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Motor and memory function in rat models of cyanide toxicity and vascular occlusion induced ischemic injury

Olalekan Michael Ogundele [a,*], Philip Adeyemi Adeniyi [a], Duyilemi Chris Ajonijebu [b], Amin Abdulbasit [c], Ansa Emmanuel Cobham [d], Azeez Olakunle Ishola [d], Gbolahan Wasiu Balogun [d]

[a] *Department of Anatomy, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria*
[b] *Department of Physiology, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria*
[c] *Department of Physiology, College of Health Sciences, University of Ilorin, Ilorin, Kwara State, Nigeria*
[d] *Department of Anatomy, College of Health Sciences, University of Ilorin, Ilorin, Kwara State, Nigeria*

Abstract

Although oxidative stress is characteristic of global vascular occlusion and cyanide toxicity, the pattern of cerebral metabolism reconditioning and rate of progression or reversal of neural tissue damage differ for both forms of ischemia. Thus, it is important to compare cognitive and motor functions in both models of ischemia involving cyanide treatment (CN) and vascular occlusion (VO).

Adult Wistar rats ($N = 30$) were divided into three groups; VO ($n = 12$), CN ($n = 12$) and Control-CO ($n = 6$). The CN was treated with 30 mg/Kg of potassium cyanide (KCN); VO was subjected to global vascular occlusion-both for duration of 10 days. The control (CO) was fed on normal rat chow and water for the same duration. At day 10, the test and control groups (CN, VO and CO) were subjected to motor function tests (Table edge tests and Open Field Test) and memory function tests (Y-Maze and Novel object recognition) while the withdrawal groups CN-I and VO-I were subjected to the same set of tests at day 20 (the withdrawal phase).

The results show that both cyanide toxicity and vascular occlusion caused a decline in motor and memory function when compared with the control. Also, the cyanide treatment produced a more rapid decline in these behavioral parameters when compared with the vascular occlusion during the treatment phase. After the withdrawal phase, cyanide treatment (CN-I) showed either an improvement or restoration of motor and memory function when compared to the CN and control. Withdrawal of vascular occlusion caused no improvement, and in some cases a decline in motor and memory function.

In conclusion, cyanide toxicity caused a decline in motor and memory function after the treatment while vascular occlusion caused no significant decline in cognition and motor function at this time. After the withdrawal phase, the effect of cyanide toxicity was reduced and significant improvements were observed in the behavioral tests (motor and cognitive), while a decline in these functions were seen in the vascular occlusion group after this phase.

Keywords: Cyanide; Ischemia; Vascular occlusion; Cognition; Memory; Motor function

1. Introduction

Cerebral blood flow is an important part of brain metabolism as it is evident from stroke and metabolic poisoning, such as cyanide toxicity [1]. The blood vessels are specialized structures and can adjust blood flow patterns to meet regional requirements of various parts of the brain during normal and oxygen deprived states [1,2]. All of these are reflected in cognition, memory, movement and neurological activities expressed in the behavior of organisms both in normal and diseased states.

Stroke is a major cause of death and disability in humans [3,4]. It is often life threatening with most patients suffering from disabilities such as palsy, memory loss and

* Corresponding author at: Department of Anatomy, College of Medicine and Health Sciences, College Building II, 2nd Floor, Room G14, Km 8.5 Afe Babalola Way, Ado-Ekiti, Nigeria. Tel.: +234 7031022702.
E-mail addresses: ola.ogundele@abuad.edu.ng, mikealslaw@hotmail.com (O.M. Ogundele).

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speech impairment requiring extra care and management therapies [5,6]. Stroke can also be described as an acute event with long term economic, psychological and social impacts on the patients as they often suffer from isolation, mood disturbances, communication difficulties and movement disorders experienced by these patients [7]. Cyanide poisoning on the other hand induces ischemia by inhibition of mitochondria respiration. The effect is rapid and death could occur within hours in extreme cases [8]. In acute slow treatment or exposure, neurological symptoms, neuropathies and degenerative effects have been described [8,9]. Osuntokun and co-workers in 1981, described several degenerative changes in the population exposed to cassava based diet; leading to loss of cognition, Parkinson like symptoms, retrobulbar neuritis, tropical ataxic neuropathy (TAN) and spastic endemic paraparesis (Konzo) [10]. The incidence of these diseases is often associated with exposure to cyanide from the environment, industrial waste and consumption of cyanophoric plants [11,12].

The role of diet in stroke and cyanide poisoning has been described by several authors [13–16]. Fruits and vegetables, being the source of flavonoids, phenols, carotenoids, and anthocyanin are important anti-inflammatory and antioxidants in stroke preventions and management [17,18]. Consumption of protein rich diets have also been reported to reduce the severity of cyanide poisoning and neurodegenerative changes in cassava endemic regions by aiding the removal of cyanide as thiocynate through the interaction between CN and sulphur containing amino acids [8,14–16]. In both forms of ischemia, that is, vascular occlusion (model for stroke) and cyanide toxicity, induction of oxidative stress, degenerative changes, cognitive impairment, movement impairment and neuropathies are common [19,20]. This is suggestive that ischemia is associated with both anatomical and behavioral deficits [21,22]. MRI studies have shown changes with basic neural networks that control and affect behavior, movement, speech, and cognition post ischemia [19,23,24]. Behavioral analysis in rodent models of GVO and cyanide treatment is important for explaining the underlying differences in the effect of the GVO and cyanide toxicity on memory and motor functions. In this study we have studied, comparatively, the variations in motor and cognitive functions in cyanide toxicity and vascular occlusion following a short-term treatment and withdrawal of the treatments.

2. Materials and methods

2.1. Animal preparation and treatment

Male adult Wistar rats ($N = 30$) were procured from the Animal Holding Facility of Afe Babalola University. The animals were then divided into three groups; $n = 12$, $n = 12$ and $n = 6$ (average weight was 250 g). The animals were allowed to acclimatize for 12 days under standard laboratory conditions and controlled environment of 12 h light/dark cycle with free access to food and water.

2.2. Treatment

A group of male rats ($n = 12$) were treated with orally administered potassium cyanide (KCN) at 30 mg/Kg body weight (BW) of KCN for 10 days by gavage (CN). A second set of adult male rats ($n = 6$) were fed on normal rat chow and treated with normal saline for the same duration (Control; CO). A separate group of $n = 12$ animals were subjected to transient occlusion of both carotid arteries, basilar artery and brachiocephalic vein with use of elastic neck cuff placed around the neck. The neck cuff was adjusted until the pressure of blood measured from the surface was about 30 mmHg above the neck cuff [36,37]. The use of elastic material as the neck cuff facilitated local irritation and inflammation around the occluded region by the 5th day. This was done for a total duration of 10 days following which the behavioral tests were administered to $n = 6$ animals each in the VO, CN and Control groups. The animals were handled carefully during the treatment using approved protocols by the institutional Animal Care and Ethics Committee. On the 11th day, KCN treatment was discontinued and the neck cuffs removed in $n = 6$ animals each, remaining in the VO and CN groups. These groups were renamed VO-I and CN-I as they represent the withdrawal groups for vascular occlusion and cyanide treatment respectively. At the end of the withdrawal phase, that is day 20, animals were subjected to motor and memory function tests.

2.2.1. Novel object recognition test (NOR)

Object recognition memory function was assessed using NOR test. A 75 cm × 50 cm × 30 cm transparent box was used. Three days prior to the habituation sessions, the rats were exposed to the box to familiarize with the environment. On the test days, they were exposed to two identical objects to acclimatize with for 5 min which is termed trial 1 (T1). The rats were then put inside a cage with food and water. Thirty minutes later, i.e. inter trial interval (ITI), the rats were placed back inside the box with one of the object replaced by a novel one for 5 min. The time used in rearing on the old (old time) and new object (new time) was recorded using a video camera suspended about 60 cm away from the habituation box. Animal rearing was measured when the nose of the animal is less than 2 cm from the object while sitting on the object is not considered [25].

$$\text{Memory index}(\%) = \frac{\text{Time spent on new object}}{\text{Total time spent on rearing both old and new object}} \times 100$$

2.2.2. Y-Maze

This is done to check the spatial working memory of the rats. The rats were placed facing the edge and were to make their arm decision. The duration for the test was 10 min. The