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Вклад 25-гидроксихолестерина в перекрёстное взаимодействие иммунной и нервной систем

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АННОТАЦИЯ

25-гидроксихолестерин (25ГХ) образуется из холестерина при участии фермента холестерин-25-гидроксилазы, экспрессия которой, как и уровень 25ГХ, значительно увеличивается в макрофагах, дендритных клетках и микроглии при воспалительной реакции. В свою очередь 25ГХ действует на многие иммунные клетки, модулируя течение воспалительной реакции и препятствуя проникновению вирусов в клетки. Накапливаются данные об участии 25ГХ в регуляции синаптической передачи как в центральной, так и периферической нервной системах. Учитывая повышенную продукцию 25ГХ не только при воспалении, но при ряде нейродегенеративных заболеваний (болезни Альцгеймера и боковом амиотрофическом склерозе), этот гидроксихолестерин может иметь значение в адаптации синаптической активности к воспалительным условиям, а также участвовать в патогенезе нейродегенеративных заболеваний и формировании синаптических дисфункций. Мишенями 25ГХ в нервной системе являются глутаматные NMDA-рецепторы, печёночные X-рецепторы и эстрогеновые рецепторы. К тому же 25ГХ может напрямую влиять на свойства синаптических мембран, изменяя формирование мембранных микродоменов (липидных рафтов) — компартментов, где сосредоточены белки, важные в синаптической пластичности. Текущие данные указывают на то, что эффекты 25ГХ сильно зависят от концентрации и «контекста» (норма, патология, наличие воспалительной реакции), в котором исследуется его действие.

В данном мини-обзоре мы сфокусировались на ключевых аспектах действия 25ГХ как локального регулятора гомеостаза холестерина и как паракринной молекулы, реализующей влияние воспаления на процессы нейропередачи в центральной и периферической нервной системе.

Ключевые слова: синаптическая передача; 25-гидроксихолестерин; скелетная мышца; везикула; липидные рафты; нейромедиатор.

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Contribution of 25-hydroxycholesterol to the cross-interaction of the immune and nervous systems

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ABSTRACT

25-hydroxycholesterol (25HC) is produced from cholesterol by cholesterol-25-hydroxylase, and its expression, similar to the 25HC level, increases significantly in macrophages, dendritic cells, and microglia during an inflammatory reaction. In turn, 25HC acts on many immune cells; therefore, it can modulate the course of the inflammatory reaction and prevent the penetration of viruses into cells. Data are accumulating about the involvement of 25HC in the regulation of synaptic transmission in both the central and peripheral nervous systems. 25HC production is increased not only during inflammation but in certain neurodegenerative diseases, such as Alzheimer's disease and amyotrophic lateral sclerosis; thus, this hydroxycholesterol can be important in the adaptation of synaptic activity to inflammatory conditions, pathogenesis of neurodegenerative diseases, and formation of synaptic dysfunctions. The targets of 25HC in the nervous system are glutamate NMDA receptors, liver X-receptors, and estrogen receptors. 25HC can also directly influence the properties of synaptic membranes by changing the formation of membrane microdomains (lipid rafts) where proteins, which are important for synaptic plasticity, are clustered. Current data indicate that the effects of 25HC strongly depend on its concentration and "context" (norm, pathology, and presence of an inflammatory reaction) in which the effect of 25HC is being investigated. This minireview focused on the key aspects of the action of 25HC as both a local regulator of cholesterol homeostasis and a paracrine molecule that realizes the influence of inflammation on neurotransmission processes in the central and peripheral nervous systems.

Keywords: synaptic transmission; 25-hydroxycholesterol; skeletal muscle; vesicle; lipid rafts; neurotransmitter.

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INTRODUCTION

Cholesterol is found in large quantities in the plasma membranes of cells (approximately 20–30 mole % [1]), where it maintains the rigidity, fluidity, and permeability of the bilipid layer. Cholesterol in combination with glycosphingolipids forms nanometer dynamic lipid microdomains that serve as a scaffold for various proteins. In addition, cholesterol has a great affinity for many transmembrane proteins (ion channels and receptors) and can modulate their activity, thereby affecting intracellular processes. In addition to its role in maintaining the structure and functioning of membranes, cholesterol is transformed into various oxysterols by enzymatic and oxidative reactions. Oxysterols have structural and functional diversity. Recent studies have indicated that oxysterols have target proteins in both the central and peripheral nervous systems. Particularly, transcription factors (liver X receptors, retinoid orphan receptors, estrogen receptor-α, glucocorticoid receptors, and sterol regulatory element-binding protein [SREBP 1]), receptors associated with G-proteins (GPR183, GPR17, CXCR2, SMO, and SLO1), ion channels (P2X7 and NMDA receptors), cell adhesion molecules ($\alpha_5\beta_1$-integrin), and oxysterol-binding proteins (ORP8) are stimulated or modulated by oxysterols [2–9].

Cytochrome P450 46A1 (CYP46A1) is one of the main enzymes of the brain that transform cholesterol into an oxidized form. This enzyme catalyzes the formation of 24-hydroxycholesterol (24HC) [10], which passes through the blood–brain barrier and enters the bloodstream with subsequent delivery to the liver [11, 12]. This pathway is responsible for removing 75–85% and 40–50% of excess cholesterol from the human and mouse brains, respectively [13, 14].

In addition to 24HC, 25-hydroxycholesterol (25HC) participates in controlling the level of brain cholesterol. Unlike 24HC, 25HC is produced in the brain in significantly smaller quantities, is not brain-specific, and is produced in the periphery. Its flow from the brain to the periphery and from the periphery to the brain is determined by the concentration gradient. 25HC is produced by the enzyme cholesterol-25-hydroxylase (CH25H). The *CH25H* gene is interferon-induced, and interferon γ and interferon type I can rapidly and STAT1-dependently enhance the expression of CH25H [15]. In general, CH25H expression increases rapidly in inflammation in macrophages, dendritic cells, and microglia. 25HC activates LX receptors, which can lead to the formation of interferon-γ [16], increasing CH25H expression. During inflammation, the blood plasma concentrations of 25HC can reach 200 ng/mL [17], whereas under normal conditions, its content ranges from 2 to 30 ng/mL [18].

25-HYDROXYCHOLESTEROL AS A REGULATOR OF CHOLESTEROL HOMEOSTASIS

25-hydroxycholesterol is an affecting regulator of cholesterol biosynthesis. By binding to LX receptors, 25HC increases the expression of cholesterol transporters ABCA1 and ABCG1 [19], which provide the outflow of excess cholesterol and phospholipids from cells [20]. An additional mechanism of action of 25HC in the regulation of cholesterol homeostasis is the inhibition of cholesterol synthesis through the binding of 25HC to insulin-induced gene 1 (INSIG). INSIG is a protein of the endoplasmic reticulum, which undergoes conformational changes by binding to 25HC and further interacts with SREBP cleavage-activating protein (SCAP), eventually forming the INSIG–SCAP–SREBP-2 complex. As part of this complex, SREBP-2 remains in an inactive form that prevents the formation of the active transcription factor SREBP-2, which enhances the expression of cholesterol biosynthesis genes [21, 22]. The results of the analysis of the interaction of INSIG and 25HC revealed the ubiquitination and degradation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which catalyzes the key stage of cholesterol synthesis [23]. Thus, the more cholesterol the cells contain, the more intensively it is synthesized into 25HC, which inhibits the synthesis of cholesterol and promotes its removal from the cell; as a result, the cholesterol level in the cell normalizes.

25-HYDROXYCHOLESTEROL AND IMMUNE RESPONSE

Numerous data have revealed the mechanisms of action of 25HC in immune cells in the presence of inflammation. 25HC has a multidirectional effect on modulating the immune response by inhibiting or increasing the production of inflammatory cytokines. 25HC can induce the secretion of proinflammatory cytokines and chemokines, for example, interleukin (IL)-1β, IL-6, IL-8, CC motif chemokine ligand 5 and macrophage colony-stimulating factor. On the contrary, 25HC suppresses inflammation by reducing the activity of inflammasomes [24, 25]. When Toll-like receptor 4 (TLR4) of macrophages is activated, there is an increase in CH25H expression and 25HC synthesis, which leads to the suppression of IL-2 production that is necessary for B-cell proliferation [17]. An increase in macrophage survival and a decrease in the innate immune response were found to be dependent on Toll receptors during the stimulation of LX receptors of macrophages by 25HC, which led to a decrease in the production of IL-6, IL-1β, monocyte chemoattractant

proteins (MCP-1 and MCP-3), inducible nitric oxide synthase, and matrix metallopeptidase-9 [26]. As mentioned above, interferon stimulates CH25H expression. In turn, 25HC can enhance interferon production and inhibit uncontrolled inflammation. 25HC, being a functional antagonist of transcriptional SREBP, also inhibits IL-1β and IL-1 formation by activated inflammasomes [27]. Such a dual role of 25HC in the immune response depends on the cellular and immunological context and can be explained by the need for an inflammatory response and protection from excessive inflammation when the production of anti-inflammatory agents leads to the restoration of homeostasis.

Interestingly, 25HC can prevent the penetration of viruses into the cell (HIV, Ebola virus, Zika virus, rabies virus, herpes simplex virus, SARS-CoV-2, etc.) [28–30]. This effect of 25HC is partly related to its ability to change the location of cholesterol by penetrating the membrane, thereby changing the properties of the membrane and lipid microdomains.

25-HYDROXYCHOLESTEROL AND THE CENTRAL NERVOUS SYSTEM

25-hydroxycholesterol is intensively synthesized by activated microglia, and its production can increase the formation of proinflammatory cytokines IL-1β, IL-1α, and tumor necrosis factor-α in response to the activation of TLR4 receptors by lipopolysaccharides [31]. In mice with *CH25H*-knockout microglia produces much less 25HC than microglia of wild-type animals [32].

25-hydroxycholesterol is a weak agonist of NMDA receptors of central synapses, which provide cognitive functions. Independently, 25HC only slightly enhances responses during activation of NMDA receptors; however, 25HC blocks the powerful potentiating effect of certain powerful positive allosteric modulators on NMDA receptors, particularly 24HC [33]. This effect of 25HC reduces the probability of excitotoxicity in hyperactivated NMDA receptors. The injection of lipopolysaccharide disrupts the long-term potentiation that is formed with the participation of NMDA receptors in the hippocampal regions of the mouse brain [32]. This impairment of long-term potentiation is not observed in mice with *CH25H*-knockout, which allows us to consider 25HC as a modulator of synaptic plasticity in neuroinflammation.

25-hydroxycholesterol is a ligand for LX receptors, which can form a complex with estrogen receptor-α [34]. 25HC can also directly activate estrogen receptors 16]. In turn, the activation of estrogen receptors by α-17β-estradiol enhances long-term plasticity by increasing the clustering of AMPA receptors in the plasma membrane [35]. However, whether 25HC can act through estrogen receptors in the brain is unknown.

25-HYDROXYCHOLESTEROL AND NEUROMUSCULAR TRANSMISSION

macrophages play a key role in adaptive and innate immunity and are abundant in skeletal muscles, where they contact motor nerves and even neuromuscular junctions, promoting regeneration processes. 25HC is intensively produced by skeletal muscle macrophages in the presence of inflammation, which may indicate the functional significance of 25HC in the interaction of the immune system and skeletal muscles. Similar to the bidirectional concentration-dependent effect of 25HC on the immune system, the same effect was observed on the exocytosis of synaptic vesicles. High concentrations (1–10 μmol) accelerate and low concentrations (0.01–0.10 μmol) slow down this process [36].

25-hydroxycholesterol is a direct ligand for LX receptors. LX receptors are nuclear receptors; however, their expression has been detected in the plasma membrane of endothelial cells, thrombocytes [34, 37], and synaptic region of the axons of motor neurons [36]. 25HC in high concentration exerts its potentiating effect through the LX receptor-dependent pathway. Being in direct connection with estrogen receptor-α, LX receptors become active under the action of 25HC [36]. The same situation is observed when LX receptors are activated by an agonist in endothelial cells [34, 37]. LX receptors and estrogen receptor-α are located in lipid rafts, and the disruption of these microdomains abolished the potentiating effect of 25HC [36].

The deficiency in LXβ receptors leads to the denervation and death of motor neurons [38], and the knockout of LXα and LXβ receptors is characterized by the production of free radicals and lipid oxidation in some parts of the brain and sciatic nerves, which is accompanied by motor dysfunction [39]. Moreover, 25HC (1 μmol) was found to increase the output of calcium ions from the endoplasmic reticulum through inositol triphosphate receptors, which is an additional contribution to the mobilization of synaptic vesicles to the active zone (exocytosis site) [36]. Zhong et al. discovered the opposite function of 25HC (1 μmol): 25HC reduces the activity of the anti-apoptotic pathway ORP4L/$G\alpha_{q/11}$/PLCβ3/IP receptors/Ca^{2+} in macrophages, which led to the induction of apoptosis [40]. Calcium-dependent protein kinases also enhance the mobilization of synaptic vesicles in Held synapses [41]. Similar data have been obtained regarding the neuromuscular synapse, where an increase in calcium output from intracellular depots under the action of 25HC (1 μmol) leads to protein kinase activation with a subsequent increase in neurotransmitter release from synaptic vesicles during high-frequency activity [36].

Returning to estrogen receptor-α, their co-localization with the α-subunit and βγ-dimer of the G_i-protein determines the nongenomic effect of estradiol on endothelial cells

[42]. Interestingly, in neuromuscular synapses, high 25HC concentrations similarly influence the activity of estrogen receptor-α, leading to the dissociation of the βγ-dimer from the G_i-protein, which potentiates the activity of phospholipase C [36].

An alternative realization of the 25HC effect on the neuromuscular synapse can be through ROS-dependent signaling. Calcium is released from the depot in response to 25HC and leads to an increase in reactive oxygen species (ROS) production by various mechanisms [36, 43]. Under the influence of 25HC (1 μmol), ROS production in the synaptic region and the concentration of hydrogen peroxide in the extracellular environment were increased. Interestingly, in this case, ROS play a signaling role because the level of lipid peroxidation under the action of 25HC was not affected [41]. In addition, like calcium, ROS can enhance the delivery of synaptic vesicles to exocytosis zones by activating protein kinase C [44–46].

25-HYDROXYCHOLESTEROL AND NEURODEGENERATIVE DISEASES

a high 25HC expression was observed in microglial cells in mice with an Alzheimer's disease. Interestingly, the microglia secreting the E4 variant of apolipoprotein E (which increases the risk of Alzheimer's disease) produce more 25HC and are more sensitive to the proinflammatory effect of 25HC than the microglia expressing apoE2 or apoE3 [31]. However, an increase in 25HC production by the microglia may also have a protective effect because 25HC reduces the clustering of the interferon-γ receptor in lipid rafts, thereby inhibiting the production of proinflammatory cytokines by microglia in response to interferon.

25-hydroxycholesterol is a potential marker of amyotrophic lateral sclerosis (ALS). ALS is characterized by progressive muscle atrophy, leading to fatality. In this pathology, 25HC concentration can reach micromolar concentrations in the spinal cord at the pre-onset disease stage in mice $SOD1^{G93A}$ (model of ALS); however, this was not observed in patients with ALS, although CH25H overexpression was detected [47]. High concentrations, 5–30 μmol, can reduce survival and induce apoptosis of motor neurons [47, 48]. For example, 25HC activated mitochondrial-dependent apoptosis by stimulating GSK-3β kinase. However, low concentrations, <1 μmol, have the opposite effects, increasing the survival of neurons [49].

Amyotrophic lateral sclerosis is characterized by a pronounced disturbance of lipid metabolism at the pre-onset stage [50, 51], including disturbances in membrane properties [52]. Lipid metabolism dysregulation is also observed in many other neurodegenerative diseases: spinal muscular atrophy [53], spinocerebellar ataxia [54], Huntington's disease [55], Parkinson's disease [56], and Alzheimer's disease [57, 58]. Recent studies have shown increased content of glycosphingolipids and an imbalance between saturated and unsaturated fatty acids in ALS [59, 60]. In the model mice with mutation of a superoxide dismutase, high ceramide levels were found as a result of oxidative stress. In turn, ceramide is a lipid that induces programmed cell death. However, low ceramide concentrations have a neuroprotective effect and enhance axonal growth [61].

Impaired lipid metabolism, including sphingolipids and cholesterol, directly influences to the state of lipid rafts, which determine the functioning of various proteins and protein complexes. Many studies have emphasized the important role of lipid rafts. For example, the level of caveolin-1 decreases in ALS, which leads to the impaired integrity of lipid rafts, contributing to disease progression [62]. In addition, a recent genomic study conducted by Zhang et al. [63] revealed changes in the content of 22 genes involved in protein expression associated with lipid rafts in patients with ALS, including ABCA1 (responsible for cholesterol efflux), CERS5 (involved in the formation of proapoptotic ceramide [64]), PLAA (phospholipase A activation), etc.

Synaptic hyperexcitability can potentiate the release of brain-derived neurotrophic factor and activation of TrkB receptors in ALS, followed by the induction of excitotoxicity and death of motor neurons [65]. In turn, TrkB receptors in combination with adenosine A2 receptors are localized in lipid rafts [66]. The extraction of cholesterol mainly from lipid rafts leads to a decrease in TrkB activity, thereby reducing excitotoxicity and death of motor neurons in ALS [65].

Changes in the properties of membranes in mice with a model of ALS at the pre-onset stage of the disease also support the important role of lipid rafts in ALS pathogenesis, indicating impaired integrity of lipid rafts. The use of various fluorescent labels disrupted the integrity of lipid rafts, increased the membrane fluidity, and destabilized the order of the lipid bilayer [52]. One of the possible causal factors of this phenomenon may be an increase in ceramide levels in the muscles, which leads to raft destabilization, for example, during hindlimb suspension [67–69]. In addition, a high ceramide level was observed in the membrane of mice with an ALS at the pre-onset stage [52].

Probably, lipid raft destabilization in ALS increases the level of extracellular choline concentration because of increased nonquantum secretion of acetylcholine [70]. In addition, the removal of cholesterol using the extracting agent methyl-β-cyclodextrin has the same effect; on the contrary, the addition of exogenous cholesterol reduces nonquantum secretion and choline levels [52]. An unregulated increase in acetylcholine level in ALS contributes to motor dysfunction and age-related morphological changes in the neuromuscular junction. For example, ALS also involved a disorder in the clustering of nicotinic acetylcholine receptors in the postsynaptic membrane [52, 71], which may explain the increase in amplitude and decrease in the rise time of miniature endplate potentials in mice with ALS [72].

Lipid raft destabilization can increase oxidative stress, for example, increased ROS production and increased lipid peroxidation in the neuromuscular junction are observed during the removal of cholesterol [73]. High hydroperoxide levels and lipid peroxidation were found in the homogenates of mouse muscles with the ALS model [50]. Interestingly, electrophilic aldehyde products that formed as a result of lipid peroxidation contribute to the aggregation of the SOD1 protein, and its mutation leads to ALS pathology [74].

As mentioned above, 25HC increases in ALS and affects the survival of motor neurons. In addition, 25HC induces lipid raft stabilization in neuromuscular synapses in mice with an ALS model at the pre-onset stage by reducing membrane fluidity and increasing its ordering. Moreover, 25HC prevents ceramide accumulation in the neuromuscular synapse. Interestingly, the synaptic membranes of mice with ALS have a significantly higher ability to bind 25HC than the membranes of wild-type mice [52]. Possibly, the number of binding sites for 25HC increases in ALS, including oxysterol-binding proteins, which can explain the high sensitivity of synaptic membranes of mice with ALS to 25HC. Data also show the involvement of oxysterol-binding proteins in ALS pathogenesis. For example, vesicle-associated protein B (VAPB) quantity, an important modulator of oxysterol-binding proteins, is reduced in the spinal cord in mice and patients with ALS at the pre-onset stage of the disease [75]. In addition, 25HC can regulate ceramide transport and cholesterol distribution in the membrane indirectly through oxysterol-binding proteins [76].

25-hydroxycholesterol can suppress synaptic changes in the neuromuscular synapse in ALS, that is, an increase in lipid peroxidation, extracellular choline levels, and disordered clustering of nicotinic acetylcholine receptors [52].

Based on the positive effect of 25HC on the properties of membranes, increased concentration in ALS can have a compensatory effect. Indeed, hypercholesterolemia has a protective effect on ALS, whereas substances that block cholesterol synthesis enhance this pathology [61, 77–80].

CONCLUSION

The class of cholesterol derivatives is diverse, and many of them have high biological activity. This study focused on 25-hydroxycholesterol, which is involved in the regulation of cellular cholesterol homeostasis and the functioning of the immune and nervous systems. Interestingly, 25-hydroxycholesterol has a concentration-dependent effect on both the immune and central nervous systems. Low 25-hydroxycholesterol concentrations promote the production of anti-inflammatory cells and improve synaptic plasticity. Higher 25-hydroxycholesterol concentrations can induce the secretion of proinflammatory cytokines and chemokines and inhibit synaptic activity, leading to synapse elimination.

25-hydroxycholesterol is produced by macrophages, including resident macrophages of the skeletal muscles. The 25-hydroxycholesterol level is increased in amyotrophic lateral sclerosis, which is characterized by the death of motor neurons and muscle atrophy. These data present the relationship between 25-hydroxycholesterol and neuromuscular transmission. Indeed, 25-hydroxycholesterol in micromolar concentrations enhances the recruitment of synaptic vesicles during the high-frequency activity of motor nerves. Membrane-associated LX receptors and estrogen receptor-α are involved in this effect of 25-hydroxycholesterol. These two receptors, forming a complex in lipid rafts, activate of the signaling pathway G_i-protein/βγ-dimer of G-protein/phospholipase C/Ca^{2+}/protein kinase C. In addition, the Ca^{2+}-dependent increase in reactive oxygen species production under the action of 25-hydroxycholesterol also contributed to the enhancement of neuromuscular transmission.

Some studies have shown that high 25-hydroxycholesterol concentrations negatively affect amyotrophic lateral sclerosis; progression; however, a positive effect of 25-hydroxycholesterol on the properties of membranes at the pre-onset stage of the disease was also reported. Particularly, 25-hydroxycholesterol can restore synaptic anomalies such as increased membrane fluidity, ceramide accumulation, and decreased membrane ordering. In addition, 25-hydroxycholesterol reduces the high level of extracellular choline in amyotrophic lateral sclerosis, which can contribute to the fragmentation of neuromuscular synapses.

This review presents the functional role of 25-hydroxycholesterol in various body systems and allows us to consider cholesterol-25-hydroxylase as a therapeutic effect target in the future.

ADDITIONAL INFORMATION

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