

Effects of Bupropion on Physiology of Reproduction in Adult Male Rats

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ABSTRACT

Introduction & objectives: Depression is a mental illness that causes persistent feeling of sadness and loss of interest. The feeling of sadness and depression is the body's natural response to the life problems. But when this feeling of extreme sadness become more than a few days or weeks, the symptoms will appear. Causes of depression can be inherited, chemical changes in the brain and nerve cell disorder with each other and use some drugs. Because Bupropion drug decreases nicotine dependence through acetylcholine receptor, it will use as a smoking cessation drug. Since this drug is a potent inhibitor of the reuptake of dopamine and epinephrine of other catecholamine in synaptic space, it is introduced as a new drug for antidepressant. This drug acts selectively on Noradrenergic and dopaminergic systems.

Materials & methods: In the present study 40 male Wistar rat, each weighting 200 ± 20 g in 5 groups of 8 were used as follow: The control group which did not receive any materials during the experiments, the witness group received only water and alcohol as solvent. Minimum, average and maximum experimental groups received orderly amount of 160,320,640 mg Bupropion drug solution orally. Prescription lasted for 28 days and after the end of this period, the heart blood was done to determine the serum concentration of LH, FSH and testosterone level and were measured with RIA. Obtained result were analyzed by T-test, Tukey and ANOVA statistical test.

Results: Based on the obtained result the activity of FSH and LH hormones, indicate significant increase at the level of $P \leq 0/05$ in experimental groups 2 and 3 compare to control group and groups with average and maximum received, the changes were observed in the level of testosterone serum. Also the testes were collected for studying of histological changes and changed in spermatogenesis and changes in testes were determined among experimental groups compared to control group for preparation of tissue sections and staining. Accordingly we can say that this drug affects cell and testicular tissue and alter spermatogonia cells, primary spermatocyte, spermatid, leydig and finally changes the number of sperm concentration in the lumen. Because the changes developed acutely cause alter in spermatogenesis process.

Conclusion: So in general we can say that high doses of this drug has negative impact on testicular issue and its cells and cause disorder in testicular function and alter hormone concentration in average and maximum doses of drug.

KEY WORDS: Bupropion, Testis, Gonadotropin, Testosterone, Rat

INTRODUCTION

The main mechanism of depression isn't fully elucidated yet. Most of researchers believe that depression caused by some deviations in the neurotransmitters secreted from brain especially dopamine, serotonin, norepinephrine. Thus, drugs that maintain these neurotransmitter's balance are effective in treating depression [1]. Bupropion is a polycyclic antidepressant that inhibit the reuptake of serotonin and norepinephrine. Bupropion increases the brain's serotonin and norepinephrine levels through the inhibition of amine (serotonin, norepinephrine) reuptake pumps in the presynaptic neurons [4]. Bupropion prescribed for the treatment of severe depression and disorders like anxiety and prolong insomnia. It is useful for quitting smoking. Bupropion use lead to some side effects on the genitourinary system which results in urinary incontinence, impotence, and abnormal ejaculation [2, 6]. Anti-depression and nicotine dependence effects of the drug is function of the acetylcholine receptors associated with dopamine and norepinephrine receptors. Bupropion have not apparent affinity for binding to dopamine, serotonin and noradrenaline receptors, however, it is capable of altering these receptors affinity to their specific ligands. This drug has effects on learning as dopamine and noradrenaline reuptake inhibitor [3]. Previous studies shown that anti-depressant drugs have detrimental effects on the sexual functions and led to erection disorders. Perhaps bupropion causes ejaculation disorders and impotence [5]. Antidepressants drugs is one of the causes of sterility in males due to damaging sperm's DNA [8]. With the increased prevalence of depression among

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communities, antidepressants such as bupropion has been used very commonly. In the present study, the effect of bupropion on the pituitary - gonad axis and testicular tissue was investigated; in order to provide an appropriate remedies for the adjustment, development or limitation on these drug use.

MATERIAL AND METHODS

This is an experimental research design conducted in the laboratory, 40 healthy adult male Wistar rats (weighting 200-230 gram) were used in this study. Animals were maintained under standard laboratory conditions on a 12 h light/dark cycle with free access to enough food and water. The rats were randomly divided into five groups; each group consisting of seven rats in the control, placebo and treatment (experiment) groups. The control group didn't receive any drug or placebo treatment. The placebo group received 2 ml/day distilled water as placebo. Treatment group received daily dose of oral bupropion with 160, 320, and 640 mg/kg for a period of 28 days. After this period, animals were weighted, then sacrificed under general anesthesia with ether, blood samples were collected from their heart. A 6 ml specimens was collected from each rat in a sterilized laboratory tubes without anticoagulant. Specimens were centrifuged under 3000 rpm for 15 minute and plasma were separated from clot content. Plasma was separated and then stored at -20 °C until measurement of LH, FSH and testosterone. Hormone measurements was performed using a radio-immunoassay (RIA) method. The hormonal kit was contain standard solutions of radioactive iodine, antibody, and washing buffer, which was purchased from Kavoshyar Company. After laparotomy, both testes of the animals of all groups were removed, and after preparation of tissue slices and staining with hematoxylin – eosin; sperm density changes in seminiferous tubules, changes of the number of interstitial cells, Sertoli and spermatogenic chain was determined using a special calibrated measuring slide (Graticule) and then, the results of histological studies was compared between the control and experimental groups. Mean and standard deviation were expressed as mean \pm standard error. Statistical tests like ANOVA, T-test and Tukey were used for data analysis. Data are presented as mean \pm standard error of means. The degree of significance was set at $P \leq 0.05$.

RESULTS

Results shown that the serum concentration of testosterone was reduced significantly at the end of 28 days in the treatment group whom received drug with 320 and 640 mg/kg (chart 1). At the end of 28 days, the serum concentration of LH and FSH was significantly higher in the treatment group which received 320 and 640 mg/kg bupropion compared with control group (charts 2 & 3).

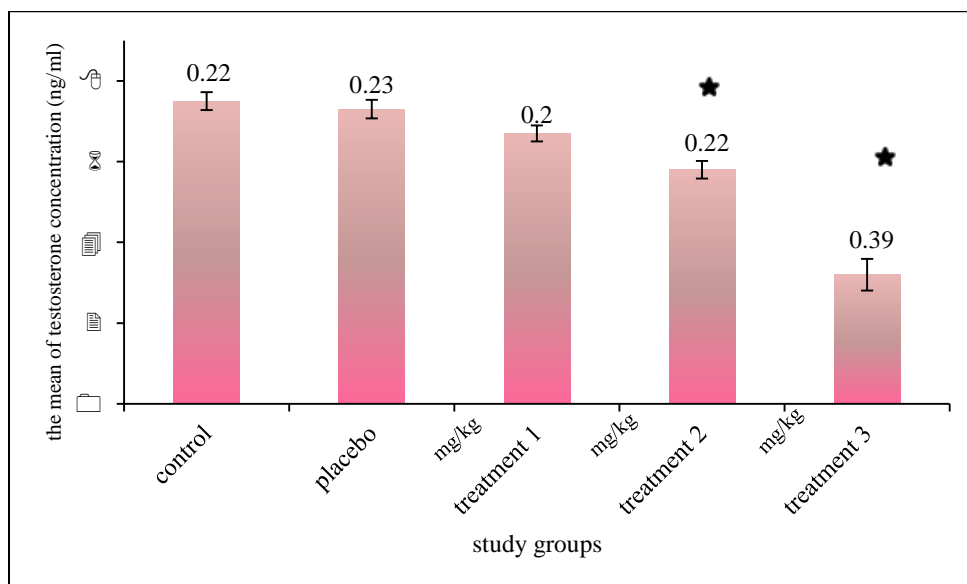


Chart 1 - Mean serum testosterone concentrations at the end of day 28. Values are shown as mean \pm standard error.

★ Indicates a significant statistical differences with the control group at $p \leq 0.05$.

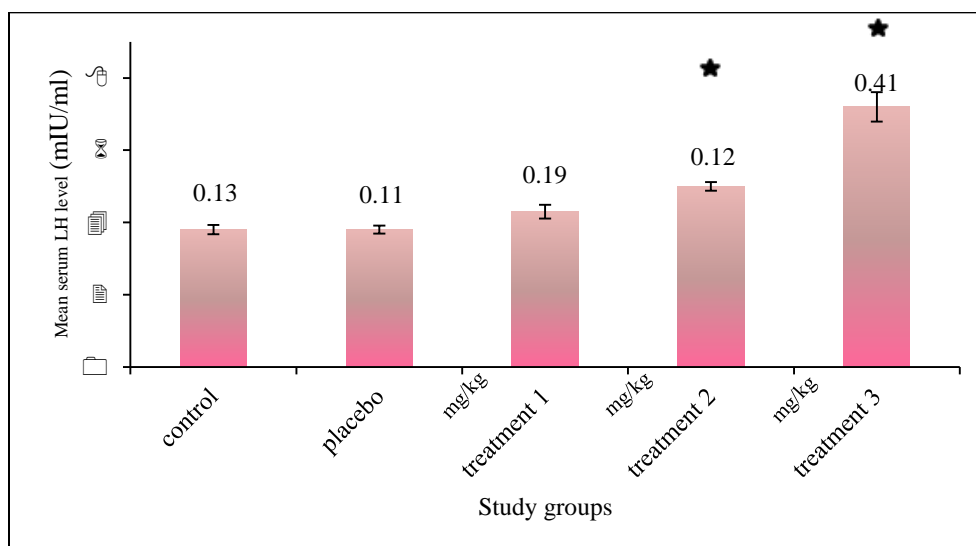


Chart 2 - Mean serum LH concentrations at the end of day 28. Values are shown as mean \pm standard error.

★ Indicates a significant statistical differences with the control group at $p \leq 0.05$.

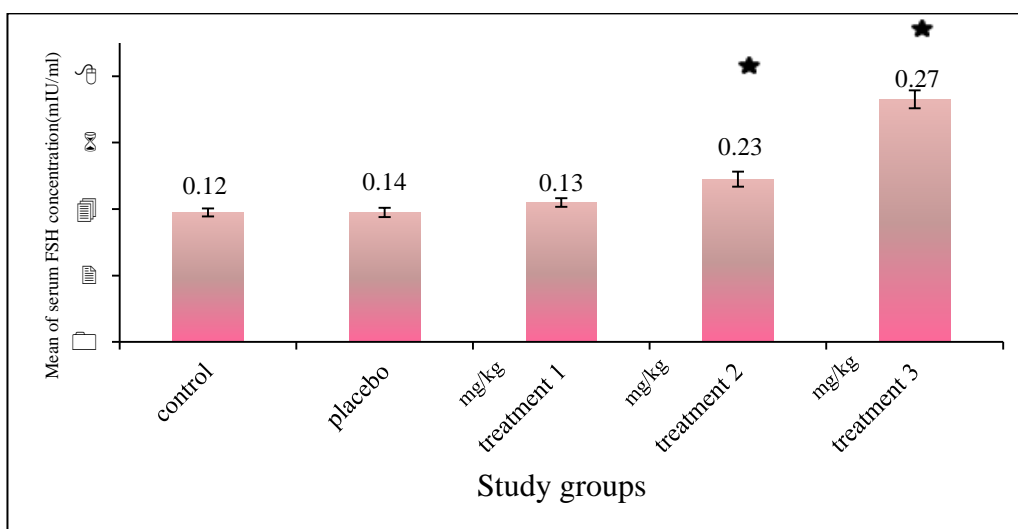


Chart 1 - Mean serum FSH concentrations at the end of day 28. Values are shown as mean \pm standard error.

★ Indicates a significant statistical differences with the control group at $p \leq 0.05$.

With the decline in serum testosterone levels in the group receiving the drug with 320 and 640 mg/kg daily, a relative reduction was observed in sperm density in the seminiferous tubules, number of spermatogonia cells, primary spermatocyte, spermatid and **Leydig cells** count (Table 1). There was not any significant differences between treatments group and control or placebo group in the Sertoli cells count at the end of 28 days (Table 2).

Table 1 - Mean (\pm SD) number of spermatozoa stem cells and Leydig cell lineages in the seminiferous tubules after oral administration of bupropion.

Groups	Drug dose mg/kg	Spermatogonia count	primary spermatocyte	Spermatid count	Leydig cells count
Control	-	64.20 \pm 1.9	120.0 \pm 1.2	128.0 \pm 3.2	16.0 \pm 0.32
Placebo	Distilled water	65.20 \pm 2.7	119.8 \pm 1.5	128.6 \pm 2.3	16.4 \pm 0.24
Treatment 1	160	60.40 \pm 2.3	114.6 \pm 4.5	122.6 \pm 3.7	14.8 \pm 0.37
Treatment 2	320	47.00 \pm 2.3 *	96.4 \pm 3.2 *	104.6 \pm 4.6 *	11.4 \pm 0.40 *
Treatment 3	640	40.80 \pm 2.3 *	85.4 \pm 3.7 *	89.6 \pm 2.1 *	9.4 \pm 0.24 *

Table 2 - Mean (\pm SD) number of Sertoli cells in the seminiferous tubules after oral administration of Bupropion

Study groups	Drug dosage, mg/kg	Sertoli cells count
Control	-	17.0 \pm 1.00
Placebo	Distilled water	16.8 \pm 0.84
Treatment 1	160	16.4 \pm 0.55
Treatment 2	320	16.0 \pm 0.71
Treatment 3	640	16.0 \pm 0.71

DISCUSSION

Based on the decline of testosterone concentration in the groups receiving dosages of 320 and 640 mg/kg, it can be assumed that bupropion increases the serotonin levels by inhibition of its reuptake; so, the increases in serotonin would inhibit the interfering enzymes in the route of steroid production in the testes which lead to testosterone reduction [4, 7]. Bupropion is a dopamine reuptake inhibitor, thus, it is likely to increase dopamine level. Increased dopamine level has an inhibitory effect on prolactin levels, and its reduction lead to low sensitivity of the LH receptor, so that this action reduce the connected LH to receptors, and increased plasma LH concentration and lack of steroids and decline of testosterone production [4, 9]. It seems that Bupropion has change the structure of LH receptors in Leydig cells that preventing it from binding to receptors, reducing steroid production which results in decreasing testosterone concentration. Also, there are possibility that bupropion reducing thyroid hormones and their settlement on the thyroid receptors in the Leydig cell line which results in lower production of steroids and testosterone [14]. Due to testosterone reduction by negative feedback path, the secretion of GnRH from hypothalamus and consequently release of LH and FSH from anterior pituitary gland will increases [17]. Bupropion can also inhibit the production of inhibin by Sertoli cells through changing the structure of adrenergic receptors which led to increases in the FSH levels. The beta-adrenergic receptors are predominant receptors in these cells and bupropion can alter the structure of β 1-adrenergic receptor; thus, it can affect the Sertoli cell functions, and reduces the Inhibin production by lowering the cAMP and protein-kinase A; which is a strong explanation for increase in the FSH levels, also consistent with the histological studies of the testes tissues [15]. Studies from other researchers show a neural pathway between the brain and the testes that stimulated by corticotropin-releasing factor (CRF) and affect the Leydig cell function [13]. Testosterone is an inhibitor for the monoamine oxidase enzyme which is involved in dopamine catabolism and reduction of this enzyme lead to raise in dopamine levels [9]. Thus, reduction of testosterone level will reduce the activity of inhibitory effects of this enzymes that followed by reduction of dopamine concentration. Dopamine inhibits production of gonadotropins by affecting the Arcuate nucleus; and reduced dopamine production will lead to rise in the gonadotropins levels [10, 16]. This study results shown that the LH and FSH levels increases in the drug recipient groups (320 & 640 mg/kg) at the end of 28th day than control group, but the testosterone level was reduced. Based on current study results, the sperm density in the seminiferous tubules was reduced in the treatments group whom received 320 and 640 mg/kg in comparison with control groups. Previous studies have shown that testosterone levels have direct effects on Sertoli cells count. Sertoli cells supports the dividing spermatid cells by releasing tubular fluids which participate in their feeding. Several proteins such as growth factor and transferrin and secrete are secreted by Sertoli cells, which have a special role in the sexual cell division and ultimately spermatogenesis. There are another role for testosterone and it is a direct effects on the proliferative reproductive cells [11, 12]. Based on the essential role of testosterone on the spermatogenesis process, it is clear that reduction of its production associate with lower sperm density; although in dire need of future researches.

In summary, it can be said that one of bupropion's side effects is reduction of steroid production in testes. High level of bupropion blood level is associated with lower serum testosterone concentration and the possibility of reproduction problems. Thus, it is recommended that these drug would be used with caution in patients with sex hormone disorders. The concurrent administration of bupropion and steroid production stimulants are suggested for prevention and reduction of side effects and drug complications.

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