

A Review on Neuronutrition

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ABSTRACT

Nutrition is a basic human need and a prerequisite to a healthy life. Since it is bonded with food, it is essential to advocate nutrition in terms of food. A proper diet is important from the very early stages (gestation period) of life for proper growth and development. Neuronutrition portrays how food affects the brain and its function. Brain is where the performances begin and end. It monitors and controls all the energy metabolism of the body and it never stops working. Neuronutrition is the nutrition needed to achieve healthy brain and good neurocognitive function. Dietary manipulations are a viable strategy for enhancing cognitive abilities and protecting the brain from damage. No single food is key to good brain health but rather a combination of food. Neurological disorders such as Alzheimer's disease, mental fatigue, and memory problems are prevalent across the world, and this opens the door to provide tailor-made products which cater to consumer's desire for better neuronutrition.

Keywords: Neurocognitive function, Neurofood, Neuronutrition, Nutrition.

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INTRODUCTION

Nutrition is defined as "the process of providing or obtaining the food necessary for health and growth"; "the sum of the processes by which an animal or plant takes in and utilizes food substances" or "the science that links food to health and disease." Food supplies energy in the form of calories and the building block nutrients that create and maintain cells (Austin, 2016). Nutrition can affect the brain with profound implications for mental health and degenerative diseases throughout the life cycle. Since it is bonded with food, it is better to advocate in terms of food rather than nutrients. The role of nutrition in neuroscience is complex with all aspects of nutrition. The concern is not with the impact of a single nutrient rather with the multiple nutrients and their interactions. The overall nutrient content in the food directly affects the structure and function of the brain as they are dependent on the nutritional input. But it is difficult to access the specificity of the nutrient with regard to their brain function (Dauncey, 2009). Food means to provide energy and are the building material of the body and can prevent and protect against diseases. For instance, a diet rich in omega -3-fatty acids supports cognitive function in the brain. Regular proper diet, exercise, and interactions with the environment have a profound effect on the health of the brain and mental function (Gomez-Pinilla, 2008). Certain deficiencies such as vitamin B12, B9, and zinc results in symptoms such as low mood, fatigue, irritability and cognitive which may lead to cognitive decline. Evidences linking diet and illness evolves the focus from specific nutrient deficiencies to an emphasis on the overall dietary pattern. High processed foods and western diet patterns have an increased risk of developing attention-deficit/ hyperactivity disorder (ADHD), depression, cognitive impairment. On the other side, whole foods, traditional foods are found to be preventive against developing mental illness (Lachance and Ramsey, 2015). Proper nutrition is interrelated with brain

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health throughout life. Deficiency in nutrition causes lower cognitive development, reduced concentration and attention and it also reduces the performance in the later stages of life. Due to these characteristics, changing the diet with balanced nutrition without any deficiencies may preserve the brain from deterioration. For instance, when food supplemented with folic acid is given to women during pregnancy period showed an increase in the neurodevelopment of fetus. To enhance the cognitive abilities, proper diet is of great importance (Banjari *et al.*, 2014). Nutritional needs vary over the lifespan of an individual but the pattern of the diet throughout the lifespan affect the health of the brain. Micronutrients such as minerals and vitamins when taken as a part of the diet, supply a greater benefit. Changing nutrition behavior life long even with a small shift can have a profound effect. For example, increased intake of fruit just 1 serving per day, had the potential to reduce cardiovascular mortality risk by 8% annually (Global Council on Brain Health, 2018). The brain is a heterogeneous organ, is comprised of multiple anatomical regions and processes. All nutrients are important for the



growth, development, and function of the brain but certain specific ones are particular during each phase of the growth of the individual. In particular, nutrition plays a versatile role in the development of the brain during conception to 3 years of age (Cusick and Georgieff, 2016).

NUTRITION AND BRAIN HEALTH

The brain is an organ where all the functions of the body begin and end. It is the controlling and monitoring unit of a human body and the important part is that it never stops working. It is a high metabolic and nutrient demanding organ. According to a study, the brain consumes 20% of an individual's daily caloric intake. It is comprised of 60% fat, a higher concentration of cholesterol and Poly Unsaturated fatty acids like omega-3-fats.

Anatomically brain comprises a million of cells known as neurons. The transmission of a signal from one neuron to the other is through a chemical compound called Neurotransmitter. These neurotransmitters are composed of amino acids that are present in food that connects the nutrition and brain functions. A WHO study showed that 14 countries had a prevalence of mental illness in relation to the deterioration in a proper diet. The process of memorization and learning is facilitated by the communication of neurons in the brain through synapses which is supported by an important nutrition factor known as omega-3-fatty acids. This omega-3 fats contained in nuts, fruits like Kiwi, fish helps in preventing mental disorders such as dementia. The common deficiencies related to mental disorders are omega-3-fatty acids, vitamin-B and Amino acids which are the precursors of neurotransmitters.

Nutrition is one of the most important epigenetic factors that have a significant effect on brain development and behavior. Development of the brain comprises a highly sequential order of events that are under the control of genetic factors but is also influenced by some epigenetic factors. Proper growth and development of the brain are essential for the normal functioning of human being ranging from simple actions such as walking, eating to complex action like thinking. This is done with the help of nearly one billion cells with specialized interconnection. From studies, it is shown that deficiency in nutrients decreases the volume of the brain, number of neurons, etc (Salonga, 2007). Nutrition can affect the brain throughout the life cycle, with profound implications for mental health and degenerative disease. From entire diets to specific nutrients, everything affects brain structure and function. The Physical, chemical and physiological development of the brain evolves from the continuous interaction of genetic and environmental factors. The environmental conditions are concerned with providing energy and nutrients needed for cellular structures and various metabolic systems. Nutritional and environmental factors may affect the central nervous system capability and performance in a variety of ways. There are two major categories of change viz anatomically, various indices of the brain structure are decreased by moderate to severe

malnutrition. Biochemically, the nutrient supply available to the brain cells is reduced, producing metabolic abnormalities with malnutrition. An adequate intake of necessary nutrients (e.g., micronutrients, EFAs) is beneficial whereas an excessive intake of some other (e.g., sugar, saturated fat) is detrimental (Food and Nutrition Board, 1973).

Amino acids and minerals, the building blocks of the production of neurotransmitter are important in the pathophysiology of mental illness. For example, folic acid/ folate, a B-vitamin being an essential vitamin has to be obtained from the diet is important for the methylation cycle, which produces a crucial co-factor for the monoamine neurotransmitter synthesis. Vitamin-B plays a major role in the metabolism of homocysteine which is an intermediate in the methionine metabolism. Elevated levels of homocysteine in the blood is a risk factor for cardiovascular disease and depression (Miller, 2008).

ROLE OF DIET IN BRAIN FUNCTION

Certain dietary components have effects on cognitive abilities. Dietary factors can affect multiple processes of the brain by regulating neurotransmitter pathways, membrane fluidity, signal transduction pathways, and synaptic transmission. The Omega-3-fatty acids, DHA is an important component of the neuronal membranes but the human body is inefficient to synthesize the required quantity of DHA and taking these through diet is the only option in maintaining Omega-3-fatty acids.

Proper nutritional status is required for proper brain development and maintenance of its normal functioning. Through biological functions, certain micronutrients affect the function of the brain. Some of the basic functions of the brain are:

Energy Metabolism of Neurons and Glial Cells

The human brain is highly metabolically active and it requires a constant supply of glucose to meet its energy needs. The blood glucose level is to be maintained properly to avoid hypoglycemia and to supply the brain with its fuel. In the initial stages of fasting, the liver glycogen breakdown to maintain the blood glucose level through gluconeogenesis pathway for which vitamin-B biotin is required. During the prolongation of the fasting period/ starvation, ketone bodies are used by the brain. But glucose is preferred than ketone bodies as they are acidic and high levels in the blood is toxic which results in ketoacidosis. Furthermore, for the complete metabolism of glucose, nutrients like magnesium, iron, manganese are essential. Moreover, vitamins, riboflavin, and niacin are required for the generation of cellular energy in the form of ATP through electron transport chain (Huskinson *et al*, 2007).

Neurotransmitter Synthesis

A neurotransmitter is a chemical substance produced by the nerve cells responsible for the transmission of signals from

one neuron to the other neuron called synaptic transmission or neurotransmission. Some of the neurotransmitters are GABA, aspartate, serotonin, acetylcholine, etc. Further, some vitamins including niacin, folate, and vitamin-B12 are required for the synthesis of neurotransmitter. For instance, zinc is essential for the proper function of GABA, norepinephrine. Vitamin C is important for the synthesis of norepinephrine (Tanphaichitr, 2001).

Neurotransmitter Binding to Receptors

Neurotransmitter functions by binding to the receptors on the cell membrane of the neuron releasing the neurotransmitters. This binding allows the ions to flow into the cell by opening the gate like ion channels. Vitamins influence the process of neurotransmitter binding to the neurons that release them (Leklem, 2001).

Nerve Impulse Propagation

The speed at which the impulses propagate is influenced by the myelination of the nerves. Myelination is a process of insulating the nerve fibers with the production of the myelin sheath which is made up of lipids and proteins. This sheath acts as an insulator which allows the rapid and efficient transmission of the nerve impulses. To maintain the integrity of the myelin sheath, folate and vitamin B12 is essential and thiamine is required for the maintenance of the nerve membrane potential and the proper conductance. Moreover, iron is an essential substance in the development of cells that produce myelin (Huskinson *et al.*, 2007).

Homocysteine Metabolism

Homocysteine is a sulfur-containing amino acid that is an intermediate in the metabolism of sulfur-containing amino acid methionine. This homocysteine can be remethylated into methionine with folate and vitamin B12 and it can also be metabolized into cysteine with vitamin B6. In the absence of these nutrients, the homocysteine level is increased. Elevated homocysteine level in the blood is linked with dementia and Alzheimer's disease (Prins *et al.*, 2002).

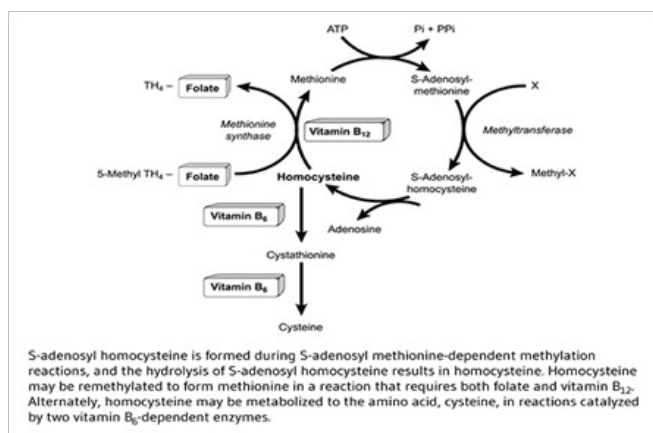


Fig. 1: Homocysteine metabolism

CONSEQUENCES OF MICRONUTRIENTS DEFICIENCY

Essential Fatty Acids

The essential fatty acids include alpha-linolenic acid, an Omega-3-fatty acid and linolenic acid, an omega-6-fatty acid. ALA and LA cannot be synthesized by the human body and must be acquired only through the diet. The long-chain omega-6 fatty acid, arachidonic acid (AA), can be synthesized from LA. Additionally, two long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can be synthesized from ALA. Omega-3 and Omega-6 PUFA play a crucial role in the functioning of vision and the nervous system. The phospholipids of the gray matter in the brain are enriched with high proportions of DHA and AA, indicating them to be the most important compound for the functioning of the central nervous system. The changes in the content of DHA in the neuronal cell membranes could alter the function of ion channels or membrane-associated receptors, as well as the availability of neurotransmitters (Food and Nutrition Board, 2002).

Zinc

The brain contains high levels of Zinc where it has catalytic, structural, and regulatory roles in cellular metabolism. Zinc has an additional role in the central nervous system as a neurosecretory product and as a cofactor. In this role, zinc is highly concentrated in the synaptic vesicles of the so-called 'zinc-containing' neurons. These neurons are exclusively found in the forebrain. Neuropsychological impairment is one major health consequence of zinc deficiency. Zinc is involved in many enzymatic reactions inside of the brain and it assists with the metabolism of omega-3-fatty acids. More than one-third of the world's population is zinc deficient. Research has linked low dietary zinc intake to depressive symptoms-the lower the zinc levels, the greater the depression. Zinc levels are 30% lower in individuals with ADHD. Sources of zinc are pumpkin seeds, beans, nuts, oatmeal, egg yolks, fresh gingerroot, etc (Sandstead *et al.*, 2000).

Magnesium

Magnesium plays an important role in the neurochemical transmission and muscular excitability. Extracellular magnesium is important for the maintenance of nerve and muscle cells and especially for the transmission of the nerve impulses for the neuromuscular junctions. More than 60% of the population is magnesium deficient. Magnesium has an essential role in supporting brain plasticity, which is the sign of a youthful, flexible brain primed for optimal learning, memory, and cognitive function. Magnesium level is decreased by excess alcohol, salt, coffee, sugar, soda, and antibiotics. Low levels of magnesium have been implicated in mood disorders, depression, and suicide. Sources of magnesium are wheat and oat bran, brown rice, nuts, dark leafy green vegetables, etc (Rude and shils, 2006).



Calcium

Calcium ion is an important intracellular signal which regulates many physiological processes. The skeleton in the human body is a large reserve of calcium which helps in maintaining the normal blood calcium level even the dietary intake of calcium is less. Change in calcium homeostasis in the brain contributes to the cognitive decline which is associated with the normal aging and the development of neurodegenerative disorders. Sources of calcium are mainly dairy products like milk, yogurt and nondairy products like seafood, leafy greens, legumes, dried fruit, tofu, etc., (Foster,2007).

Iron

Iron is an important component of many proteins and enzymes. It is essential for the development of brain cells that produce myelin (Oligodendrocytes) and it is also an important mineral required for the synthesis of many neurotransmitters. Deficiency of iron in various stages of the development of the brain has detrimental consequences. Maternal deficiency of iron has serious consequences for the woman and the fetus. Though iron is an essential mineral for the functioning of the brain, it is toxic in higher concentration in the neuron. Sources of iron are lean beef, oysters, chicken, beans and lentils, tofu, baked potatoes, cashews, dark green leafy vegetables such as spinach, etc (Gambling and McArdle,2004).

Vitamin C

Vitamin C in high concentrations is mostly distributed in the pituitary gland and the brain. Vitamin-C is essential in the synthesis of the neurotransmitters dopamine and noradrenaline. Ascorbate (vitamin C) is a vital antioxidant molecule present in the brain. The functions of ascorbate in the CNS and brain are numerous. It directly acts to scavenge oxygen or nitrogen-based radical species generated during normal cellular metabolism. This is required for the enzymatic reaction that synthesis the neurotransmitter norepinephrine from dopamine. Sources of vitamin C are bell peppers, dark leafy greens, kiwis, broccoli, berries, citrus fruits, tomatoes, peas, papayas, etc., (Harrison and May 2009).

Vitamin D

The vitamin D receptor is expressed in brain tissue. Vitamin D is essential for the normal development and functioning of the brain and its deficiency may impair cognitive abilities which is a major problem worldwide, with an estimated one billion people having an insufficient level. Cognitive impairment, memory loss, and vitamin D deficiency are correlated. Sources of vitamin D are Cod liver oil, salmon, shrimp, egg yolk, etc., (Holick,2007).

Vitamin E

The α -tocopherol is a form of vitamin E which is an important fat-soluble antioxidant. The α -tocopherol plays a vital role in maintaining the integrity of cell membranes as it prevents oxidation induced lipid destruction in the brain.

The deficiency of vitamin E causes lipid peroxidation in brain tissues. They are believed to play a role in certain conditions related to aging. Severe vitamin E deficiency results mainly in neurological symptoms such as impaired balance and coordination, injury to the sensory nerves, muscle weakness and damage to the retina of the eye. Sources of vitamin E are nuts, such as almonds, peanuts and hazelnuts, and vegetable oils, such as sunflower, wheat germ, safflower, corn and soybean oils, etc., (Macevilly and Muller,1996).

BRAIN AND GUT HEALTH

The brain and gut are connected physically and biochemically in numerous ways. The gut and brain are connected chemically through neurotransmitters that enable neurotransmission. The gut is also called as the "second brain" as it synthesizes many neurotransmitters that brain synthesizes like serotonin, dopamine, and gamma-aminobutyric acid, which plays a key role in regulating the mood. Gut microbes produce chemicals that affect brain health. Studies of gut flora is on its infancy. Gut flora serves many purposes in the human body and some of them are digestion and absorption of the food, synthesis of nutrients like vitamin k, pantothenic acid, amino acids, proteins, etc., acts as a housekeeper of the digestive tract by coating it with antimicrobial substances. The gut and psychology syndrome (GAPS) provides the connection between gut health and the functioning of the brain (Campbell,2008). The gut and gut microbes play a vital role in the immune system and inflammation. The gut microbiota is the collection of microorganisms live within mammals which provide crucial signals for the development and functioning of the immune system. The gut microbiota and the immune system are connected in a complex structure that communicates even across a long distance within the human body. The microbial metabolites which are produced by the interactions between microorganisms play a vital role in human physiology with effects on the immune system. These observations support the concept that mammals are holobionts (Rooks and Garrett, 2016).

The gut bacteria affect brain health and improving gut microbiome may improve the health of the brain. The gut microbiome is a complex ecosystem and a normal adult is inhabited by 10^{13} to 10^{14} microorganisms which are at least 10 times higher than the number of human cells and 150 times greater than the genes present in a human body. Nearly more than 1000 species of organisms are present in a human gut. The colonization of the infant microbiota commences at the time of delivery and the initial microbiome will be of maternal signature. Currently, probiotics are defined as a live organism that, when ingested in adequate amounts, exerts a health benefit and those that affect the brain are often referred to as "psychobiotics". Some probiotics have the potential to act as psychotropic agents as they mechanistically function as delivery vehicles for certain neuroactive compounds. Probiotic bacteria manufacture and secrete neurochemicals. For instance, certain strains of *Lactobacillus* and *Bifidobacterium*

secrete gamma-aminobutyric acid (GABA) which is the main inhibitory neurotransmitter responsible for regulating many physiological and psychological processes (Dinan *et al.*, 2016).

The microbiome is a critical component in the brain-gut axis and has an impact on the behavior and mood at the CNS level. A staple gut microbiota must be important for proper signaling along the gut-brain axis. Stress at the CNS level may also affect the gut microbiota. For instance, Signaling molecules released into the gut from brain cells can result in changes in gastrointestinal motility and secretion of the microbiota (Grenham *et al.*, 2011).

NEURODISEASES AND DIET

A neurologic deficit refers to the abnormal function of a specific body area. This altered function is due to the weaker function of the nerves system causing neurodegenerative diseases. They are caused by degeneration (dysfunction and death) of neurons within the brain. Neurological disorders are now the leading source of disability globally, and aging is increasing the burden of neurodegenerative disorders. Some of the most leading neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, dementia, and cognitive decline, etc which can be prevented by changing the form of diet.

Alzheimer's disease (AD) is characterized by a massive neuronal death-causing memory loss, cognitive impairment and behavioral alteration that ultimately lead to dementia and death. Hyperphosphorylation of tau protein and beta-amyloid results in "protein misfolding disorder" which in turn leads to Alzheimer's disease. The number of AD patients in the world is estimated at 46.8 million and is expected to increase up to 131.5 million by 2050. A higher dietary intake of vitamin C, E, B₁₂, flavonoids, antioxidants can reduce the risk of developing AD. The polyphenols containing beverages have a positive effect on the treatment of AD as they reduce the homocysteine concentration. Several polyphenols have the potential to scavenge reactive oxygen species (ROS) and

superoxide radical. A diet containing a minimum amount of saturated fatty acids and a high amount of unsaturated fatty acids, polyphenols, vitamins and regular intake of fruits helps in reducing the risk of developing AD. According to the World Health Organization, the Mediterranean diet is a positive approach in preventing many diseases including AD. It is proved through numerous experimental data that nutrients such as PUFA, polyphenols, vitamins can enervate the neurodegenerative process in AD (Ravi *et al.*, 2018).

Parkinson's disease is a second most chronic degenerative disorder normally defined as a disorder of movements that affects nerve cells in the part of the brain controlling muscle movements. In a normal person, brain Cells in Substantia Nigra produce and release dopamine which lands on neurons of the other parts of the brain which is responsible for the regulation of muscle movement. But in the case of Parkinson's disease patient, the Substantia Nigra degenerates which no longer able to produce dopamine which leads to loss of control of muscle movements resulting in Parkinson's disease. In working up with the PD patients, it is advised to include the nutritional assessment as it may ameliorate (Barichella *et al.*, 2009). Fruits and vegetables with a high amount of phytochemicals and antioxidants may slow down the progression of PD. Omega 3 fatty acids have a protective effect on neurodegenerative disorders. Normally a diet that is rich in phytochemicals, bioconstituents can be used for disease management (Seidl *et al.*, 2014). Dietary intake of vegetables from Solanaceae family such as tomatoes, peppers showed reduced risk towards PD (Nielsen *et al.*, 2013).

CONCLUSION

No single food is key to good brain health but rather a combination of healthy foods is likely to help protect the brain. From this review, it is important to notice that the pattern of diet over life span affects brain health. Most of the population does not meet the recommended dietary allowance (RDA) of important brain vitamins and minerals. These are only the minimum recommended intakes. Diet, an exercise in our daily routine have the potential to alter brain health and mental function. The studies relating to diet and brain health are at its infancy stage and hence further clinical studies are needed for the effect of diet, exercise, nutrition with neurodegenerative diseases. Ultimately the success in clinical trials will results in the incorporation of the nutrients in daily diet.

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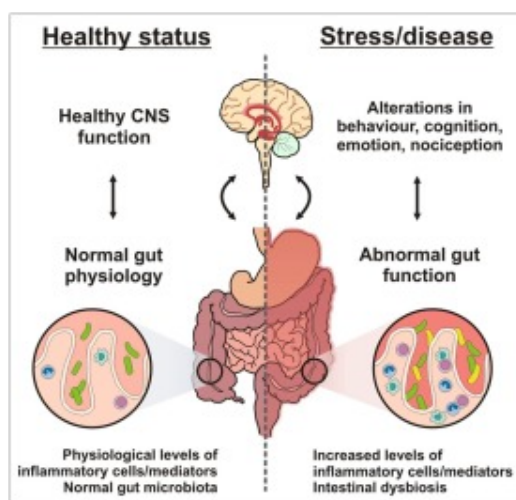


Fig. 2: Gut-brain connection



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