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Original Article

Sodium Fluoride Toxic Impact on the Histology of Albino Rat Cerebellar Cortex and Protective Role of Resveratrol

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ABSTRACT

Background: Fluoride is a toxic element that has a hazardous effect on the nervous tissue. Resveratrol (RSV) is a polyphenolic compound with strong antioxidant properties.

Aim: Using histopathological and immunohistochemical studies to evaluate the impact of NaF on the cerebellar cortex of albino rats and the protective effect of RSV.

Methods: In this investigation, forty adult male albino rats had been used. The animals were randomly divided into four groups, 10 in each. **Group I:** (**Negative control group**): No medications were given. **Group II: (Positive control group)**: Animals were given 30 mg/kg of RSV one time per day. **Group III: (NaF group):** Animals were given 10 mg/kg NaF one time per day. **Group IV: (NaF+RSV group):** Animals were given 10 mg/kg of NaF and 30 mg/kg of RSV one time per day. At the end of the 30-day experiment, the body weight of all animals was recorded, and then they were sacrificed. The cerebella were separated and weighed. Samples were processed for hematoxylin and eosin staining (H&E) for general structure and cytosolic aspartate specific cystiene protease (Caspase-3) immunohistochemical staining for apoptosis.

Results: NaF exposure obviously affected the rats' body weight and caused histopathological changes in the cortex of rats' cerebellum. RSV protected against such changes and reduced the apoptotic activity of NaF.

Conclusion: NaF exposure seriously affects the cortex of the cerebellum and induces apoptotic activity via the caspase-3 pathway. Co-administration of RSV along with NaF protected against the neurotoxic effects of NaF.

Keywords: Cerebellum, Sodium fluoride, Resveratrol, Caspase-3

INTRODUCTION

Fluoride is a natural component of the earth's crust and is frequently present in different environments [1]. It does not exist in an isolated form, always being associated with other elements forming fluoridated compounds [2]. NaF is one of the commonest inorganic forms of fluorides. Fluoride reaches our bodies through a variety of means, including toothpaste, mouthwashes, food supplements, and fluoride-containing polymeric surfaces in easily cleaned cookware. Water, on the other hand, continues to be the primary source of fluoride, accounting for more than 60% of overall fluoride consumption [3, 4]. Fluoride in small amounts is beneficial for normal bone mineralization and dental enamel formation [5]. Excess intake of fluoride can exhibit toxic effects on various organs and tissues [6]. Fluoride has the ability to pass through the blood barrier of the brain and accumulate in the CNS, causing neurological complications such as limb paralysis and spasticity, vertigo, and impaired mental acuity [7]. The cerebellum is a target organ for fluoride toxicity leading to degenerative changes in rat cerebellar cortex layers and cells especially the Purkinje cells [8,9]. Oxidative stress, free radical generation and lipid peroxidation were thought to be responsible for the pathogenesis of NaF-induced neurodegeneration [10]. Resveratrol is a naturally occurring non-flavonoid polyphenol that can be found in the skin of grapes, blueberries, peanuts and Senna. It has cardioprotective, antidiabetic, anticancer and neuroprotective

effects against depression and Alzheimer disease (AD) [11].

Using histopathological and immunohistochemical studies, the aim of this research was to assess the impact of NaF on the cortex of the cerebellum in relation to the beneficial effect of RSV.

MATERIAL AND METHODS

Chemicals

1- Sodium fluoride: It was purchased from Al-Kahira Company for pharmaceutical industries as a powder.

2- Resveratrol: It was purchased from the United Arab Emirates and manufactured by California Gold Nutrition as veggie capsules.

Experimental animals

In this investigation, forty adult male albino rats, weighing 250-300 gm, had been used. The animals were randomly divided into four groups, 10 in each. The animals were gotten from the animal house at Zagazig University's Faculty of Medicine. The animals were kept in a laboratory under proper control. All study procedures were carried out in compliance with the Zagazig University Institutional Animal Care and Use Committee's guidelines (ZU-IACUC) with an approval number of ZU-IACUC/3/F/181/2019.

Group I: (**Negative control group)**: They were given 2.5 ml distilled water without any medications.

Group II: (Positive control group): Animals were given 30 mg/kg of RSV [12] dissolved in 2.5 ml distilled water and mixed well before giving, one time per day by IGT.

Group III: (NaF group): Animals were given 10 mg/kg of NaF dissolved in distilled water one time per day by IGT [13].

Group IV: (NaF+RSV group): Animals were given 10 mg/kg of NaF and 30 mg/kg of RSV one time per day by IGT.

Methods

The animals were weighed at the end of the experiment, which lasted 30 days, then anaesthetized by intra-peritoneal injection of thiopental 75mg/kg [14]. The cranial cavity was opened, and then the cerebella were separated, weighed and managed for light microscopic examination and caspase-3 immunohistochemical staining. Area percent of caspase-3 immunoreactivity was measured by using the "Image J 1.49v/Java 1.6.0_244" software. Data analysis was done by the Statistical Package for Social Science (SPSS), software version 24.0. The data was shown in the form of mean ± standard deviation (SD). There is significance at P-value<0.05, high significance at P<0.001, and no significance at P≥0.05.

RESULTS

1- Rat body weights.

Data analysis regarding the mean final body weights showed a highly significant decrease in the NaF group in relation to control groups (P<0.001) and a significant decrease in relation to the NaF+RSV group (p<0.05). When compared to control groups, the NaF+RSV group had a significant decrease in mean final body weight (P<0.05) **(Table).**

2- Cerebellar weights

ANOVA test revealed no significant differences between the groups (p>0.05) regarding the cerebellar weight **(Fig. 1)**.

3- Light Microscopic Examination

H&E stain

The control (–ve) and control (+ve) stained sections revealed the same histological structure of the cerebellar cortex, so they were considered as one group, which was the control group. The control sections of adult male albino rats' cerebellar cortex showed that the superficial molecular cell layer (MCL) contained few scattered cells and fibers; the middle Purkinje cell layer (PCL) is one row of pear-shaped cells with vesicular nuclei, which are the Purkinje cells. The densely packed deep granular cell layer (GCL) is formed of small rounded granular cells and cerebellar islands between them **(Fig. 2A, 3A)**. As regarding the NaF sections, the PCL exhibited noticeable disturbances in the form of deeply stained irregular shrunken cells with hardly identified nuclei. Also, there was disarrangement of the Purkinje cells in addition to vacuolations in all layers **(Fig. 3B)**. Some congested blood capillaries were also observed **(Fig. 2B)**. Sections of the NaF+RSV group showed that some of the Purkinje were shrunken with hardly identified nuclei; others were normal and pyriform in shape with normal vesicular nuclei. Some vacuolations were also observed, but less than in the NaF group **(Fig. 2C, 3C)**.

Caspase-3 immunohistochemically stained sections showed:

In the control group, there was negative immunoreaction of caspase-3 within the 3 layers of the cortex **(Fig. 4A)**. Regarding the NaF group, there was strong positive immunoreaction of caspase-3, mainly nuclear, as shown in the nuclei of Purkinje cells with scattered immune positive cells in the MCL, PCL and GCL **(Fig.4B).** On the other hand, the NaF+RSV group showed moderate positive immunoreaction of caspase-3 mainly cytoplasmic as shown in the cytoplasm of Purkinje cells with scattered immune positive cells in the MCL, PCL and GCL **(Fig. 4C).**

4- Morphometric study

Data analysis considering the area percent of caspase-3 showed a highly significant increase in the NaF group in relation to control and NaF+RSV groups (P<0.001). When compared to the control group, the NaF+RSV group had a highly significant increase in the area percent of caspase-3 (P<0.001) **(Fig. 4D).**

Table 1: Comparisons between initial and final body weights.

	Control ve	***Control +ve***	***NaF group***	***NaF+RSV group***	***F***	***P*-value**	***Games-Howell***
Initial BW (gm)	287.3± 7.12	287.9± 8.5	286.1±8.75	287.7± 7.04	0.104	0.957 NS	-----
Final BW (gm)	321.8±6.2	320.2±7.76	252.7±28.24	292.55±18.16	34.1	<0.001**	0.956 NS [a] <0.001** [b] 0.003* [c] <0.001** [d] 0.004* [e] 0.009* [f]
	Control ve	***Control +ve***	***NaF group***	***NaF+RSV group***	***F***	***P*-value**	***Games-Howell***
Paired t	10.67	7.59	4.34	0.79			
p-value	<0.001**	<0.001**	0.002*	0.449 NS			

One-way ANOVA (F-test) followed by Games-Howell test. Paired t: Paired t test.
a: control -ve versus control +ve b: control -ve versus NaF group
c: control -ve versus NaF+RSV group d: control +ve versus NaF group
e: control +ve versus NaF+RSV f: NaF group versus NaF+RSV group
*: Significant (P<0.05) **: highly significant (p< 0.001).
NS: Non significant (P>0.05)

Figure 1: Bar chart showing comparison between different studied groups regarding mean values of cerebellar weight.

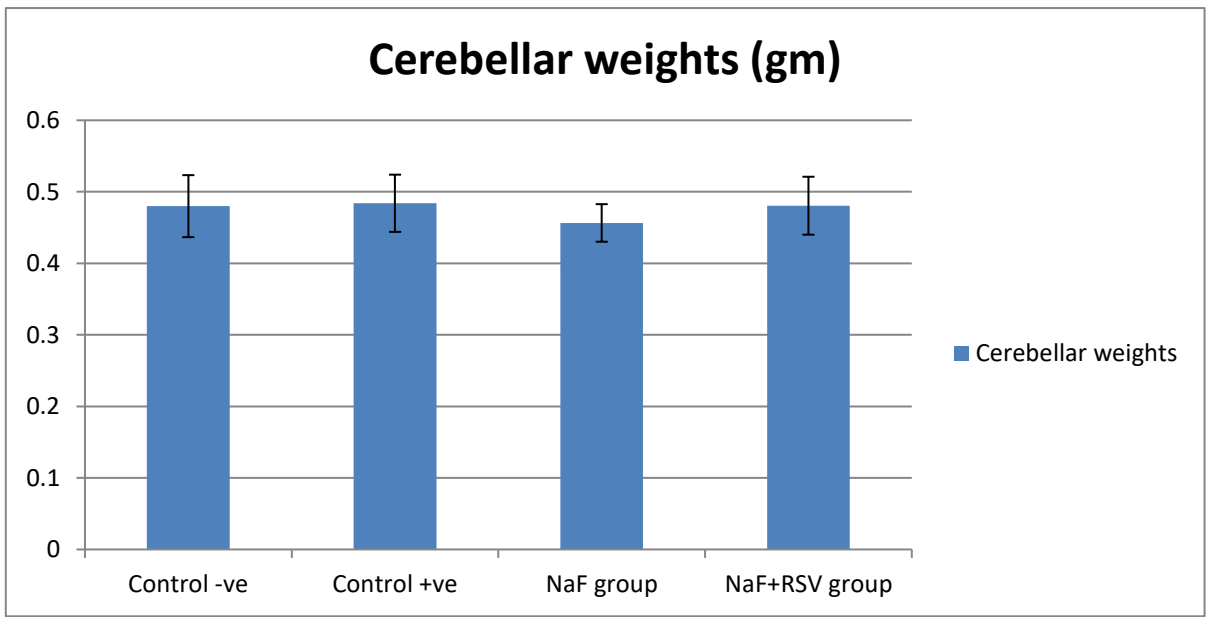

Figure 2: Photomicrographs of cerebellar cortex sections of different groups showing the cerebellar folia **(F)** separated by deep long sulci **(S)** and formed of 3 layers: outer **MCL**, middle **PCL** and inner **GCL** with a well-defined core of white matter **(WM)**. **A)** is the control group. **B)** is the NaF group with some congested blood capillaries **(Arrow heads). C)** is the NaF+RSV group. **[H&E X100]**

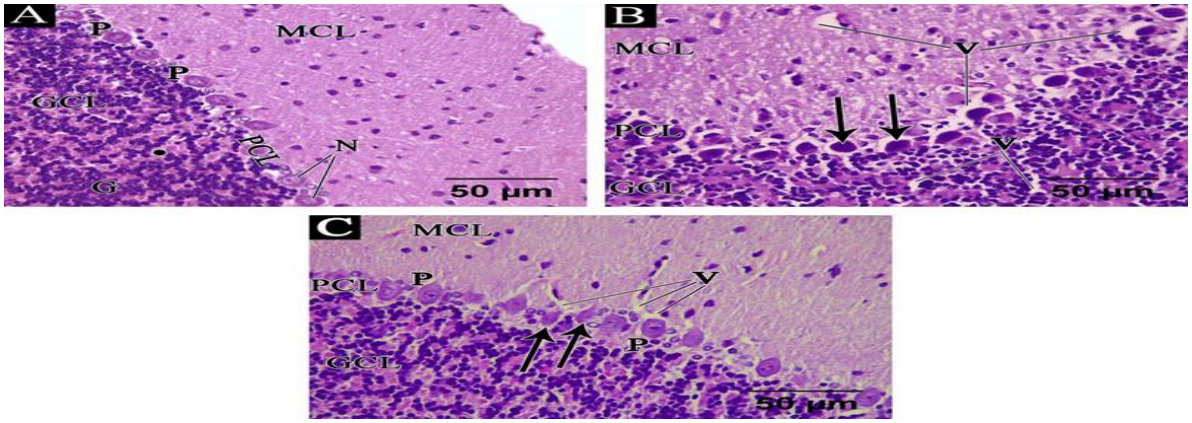

Figure 3: Photomicrographs of cerebellar cortex sections of different groups: **A)** Control group showing, outer **MCL**, **PCL** is formed of Purkinje cells **(P)** arranged in one row, they are large pear-shaped cells with central vesicular nuclei **(N)**. **GCL** is densely packed with small rounded granular cells **(G)** and cerebellar islands in-between **(Black star)**. **B)** NaF group showing deeply stained and shrunken Purkinje cells **(Arrows)** with irregular outlines and hardly identified nuclei. There are also vacuolations in all layers **(V)** . **C)** NaF+RSV group showing the **PCL** containing some cells which are shrunken **(Arrows)** with hardly identified nuclei. Others are normal and pyriform shaped **(P)** with normal vesicular nuclei. Some vacuolations were also observed **(V)**. **[H&E X400]**

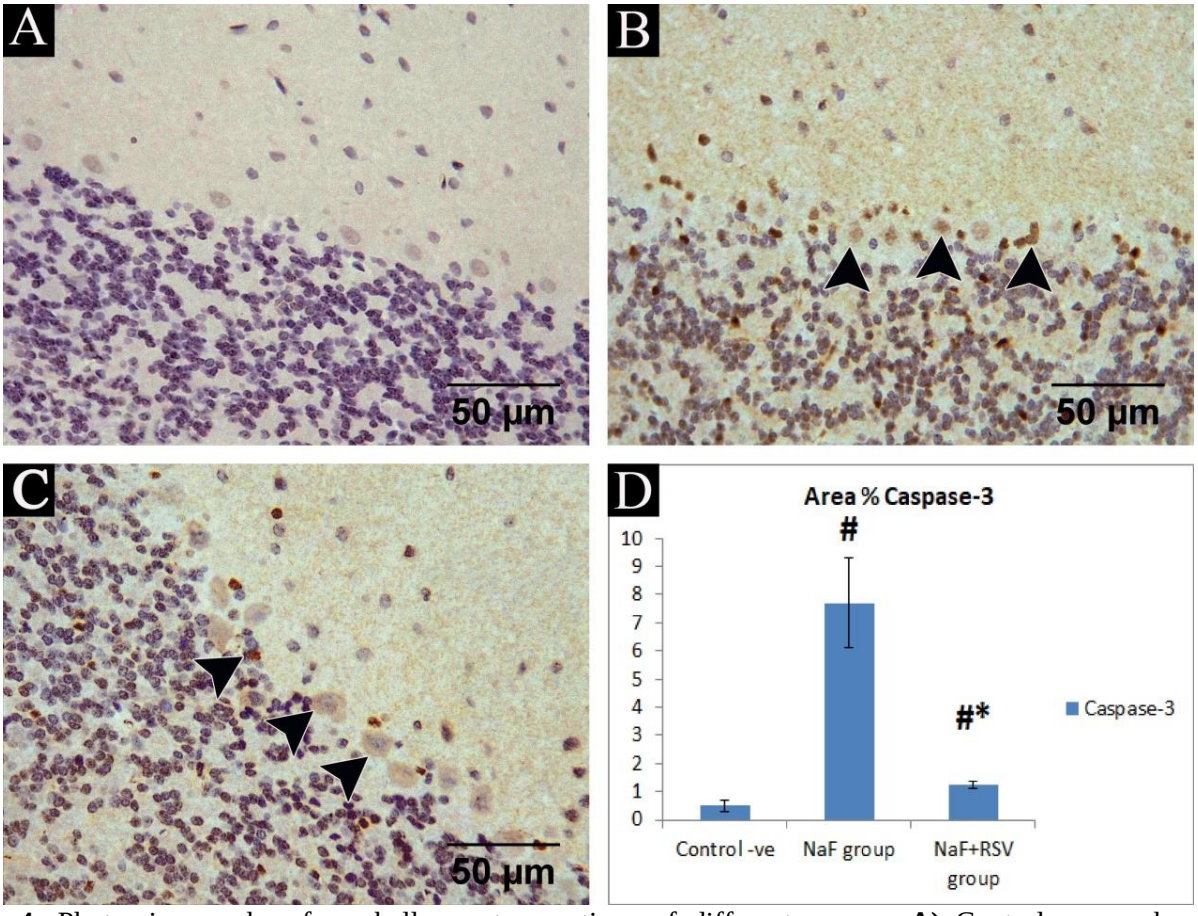

Fig. 4: Photomicrographs of cerebellar cortex sections of different groups: **A)** Control group showing negative caspase-3 immunoreaction within the **MCL**, **PCL** and **GCL**. **B**) NaF group showing strong positive immunoreaction of caspase-3 **(Arrow heads)** mainly nuclear as showed in the nuclei of Purkinje cells with

scattered immune positive cells in the **MCL**, **PCL** and **GCL**. **C)** NaF+RSV group showing moderate positive immunoreaction of caspase-3 **(Arrow heads)** mainly cytoplasmic as showed in the cytoplasm of Purkinje cells with scattered immune positive cells in the **MCL**, **PCL** and **GCL. D)** bar chart showing comparison between different studied groups regarding area percent of caspase-3, **#** Highly significant difference compared to the control group, $p<0.001$. ***** Highly significant difference compared to the NaF group, $p<0.001$. **[Caspase-3 × 400]**

DISCUSSION

In the present investigation, the mean final body weight of the NaF group was highly significantly lower than that of the control groups. This was consistent with the observations conducted by **Paul et al.** [15] who reported that decreased food intake together with the depletion of protein in soft tissues such as the liver and skeletal muscles led to inhibition of body weight gain. In addition, **Pal and Sarkar** [16] recorded a decrease in the organo-somatic index after fluoride exposure and related that to diminished food desire and malnourishment caused by fluoride, leading to retardation of animal growth. **Pushpalatha et al.** [17] confirmed that fluoride intake might cause digestive and absorption problems, resulting in brain malnutrition and retarded growth. Also, the decrease in body weight may be correlated to the direct corrosive effect of fluoride on the mucosa of the GIT [18]. On the contrary, **Agustina et al.** [13] documented that NaF treatment showed a highly significant increase in the mean body weight of rats compared to the control group. Also, **Lopes et al.** [19] stated that fluoride treatment did not impair the body weight gain of mice as changes in motor tasks were not related to differences in nutritional factors. Regarding the NaF+RSV group, there was a significant increase in the mean final body weight when related to the NaF group and a significant decrease when related to the control groups. In terms of cerebellar weights, the current study found that there were no statistically significant differences between groups and this was in agreement with **Agustina et al.** [13]. As regarding H&E stained sections, the NaF group displayed disruption of the histological architecture of the cortex of the cerebellum, chiefly the Purkinje cell layer. This was in line with **Al-Hayani et al.** [9] who gave NaF treatment for 6 weeks using a dosage of 20 mg/kg. **El-Dien et al.** [8] accounted for the irregularity of shape and disarrangement of Purkinje cells as an adaptation to rebuild new synaptic connections with other nerve cells. There were also areas of congestion in the cerebellar cortex. This was similar to the findings of **Al Badawi et al.** [20] who declared that NaF treatment caused blood capillary damage, resulting in cerebellar ischaemia and neuronal loss. The H&E stained sections regarding the NaF+RSV group exhibited that most Purkinje cells were keeping their usual form with a few cells which were affected. There were vacuolations to a lesser extent than in the NaF group. In the present study, caspase-3 immunostained sections of the NaF group showed strong positive immunoreaction of caspase-3 mainly nuclear with scattered immune positive cells in the three cortical layers. Caspase-3 is an apoptotic marker expressed in the cytoplasm and nucleus of cells. It plays a chief role in developmental and pathologic death in the nervous system. After caspase-3 cleavage and activation, it is translocated from the cytoplasm of the cell into its nucleus. This translocation results in DNA fragmentation and nuclear disruption [21,22,23]. Our results were consistent with those of **El-Khair et al.** [18] who declared positive caspase-3 immunoreactivity with brownish discoloration of the nucleus and cytoplasm of the neurons of the gray matter of the spinal cord in NaF treated rats. **Song et al.** [24] also discovered caspase-3 and caspase-9 proteins in the livers of NaF-treated rats. **Thangapandiyan and MiltonPrabu** [25] correlated fluoride's neuropathological implications with the binding of fluoride ions with antioxidants, which causes oxidative stress leading to cell damage and apoptosis. Moreover, **Refsnes et al.** [26] recorded that NaF toxicity leads to induction of apoptosis via release of reactive oxygen species (ROS) and inhibition of oxidative phosphorylation and glycolysis. Regarding the NaF+RSV group, caspase-3 immunostained sections showed moderate positive immunoreaction of caspase-3, mainly cytoplasmic as shown in the cytoplasm of Purkinje cells with scattered immune positive cells in the three cortical layers. This was in line with **Ghorbani et al.** [27] who clarified that RSV considerably reversed the up-regulated expression of active caspase-3 in a rat model of cerebellar ataxia treated by 3-AP. The findings of the current work were also in concordance with **Amer and Karam** [28] who reported a weak positive caspase-3 reaction in some Purkinje cells of zinc oxide nanoparticles and curcumin (antioxidant and anti-inflammatory polyphenol) treated animals. Also, **Alsemeh et al.** [29] reported that fewer caspase-3 immunostained cells were observed, especially in the PCL of the dimethoate and quercetin (antioxidant bioflavonoid) treated group. The anti-apoptotic properties of RSV may be correlated with the inhibition of p53 and the activation of

silent information regulator-1 (SIRT1), which has a neuroprotective effect via regulation of ROS, proinflammatory cytokine production, and amyloid-β (Aβ) expression in the brains of AD patients [30,31,32,33,34].

CONCLUSIONS

It can be concluded that NaF exposure produces marked degenerative changes in the cortex of the cerebellum of adult male albino rats. Co-administration of RSV along with NaF protected against the neurotoxic effects of NaF.

CONFLICT OF INTEREST

No interest conflict was announced by the authors.

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