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Review Article

Metabolic Reprogramming in Nerve Cells

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Abstract

Mammalian physiology has a complex networked system which is called the nervous system. Nerve cells can undergo degeneration due to injury and stress. Regeneration is a difficult process, and axonal regeneration may succeed or may not. Metabolic changes can lead to the development of many diseases including neurodegenerative diseases. Survival of the metabolically impaired state of the nerve cells is referred to as metabolic reprogramming of the nerve cells in the present review. Metabolic rewiring dependent on intrinsic and extrinsic factors is a necessity for neuron regeneration and can act as curative in neurogenesis. These events highlight the importance of understanding molecular mechanisms of nerve cells metabolism. The knowledge can help us to understand the process of reprogramming in nerve cells that will be useful for nerve cell regeneration. Different plant extracts, or food components or physical activity may help in the process of metabolic reprogramming of nerve cells, but there is a need for scientific studies to understand the process that can support neural regeneration process along with the first line of therapy. The present review discusses neuron metabolism, effects in nervous disorders, and suggests possible interventions that can be exercised as therapeutic interventions.

Keywords: Neural metabolism, Metabolic transitions, Glial cells, Astrocytes, Neurodegenerative diseases, Neural regeneration, Dietary components, Nerve growth factors

Introduction

The mammalian system is composed of different types of systems and networks, and one of the communicating systems is the nervous system. The nervous system along with the endocrine system is responsible for maintaining homeostasis in the human body [1]. The fundamental unit of the nervous system is neuron, or also called as 'nerve cell'. Apart from neurons, the nervous system also bears neuroglial cells. The nerve cell carries electrical impulses, and consists of dendrite, axon and a cell body and communication between nerve cells occurs by structures called 'synapse' [2]. The nervous system is not only responsible for the cognitive functions in our body but also the movement, digestion, and other activities [3]. The nervous system in vertebrates is divided into two categories, central nervous system (CNS) and peripheral nervous system (PNS) [4].

Impairment of functioning of the nervous system and nerve cells leads to the generation of neurodegenerative disease. Functional impairment of neurons and behavioral abnormalities are evoked by neural cells [5]. Neural non-coding RNAs play a critical regulatory role in brain functions [6]. Neurodegenerative diseases occupy an important viewpoint in public health because of the complexity involved in prevalence, time, and cost in treatment. The prevalence is due to a reason of multiple factors, and one of these is due to the lifestyle of an individual. Effective treatment for neurodegenerative diseases is difficult, and this gives the importance to finding out new therapeutic interventions. Metabolic factors play prime in the development of many complex diseases, and the same cause lies in the development of neurodegenerative diseases [7,8]. Low nutrient and oxygen conditions leads to an environmental adaptation of the cells, primarily tumour cells by the process called as metabolic rewiring, whereas metabolic plasticity refers to the ability of the cells to adapt their metabolic status to specific needs during development, differentiation, or response to stimuli [9-11].

Again, metabolic reprogramming used in context to tumour cell metabolism refers to ability of tumour cells to alter their metabolism for growth and energy requirements [12]. The mechanism of metabolic plasticity meets gene regulation, which is observed in metabolic rewiring also [13]. Metabolic functions of nerve

cells alter neurodegeneration and ageing and other pathological conditions. This can also be an adjustment of the nerve cells to grow and sustain themselves under different pathological situations. Thus, here in this work, the survival of metabolically impaired state of nerve cells is referred to as 'metabolic reprogramming' of nerve cells. The situation can be altered or enhanced by different factors that can be intrinsic, or extrinsic like diet, exercise, etc. The concept of metabolic reprogramming emphasizes on the need for development of therapeutic strategies that can be based on drugs, food, lifestyle, exercise, and social interactions in cure for neurodegenerative diseases [14]. The present work within the limited scope is looking at the metabolic aspects in functioning and dysfunctioning of the nerve cells and suggest on the possible interventions that can be exercised as therapeutic interventions.

Neural Metabolism

Understanding metabolism of the neurons can unravel reasons behind nerve cell damages as in stroke, memory loss as well as in Parkinson's and Alzheimer's disease [15]. Brain neurons together with astrocytes possess a high energy demand [16].

Microglia is understood to be a reactive contributor in neurological disorders [5]. Growth of dendrite, a highly branched network system in human brain is a complex process and is controlled by a few signaling pathways. In this process, active Nedd4-1 prevents protein degradation by ubiquitylation, and dendrites can grow due to the functions played by Nedd4/Rap2/TNIK [17].

In situations of injury to the brain, nerve cells cannot be replenished, as they cannot renew themselves. However, in events of stroke, treatment with stem cells shows a promising approach [18]. Furthermore, nerve growth factors, or neutrophins also help in the regeneration process [19].The transcription factor family, E2F playing role in cell cycle also plays important role in neuronal differentiation, and E2F4 is important for terminal differentiation of neuroblasts [20]. Communication between neurons demands high energy, and glucose supply can vary in the nerve cells. Excess concentration of glucose can lead to mitochondrial inactivation in the neurons [21]. The process can lead to abnormal neuronal firing and axonal shearing and consequently death of the neurons. This is seen in Alzhemier's disease, as well as in Dementia, and ability of a person to understand and respond to any signal comes down [22]. Energy demand in the brain rises with large number of neurons and is essential to maintain functioning of the neurons. Bulk of the energy consumption occurs at synapses, which is balanced by the activity of Na+/K+ ATPase pump with regulation of other ions like Ca2+, Mg2+, HCO3-, Cl- and H+. Astrocytic end feet mediate supply of glucose to the brain cells. Astrocytes can store glucose as glycogen or convert glucose to lactate and supply lactate to neurons by Glucose transporters (GLUT 3) for conversion to pyruvate and entrance to the citric acid cycle. Additionally, glucose can directly enter neurons by GLUT 3 for generation of pyruvate by glycolysis or enter to pentose phosphate pathway (PPP) to generate NADPH and other molecules [23]. Intermediates from PPP act as nucleotide precursors, whereas intermediates from glycolysis can serve as precursors for many biosynthetic metabolic pathways [24]. Lactate shuttle in brain occurs by mono-carboxylate transporters, key molecules for interaction between glia and neurons mediated by carbonic anhydrases (CA), playing role in bicarbonate transport [23,25]. Glucose reaches brain astrocytes, oligodendrocytes via GLUT 3 and microglial cells via GLUT 5 [26]. Glycogen is unevenly distributed in the brain, and concentrations are highest in regions with the highest synaptic density [27,28]. During stress, or any activity requiring more energy, glycogen from astrocytes is immediately converted to lactate, and lactate provides neuro protective effect against hypoglycemia, or ischemia [25]. Synaptic activity also involves uptake of K+ ions by astrocytes released by neurons with energy derivation from the breakdown of glycogen reserves [29-32]. Neurons can increase their glycolytic ability in response to stimulation and the metabolic resupply of energy in neurons can be regulated by feedback signaling by adenosine diphosphate and feedforward signaling by calcium ions. The choice between glycolysis and oxidative phosphorylation has an important effect on health and disease. However, during brain stimulation there is transient uncoupling between glycolysis and oxidative phosphorylation [33]. Astrocytes can flourish under hypoxia and depend on glycolysis, whereas neurons depend on oxidative metabolism and can succumb to ischemia [34]. Axonal myelination and regeneration are supported by monocarboxylate transporters [35]. Apart from glucose and lactate, acetate also serves as energy source to nerve cells. ATP generation in the brain is triggered mainly by glucose metabolism, and glucose supply to the brain is controlled by neurovascular coupling, and cross blood brain barrier by GLUTs. Disturbances in glucose metabolism leads to many neurological diseases [36,37]. Disruption of monocarboxylate transporters can also lead to neurodegeneration. The peripheral nervous system depends on lactate as fuel source [38-42]. Astrocytes, however, use acetate which later enters the citric acid cycle [43-48].

Glucose is needed in resting physiology, whereas lactate and acetate are essential in times of increased neuronal activities, including situations of limited oxygen or glucose supply. However, neuronal stimulation has also been reported to lead to an increased glucose consumption [33,48]. The homeostatic tone of the nervous system is regulated by lactate [49]. Furthermore, peroxisomal β-deficiency leads to metabolic disorder with involvement of the central nervous system (CNS) [5].

Molecular motors apart from playing role in neural disease pathogenesis also play role in brain wiring and neuronal plasticity, as well as regulates CNS and PNS. The molecular motors KIF 3 and KIF17 function for anterograde transport, whereas cytoplasmic dynein 2 plays role in retrograde transport. The myosin family proteins functions in short range transport processes. The KIF3 motor also acts as a tumour suppressor [50,51]. Alterations in the NAD+ level impair the metabolic signaling pathways and lead to different neurodegenerative disorders, ageing and tumourigenesis [52].

Metabolic Interactions

Metabolic interactions between astrocytes and neurons directs brain activity. Disruption of this interaction can lead to the development of generation of neurological diseases. Astrocytes act as sites for L-serine synthesis and mitochondrial reactive oxygen species (ROS) production [24]. Synapse generated glutamate (Glu) and ammoniacal ions (NH4+) is uptaken by the glial cells, and releases glutamine to neurons [53,54]. The functioning of NMDA receptors regulates synaptic plasticity and memory due to D-Serine released from 3-phosphoglycerate (PG) in astrocytes [55,56]. On the other side, L-serine plays a critical role in neurotransmission [57,58]. Simultaneously, glycine synthesized from serine acts as inhibitory neurotransmitter via ionotrophic glycine receptors located primarily in brain stem and spinal cord. The L-serine to glycine conversion coupled to the folate cycle, catalyzed by serine hydroxymethyl transferase leads to the generation of N-5, N-10-methylenetetrahydrofolate (5,10-meTHF) from tetrahydrofolate (THF). L-serine, important for neurotransmission, also provides carbons for the generation of GSH (γ-L-glutamyl-L-cysteinyl-glycine), an antioxidant [59,60]. Astrocytes with the help of syncytia help in the intra-astrocytic transfer of glucose, water, Ca2+, K+, etc. Immature astrocytes are embedded within astrocytoma which lack neurons [35]. In contrast to neurons, astrocytes can preserve energy stores such as glycogen which later is converted to glucose or lactate [61-63]. Phosphatidylserine, present in neuronal membranes modulates synaptic receptors, proteins, and release of neurotransmitters by exocytosis with Ca2+ -dependent membrane fusion reactions. Impairment of phosphatidylserine functioning results in cognitive impairment and Alzheimer's disease [64].

Neuron-astrocyte metabolic interaction functions to maintain cellular homeostasis of glutamate, the excitatory neurotransmitter of the brain. Glutamate also plays a role in networking glucose and amino acid metabolism between neurons and astrocytes. Glutamate metabolic shifts lead to the generation of neurodegenerative diseases, like Alzheimer's disease, Huntington's disease. Glutamate is recycled between neurons and astrocytes as glutamate and glutamine by glutamate-glutamine cycle [65]. Glutamate also serves as the key metabolite in malate-aspartate shuttle (MAS). The MAS activity transfers cytosolic reducing equivalents of NADH or NAD+ to the mitochondrial matrix, essential for sustained glycolytic activity [66,67]. Dysfunction of glutamate metabolism can lead to neurodegenerative diseases, like Alzheimer's and Huntington disease. One of the features of Alzheimer's disease is reduced levels of glutamate levels in the brain, as well as due to disturbed astrocyte glutamine support [68,69].

The blood-brain barrier (BBB), formed by capillary endothelial cells is essential to prevent entry of neurotoxins and pathogens to brain, and functionally interacts with its surrounding of astrocyte perivascular end feet, pericytes and basement membrane [70]. Disturbances in the functioning of BBB leads to loss of synaptic transmission, neuronal connectivity, and functioning [71]. The blood brain barrier is formed by capillary endothelial cells surrounded by basement membrane, pericytes and astrocyte perivascular end feet. Tight junctions between endothelial cells prevent entry of water-soluble molecules, and nutrients can be transported by passive or active-mediated transporters. However, gases and small nonpolar lipids can enter by passive diffusion [70].

Energy Metabolism in Brain

Brain energy metabolism involves networking between energy demand and supply coupled with changes in local blood flow and glucose utilization, also referred to as neurovascular and neurometabolic coupling. Astrocytes play an important role in neurovascular coupling, and astrocyte-neuron interactions regulate cerebral blood flow [72]. Neurons depend on oxidative metabolism to meet their energy needs, whereas astrocytes (glial cells) are highly glycolytic. However, it is the astrocytes that play a critical role in neurotransmitter recycling and anaplerosis, and mobilization of astrocytic glycogen stores is critical for long-term memory formation in rats [73-76]. Interaction between astrocyte and neuron is important for defense against oxidative stress, and reduced form of glutathione peroxidase is essential for the detoxification of reactive oxygen species [77].

Metabolic Transitions

Metabolic reprogramming, or transitions occurring in neurons, like changes in oxidative stress and induction of transcriptional sensors of oxidative stress are important in regulating physiological neuronal function, and brain plasticity and cognitive function. Metabolic pathways are disrupted in neurodegenerative diseases and can be due to oxidative stress [78].

Astrocytes have more metabolic plasticity than neurons. Upon nitric oxide exposure, astrocytes elevate their glucose metabolism through glycolysis and thus limiting fall in ATP levels and apoptosis of astrocytes. In contrast, nitric oxide exposure makes neurons lose their ATP levels and apoptosis. If neurons grow in low ATP energy levels, neurons can be deformed leading to death of the cell [15]. Even though metabolic plasticity of astrocytes is beneficial for their beneficial for their homeostatic and neuroprotective functions in physiological conditions, it can turn out to be harmful in pathological conditions [79-81]. Energetic interactions between astrocytes and neurons can also lead to neuronal excitability [72]. Similarly, neuroenergetics or coupling between neuronal activity and energy metabolism plays a critical role in neuron-astrocyte metabolic interactions [82]. Thus, wherein impairment of astrocyte functions can lead to neurodegenerative diseases, restoration of astrocyte function can provide lights for therapeutic opportunities in neurodegenerative diseases [83].

In Alzheimer's disease, induction of hypoxia leads to an elevation of HIF-1α target, β-site β-amyloid precursor protein cleavage enzyme 1 (BACE 1) that cleaves amyloid precursor protein (APP) to form Aβ. In neuronal mitochondria, oxidative metabolism is disrupted by accumulation of Aβ. This leads to reduction in TCA cycle entry, acetyl-CoA production, α-ketoglutarate dehydrogenase complex, and elevated reactive oxygen species formation and transglutaminase activity leading to increased α-synuclein aggregation with reduction in oxidative respiration [84-90].

Changes in zinc and copper level are coupled to Alzheimer's disease pathology, and co-localization of copper is seen in Aβ plaques Simultaneously, iron is also co-localized with Aβ-plaques and neurofibrillary tangles [91-97]. Increased iron levels have been reported to be linked with APOE-4 AD risk allele [98]. Ageing is one of the risk factors for developing Alzheimer's and Parkinson' s disease (PD). Genetic and environmental factors can also lead to PD and Huntington's disease (HD). Parkinson's disease affects patient motor function with formation of α-synuclein aggregates. Huntington's disease is characterized by formation of expanded CAG repeats in the Huntingtin (HTT) gene leading to neuronal degeneration and cell death in the brain [78]. Development of Parkinson's disease can result also due to the mutations in mitochondrial genes and exposure to the neurotoxin, MPP+ that inhibits ETC complex I and oxidative respiration leading to permanent Parkinsonism [99-101]. Retention of memory in brain for long term is due to the lactate presence [102]. However, the essential energy substrates during development are ketone bodies, 3-β-hydroxybutyrate (3HB) and acetoacetate (AcAc) [103-105]. Ketone utilization during brain maturation and development is not only essential for energy metabolism, but also for amino acid and lipid metabolism as well as in postnatal period [106,107]. Ketone oxidation in the adult brain increases under conditions of limited glucose availability, wherein ketone bodies are produced in liver from fatty acid and ketogenic amino acid oxidation. In the brain, astrocytes can only generate ketone bodies and uptake of ketone bodies in brain occurs by mono carboxylate transporters [108]. Ketosis in the brain is regulated by blood concentration which is coupled with reduced glucose utilization [109-111].

Consequences of Metabolic Dysfunction

Spontaneous coordinated behavior and nerve cells involves role of gap junction protein, innexin 2 [112]. Ageing reduces gray matter in the brain by dendritic arborization and reduction in synapse numbers. Additionally, white matter density also reduces in the brain with ageing coupled with an increase in the number of white matter lesions and decline in ATP levels. This also leads to structural alterations in mitochondria as well as downregulated association of mitochondria with endoplasmic reticulum [113-116]. Ageing also leads to a gradual decline in energy utilization by the brain, reduced NAD and NAD+ levels and elevated levels of NADH [117,118]. With reduction in ability of the neurons to generate required amount of ATP, synapses initiate their degeneration and dysfunction [119]. Loss of blood-brain-barrier integrity results in parenchymal accumulation of blood-derived proteins and immune cells leading to the development of inflammation [120]. Thus, hypometabolism leads to cognitive dysfunction in ageing as well as the development of adaptive signaling pathways in brain [121]. The neuronal firing patterns leading to neuroanatomical changes result in coginitive deficits with age. Neurons also with age lose their tree branching pattern and turnover [70]. Endothelial transporter proteins are altered in amylotrophic lateral sclerosis (ALS) patients with degeneration of astrocyte endfeet and abnormal level of blood protein in the cerebrospinal fluid. There is also deposition of IgG and complents in spinal cord and motor cortex [122-126]. The ALS patients also exhibit glucose intolerance, insulin resistance and hyperlipidemia [127-129]. Impairment of mitochondrial functions in mitochondria results from the mutations in the genes encoding α-synuclein, Parkin (Park 2), PTEN induced putative kinase-1 (PINK1), Leucine rich repeat kinase-2 (LRRK2), DJ-1 (Park 7) [130].

Sleep apnea

The healthcare issues in neurological patients can also lead to the development of obstructive sleep apnea [131]. Obstructive sleep apnea (OSA) is a complex disease related to the dysregulation of the molecular clock and other associated biological processes [132]. The hypothesis being put forth in OSA is that the monoaminergic neurons (noradrenergic and serontonergic) inhibit cholinergic neurons leading to suppression of REM sleep and upregulating NREM sleep. This is due to the decrease in firing frequency of monoaminergic neurons in NREM sleep, and increase in firing of cholinergic neurons in REM sleep. The process leads to the development of a recurring cycle [133]. Sleep apnea is associated with many other complications including Down's syndrome [134]. Understanding molecular biology of sleep apnea can lead to the development of new treatments [135]. There are a few reports that have shown the molecular domains affected in OSA, adipokines, cell-adhesion molecules and molecules responding to the endoplasmic reticulum stress [136].

Reprogramming

The cellular and molecular mechanisms of cognitive functions need to undergo more research. Though there are several reports on neuronal reprogramming, the mechanisms of cell fate conversions are not being well studied. Reports observe the co-expression of Bcl-2 and anti-oxidative treatments to improve glial to neuron conversion after traumatic brain injury [137]. The neural transcription factor, Neuro D1 could also reprogram glial cells to functional neurons, as well as human cortical cells to functional neurons [138]. Furthermore, the transcription factor ATF3 induced after early peripheral nerve injury developed cellular plasticity in sensory neurons to transform into a regenerative state [139]. Additionally, animal models have shown that Muller glia in zebrafish can be reprogrammed to regenerate retinal neurons [140].

In Drosophila, gut derived cytokines metabolically reprogrammed glial cells [141]. Glia has also been evidenced to undergo metabolic reprogramming in amyotrophic lateral sclerosis (ALS) due to mitochondrial dysfunctions [142]. Synaptic plasticity is a critical mechanism at the neuronal level [143]. Research work evidences the role of astrocytic ApoE to reprogram lipid metabolism and regulate neuronal epigenetic conditions. Brain function with memory activity is modulated in the process. However, comparatively ApoE4 is able to reprogram neurons than ApoE3 [144].

Neural Regeneration

Nerve injuries can result in loss of body parts. Regeneration is a difficult process, and stem cell replacement therapy is one of the possible interventions. Studies also suggest the use of growth factors

in regeneration of the nerve cells [145]. Neurological dysfunctions and neurological disease are associated with alterations in neural stem cell (NSC) differentiation [146]. The molecules, p53 and p73, play key role in brain development and regulation of CNS development, and transition of GABA from excitatory to inhibitory coupled with glutamate excitatory inputs plays critical role in neurogenesis [147-151]. The mTOR (mammalian target of rapamycin) signaling plays an important role in differentiation, neurite outgrowth and synaptic formation, whereas HDAC inhibitors act as neuroprotective in neurodegeneration [152-154]. In summary, extrinsic, and intrinsic factors regulate neurogenesis and impairment of neurogenesis contributes to development of neurodegeneration and cognitive impairment [155]. Of the important players in synaptic circuit, gap junction protein connexin-36 plays a critical role [156].

Furthermore, nerve growth factor, a target derived neutrophic factor essential for the survival, growth and functioning of the peripheral and central nervous system also plays role in chemotactic movement of rat peritoneal mast cells by influencing survival and differentiation of the mast cells. The mechanism involves drastic morphological change and distribution of F-actin fibres and use of mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathway [157]. Different types of cells of the central nervous system arise from the ability of neural stem cells to undergo symmetric divisions and proliferation, as well as differentiation by asymmetric divisions. The NSCs generate neural precursor cells that again give rise to functional neurons in embryonic neuron development and adult central nervous system. The process for generation of pluripotentiality in NSCs to create young neurons called as neurogenesis, involves development of neuroblasts which differentiate to new neurons that migrates to the existing neural networks due to regulation by intrinsic and extrinsic signals [158,159]. The extrinsic factors includes transcriptional regulators, Sonic Hedgehog (Shh), Notch, Wnt, Bone morphogenetic proteins (BMP), Oct4, Sox2 and Nanog, whereas the intrinsic factors includes epigenetic regulators [160]. Interaction between microRNAs (miRNA) and nuclear receptor TLX plays role in dedifferention process of NSCs. Crosstalk between let-7b and cyclin D1 through TLX initiates stages of development [161,162]. Additionally, neurogenesis is mediated by growth factors and neutrophic factors. The identified neutrophic factors playing role here are four, namely nerve growth factor (NGF), BDNF, neurotrophin 3(NT-3), and neurotrophin 4/5(NT-4/5), wherein neutrophins binds to tyrosine kinase receptors [163-166].

Neural transcription factors are involved in the development of neural stem cells right from the embryonic stage [167]. For development of brain, subgroup of the basic-helix-loop-helix (bHLH) transcription factor, a neural lineage bHLH transcription factor, Neurod family is essential for development of CNS. The participating members of the Neurod family are four, namely Neurod 1, Neurod 2, Neurod 4 and Neurod 6 [168].

The bHLH transcription factor, NeuroD1, critical to initiate neuronal development program can reprogram other cell types to neurons. NeuroD1 binds directly to the regulatory elements of neuronal genes that can be developmentally silenced by epigenetic mechanisms [169]. The LIM homeodomain transcription factor, ISL1 plays a key role in the development of sympathetic nervous development by controlling cell cycle gene expression. This is essential for glial differentiation repression and neuronal differentiation [170].

Neural morphogenesis is regulated by the cell-adhesion molecules and actin-associated proteins. The movement mechanism of nerve growth cones with actin fibers determines axonal pathfinding in embryogenesis [171].

Long distance signaling in neurons is mediated by calcium signaling and bidirectional transport of proteins, vesicles, and mRNAs along microtubules. This is also helped by the axonal lengths and characteristic feature of the neurons being polarized cells. The process mediates in communication about axon injury to the soma, so as to enable initiation of the repair mechanisms [172]. Glial cell derived neurotrophic factor has been observed not only to prolong survival and induce enteric neurogenesis, but also improve colon structure and function in Hirschsprung disease [173]. Reports also observe the use of exosomes for the treatment of peripheral nerve injury [174].

The fibroblast growth factor (FGF) signaling is responsible for the development of spinal cord [175]. Insulin Growth factor 1 (IGF) signalling plays role in adult neurogenesis, as well as stimulating differentiation of adult hippocampal progenitor cells to oligodendrocytes by inhibiting BMP signaling [176]. Vascular endothelial growth factor (VEGF) functions in the regulation of growth and maturation of neurons during development [177,178]. The three growth factors, FGF, IGF and VEGF functions by associating with tyrosine kinases [146]. Microenvironmental resource competition regulates differentiation of oligodendrocytes [179]. Neurotransmitters, like glutamate playing critical role in neural communication also function in neurogenesis [180,181]. In contrast to the role of neurotransmitter glutamate, GABA acts as the main inhibitory neurotransmitter in the brain. GABA acts in dual role, either as depolarizer, or as hyperpolarizer but decides based on the intracellular chloride content that decides on the transmembrane gradient [182]. Dopamine is another neurotransmitter of catecholamine involved in ontogenesis and embryonic proliferation of the germinal zone in development [183]. Chemical factors and intercellular contacts also play a critical role in remodeling of the dorsal root ganglion (DRG) cells. Primary sensory neurons are enclosed in DRG, and DRG cells can differentiate to different neuronal subpopulations [184]. In summary, the process of differentiation can be modulated by kinetics of protein metabolism in ganglion cells preganglionic nerve endings [185].

Axonal Regeneration

Axonal degeneration results from damage to the CNS, and CNS inflammation induces axonal degeneration. Axon growth is inhibited by RhoA. However, stimulation of cyclic adenosine monophosphate (cAMP) by prostacyclin leads to axonal regeneration [186]. Regeneration of axons is signaled by several intrinsic and extrinsic factors [186,187]. The first step of axon regeneration is initiated by growth cone formation. Nonregenerative response leads to the formation of retraction bulbs. Long range anterograde transport helps in axon extension, but in situations of injury, transport gets inhibited and that leads to the regeneration failure [187].

Curative Approaches

Cognitive performance in animals along with neurogenesis and synaptic plasticity improves with dietary energy restriction or fasting and exercise [188]. Experiments in Drosophila melanogaster has shown that short-term fasting results in increased long-term memory, whereas protracted fasting prevents aversive and not pleasant memory formation leading to conclude upon that intermittent bioenergetic changes are good for brain works [189,190]. This phenomenon can be related to the increase in brain functions and neuro protection under metabolic shocks conferring resistance to dysfunction and degeneration [191-193]. Brain ageing is accelerated by sluggish lifestyle, reduced physical and social activity, excessive calories intake, etc., whereas good lifestyle habits with dietary energy restriction, macro- and micro-nutrients in diet, intellectual and social stimulations, reduction of stress uplifts cognitive abilities in an individual [188]. At the cellular level, neuronal resilience is improved by upregulation of the transcription factors, cAMP response element-binding protein (CREB), nuclear factor κB (NF-κB), and nuclear factor erythroid-derived 2 (NRF2) and genetic expression of proteins counteracting cellular stress at multiple subcellular sites, and by different mechanisms [194]. Antioxidant enzymes, antiapoptotic protein, chaperones, neutrophic factors, etc. are upregulated by physical activity and intermittent fasting [194,195]. Adaptive cellular stress response upregulates cytoprotective signaling pathways by secreted neutrophins [196]. Amylin the food intake satiation hormone, and controller of blood glucose levels, and with ability to form amyloid plaques is not only restricted the pancreatic islet cells, but also extends to the CNS, wherein it co-localizes with Aβ-plaques in AD patients. Amylin thus lies at the interface between metabolic and neurodegenerative disorders [197-200]. These suggest that intake of drugs and food promotes brain health development.

Dietary Influence

Food components in terms of dietary intake can help in recovery from neurogenic diseases, or can act as predictive for neurogenic diseases. Of the extrinsic factors to regulate neurogenesis, dietary factor is one of the factors to regulate molecular events in energy metabolism and synaptic plasticity, as well as can complement the cation of exercise [201]. Diet modulates sympathetic nervous system (SNS) role, and intake of sucrose upregulated SNS activity in rat study [202]. Multiple sclerosis (MS) proceeds with the loss of oligodendrocytes and destruction of myelin sheath. Intake of some foods like more of fish, polyunsaturated fatty acids (PUFA), exercising calorie restriction can either decrease, or lead to the development of MS. Adolescent obesity or intake of insufficient vitamin D levels enhance possibility for MS development. Consumption of ketogenic diet can lead to modulate vulnerability to MS [203]. Development of MS may collocate itself with initiation of metabolic syndrome [204-206]. The situation can aggravate loss of healthy gut microbiota and short chain fatty acid producing bacteria, and encouragement of pathogenic species, like Enterobacter spp [207-209]. Dietary carbohydrates regulate nervous system function. Vagus nerve, acting as the communication pathway between gut, live and brain senses peripheral glucose availability to the brain sites. Intake of carbohydrates also enhances tryptophan concentration in the brain [202]. Enteroendocrine cells can sense bacterial tryptophan catabolites to activate enteric and vagal neuronal pathways [210]. Furthermore, glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake by CNS-GIPR signaling [211]. In situations of nerve injuries, nutrients show neuroprotective properties, apart from recovery of injured nerve tissue [212].

Caffeine helps to improve memory power by increasing cAMP (cyclic Adenosine monophosphate) levels. Curcumin from turmeric crosses the blood-brain barrier, boosts serotonin, dopamine and neutrophic factor and activates NRF2. This helps in new brain cell growth and is beneficial in animal models of traumatic brain injury, stroke, AD and PD. However, turmeric constitutes only 3-6% of curcumin [213-216]. The peripheral nervous system, susceptible to injury, can be regenerated by following a tailored diet [217].

Magnesium, involved in different and many enzymatic reactions leads to regeneration of the peripheral nerves [218]. Plant derived compounds can help in regeneration of the peripheral nerves [219]. Axonal regrowth in the nerve cells can be affected by DHA, part of neuronal membrane phospholipid by elevating expression of Bcl-2, as well as by inhibiting caspase 3-downstream effects [220-222]. Vitamin D expresses regulatory effect on neutrophic factors involved in nerve regeneration [223-225]. Polyphenols and polyphenol-rich foods benefit the regeneration of peripheral nerves and give neuroprotective effects in neuro degenerative diseases [226,227]. Methylcobalamin (MeCbl), activated form of vitamin B12, improves nerve conduction, regenerates nerves from injuries and is used in treatment of Ad and rheumatoid arthritis [228]. Also, a high fat diet can lead to hypothalamic dysfunction [229]. There are many nutrients that are beneficial for neuroprotective effect and brain functioning [230]. Ageing populations need brain health supplements. Vitamins C, D and B12 offer neuroprotective support and B family vitamins prevent dementia and boosts neurotransmitter production [229]. A few of those that affect the neural health of a person have been listed in Table 1 [231-239].

Table 1: Essential food ingredients for healthy neuro functioning. The Table highlights a few of the essential ingredients required in diet for neuroprotective functioning.

Authors	Food	Role	Quantum Requirement
Johnson [231], Mayoclinic [232], TimesofIndia [233], Medical News Today [234], Webmd [235], Healthshots [236], Healthline [237],	Vegetables	Green leafy vegetables (kale, collards, spinach, lettuce) beneficial to reduce dementia risk and cognitive decline. Supplies Vitamin B complex (acts as Neurotransmitters), C, E (acts as neuroprotectors and Magnesium (calms nerves).	One serving a day in groups or as single item/by change
NIA [238], SCL Health [239]	Berries	Blueberries, Strawberries For reduced cognitive decline	Two or more servings/week
	Nuts and Eggs	A handful of nuts and an egg [supplies vitamin E for Neuroprotection, egg provides choline (not more than 3500mg/day) essential to make acetylcholine)	Nuts: Five times/week Egg: one/day
	Legumes	supplies protein, fiber, Vitamin B complex Supports brain health	Four times/ week
	Fish, walnuts and almonds	supplies omega-3-fatty acids for brain and nerve health	Once a week, or 100grams/day serving
	Wine	Lowers risk of dementia	Light to moderate
	Dark Chocolates	contains flavanol and gives anti-inflammatoryand antioxidant properties	One serving/Week
	Broccoli	contains glucosinolates that reduces rate of breakdown of acetylcholine provides Vitamin K and folate (not more than 1000 mg/day for adults) that protects from blood clot and stroke. Improves memory and concentration	one serving/day
	Pumpkin (ripe) seeds	provides Magnesium, iron (essential for neurotransmitter synthesis, neuron myelination,mitochondrial functioning and consumption not more than 45 mg/day for adults), copper and zinc. [low Magnesium levels is linked to migraines,depression and epilepsy, copper (not more than 8000 mg/day for adult) s, and zinc (essential for neural regeneration, axonal and synaptic transmission), can reduce chances of Alzheimer's, Parkinson's disease and depression]	one serving/day
	Protein	essential for brain functioning and for production of neurotransmitters (sources: pulses, legumes,egg, meat, poultry, dairy products, fish)	0.8gram/kg body weight
	Coffee	Caffeine and antioxidants [increase alertness by blocking adenosine; improves mood by upregulating neurotransmitter, dopamine; increases concentration]	3-4cups/day

The probable dosage as per the recommendations and traditional culinary knowledge has been put forth over in Table 1, but one needs to look for quantum availability of that dosage from food product(s) as per the first line of therapy. Though there is less scientific evidence, Bacopa monnieri is consumed to improve brain health [240]. In general, the beneficial nutrients for balanced neurotransmitter supply to the brain includes amino acids, glucose, vitamins C, E, D, B-complex, β-carotene, minerals, arachidonic acids, docosahexaenoic acid, eicosapentaenoic acid, gamma-linolenic acid, apart from antioxidants for neuroprotective functions [241].

The presence of antioxidants in the diet protects against oxidative damage to nervous system cells. Biochemical data indicate that polyunsaturated fatty acids such as arachidonic acid (AA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA) as structural components of the nervous system play a key role in its function. The nutrition of the entire body also influences the production of neurotransmitters in the brain.

Conclusion

Therapeutic approaches have been adopted in patients with nervous system impairment using electrical stimulation of the CNS. However, it is unclear about the cells or cellular elements that activated upon electrical stimulation of the CNS [242]. There are many reports detailing the signaling and transcription factors that play a critical role in neural progenitor differentiation to neurons and glia cells. Even, long term memory is fuelled by pentose phosphate pathway of glial glucose [243]. Therapeutic strategies for ALS can stem out from glial mitochondrial function and metabolic reprogramming [244]. Development and induction of stem cells can help in replacement of the specific cells affected by neurodegenerative disease and injuries [245]. Direct regeneration of the neurons is a difficult process, however research understandings from the effect of growth factors, or any other component from the diet, or food component including lifestyle may help in regeneration studies under in vivo and in vitro conditions. The knowledge can be useful in the treatment of brain tumours also. The most common brain tumours in adults are glioma, and neuroblastoma in children. Loss of miRNA-34a leads to the loss of p53 that directs formation of adrenergic fibers in head and neck cancer [246]. Reports have identified molecular targets for therapeutical recovery procedures in brain tumours [247]. Experimenters have also uncovered a new class of memory cells, 'grandmother neuron' that is the crossroads of sensory perception and memory [248]. Exogenously administered growth factors also led to regeneration of peripheral nerves [249]. Reports also confirm the reversal of neurodegeneration at advanced stage by neuronal metabolic rewiring [250]. Furthermore, calmodulin kinases may also contribute to the pathology of neuropsychological disorders. Stress coupled with neuroinflammation leads to neurodegeneration. Herbal medicine in nerve regeneration is a therapeutic option in this situation, and Ginkgo biloba, an antioxidant can help in nerve regeneration. Higher dosage of Ginkgo biloba extract reported better results [251-254]. Lastly, neurons adjust fuel utilization under conditions of pathogenic reprogramming in amyotrophic lateral sclerosis (ALS) [255]. Metabolic reprogramming in astrocytes can distinguish region specific neuronal susceptibility [256].

The physical way of brain communication occurs via neurons. Mapping the total circuitry can help one to understand different functions, like cognitive functions. The question arises here, if food components, or any activities can lead to rewiring of the circuitry in adult brain? Can these components lead to neurogenesis? It is certain that regulatory pathways influence the process of neurogenesis. There is also dependence on mitochondrial activity, energy consumption and Gibb's energy consumption [257,258]. Mitochondria also serves as the central regulator in the process of neurodifferentiation and for neural stem cell fate decisions [259]. Glial metabolites can lead to glial reprogramming to facilitate morphological and functional regeneration in the central nervous system after injury [260]. Neuroplasticity or brain plasticity shapes brain morphology and physiology, and neuroplasticity is regulated by intrinsic and extrinsic stimuli [261]. The hypothesis that can be put forth here is that can dietary components or physical and or social activities have a direct influence on the process of neurogenesis and neuroplasticity? Nevertheless, it is essential to understand the molecular effects of herbs, or any other food components to support the first line of therapy in treatments for nerve injury. The knowledge gained will also help to understand metabolic reprogramming in nerve cells. With the understanding of metabolic reprogramming mechanism in nerve cells, therapeutic possibilities using food, social interactions, exercise with the first line of therapy can highlight upon the curative options for neurodegenerative diseases. The axonal regeneration is regulated by intrinsic and extrinsic factors; however, the question remains whether any specific dietary components initiate or stimulate axonal regeneration. The hypothesis can also be experimented in cultured stem cell conditions to allow manipulation of NSCs for therapeutic uses. It is thus essential to understand molecular basis of the effect of diet on food cognition to manipulate diet for sustaining neuron health.

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