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Neuro-Protective Effect of Omega-3 against Valproic Acid on the Cerebral Cortex of Rats

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Abstract: Research from both retrospective and prospective clinical investigations has shown that prenatal VPA exposure can cause signs of autism spectrum disorder (ASD) in children, including social impairment, communication impairments, anxiety, obsessive/repetitive behaviour, and impaired motor abilities. Bipolar illness, migraine, and epilepsy are all treated with valproic acid (VPA), an anti-epileptic medication. As an inhibitor of histone deacetylases and an epigenetic modulator, VPA is a powerful teratogen for the progeny of human females undergoing pregnancy. The teratogenicity of VPA revealed foetal valproate syndrome, a condition in which offspring have characteristics of autism spectrum disorder (ASD), dysmorphic features, cardiac abnormalities, neural tube malformations, and neurodevelopmental delay. Omega-3 is polyunsaturated fatty acids (PUFAs). They are present in seafood like krill and algae as well as fish. These polyunsaturated fatty acids (PUFAs), which are found in membrane phospholipids. For some high-fat tissues, such as brain and retinal tissue, OM3FAs have a stabilizing and protective impact. Because docosahexaenoic acid (DHA) is a crucial component of the brain's phospholipid membranes, OM3FAs capacity to preserve the cell membrane integrity of neural tissues improves cognitive function, Alzheimer disease, and dementia. There for, Omega-3 protects against Valproic acid

Keywords: *Polyunsaturated fatty acids ; Autism spectrum disorder ; central nervous system.*

Introduction

Two divisions of the nervous system are the peripheral and central nervous systems (PNS and CNS, respectively). The cerebral hemispheres, which include the medulla, pons, and midbrain; the brain stem, which includes the medulla, pons, and midbrain; the diencephalon, which includes the thalamus and hypothalamus; and the cerebellum comprise the four main regions of the brain.The nervous system is composed of enormous neural networks, and every function and experience, including thinking, speaking, feeling, learning, and memory, is made possible by signalling within these circuits **[1]**

Gross anatomy of the human cerebrum:

EXTERNAL FEATURES

The outermost layer that envelops the brain is called the cerebral cortex. It has billions of neurons that perform high-level executive processes, and it is made of grey matter. Different sulci in the cortex separate it into frontal, parietal, occipital, and temporal lobes **[2].**

The corpus callosum, a bundle of white fibers, connects the two cerebral hemispheres that make up the cerebrum's median longitudinal fissure.

Each cerebral hemisphere has three types of brain matter: cortical grey matter, white matter underneath the grey matter, and a collection of subcortical neuronal masses inside the white matter known as the basal ganglia. The interventricular foramen of Monroe connects the third ventricle to the lateral ventricles, which are cavities located in each cerebral hemisphere. Cerebrospinal fluid, a nutritional substance for the brain tissue, is found in the ventricles **[3].**

Poles

Each cerebral hemisphere contains three poles: the frontal, temporal, and occipital. The anterior most extremity of the cerebral hemisphere is called the frontal pole, and it correlates with the super-ciliary arch. The cerebral hemisphere's rear end is known as the occipital pole, while the anterior end of the temporal lobe is known as the temporal pole **[3].**

Surfaces

The supero-lateral, medial, and inferior surfaces are the three surfaces found on each cerebral hemisphere. The largest surface of all is the supero-lateral surface, which is convex and faces the cranial cap **(Fig. I) [4].**

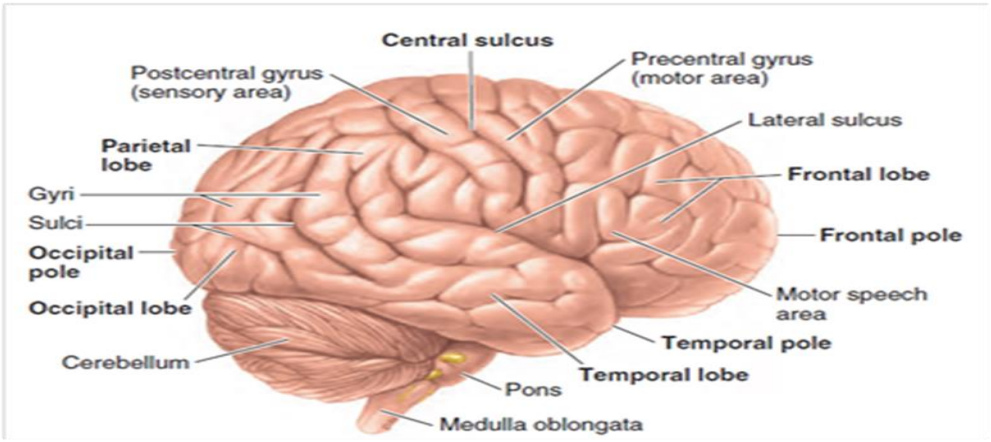

Fig. I. Lateral view of the right hemisphere **[21].**

The medial surface is oriented towards the medial surface of the opposing hemisphere and is flat. Falx cerebri is located in what is referred to as the longitudinal cerebral fissure, which is the gap between the medial surfaces of two hemispheres. The medial surface of the corpus callosum has a C-shaped cut portion **[3].**

The base of the skull is the target of the inferior surface. The stem of the lateral sulcus divides the inferior surface into tentorial and orbital parts. The anterior part of the inferior surface, which is situated above the orbital plate and anterior cranial fossa, is known as the orbital component. The posterior large segment located over the tentorium cerebelli is referred to as the tentorial component **(Fig. II) [3].**

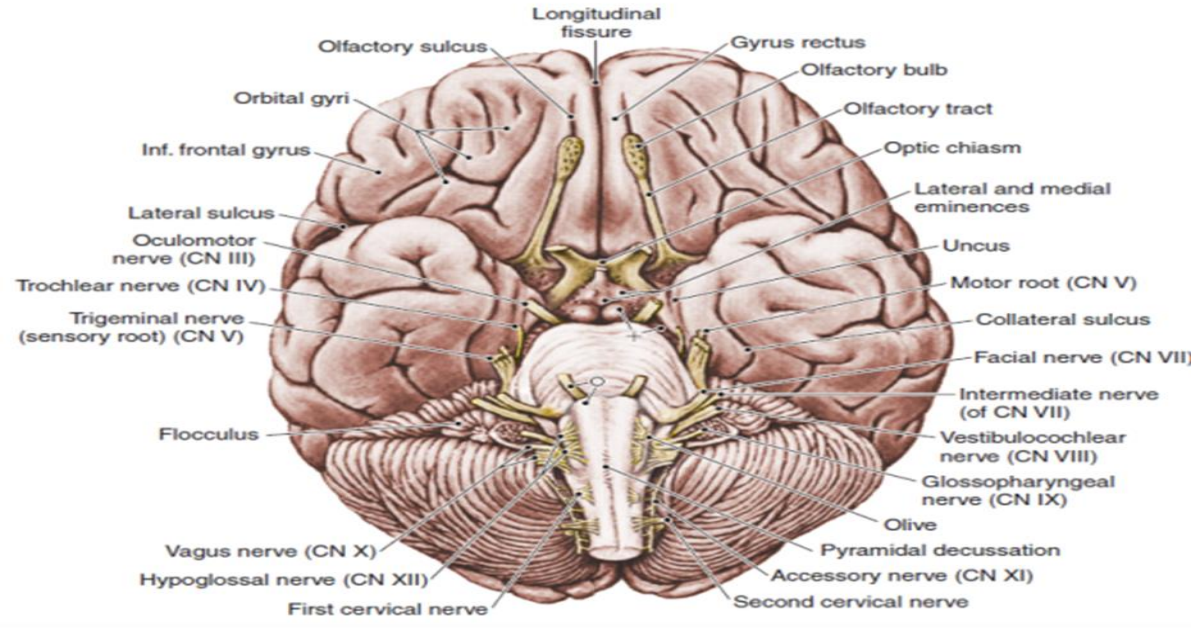

Fig. II. Inferior surface of the brain **[22].**

Borders

The superomedial border, which divides the superomedial surface from the medial surface, runs from the frontal pole to the occipital pole **[5].**

The inferolateral barrier separates the inferior surface of the cerebral hemisphere from the superolateral surface. The part of the inferolateral border that comes before the lateral sulcus stem is known as the superciliary border. The inferomedial border separates the inferior surface from the medial surface. The brainstem and diencephalon split it at the anterior medial orbital boundary and posterior medial occipital border **[4].**

The orbital surface and medial surface are divided by the medial orbital boundary. The medial surface and the tentorial surface are divided by the medial occipital boundary. Two other boundaries are the infero-medial border, which encircles the cerebral peduncle, and the super-ciliary border, which is located at the intersection of the supero-lateral and orbital surfaces **[6].**

HISTOLOGICAL STRUCTURE OF THE HUMAN CEREBRAL CORTEX

There are areas of the nerve tissue that are mostly made up of cell bodies and there are other areas that are primarily constituted of axons. These two areas of the nervous system's structures are frequently referred to as grey matter or white matter, respectively. The cerebral medulla, an internal white matter area, the superficial cerebral cortex of grey matter, and the basal nuclei, deep inside the white matter of the brain, are the three main regions that make up the cerebrum **[7].**

Among the several neuronal types found in the cerebral cortex are Fusiform, pyramidal, stellate, horizontal Cajal, and cells of Martinotti cells. The outer layer is faced by the pyramidal cells' apices. Axons arise from the centre of the base, whereas dendrites emerge from the corners of pyramidal cells **[8].**

The pyramidal cell axons extend as projection fibers into the white matter. There are three further sizes of pyramidal cells: small, medium, and giant. The stellate/granule cells have a diameter of around 8 μm and resemble stars in size **[9].**

Stellate cells resemble the granule cells that are known as nizzle-stained granules. Granule cells feature many dendrites and little axons. The term Koniocortex (Konio = Cloud) refers to regions of the cerebral cortex where there is clouding of the granule cells **[8].**

The cortical layer that is most superficial contains the fusiform horizontal cells of Cajal. These cells are oriented horizontally. Although they are located in the deep layer of the cortex and have a fusiform shape, the fusiform cells are orientated vertically. Small multipolar cells known as Martinotti cells are present in every layer of the cerebral cortex **[10].**

Laminar organization in the human cerebral cortex

According to García **[8]** these horizontal arrangements of cellular layers are seen under a microscope:

i. Molecular (Plexiform) layer I: made up of glial cells, Cajal-Retzius cells, horizontally arranged axons, and apical dendritic tufts of pyramidal neurons.

ii. The external granular layer II is mostly made up of tiny pyramidal and granular cells.

iii. The third external pyramidal layer is made up of medium- and small-sized pyramidal cells.

iv. The internal granular layer IV is made up of tiny pyramidal and granular cells.

v. The biggest pyramidal cells are found in internal pyramidal layer

vi. Multiform (Polymorphous) layer VI: This layer contains excitatory cells such as bipolar/fusiform cells, pyramidal cells, inverted pyramidal neurons, and odd-shaped cells.

Myelinated axons in three different types of tracts—association, commissural, and projection tracts—make up the majority of the cerebral white matter. Axons in the association tracts carry nerve signals from gyri in the same hemisphere to each other **[11].**

Anatomy of rat brain

Rats have a central nervous system made up of the brain and spinal cord, which is covered in three layers of meninges. The outermost cerebral hemisphere is called the dura, and it is folded to separate the two hemispheres that comprise the falx cerebri. The cerebellum and cerebrum are further separated by the tentorium cerebelli. The innermost meninge is called the pia mater, and it is connected to the brain and spinal cord. Arachnoid matter is a network of microscopic fibres that is located between the dura and pia matter **[12].** The most noticeable differences are that rodent brains contain less white matter and are small (rat brains weight around 2.0 g). Since they lack gyri and sulci, they are classified as lissencephalic species. Therefore, using surface topography to distinguish between different areas of the rodent cerebrum is not feasible. The prominence of the olfactory bulbs and pathways is the primary ventral characteristic that separates humans from rodents. Since smell is a rodent's primary sensory modality, its olfactory bulbs are enormous, making about 6-7% of the total weight of the brain **[13].**

Histology of rat brain

Table 1 provides a summary of the cerebral cortex's layers. A large portion of our knowledge about the histology of the cortex comes from research done on cats and primates. The arrangement of the layers differs significantly between areas within the cortex. Paxinos **[14]** provides further information on the rats' cerebral cortex.

Table 1: Layers of the Cerebral Cortex **[14].**

Layer Number	Layer Name	Descriptive Notes	Horizontal/Tangential Bundles of Nerve Fibres
I	Molecular layer	Largely horizontal fibres: dendrites of pyramidal cells, axons of cells of Martinotti and both of cells of Retzius Cajal	
II	External granular layer	Many small pyramidal cells (pyramidal cells are not confined to the pyramidal layers) and inter-neurons	
III	External pyramidal layer	Typical pyramidal cells, cell bodies tending to become larger towards the inner aspect of the layer. Axons project to other parts of the cerebral cortex as association fibres and fibres of commissures	
IV	Internal granular layer	Mainly stellate cells, other types of inter-neurons and some pyramidal cells present	Outer line of Baillarger: line of Gennari in primate visual cortex
V	Internal pyramidal layer	Largest pyramidal cells present, largest of all (Betz cells) in primary motor cortex. Axons project to extra-cortical locations: basal ganglia, brainstem and spinal cord	Inner line of Baillarger
VI	Multiform layer	Fusiform cells, small pyramidal cells, interneurons. Axons of pyramidal cells project to thalamus	

The Valproic Acid

Bipolar illness, migraine, and epilepsy are all treated with valproic acid (VPA), an anti-epileptic medication. VPA can alter gene activity, damage DNA, interfere with mitochondrial energy metabolism, and increase foetal oxidative stress since it is an epigenetic modulator and an inhibitor of histone deacetylases. VPA is therefore a strong teratogen for children born to human females who are pregnant **[15].**

Foetal valproate syndrome, which includes neural tube malformations, neurodevelopment delay, dysmorphic traits, cardiac anomalies, cognitive deficits, and signs of autism spectrum disorder (ASD) in children, was shown by the teratogenicity of VPA **[16].**

The information that is now available shows that VPA is the most teratogenic anti-epileptic drug and that the dosage of this AED is strongly connected with the incidence of abnormalities. The potentiation of GABA-mediated processes is one of the primary mechanisms by which VPA acts **[15].**

This AED has also been shown to block histone deacetylases, which means that it may affect the way in which several genes are expressed involved in cellular differentiation and cell cycle regulation through epigenetic alterations **[16].**

In comparison to the morning, absorption is slower in the afternoon after lunch. After breakfast, is explained by if the medicine is taken two or three hours after a meal, it will always be delayed. Low clearance rates (6–20 ml/h/Kg) are caused by VPA's strong protein binding (87-95%) **[17].**

The OMEGA-3

Polyunsaturated fatty acids (PUFAs) having several carbon-carbon double bonds in their backbone are known as omega-3 PUFAs. They are present in seafood like krill and algae as well as fish including sardines, salmon, tuna, and halibut as well as in nut oils, some plants, and lake trout. These polyunsaturated fatty acids (PUFAs), which are found in membrane phospholipids, are essential for many physiological processes, such as signalling, cell-to-cell communication, and membrane shape and fluidity preservation **[18].**

In addition to potentially lowering the risk of chronic illnesses including cancer, arthritis, and heart disease, N-3 PUFAs can also decrease inflammation. Additionally, they control the development and activities of the nervous system, blood pressure, hematic coagulation, glucose tolerance, and more. For some high-fat tissues, such as brain and retinal tissue, OM3FAs have a stabilizing and protective impact. Because docosahexaenoic acid (DHA) is a crucial component of the brain's phospholipid membranes, OM3FAs capacity to preserve the cell membrane integrity of neural tissues improves cognitive function, Alzheimer disease, and dementia **[19].**

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 for the growth of the children in the diets of expectant and nursing mothers **[20].**

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