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Full Length Research Paper

Effect of rosmarinic acid on sexual behavior in diabetic male rats

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One of the disorders that are caused by diabetes disease is reproductive problem, infertility and decrease libido. Antioxidants have essential effect on diabetes as enhanced oxidative stress, and changes in antioxidant capacity play an important role in the pathogenesis of chronic diabetes mellitus. So, the aim of this work was to study antioxidant effect of rosmarinic acid on sexual behavior of the diabetic rats. Rosmarinic acid from the plants reduced superoxide radicals from xanthine oxidase and inhibited cyclooxygenase I and II enzymes. Eighty Wistar male and female rats were selected for this research, male rats (n = 40) were allocated into four groups, control group (n = 10), rosmarinic acid (Ro) treated group that received 5 mg/rat (gavage) (n = 10) and diabetic group that received streptozotocin in dose of 55 mg/kg (IP) streptozotocin (STZ) (n = 20) which was subdivided to two groups of 10; STZ group and treatment group. Treatment group received 55 mg/kg body weight via intraperitoneal injection (IP) STZ plus 5 mg/rat Ro daily for 4 weeks, respectively; however, the control group just received an equal volume of distilled water daily (gavage). Diabetes was induced by a single (IP) injection of streptozotocin (55 mg/kg). On the 28th day of research, forty female rats prepared to sexual stimulation and on the 30th day, they were caged with male rats. Level of sexual behavior (according video observation) and testosterone significantly increased in groups that received Ro, in comparison to the whole groups ($P < 0.05$). At the end of the study 5 ml of blood samples were collected for measurement of testosterone levels of male rats in control and treated groups. We could conclude that the treatment with rosmarinic acid have significantly preventive and curative effect on diabetic disorder in rats.

Key words: Diabetic, rosmarinic acid, streptozotocin, sexual behavior, testosterone.

INTRODUCTION

Oxidative stress occurs when the production of potentially destructive reactive oxygen species (ROS) exceeds the bodies own natural antioxidant defenses, resulting in cellular damage. Oxidative stress is a common pathology seen in approximately half of all infertile men. ROS, defined as including oxygen ions, free radicals and peroxides are generated by sperm and seminal leukocytes (koca et al., 2003). Bal et al., (2011) showed many bio antioxidant such as hydrated C(60) that could significantly reduces diabetes-induced oxidative stress and associated complications such as testicular dysfunction and spermatogenic disruption (Bal et al., 2011). Rosmarinic acid was identified as a major anti-oxidant compound (0.22 to 0.97%) in all seven herbs, confirmed by nuclear magnetic resonance. Rosmarinic acid from the plants quenched superoxide radicals from xanthine oxidase and inhibited cyclooxygenase I and II enzymes (Park, 2011). Diabetes is associated with gender-specific changes in sex steroid hormones; however, the mechanisms responsible for these associations as well as the link to sexual dysfunction are not well understood (Bitzer and Alder, 2009). Imbalances in sex steroid hormone levels are strongly associated with diabetes and this may negatively impact upon sexual function (Kim, 2009). Although, numerous factors are likely to contribute

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to the development of diabetes and its complications, the role of sex steroid hormones must be recognized (Kim, 2009). Antioxidants secreted by the reproductive tract protect spermatozoa against the toxic effects of reactive oxygen species (ROS) after ejaculation (Koziorowska-Gilun et al., 2011). Antioxidants such as vitamin E can regulate apoptosis-related protein Bcl-2, Bax expression and confront free radical damage which contributes to a protective effect for ovarian grandiose cells (Lu et al., 2009). Zhang et al. (2011) evaluated that the effect of rosmarinic acid (RosA) on the proliferation and apoptosis in activated hepatic stellate cells (HSC-T6), which is useful to decrease this cell population. Rosemary (*Rosmarinus officinalis*), a culinary spice and medicinal herb, has been widely used in European folk medicine to treat numerous disorders (Cheng et al., 2011). Many studies have shown that rosemary extracts play important roles as anti-inflammatory, anti-tumor and anti-proliferative in various *in vitro* and *in vivo* settings (Cheng et al., 2011). Rosemary (*Rosmarinus officinalis*) leaves, possess a variety of bioactivities (Kuo et al., 2011). Previous studies have shown that the extract of rosemary leaves from supercritical fluid extraction inhibits the expression of inflammatory mediators with apparent dose-dependent responses (Kuo et al., 2011). These experiments were designed to evaluate the hypothesis that diabetes-induced sexual dysfunction in male rats by testosterone unbalancing events that normally facilitate sexual behavior. So, the aim of this work was to study antioxidant effect of rosmarinic acid on sexual behavior of the diabetic male rats.

MATERIALS AND METHODS

Animals

Eighty adult 8 weeks old Wistar albino male rats 250 ± 10 g (n = 40) and female Wistar albino rats 230 ± 10 g (n = 40) were obtained from Animal Facility of Pasture Institute of Iran. Male rats were housed in temperature controlled rooms (25°C) with constant humidity (40 to 70%) and 12 h/12 h light/dark cycle prior to use in experimental protocols. All animals were treated in accordance to the principles of laboratory animal care (National Institutes of Health). The experimental protocol was approved by the animal ethical committee in accordance with the guide for the care and use of laboratory animals prepared by Tabriz Medical University. All rats were fed a standard diet and water. The daily intake of animal water was monitored at least one week prior to start of treatments in order to determine the amount of water needed per experimental animal. Thereafter, the rats were randomly selected and divided into control (n = 10) and rosmarinic acid (Ro) group that received 5 mg/rat (gavage) (n = 10) and diabetic group that received 55 mg/kg (IP) streptozotocin (STZ) (n = 20) which was subdivided into two groups of 10; STZ group and treatment group. Treatment group received 55 mg/kg (IP) STZ plus 5 mg/rat of Ro (gavage). The control group just received an equal volume of 1 cc distilled water daily (gavage). Diabetes was induced by a single (IP) injection of streptozotocin (STZ, Sigma- U.S.A.) in 0.1 M citrate buffer (pH 4.0) at a dose of 55 mg/kg body weight. Rosmarinic acid (Ro) inducements were continued to the end of the study (for 4 weeks) according to the method (Khaki et al., 2010) described. After then, male rats were prepared for sexual behavior examination; the rate of ejaculation, mounted and lordosis were recorded (for each positive reaction equal to one (+) mark).

Female stimulation

48 h before male behavioral test recording, forty Wistar albino female rats were injected subcutaneously with 20 µg estradiol benzoate in oil 4 h, before the test they received subcutaneously injection of 500 µg progesterone in oil. These female rats were prepared to be caged one by one to each male rat.

Sexual behavior of male tests

For sexual behavior displayed by the experimental males were conducted in a Plexiglas observation chamber (46 × 58 × 51 cm). During the test, the examined forty male had unrestricted access to the stimulus animal (either male or female). The tests lasted 25 min or until ejaculation, whichever occurred first. Behavioral testing took place under dim red light illumination in the middle part of the dark phase of the light-dark cycle. Video recordings of these tests were analyzed to determine frequency of mounts, intromissions and ejaculations shown by the examined males and the latency to show these behaviors (Henley et al., 2010).

Induction of experimental type 1 diabetes

Experimental type 1 diabetes was induced in rats by intraperitoneal (IP) injection of 55 mg/kg streptozotocin (STZ) in distilled water. Control rats received distilled water, only (khaki et al., 2010).

Determination of blood glucose level

Blood samples were collected from the tail vein male rats in all groups. Basal glucose levels were determined prior to STZ injection, using an automated blood glucose analyzer (Glucometer Elite XL). Sample collections were then made 48 h after STZ injection and blood glucose concentrations were determined and compared between groups. Rats with blood glucose concentrations above 300 mg/dl were declared diabetic and were used in the experimental group. One week after the induction of experimental diabetes, protocol was started.

Testosterone hormone assay

Total serum concentration of testosterone from male rats was measured using a double-antibody RIA kit (Immunotech Beckman Coulter Co., USA). The testosterone detection sensitivity per assay tube was 0.025 ng/ml.

Surgical procedure

On the 28th day (at the end of the treatment period), the blood samples in control and experimental groups of male rats were immediately obtained.

Statistical analysis

Statistical analysis was done using the ANOVA test to test for comparison (Kolmorogov-smirnov) of data in the control group with

Table 1. Measurement of serum testosterone hormone and blood glucose, rate of ejaculation, mounts and lordosis in male rats in all groups.

Groups	Control	Extracts	STZ	Extract with STZ
Testosterone (ng/ml)	2.1 ± 0.05	2.9 ± 0.05	1.1 ± 0.05*	1.9 ± 0.05
Ejaculation	+ + + + +	+ + + + +	+ +*	+ +*
Mounts	+ + + +	+ + + + +	+ +*	+ + +*
Lordosis	+ + + +	+ + + +	+*	+ +*
Blood glucose (g/L)	1.1 ± 0.05	0.9 ± 0.05	5.1 ± 0.10*	2.1 ± 0.10*

*Statistical analysis of Dunnett (one side) shows significant differences between experimental groups in comparison to control group ($P < 0.05$).

the experimental groups. The results were expressed as mean ± S.E.M (standard error of means). P-value less than 0.05 were considered significant and are written in the parentheses.

RESULTS

Testosterone hormone, blood glucose, rate of ejaculation, mounts and lordosis

Testosterone level in control group was 2.1 ± 0.05 ng/ml and in extract, STZ, extracts with STZ groups were 2.9 ± 0.05, 1.1 ± 0.05 and 1.9 ± 0.05 ng/ml, respectively (Table 1). Blood glucose level in control group was 1.1 ± 0.05 g/L and extract, STZ, extracts with STZ groups were 0.9 ± 0.05, 5.1 ± 0.10 and 2.1 ± 0.10 g/L, respectively (Table 1). The rate of ejaculation, mounts and lordosis in whole groups were analysed and data showed that mean of ejaculation, mounts and lordosis in extract, extract with STZ and STZ groups were significantly decreased ($P < 0.05$) when compared with control group.

DISCUSSION

In nowadays sexual function of older (elderly) individuals, becomes an important issue particularly for men. Sexual functional in male mammals is roughly classified into fertility and sexual potency (Terada et al., 2009). There is much interest in worldwide in developing an animal model of human potency (Kinsey et al., 1948; Kruger et al., 2003). Libido and copulatory behavior decline in human and animals with increasing age, exposed to chemical and many disease such as blood pressure and diabetes (Terada et al., 2009). Testosterone is necessary for normal development of male sexual behavior, exogenous perinatal testosterone treatment of an intact male result in disruption of normal male sexual behavior (Diamond et al., 1973; Piacsek and Hostetter, 1984; Pollak and Sachs, 1975; Zadina et al., 1979). One factor that could mediate this effect of testosterone exposure is the possibility that the hyper-androgen treatment is reducing the male's motivation to approach the female. Support for this idea can be found in both the animal and human literature. This finding about testosterone role agreed with our results that confirmed that the level of testosterone can play important role in enhancement of sexual behavior in male rats in all groups. Although, not statistically significant, male ferrets treated with testosterone perinatally appear less likely to approach a stimulus female than a stimulus male as compared to control males (Baum et al., 1990). Prenatal hyper-androgen exposure has also been suggested to play a role in sexual orientation in humans (Henley et al., 2010). Some homosexual men have been shown to have larger genitalia (Bogaert and Hershberger, 1999), more masculine auditory evoked potentials (McFadden and Champlin, 2000), and more masculine 2D:4D digit length ratios (Rahman, 2005; Rahman and Wilson, 2003; Robinson and Manning, 2000) than heterosexual men (Berenbaum et al., 2009). All of these measures appear to be androgen-dependent during development, indicating that some homosexual men may be exposed to a higher level of androgen during development as compared to heterosexual men (Henley et al., 2010). Whereas several studies (Diamond et al., 1973; Piacsek and Hostetter, 1984; Pollak and Sachs, 1975; Zadina et al., 1979) have focused on the consummatory aspects of male sexual behavior after early exposure to elevated levels of testosterone, the current study expands these findings to include appetitive aspects of male sexual behavior including measures of partner preference. A male's motivation to approach a partner can be measured in a preference test by examining the amount of time spent with each stimulus animal. An increase in the oxidative stress and a decrease in the antioxidant levels have been described in diabetic patients, that have been related with the etiopathogenesis of diabetes and its chronic complications (Cuerda et al., 2011). The inter-vention studies including different antioxidants have not demonstrated any beneficial effect on cardiovascular and global morbidity and mortality in different populations, including diabetic patients. Neither of these studies has demonstrated a beneficial effect of antioxidant supplementation on the prevention of diabetes. According to these studies, these substances can decrease lipid peroxidation, LDL-cholesterol particles oxidation and improve endothelial function and endothelial-dependent

vasodilatation, without significant improvement in the metabolic control of these patients (Cuerda et al., 2011). Quercetin potentiated glucose and glibenclamide-induced insulin secretion and protected β-cells against oxidative damage suggested that ERK1/2 played a major role in those effects. The potential of quercetin in preventing β-cell dysfunction associated with diabetes deserves further investigation (Youl et al., 2010). The role of diabetic complications is controversial. Most trials on the effect of exercise on patients with diabetes mellitus focused on their glycemic control, only a few focused on sexual dysfunction. khaki et al. (2010) confirmed that diabetes has impair germinal cells and testosterone levels was affected by increased oxidative stress and quercetin is an anti-oxidative effects and could recover testes tissue and reversible testosterone in diabetics rats. In this study, our data's showed that diabetes can decreased testosterone levels and cause sexual dysfunction, and this is to our previous study (khaki et al., 2010). Sexual dysfunction in general, links between diabetes and sexual dysfunction, and management options for sexual dysfunction including therapeutic exercises were reviewed (Adeniyi and Adeleye, 2010). Thakur et al., (2010) showed experimental diabetes mellitus that leads to dysfunctional in sexual behavior in male rats, and using *Chlorophytum borivilianum* extract, it significantly ameliorate diabetes-induced sexual dysfunction. Kruger et al. (2003) showed that besides a neuroendocrine reproductive reflex, a post-orgasmic prolactin increase may represent one factor modulating central nervous system centers controlling sexual drive and behavior. In another study, researchers showed that melatonin with its anti-oxidative potential ameliorate oxidative stress in male rats and recurrence of sexual disability (Brotto et al., 2001). Traditionally, the role of sexual steroid hormones was focused primarily on reproductive organs: the breast, female reproductive tract (uterus, mammary gland, and ovary), and male reproductive tract (testes, epididymis and prostate), the endocrine pancreas has a pivotal role on carbohydrate homeostasis and deterioration in function, produces diabetes.

However, oxidative stress occurs from an imbalance between ROS and antioxidant actions. During chronic oxidative stress caused by environmental factors (that is, UV light, ionizing radiation and toxic substances), infections, diabetes, or lack of dietary antioxidants, an inequity of cellular reducing equivalents capable of detoxifying the increased burden of ROS has marked effects on normal cellular processes. However, in times of oxidative stress, normal cellular respiration is also still functioning, resulting in dysregulated mitochondrial free radical production and disparity between ROS generation and antioxidant defenses (Schriner et al., 2005; Limón and Gonsebatt, 2009). In male rodents, sexual behavior is a rewarding and reinforcing behavior, composed of various elements, including anogenital investigation, mounts, intromissions and ejaculation (Tenk et al., 2009). Ejaculation appears to be the most reinforcing component of sexual behavior (Coolen et al., 2004; Pfaus et al., 2001). For example, in contrast to males allowed to only intromit or mount, but not ejaculate, males allowed to copulate to ejaculation developed faster running speeds in T-mazes (Kagan, 1955), straight-arm runway (Lopez et al., 1955) or hurdle climbing (Sheffield et al., 1951). In addition, ejaculation is essential for the formation of conditioned copulatory preferences.

Our results could revealed that rosmarinic acid (Ro), had ability to increasing serum testosterone and sexual behavior such as ejaculation, mounts and lordosis per cases in whole groups ($P < 0.05$). In other hands, level of serum testosterone and ejaculation, mounts and lordosis in STZ group were significantly decreased as compared to control group ($P < 0.05$). In conclusion, rosmarinic acid via increasing serum testosterone levels causes the protective effects of diabetes decreasing libido, so treatment with Ro can increase libido rates in diabetic group. It will be suggested that using rosmarinic acid has beneficial effect in diabetic patients that have sexual disorders.

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