B.W.) and atenolol at dose (100mg/kg/B.W.) orally.

Results: serum level of serum testosterone in control group was 1.51 ± 0.21 ng/ml, and it significantly decreased in atenolol treated group (0.74 ± 0.008 ng/ml). Serum level of FSH in the control group was (4.87 ± 0.03 mIU /ml) while it significantly reduced in atenolol treated group (2.69 ± 0.15 mIU/ml), also the results showed that atenolol was a significantly decrease the Ca^{+2} concentration to (1.20 ± 0.15 mg/dl) in contrast to control group.

Conclusion: Vitamin E improve significantly the levels of serum FSH and testosterone in in atenolol treated rats.

Key words: atenolol, vitamin E, male reproductive system.

الخلاصة :

على الهرمونات الذكورية وضعف الخصوبة بسبب الاجهاد E صممت هذه الدراسة لمعرفة التأثير المحسن لفيتامين التاكسدي الناتج من اعطاء الاتينولول لذكور الجرذان البالغة) جمعت T₁, T₂, T₃ C, تم استخدام (32) من ذكور الجرذان البالغة. وقسمت عشوائيا وبشكل متساوي الى اربع مجاميع هي (جمعت عينات الدم في الفترات 0 و 56 يوم من التجربة وتم سحب الدم بطريقة الوخز القلبي. تشير النتائج الى أنالعلاج بالاتينولول قد أدى الى حصول انخفاض معنوي في تركيز هرمونات التيستوستيرون والهرمون) ($P < 0.05$) وبالمقابل يلاحظ حصول ارتفاع معنوي (T₂) فيمجموعة ($p < 0.05$) المحفز للجريبات E عند العلاج بفيتامين (T₂) لمستوى تركيز الهرمونات في المجموعة اخيرا تم الاستنتاج من خلال نتائج هذه الدراسة بأن فيتامين E له تأثير فعال للتخفيف من الآثار الجانبية للاتينولول على الهرمونات الذكورية.

Introduction:

Antihypertensive operators are group of pharmaceuticals that are use to repress fast rhythms of the heart such as ventricular fibrillation, atrial flutter, ventricular tachycardia and atrial fibrillation.. Atenolol have been in

employ for near 25-30 years., it is a β_1 -selective (Cardioselective) β -adrenergic receptor blocking agent. It was accepted by the FDA in August 1981. Also atenolol changed physiological secretion of sexual hormone in adult male rat by different

mechanisms, Vitamin E is another antioxidant that is found in cell membranes and protects the cell membranes against the hydrogen peroxides. α -tocopherol is the natural form of vitamin E with high biological activity [1].vitamin E restored their levels to an optimum rate affected on animal fertilization potential. In accordance with the current result, also found that the serum FSH and testosterone improved by oral administration of vitamin E [2].

Aim of the study: This study was designed to reveal the protective effect of vitamin E on reproductive efficiency in male rats exposed to atenolol

Materials and Methods:Animals and Study Design

Sexually mature male Wistar albino rats weighing 150 ± 10 g were used in the present study. Animals were kept in the laboratory under constant temperature ($25 \pm 3^\circ\text{C}$) throughout the experimental work. They were maintained on a standard rodent diet composed of 20% casein, 15% corn oil, 55% corn starch, 5 % salt mixture and 5% vitaminized starch (green world Company,Iraq).Water was available ad libitum.Maintenance of animals and experimental procedures was approved by the animal ethical committee in accordance with the guide for care and use of laboratory animals prepared by Baghdad University,Iraq. Thirty-two healthy adult males rats at random divided into four equal groups and treatment for 56 days as follows:-First group (control):Animals in this group received tap water and served as control.Second group (group T1):Animal in this group will be receive atenolol orally at dose. Third group (group T2):Animal in this group

will be receive Vit.E orally.vitamin E is capsule, at dose (800 IU /B.W.) and atenolol is tablet at dose (100mg/kg/B.W.), the dose of vitamin E and atenolol calculated according to animal weight. Rats were regularly orally administered with atenolol and vitamin E at a dose level of (2 mg/ml and 12 IU /ml respectively). Fourth group (group T3):Animal in this group will be receive Vit.E and atenolol orally

Preparation of samples and measurement of serum level of testosterone and FSH hormones:

Blood samples was obtained after end of the procedure. After centrifugation, serum samples was stored in deep freeze for further analysis. Kits for measurement testosterone and FSH hormone for rats was obtained. Enzyme linked immune-sorbent assay (ELISA) was used for measurement of serum testosterone and FSH hormon.

Results: Analysis of variant (ANOVA) was used for analysis of data to compare between mean of the four groups. The results are expressed as mean \pm SEM.

1.Effect of Vitamin E on serum testosterone hormone concentration in rats treated with Atenolol: In control group, serum level of testosterone was (1.51 ± 0.21 ng/ml) in comparison to T₁ group which was (0.74 ± 0.008 ng/ml), while serum testosterone concentration significantly ($P < 0.05$) increased in atenolol plus vitamin E treated group (1.53 ± 0.008 ng/ml) as shown in table (1). Atenolol was significantly decreases serum testosterone concentration.Multiple comparisons among the groups are shown in table(1).

Table 1: Effect of Vitamin E on serum testosterone hormone concentration (ng/ml),in adult male rats treated with Atenolol.

Groups Times	Control group	Group T ₁ (Atenolol)	Group T ₂ (Atenolol+ VitE)	Group T ₃ (Vit E)
Zero day	1.48 ±0.1	1.73± 0.11*	1.69±1.01*	1.74 ±0.01*
56days	1.51±0.21*	0.74±0.008*	1.53±0.008*	3.06±0.23*

* Significant differences

2. Effect of Vitamin E on serum Follicle-stimulating hormone concentration in rats treated with Atenolol: serum level of FSH was significantly lower in atenolol treated group (2.69±0.15 mIU /ml) in comparison to control group (4.87±0.03 mIU /ml) (p<0.05). Vitamin E significantly increases serum level of FSH to 5.10±0.06 mIU /ml (p<0.05) in vitamin E plus atenolol treated group as shown in table 2. Multiple comparisons among the groups are shown in table(2).

Table 2: Effect of Vitamin E on serum FSH concentration (mIU /ml), in adult male rats treated with Atenolol.

Groups Times	Control group	Group T ₁ (Atenolol)	Group T ₂ (Atenolol +Vit E)	Group T ₃ (Vit E)
Zero day	4.88±0.05	4.76±0.08*	4.97 ±0.05*	4.87 ±0.05
56 days	4.87±0.03*	2.69±0.15*	5.10±0.06*	5.54 ±0.08*

* Significant differences

3.Effect of Vitamin E on serum Ca⁺² concentration in rats treated with Atenolol: A significant (P<0.05) increase in the Ca⁺² concentration was detected during 56 days after treatment in T₂ group as compared with the T₁ group, with mean value of (2.62±0.15) and (1.20±0.15) respectively for groups T₂ and T₁ at the end of experiment as shown in table(2).

Effect of Vitamin E on Ca⁺ concentration (mg/dl) in adult male rats treated with Atenolol.

Groups Time	Control group	Group T ₁ (Atenolol)	Group T ₂ (Atenolol+Vit E)	Group T ₃ (Vit E)
Zero day	3.47 ±0.17	3.03± 0.16*	3.00±0.17	3.05±0.15
56 days	3.56±0.18*	1.20±0.15*	2.62±0.15*	3.44 ±0.12*

* Significant differences

Discussion:

In our present study low level of FSH and testosterone is observed by action of atenolol. It is well established that Gonadotropin-releasing hormone (GnRH) can enhance the formation and release of LH,FSH and increase testosterone formation [3].

Khan et al. (2004) [4] suggest that atenolol inhibits testosterone release via mechanism involving decrease production of c-AMP but not affecting the enzyme activities of steroidogenesis. In this study when rat Leydig cells incubated with atenolol causes significant reduction in testosterone release by these cells. Furthermore, this study is consistent with the result of [5] they referred that atenolol inhibited the action of noradrenaline on testicular Leydig cell hyperactivity in rat treated with cadmium. In this study may be possibly due to the direct effect of β -blocker atenolol on testosterone production by the disruption of adrenergic-stimulated c-AMP transduction pathway. Further, it is generally accepted that sympathetic nervous system participate in the regulation of testosterone release. Because there is no studies on effect of atenolol on FSH significantly low serum levels of FSH observed in this study after treatment with atenolol may be due to the reduction in calcium concentration which in turn reflect on FSH production by GnRH stimulation. Another possible mechanism for reduction FSH is that hypercholesterolemia

The present study, showed that atenolol changed physiological secretion of sexual hormone in rat serum and vitamin E restored their levels to an optimum rate affected on animal fertilization potential. In accordance with the current result [6], also found that the serum FSH and testosterone improved by oral administration of vitamin E. Vitamin E is another antioxidant that is found in cell membranes and protects the cell membranes against the hydrogen peroxides. Some reports indicated that the key role of vitamin E in reducing oxidative stress in the testis [7,8]. Vitamin E impression on both neuroendocrine gonadal axis and testicular cells may be created condition that the deleterious process. The second assumption is vitamin E; due to enhance steroid hormones levels to Sertoli cells, can have a positive effect on nutrition of germ cells [6]. Therefore, vitamin E have a direct effect on sexual hormones production or decreased level of FSH and LH may be as a compensatory mechanism to elevate testosterone level. Results of the present study also in-line with [9] who showed that vitamin E treatment on lead intoxicated animals showed a significant increase in reproductive hormones and ameliorative effect on semen quality. [10] reported that the primary receptor of vitamin E in the endocrine system is found in the pituitary. However, **Kitabchi et al. (1978)** [11] and **Nathans and Kitabchi (1975)** [12] have reported a decrease in ACTH-induced steroidogenesis and adenylatecyclase activity in vitro

experiment on the adrenal cortex of vitamin E deficient rats. Furthermore, the present study demonstrates that vitamin E administration enhances testosterone production in rat. It was found recently that a specific binding material for vitamin E is present in cytosol and nuclei from liver [13]. It can be presumed that this specific receptor may also be present in the pituitary and testis.

The finding of present study refers that calcium concentration significantly decreased by atenolol administration to male rats.

There are different mechanisms for the effect of atenolol on calcium concentration. One of them is that atenolol has a suppression effect on rennin-angiotensin-aldosterone pathway [14]. Concomitantly, this will cause a decrease in serum sodium concentration due to increased excretion of sodium in the absence of this pathway during atenolol treatment. At the same time, this will impact on calcium concentration and decrease this may be due to the activation of Na-K ATPase by β -blocker atenolol in heart and kidney tissue, the decrease in tissue sodium will cause a decrease in calcium influx through Na-Ca exchange mechanism and thus caused a decrease in intracellular calcium. Therefore, the decreased intracellular calcium results in a vasorelaxant effect and lowering blood pressure [15]. **Hasan et al. (2006)** [16] found out that the effect of atenolol on plasma calcium was significantly reduced to the half of the normal values in rabbits after 27 days, these findings suggest that atenolol may control blood pressure by the suppression of rennin-angiotensin-aldosterone pathway which is accompanied by a reduction of sodium and calcium concentration. So, this

study refers to the diuretic action of atenolol concomitantly, the positive impact of atenolol is due to decreases in sodium and calcium by decreases in sympathetic overactivity and excretion of sodium and calcium by improvement in kidney function, and this will inhibit the renal sympathetic stimulation to renin release by β 1-adrenergic receptors and sodium reabsorption [17]. A significant difference in the mean value of Ca^{+2} in atenolol plus vitamin E group through the experimental period as compared to each other. Recent study demonstrated that in quails, broilers exposed to heat stress and supplemented with vitamin E, blood calcium and potassium had increased and blood sodium had decreased [18]. Therefore, this could be the reason behind the increase in bone mineral density in vitamin E deficient rats upon supplementing with calcium [19].

In conclusion, the results suggest that administration of vitamin E to rats with decreasing reproductive hormones induced by atenolol may be beneficial for reducing this side effect.

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