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Neuroprotective influence of taurine on fluoride-induced biochemical and behavioral deficits in rats

Isaac A. Adedara*, Amos O. Abolaji, Umar F. Idris, Bolanle F. Olabiyi, Esther M. Onibiyo, TeminiJesu D. Ojuade, Ebenezer O. Farombi

Drug Metabolism and Toxicology Research Laboratories, Department of Biochemistry, College of Medicine, University of Ibadan, Ibadan, Nigeria

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ABSTRACT

Epidemiological and experimental studies have demonstrated that excessive exposure to fluoride induced neurodevelopmental toxicity both in humans and animals. Taurine is a free intracellular β-amino acid with antioxidant and neuroprotective properties. The present study investigated the neuroprotective mechanism of taurine by evaluating the biochemical and behavioral characteristics in rats exposed to sodium fluoride (NaF) singly in drinking water at 15 mg/L alone or orally co-administered by gavage with taurine at 100 and 200 mg/kg body weight for 45 consecutive days. Locomotor behavior was assessed using video-tracking software during a 10-min trial in a novel environment while the brain structures namely the hypothalamus, cerebrum and cerebellum of the rats were processed for biochemical determinations. Results showed that taurine administration prevented NaF-induced locomotor and motor deficits namely decrease in total distance travelled, total body rotation, maximum speed, absolute turn angle along with weak forelimb grip, increased incidence of fecal pellets and time of grooming, immobility and negative geotaxis. The taurine mediated enhancement of the exploratory profiles of NaF-exposed rats was supported by track and occupancy plot analyses. Moreover, taurine prevented NaF-induced increase in hydrogen peroxide and lipid peroxidation levels but increased acetylcholinesterase and the antioxidant enzymes activities in the hypothalamus, cerebrum and cerebellum of the rats. Collectively, taurine protected against NaF-induced neurotoxicity via mechanisms involving the restoration of acetylcholinesterase activity and antioxidant status with concomitant inhibition of lipid peroxidation in the brain of rats.

1. Introduction

Fluoride is an essential chemical in the manufacture of fluoridated dental preparations and the fluoridation of drinking water [1]. The main sources of human exposure to fluoride are drinking water, food, dental products, and pesticides [2]. The acceptable limit of fluoride in drinking water ranged from 0.7 to 1.0 mg/L [3]. However, certain parts of the world including Africa, Asia and the Eastern Mediterranean could be exposed to contaminated water with fluoride concentration reaching up to 20 mg/L [4]. Excessive exposure to fluoride is well reported to cause several health problems including dental and skeletal fluorosis [5,6]. Furthermore, excessive fluoride exposure reportedly induced neurotoxicity which is associated with neurodegenerative changes. Epidemiological studies showed that children in high-fluoride areas had significantly lower intelligence quotient scores than those who lived in low-fluoride areas [7,8]. Consumption of fluoride in drinking water is associated with developmental neurotoxicity in children and adults [9] and psychiatric manifestations including lethargy, memory impairment and thinking difficulties were evident in industrial workers chronically exposed to fluoride [10].

The simultaneous occurrence of fluoride and aluminum in drinking water has been demonstrated to result in the formation of lipid-soluble complexes (Aluminofluoride complexes) which cross the blood brain barrier and accumulate in the cerebral tissues [11,12]. The penetrated fluoride complexes consequently impair the central nervous system function via different neurotoxic mechanisms. Specifically, fluoride neurotoxicity has been reported to include alterations in metabolism of brain protein, biogenic amine levels, nucleic acid content, proteolytic enzymes activities along with increased oxidative stress and DNA damage in the brain [13].

* Corresponding author.
E-mail address: dedac2001@yahoo.co.uk (I.A. Adedara).

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Moreover, subchronic fluoride exposure caused a significant reduction in the levels of glutamate transporters, nicotinic acetylcholine receptor and mitochondrial energy enzymes [14,15]. Moreover, acetylcholine is an essential neurotransmitter required for the regulation of motor function, locomotion and exploration [16]. The hydrolysis acetylcholine at synapses by acetylcholinesterase (AChE) is one of the most important mechanisms responsible for normal cholinergic function. Alteration in AChE activity has been associated with cognitive and neurobehavioral deficits observed in patients with neurodegenerative diseases [17,18].

Taurine (2-aminoethane sulfonic acid) is a free intracellular β-amino acid. The biosynthesis of taurine in human occurs primarily in the liver via oxidation and decarboxylation of the amino acid, cysteine [19]. However, dietary taurine is ingested from meat and especially from sea foods. Taurine is well reported to elicit numerous physiological functions including cytoprotective effects, membrane stabilization, antioxidant and anti-inflammatory activities, modulation of intracellular calcium and neurotransmitters concentration [19–21]. Interestingly, the cytoprotective influence of taurine on fluoride-induced oxidative stress and cell death in hepatocytes *in vitro* has been reported [22]. Recently, taurine reportedly ameliorated fluoride-induced renal and thyroid dysfunctions in rats via mechanisms involving the reduction of oxidative stress indices, augmentation of antioxidant enzymes activities, and enhancement of the functional status of the thyroid system [23]. Although the widely reported beneficial health effects of taurine have been attributed to its multiple actions on cellular functions, there is no information in literature on the effects of taurine on the neurotoxicity due exposure to fluoride.

Thus, the present study was designed to investigate the relevance of taurine in the protection against fluoride-induced neurotoxicity by assessing some biochemical endpoints and the neurobehavioral characteristics namely the locomotor and exploratory profiles in rats. A standard behavioral protocol for evaluating novelty-associated behavioral stress responses [24,25] was employed, using a video-tracking software (ANY-maze, Stoelting CO, USA). Subsequently, acetylcholinesterase (AChE) activity, as well as antioxidant and oxidative stress biomarkers were analyzed in the hypothalamus, cerebrum and cerebellum of the experimental rats.

2. Materials and methods

2.1. Chemicals

Sodium fluoride (NaF), taurine (2-aminoethanesulfonic acid), thiobarbituric acid (TBA), epinephrine, glutathione, hydrogen peroxide, 1-chloro-2,4-dinitrobenzene (CDNB), trichloroacetic acid (TCA) and 5′,5′-dithio-bis-2-nitrobenzoic acid (DTNB) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All other reagents were of analytical grade and were obtained from the British Drug Houses (Poole, Dorset, UK).

2.2. Animal model

Sixty adult male Wistar rats weighing between 120 g and 140 g obtained from the Department of Biochemistry, University of Ibadan, Ibadan were used for this study. The animals were housed in plastic cages placed in a well-ventilated vivarium and subjected to natural photoperiod of 12-hr light: 12-hr dark. They were fed with rat chow and given drinking water *ad libitum* for a week before the commencement of the experiment. All the animals received humane care according to the conditions stated in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science (NAS) and published by the National Institute of Health. The experimental protocols were carried out after approval by the University of Ibadan Ethical Committee.

2.3. Experimental protocol

The animals were randomly assigned to five groups of twelve rats each and were treated for 45 consecutive days as follows:

Group I (Control): Rats received drinking water alone.
Group II (NaF alone): Rats were exposed to NaF alone in drinking water at 15 mg/L.
Group III (TAU alone): Rats were orally administered taurine alone at a dose of 200 mg/kg.
Groups IV (NaF + TAU 1): Rats were co-administered with NaF and taurine at 100 mg/kg.
Groups V (NaF + TAU 2): Rats were co-administered with NaF and taurine at 200 mg/kg.

Stock solution of taurine (100 mg/ml) was prepared fresh every other day using drinking water as a vehicle. The doses of NaF and taurine used in the present study were selected based on the previously published data [23,26]. The gavage volumes for 100 and 200 mg/kg of taurine were about 160 and 320 μL of the stock solution, respectively.

2.4. Behavioral experiments in a novel environment

Twenty-four hours following the last treatment, the novel environment test was performed to assess the behavioral pattern of rats according to a standard procedure [24]. Briefly, the rats were randomly selected and placed in the center of the apparatus (wooden box of 56 cm width x 56 cm length x 20 cm height) and allowed to freely explore the arena. The behavior of the rats was filmed during a 10-min trial using a webcam (DNE webcam, Porto Alegre, Brazil) mounted above the apparatus and attached to a laptop. All experiments were conducted during the same time-period each day (from 10:00 a.m. to 4:00 p.m.) to maintain the same experimental conditions. The behavioral endpoints were automatically computed at a rate of 30 frames per second using video-tracking software (ANY-maze, Stoelting CO, USA). Necessary care was taken when transferring the rats from home cages to the novel environment to avoid stress associated with handling. All the rats were handled and tested using a standardized protocol (similar illumination, manipulation and time period in a day).

2.5. Determination of neurobehavioral parameters

Locomotor, motor and exploratory activities were analyzed in the novel environment in order to reflect habituation to novelty stress. The locomotor and motor patterns of the experimental rats were evaluated by behavioral endpoints including the maximum speed, total distance travelled, total time immobile, absolute turn angle and body rotation along with grooming time and fecal pellets. Analysis of the exploratory profile of the rats was performed using representative track and occupancy plots in order to evaluate the exploratory activity in the novel environment. The home base formation in the new environment during a trial was defined as a place in the arena for which the experimental animal showed a preference in terms of occupancy, and as a starting and ending point of exploratory tours [27]. The home base formation of the rats was confirmed by both track and occupancy plots.

2.6. Negative geotaxis

The rats were placed head down on an inclined board (45°) of