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Full Length Research Paper

Histological Analysis of Sildenafil Citrate's Impact on the Medial Geniculate Body in Adult Wistar Rats

A. O. Eweka[1]* and A. B. Eweka[2]

[1]Department of Anatomy, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Edo State, Nigeria.

[2]School of Nursing, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria.

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The histological effect of oral administration of sildenafil citrate (Viagra), commonly used as an aphrodisiac and for the treatment of erectile dysfunction on the medial geniculate body of adult Wistar rat was carefully studied. The rats of both sexes (n=24), average weight of 202 g 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, 0.25, 0.70 and 1.43 mg/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 medial geniculate body 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 medial geniculate body showed some decreased cellular population, degenerative changes, cellular hypertrophy, with some vacuolations appearing in the stroma, with the group that received higher doses of sildenafil citrate (1.43 mg/kg) more severe. These findings indicate that sildenafil citrate consumption may have some deleterious effects on the medial geniculate body of adult Wistar rats at higher doses and by extension may affect the functions of the medial geniculate body and this may probably have some adverse effects on auditory sensibilities by its deleterious effects on the cells of the medial geniculate body of adult Wistar rats. It is therefore recommended that further studies aimed at corroborating these observations be carried out.

Key words: Sildenafil citrate, medial geniculate body, degenerative changes, Wistar rats.

INTRODUCTION

Sildenafil citrate is widely used as an effective and safe oral treatment for erectile dysfunction of various etiologies (Goldstein et al., 1998; Cheitlin et al., 1999; Benchekroun et al., 2003). It is a potent and selective inhibitor of phosphodiesterase type 5 enzymes that acts to break down cyclic guanosine monophosphate (cGMP) (Boolell et al., 1996). The medication amplifies the effect of sexual stimulation by retarding the degradation of this enzyme. Sildenafil has been found effective in several subpopulations of men with erectile dysfunction, including sufferers from diabetes (Basu and Ryder, 2004), hypertension (Feldman et al., 1999), spinal cord injuries (Hultling et al., 2000; Deforge et al., 2006), multiple sclerosis (Fowler et al., 2005), depression (Seidman et al., 2001; Rosen et al., 2004; Tignol et al., 2004; Fava et al., 2006), PTSD (Orr et al., 2006), and schizophrenia (Aviv et al., 2004; Gopalakrishnan et al., 2006), men after resection of the prostate or radical prostatectomy (Nandipati et al., 2006), after renal transplant (Sharma et al., 2006), men on dialysis (Dachille et al., 2006), and men aged 65 years and older (Wagner et al., 2001;

*Corresponding author. E-mail: andreweweka@yahoo.com. Tel: +2348023390890, +2348038665346, +2348055216031.

Carson, 2004).

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 (McMahon et al., 2000). It is likely that performance anxiety and sympathetic over-tone are the cause of this unresponsiveness to sildenafil citrate during awakening, though data supporting this assumption are lacking (Rosen, 2001). 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 (Eardley, 2001).

With the presence of PDE5 in choroidal and retinal vessels sildenafil citrate increase choroidal blood flow and cause vasodilation of the retinal vasculature. The most common symptoms are a blue tinge to vision and an increased sensitivity to light (Kerr and Danesh-Meyer, 2009). Adverse effects include headache, visual and retinal disturbances, dizziness and pupil-sparing third nerve palsy (Monastero et al., 2001). There have been reports of non-arteritic anterior ischaemic optic neuropathy and serous macular detachment in users of PDE5 inhibitors, although a causal relationship has not been conclusively shown. Despite the role of cGMP in the production and drainage of aqueous humor these medications do not appear to alter intraocular pressure and are safe in patients with glaucoma. All PDE5 inhibitors weakly inhibit PDE6 located in rod and cone photoreceptors resulting in mild and transient visual symptoms that correlate with plasma concentrations. Psychophysical tests reveal no effect on visual acuity, visual fields or contrast sensitivity; however, some studies show a mild and reversible impairment of blue-green colour discrimination. PDE5 inhibitors transiently alter retinal function on electroretinogram testing but do not appear to be retinotoxic. Despite the role of cyclic nucleotides in tear production there is no detrimental effect on tear film quality. Based on the available evi-dence PDE5 inhibitors have a good ocular safety profile (Kerr and Danesh-Meyer, 2009).

It has been reported that sildenafil citrate significantly improves nocturnal penile erections in sildenafil non-responding patients with psychogenic erectile dysfunction (Abdel-Naser et al., 2004). Several pharmacological and physiological properties of sildenafil have been described (Cheitlin et al., 1999; Aviv et al., 2004; Galie et al., 2005; Hoeper et al., 2006).

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. Thus, preclinical and very limited clinical data suggest that sildenafil may have therapeutic potential in selected neurological disorders. However, numerous reports are available regarding neurological adverse events ascribed to the drug. 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 (Farooq et al., 2008).

The inferior colliculus and medial geniculate body constitute the intracranial auditory relay centres. The medial geniculate body is the target of ascending projections from the inferior colliculus and descending input from the auditory cortex; this is the obligatory synaptic target in the thalamus for hearing. It contains interleaved and overlapping tonotopic and aural bands (Fall, 1999). The cerebral cortex strongly affects the medial geniculate body through descending projections which are thought to consist primarily of small areas with slow conduction velocities (Winner, 1996). Cerebral nuclei such as the medial and lateral geniculate bodies, inferior and superior colliculi have higher glucose utilization than other structures. There is also a correlation between functional activity and metabolic rate such as in the visual and auditory system (Siesjo, 1978). The effects of sildenafil citrate on the intracranial auditory relay centre may not have been documented, but there have been reports that it may be implicated in varied symptoms of dizziness, vomiting, headaches, diarrhea, tinnitus, increase hearing loss, macular rash, neutronpenia, migraine, seizure, transient global amnesia, nonarteritic anterior ischemic optic neuropathy, macular degeneration, branch retinal artery occlusion, and ocular muscle palsies.

It is probable that the adverse effects of sildenafil citrate on hearing such as tinnitus may be due to direct effect of sildenafil citrate on this auditory relay centre. This present study was to elucidate the histological effects of sildenafil citrate on the medial geniculate body of adult Wistar rats.

MATERIALS AND METHODS

Animals

Twenty-four (24) adult Wistar rats of both sexes with average weight of 202 g 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 grower's marsh 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. Sildenafil citrate tablet were obtained from the University of Benin Teaching Hospital Pharmacy, Benin City, Edo state, Nigeria.

Sildenafil citrate administration

The rats in the treatment groups (A, B, and C) received respectively, 0.25, 0.70 and 1.43 mg/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 medial geniculate body was quickly dissected out and fixed in10% formal saline for routine histological techniques.

Histological study

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 (Drury, 1967). The digital photomicrographs of the desired sections were made in the Department of Anatomy research laboratory, University of Benin, Nigeria for further observations.

RESULT

Photomicrographs of the sections of the medial geniculate (MGB) 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 medial geniculate body from the treatment (A, B, and C) groups showed some decrease in cellular population, degenerative changes, cellular hypertrophy and vacuolations appearing in the stroma (Figures 2, 3 and 4).

DISCUSSION

The results (H & E) revealed that administration of sildenafil citrate showed some varied degree of cellular degenerative changes, cellular hypertrophy, decrease cell population and intercellular vacuolations appearing in the stroma of the treatment groups compared to the control section of the medial 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 (Wyllie, 1980). 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 (Farber, 1981). It was reported that cell death in response to neurotoxins might trigger an apoptotic death pathway within brain cells (Waters, 1994).

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

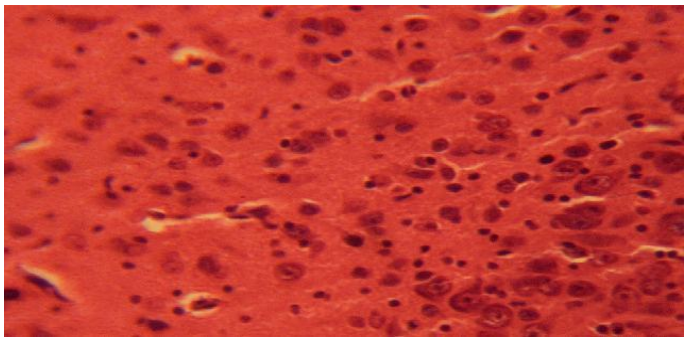

Figure 1. Group D: Control section of the medial geniculate body (Mag. x400).

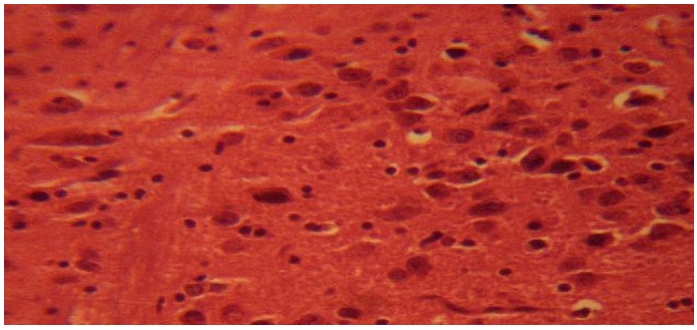

Figure 2. Photomicrograph of treatment section of the medial geniculate body of rats that received 0.25 mg/kg of sildenafil citrate base dissolved in distilled water daily for 30 days (Mag. X400).

environmental perturbation and departure from the normal physiological conditions (Martins, 1978). There is the need to further investigate the actual mechanism by which sildenafil citrate induced neuronal degeneration in the medial geniculate body of adult Wistar rat in this study.

Extensive cell death in the central nervous system is present in all neurodegenerative diseases (Waters, 1994). The type of nerve cell loss and the particular part of the brain affected dictate the symptoms associated with an individual disease (Waters, 1994). In this study sildenafil citrate may have acted as toxin to the cells of the medial geniculate body, 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 (Martins, 1998). The prime candidates for inducing the massive cell destruction observed in neurodegeneration are neurotoxins (Waters, 1994). The latter when present at a critical level can be toxic to the brain cells they normally excite (Waters, 1994). It is inferred from this results that prolonged and high dose of sildenafil citrate resulted in increased toxic effects on the medial geniculate body.

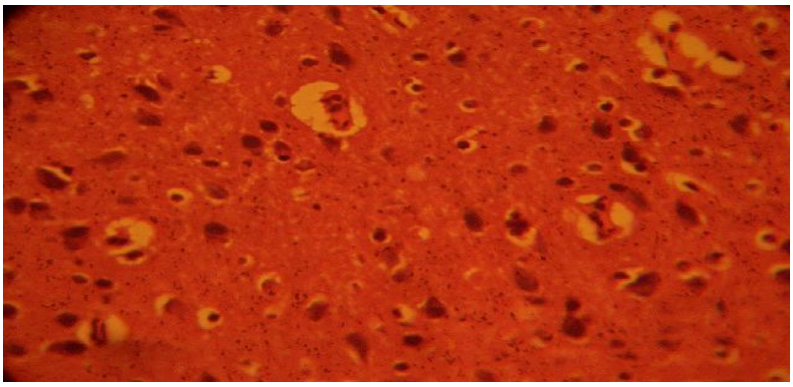

Figure 3. Photomicrograph of treatment section of the medial geniculate body of rats that received 0.70 mg/kg of sildenafil citrate base dissolved in distilled water daily for 30 days (Mag. X400).

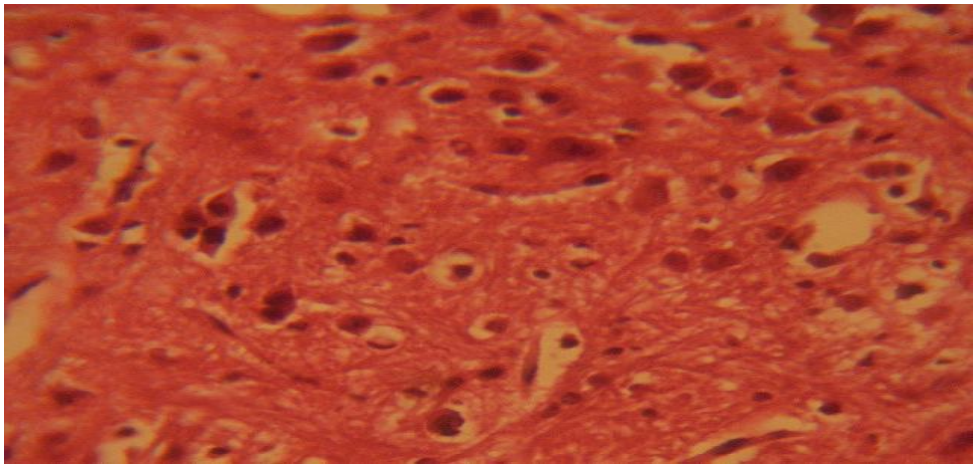

Figure 4. Photomicrograph of treatment section of the medial geniculate body of rats that received 1.43 mg/kg of sildenafil citrate base dissolved in distilled water daily for 30 days (Mag. X400).

The vacuolations observed in the stroma of the medial 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 medial 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 (Cunningham and Smith, 2001; Pomeranz et al., 2002; Pomeranz and Bhavsar, 2005).

CONCLUSION

Our study revealed that high doses and long term administration of sildenafil citrate caused some varied degree of cellular degenerative changes, cellular hypertrophy, clustering of cells and intercellular vacuolations in the medial geniculate body of adult Wistar rats. These results may probably affect the functions of the medial geniculate body in auditory sensibility in adult Wistar rats. It is recommended that further studies be carried out to examine these findings.

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