Effects of Chronic Administration of Efavirenz on the Inferior Colliculus of Adult Wistar Rats

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Efavirenz is used for highly active antiretroviral therapy for the treatment of human immunodeficiency virus type-1. We studied the effect of chronic administration of efavirenz on the inferior colliculus of adult Wistar rats. Rats of both sexes (n=16) were randomly assigned into treatment (n=8) and control (n=8) groups. The treatment group received 600mg/70kg body weight of efavirenz dissolved in distilled water daily for 30 days through an orogastric tube, and controls received distilled water. The rats were sacrificed on the 31st day of the experiment. We found that treated rats had cellular degenerative changes such as a sparse cellular population, hypertrophy, microcystic changes, and vacuolation in the stroma of the inferior colliculus in treated rats compared with controls. Chronic administration of efavirenz may adversely affect the auditory system by affecting the microanatomy of the inferior colliculus of adult Wistar rats.

Key Words: efavirenz; human immunodeficiency virus; inferior colliculus; Wistar rats

Introduction

Efavirenz is an antiretroviral drug that belongs to the class of drugs called nonnucleoside reverse transcriptase inhibitors used as part of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) type-1. Efavirenz is effective in many combination regimes for the treatment of HIV infection, in both previously untreated individuals and in those undergoing treatment. It has been successfully combined with nucleoside analogs consisting of lamivudine or emtricitabine plus abacavir, didanosine, stavudine, tenofovir or zidovudine to achieve virological suppression in a high percentage of recipients. Most antiviral agents do not efficiently penetrate the blood brain barrier or are actively transported out of the central nervous system. Even after antiviral treatment successfully controls the virus in the treatment compartments, the central nervous system may suffer continued damage induced by HIV infection. Efavirenz may be taken once a day without a meal, and it can penetrate the central nervous system and spinal fluids.

Efavirenz has emerged as a cornerstone of HAART regimens. However, some adverse effects in the central nervous system have been associated with efavirenz. The most common central nervous system effects include confusion, insomnia, abnormal vivid dreams, dizziness and headaches. The side effect profile of the drug is generally regarded as satisfactory, despite some conflicting study results.
in the medical literature, as well as conflicting studies from patients and physicians regarding the neuropsychiatric problems associated with efavirenz. Lipodystrophy, moderate or severe pain, abnormal vision, arthralgia, asthenia, dyspnea, gynecomastia, myalgia, myopathy, and tinnitus have been reported with efavirenz use.

The inferior colliculus is the obligatory midbrain synaptic target of the ascending auditory pathway in which the contralateral ear is primarily represented. The inferior colliculus is essential for normal hearing and for the startle reflex. It receives its ascending input mainly from the contralateral cochlear nucleus and the superior olive, and it sends axons to the medial geniculate body.

Cortical structures such as the medial and lateral geniculate bodies, and inferior and superior colliculi exhibit higher glucose use than other structures. There is a correlation between functional activity and metabolic rate in the visual and auditory system. Since efavirenz crosses the blood brain barrier, it is important to determine its effect on the inferior colliculus. It is probable that the adverse effects of efavirenz on hearing, such as tinnitus, may be due to direct effects of efavirenz on the inferior colliculus. The present study aimed to elucidate the effects of chronic administration of efavirenz on the inferior colliculus of adult Wistar rats.

Materials and Methods

Animals

Adult Wistar rats of both sexes (n=16), with an average weight of 200 g, were randomly assigned into two groups: control (n=8) and treatment (n=8). The rats were obtained and maintained in the Animal Holding of the Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin City, Edo State, Nigeria. They were fed with grower’s mash obtained from Edo Feeds and Flour Mill Limited (Ewu, Edo State, Nigeria) and given liberal access to water. Efavirenz was obtained from the President’s Emergency Plan for Aids Relief unit, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria.

Drug administration

The rats in the treatment group received the recommended daily dosage of 600 mg/70 kg body weight of efavirenz dissolved in distilled water for 30 days through orogastric tube administration, while the control rats received an equal volume of distilled water through the same route and for the same period of time. The rats were sacrificed by cervical dislocation on the 31st day of the experiment.

Histological study

The tissues were dehydrated in an ascending grade of alcohol (ethanol), cleared in xylene, and then embedded in paraffin wax. Serial sections 7 μm in thickness were obtained using a rotatory microtome. The deparaffinized sections were stained routinely with hematoxylin and eosin.

Photomicrographs of the results were obtained using a research photographic microscope in the Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin city, Edo State, Nigeria.

Results

Sections of the inferior colliculus from control animals showed normal histological features with the neurons appearing distinct and within the normal range of sizes. Neuronal and glial cells appeared normal, and no vacuolation in the stroma of the sections was observed (Figure 1).

The inferior colliculus of the treated group showed cellular degenerative changes such as a sparse cellular population, hypertrophy, microcystic changes, and vacuolation in the stroma compared with the control group (Figure 2).

Discussion

Our study showed that efavirenz treatment resulted in various cellular degenerative changes such as a
Effects of efavirenz on the inferior colliculus

Sparse cellular population, hypertrophy, microcystic changes and vacuolation in the stroma of the inferior colliculus compared with controls.

Neuronal degeneration has been reported to result in cell death, which consists of two types, apoptotic and necrotic cell death. These two types of cell death differ morphologically and biochemically. Pathological or accidental cell death is regarded as necrotic, and can result from extrinsic insults to the cell such as osmotic, thermal, toxic, and traumatic effects. It has been reported that cell death in response to neurotoxins might trigger an apoptotic death pathway within brain cells. The process of cellular necrosis involves disruption of the structural and functional integrity of the membranes. Cellular necrosis is not induced by stimuli intrinsic to cells as in programmed cell death, but by an abrupt environmental perturbation and departure from normal physiological conditions. Further investigation into the actual mechanism by which efavirenz induces neuronal degeneration in the inferior colliculus of adult rats is required.

Extensive cell death in the central nervous system is present in all neurodegenerative diseases. The type of nerve cell loss and the particular part of the brain affected dictate the symptoms associated with an individual disease. In our study, efavirenz may have acted as a toxin to cells of the inferior colliculus, affecting their cellular integrity and causing defects in membrane permeability and cell volume homeostasis.

In cellular necrosis, the rate of progression depends on the severity of the environmental insult. The greater the severity of the insult, the more rapid the progression of neuronal injury. This principle holds true for toxicological insults to the brain and other organs. Prime candidates for inducing massive cell destruction observed in neurodegeneration are neurotoxins. These substances may be present in small amounts in the environment, or even naturally occurring chemicals such as glutamate used by the brain as transmitter’s substances. When glutamate is present at a critical level it can be toxic to brain cells. Our study results suggested that prolonged administration of efavirenz resulted in increased toxic effects on the inferior colliculus. The decrease in cellular population observed in this study may have resulted from cell death caused by the toxic effects of efavirenz. Similarly, it has been reported that chronic administration of chloroquine results in cellular degenerative changes, a sparse cellular population and vacuolation appearing in the stroma with some autophagic vacuoles in the inferior colliculus and medial geniculate body of adult Wistar rats. The microcystic changes and vacuolation observed in the stroma of the inferior colliculus in this experiment may have been due to efavirenz interference, since it is known to cross the blood brain barrier, and thus access cells of the brain. The results observed in this experiment may have been due to the adverse effects of efavirenz on the inferior colliculus, since it has been reported that chronic administration of efavirenz affects the weight of the brain and inferior colliculus in adult Wistar rats. This previous study showed that there was a significant decrease (p<0.05) in dry brain weight, and an increase in the relative dry brain weight of the treatment group compared with controls. There was also a significant increase (p<0.05) in the relative weight of the dry inferior colliculus as well as per total dry brain weight in the treatment group compared with controls. Since the neurons of the central nervous system are affected by efavirenz, it is probable that the results obtained in our experiment may have been due to the neurotoxic effects of efavirenz on the neuronal cells of the inferior colliculus of adult Wistar rats.

Ischemic or pharmacologic disruption of cellular transporters can cause swelling of the brain parenchyma. Under such conditions, there is a net shift of water from the extracellular space to the interior of the brain cells. Cytotoxic edema usually involves intracellular swelling of glial, endothelial, and neuronal cells. The microcystic changes and vacuolation in the stroma of the treated inferior colliculus reported in our experiment may have been due to the neurotoxic effect of efavirenz on cells of the inferior colliculus. Regulation of brain water content, and therefore, volume, is critical for maintaining the intracranial pressure within tolerable limits. Since efavirenz affects the weight of the brain and that of the inferior colliculus in adult Wistar rats, in our study, efavirenz could have acted as a toxin to

Figure 2. Treated section of inferior colliculus (hematoxylin and eosin, 400×).
cells of the inferior colliculus, thus affecting their cellular integrity and causing a defect in membrane permeability and cell volume homeostasis. The prime candidates for inducing a massive increase in cell volume observed in neurodegeneration are neurotoxins.  

As brain tissue shrinks or swells, as reported in this study, the activity of cellular transporters is modified by up-regulation or down-regulation such as in the case of hyponatremia or hypernatremia.  

Ischemia or pharmacological disruption of cellular transporters can cause swelling of parenchyma of the brain and in the inferior colliculus. Pharmacological disruption of the inferior colliculus caused by efavirenz was a cardinal feature of our experiment. However, there are many different causes of cellular swelling, including drug poisoning, water intoxication, hypoxia, and acute hyponatremia. Under such conditions, there is a net shift of water from the extracellular space to the interior of the brain cells. In our experiment, we observed intracellular swelling of glial, endothelial and neuronal cells. Brain swelling along with severe cytotoxic edema may lead to a marked reduction in the size of the ventricular system and basal cisterns.

The toxic effects of efavirenz on the microanatomy and weight of the inferior colliculus on rats highlights the potential neurological symptoms, such as lipodystrophy, moderate or severe pain, abnormal vision, arthralgia, asthenia, dyspnea, gynecomastia, myalgia, myopathy and tinnitus reported among patients receiving efavirenz treatment.

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