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Review Article

Experimental Neurobiology

Impaired Cholesterol Metabolism, Neurons, and Neuropsychiatric Disorders

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Cholesterol metabolism plays an essential role in cellular functions (including as a component of the plasma membrane, as an energy source, and in hormone production) under normal conditions. Dysregulated cholesterol metabolism causes a wide spectrum of pathological conditions, leading to neuropsychiatric disorders, such as anxiety and depression. In addition, patients with neuropsychiatric disorders also have impaired cholesterol metabolism. Therefore, metabolic disturbances are closely associated with the neuropsychiatric disorders. Although immune disturbance, neuroinflammation, a dysregulated neurotransmitter system, and oxidative stress have been suggested as pathophysiology of neuropsychiatric disorders, dysregulation of cholesterol metabolism is also found in patients with psychiatric diseases. As expected, patients with mental illness appear to be at risk of metabolic disorders, including metabolic syndrome, in which cholesterol influences altered neuronal homeostasis, such as neuronal cell toxicity, neuronal cell death, and neuronal structures and functions, including synaptogenesis, neurogenesis, axonogenesis, and action potential. Therefore, reversing impaired or abnormal cholesterol metabolism may help restore neuronal injury found in mental illness. This review is aimed to discuss the links between cholesterol metabolism impairment and neuropsychiatric disorders and provides insights into neuronal dysfunction due to abnormal cholesterol metabolism in neuropsychiatric disorders.

Key words: Cholesterol, Major depressive disorders, Anxiety disorders, Neurons, Synapse, Neurotransmission

INTRODUCTION

Cholesterol is the main component of the cell membrane; it aids cellular influx and efflux by interacting with transmembrane molecules and regulates membrane homeostasis, such as permeability and rigidity [1]. Cholesterol contributes to cellular trafficking and transmembrane signal transduction [1]. Additionally, cholesterol is a precursor of steroid hormones and bile acids [2, 3]. Cholesterol is derived from dietary sources or *de novo* synthesis [1, 2]. The cholesterol balance is maintained by cholesterol ingestion, absorption in the gastrointestinal tract, synthesis, storage, and excretion [4]. Excessive cholesterol is stored as cholesteryl esters in lipid droplets (LDs) and released into the circulation as cholesterol-containing lipoprotein particles, including chylomicrons and very-low-density lipoproteins (VLDL) [4, 5]. LDs are consumed by lipolysis or autophagic degradation of lipids, termed as lipophagy; therefore, LDs regulate the intracellular cholesterol level and prevent lipotoxicity [5]. Dysregulated cholesterol metabolism and overload can initiate cellular toxicity and cell death [6]. Ectopic LDs are associated with the development of metabolic disorders [7]. Deficits in cholesterol synthesis result in cholesterol deficiency and the generation of toxic sterol precursors [8]. Alterations in lipid metabolism have also been observed in neurological diseases [9].

Neuropsychiatric disorders are leading causes of disability and morbidity and are a global burden [10, 11]. Patients with neuropsychiatric disorders have homeostatic imbalance [11]; therefore, there is a high prevalence of metabolic syndrome (MetS) due to obesity, dyslipidaemia, hypertension, or dysglycaemia among these

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patients [12]. In particular, central obesity and dyslipidaemia are highly associated with mental illness [13]. A previous study demonstrated that hypercholesterolaemia, induced by a high-cholesterol diet, promotes cognitive impairment, including learning disabilities, triggers cerebrovascular dysfunction, and induces white matter inflammation by astrogliosis and microgliosis [14]. Patients with familial hypercholesterolaemia have an increased incidence of mild cognitive impairment [15]. Animal models of familial hypercholesterolaemia manifest cognitive impairment with impaired blood-brain barrier (BBB) and neuroinflammation [16, 17]. Animal models of hypercholesterolaemia have been reported to present with depression and anxiety [18, 19]. Additionally, animals with hypocholesterolaemia display depression-like behaviours [20]. In a clinical study, abnormal cholesterol levels were observed in patients with depression, and patients with anxiety exhibited high cholesterol levels [21]. In the case of patients with mental illness accompanied by impaired cholesterol metabolism, improvement in symptoms may be expected by restoring it. Therefore, this review focuses on the relationship between impaired cholesterol metabolism and neuropsychiatric conditions with regard to neuronal dysfunction.

Cholesterol metabolism in the brain and brain diseases

Cholesterol plays a pivotal role in the brain, where cholesterol levels are higher than those in other organs [2]. Unlike other peripheral organs, the brain has limited cholesterol uptake owing to the presence of the BBB [9]. In the brain, cholesterol supply mainly depends on *de novo* synthesis [9]. Several enzymes, including 3-hydroxy-3-methyglutaryl coenzyme-A reductase (HMGCR), synthesise cholesterol [22]. Cholesterol synthesis is controlled by the sterol regulatory element-binding protein (SREBP) [22]. Specifically, SREBP2 is responsible for cholesterol synthesis [22]. Resident brain cells, such as astrocytes, microglia, oligodendrocytes, and neurons, can regulate cholesterol metabolism [23]. During brain development, neurons produce large amounts of cholesterol [24]. However, cholesterol synthesis in neurons gradually declines and cholesterol produced by glial cells is supplied [23]. In particular, myelin-forming oligodendrocytes, which play an important role in the transmission of nerve impulses by insulating axons, contain higher amounts of cholesterol than other cell types in the brain [25]. Cholesterol is an essential constituent of the cellular membrane and is essential for the maintenance of lipid rafts [26]. Cholesterol regulates cell morphology, ion permeability, and cell-to-cell interactions [27].

Impaired cholesterol metabolism is relevant to a wide spectrum of brain disorders and diseases [9, 26]. Abnormal brain cholesterol metabolism causes neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [27]. Low-density lipoprotein cholesterol (LDL-C) is linked to the neuropathology of AD [28]. Therefore, neurofibrillary tangles, β-amyloid, and cerebral angiopathy are significantly associated with LDL-C levels [28]. Similarly, increased brain β-amyloid levels are caused by hypercholesterolaemia [29]. It has been observed that in statin-free patients with PD, low LDL-C levels tend to be associated with a high occurrence of PD [30]. In a meta-analysis, high levels of cholesterol and triglycerides in the serum had protective properties in PD [31]. Furthermore, higher plasma 24(S)-hydroxycholesterol levels are consistent with a better olfaction, and loss of smell is one of the symptoms preceding the onset of PD [32]. α-Synuclein-containing Lewy bodies are pathological hallmarks of PD [22]. Cholesterol can regulate the expression and inclusions of α-synuclein observed in PD [22]. Extracellular α-synuclein attaches to the plasma membranes of neurons and glial cells and translocates into cells [22]. In HD, polyglutamine expansion is closely associated with cholesterol metabolism [33]. HD is accompanied by cholesterol abnormalities, including hypocholesterolaemia, a decline in cholesterol synthesis, and cholesterol deposition in neurons [33]. Additionally, the progression of ischaemic stroke and cerebral small vessel disease is influenced by hypercholesterolaemia [34]. Hypercholesterolaemia is a risk factor for vascular disease, which is likely to induce vascular dementia [35]. In addition, dysregulated cholesterol catabolism and its catabolites, such as oxysterols and bile acids, are associated with a risk of dementia [36]. Thus, these studies have provided important correlations between the cholesterol metabolism and brain health and diseases.

Impaired cholesterol metabolism and neurons

Cholesterol balance is correlated with normal neuronal structure and function [37-39] (Fig. 1). Cholesterol is required for axon outgrowth [37]. It is necessary for synaptogenesis and synaptic plasticity [38]. Cholesterol induces synaptic development, enhances pre-synapse differentiation, increases synapse-associated molecules, and stabilises synaptic transmission [38, 39]. Additionally, neuronal cholesterol metabolism is responsible for increased dendritic outgrowth [39]. Therefore, cholesterol in neurons and glial cells influences learning and memory [23]. Defects in cholesterol metabolism are linked to abnormal neurological features [37-39]. Cholesterol deposition is deleterious to neurons [40]. A previous study showed that an animal model of hypercholesterolaemia exhibited cognitive impairment with altered neurons in the hippocampus [41]. In addition, cholesterol imbalance is responsible for hippocampal neural degeneration, and the absence of cholesterol absence results in the breakdown of the neurofilament integrity

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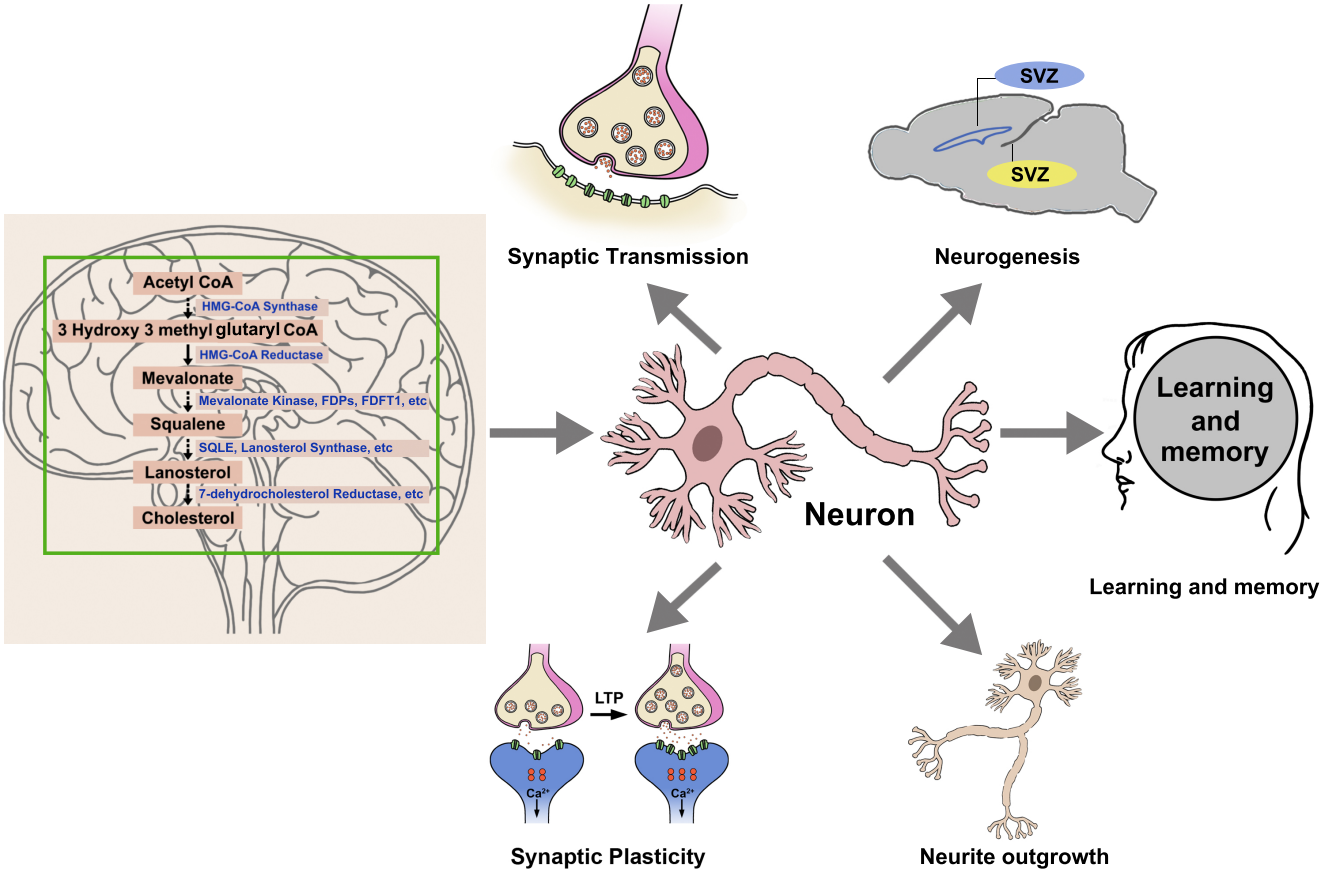

Fig. 1. Cholesterol metabolism and neurons. Cholesterol metabolism is essential for synaptic transmission, synaptic plasticity, neurite outgrowth, neurogenesis, and learning and memory. FDPs, Farnesyl-Diphosphate Synthase; FDFT1, Farnesyl-Diphosphate Farnesyltransferase 1 or Squalene Synthase; SQLE, Squalene Epoxidase.

[42]. High levels of cholesterol in the diet lead to impairment of long-term potentiation (LTP) [42, 43]. Moreover, oxygenated derivatives of cholesterol, 24(S)-hydroxycholesterol, exhibit cytotoxic properties and induce neuronal cell death [40]. Individuals with hypercholesterolaemia are at risk of cognitive deficits [27]. Similarly, cholesterol depletion or insufficient cholesterol in neurons reduces LTP and damages learning and memory [23]. Increased amounts of neuronal cholesterol increase endoplasmic reticulum stress and induce apoptotic neuronal cell death in the hippocampus, resulting in the loss of cognitive function and brain atrophy [44]. Hence, many studies demonstrated the importance of cholesterol metabolism in neurons [37-39, 42, 43].

Synapse requires the support of cholesterol as a source of presynaptic and postsynaptic membranes; that is, cholesterol is involved in synaptic transmission [45]. However, abnormal cholesterol levels can disrupt neurotransmission [42]. In a previous study, rats that were fed a hypercholesterolaemic diet showed hypercholesterolaemia with high levels of total cholesterol, triglycerides, and LDL-C, which have an impact on brain cholesterol metabolism [46]. As expected, cerebral total cholesterol, triglyceride, and LDL-C levels are elevated, and morphological changes in neurons with an imbalance of neurotransmitters are observed in the hippocampus [46]. They display increases in glutamate, dopamine, and N-methyl-D-aspartate (NMDA) levels, while gamma-aminobutrylic acid (GABA), 5-hydroxytryptamine (5-HT), and low-density lipoprotein receptor (LDLR) levels are decreased in the brain [46]. Similarly, mice induced by high-cholesterol diet showed psychomotor impairment and depression-like behaviour, accompanied by altered neurotransmitters, such as reductions in serotonin in the cortex and dopamine in the striatum [47]. Hypercholesterolaemia induced by LDLR knockout contributes to changes in acetylcholinesterase activity in the brain [48]. In contrast, cholesterol depletion leads to a decline in neurotransmission; for instance, evoked excitatory postsynaptic currents mediated by NMDA receptors (NMDAR) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors (AMPAR) are altered after the deletion of cholesterol [45]. Cholesterol is involved in NMDAR function, including open

probability, and NMDAR stabilisation [45].

Cholesterol metabolism is involved in adult hippocampal neurogenesis [41]; therefore, abnormal cholesterol levels lead to impaired neurogenesis [41]. An animal model of familial hypercholesterolaemia by established knockout of LDLR exhibited downregulated expression of cholesterol synthesis-associated genes, such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMGCR) and squalene synthase (FDFT1) [41]. This model shows that adult neurogenesis is damaged in the hippocampus and is responsible for impaired proliferation and differentiation of neural precursor cells in the hippocampus [41].

Moreover, cholesterol dysregulation results in neurodegeneration [49]. An imbalance in cholesterol levels can lead to impaired neural plasticity [42]. Cholesterol-fed mice display impaired LTP [42]. Further, action potential propagation is also influenced by cholesterol [45]. In a previous study, cholesterol-fed rats exhibited loss of synaptic plasticity and neurodegeneration [49]. After treatment with 27-hydrocholesterol, hippocampal primary neurons showed reductions in dendritic length, dendritic spine density, and the postsynaptic marker PSD-95 [50]. Moreover, DNA damage was observed in primary hippocampal neurons after treatment with 27-hydrocholesterol [50]. In Cyp27 Transgenic (Tg) mice with high systemic expression of 27-hydrocholesterol, reduced spine density and dendritic arborisation were found in the hippocampus [50]. Moreover, structural and functional alterations were observed in hippocampal synapses of Cyp27 Tg mice [51]. Cyp27 Tg mice displayed abnormally high LTP and larger dendritic spines in CA1 pyramidal neurons, indicating that high cholesterol can modify synaptic potentiation and neuronal circuits [51].

Cholesterol metabolism is important for cognitive function [16]. Patients with familial hypercholesterolaemia have a higher incidence of cognitive impairment, which may be caused by high cholesterol levels or LDLR dysfunction [15]. In addition, elderly individuals with hypercholesterolaemia (higher total cholesterol and LDL-C concentrations) are vulnerable to cognitive decline [52]. A familial hypercholesterolaemia animal model with deletion of LDLR showed BBB breakdown and cognitive dysfunction [16]. In particular, a hypercholesterolaemic diet increased the permeability of the BBB in the prefrontal cortex and hippocampus in wild-type and LDLR-deleted mice [16]. In a similar model, LDLR knockout resulted in impairment of spatial memory with morphological changes in the dentate gyrus in the hippocampus [53]. Wider synaptic clefts and reduced synaptic markers were detected in the hippocampus [53]. Moreover, apoptotic cell death and oedema have been observed in the hippocampus of LDLR deleted mice [53].

In another study, LDLR knockout mice exposed to high cholesterol from an early age exhibited memory loss in the working, spatial, and procedural domains with age [48]. Furthermore, hypercholesterolaemia caused by knockout of apolipoprotein E with injection of amyloid beta promoted cognitive impairment, such as loss of spatial learning and memory function, after a high-fat diet [54]. Taken together, proper cholesterol metabolism or balance is essential for maintaining the normal structure and function of the neurons.

Cholesterol metabolism in psychiatric disorders

Changes in cholesterol metabolism can alter mental status [55] (Fig. 2). Emerging evidence indicates that patients with psychiatric disorders exhibit abnormal cholesterol metabolism [56, 57]. An imbalance in serum cholesterol levels is easily observed in individuals with mood disorders [57]. Impairments of synaptic outgrowth and myelin formation due to the influence of cholesterol on neurotransmitters, such as serotonin receptor, GABA receptors, and NMDARs, affect mental condition [45, 56]. Moreover, cholesterol, as the main source of steroid hormones, plays a key role in the activity of the hypothalamic-pituitary-adrenal (HPA) axis, which is involved in circadian rhythms, stress, and neuropsychiatric disorders [58]. Stress is also closely associated with cholesterol metabolism [59]. Psychological stress leads to altered lipid levels, including hypercholaesterolaemia and a high incidence of metabolic diseases [59]. Under stress conditions, individuals display increased serum cortisol, total cholesterol, LDL-C, and adrenaline levels [60]. Stress contributes to activation of the HPA axis, which is known to regulate glucocorticoid levels [61]. On the basis of previous literatures, cholesterol metabolism is critical for mental health [55-57].

Major depressive disorder (MDD)

MDD is common and leads to poor quality of life [62]. MDD is diagnosed using criteria, such as the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) and Patient Health Questionnaire-9 (PHQ-9), and is characterised by impairment of functioning, including home or work life, and inability of personal care [63, 64]. MDD symptoms include changes in weight, abnormal sleep patterns, and psychomotor problems, and persistent depression and sadness [63]. Multiple studies demonstrated that genetic, environmental, and psychological components can lead to the development of MDD [65, 66]. The pathogenesis of MDD is associated with abnormal neurotransmitters, neural plasticity, an impaired immune system, and dysregulation of the HPA axis [66]. In addition, abnormal monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine, are associated with MDD [67]. It has been demonstrated that the serotonin receptor 5-HT2A is highly expressed in patients with MDD [66,

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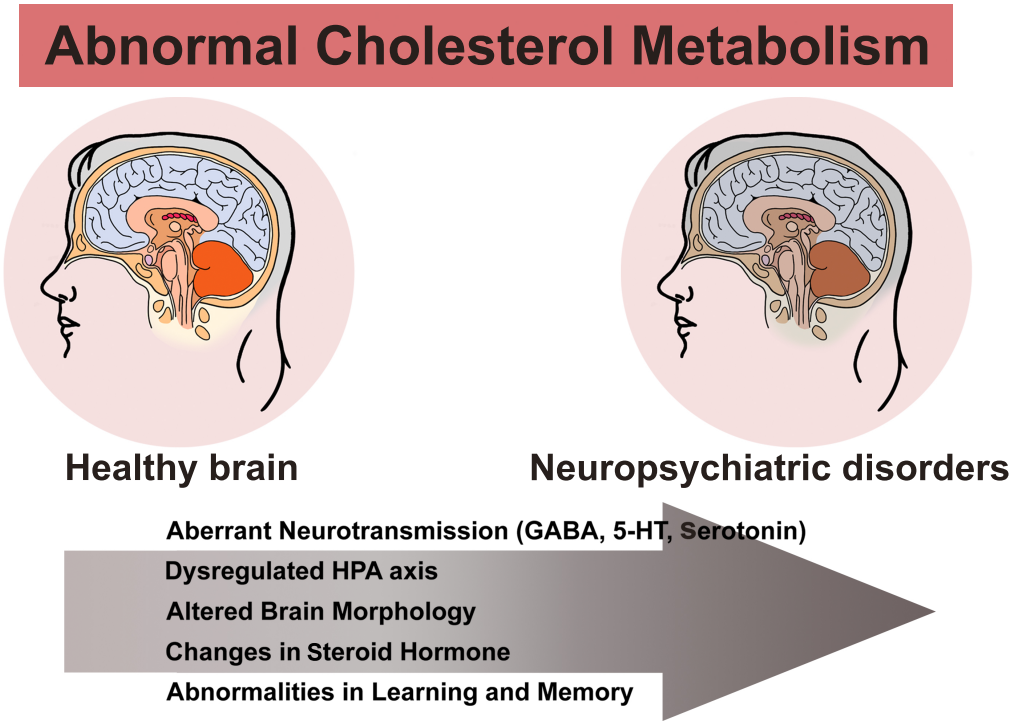

Fig. 2. The relationship between abnormal cholesterol metabolism and neuropsychiatric disorders. Cholesterol imbalance is involved in aberrant neurotransmission, dysregulated HPA axis, altered brain morphology, changes in steroid hormone and abnormalities in learning and memory. HPA, Hypothalamic-pituitary-adrenal.

68]. High cholesterol levels are responsible for the low sensitivity of 5-HT receptors and suppression of dendritic branching [21]. A disrupted dopamine system contributes to anhedonia, found in MDD patients, and animal models of depression display dysregulated dopaminergic systems [69, 70]. Altered norepinephrine neurotransmission is involved in MDD [70].

In particular, compromised cholesterol metabolism is a pathomechanism of MDD [57]. For instance, patients with hyperlipidaemia are vulnerable to depression [71], and depressive patients exhibit high levels of plasma cholesterol, which contribute to brain damage [72]. High serum LDL-C levels have been detected in patients with depression, and these levels correlate with depression severity [73]. This relationship is not limited to a specific age group but appears in various age groups [74]. Depressive adolescent males (aged 12~18 years) show that depressive mood is related to high levels of serum LDL-C [74]. In the elderly male population, depressive mood is closely associated with lower levels of LDL-C in serum [75], although a recent study using data from the National Health and Nutrition Examination Survey showed no correlation between depressive mood and low cholesterol levels, including low total cholesterol, low LDL-C, and low high density lipoprotein (HDL)-C levels in both women and men [76]. That is, abnormally high or low cholesterol levels are linked to depression [74, 75]. Patients with MDD and hypercholesterolaemia exhibit poorer outcomes in spite of antidepressant drug than those without hypercholesterolaemia, and high levels of cholesterol result in decreased serotonin receptors [57]. A previous study showed that serum cholesterol levels are closely related to polymorphisms in the promoter region of the serotonin transporter gene in neurons [77]. In addition, MDD patients manifest changes in white matter, which mostly consists of myelinated nerve fibres, and show abnormal cerebral blood flow (CBF) and BBB [78]. Magnetic resonance imaging (MRI) reveals that patients with MDD show abnormally low myelin content in brain regions, including the nucleus accumbens, medial prefrontal cortex, insula, lateral prefrontal cortex, and subgenual anterior cingulate cortex [79]. In particular, the myelin contents of the lateral prefrontal cortex, insula, and whole brain reflect the severity of depression [79]. SREBP-2 was decreased in the hippocampus of an animal model of depression, thereby reducing of cholesterol synthesis [80]. Hypercholesterolaemic mice with knockout of the LDLR show depression-like behaviour and altered monoaminergic metabolism [17]. In contrast, HMGCR inhibitors, statins, which are cholesterol-lowering drugs, have an impact on the treatment of depression [81]. Statins can decrease cholesterol *de novo* synthesis and reduce steroid hormone precursors, such as cortisone and corticosterone [82]. In addition, statins are involved in the regulation of serotonin receptor dynamics, leading to the upregulation of serotonin levels in the hippocampus [81]. Given these studies, cholesterol dysregulation has been implicated in the neurological abnormalities found in MDD.

Anxiety disorders

Anxiety disorders are common and occur at various ages ranging from childhood to adulthood [83]. Anxiety disorders are comorbid with MDD [83, 84]. Anxiety disorders include generalised anxiety disorders (GAD), panic disorder, posttraumatic stress disorder (PTSD), and social anxiety disorder [85]. Anxiety disorders are characterised by persistent and excessive anxiety or fear, avoidance behaviour, and unexpected treats [84, 86]. Physical characteristics include dizziness and irregular heart rate [86]. DSM-5, the International Classification of Diseases, Tenth Edition (ICD-10), or Generalized Anxiety Disorder-7 is used to diagnose an anxiety disorders [86, 87]. The pathogenesis of anxiety disorders includes disruptions in neurotransmission, neuronal structure, and neuroendocrine systems [85]. Lower inhibitory actions of GABA and higher excitatory actions of glutamate are observed in patients with anxiety disorders than healthy controls [85]. Similar to MDD, abnormal serotonin, dopamine, and norepinephrine levels are found in patients with anxiety disorders [85]. Patients with GAD—a common type of anxiety disorder—experience insomnia, irritability, or fatigue and show aberrant functional activity or structural connectivity in brain regions, including the hippocampus, prefrontal cortex, and amygdala [88, 89]. In GAD, the ventrolateral prefrontal cortex is activated compared to healthy controls, which correlates with symptom severity [85]. Activation of the amygdala and insula is detected under negative emotional conditions [85], and abnormalities in GABA and serotonin have been detected in patients with GAD [90]. Patients with GAD have lower levels of serotonin in the cerebrospinal fluid (CSF) compared to heathy controls [90]. Patients suffering from panic disorder display reduced cerebral blood flow in the temporal lobe [91], lower GABA levels in the brain regions, such as the basal ganglia and anterior cingulate [92], and decreased/disrupted serotonin type 1A receptor function [93]. Additionally, patients with panic disorder tend to present excessive amounts of 5-HT and/or serotonin receptor hypersensitivity [93]. Also, patients with PTSD exhibit abnormalities in fear memory, emotion regulation, and threat regulation, as well as abnormal activity of the amygdala [94]. Aberrant volumes of brain regions, such as the hippocampus and anterior cingulate, and abnormal functions of brain regions, such as the amygdala and medial prefrontal/anterior cingulate, appear in PTSD [95]. It is known that PTSD is related to chronic dysregulation of the HPA axis, including increased levels of corticotropin-releasing hormone (CRH) in CSF and insensitive adrenocorticotropin (ACTH) [95]. Also, changes in serotonin neurotransmission have been observed in patients with PTSD [95]. For instance, decreased concentration of 5-HT in serum and reduced density of 5-HT1B receptor in the brain appear in PTSD [96, 97].

Cholesterol dysregulation is also one of the main pathological factors in anxiety disorder [18]. In GAD, high levels of cholesterol and triglycerides are detected in the serum owing to the elevated activity of noradrenaline [98]. Moreover, patients with comorbid GAD and MDD display elevated levels of total cholesterol and LDL-C [99]. Similarly, hypercholesterolaemia due to enhanced noradrenergic activation occurs in individuals with panic disorder [100], indicating the elevation of autonomic arousal [101, 102]. Patients with PTSD have increased levels of serum cholesterol, triglycerides, and LDL [103]. In a preclinical study, adult rats with high total cholesterol and LDL-C levels after feeding a high-cholesterol diet showed anxiety-like behaviour with lower levels of hippocampal brain-derived neurotrophic factor (BDNF) [104]. The reduction of 5-HT is obvious in the hippocampus of adult rats that were fed a high-cholesterol diet [104]. Another study demonstrated that a high-cholesterol diet induces anxiety- and depression-like behaviour in mice and promotes an increased concentration of 5-HT in the hippocampus [105]. In particular, 5-HT2A receptor expression is elevated in the hippocampus after a high-cholesterol diet; however, in the prefrontal cortex and hypothalamus, 5-HT2A receptor expression is reduced despite high-cholesterol feeding [105]. There is an evidence that high cholesterol is responsible for anxiety disorders via changes in GABA receptor sensibility [21]. Therefore, neurological malfunctions in anxiety disorders are closely associated with cholesterol metabolism.

CONCLUSION

Although an appropriate concentration of cholesterol is necessary to sustain various neurophysiologies, it remains controversial whether plasma cholesterol level correlate with brain function and behaviour. Moreover, cholesterol in the brain is metaboised independently of the rest of the body [106]. Further research is needed to elucidate the link. However, accumulating evidence shows that cholesterol imbalance due to over- or under- supply of cholesterol or a dysfunctional cholesterol metabolic system results in neuropathologies, which can contribute to the development of different neuropsychiatric disorders. Impairment of cholesterol metabolism is associated with neuronal dysfunction, such as abnormal neurite outgrowth, and dysregulated neurotransmission, and neuronal cell death in the central nervous system. Balancing cholesterol metabolism may be a novel way to resolve neurological symptoms in patients with neuropsychiatric disorders.

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CONFLICT OF INTEREST

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