Brief Insight about Cerebral Cortex and Possible Role of FG Loop Peptide in Neurological Disorders

Eman Samy Abd Elkreem Ali Elsheikh [1], Asmaa Alhosiny Kattaia [2] Hala Elwy Hashem[3], Hoda Hussein Anan [4]
1 Assistant Lecturer of Histology and Cell Biology, Faculty of Medicine, Zagazig University, Egypt
2 Professor of Histology and Cell Biology, Faculty of Medicine, Zagazig University, Egypt.
3 Professor of Histology and Cell Biology, Faculty of Medicine, Zagazig University, Egypt
4 Professor of Histology and Cell Biology, Faculty of Medicine, Zagazig University, Egypt
Corresponding author: Eman Samy Abd Elkreem Ali Elsheikh
E-mail: emanelsheikh942@gmail.com, Eselsheikh@gmail.com, ISSheikh@medicine.zu.edu.eg
Conflict of interest: None declared
Funding: No funding sources

Abstract
The human nervous system arises from the ectoderm which one of the three distinct embryonic germ layers that arise in the third week after conception. The cerebral cortex is formed from neuroepithelial cells (NECs). In humans, NEC proliferation begins in the 4th week of development in the neural plate. NECs proliferate in a symmetric fashion (one stem cell divides into two stem cells) until neural tube closure is complete. Afterwards, proliferation changes to asymmetric division in which one stem cell produces one stem cell and one neuron. The differentiated neurons are located in the periphery (primordial plexiform layer or preplate PP) and as a consequence, the stem cells are placed in the deep germinative zone called the ventricular zone (VZ). In early developmental stages when the distance between the VZ and PP is short, the neurons move by somal translocation (nucleokinesis). Nucleokinesis occurs by the neuron extending a process toward the PP meningeal surface, and the nucleus moves toward the surface as the ventricular process shortens and is detached from the ventricle. The FG loop peptide (FGL, EVYVVAENQQGKSKA), is a neural cell adhesion molecule-mimetic peptide (NCAM – mimetic peptide). Neural cell adhesion molecule NCAM is a cell surface glycoprotein expressed mainly in three isoforms, NCAM120, NCAM140 and NCAM180, named according to their apparent molecular weights. Extracellularly, all three isoforms consist of five Ig-like modules followed by two fibronectins type III (FN3) modules. NCAM signal interacts through its growth factor receptors including fibroblast growth factor receptor (FGFR). The FGFR-1 binding site of NCAM is a 15 amino acid small loop peptide that is is called the FGL peptide. NCAM plays an important role in the nervous system in development, plasticity and learning and memory. FGL has been shown to rapidly enter the bloodstream, to penetrate the blood–brain barrier, and to circulate within the cerebrospinal fluid upon systemic administration. FGL was reported to be the most promising NCAM mimetic peptide for clinical translation

Keywords: FG Loop peptide, Cerebral Cortex

Tob Regul Sci. ™ 2023 ;9(1): 6084-6096
DOI: doi.org/10.18001/TRS.9.1.424

Introduction

The human nervous system arises from the ectoderm which one of the three distinct embryonic germ layers that arise in the third week after conception. Neurulation, the process of the development of the neural tube, begins during the fourth week of fetal development. During primary neurulation, the neuroepithelium elevates around the midline, forming the neural groove with the two neural folds on either side **(1)**.

Fusion of these folds forms the neural tube, whose lumen becomes the neural canal. The cranial opening of the tube closes on roughly the 25th day and the caudal one closes on the 27th day **(2)**.

This process forms three dilations in the cranial end of the neural tube, known as the primary brain vesicles; the prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hindbrain), respectively. The prosencephalon divides into the telencephalon and diencephalon in three stages; formation, cleavage, and the development of the midline **(3)**.

The posterior portion of the forebrain becomes the diencephalon; whose central cavity forms the third ventricle alongside the median part of the telencephalon. The diencephalon, midbrain and hindbrain are all covered as the cerebral hemispheres enlarge, eventually meeting together in the midline, giving rise to the cerebral falx as mesenchyme is trapped in the longitudinal sulcus between them **(2)**.

Normal Development Of The Cerebral Cortex

The cerebral cortex is formed from neuroepithelial cells (NECs). In humans, NEC proliferation begins in the 4th week of development in the neural plate. NECs proliferate in a symmetric fashion (one stem cell divides into two stem cells) until neural tube closure is complete. Afterwards, proliferation changes to asymmetric division in which one stem cell produces one stem cell and one neuron. The differentiated neurons are located in the periphery (primordial plexiform layer or preplate PP) and as a consequence, the stem cells are placed in the deep germinative zone called the ventricular zone (VZ) **(4)**.

In early developmental stages when the distance between the VZ and PP is short, the neurons move by somal translocation (nucleokinesis). Nucleokinesis occurs by the neuron extending a process toward the PP meningeal surface, and the nucleus moves toward the surface as the ventricular process shortens and is detached from the ventricle. New-born excitatory, pyramidal neurons must migrate from the VZ where they are born, to near the surface of the cortex. This migration is accomplished through a process called radial migration **(5)**

Radial migration uses radial glial fibers of radial glial cells (RGCs) as a scaffold. RGCs are neuroepithelial progenitors that form bipolar radial fibers between the ventricular and meningeal surfaces. The newly formed neurons travel along the radial glial fiber in the direction perpendicular to the cortical surface and are induced to detach from the radial glia **(5))**.

Formation of layers:

The cerebral cortex is divided into layers, each layer is formed by radial glial cells located in the ventricular zone or subventricular zone, and then migrate to their final destination (5).

Layer 1

Layer I, the molecular layer, is the first and most superficial cortical layer produced during neurogenesis and is composed of Cajal–Retzius cells and pyramidal cells. This layer is unique in the aspect that these cells migrate to the outer edge of the cortex opposed to the migration experienced by the other 5 layers (6).

Layers 2 and 3

The second and third layers are also called the External Granular layer and External Pyramidal layer respectively. These layers are the last to form during corticogenesis and include pyramidal neurons, astrocytes, stellates, and radial glial cells. (5).

Layers 4, 5 and 6

The fourth, fifth and sixth layers are also called the Internal Granular layer, Internal Pyramidal layer, and Polymorphic or Multiform layer respectively. Included in these layers are stellates, radial glia, and pyramidal neurons.The layer six is adjacent to the ventricular zone. (5).

Anatomy of Cerebral Hemispheres

The Hemispheres :

The surface of the cerebrum is covered by a layer of grey matter convoluted into many folds (gyri) and valleys (sulci); these maximize the surface area of the cerebrum, which represents between 81% and 85% of the brain's mass. The outer grey matter, also known as the cerebral cortex, consists of dendrites and interneuron cell bodies, with their associated glia and vasculature. Grey matter neurons lack the myelin sheath that gives other parts of the brain a white coloring (7).

Large sulci separate the cortex anatomically into individual lobes. The longitudinal cerebral sulcus separates the cortex of the cerebrum into the left and right hemispheres, which remain connected via the corpus callosum, a fibrous structure of nerves ensuring communication between the two. Largely symmetrical, the two hemispheres are not completely identical in anatomy or in function (8).

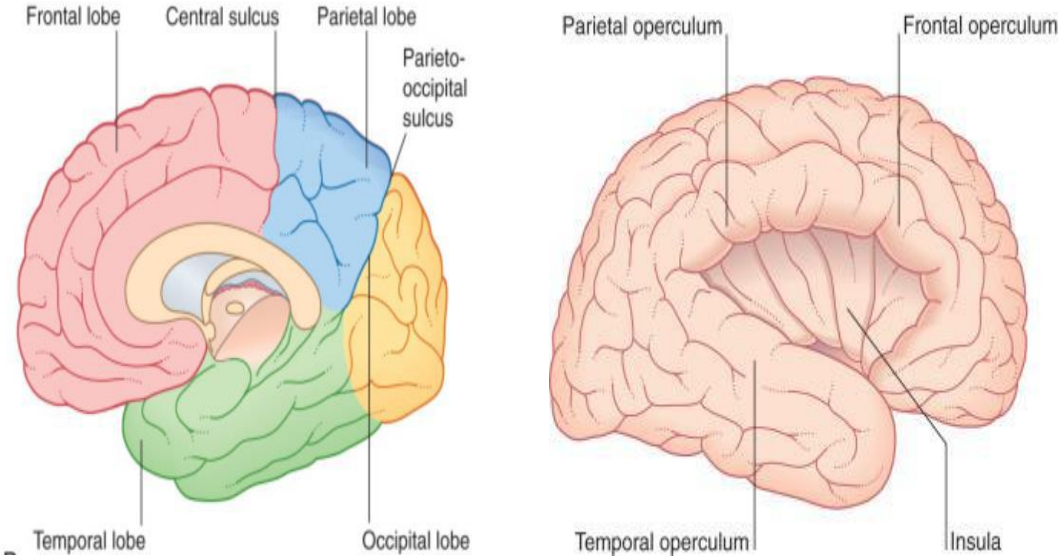

Diagram (1) Medial surfaces of the right brain hemisphere with lobes indicated. The insula through the lateral sulcus (9).

The Lobes :

The hemispheres are separated by various sulci into five lobes, they are named after bones of the skull beneath which they are located and have evolved distinct functions **(10).**

1- The frontal lobes:

The most anteriorly located lobes (under the frontal bone of the forehead). On each side, the frontal lobe is separated from the parietal lobe (situated under the parietal bone) via the central sulcus and from the temporal lobe by the lateral sulcus. The frontal lobes are the largest lobes of the cerebrum and contain a number of important functional areas. The cortex of the frontal lobe contains some noticeable gyri: anteriorly to the central sulcus is the precentral gyrus (containing the somato-motor cortex) **(10).**

The frontal lobe's lateral surface is divided into three further gyri: the superior, middle, and inferior frontal gyri. Interesting landmarks on the inferior aspect of the frontal lobe are the orbital gyri, the gyrus rectus and the olfactory sulcus. The olfactory bulb and its associated structures lie on the anterior surface of the frontal lobe and are functionally related to the limbic system **(11).**

The functional roles of the frontal lobe include the control of prospective memory (memory associated with planning) as well as speech and language. Broca's area is a region of the frontal lobe located in the posterior inferior frontal gyrus, which mediates sensory information between the temporal and motor cortices. Additionally, the regulation of personality, social behavior, and decision-making appears to be significantly modulated by the frontal lobe. **(8).**

2-The parietal lobes:

They are bounded posteriorly and inferiorly by the occipital and temporal lobes, is limited anteriorly by the central sulcus. Its two main sulci are the postcentral and the intraparietal sulci. The superior lobule contains the somatosensory association cortex, which is involved in motor planning, while the inferior lobule, contains the secondary somatosensory cortex (SII), which receives somatosensory stimuli from the thalamus and contralateral SII and integrates them with visual or auditory input to perform a variety of higher-order functions, including sensorimotor planning, spatial recognition, and stereognosis, as well as a some involvement in learning and language**(12).**

3-The temporal lobes

They are often referred to as the neocortex. Situated anteriorly to the occipital lobe, posteriorly to the frontal lobe and inferior to the lateral sulcus, the temporal lobe is divided into superior, middle and inferior gyri. The superior temporal gyrus (STP) contains the primary auditory cortex, located within Herschl's transverse temporal gyri. The primary auditory cortex is responsible for processing auditory stimuli. The inferior temporal gyrus occupies the lateral and basal surfaces of the cerebrum, and plays a role in visual and facial perception through the ventral visual pathway **(12).**

4-The occipital lobes

Form the caudal section of the hemisphere. On its medial surface, the parieto-occipital sulcus separates the precuneus of the parietal lobe from the cuneus of the occipital lobe. The gyri which contains the primary visual cortex lie on either side of this sulcus. The occipital lobe has visual processing and interpretation roles **(12).**

5-The hidden lobes known as the insula:

They lie buried behind the lateral sulcus. They function like a shield, covering and protecting the basal nuclei and thalamus located below. **(13).**

Anatomy of Middle Cerebral Artery

The middle cerebral artery (**MCA**) is one of the three major paired arteries that supply blood to the cerebrum and is considered as a critical artery which has an extensive clinical significance. The MCA is part of the circle of Willis anastomotic system within the brain, which forms when the anterior cerebral arteries anastomose anteriorly with each other through the anterior communicating artery and posteriorly with the two posterior communicating arteries bridging the MCA with the posterior cerebral artery on each side. The MCA was reported to be the most common pathologically affected blood vessel in the brain. **(14).**

Origin and course

The aortic arch gives rise to the brachiocephalic artery, from which subsequently stems the right common carotid artery; the left common carotid artery branches off the aortic arch

just downstream the brachiocephalic trunk. The left and right common carotid arteries run along parallel to each other and divide near the angle of the mandible to the external and internal carotid arteries. The external carotid supplies the face and neck branching off immediately, while the internal carotid arteries do not branch until the origin of the ophthalmic artery bilaterally. Subsequently, the internal carotid arteries bifurcate onto the anterior, middle and posterior cerebral arteries, on each internal carotid artery. The largest terminal branch of the internal carotid artery is the MCA. The MCA divides into four main surgical segments, denominated M1 to M4. The M1 segment extends from the ending of the internal carotid artery, perforating the brain up to its division. The M2 segment bifurcates or occasionally trifurcates. It travels laterally to the Sylvian fissure, and its branches end in the cerebral cortex. The M3 segment travels externally through the insula into the cortex. Finally, the M4 segments are thin and extend from the Sylvian fissure to the cortex. (14).

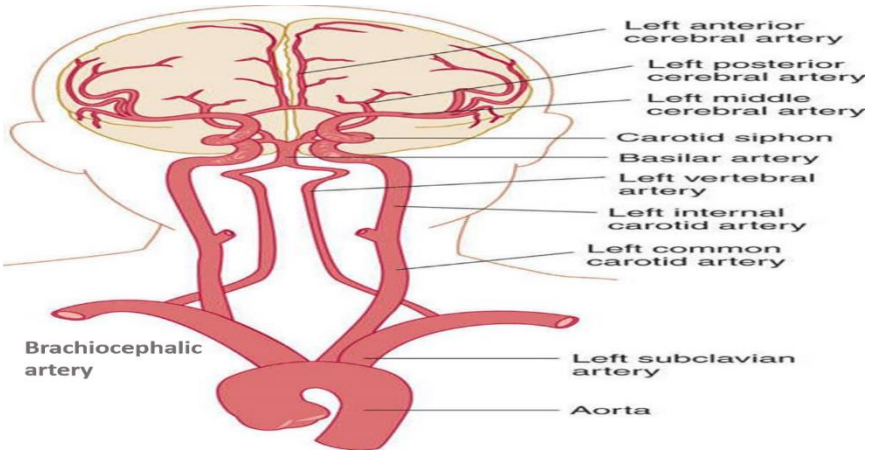

Diagram (2) Anatomy of Middle cerebral artery (15).

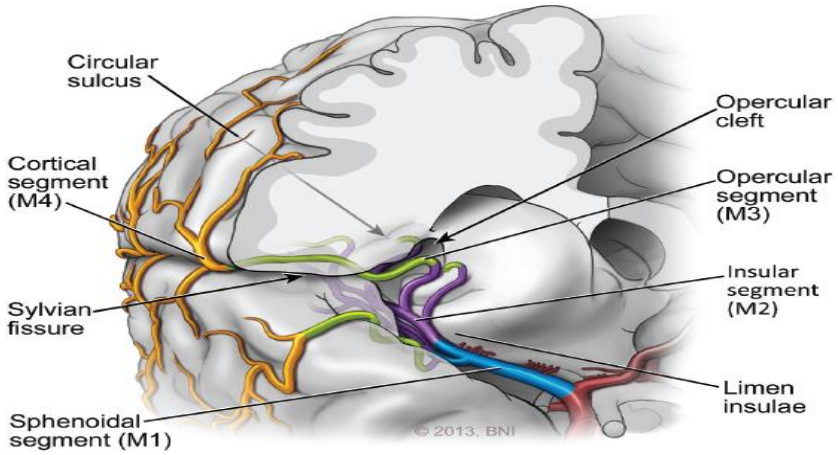

Diagram (3) Artist's illustration depicting the anatomy of the four segments of the middle cerebral artery. (Used with permission from Barrow Neurological Institute, Phoenix, AZ.) (16).

Branches and area supplied by MCA:

The primary function of the MCA is to supply specific regions of brain parenchyma with oxygenated blood. The cortical branches of the MCA irrigate the brain parenchyma of the primary motor and somatosensory cortical areas of the face, trunk and upper limbs, apart from the insular and auditory cortex. The small central branches give rise to the lenticulostriate vessels, which irrigate the basal ganglia and internal capsule. The superior division irrigates the lateral and inferior frontal lobe, which involves the Broca area responsible for speech production, language comprehension, and writing. The inferior division of the MCA irrigates the superior temporal gyrus, which involves Wernicke's area responsible for speech comprehension and language development **(14).**

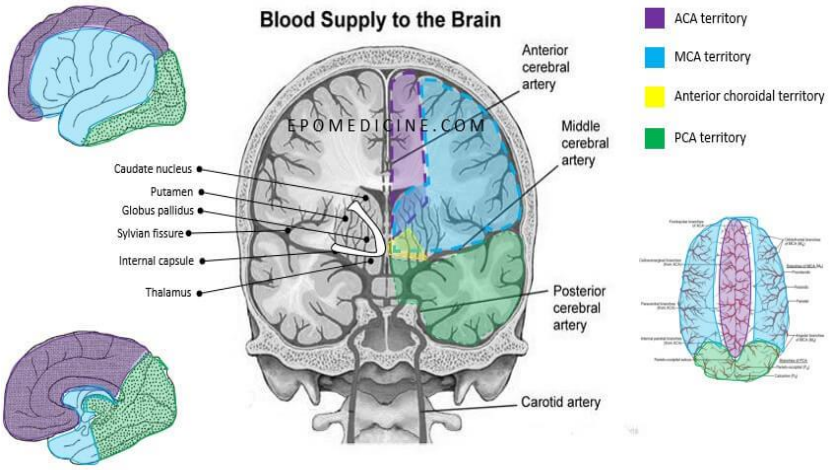

Diagram (4) Blood Supply of the brain and blue areas are supplied by the Middle cerebral artery. (17).

Parts affected by middle cerebral artery occlusion:

Middle artery syndrome presents with contralateral sensory loss of the legs, arms, and lower two-thirds of the face due to tissue necrosis of the primary somatosensory cortex. Contralateral paralysis of the arms, legs, and face may be observed due to necrosis of the primary motor cortex, which is observed clinically as muscle weakness, spasticity, hyperreflexia, and resistance to movement (upper motor neuron signs). Ipsilateral eye deviation is observed due to frontal cortex Brodmann area 8 becoming ischemic, impairing planning of eye movement, symptoms that are exacerbated by contralateral homonymous hemianopsia. dominant, most commonly left-sided, hemisphere stroke results in Broca aphasia if the superior division of the MCA is affected. In contrast, Wernicke's or conduction aphasia may be seen if the inferior division of the MCA is affected. A non-dominant, most commonly right-sided, hemisphere stroke results in hemineglect syndrome, presenting with anosognosia, apraxia, and hemispatial neglect **(14).**

The MCA supplies blood to a portion of the frontal lobe and the lateral surface of the temporal and parietal lobes. Strokes that occur in this area result in primary motor and sensory deficit of the face, throat, hand, and arm; if the stroke occurs in the dominant hemisphere, it also can affect speech. **(17)**

Histology of cerebral cortex

Cerebral cortex is formed histologically of six layers. From the outer most layer I near to the pia matter ,to the inner most layer VI near to underlying white matter .

I: The plexiform layer (or molecular layer) consists largely of fibers, most of which travel parallel to the surface, and relatively few cells, mostly neuroglial cells and occasional horizontal cells of Cajal.

II: The small pyramidal cell layer (or outer granular layer) consists mainly of small pyramidal cells and granule cells, also called stellate cells.

III: The layer of medium pyramidal cells (or layer of outer pyramidal cells) is not sharply demarcated from layer II. However, the pyramidal cells are somewhat larger and possess a typical pyramidal shape.

IV: The granular layer (or inner granular layer) is characterized by the presence of many small granule cells (stellate cells).

V: The layer of large pyramidal cells (or inner layer of pyramidal cells) contains pyramidal cells that, in many parts of the cerebrum, are smaller than the pyramidal cells of layer III but in the motor area are extremely large and are called Betz cells.

VI: The layer of polymorphic cells contains cells with diverse shapes, many of which have a spindle of fusiform shape. These cells are called fusiform cells. In addition to pyramidal cells, granule cells, and fusiform cells, two other cell types are also present in the cerebral cortex: the horizontal cells of Cajal, which are present only in layer I and send their processes laterally, and the cells of Martinotti, which send their axons toward the surface (opposite to that of pyramidal cells) **(18).**

The FG loop peptide (FGL, EVYVVAENQQGKSKA), is a neural cell adhesion molecule-mimetic peptide (NCAM – mimetic peptide) **(19).**

Structure

Cell adhesion molecules (CAMs) constitute a large class of plasma membrane-anchored proteins that mediate attachment of cells to neighboring cells and to the surrounding extracellular matrix. Furthermore, CAMs often form heterophilic cis-interactions through which they can regulate intracellular signal transduction cascades and thereby modulate a number of processes including cellular proliferation, survival, differentiation, and migration **(.** In addition, CAMs expressed in the nervous system can regulate processes such as neurite outgrowth, synaptic maturation and synaptic plasticity in relation to learning and memory formation **(20).**

Neural cell adhesion molecule NCAM is a cell surface glycoprotein expressed mainly in three isoforms, NCAM120, NCAM140 and NCAM180, named according to their apparent molecular weights. Extracellularly, all three isoforms consist of five Ig-like modules followed by two fibronectins type III (FN3) modules The extracellular part of NCAM is engaged

in both NCAM homophilic binding and heterophilic interactions with a variety of different molecules **(19).**

The extracellular domains of adhesion molecules extend from the cell and bind to other cells or matrix by binding to other adhesion molecules of the same type (homophilic binding), binding to other adhesion molecules of a different type (heterophilic binding), or binding to an intermediary "linker" which itself binds to other adhesion molecules **(20).**

One important heterophilic interaction partner of NCAM is the fibroblast growth factor receptor (FGFR) Both the first(FN3,1) and second (FN3,2) NCAM FN3 modules were shown to be involved in the interaction with FGFR **(19).**A number of synthetic peptides derived from sequences in the NCAM (FN,3) domains are reported to bind and activate FGFR. Most notably, a synthetic peptide, FGL **(21).**

NCAM signal interacts through its growth factor receptors including fibroblast growth factor receptor (FGFR). The FGFR-1 binding site of NCAM is a 15 amino acid small loop peptide that is is called the FGL peptide **(22)**

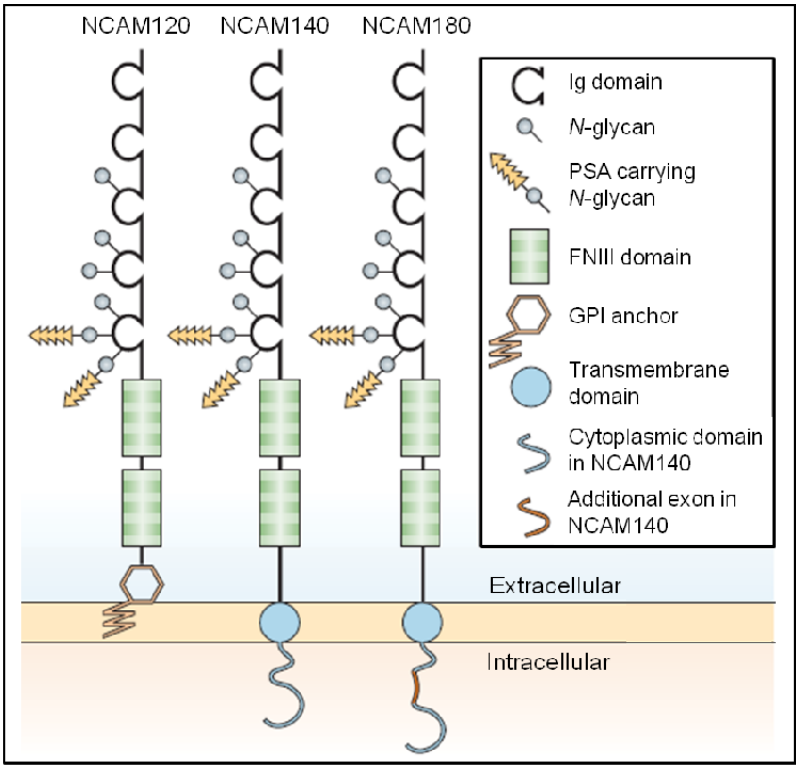

Diagram (5) The three main isoforms of NCAM: - NCAM120, NCAM140 and NCAM180. Extracellularly, all three isoforms consist of five Ig-like modules followed by two fibronectins type III (FN3) modules (23).

NCAM plays an important role in the nervous system in development, plasticity and learning and memory **(21).**

FGL is a 15 amino acid peptide synthesized from the interconnecting loop region of the second fibronectin type III module in the extracellular domain of NCAM, which interacts with the binding site of FGFR1 **(19).**

Mechanism of action

FGL (FnIII2) are reported to bind and activate FGFR. Interaction with FGFR1 results in receptor phosphorylation without prior hemophilic NCAM binding **(24).**

The Neural Cell Adhesion Molecule (NCAM) plays a crucial role in development of the central nervous system regulating cell migration, differentiation and synaptogenesis. NCAM mediates cell–cell adhesion through homophilic NCAM binding, subsequently resulting in activation of the fibroblast growth factor receptor (FGFR). NCAM-mediated adhesion leads to activation of various intracellular signal transduction pathways, including the Ras-mitogen activated protein kinase (MAPK) and the phosphatidylinositol-3-kinase (PI3K)-Akt pathways. A synthetic peptide derived from the second fibronectin type III module of NCAM, the FGL peptide, binds to and induces phosphorylation of FGFR without prior homophilic NCAM binding. FGL peptide is able to mimic NCAM heterophilic binding to the FGFR by inducing neuronal differentiation as reflected by neurite outgrowth through a direct interaction with FGFR in primary cultures of three different neuronal cell types all expressing FGFR subtype 1: dopaminergic, hippocampal and cerebellar granule neurons. Moreover, the FGL peptide promotes neuronal survival upon induction of cell death in the same three cell types. The effects of the FGL peptide are shown to depend on activation of FGFR and the MAPK and PI3K intracellular signalling pathways, all three kinases being necessary for the effects of FGL on neurite outgrowth and neuronal survival **(24).**

This peptide promotes e.g. neurite outgrowth and neuronal cell survival in vitro. Furthermore, it has multiple effects in vivo including reduction of inflammation, promotion of learning and memory formation, and the reduction of signs neuropathology and cognitive impairment in an Alzheimer's disease model **(21).**

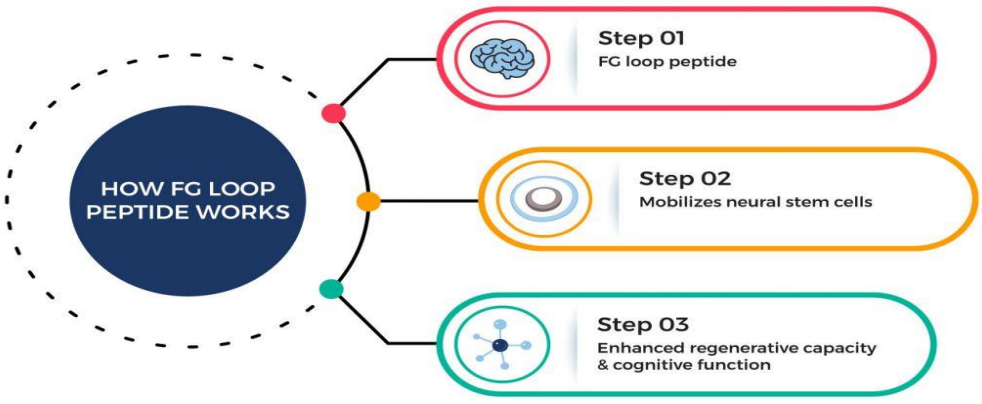

Diagram (6) The neural cell adhesion molecule (NCAM) plays vital roles in the development and function of the nervous system, promoting neurogenesis, neurite outgrowth, neuronal sur-vial and plasticity and learning and memory. (19).

NCAM-derived peptide, FGL, can act as a novel anti-inflammatory agent in models of ageing and age-related diseases, restoring cognitive function and averting neuropathology **(24).**

The NCAM signaling transduction cascade is initiated by direct interaction of NCAM with fibroblast growth factor receptor (FGFR), expressed on both neurons and glial cells **(21).**

It enhances hippocampal function and plays a role in neuronal development. FGL has also been shown to be protective against 6-hydroxydopamine and amyloid-β (Aβ) in vitro **(22)**

FGL has been shown to rapidly enter the bloodstream, to penetrate the blood–brain barrier, and to circulate within the cerebrospinal fluid upon systemic administration. FGL was reported to be the most promising NCAM mimetic peptide for clinical translation **(25).**

FGL was observed to be able to both mobilizes endogenous neural stem cells (NSC) and enhances the generation of oligodendrocytes in vitro. Furthermore, **Skibo et al. (26**) reported that FGL conveys neuroprotection after stroke. Hence, FGL constitutes an attractive candidate molecule for enhancing the therapeutic potential of endogenous NSC and may thus open a new therapeutic strategy for stroke **(27).**

FGL improves cognitive function through enhancement of synaptic function. that FGL induces large changes in the fine structure of synapses and dendritic spines in hippocampus of aged rats, complementing data showing its effect on cognitive processes. FGL increases the length of neurites from rat embryonic hippocampal neurons with a bell-shaped dose–response curve characteristic of growth factor-induced neurite extension. This stimulatory response can be blocked with an antibody against FGFR, indicating that the NCAM-derived FGL peptde is an agonist of the FGFR **(24).**

Side effects.

Up to now no side effects have been described regarding FGL treatment in rodents. In addition, icv injection in young rats (twice in two consecutive days) did not alter their locomotive capacities, as assessed by an open field test, and also it did not alter weight gain or cause any signs of illness **(28).**

No Conflict of interest.

References:

[1] Dias, M., Partington, M., & SECTION ON NEUROLOGIC SURGERY (2015). Congenital Brain and Spinal Cord Malformations and Their Associated Cutaneous Markers. Pediatrics, 136(4), e1105–e1119.

[2] Moore, K. L., Persaud, T. V. N., Torchia, M. G., & Elsevier. (2020). The developing human: Clinically oriented embryology (Eleventh ed.). Edinburgh: Elsevier.

[3] Rewane, A., & Munakomi, S. (2020). Embryology, Central Nervous System, Malformations. In StatPearls. StatPearls Publishing.

[4] Zecevic, N., Milosevic, A., Rakic, S., & Marín-Padilla, M. (1999). Early development and composition of the human primordial plexiform layer: an immunohistochemical study. Journal of Comparative Neurology, 412(2), 241-254.
[5] Rakic, P. (1995). A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends in neurosciences, 18(9), 383-388.
[6] Kwon, H. J., Ma, S., & Huang, Z. (2011). Radial glia regulate Cajal–Retzius cell positioning in the early embryonic cerebral cortex. Developmental biology, 351(1), 25-34.
[7] Song, J., Yang, X., Zhou, Y., Chen, L., Zhang, X., Liu, Z., . . . Li, W. (2019). Dysregulation of neuron differentiation in an autistic savant with exceptional memory. Molecular Brain, 12(1), 1-12.
[8] Marieb, E. N. & Hoehn, K. (2018). Human anatomy & physiology (Global; Eleventh; ed.). Harlow, England: Pearson Education Limited.
[9] Mtui, E., Gruener, G., Dockery, P., Fitzgerald, M. J. T., & Elsevier. (2017). Fitzgerald's clinical neuroanatomy and neuroscience (7.th ed.). Philadelphia, PA: Elsevier.
[10] El-Baba RM, Schury MP. Neuroanatomy, Frontal Cortex. (2020). [Updated 2020 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/books/NBK554483/
[11] Haines, D. E., Mihailoff, G. A. (2018). Fundamental neuroscience for basic and clinical applications (Fifth ed.). Philadelphia, PA: Elsevier.
[12] Jawabri, K. H., & Sharma, S. (2019). Physiology, cerebral cortex functions.
[13] Winn, H. R., (2017). Youmans and winn neurological surgery (Seventh ed.). Philadelphia, PA: Elsevier.
[14] Navarro-Orozco, D., & Sánchez-Manso, J. C. (2021). Neuroanatomy, middle cerebral artery. StatPearls [Internet].
[15] Waxman, S. G. (2017). Clinical neuroanatomy, 28th edition McGraw-Hill.
[16] Song, J., Yang, X., Zhou, Y., Chen, L., Zhang, X., Liu, Z., . . . Li, W. (2019). Dysregulation of neuron differentiation in an autistic savant with exceptional memory. Molecular Brain, 12(1), 1-12.
[17] Epomedicine. Circle of Willis and Forebrain Blood Supply [Internet]. Epomedicine; 2016 Aug 1 [cited 2023 Nov 20]. Available from: https://epomedicine.com/medical-students/circle-willis-forebrain-blood-supply/.
[18] Ross, M., & Pawlina, W. (2016): Histology: a text and atlas: with correlated cell and molecular biology. 7th ed., p.p. 698-720. Barcelona: Wolters Kluwer.
[19] Hansen, S. M., Køhler, L. B., Li, S., Kiselyov, V., Christensen, C., Owczarek, S., ... & Berezin, V. (2008). NCAM-derived peptides function as agonists for the fibroblast growth factor receptor. Journal of neurochemistry, 106(5), 2030-2041.
[20] Walmod, P. S. (2014). Introduction. Cell adhesion molecules: implications in neurological diseases. Advances in neurobiology, 8, xvii-xxi.
[21] Berezin, V., & Bock, E. (2010). NCAM mimetic peptides: an update. Structure and Function of the Neural Cell Adhesion Molecule NCAM, 337-353.

[22] Cox, F. F., Berezin, V., Bock, E., & Lynch, M. A. (2013). The neural cell adhesion molecule-derived peptide, FGL, attenuates lipopolysaccharide-induced changes in glia in a CD200-dependent manner. Neuroscience, 235, 141-148.
[23] Wobst, H. J. (2014). Identification of novel cytosolic binding partners of the neural cell adhesion molecule NCAM and functional analysis of these interactions (Doctoral dissertation, Universitäts-und Landesbibliothek Bonn
[24] Neiiendam JL, Kohler LB, Christensen C, Li S, Pedersen MV, Ditlevsen DK, Kornum MK, Kiselyov VV, Berezin V, Bock E (2004) An NCAM-derived FGF-receptor agonist, the FGL-peptide, induces neurite outgrowth and neuronal survival in primary rat neurons. J Neurochem 91:920-935.
[25] Secher, T., Novitskaia, V., Berezin, V., Bock, E., Glenthøj, B., & Klementiev, B. (2006). A neural cell adhesion molecule–derived fibroblast growth factor receptor agonist, the FGL-peptide, promotes early postnatal sensorimotor development and enhances social memory retention. Neuroscience, 141(3), 1289-1299.
[26] Skibo, G. G., Lushnikova, I. V., Voronin, K. Y., Dmitrieva, O., Novikova, T., Klementiev, B., ... & Bock, E. (2005). A synthetic NCAM-derived peptide, FGL, protects hippocampal neurons from ischemic insult both in vitro and in vivo. European Journal of Neuroscience, 22(7), 1589-1596.
[27] Klein, R., Blaschke, S., Neumaier, B., Endepols, H., Graf, R., Keuters, M., ... & Rueger, M. A. (2014). The synthetic NCAM mimetic peptide FGL mobilizes neural stem cells in vitro and in vivo. Stem cell reviews and reports, 10, 539-547.
[28] Cambon K, Hansen SM, Venero C, Herrero AI, Skibo G, Berezin V, Bock E, Sand i C (2004) A synthetic neural cell adhesion molecule mimetic peptide promotes synaptogenesis, enhances presynaptic function, and facilitates memory consolidation. J Neurosci 24:4197-4204.