https://doi.org/10.48047/AFJBS.6.2.2024.3747-3754

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

# Could Omega-3 have beneficial neuroprotective roles of the cerebellum?

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Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 August 2024

Accepted: 15 August 2024

Published: 15 August 2024

*doi: 10.48047/AFJBS.6.2.2024.3747-3754*

**Abstract:** Background: The cerebellum is located at the anterior end of the hindbrain, the cerebellum, also known as the "little brain," is mostly recognized for its function in sensory-motor processing. One of the most significant antiepileptic medications, valproic acid (VPA), has shown to be essential for pregnant epileptic patients in order to reduce the risk of convulsions for both the mothers and the foetuses. Omega-3 supplements were looked into as a potential preventative measure against a number of birth abnormalities. Its protection against VPA-induced cerebellar toxicity, however, was not adequately studied. We intended to provide an outline if Omega-3 have beneficial neuroprotective roles of the cerebellum.
Conclusion: A persistent neurological condition called epilepsy is typified by frequent, erratic seizures that are caused by spikes in the brain's electrical activity. The information that is now available supports the possibility of using omega-3 fatty acids as a coadjuvant treatment in conjunction with anticonvulsant medications to treat epilepsy. Numerous studies have reported a preventive effect against cardiovascular disease as well as an increase in seizure thresholds and latency to seizures. To validate their therapeutic potential, more extensive human clinical studies are required as the majority of the data have come from animal models.

**Keywords:** Omega-3, valproic acid, cerebellum

## Introduction

Located at the anterior end of the hindbrain, the cerebellum, also known as the "little brain," is mostly recognised for its function in sensory-motor processing. It is one of the most intricately designed areas of the central nervous system (CNS) in amniotes, and in humans, it houses more than half of the adult brain's mature neurons [1].

According to Martin. [2]., the cerebellum's overall function in motor control is dependent upon its linkages with other areas of the brain. Information from the brain stem, spinal cord, extraocular muscles, limbs, and the majority of sensory systems is gathered by the cerebellum.

There is a developmental gradient in every anatomical region during the central nervous system's (CNS) development. This indicates that not every neuron in a particular anatomical location is produced at the same time. There is additionally another gradient (the caudo-rostral). With a few exceptions, such as the cerebellum, which develops later and is a late offshoot of the neural tube, the spinal cord develops first, followed by the brain stem and then the encephalon [3].

The development of the cerebellum in mice happens in multiple separate but related stages. The establishment of the cerebellar territory along the dorso-ventral (DV) and antero-posterior (AP) axes of the neural tube is one of them. Other processes include the initial specification of the cell types that make up the cerebellum, their subsequent migration, differentiation, and proliferation, and the formation of the cerebellar circuitry [4].

The central nervous system's anterior-posterior patterning starts during neural induction and gastrulation, two early stages of development. Homeo-box genes (HOX genes), which are expressed in the notochord, pre-chordal plate, and neural plate, provide signals for the segregation of the brain into forebrain, midbrain, and hindbrain regions once the neural plate has been formed. These genes identify the rhombomeres and define their derivatives, as well as confer positional value along the hindbrain's antero-posterior axis [5].

Several new processes appeared in the granular layer of the rat cerebellum during the first postnatal week, emerging from focal swellings along the first segment of the Purkinje neurite. The following week saw a great deal of structural flexibility, including remodelling of terminal arbours and trimming of collateral branches. About day 15 postnatally, the Purkinje infra-ganglionic plexus, which is located in the most superficial part of the granular layer, reached its mature distribution [6].

In the first two years following birth, the human cerebellum experiences significant expansion and neuronal reorganisation as it matures postnatally [1,7].

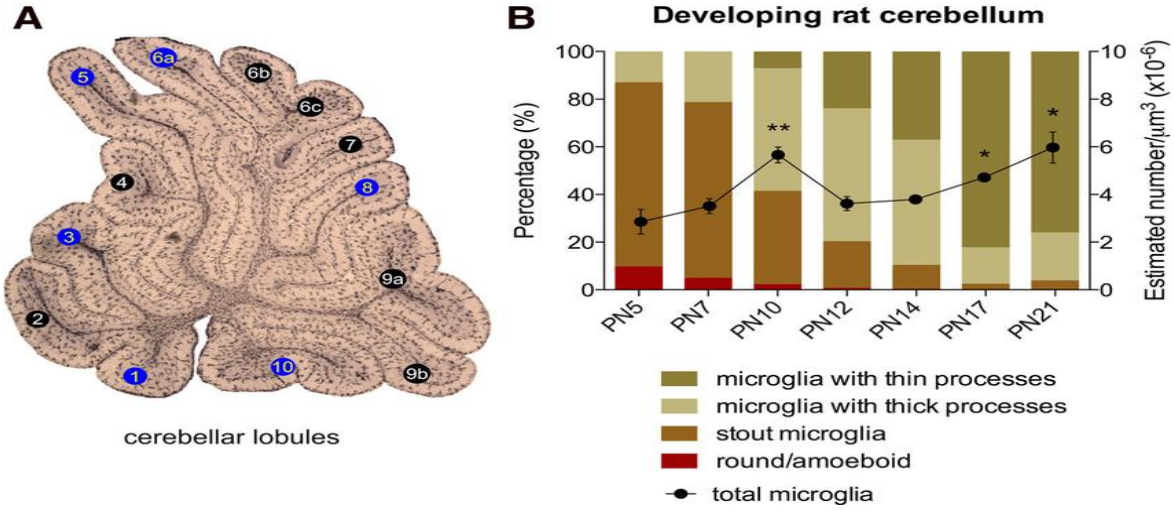


Fig 1:Microglia in the developing cerebellum during pregnancy

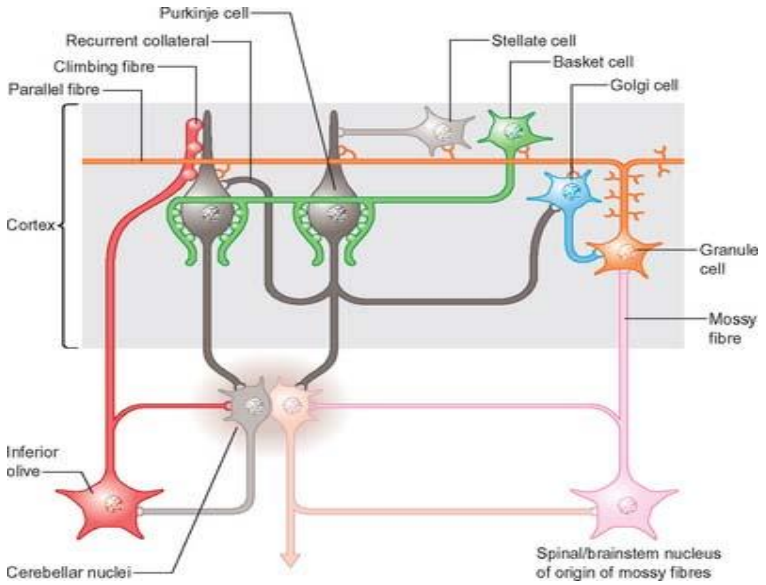


Fig.2 The main intrinsic connections of the cerebellar cortex

Neuro-trophins may have a variety of effects in the developing postnatal cerebellum after interacting with their specific tyrosine kinase (Trk) receptors. By activating the phospholipase Cγ (PLCγ) pathway, they can boost neurotransmitter release. They can also improve synaptic delivery by activating protein kinase C (PKC) and Ca2+-/calmodulindependent kinase II (CaMKII). Through its interaction with TrkB, brain-derived neutrophic factor (BDNF) promotes dendritic development and spine maturation. Trk signalling can influence the actin cytoskeleton, which is crucial for brain function, by stimulating the guanosine triphosphate (GTP) ases of the small Ras homolog gene (Rho). By activating the phosphoinositide 3-kinase (PI3K)–AKT pathway and transcription of activity-regulated genes like FOS and ARC, Trk signalling also enhances mRNA translation on a global scale [8].

The Purkinje cell's development and the ascending fibres' closely correspond. Cajal identified four distinct stages of the climbing fiber's life cycle: the early peri-cellular nest stage, where the climbing fibre develops an infra-cellular plexus; the stage of the juvenile climbing fibre arborization; the place of the supra-nuclear capuchon; and, lastly, its adult form. The inhibitory synapses of the basket cell axons have replaced the climbing fibre synaptic connections with the filopodia of the Purkinje cell soma, which were formerly located on stubby spines on the smooth proximal dendrites of the Purkinje cells [9].

Cingolani et al. [10] also noted that Purkinje neurons organised themselves into a distinct monolayer and gradually developed their characteristic, elaborated dendritic tree and synaptic contacts during the first three weeks of postnatal development, when Purkinje cell differentiation was completed. The maturation of mature synaptic connections on Purkinje cells and the creation of the dendritic tree, which were finished by postnatal three weeks, were mirrored by the postnatal alteration in the expression of small-conductance Ca+2-activated K+ channels.

The precise form of Ca2+ signals at presynaptic terminals is a significant determinant since transmitter release at presynaptic terminals is a Ca2+-dependent process [11].

**Valproic Acid**

One of the most significant antiepileptic medications, valproic acid (VPA), has shown to be essential for pregnant epileptic patients in order to reduce the risk of convulsions for both the mothers and the foetuses. Omega-3 supplements were looked into as a potential preventative measure against a number of birth abnormalities. Its protection against VPA-induced cerebellar toxicity, however, was not adequately studied. The goal of the current investigation was to assess Omega-3's ability to protect against cerebellar neurotoxicity caused by VPA. Valproic acid, also known as VPA, is a broad-spectrum antiepileptic medication used to treat

and prevent various forms of partial and generalized epileptic seizures in adults and children. It also serves as a mood stabilizer for people with schizoaffective disorders, bipolar disorder, neuropathic pain, and social anxiety [12].

By increasing GABA functions, inhibiting NMDA glutamate receptors, blocking sodium and calcium channels, and potentially lowering aspartate levels and changing dopaminergic and serotoninergic neurotransmissions, VPA appears to reduce neuronal excitation . A broad-spectrum antiepileptic medication, valproic acid (VPA) is used to treat a variety of partial and generalized epileptic seizures in children and adults. It also serves as a mood stabilizer for people with schizoaffective disorders, social anxiety, and neuropathic pain [13].

Prior research has demonstrated that VPA can harm neurons and impair cognition in epileptic individuals and rodents. Moreover, VPA causes oxidative stress, interferes with the CNS's proper growth, and may compromise cognitive function . Furthermore, exposure to VPA during pregnancy is linked to birth abnormalities and a higher chance of autism [14].

A carboxylic acid with branched chain is valproic acid (VPA). Because of its significant effect on a wide variety of seizure types, it is the most often used antiepileptic medication. Pregnant women with epilepsy were found to be susceptible to VPA and could not be excluded [15]. Uncontrolled epileptic seizures during pregnancy carry a significant risk of harm to the developing baby as well as the mother [16]. VPA**,** however, has been demonstrated to cause toxicity and teratogenicity after crossing the placenta and accumulating in the foetal circulation at a higher concentration than in the mother's blood [17].

Various studies have found that exposure to VPA during pregnancy causes a noticeable deterioration of the cerebellar Purkinje and granular cells Main SL, [18]**,** a shrinkage of the Purkinje and cerebellar hemispheres cell number was discovered in rats on day 12 of gestation following VPA administration [10]. Few research, meanwhile, have looked into how VPA affects gliogenesis in the growing brain. Following prenatal VPA injection, they discovered changes in the postnatal density of microglia and astrocytes [19].

It was shown that VPA started the toxicity of genes and proteins that play crucial roles in controlling development and differentiation during organogenesis by generating several apoptotic cascades [20]. It has been claimed that an increase in the body's overall free radical level is what causes fetal deformity and cellular damage brought on by VPA [21]. It has been discovered that vitamin B9, or folate, is a crucial co-factor in the control of gene expression and the synthesis of new proteins, both of which are necessary for the differentiation, development, and proliferation of fetal cells [22].

Even so, there was inadequate research done on the protective effect of Omega_3 against prenatal VPA cerebellar damage. Therefore, the current study's goal was to investigate any potential protective effects of Omega_3 on the postnatal changes in the histology and ultrastructural development of the cerebellar cortex following prenatal VPA treatment. An anti-epileptic medication called valproic acid (VPA) is used to treat migraine, bipolar disorder, and epilepsy. As an epigenetic regulator and inhibitor of histone deacetylases, VPA can alter gene activity, damage DNA, interfere with mitochondrial energy metabolism, and increase oxidative stress in foetuses. Accordingly, VPA is a strong teratogen for the progeny of human pregnant females [23].

According to Gottfried et al. [23], the teratogenicity of VPA revealed foetal valproate syndrome, which is characterised by neural tube malformations, neurodevelopment delay, dysmorphic features, cardiac anomalies, cognitive deficits, and antiseptal defect (ASD) symptoms in offspring.

ASD, cognitive-emotional disorders, schizophrenia, and addictive behaviours have all been linked to cerebellar impairment. Additionally, a prior study that used an experimental model of ASD and involved injecting VPA into rats found that both the size of the cerebellar hemispheres and the quantity of cerebellar Purkinje cells had significantly decreased [24]**.**

In contrast, human cerebellum development starts during the fourth week of embryonic development and continues until birth**.** However, according to Altman and Bayer. [25], cerebellar development in mice takes place over the course of six weeks, from embryonic day 7 to postnatal day 30. The interaction of two germinal

epithelia—the ventricular zone of the fourth ventricle, which gives rise to Purkinje cells, and the outer granular layer, which gives rise to granule cells—largely regulates the formation of the cerebellum [26].

In the rat cerebellar cortex, these distinct neuronal groupings emerge at widely differing times. Microneurons like granule, stellate, or basket cells grow postnatally, while macroneurons like Purkinje cells or neurons in the cerebellar nuclei develop during pregnancy. Additionally, the neurogenesis of these cells peaks on the E15th day, while the prenatal development of Purkinje cells is finished between the 13th and 16th embryonic days. Furthermore, during the second and third postnatal week—or, at most, between the tenth and eleventh day—granule cell modifications are finished [25].

It appears that oxidative stress plays a role in VPA's neurotoxic effects. VPA causes oxidative damage to proteins and lipids in the brain. Moreover, glutathione—the main non-enzymatic antioxidant defence in the brain—is decreased by VPA. Oxidative stress may be initiated or exacerbated by AChE and Na+, K+ inhibition.v Oxidative stress in the rat brain's cerebellum and cerebral cortex was produced by VPA [27].

**Omega-3**

Long-chain polyunsaturated fatty acids found in plants and marine environments are known as omega-3 fatty acids. Alpha linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid are the three major physiological Omega-3 that are available [28]. It has anti-inflammatory and vascular qualities [28].

There are several sources of omega-3 fatty acids in diets today, including the flesh of oily fish (like mackerel, salmon, sardines, and anchovies), animal sources (like meat and poultry), and vegetarian sources (like alpha-linolenic acid, which is found in the lipid portions of leafy green plants and some seeds and supplements). For people who don't like fish or who can't get enough of it from diet alone, these sources are a great alternative [29].

Age-related cognitive decline, rheumatoid arthritis, diabetes, cancer, depression, and other mental diseases are among the ailments for which omega-3 is beneficial. Additionally, it is critical to the developing child's diet for women who are pregnant or nursing. Omega-3 fatty acids are essential for the body's healthy operation and are involved in numerous physiological processes in the brain. They are energy substrates as well as essential membrane components. In particular, it has been discovered that omega-3 fatty acids are essential for the growth and development of neurons as well as being vital regulators of brain activity and oxidative stress management in both neuronal health and illness. As the primary fatty acid in the brain, docosahexaenoic acid (DHA) is an omega-3 fatty acid with 22 carbons that accumulates in the lipid and synaptic membranes of the cortex, making up to 35% of the content of the membranes [30].

The essential fatty acids omega-3 (o-3) consist of a-linolenic acid (ALA, C18: 3n-3), eicopentaenoic acid (EPA, C20: 5n-3), and docosahexaenoic acid (DHA, C22: 6n-3). Omega-3 fatty acids are crucial for the neurological system's histological, anatomical, and metabolic integrity**.** Fish oil is rich in omega-3 polyunsaturated fatty acids (PUFAs) like EPA and DHA, while vegetable oils like soybean and linseed oil include omega-6 PUFAs like ALA. Only 5% of ALA can reach this metabolic route, but only after specific enzyme-catalyzed chain reactions can EPA be generated from ALA and DHA from EPA [30].

However, when ALA is consumed by diet, the tissue EPA level rises while the DHA level stays the same**.** As a result, it has been suggested that fish products supply DHA, which is found in the phospholipid structures of the brain's cellular membranes.

DHA are widely distributed throughout the brain and play a role in, or modify, the way that brain neurons communicate [31].

DHA and arachidonic acid are necessary for the retina and brain to grow normally, especially in premature babies. DHA plays a unique role in the tissues of neurons and makes about 15%–20% of the lipid molecules in the cerebral cortex. Additionally, studies in brain tissues have indicated that omega-3 fatty acids have neuroprotective properties [32].

DHA oil has been utilized as an adjuvant in cancer therapy for conditions such breast tumors and colon tumors, as well as for the treatment of autoimmune illnesses, rheumatoid arthritis, glomerulonephritis, allergic asthma,

and hypertension. Long-term studies on the effects of omega-3 fatty acids on the heart, the reduction of inflammation, and the management of specific mental health conditions Their use as dietary supplements has expanded as a result of (such as inattention, hyperactivity, and other disruptive behaviors) [32].

To far, however, no experimental research has been done on how omega-3 fatty acids protect against valproic acid-induced neuronal damage in the cerebellum. Reactive oxygen species (ROS) production and accumulation are out of equilibrium, which is known as oxidative stress. There is strong evidence that fish oil supplements help treat conditions like cancer and arrhythmia that are caused by an imbalance in ROS. Additionally, supplements have a positive impact on the levels of uric acid, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and plasma triglycerides (TG). In female transgenic mice , the development of atherosclerotic lesions is inhibited by an anti-inflammatory dietary combination containing fish oil. Since the human body lacks the desaturase enzymes Δ-15 and Δ-12, it is unable to complete the de novo biosynthesis of necessary FAs. Thus, diet has to include necessary FAs [33].

Traditionally, it was believed that polyunsaturated fatty acids (PUFA) were primarily responsible for the creation of cellular membranes and were relatively inert structural elements of the brain. In the last ten years, a variety of bioactive lipid mediators that are enzymatically derived from the primary n-6 PUFA in the brain, arachidonic acid, and the primary n-3 PUFA, docosahexaenoic acid (DHA), have been found in the brain and demonstrated to control microglia activation. DHA is also known to regulate peripheral immune function.

The regulation of microglia's molecular signalling by PUFA has been the subject of recent research, particularly in relation to neuroinflammation and behaviour. A number of effective medications control brain lipid signalling and offer evidence of concept for brain targeting. Many pathways can be disrupted, resulting to altered brain lipid homeostasis, because brain lipid metabolism depends on a complex integration of nutrition, peripheral metabolism, including the liver and blood, which supply the brain with PUFAs that can be affected by genetics, sex, and ageing. Neurologic illnesses cause changes in brain lipid signalling pathways, which could be useful targets for the creation of new treatments. In this work, we specifically address the ways in which n-3 PUFAs and their metabolites control the phenotypic and function of microglia in order to carry out their anti-inflammatory and proresolving effects in the brain [33].

The structure of omega-3 polyunsaturated fatty acids contains many double bonds. The most significant omega-3 fatty acids, alpha-linolenic, eicosapentaenoic, and docosahexaenoic, are not produced in sufficient proportions by the body and must thus be received through diet. These fatty acids perform vital physiological roles in the brain and are necessary for the organism to function properly.

A persistent neurological condition called epilepsy is typified by frequent, erratic seizures that are caused by spikes in the brain's electrical activity. The information that is now available supports the possibility of using omega-3 fatty acids as a coadjuvant treatment in conjunction with anticonvulsant medications to treat epilepsy. Numerous studies have reported a preventive effect against cardiovascular disease as well as an increase in seizure thresholds and latency to seizures.

To validate their therapeutic potential, more extensive human clinical studies are required as the majority of the data have come from animal models.

**Conclusion**

SP has the potential to become a valuable food in the future. SP has been used in the formulation of several food products, and each year more and more innovative foods are introduced to the market that use this beneficial ingredient. SP is both trendy and nutritious, containing proteins, PUFAs, and bioactive pigments like carotenoids, chlorophylls, and phycobiliproteins. SP has beneficial effects in the treatment of neurodegenerative disorders and had positive effect in enhancing the locomotor function of the hind limb and diminishing the morphological injury of the spinal cord.

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