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Original Article:

The effects of sildenafil ciltrate on the lateral geniculate body of adult Wistar rats (*Rattus norvegicus*)- A histological study

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Abstract:
The histological effect of oral administration of sildenafil citrate (Viagra), commonly used as an aphrodisiac and for the treatment of erectile dysfunction on one of the visual relay centres namely the lateral geniculate body (LGB) of adult Wistar rat was carefully studied. The rats of both sexes (n=24), average weight of 202g were randomly assigned into three treatment (n=18) and control (n=6) groups. The rats in the treatment groups 'A', 'B' and 'C' received respectively, 0.25mg/kg, 0.70mg/kg and 1.43mg/kg body weight of sildenafil citrate base dissolved in distilled water daily for 30 days, through orogastric feeding tube, while that of the control group D, received equal volume of distilled water daily during the period of the experiment. The rats were fed with growers' mash obtained from Edo Feeds and Flour Mill Ltd, Ewu, Edo State, Nigeria and were given water liberally. The rats were sacrificed on day thirty-one of the experiment. The lateral geniculate body (LGB) was carefully dissected out and quickly fixed in 10% formal saline for histological studies. The histological findings after H&E method indicated that the treated section of the lateral geniculate body (LGB) showed some varying degree of reduced cellular population based on its sparse distribution, degenerative changes, cellular hypertrophy, and intercellular vacuolations appearing in the stroma. Varying dosage and long administration of sildenafil citrate may have some deleterious effects on the neurons of the intracranial visual relay centre and this may probably have some adverse effects on visual sensibilities by its deleterious effects on the cells of the lateral geniculate body (LGB) of adult Wistar rats. It is therefore recommended that further studies aimed at corroborating these observations be carried out.
Key Words: Sildenafil citrate, lateral geniculate body, decreased cellular population, cellular hypertrophy, vacuolations, Wistar rats

Introduction:
Erectile dysfunction (ED or "male impotence") is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis sufficient for satisfactory sexual performance (1) and is indicated when an erection is consistently difficult or impossible to produce, despite arousal.(2) There are various and often multiple underlying causes, some of which are treatable medical conditions such as cardiovascular disease and diabetes, neurological problems (for example, trauma from prostatectomy surgery), hormonal insufficiencies (hypogonadism) and drug side effects or psychological. It is important to realize that erectile dysfunction can signal underlying risk for cardiovascular disease.(3) ED is a serious medical and social problem which occurs in 10%-52% in men and 25%-63% in women.(4)

An understanding of the physiological mechanism of erection has led to the development of new oral therapies for erectile dysfunction that target different sites in the sexual arousal process. Apomorphine activates the arousal center of the brain. Phentolamine increases penile blood flow. Sildenafil enhances the action of nitric oxide, an endothelial-derived vasodilator and smooth muscle relaxant. These developments constitute a significant advance in a much-neglected area of male medicine.(5)

Sildenafil citrate is widely used as an effective and safe oral treatment for erectile dysfunction of various etiologies.(6) It is a potent and selective inhibitor of phosphodiesterase type 5 enzymes that acts to break down cyclic guanosine monophosphate (cGMP).(7) Accumulation of cGMP inhibits the degradation of nitric oxide that is responsible for smooth muscle relaxation within the corpora cavernosa. Nitric oxide is released by intracavernous nonadrenergic noncholinergic nerve terminals not only following a central or local erectogenic stimulus but also during rapid eye movement (REM) sleep.(8) Psychogenic erectile dysfunction (ED) patients are excellent candidates for sildenafil citrate therapy due to the intact neurovascular pathway. Nevertheless, the drug has been reported to be effective only in about 78% of patients with psychogenic ED.(9) It is likely that performance anxiety and sympathetic overtone are the cause of this unresponsiveness to sildenafil citrate during awakening, though data supporting this assumption are lacking.(10) The drug has been found to be effective and well tolerated in men with mild to moderate erectile dysfunction of no clinically identifiable organic cause.(11)

With the presence of PDE5 in choroidal and retinal vessels sildenafil citrate increase choroidal blood flow and cause vasodilatation of the retinal vasculature. The most common symptoms are a blue tinge to vision and an increased sensitivity to

light.(12) Adverse effects include headache, visual and retinal disturbances, dizziness and pupil-sparing third nerve palsy. (13) It has been reported that Sildenafil citrate significantly improves nocturnal penile erections in sildenafil non-responding patients with psychogenic erectile dysfunction.(14) Several pharmacological and physiological properties of sildenafil have been described.(15-18)

In Nigeria, most individuals often use sildenafil citrate indiscriminately for sexual arousal. There is a growing apprehension that it could be harmful or injurious to the body. Though sildenafil is currently being used to treat erectile dysfunction in patients with multiple sclerosis, Parkinson disease, multisystem atrophy, and spinal cord injury by improving their neurologically related erectile dysfunction, conversely, it has been implicated in a number of neurological problems, such as intracerebral hemorrhage, migraine, seizure, transient global amnesia, nonarteritic anterior ischemic optic neuropathy, macular degeneration, branch retinal artery occlusion, and ocular muscle palsies. Although sildenafil shows some promise as a therapeutic agent in selected neurological disorders, well-designed clinical trials are needed before the agent can be recommended for use in any neurological disorder.(19)

The lateral geniculate body and superior colliculus constitute the intracranial visual relay centres. The Lateral geniculate body in mammals is considered as part of the thalamic nuclei for processing visual information.(20) In rats the Lateral geniculate body receives input from the geniculate leaflet, which participates in the regulation of circadian function through its projection to the circadian pacemaker of the hypothalamus. (21)

The effects of sildenafil citrate on the intracranial visual relay centre may not have been documented, but there have been reports that it may be implicated in varied symptoms of dizziness, headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision, severe hypotension, myocardial infarction (heart attack), ventricular arrhythmias, stroke, increased intraocular pressure and sudden hearing loss.(22,23)

Some sildenafil users have complained of seeing everything tinted blue (cyanopsia).(24)

In July 2005, the U.S. Food and Drug Administration found that sildenafil could lead to vision impairment in rare cases (25), and a number of studies have linked sildenafil use with nonarteritic anterior ischemic optic neuropathy.(26-30)

This work was performed in order to investigate potential histological effects of sildenafil citrate on the lateral geniculate body of adult Wistar rats

Materials and Methods:
Twenty-four (24) adult Wistar rats of both sexes with average weight of 202g were randomly assigned into four groups A, B, C and D of (n=6) in each group. Groups A, B, and C of (n=18) serves as treatments groups while group D (n=-6) was the control. The rats were obtained and maintained in the Animal holdings of the Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin city, Nigeria. They were fed with growers' mash obtained from Edo feed and flour mill limited, Ewu, Edo state, and were given water liberally. The rats were allowed to gain maximum acclimatization before the actual commencement of the experiment. The sildenafil citrate tablets were obtained from the University of Benin Teaching Hospital Pharmacy, Benin City, Edo state, Nigeria.

The rats in the treatment groups (A, B, & C) received respectively, 0.25mg/kg, 0.70mg/kg and 1.43mg/kg body weight of sildenafil citrate base dissolved in distilled water daily for 30 days, through orogastric feeding tube, while that of the control group D, received equal volume of distilled water daily during the period of the experiment. The rats were sacrificed by cervical dislocation on day thirty-one of the experiment. The skulls were opened using bone forceps to expose the brain of the rat, and the lateral geniculate body was quickly dissected out and fixed in10% formal saline for routine histological techniques.

The tissue was dehydrated in an ascending grade of alcohol (ethanol), cleared in xylene and embedded in paraffin wax. Serial sections of 7 microns thick were obtained using a rotatory microtome. Some of the deparaffinized sections were stained routinely with hematoxylin and eosin (H&E) method. (31) The digital photomicrographs of the desired sections were made in the Department of Anatomy research laboratory, University of Benin, Nigeria for further observations.

Results:
Photomicrographs of the sections of the lateral geniculate body (LGB) from the control group (D) showed normal histological features, with the neurons appearing distinct and the glial cells normal without vacuolation in the stroma (Figure 1). The sections of the lateral geniculate body (LGB) from the treatment (A, B, & C) groups showed some varying degree of reduced cellular population, based on its sparse distribution, degenerative changes, cellular hypertrophy, and intercellular vacuolations appearing in the stroma. (Figure 2, 3 &4)

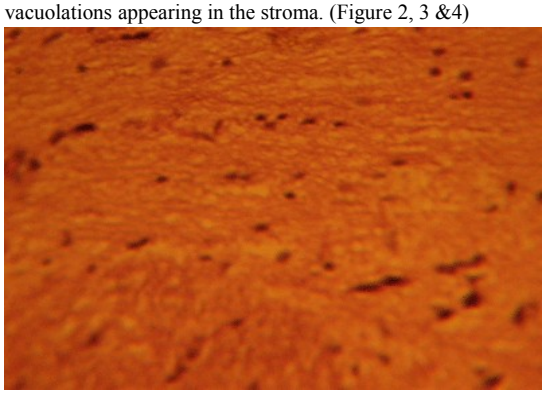

Fig.1: Control section of the lateral geniculate body (Mag. x400)

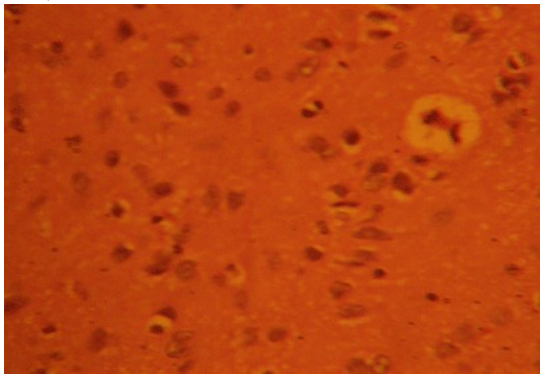

Fig. 2: Photomicrograph of treatment section of the lateral geniculate body of rats that received 0.25mg/kg of sildenafil citrate base dissolved in distilled water daily for 30 days (Mag. X400)

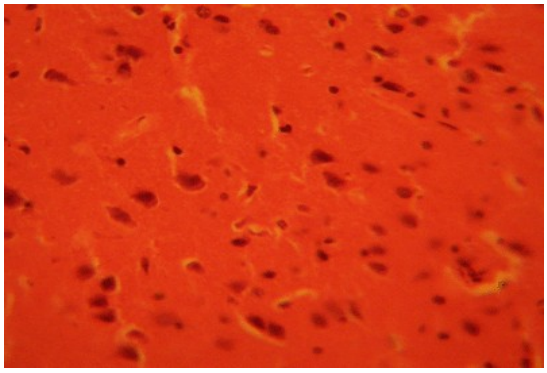

Fig. 3: Photomicrograph of treatment section of the lateral geniculate body of rats that received 0.70mg/kg of sildenafil citrate base dissolved in distilled water daily for 30 days (Mag. X400)

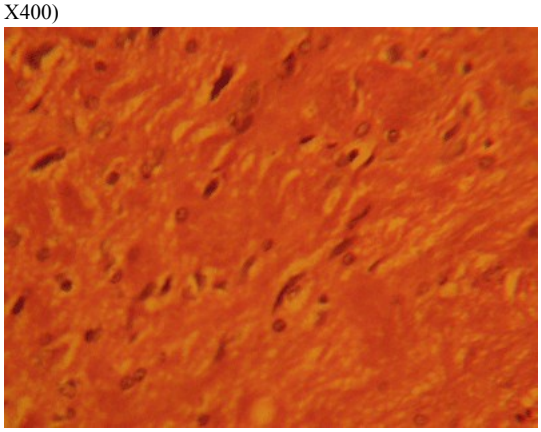

Fig. 4: Photomicrograph of treatment section of the lateral geniculate body of rats that received 1.43mg/kg of sildenafil citrate base dissolved in distilled water daily for 30 days (Mag. X400)

Discussion:

The results (H & E) revealed that administration of sildenafil citrate showed some varied degree of cellular degenerative changes, cellular hypertrophy, clustering of cells and intercellular vacuolations appearing in the stroma of the treatment groups compared to the control section of the lateral geniculate body of the adult Wistar rat. Neuronal degeneration has been reported to result in cell death, which is of two types, namely apoptotic and necrotic cell death. These two types differ morphologically and biochemically.(32) Pathological or accidental cell death is regarded as necrotic and could result from extrinsic insults to the cell such as osmotic, thermal, toxic and traumatic effects.(33) It was reported that cell death in response to neurotoxins might trigger an apoptotic death pathway within brain cells.(34)

The process of cellular necrosis involves disruption of the membranes structural and functional integrity. Cellular necrosis is not induced by stimuli intrinsic to the cells as in programmed cell death (PCD), but by an abrupt environmental perturbation and departure from the normal physiological conditions.(35) There is the need to further investigate the actual mechanism by which sildenafil citrate induced neuronal degeneration in the lateral geniculate body of adult Wistar rat in this study.

Extensive cell death in the central nervous system is present in all neurodegenerative diseases.(34) The type of nerve cell loss and the particular part of the brain affected dictate the symptoms associated with an individual disease.(34) In this study sildenafil citrate may have acted as toxin to the cells of the lateral geniculate body (LGB), affecting their cellular integrity and causing defect in membrane permeability and cell volume homeostasis.

In cellular necrosis, the rate of progression depends on the severity of the environmental insults. The principle holds true for toxicological insult to the brain and other organs.(35) The prime candidates for inducing the massive cell destruction observed in neurodegeneration are neurotoxins.(34) The latter when present at a critical level can be toxic to the brain cells they normally excite.(34) It is inferred from this results that prolonged and high dose of sildenafil citrate resulted in increased toxic effects on the LGB.

The vacuolations observed in the stroma of the lateral geniculate body in this experiment may be due to sildenafil citrate interference. The cellular hypertrophy observed in this experiment may be due to the adverse effects of sildenafil citrate on the lateral geniculate body. This study may underlie the possible neurological symptoms such as dizziness and tinnitus. Sildenafil citrate has been implicated as a possible cause of blindness: diagnosed as nonarteritic anterior ischemic optic neuropathy.(26,28-30)

Conclusions:

Our study revealed that high doses and long term administration of sildenafil citrate caused some varied degree of cellular degenerative changes, spares cellular population, cellular hypertrophy and vacuolations in the lateral geniculate body of adult Wistar rats. These results may probably affect the functions of the lateral geniculate body in visual sensibility in adult Wistar rats.

It is recommended that further studies be carried out to examine these findings.

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