ORIGINAL COMMUNICATION

Anatomy Journal of Africa. 2015. Vol 4(1): 534 - 548

MORPHOLOGICAL EFFECTS OF CHRONIC ADMINISTRATION OF ZIDOVUDINE ON THE VISUAL RELAY CENTRES OF ADULT WISTAR RATS

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ABSTRACT

The oxidative stress effects in chronic administration of Zidovudine (ZDV) on vision had also been reported. The objective of this study was to investigate how ZDV induced morphological changes in the tissues. The rats of both sexes (N=40), with an average weight of 200g were equally but simple randomly assigned into treatment and control groups. Each animal in the treatment group received approximately 0.857mg/200g of ZDV twice daily (on the basis of 300mg/70kg body weight dosage). The findings indicated that there was a significant ($p < 0.05$) increase in the weight of the treated superior colliculus and decrease in the weight of the treated lateral geniculate body as compared to their corresponding control group. The morphological changes were consistent with previous findings, which include cellular changes such as hypertrophy, unevenly distributed cellular population, and vacuolations in the stroma of the treated tissues as compared to the control group. The toxic effects of ZDV on the morphology of the intracranial visual relay centres of the tested adult wistar rats observed in this experiment may underline some of the possible neurological symptoms reported concerning ZDV treatments in human.

Keywords: Zidovudine, Morphological effects, Superior Colliculus, Lateral Geniculate Body, Wistar Rats

INTRODUCTION

The lateral geniculate body (LGB) and superior colliculus (SC) constitute the intracranial visual relay centres responsible for visuomotor behavior (Peck *et al*., 1979; Marotte, 1990). While the lateral geniculate body in the thalamic nuclei may be processing visual information (Piscopo *et al*., 2013), the superior colliculus is concerned with ocular movement including control and regulation of many movements of the eye and head (Altman and Bayer, 1981; Leigh *et al*., 1997). Previous studies have indicated that common HIV antiretroviral drugs have adverse effects on the intracranial visual relay centres of adult Wistar rats. For instance, chronic administration of efavirenz was reported to cause cellular degenerative changes (Adjene *et al*., 2010), and oxidative stress (Adjene *et al*., 2011).

Just like efavirenz, Zidovudine is yet another antiretroviral drug that has loss of vision as one of the side effects (Lalonde *et al*., 1991; Geier *et al*., 1993). However, the effect of chronic administration of ZDV on the microanatomy of intracranial relay centres has yet to be really studied. Radiological case studies have indicated that vision impairment could be associated with lesion and neuronal inflammations in lateral geniculate bodies and superior colliculus (Bert *et al*., 2004). On this basis, coupled with previous finding of cellular degeneration in experimental chronic administration of efavirenz (Adjene *et al*., 2010), the objective was to investigate morphological effects of chronic administration of ZDV on intracranial visual relay centres of adult Wistar rats, especially with a view to determine corroboration with previous findings.

MATERIALS AND METHODS

Animals care and Ethics: This study was a continuation of a series of doctoral research work on brain, including the intracranial visual relay centres. The Faculty of Basic Medical Sciences, Delta State University, Abraka granted approval before the commencement of the work. Forty adult wistar rats of both sexes with average weight of about 200g were randomly assigned into two groups: control (n_1=20) and test (n_2=20). The rats were obtained and maintained in the Animal Holding of the Department of Anatomy and Cell Biology, Faculty of Basic Medical Science, Delta State University, Abraka. They were fed with grower's mash obtained from Edo Feeds and Flour Mill Limited, Ewu, Edo State, Nigeria and given water liberally. ZDV was obtained from the President Emergency Plan for AIDS Relief (PEPFAR) Unit, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria.

Drug administration: The rats in the test group received 300mg/70kg (0.857mg/200g) body weight of ZDV being the dosages required twice daily. The drug was dissolved in distilled water and administered twice daily for thirty days through the orogastric tube while the control rats received equal volume of distilled water through the same route and for the same period.

Dissection of superior colliculi and lateral geniculate body: The head of the sacrificed rat was recovered after cervical dislocation and the skull was quickly opened with the aid of a pair of bone forceps to expose the brain, dried and weighed. The superior colliculi and lateral geniculate body were carefully dissected out using a sharp scapel blade, blotted dried, weighed using Toledo weighing balance and were quickly fixed in 15% formal saline for further routine histological techniques.

Histological study: The tissues were dehydrated in an ascending grades of alcohol (ethanol), cleared in xylene and embedded in paraffin wax. Serial sections of about 6μm thick were obtained using a rotatory microtome. The deparaffinised sections were stained routinely with haematoxylin and eosin method (Drury *et al.*, 1976). Photomicrographs of the desired results were obtained using research photographic microscope in the Department of Anatomy and Cell Biology, Faculty of Basic Medical Science, Delta State University, Abraka, Nigeria.

Data Management: The parametric data were analyzed using the statistical package for social sciences (SPSS version 21) for unpaired student t-test. A p value of <0.05 was considered significant.

RESULTS

The findings indicated that there was a significant ($p < 0.05$) increase in the weight (g) and relative weight (%) of the tested superior colliculus and a significant ($p < 0.05$) decrease in the weight (g) and relative weight (%) of the tested lateral geniculate body as compared to their corresponding control group (Table 1).

The desired histological sections of the superior colliculus and lateral geniculate body from the control animals showed normal histological features with the neurons appearing distinct and of various sizes. The neurons and glial cells appeared normal and there was no vacuolation in the stroma of the sections (Figures 1 & 3). The histological section of the superior colliculus and lateral geniculate body of the tested group revealed some cellular changes such as hypertrophy, unevenly distributed cellular population, pyknotic nuclei with some cellular congestions and vacuolations in the stroma of the superior colliculus and lateral geniculate body as

compared to their corresponding control group (Figures 2 & 4).

Table 1: The mean weights (g) and mean relative weights (%) of the superior colliculus (SC) and lateral geniculate body (LGB) of the animals

		Control (n=20)	Treatment (n=20)
Brain weight. (g)		1.65 ± 0.03	1.81 ± 0.04
Superior colliculus	Absolute weight (g)	0.08 ± 0.01	0.16 ± 0.03
	Relative weight (%)	4.84 ± 0.48	9.07 ± 1.42
Lateral geniculate body	Absolute weight (g)	0.28 ± 0.02	0.21 ± 0.02
	Relative weight (%)	17.28 ± 1.11	11.81 ± 1.10

*Significant (P< 0.05)

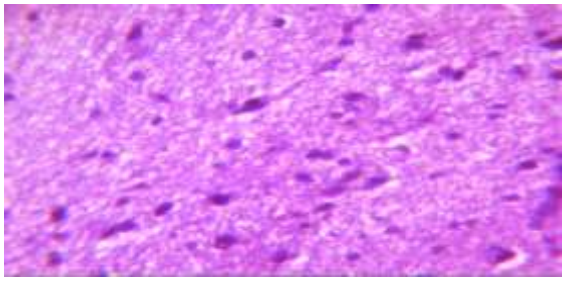

Figure 1: Control section of SC (H&E method x400)

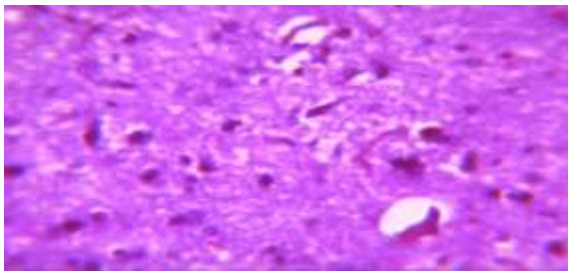

Figure 2: Tested section of SC with AZT (H&E method x400)

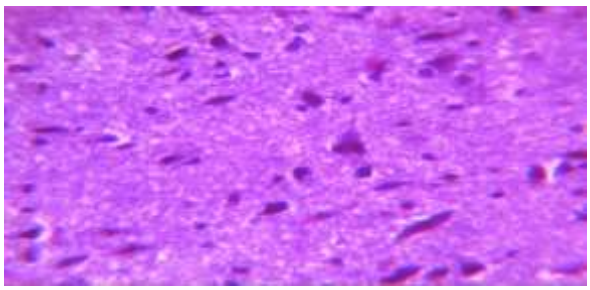

Figure 3: Control section of LGB (H&E method x400)

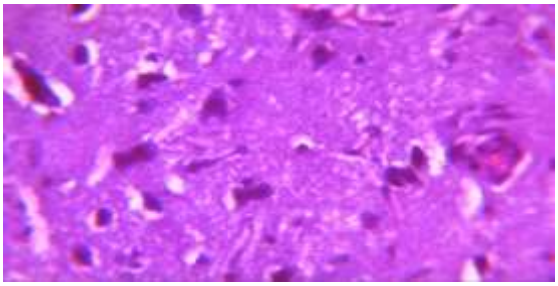

Figure 4: Tested section of LGB with AZT (H&E method x400)

DISCUSSION

Ischemic or pharmacologic disruption of cellular transporters can cause swelling of the brain parenchyma (Johanson, 1995). Under such conditions, there is a net shift of water from the extracellular space to the interior of the brain cells (Johanson, 1995). Cytotoxic edema usually involves intracellular swelling of glial, endothelia and neurons (Johanson, 1995). The significant ($p < 0.05$) increased in weight of the superior colliculus and significant ($p < 0.05$) decrease in weight of the lateral geniculate body might be due to neurotoxic effects of ZDV on the cells of the brain of the adult wistar rats.

Regulation of brain water content and therefore of the volume is critical for maintaining the intracranial pressure within tolerable limits (Johanson, 1995). In this study, ZDV could have acted as toxins to the cells of the superior colliculus and lateral geniculate body thus affecting their cellular integrity and causing a defect in membrane permeability and cell volume homeostasis. ZDV is known to cross blood brain barrier and could get access to the cells of the brain. As brain tissue swells or shrinks as reported in this study, the activity of the cellular transporters is approximately modified by the up or down regulations as reported in the case of hyponatremia or hypernatremia (Johanson, 1995). Ischemia or pharmacologic disruption of cellular transporters can cause swelling of parenchyma of the superior colliculus and lateral geniculate body. The pharmacologic disruption of ZDV is a cardinal feature in this experiment. There are many different causes of cell swelling, including drug poisoning, water intoxication, hypoxia, and acute hyponatremia (Johanson, 1995). Under such conditions, there is a net shift of water from the extracellular space to the interior of the brain cells (Johanson, 1995). This usually involves intracellular swellings or shrinkage of the glial, endothelia and neurons (Johanson, 1995). Brains swelling attendant to severe cytotoxic oedema may lead to marked reduction in the size of the ventricular system and basal cisterns (Johanson, 1995).

The histological section of the tested superior colliculus and lateral geniculate body revealed some cellular changes such as hypertrophy, uneven distribution of cellular population, pyknotic nuclei with some cellular congestions and vacuolations as compared to the corresponding control group. Neuronal degeneration was reported to result in cell death, which could differ morphologically and biochemically (Wyllie, 1980). The process of cellular necrosis involves disruption of the membranes structural and functional integrity. The vacuolations observed in the stroma of the superior colliculus and lateral geniculate body in this experiment may be due to ZDV interference, since it is known to cross blood brain barrier and thus getting access to the cells of the brain.

Extensive cell death in the central nervous system is present in all neurodegenerative diseases (Waters *et al.*, 1994). The type of nerve cell loss and the particular part of the brain affected dictate the symptoms associated with an individual disease (Waters *et al.*, 1994). In this study, ZDV may have acted as a toxin to the cells of the superior colliculus and lateral geniculate body, thus affecting their cellular integrity and causing defect in membrane permeability and cell volume homeostasis.

It could be inferred from this study that chronic administration of ZDV to adult wistar rats resulted in increased toxic effects on the superior colliculus and lateral geniculate body. This study is in consonance with the earlier reports which documented that chronic administration of efavirenz to an adult wistar rats revealed some cellular degenerative changes and vacuolations in the colliculi and geniculate bodies (Adjene *et al.*, 2010; Adjene and Momah, 2010; Adjene and Igbigbi, 2010; Adjene *et al.*, 2011). The decrease in cellular population observed in this study may have been due to cell death caused by the ZDV.

The cellular congestion and vacuolations observed in the stroma of the superior colliculus and lateral geniculate body in this experiment may be due to ZDV interference, since it is known to cross blood brain barrier and thus getting access to the cells of the brain. Since the neurons of the central nervous system are affected by ZDV (Igbigbi *et al.*, 2013; Igbigbi *et al.*, 2014a; Igbigbi *et al.*, 2014b), it is probable that the results obtained in this experiment may have been due to the neurotoxic effect of ZDV on the neuronal cells of the superior colliculus and lateral geniculate body of the tested adult wistar rats.

The toxic effects of ZDV on the morphology of the intracranial visual relay centres of the

tested adult wistar rats observed in this experiment may underline some of the possible neurological symptoms reported concerning ZDV treatments in human.

Conflict of interest: The authors declare that there is no conflict of interest.

Acknowledgement: We sincerely acknowledge with thanks the PEPFAR unit of the University of Benin Teaching Hospital for the gift of zidovudine used in this study.

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