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Effect of Selegiline on Concentration of Testosterone and Spermatogenesis in Rats

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Abstract: The aim of this research was to evaluate the effect of deprenyl (selegiline), a monoamine oxidase-B inhibitor (MAO-B) on pituitary-gonad axis and spermatogenesis in rats. In this study 32 adult male rats in the form of experimental and control groups were used. The experimental groups (B, C and D) were given oral doses 5, 10 and 15 (mg kg⁻¹ B.W) selegiline for the period of 30 days and the control group (A) received normal saline. The blood samples were taken 8 h after receiving last dose on 30th day and the concentrations of Lutein Hormone (LH), Follicle Stimulating Hormone (FSH) and testosterone were measured by RIA. In addition, on the 30th day the testes were separated and histological changes were studied among experimental and control groups. The difference in concentration of hormones between groups were studied by one-way analysis of variance (ANOVA), followed by Tukey test. The level of significance was considered at $p \leq 0.05$. The results indicates that receiving different dosage of selegiline shows a significant increase in concentration of LH hormone in comparison with control group, but concentration of FSH did not show significant difference in comparison with the control group. In addition the concentration of testosterone in response to different dosage in relative to the control group shows a significant decrease. According to the results we suggest that selegiline causes a decrease in concentration of testosterone via down-regulation receptors on leydig cells by LH. Furthermore, as an inhibitor of MAO-B, causes increase in dopamine concentration in striatum area and in turn causes decrease in concentration of prolactin. The decrease of prolactin secretion reduce the effect of LH hormone on leydig cell. Besides, histological studies showed a significant effect caused by selegiline such as decrease of sperm in seminiferous tubules, leydig cells and reduced spermatogenesis.

Key words: Selegiline, LH, FSH, testosterone, spermatogenesis, rat

INTRODUCTION

The pituitary-gonad axis is one of the most complicated and active sites in the body which controls not only reproductive functions, but also many of the individual's physiological aspects including sex differentiation, the development of sex secondary characteristic and behavior through the synthesis and secretion of androgens. Recognizing the factors which, in some way, affect this center and ways for controlling or escalating these effects have always been addressed by researchers. It has been postulated that Selegiline as monoamine oxidase B (MAO-B) is an inhibitor which alter disease progression in Parkinson's disease (Macleod *et al.*, 2005) and improve memory and learning in dementia of alzheimer's type (Takahata *et al.*, 2005) and depression (Olanow, 1996). MAO-B is recognized as an enzyme of crucial interest to pharmacologists because it catalyzed the major inactivation pathway for the catecholamine neurotransmitters, noradrenaline, adrenaline and dopamine (Youdim and Bakhle, 2006). The amount of this drug to be taken in is 10 mg day⁻¹. It is sometimes used in a single dose in the morning; but in most studies, it is used in two 5 mg day⁻¹. Studies show that it is better to administer this drug both in the morning and in the afternoon (Lange, 1994). Clinical findings have revealed that the amount of 10 mg day⁻¹ is an effective one (Frankel and Kempster, 1989). Studies

carried out using selegiline marked by carbon 14 indicate that this drug is quickly absorbed from the gastro-intestinal system within 0.5-2 h following oral administration when concentration reaches the maximum level (Magyar, 1984). The half life of its absorption is 0.4 an hour for man and is characterized by hydrophilicity and a little alkaline property and quickly permeates the tissues and is distributed throughout the body.

Studies on animals using autoradiography also indicate that selegiline quickly gets into the brain and the spine and after thirty seconds, its concentration reaches an amount 3.5 times larger than the amount of the blood serum. Its rapid distribution throughout the whole blood-brain barrier is due to its low polarity (Fowler, 1987). Studies show that the selegiline marked by carbon 14 can connect to some parts of the brain such as the thalamus, the striatum of the brain's cortex and the whole brain stem which are rich with MAO-B enzyme. Given the fact that a thorough investigation into the effects of this drug on the pituitary gonad axis and spermatogenesis has not been carried out yet, in this study, the effect of this drug on one of the most important endocrine axis of the body has been investigated. Since the testes are vital parts of the individual's body, the effect of this drug on the activity of the testicular function and concentration of LH, FSH and testosterone hormones is of great importance in terms of endocrine and reproduction aspects.

MATERIALS AND METHODS

The animals used in this study included 32 adult male Wistar rats having weights between 200-220 g which had been brought from the Animal Raising Department of Iran's Pasteur Institution.

Having been carried to the cite of the experiment (The Medical College of Isfahan University,) the animals were given 15-20 days' time to adapt themselves to the surroundings and get to the desirable age and weight. During the time of the experiment, the temperature of the environment was $24\pm 2^{\circ}\text{C}$ (Grizard and Artonne, 1997). All the animals were under standard light conditions which consisted of 12 h of lighting and 12 h of darkness (Cabanillas and Masini Repiso, 1994). They had access to sufficient amounts of water and food. The animals were randomly divided into four eight-member groups which comprised the control group (A) and experimental groups (B, C and D). The experimental groups were given selegiline at the doses of 5, 10 and 15 (mg kg^{-1} B.W) for 30 days in two morning and afternoon shifts with an interval of 12 h (Cedarbaum, 1990). Animals of the control group only received normal saline. An instrument called animal feeding which was especially designed for rats was used to administer the drug and normal saline. At the end of the 30th day and 8 h after the administration of the last dose of the drug, cupping was carried out for all the animals by drawing some blood from the corner of their eyes. The blood was collected from each rat in sterilized tubes which contained no anti-coagulation substance. The collected blood samples were centrifuged at the rate of 3000 rounds/min for 15 min, for the serum to be separated from the coagulum. Then, the serum in each sample was separated from the coagulum using a sampler and was kept at the temperature of -20°C till the time of hormone assay for measurement of hormones and histological studies. The hormone measurement was carried out using common methods and according to the Radio Immuno Assay (RIA) method.

After opening the abdomens of the animals, both of the testes were removed from all groups and after taking some tissue segments and painting according to the hematoxylin and eosine method, were determined between the experimental groups and the control one by histological studies. Changes related to the density of sperm in the seminiferous tubules, changes in the number of the leydig cells and sertoli cells and the cascade of spermatogenesis.

The statistical tests used for the analysis of the results obtained from the experimental and control groups included the ANOVA and Duncan tests. The average and standard deviation were expressed as follows: $\bar{X} \pm \text{SEM}$.

The level of significance was considered at $p \leq 0.05$ between the control and experimental groups. Significant difference among the groups has been identified with a star (*).

Table 1: Concentrations of LH, FSH and testosterone in different groups on 30th day

Groups		Concentration of LH (μmL^{-1})	Concentration of FSH (μmL^{-1})	Concentration of testosterone (ng mL^{-1})
A	Control	0.306±0.12	0.94±0.55	0.276±0.23
B	5 mg kg^{-1} .B.W	0.327±0.25*	0.24±0.13	0.353±0.33*
C	10 mg kg^{-1} .B.W	0.296±0.18	0.36±0.39	0.288±0.41 *
D	15 mg kg^{-1} .B.W	0.328±0.15*	0.44±0.52	0.320±0.15*

The average±Standard deviation ($\bar{x} \pm \text{SEM}$). The average amounts marked by *have a significant difference with the control group. The number of samples in each group is: n = 8

RESULTS

The results of the experiments carried out in hormone assay, along with the statistical calculations between the control and experimental groups have been presented in the form of Table 1.

Statistical analysis of the data showed that the application of the drug at the aforesaid doses significantly increases the concentration of LH in the groups receiving the selegiline at the doses of 5 and 15 (mg kg^{-1} B.W) at the end of the 30th day as compared with the control group (Table 1). There was no significant difference between the experimental and control groups as in the concentration of FSH hormone (Table 1).

At the end of the 30th day, the concentration of testosterone showed a significant increase in all the experimental groups compared with the control group (Table 1). The amounts have been presented as follows:

The results of histological changes show a significant decrease of sperms in seminiferous tubules, disorders in the spermatogenesis, the destruction of intestinal space and thus, the decrease of leydig cells in the experimental groups which received the drug after a long time (30 days) in comparison with the control group.

DISCUSSION

Numerous studies are in progress all over the world, aimed at doing more investigations into the mechanisms regulating the function of different parts of the body and their position of influence. These studies are carried out for the purpose of clarifying vague issues as much as possible; because the clarification of these vague points sometimes can be helpful for offering better solutions and explaining issues more accurately.

In the present study, the effect of selegiline on the concentration of LH, FSH and testosterone and also on histological changes in the testes has been investigated. The results obtained by investigating the effect of the administration of selegiline on the concentration of LH indicate that using this drug at the doses given, increases the concentration of this hormone in the experimental groups as compared with the control group at the end of the 30th day. This is an increase which is significant, given the following probability: $p \leq 0.05$.

Studies indicate that selegiline directly affects the pituitary gland as an inhibitor of MAO-B and escalates the secretion of LH from the pituitary gland. An increase in the concentration of LH, possibly has decreasing effects on the activities of the receptors in leydig cells which exist may down regulation in the testis (Knoll and Dallo, 1989) and in turn, decreases the secretion of testosterone. Selegiline also increases the dopamine concentration from the striatum of the brain and the secreted dopamine is transmitted to the portal blood circulation system via tubero-infundibular neurons and dopaminergic activities and reduces the secretion of prolactin. Probably a decrease of prolactin secretion reduces the effects of LH on the leydig cells.

Studying the effects caused by different doses of selegiline on the concentration of the FSH indicates that at the end of this period, this drug used causes a non significant difference in the FSH between the control and experimental groups. According to the results of this study and those carried out by other researchers, there are possibly a large number of mutations in the receptors of LH in the leydig cells (Beak Peccoz and Romoli, 2000), but these mutations rarely occur in the sertoli cells. One of the reasons for the unchanging and stable FSH, may be the stability which exists in the operation of FSH following the application of the drug. However, further studies and investigations have to be carried out regarding this issue. This neuropharmacological agents have been reported to increase sexual behavior in male rats. So sexual dysfunction frequently occurs in patients with schizophrenia under antipsychotic therapy and the presence of sexual side effects may affects compliance (Costa *et al.*, 2006).

Studies of the effects of different doses of this drug on the concentration of testosterone show that the doses of 5, 10 and 15 (mg kg⁻¹ B.W) cause a significant difference in the experimental groups at the end of the 30th day as compared with the control group. Studies of procarbazine, which is an inhibitor of the MAO enzyme and as being equivalent to selegiline indicate that this drug accelerates spermatogenesis and increases fertility in most studies has been introduced (Meistrich and Wilson, 1999) in the short term, but in the long term, it hampers both. Studies carried out by other researchers also indicate that treatment with carbozin degenerate all 70% of the seminiferous tubules and hampers the secretion of testosterone and also the process of spermatogenesis (Kangasniemi and Wilson, 1995).

Results from histological studies demonstrate the reduction of the sperm in the seminiferous tubules, the destruction of interstitial spaces and thus, a decrease in the number of leydig cells in the experimental groups, particularly at the maximum doses of 15 (mg kg⁻¹ B.W). This confirms the general conclusion that in this period of time, selegiline reduces the secretion of testosterone and damages the process of spermatogenesis.

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