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Sub-Chronic Treatment of Sildernafil Citrate (Viagra) on some Enzymatic and Non-enzymatic Antioxidants in Testes and Brain of Male Rats

Akintunde JK[1*], Ajiboye JA[2], Siemuri EO[3], Oyelowo SB[2], Sunday OJ[4], Abam EO[2] and Irondi AE[5]

Abstract

Sildenafil citrate, a specific phosphodiesterase-5 (PDE-5) inhibitor drug currently used for the treatment of erectile dysfunction in men. The present study investigates the effects of Sildenafil citrate on antioxidant defense systems of testes and brain tissues of male rats by measuring the GSH, SOD, and CAT activity. Lipid peroxidation was also estimated by measuring the MDA levels, a Thiobarbituric Acid Reactive Substrate (TBARS) as biomarker of oxidative stress. Sildenafil citrate was orally administered at the different dose levels of 20 mg/kg body weight per 30 days in four divided doses of 50, 100, 150 and 200 mg/kg body weight while control rats were given distilled water. The result revealed that Sildenafil citrate significantly increased MDA levels in testes. Conversely, the MDA levels in brain tissue was significantly reduced $P<0.05$. However, a significant increase in GSH content of testes and brain was observed. Similarly, superoxide dismutase (SOD) and catalase (CAT) activities for both tissues increased significantly ($p<0.05$) compared to their corresponding control. The histological examination of the testicular tissues revealed no visible lesions. Collectively, the results suggest that therapeutic dose of Sildenafil citrate elicits modulatory roles by stabilizing/boosting antioxidant defense systems in male rat.

Keywords: Sildenafil citrate; Antioxidant defense system; MDA; Testes; Brain

Introduction

Sildenafil citrate popularly known as Viagra is a powerful therapy for male erectile dysfunction. It is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) [1,2]. Sildenafil citrate is designated chemically as 1-[[3-(6, 7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate. It was initially used to treat cardiovascular diseases. In the process, its penile erection effect was discovered [3,4]. The physiologic mechanism of penile erection involves the release of nitric oxide (NO) in the erectile tissues during sexual stimulation.

Nitric oxide (NO·) is referred to as endothelium derived relaxing factor [5]. This is synthesized from the amino acid L-arginine, oxygen, and a variety of cofactors, by nitric oxide synthase enzymes [6]. Nitric oxide is also used as a gaseous chemical compound that acts as an important signaling molecule within the human body. It also facilitates a variety of critical functions by enhancing blood flow and increasing immune defense system [7]. However, NO enhances blood flow by activating guanylate cyclase as shown in figure 2. This leads to increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation (vasodilation) in the corpus cavernosum and allowing inflow of blood which ensures prolong steady penile erection [8,9].

The formation of free radicals is a naturally occurring intracellular

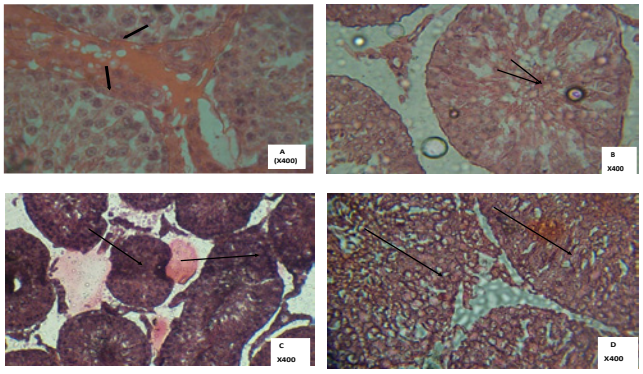


Figure 1: Representative photomicrographs of testes from Viagra treated animals (original magnification: 400 X (A) control rat showing mild interstitial congestion and oedema (Black arrows), (B) rat treated with Viagra shows no visible lesions seen (Red arrows) (C) rat treated with Viagra shows no visible lesions (Orange arrows) (D) rat treated with Viagra shows no visible lesions (Green arrows). Thus, sildenafil citrate may be considered as safe therapeutic drug during the treatment of erectile dysfunction in males as it inhibits free radical generation.

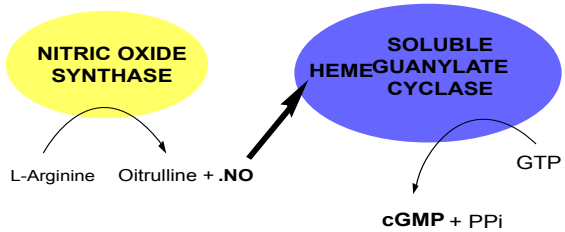


Figure 2: N0 mediated cGMP production. In the reproductive system, during stimulation, nitrous oxide (NO) is released locally from nerve endings in the endothelial cells of the erectile tissue (corpus carvenosum).Nitrous oxide is made with the aid of the enzyme NO synthase, which deaminates the amino acid L-arginine, thus producing NO and citrulline. The NO then diffuses out of the cell in which it was synthesized into neighbouring cells. NO then acts with iron in the enzyme guanylyl cyclase to produce the intracellular mediator (second messenger) guanosine monophosphate (3':5'cyclic GMP) from guanosine triphosphate (GTP).

***Corresponding author:** Akintunde JK, College of Pure and Applied Sciences, Department of Biosciences and Biotechnology, Biochemistry unit (Drug metabolism and Toxicology), Kwara State University, Malete, Ilorin, Nigeria, Tel: +23408064156056; Fax: +23408064156056; E-mail: akintundejacob@yahoo.com

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metabolic process. These cause oxidative damage to a number of molecules in cells including membrane lipids, proteins and nucleic acid [10,11]. The potential harmful effects of these species are controlled by the cellular antioxidant defense system [12]. Reduced glutathione (GSH) is the predominant defense against ROS free radicals in testes tissues of the body [13]. In addition, antioxidant enzymes, such as Super Oxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GPx) are essential in both scavenging process of (ROS) free radicals and maintaining cellular stability [14-16]. When the generation of ROS in cells impairs antioxidant defenses or exceeds the ability of the antioxidant defense system to eliminate them, it leads to oxidative stress [17,18]. Thus, the present study aimed at investigating the effects of Viagra Sub-Chronic Treatment on some Enzymatic and Non-enzymatic Antioxidants in Testes and Brain of Male Rats. This to ascertain whether the drug (Viagra) used to increase libido during sexual exercise has some negative side effects on the brain.

Materials and Methods

Chemicals

Sildenafil citrate (Viagra), hydrogen peroxide, and thiobarbituric acid (TBA) were purchased from Sigma (St Louis, MO, USA).All chemicals and reagents used in the present study were of analytical grade and were obtained from Sigma Chemical Company, Saint Louis, USA

Animal treatment

Twenty-five healthy adult male wistar rats weighing approximately 200–220 g obtained from the Department of Physiology, University of Ibadan, Nigeria were randomly assigned into 5 groups of 5 animals per group. They were housed in a plastic suspended cage placed in a well ventilated rat house, provided rat pellets and water *ad libitum*, and subjected to a natural photoperiod of 12 h light and 12 h dark cycle, 50% humidity and at 30 ± 2°C. Rats in Group I served as control and were administered distilled water. Animals in Groups II, III, IV and V were orally administered at the different dose levels of 20 mg/kg body weight per 30 days in four divided doses of 50, 100, 150 and 200 mg/kg body. The control rats were given distilled water.

Necropsy

The animals were fasted overnight, weighed and sacrificed by decapitation 24 h after the last treatment. Testes and brains were removed and cleared of adhering tissues, washed in ice cold 1.15% potassium chloride and dried with blotting paper. The blood was allowed to clot and centrifuged at low speed (3000 g) at room temperature for 15 min. The supernatant (serum) was removed and used for biochemical analysis.

Enzymatic and non-enzymatic antioxidant assays

The testes and brains were homogenized in 50 mM Tris–HCl buffer (pH 7.4) containing 1.15% KCl and the homogenate was centrifuged at 10,000 g for 15 min at 4°C. The supernatant was collected for the estimation of CAT activity using hydrogen peroxide as substrate according to the method of Sinha, (18). SOD activity was determined by measuring the inhibition of autoxidation of epinephrine at pH 10.2 at 30°C according to [19]. Protein concentration was determined by the method of Lowry et al. [20]. Reduced GSH was determined at 412 nm using the method described by Jollow [21].

Lipid peroxidation assay

Lipid peroxidation was quantified as malondialdehyde (MDA) according to the method described by Ohkawa [22] and expressed as mmol/g tissue.

Histological examination

The testes were collected and cut into two pieces, fixed in Bouin's fixative for 6 h, then transferred to formalin, sectioned and stained routinely with hematoxylin and eosin for histopathologic examination.Permanent photomicrograph was obtained using light microscope.

Statistical analysis

All the results obtained are expressed as Mean ± SD of five rats in each group. Statistical evaluation was done by using analysis of variance (ANOVA) followed by Duncan's Multiple Range Test (DMRT). The statistical significance was at a $p<0.05$ [23].

Results

The effect of Viagra on microsomal lipid Peroxidation (LPO) levels of the testes and brain of male rats was investigated. The results revealed that the LPO (MDA) levels of the testes were significantly ($p<0.05$) increased in testes in a dose dependent manner by 111.87%, 144.54%, 202.72% and 278.94% respectively compared with the control group. Conversely, the LPO levels in brain tissue decreased significantly ($p<0.05$) in dose dependent fashion by 19.8%, 39.59%, 59.62% and 79.41% respectively against the corresponding control (Table 2). There was a significant ($p<0.05$) marked elevation of SOD levels in a dose-dependent manner by 98.34%, 118.56%,132.04% and 183.54% respectively compared to the control (Table 1). Similarly, the SOD activity of the brain increased significantly ($p<0.05$) by 45.15 %, 41.63%, 64.05% and 84.78% respectively compared with the control group (Table 2).

Sub-chronic treated-rats with Viagra caused a significant ($p<0.05$) increased in the activity of Catalase (CAT) in rat testes (Table 1) by 9.84%, 10.573%, 11.30%, and 12.03% respectively while brain increased by 8.01%, 16.03%, 24.04% and 32.05% respectively (Table 2) against their corresponding control.

Also, reduced testes GSH levels were significantly ($p<0.05$) elevated in a dose-dependent manner by 219.44%, 308.38%, 331.13% and 374.95% respectively (Table 1) against the control group. Similarly, the brain GSH levels of treated-rats with the drug (Viagra) increased significantly ($p<0.05$) in dose dependent manner by 31.64%, 69.29%, 81.74% and 102.71% respectively compared to the control group (Table 2).

Additionally, the histopathological examination revealed that therapeutic doses of Viagra showed no visible lesions in the testes of rats (as shown in figure 1) compared with the control.

Discussion

Sildenafil citrate commonly known as Viagra is being used therapeutically for the treatment of erectile dysfunction in folk men. It had been reported that Viagra induced cardiovascular diseases due to its cardiovascular properties [24-27]. The lipid peroxidation may occur as a result of the imbalance between the production of oxidants and antioxidants [28-30]. Our present study investigated the effects

Table 1: The effects of therapeutic doses of sildenafil citrate on lipid peroxidation, antioxidant enzymes and non-enzymatic antioxidant in testes of wistar albino rats.

Dose	LPO[a]	GSH[c]	SOD[d]	CAT[e]	Total protein[f]
Control	19.126 ± 5.488	34.563 ± 2.431	9.051 ± 2.751	26.852 ± 5.112	0.258 ± 0.049
50mg	40.534 ± 5.856[b]	110.397 ± 22.669[b]	17.946 ± 0.673[b]	32.402 ± 4.547[b]	0.147 ± 0.041[a]
100mg	46.764 ± 18.275[b]	141.135 ± 34.569[b]	19.777 ± 2.560[b]	35.62 ± 9.930[b]	0.1112 ± 0.059[a]
150mg	54.907 ± 22.367[b]	149.890 ± 6.656[b]	21.001 ± 4.708[b]	48.160 ± 4.560[b]	0.0920 ± 0.0172[b]
200mg	72.492 ± 11.720[b]	164.142 ± 38.773[b]	25.656 ± 2.144[b]	52.547 ± 2.488[b]	0.082 ± 0.0153[b]

Values are means ± SD for five rats per group
[b]p<0.05 (ANOVA) against control
a unit/mg protein, c mmole/min/mg protein
d U/mg protein, **e** mmoles /min/mg protein
f mg protein

Table 2: The effects of therapeutic doses of sildenafil citrate on lipid peroxidation, antioxidant enzymes and non-enzymatic antioxidant in brain of wistar albino rats.

Dose	LPO[a]	GSH[c]	SOD[d]	CAT[e]	Total Protein[f]
Control	8.842 ± 0.420	32.141 ± 1.339	5.980 ± 1.762	9.110 ± 1.752	0.366 ± 0.051
50mg	7.087 ± 0.219	42.313 ± 4.029[b]	8.677 ± 2.308[b]	9.840 ± 2.186	0.409 ± 0.117
100mg	5.337 ± 0.737[b]	54.411 ± 4.569[b]	8.474 ± 1.747[b]	10.573 ± 0.611[b]	0.424 ± 0.025
150mg	3.577 ± 0.727[b]	58.813 ± 8.711[b]	9.806 ± 1.017[b]	11.3 ± 2.109[b]	0.450 ± 0.063
200mg	1.822 ± 0.726[b]	65.151 ± 5.087[b]	11.051 ± 0.958[b]	12.03 ± 1.471[b]	0.473 ± 0.0112

Values are means ± SD for five rats per group
[b]p<0.05 (ANOVA) against control
a unit/mg protein, **c** mmole/min/mg protein
d U/mg protein, **e** mmoles /min/mg protein
f mg protein

of Viagra on the antioxidant status of both testes and brain. It was observed that the Viagra significantly induced lipid peroxidation only in the testes of the experimental animals in a dose dependent manner compared to the control group. The MDA brain tissue decreased significantly in a dose dependent fashion in rats administered with Viagra. The induced lipid peroxidation in the testes may be attributed to the fact that Viagra is a testes-target drug where most reproductive actions are elicited [31,32]. Our data are in agreement with findings of Sivasankaran et al. [33] who reported that concomitant ethanol treatment with Viagra increased MDA levels in adult male rats. However, the significant reduction in MDA levels of brain tissue indicates that the drug does not suggest any deleterious effects to the brain. High antioxidant levels of GSH, CAT and SOD of the present study are in consonance with work of [34-36] who reported a significant decrease in MDA levels and increase in antioxidant (GSH) levels during alloxan- induced non-insulin dependent diabetes mellitus (NIDDM) of male rats. Our data suspected Viagra as a preventive therapy against oxidative stress in the brain [37].

Furthermore, Viagra may exert beneficial actions through the direct inhibition of xanthine oxidase (XO). This is a source of ROS and RNS [34]. Our data depicted direct inactivation of free radical species in brain by boosting and stabilizing the antioxidant content (GSH, SOD, and CAT). Hence, Viagra can control hyperglycemia which promotes free radical formation [38]. And it has a long-term protective effect on brain oxidative stress [35]. This is achieved by direct inhibition of oxidase activities and ROS formation [39,40]. Also, it has been shown that the anti-oxidative action of Viagra may have a crucial role in modifying the vascular complications in the brain of diabetic patients [38,41]. From our present study, the inhibitory effect of Viagra on lipid peroxidation and high antioxidant levels may be attributed to increased bioactive NO whose main action is to activate soluble guanylate cyclase which results in increased cGMP level [42].

Natural compounds or synthetic drugs that possess high antioxidant properties are regarded as intervention of oxidative damage [43]. The levels of GSH of our present study in the testes and brain were significantly elevated. The GSH levels were much higher in the testes than the brain. The marked elevation of GSH levels in testes may be linked to the high accumulation of the drug. This indicates that the therapeutic dose of the drug (Viagra) is not deleterious when taken for erectile dysfunction. This may also protect sperm from the endogenous havoc induced by free radicals and reacting oxygen species. Similarly, therapeutic dose of Viagra protects the brain from many assaults that may arise from reactive oxygen species.

Generally, Superoxide dismutase (SOD) catalyzed to scavenge excess superoxide anions and convert them to H_2O_2 [32]. Biphasic fluxes of SOD activities are common, increase or decrease may relate to the presence of excess superoxides [44]. In our present investigation, SOD activity in both testes and brain tissues increased significantly in dose dependent manner. Testes SOD activity was higher than brain SOD activity. Increased SOD activity in both tissues may be linked to increased de novo synthesis of SOD protein or irreversible activation of enzyme proteins from either decreased or increased free radical production resulting from oxygen metabolism in the mitochondria [18,45,46].Study had reported that decreased SOD activity reflects oxidative stress. Hence, our results showed increased SOD activity suggesting quick elimination of superoxide anions from the body.

Moreover, CAT scavenges H_2O_2 generated by free radicals or by SOD during the removal of superoxide anions and converts it to water [46]. Catalase also has a secondary role in the metabolism of ethanol [17]. Our data revealed that CAT activity in both tissues increased significantly. The CAT activity of the testes was higher than the brain. This may be linked to its prolonged effects on the erectile tissue by inhibiting the hydrolysis of cGMP, thereby making nitric oxide to act longer. Also, increased CAT activity may be attributed to excess H_2O_2 production resulting from other intermediary metabolism or induction of lipid peroxidation in the testes. Therefore, an increased

CAT activity in the testes indicates efficient elimination of toxic H_2O_2 from the tissues.

Natural adverse histopathologic changes in the testes ranging from mild congestion to interstitial oedema were observed in the control of experimental rats. The present data elucidated that Viagra was able to naturally protect these histopathologic changes. Collectively, the present study reveals that sub-chronic administration of therapeutic dose of Viagra to male rats induced lipid peroxidation only in the testes. It potentiated the antioxidant defense systems both in the brain and testes. This suggests the adverse effect of Viagra on testicular lipid peroxidation. In view of the importance of this drug in clinical practice, the relevance of our study to humans merits further investigation on the modulatory effects of medicinal plants over the drug.

Conflict of Interest

The authors declare that there are no conflicts of interest and that the authors of this manuscript have no financial or personal relationship with any organization which could influence the work.

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Author Affiliations

Top

[1]*College of Pure and Applied Sciences, Department of Biosciences and Biotechnology, Biochemistry unit (Drug Metabolism and Toxicology), Kwara State University, Malete, Ilorin, Nigeria*
[2]*Department of Chemical Sciences, Biochemistry unit, College of Natural and Applied Sciences, Bells University of Technology Ota, Ogun State, Nigeria*
[3]*Faculty of Basic Medical Sciences, Department of Biochemistry, Membrane Biochemistry and Biotechnology, University of Ibadan, Nigeria*
[4]*College of Pure and Applied Sciences, Department of Biosciences and Biotechnology, Plant and Environmental Biology unit, Kwara State University, Malete, Ilorin, Nigeria*
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