How Overnutrition Alters Brain Activity

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Abstract

Lipids as one of the main energy sources for cells make plasma membrane structure. About the brain, the only energy fuel is a glucose which makes wide various signaling pathways in the neurons. Most functions for lipids in the brain are narrowed to structural purposes such as myelin sheath. By increasing the rate of obesity and diabetes in the industrialized countries, researchers attempt to find out more about cellular and molecular details of this problems. Interestingly, the prevalence of the neurological disorders is high in western countries and some evidences show that obesity and diabetes have correlation with occurrence of the neuropathological conditions. Overnutrition or high calorie intake are the most important factors which can accelerate or trigger the pathological circumstances in the CNS. This review focuses on the various lipids and their functions in normal and high calorie intake conditions. We summarize roles of various lipids in the neurodegenerative e.g. AD and neuropsychiatric e.g. bipolar disorders.

Keywords: Lipid; High Fat Diet; Neurodegenerative Diseases; Neuropsychiatric Disorders

Abbreviation

Aβ: Amyloid Beta; AD: Alzheimer's Disease; ALA: α-Linolenic Acid; AMPK: AMP-Activated Protein Kinase; APP: Amyloid Precursor Protein; ARA: Arachidonic Acid; ASDs: Autism Spectrum Disorders; Atg: Autophagy-Related Proteins; BBB: Blood Brain Barrier; BDNF: Brain Derived Neurotrophic Factor; CNS: Central Nervous System; COXs: Cyclooxygenases; CSF: Cerebrospinal Fluid; CVDs: Cardiovascular Diseases; DHA: Docosahexaenoic Acid; DISC1: Disrupted in Schizophrenia 1; EPA: Eicosapentaenoic Acid; ER: Endoplasmic Reticulum; FXS: Fragile X Syndrome; GABA: γ-Aminobutyric Acid; GalCer: Galactosylceramide; GAP: GTPase Activating Proteins; GSLs: Glycosphingolipids; HD: Huntington's Disease; LA: Linoleic Acid; LC3: Light Chain 3; LRRK2: Leucine-Rich Repeat Kinase 2; MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; mTOR: Mammalian Target Of Rapamycin; NF1: Neurofibromatosis Type 1; NFTs: Neurofibrillary Tangles; NGF: Nerve Growth Factor; NPD1: Neuroprotectin-D1; PBDs: Peroxisome Biogenesis Disorders; PC: Phosphatidylcholine; PD: Parkinson's Disease; PEDs: Peroxisomal Enzyme Deficiencies; PEXs: Peroxins; PG: Phosphatidylglycerol; PGC1α: Peroxisome Proliferator-Activated Receptor γ Coactivator 1α; PS1: Presenilin1; PUFAs: Poly Unsaturated Fatty Acids; Rheb: Ras Homolog Enriched in Brain; SM: Sphingomyelinase; SMS: Sphingomyelin Synthase; SN: Substantia Nigra; SREBP: Sterol Regulatory Element Binding Proteins; SVZ: Subventricular Zone; T2D: Type 2 Diabetes; TFEB: Transcriptional Function of the EB; TLR4: Toll like Receptor 4; TSC: Tuberous Sclerosis Complex; UCHL1: Ubiquitin Carboxyl Terminal Hydrolase L1; ULK1/2: UNC-51-like Kinases 1/2

Introduction

Food as the main source of the energy and providing fuel for metabolism could contain various ingredients. Wide assortment in the compositions of foods causes physiological alteration in the body. Most recent researches have provided evidences about two main mac-

romolecules which are play roles in the brain structure and function. Lipids are the highest components of the central nervous system (CNS) and sugar in the form of the glucose is the main source of energy for brain. Sugar is the main fuel for brain and it cannot use other sources of energy. Half of all energy in the body is consumed by brain as a fuel. Modern life makes calorie abundant foods which lead to overfeeding related disorders such as obesity, type 2 diabetes (T2D), and cardiovascular diseases (CVDs) [13]. The influences of the over-feeding on the commencement of the pathophysiological abnormalities such as obesity, insulin resistance, impaired glucose tolerance, dyslipidemia and high blood pressure have been provided [47]. Cross disciplinary studies showed over nutrition and excess energy trigger neurological disorders in human and mice [8,9]. Abnormalities in the CNS can be categorized in widescreen like mental illness, brain injuries and neurodegenerative disorders [1012]. Moreover, metabolic syndromes associated with neural inflammation and neuropathy in the patients with T2D, obesity etc. are the main symptomatic hallmarks after few years [13]. Malnutrition affects brain development from the birth to 3 years of ages. Lipids are the main structural components of the myelin sheaths which are surrounding neurons [14]. Connection between general metabolism in the body and brain activity can harm the brain in the pathophysiological conditions such as T2D and obesity [15]. The effects of nutritional factors especially lipids on brain activity and function have been investigated during last few years. In this review we consider the role of overnutrition in the human brain during development and aging. Relative mentality and pathologically abnormalities with disturbing in lipid metabolism are categorized based on biochemical and pathophysiological features. Finding the correlation between general abnormalities in the metabolism and changing in the brain activity can be considered as the new therapeutic avenues in the neurobiology of disorders.

Lipids of the brain

Most weight of the brain contains lipids which have wide varieties from the most elusive to complicated structures. Lipids work in brain for membrane function, releasing neurotrophic factors, signal transduction and apoptosis [16]. Brain contains various types of lipids which are different based on sex, age, intake of nutrition and disorders.

Poly unsaturated fatty acids (PUFAs) contain more than 20 carbons in the structure. Beside the number of carbon, presence of the double bonds is the main character for this type of fatty acids. The main sources for PUFA are Linoleic acid [LA, 18:2(n-6)] and α-linolenic acid [ALA,18:3(n-3)] that are received from diet as essential fatty acids. LA and ALA can act as precursor for eicosapentaenoic acid [EPA; 20:5(n-3)], docosahexaenoic acid [DHA; 22:6(n-3)], and arachidonic acid [ARA; 20:4(n-6)] [17]. Transportation of the PUFAs into the brain are detected in two forms: free fatty acids as unesterified or in the form of lysophospholipids and lipoproteins as esterified. Brain visual cortex and retina development need DHA and transport through placental by gaining from maternal diet. After birth DHA can be provided by mother's milk [18]. After entering into the brain, DHA and ARA convert to the phospholipids of cell membrane but PUFAs start βoxidation process [19]. ARA and EPA are transformed by oxygenase enzymes to the precursor of the inflammatory signaling such as eicosanoids. But DHA generates anti-inflammatory agents like resolvins and protectins such as neuroprotectin-D1 (NPD1) [20].

Sphingolipids are the other abundant lipid in the brain consists polar head group and nonpolar tails and classified into ceramides, sphingomyelins and glycosphingolipids (GSLs). Ceramide is the nonpolar part of the sphingolipids and contains fatty acid with 236 carbons and its synthesis is initiated by palmitic (16:0) and serine [21]. Endoplasmic reticulum (ER), Golgi apparatus and lysosomes are the main places for synthesis and degradation of the sphingolipids [22]. Ceramide is the main precursor for the last steps in the synthesis of various products such as galactosylceramide (GalCer), ceramide-1-phosphate, sphingosine, free fatty acid and sphingomyelin as the sphingolipid analogue of the phosphatidylcholine (PC) which makes 10% of brain lipid. Diacylglycerol is the byproduct of the sphingo-myelin synthesis [2326]. Sphingomyelinase (SM) responsible for converting sphingomyelin into ceramide and phosphocholine while sphingomyelin synthase (SMS) is the critical enzyme in the metabolism of the sphingomyelin from substrates, ceramide and PC. Metabolic pathway of the SM activity is related to neurogenesis in the hippocampus [27]. Reducing the ceramide level in the brain correlates with the psychiatric disorders like anxiety and depression [28]. Ceramide has crucial role in the neural differentiation, senescence, survival and apoptosis. Increasing in the ceramide level cause neuropathological symptoms in the brain and the high level of it is detectable in

tissues undergoing neurodegeneration [29]. In addition to ceramide level, sphingomyelin homeostasis has imperative character in the neuropathological conditions. Recent studies show high sphingomyelin level can alter autophagy process in cultured neurons [30].

GSLs as the main component of the membrane structure in the neurons and they have neutral or charged heads in PH 7. In the neural cells the charge of the GSLs are negative because of the sulfate group (Sulfatide) and sialic acid (Ganglioside) [31]. GM1, GD1a, GD1b, and GT1b as the main gangliosides of the CNS contribute in the neurogenesis, brain development, aging and synaptic transmission [32]. Nerve growth factor (NGF) is used for differentiation of PC12 cells to the dopaminergic cells and GM1 plays crucial role in this process [33]. GM1 mediates the signaling triggers from serotonin receptors to downstream cascade [34]. Studies show that various types of GSLs have abilities to bind to various receptors which are specific for insulin, EGF and PDGF [3537].

Cholesterol of the brain is uptake from the body cholesterol contents. The main role of the cholesterol in the brain is about myelination process of neurons. After myelination during the development cholesterol content is decreased in the brain [38]. Synthesis of the cholesterol in the brain can be affected by brain derived neurotrophic factor (BDNF) which plays various roles in brain development and function [39]. Not only neurons synthesis the cholesterol but also oligodendrocytes make it for cells in CNS [40]. The concentration and interaction of the cholesterol in the membranes of neurons determine captivating of the cholesterol by neurons. Interaction of the cholesterol in the neuron membrane comprises hydroxyl group of the cholesterol with polar head of the sphingolipids through hydrogen bonds [41]. Their interactions make lipid raft in the membrane which segregates membrane proteins from each other [42]. Lipid rafts contribute to many aspects of the neuronal activities such as synaptic formation and signal transduction [43]. Fatty acids, cholesterol and gangliosides in the dietary can alter the lipid raft [44]. Cholesterol in lipid rafts increase the aggregation of the pre/postsynaptic proteins in the axon terminals [45].

These observations raised basic questions about brain lipids and their contribution in various cellular and molecular mechanisms of the brain. Specifically, the open question is about how dietary or non-dietary lipids enhancement in the brain can affect CNS in the pathological level? The evidence focus on lipid alteration and neurological disorders based on their molecular aspects which could be clues for understanding these types of questions.

Autophagy and lipids

Protein misfolding is the main character of the neurological disorders. Toxicity of the deposited proteins triggers degeneration of the neurons during pathological conditions [46]. Macroautophagy is a process that by making double membrane vesicles (autophagosome) around accumulated proteins starts to degrade proteins. Fusion of the autophagosome to lysosome provide autolysosome that leads to breaking down of the material through hydrolysis. Autophagy-related proteins (Atg) are recruited during the formation of the autophagosome in the yeast. Development of the autophagosome includes nucleation of the phagophore, Atg conjugation to the complex, microtubule-associated protein light chain 3 (LC3) insertion into the membrane of the complex, taking the target proteins and finally fusing into the lysosome to digests and clear target proteins [47]. Mammalian orthologues for Atg proteins are UNC-51-like kinases 1 and 2 (ULK1 and ULK2). Atg/ULKs have central roles in the formation and function of the autophagosome and autophagy process [48]. Nutrient deprivation, stress and starvation are the main inducers of the autophagy in the cell. AMP-activated protein kinase (AMPK) is the main sensor for detecting the energy status of the cell and by phosphorylating wide various of enzymes improves metabolic circumstances of the cell [49]. In the starvation condition one of the strategies that is used by cell is activation of the AMPK and triggering the autophagy process [50]. The first target for AMPK is the mammalian target of rapamycin (mTOR) that integrates nutrient signals. mTOR is the negative regulator of the autophagy which is accelerated by using rapamycin as mTOR inhibitor [51]. mTOR includes two complexes: mTORC1 and mTORC2. Multiple proteins arrange mTORC complexes, RAPTOR and PRAS40 are specific for mTORC1 while RICTOR, mSin1, and PROCTOR1/2 have role in the formation of the mTORC2 [52,53]. mTORC1 integrates with nutrient and growth factor signals and it can induce anabolism such as lipid synthesis in the cell. about the catabolic pathways mTORC1 works as an inhibitor and prevents lysosome biogenesis and autophagy. mTORC1 inhibits autophagy by phosphorylating of the ULK components. In the yeast it can phosphorylate Atg1

and disrupt the formation of the autophagosome [54,55]. Moreover, mTORC1 modulate the transcriptional function of the EB (TFEB) that is regulator of the lysosmal and autophagosomal genes expressions. TFEB controls lipid metabolism through peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1α) during the starvation [56,57]. Are lipids conquest the starvation and inhibit autophagy? This is the main question which has been raised and recent studies show some evidences to answer it. PUFAs like DHA and EPA with n3 inhibit the formation of the autophagosome at the initial stage of the autophagy. In addition, they can increase phosphorylated level of mTOR (activated form) which leads to inhibition of the autophagy [58]. mTOR controls lipid synthesis beside the potential of the autophagy procedure. In the present of the active mTOR the synthesis of the ceramide is increased [59]. Previous studies show the correlation between increased level of the ceramide and degeneration undergoing in the nervous system (29). Inhibition of the mTOR by rapamycin increase PC, PUFAs, saturated fatty acids and phosphatidylglycerol (PG) accumulation in the cells [60]. Cholesterol as another important lipid in the membrane structures of neurons play a role in autophagy process. Depletion of the cholesterol and using the inhibitor of cholesterol synthesis enzymes trigger autophagy in various types of cells [61,62]. In addition, mTOR as the inhibitor of the autophagy has central role in the synthesis of the cholesterol. sterol regulatory element binding proteins (SREBP) are the family of proteins with three members: SREBP1a, SREBP1c, and SREBP2. These proteins control homeostasis of the cholesterol by controlling its synthesis [63]. SREBP functionality depends on the mTORC1 activity. By inducing SREBP activity, mTORC1 participates in the cholesterol biosynthesis [60].

Based on evidences, autophagy is influenced by various factors such as lipid accumulation, stress and nutrient deprivation. But in many cases related to neurological and neuropsychiatric abnormalities, autophagy plays central role in the various stages of the anomalies. Accumulation of the lipids in the cell through activation of the mTOR is another critical factor in the disorders related to CNS.

Peroxisome and lipids

Peroxisomes as single membrane organelles responsible for various biochemical reactions have different shapes, numbers and enzymatic activities upon changes in the environment [64]. Impairments in the functionality of the peroxisomes can cause neurological disruptions such as dysmyelination, defects in neuronal migration and neurodevelopment [65,66]. Peroxisomal diseases are categorized into two groups: peroxisome biogenesis disorders (PBDs) which show disruption in the biogenesis of the functional peroxisomes and peroxisomal enzyme deficiencies (PEDs) which is occurred because of inattentive specific peroxisomal enzyme activity [67,68]. All peroxisomal proteins have signal peptide which is perceived by specific receptors termed peroxins (PEXs).

Peroxisomes are responsible for degrading the various types of fatty acids such as PUFAs, saturated fatty acids, branched chain fatty acids and very long unsaturated fatty acids [69]. Beside oxidation of fatty acids peroxisomes has important roles in the synthesis of the diacyl phospholipids, glycerol backbone with bind fatty acyls [70]. DHA as a critical n-3 PUFA is synthesized in the ER from dietary LA. After elongation and desaturation processes in the ER, the final product C24:6 n-3 is transported into the peroxisomes and by passing beta oxidation generates C22:6-CoA [71]. Two fates are recognized for the generated C22:6-CoA: continue further beta oxidation in the peroxisome or export from peroxisome to incorporate into lipids in ER. Recent studies show that in the PBD patients the amount of GM2, GM1 and GD1 is higher than control group. This evidence demonstrates peroxisome role in the ganglioside metabolism [72]. Accumulation of the GM2 in the mouse model showed neuronal death and apoptotic pathway which is prompted by GM2 [73]. GD1 has high concentration in the Purkinje cells but the accumulation and enhancement in the GD1 level is detected in the degenerated neurons [74]. In the Zellweger patients, PBD syndrome, the amount of ceramide is severely high in the brain and it can demonstrate the role of ceramide in the pathogenesis of this disease [75].

Tuberous sclerosis complex (TSC) is a negative regulator of the mTOR activity includes TSC1 (also known as hamartin) and TSC2 (also known as tuberin). TSCs complexes have GTPase activating proteins (GAP) activity and convert GTP to GDP in Ras homolog enriched in brain (Rheb) protein [76]. Rheb-GTP is an active form triggers mTORC activity but converting of the GTP to GDP by TSC complexes inactivates Rheb and inhibits mTOR function [77]. TSC complexes and Rheb are localized into the cytoplasmic face of the peroxisome and by function of the TSC on the Rheb the autophagy is prompted. In PBD diseases like Zellweger TSC complexes cannot localize into the peroxisome and autophagy is inhibited due to activity of mTORC [78].

So, beside the biosynthesis of various lipid peroxisome can influence autophagy indirectly. Localization of the TSCs complexes by PEX proteins into the peroxisome plays crucial role in the inactivation of the Rheb which is caused mTOR inhibition. Peroxisome dysfunction not only disturb lipid biogenesis and cause accumulation of some types of lipids which are toxic for cell but also has a role in the control of the autophagy.

Autophagy in neurodegenerative and neuropsychiatric disorders

Protein misfolding is controlled by chaperones but stressful situations and mutations interrupt protein folding and generate aggregate form of them. This phenomenon is the central player of the neurodegenerative disorders and neuropsychiatric diseases. amyloid beta (Aβ) peptide deposit in the Alzheimer's disease (AD), αsynuclein in the Parkinson (PD) patients and Huntingtin in the model of Huntington's disease (HD) are the main samples of aggregate proteins in neurodegenerative disorders. Disrupted in Schizophrenia 1 (DISC1) is a crucial protein in the synapse formation and can be found in dimers, octamers, higher oligomers. Aggregation of this protein in insoluble form has dominant character in some neuropsychiatric disorders such as schizophrenia, bipolar disorder, depression and autism. Aggregate proteins should be cleared by autophagy mechanism before coming to toxic form. But dysfunction in the autophagy process has been implicated in wide variety of neurological and psychiatric disorders.

Autism spectrum disorders (ASDs) with symptoms like impaired social interactions, abnormal repetitive behavior and intellectual disability are common neurodevelopmental disorders [79]. Keeping the mTOR in active form causes changes in synaptic formation and structure in the autistic patients. Some mutations in the TSCs complexes have been sensed in the autism patients [80]. Inactivation of TSC1 in animal models showed seizure, microcephaly and death in neural cells [81]. Conditional mutation of TSC1 in the Purkinje cells cause ASD like behaviors such as anti-social and non-repetitive abnormalities [82]. γ-aminobutyric acid (GABA) as an inhibitory neurotransmitter controls movement, motor control, vision and anxiety. TSC1 mutation inhibits GABA transmission which is detectable in the neurofibromatosis type 1 (NF1), Fragile X syndrome (FXS) and Down syndrome [83,84]. Treatment with the mTOR inhibitor, rapamycin, show amelioration in the symptoms of the FXS models [85]. Dysfunctionality of autophagy process leads to depression which has symptoms like depressed mood, anhedonia, low energy or fatigue, and altered cognitive function [86]. amitriptyline and selective serotonin reuptake inhibitor citalopram as antidepressant drugs increase the expression of autophagy markers [87]. Lithium as sentimental therapy for unstable mood such as bipolar disorder induces autophagy process [88]. Formation of insoluble DISC1 protein in the schizophrenia and mental disorders can be ameliorate by inhibiting mTOR which is caused autophagy initiation [89,90].

Aggregate and insoluble proteins are the hallmark of the neurodegenerative disorders. In these types of neurological diseases autophagy is inhibited and clearance of the insoluble proteins is not completed. Aggregation of proteins triggers other pathological mechanisms which accelerate further degeneration of neurons in the brain.

PD is characterized by progressive loss of dopaminergic neurons in the substantia nigra (SN) and the presence of the aggregate proteins known αsynuclein which make Lewy Bodies in the cell [91]. αsynuclein can be degraded by autophagy mechanism [92] and therapeutic attempts to induce autophagy help clearance of the αsynuclein and disease pathology [93]. Mutants αsynuclein (A30P, A53T) inhibit autophagy by binding to receptors on the lysosomes and reducing the transportation of substrates into the lysosome [94,95]. Ubiquitin carboxyl terminal hydrolase L1 (UCHL1) and leucine-rich repeat kinase 2 (LRRK2) as genes involve in the PD pathology influence autophagy machinery [96,97]. Activation of autophagy by Pramipexole, dopamine D2/3 receptors agonist, clear αsynuclein aggregation [98].

AD is the most prevalent neurodegenerative disorder is hallmarked with the presence of the extracellular senile plaques and intracellular neurofibrillary tangles (NFTs). Senile plaques are made from Aβ which is generated by cleaving the amyloid precursor protein (APP) [99,100]. Defects in the autophagy system is the main reason for the accumulation of NFTs and Aβ in AD. Mutant presenilin1(PS1) causes familial autosomal dominant AD, PS1 is the component of enzyme that cleaves APP [101]. Mutation in PS1 leads to accumulation

of the undegraded autophagosomes. Mutant PS1 disrupts assembly of the H^+-ATPase (v-ATPase) pump in the lysosomal membrane [102]. Intracellular aggregation, NFTs, is composed hyperphosphorylated tau and autophagy system responsible for degrading them. 3-methyl amphetamine (3-MA) is an inhibitor of the autophagy increase aggregation of the tau and delay their clearance [103]. But rapamycin using ameliorate AD pathogenesis about aggregated proteins [104]. Therefore, AD may correlate with autophagy machine and it is associated with autophagosome formation.

HD as autosomal dominant neurodegenerative disorder is characterized by loss of motor function because of expanded CAG repeats in the huntingtin gene which encode poly glutamine (PolyQ) in the protein [105]. Huntingtin protein with extra Poly Q tract aggregate as an intracellular inclusion and autophagy is responsible for degrading and clearing of it [106]. Overexpression of the huntingtin without CAG repeats showed the inducer role of Huntingtin protein for autophagy [107]. Previous studies showed that rapamycin has ability to induce autophagy and ameliorate HD pathology by reducing aggregate huntingtin [108,109].

Taken together, autophagy could be proper candidate for neurodegenerative disorders but other factors can influence this clearance mechanism. Attending of the environmental factor will help to understand the autophagy and related mechanisms to alleviate symptoms in psychiatric and neurologic disorders.

Overnutrition and brain

Prevalence of the obesity in the industrialized nations has been increased. This change in the rate of obese people, enhances onset of various diseases such as type 2 diabetes, cardiovascular disease, stroke, cancer and neurological disorders [110]. Consumption of high lipid content foods and alteration in the life style are the main factors which can influence the rate of neurologic and neuropsychiatric disorders in the society. Based on evidences we can categorize types of lipids which are intake by overnutrition and their affections on brain activity and function.

High fat diet contains PUFAs, cholesterol, saturated and unsaturated fatty acids (C14C24). Formula of high fat diet that has been used in wide various experiments is summarized in table 1.

Fatty acid	Standard diet	High fat diet
Myristic C14	0.006	0.2 0.9
Myristoleic C14:1	0	0 0.5
Palmitic C16	0.764	13 21.8
Palmitoleic C16:1	0	0.2 3.8
Stearic C18	0.15	10.2 12.4
Oleic C18:1	1.26	39.3 62
Linoleic C18:2	3.13	12.8 12.9
Linolenic C18:3	0.28	0.7 1.6
Arachidic C20	0. 01	0 0.3
Arachidonic C20:4	0	0 1.7
Behenic C22	0. 003	0 0.3
Lignoceric C24	0	0 0.1
Cholesterol		0.03 0.035

Table 1: *Fatty acids compositions in diets (g/100 g of diet).*

Free fatty acids circulate in the blood in the forms of non-esterified and bind to albumin. Dissociation from albumin helps them to pass through the blood brain barrier (BBB) and enters into neural cells. In the next step they can participate in the structure of the plasma membrane or jump into βoxidation process to generate ATP [111113].

Myristic acid (C14) presence in the high fat diet caused loss of spontaneous locomotion in the mouse models for psychiatric disorders [114]. Using high fat diet leads to increase the level of the myristic acid in the brains of male mouse while its concentration in the plasma was unchanged [115]. Palmitic acid (C16) has wide various of effects on the brain activity and function by using high fat diet. Previous *in vitro* studies implicate the role of palmitic acid in the induction of the inflammation in the macrophages and acceleration of amyloid processing in neurons [116118]. In cultured astrocytes palmitic acid reasons for secretion of the cytokines such as TNFα and IL-6, as well as IL-1β [119]. Cytokines as the main inflammatory secreted responses from glial cells in the brain can trigger the degeneration and inflammation in the neurons [120]. Anxiety disorders include anxiety disorder, obsessive-compulsive disorder, panic disorder and post-traumatic stress disorder. Palmitate using in high fat diet causes anxiety like behavior in the mouse models [114]. Disruption in the metabolism and process of neurotransmitters correlates with the onset of memory loss, depression, delirium and anxiety [121123]. Presence of the palmitate in high fat diet which is intake by mouse shows enhancement of the dopamine and serotonin in the hippocampus and amygdala [114]. Palmitic acid is increased in the male mouse brains like myristic acid after administration of high fat diet while its concentration in plasma is increased in both genders after using high fat diet [115]. In addition, human and animal models studies showed decline in cognitive in the presence of the high amount of palmitic acid in the diet [124126]. Palmitic acid causes neurodegeneration in cortical primary neurons which leads to AD like pathogenesis [117]. Neurogenesis is the replacement of the degenerated or injured neurons with new ones and that process comes from dentate gyrus and the subventricular zone (SVZ) of the brain [127]. Growth factors such as BDNF improves neurogenesis, palmitic acid in high fat diet reduces the expression of BDNF in the hippocampus of the mouse and inhibits neurogenesis [128,129]. Disruption in the cell cycle is another hallmark for neurodegeneration and palmitic acid is one of the main suppressor of the cell cycle in *in vitro* studies [130]. Moreover, palmitic acid has correlation with the PD onset [131]. PGC1α is the mediator of the mitochondrial biogenesis and it can work as neuroprotective agent in neurodegenerative disorders especially PD [132]. On PD patients PGC1α promoter is hypermethylated that is caused decreasing in the expression of some genes and mitochondrial biogenesis. In mouse models administration of palmitic acid in the high fat dietary leads to hypermethylation of the PGC1α promoter [133]. High amount of palmitic acid could be trigger for the palmitoylation of the Huntingtin protein in the N terminus which is increase the stability and aggregation of protein. Aggregated form of the Huntingtin is the main pathologic character of the HD [134]. Stearic acid (C18) as a component of the high fat diet influence the hyperphosphorylation of tau protein which is caused AD [117]. In human trophoblast stearic acid increases the expression of the cytokine, TNFα and toll like receptor 4 (TLR4). Enhancement of the stearic acid in the macrophages triggers inflammatory signaling pathways [135,136]. On the other hand, stearic acid influences TLR4 expression in the embryonic mouse hypothalamus cell line [137]. Cholesterol contributes in the cell membrane and circulate in the plasma in free form. Evidences showed high level of serum cholesterol increases the risk of AD and dementia [138]. Increasing in the level of cleaved APP in the form of Aβ is the main output for the high cholesterol level in AD models [139]. Actually one of the main mechanism that can be controlled by cholesterol level is autophagy. Cholesterol by inhibiting the autophagy arrest cellular clearance mechanism about misfolded or aggregate proteins in neuropsychiatric and neurological disorders. By eliminating the cholesterol mTOR is converted to inactive form that leads to triggering the autophagy [61]. About the PD researches have controversial results, in some finding evidences show the correlation between PD and high level of cholesterol in plasma while other groups regret any link between cholesterol level and PD [140,141]. But most derivative of cholesterol increase the aggregation of the αsynuclein and reduce neuronal growth [142]. Arachidonic acid (C20 n4) belongs to ω6 lipid groups and is generated from LA. High level of LA increases the level of ARA in the tissues [143]. Circulated arachidonic acid after entering into the brain has two pathways: incorporate in the synthesis of the membrane phospholipids or recruits metabolizing enzymes. Metabolism of ARA produces various products such as eicosanoids. Prostaglandins (PGs), thromboxanes, leukotrienes and epoxy fatty acids as known eicosanoids play role in the neurotransmission, neuronal firing and neuroinflammation in the brain [144146]. Production of eicosanoids depends on prostaglandin G/H synthase, or cyclooxygenases (COXs) activity. COX-1 and COX-2 are the distinct isoforms

of the COXs which have different expression patterns. COX-1 expresses in most of tissues constantly while expression of COX-2 is the responsibility of it to acute and chronic inflammation conditions [147,148]. Hamilton., *et al*. implicated that ARA and COX2 expression have synergetic correlation and by increasing ARA supply the expression of COX2 is increased [149]. Most of neurological disorders show high expression of the COX2 in the pathological conditions. Analyzing of the AD brains show high expression level of the COX2 but at the end of this disease the numbers of COX2 positive neurons are decreased [150,151]. PGE2 as a derivative metabolite of the PG shows high level in the cerebrospinal fluid (CSF) in the AD patients [152]. Recent studies showed the high level of the COX2 in PD patients and the same results were gotten from using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mouse model [153]. Moreover, Amyotrophic lateral sclerosis (ALS) as a neurodegenerative disease has high COX2 level in the spinal specimen and elevated PGE2 in the CSF [154156]. In the psychiatric disorders such as depression and schizophrenia, PGE2 shows elevated level and the expression of the COX2 is increased [157]. Yoo., *et al*. found the association between polymorphism in the COX2 gene and ASD in the Korean population. That polymorphism increases the activity of the COX2 [158]. Lithium and valproate as known drugs in the treatment of the bipolar disorder attenuate the symptoms of disease by decreasing the expression of the COX2 [159,160].

By surfing in the recent studies which try to find therapeutic avenues for treatment of the neurodegenerative and neuropsychiatric disorders, we can find COX2 as the central player in this scenario. Most of the experiments focus on alteration in the COX2 expression and activity which can attenuate the symptoms of most neurologic and psychiatric abnormalities. ARA level has correlation with the COX2 level and activity [149], so presence of the ARA in the dietary could be alter the COX2 expression level.

Conclusion and Future Direction

High fat diet has been known for their affects in the various disorders such as obesity, T2DM and heart diseases. Improving researches in the field of neuroscience has fascinated most scientists to focus on diet and brain activity. Their findings during recent years open new views in the neuroscience and brain researches. Alteration in the fat contents in the diet easily changes brain activity and even in some cases work as a fuel for combusting the pathological conditions. Beside neurological abnormalities high fat diet and alteration in lipid intake show close relationship with changing of the behavior and cognition in animal models. On the contrary, obesity and brain activity approach to the common point that approves the linkage between overweight and brain function. Todays, obesity and neurodegenerative disorders are the main problems of the health in industrialized countries that people use high calorie diet there. This connection between the ratio of the obesity and neurological disorders suggests that treatment of one of them can attenuate another one. But which one has to be target, obesity or neurology?

For example, Mediterranean diet which includes vegetables and fish is the powerful tool in the alleviation of neurodegenerative disorders especially AD.

In this review we tried to find out how lipid alteration can change brain activity and explain cellular pathways which are triggered by various lipids in disorders. Improving the knowledge of society about dietary lipids and their effects on the health of the brain would be helpful policy. But on the research bench scientists need to do further experiments to find out all details about pathological and behavioral changes in the presence of the various dietary lipids.

By improving information about cellular and molecular mechanisms that come from high lipid contents in the brain, therapeutic approaches will be opened in front of neuroscience to control or treat wide varieties of the neurological and neuropsychiatric disorders.

Conflict of Interest

None of the authors has any conflicts of interest to disclose and all authors support submission to this journal.

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Volume 10 Issue 2 February 2018