REVIEW

Cysteinyl Leukotrienes and Their Receptors: Emerging Therapeutic Targets in Central Nervous System Disorders

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Alzheimer's disease; Cerebral ischemia; Cysteinyl leukotrienes type 1 receptor; G-protein-coupled receptor 17; Multiple sclerosis.

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Received 9 June 2016; revision 14 July 2016;

accepted 18 July 2016

SUMMARY

Cysteinyl leukotrienes are a group of the inflammatory lipid molecules well known as mediators of inflammatory signaling in the allergic diseases. Although they are traditionally known for their role in allergic asthma, allergic rhinitis, and others, recent advances in the field of biomedical research highlighted the role of these inflammatory mediators in a broader range of diseases such as in the inflammation associated with the central nervous system (CNS) disorders, vascular inflammation (atherosclerotic), and in cancer. Among the CNS diseases, they, along with their synthesis precursor enzyme 5-lipoxygenase and their receptors, have been shown to be associated with brain injury, Multiple sclerosis, Alzheimer's disease, Parkinson's disease, brain ischemia, epilepsy, and others. However, a lot more remains elusive as the research in these areas is emerging and only a little has been discovered. Herein, through this review, we first provided a general up-to-date information on the synthesis pathway and the receptors for the molecules. Next, we summarized the current findings on their role in the brain disorders, with an insight given to the future perspectives.

doi: 10.1111/cns.12596

Background

The importance of the lipid inflammatory mediators in health and disease has been emerging area of interest. Leukotrienes (LTs), along with prostaglandins, thromboxanes, and lipoxins, are the major constituents of a group of biologically active, oxygenated, polyunsaturated, long-chain fatty acids, known as the eicosanoids. They are secreted by mast cells, eosinophil, and leukocytes during inflammation and possess a wide range of biological activities such as leukocyte chemotaxis [1], vascular leakage [2], endothelial cell migration (but not proliferation) [3], smooth muscle cells proliferation [4], and astrocytes proliferation [5,6]. In the human body, they are derived *de novo* from arachidonic acid [7] and include five types, namely leukotriene A4 (LTA4), leukotriene B4 (LTB4), leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4). LTA4 and LTB4 (non-cysteinyl leukotrienes) are structurally different from the cysteinyl leukotrienes (Cys-LT) as they lack the cysteine moiety, which is present in the Cys-LT (LTC4, LTD4, and LTE4) [8]. Their hospitality is also welcomed by other type of receptors such as BLT₁ and BLT₂ [9], whereas LTC4, LTD4, and LTE4 are the ligands majorly for cysteinyl leukotrienes type 1 (CysLT₁R) and type 2 receptor (CysLT₂R) [10]. The rank of order is LTD4 > LTC4 > LTE4 by means of their affinity

toward CysLT₁R [11], whereas the order to that of CysLT₂R is LTC4 = LTD4 >> LTE4 [12]. Apart from these two main receptors, several other receptors have been reported but their role as Cys-LT receptors is very little known. These additionally reported receptors are GPR17 [13], GPR99 [2], PPAR γ [14], and P2Y₁₂ [15,16]. The latter three receptors, that is, GPR99, PPAR γ , and P2Y₁₂, have been reported to have preferential binding to LTE4, which, in general, has less preference for CysLT₁R or CysLT₂R (Figure 1). Structurally, CysLT₁R and CysLT₂R are 38% homologous to each other [12], and they also share a phylogenetic relationship with the purinergic (P2Y) class of GPCRs [15,17] and receptors for proteases (PARs), and platelet-activating factor receptor (PAFR) [18,19]. Apart from these, a cross talk between the toll-like receptors (TLRs) and CysLT₁R in dendritic cells has also been reported [20].

Ever since the elucidation of chemical structure of the Cys-LT and their association with inflammation [7], their role has been mainly studied in the pathophysiology of asthma [21–23]. However, in more recent days, their role in other diseases has been emerging and pathophysiological role of these lipid mediators in diseases such as cardiovascular diseases including vascular inflammation and atherosclerosis [24–26], cancer [27–29], and many CNS diseases (discussed in the later parts of this review) has been

Figure 1 Biosynthesis pathway of the Cys-LT and their receptors. cPLA2-derived arachidonic acid is converted to LTA4 by the action of 5-LOX and FLAP (this step can be blocked by 5-LOX/FLAP inhibitor zileuton). LTA4 is then rapidly converted to LTB4 by LTA4-H or to LTC4 by LTC4-S; LTC4 is further converted to LTD4 and LTE4. LTC4, LTD4, and LTE4 can bind to CysLT₁R, CysLT₂R, and GPR17 (CysLT₁R antagonists can block the activity of CysLT₁R or GPR17, but not CysLT₂R). Among the Cys-LT, only LTE4 shows preferential binding toward GPR99, PPAR γ , and P2Y₁₂.

shown. Herein, a summary has been made on the research findings on Cys-LT and their receptors in different CNS diseases and the underlying mechanism by which they might play a crucial role in such mediation of the CNS diseases.

Synthesis of the Cys-LT through Arachidonic Acid Metabolism

Free arachidonic acid (AA), a ubiquitous, 20-carbon chain fatty acid [30], which is liberated from membrane phospholipids through calcium-dependent cPLA2 (cytosolic phospholipase A2) in the cytosol [31], is metabolized enzymatically to eicosanoids through three major pathways, namely cytochrome P450, cyclooxygenase (COX), and lipoxygenase (LOX) pathways [28]. In the cytochrome P450 pathway, AA is converted into epoxyeicosatrienoic acids (EETs), hydroxyeicosatetraenoic acids (HETEs), and hydroperoxyeicosatetraenoic acids (HPETEs). In the COX pathway, AA is metabolized to prostaglandin H₂ (PGH₂), which is further metabolized, by particular prostaglandin and thromboxane synthases, to prostanoids, together with prostaglandins (PGs), for example, PGE₂, PGF₂, PGD₂ and PGI₂ and thromboxanes (TXs), for example, TXA₂. In the LOX pathway, AA is metabolized to 8-, 12- and 15-HPETE by 12- and 15-LOX or to 5-HPETE by 5-LOX and 5-lipoxygenase-activating protein (FLAP). 5-HPETE instantly undergoes dehydration to form LTA₄, which is unstable in nature and rapidly metabolized either to produce LTB₄ by the act of LTA₄ hydrolase (LTA₄-H) or to generate LTC₄ by the action

of LTC₄ synthase (LTC₄-S); LTC₄ is further converted to LTD₄ and LTE₄ [32] (Figure 1).

Although the biosynthesis process of the Cys-LT mainly occurs in a cell-specific manner in the nuclear envelope [33], a nonspecific mechanism may also be followed by cells like vascular endothelial cells [34,35], and platelets [36] to produce Cys-LT. Although these cells lack the enzymes to produce LTA₄, they can use the LTA₄ from the surrounding neutrophils and produce LTC₄ - an alternate route for Cys-LT biosynthesis known as transcellular biosynthesis [33]. Such transcellular biosynthesis has also been observed in neuronal and glial cells when these cells are cocultured with neutrophils [37]; similar trend was found in brain endothelial cells in a CysLT₂R-dependent manner [38]. Neutrophils infiltrate the brain regions following injury and donate LTA₄ to these cells, which is further utilized to generate Cys-LT in a similar manner to that of followed in the traditional Cys-LT biosynthesis (Figure 2).

Receptors for the Cys-LT

The main two receptors for Cys-LT, namely CysLT₁R and CysLT₂R, are the members of G-protein-coupled receptors (GPCRs) [39,40]. Recombinant CysLTRs activate the Gq/11 pathway that involves modulation of inositol phospholipids hydrolysis and calcium mobilization, whereas the native systems involve activation of a pertussis toxin-insensitive Gi/o-protein [39]. The internalization and signaling of CysLT₁R, as a GPCR, largely depends on protein kinase C (PKC) [41,42], which is the principal regulator of both rapid agonist-dependent internalization and rapid agonist-dependent desensitization of the receptor [41]. No data are yet available on the functional regulation of CysLT₂R [39].

CysLT₁R (Cysteinyl Leukotrienes Type 1 Receptor)

The first known receptor of the Cys-LT, CysLT₁R, was reported in 1999 [11,43]. The receptor showed highest affinity toward LTD₄ (EC₅₀ = 2.5 nM), with much lower affinity toward LTC₄ (EC₅₀ = 24 nM) and LTE₄ (EC₅₀ = 240 nM) [43]. The human CysLT₁R shares a homology of 38% with CysLT₂R [12], 32% with the purinergic receptor P2Y₁ and the receptor for platelet-activating factor, and 28% with BLT receptor [11]. The receptor contains 336 amino acid residues with found mRNA expression in the spleen, lung tissue, smooth muscle cells, leukocytes, macrophages, and mast cells [10,33]. Later interpretation in mouse led to the discovery that the mCysLT₁R was composed of 339 amino acid residues with 87.3% identity with the hCysLT₁R [44]. The receptor is the primary target in the treatment of asthma and can be targeted by agents such as montelukast, pranlukast, and zafirlukast.

CysLT₂R (Cysteinyl Leukotrienes Type 2 Receptor)

One year after CysLT₁R was cloned, another receptor for the Cys-LT was reported in 2000. The receptor was named CysLT₂R that showed an equal affinity both toward LTC₄ and LTD₄ with a lower affinity toward LTE₄ [12,45]. More recently, it has been confirmed that LTC₄ selectively binds to CysLT₂R and works on a

Figure 2 Transcellular biosynthesis of Cys-LT in the brain. Neutrophils, which infiltrate the inflamed brain area, transfer LTA4 to the surrounding neurons, glial cells, and brain endothelial cells. This LTA4 then can further be utilized by these brain resident cells to produce Cys-LT.

CysLT₂R-dependant manner and that LTC₄ is inactivated in CysLT₂R^{-/-} mice [46]. The receptor contains 345 amino acid residues and is expressed in the adrenal gland, heart, spleen, leukocytes, placenta, brain, and lymph nodes, with lower expression in the lung [10,33]. Later studies carried out on mCysLT₂R found that the homology of mCysLT₂R to that of hCysLT₂R was 73.4% and it consisted of 309 amino acids [47]. It is interesting that CysLT₂R uses different activation niche for the mediation of its inflammatory responses [48].

GPR17 (G-protein-coupled Receptor 17)

GPR17, a receptor with close phylogenetic relationship with the purinergic receptors [49], is a G-coupled dual receptor activated by both uracil nucleotides and Cys-LT [13], and LTD₄ can induce migratory function of the receptor [50]. Whereas several studies support the idea that GPR17 is a receptor for Cys-LTs, other studies also exist contradicting the same. One study represented that GPR17 is not a cognate receptor for Cys-LT [51], and rather, it acts a negative regulator of CysLT₁R [52].

GPR99 (G-protein-coupled Receptor 99)

GPR99, another GPCR belonging to the P2Y subfamily of GPCRs [53], was recently identified to be a receptor for LTE₄ [2]. LTE₄, which generally has the lowest affinity toward CysLT₁R and CysLT₂R, was shown to be involved in vascular leakage through GPR99-mediated actions [2].

PPAR γ (Peroxisome Proliferator-activated Receptor γ)

Although LTB₄, the most important subtype of the noncysteinyl leukotrienes, is known as an important regulator of the functions of the PPAR family of receptors [54], only a single study exists representing PPAR γ as a receptor for the Cys-LT [14]. Paruchuri and colleagues, in 2008, using culture of human mast cells, showed

that PPAR γ is involved in LTE₄-mediated ERK (Extracellular signal-Regulated Kinases) activation and that treatment with GW9622, a selective PPAR γ antagonist, can block the LTE₄-induced, but not LTD₄-induced, activation of ERK, suggesting a selective binding of LTE₄ with PPAR γ [14].

P2Y₁₂

P2Y₁₂ was shown as a receptor for LTE₄ [15,16]. However, a recent study has opposed that LTE₄ or other Cys-LT do not bind to P2Y₁₂ [55]. On the contrary, again, even a more recent study showed LTE₄ as a ligand for the P2Y₁₂ [56], suggesting a need for more studies confirming the crosstalk between LTE₄/P2Y₁₂. P2Y₁₂ has also been recognized as to support the cross talk between LTC₄ and CysLT₂R [46].

P2Y₆ (A Supporting Receptor)

Although this purinergic subfamily of receptor does not bind to the Cys-LT, the activity of the Cys-LT/their receptors depends on these receptors. P2Y₆ has been identified as a mediator of chemokine generation and promoter of cell survival that supports the activity of CysLT₁R [57]. CysLT₁R antagonists also show differential inhibitory effect on the P2Y₆ receptor [58].

Therapeutic Interventions: Cys-LT Biosynthesis Blockers and the CysLTR Antagonists

Currently, there are two available approaches to therapeutically block the Cys-LT. The 5-LOX pathway of Cys-LT production during AA metabolism can be blocked by FLAP inhibitors such as zileuton, which is a choice of drug in asthma. Drugs targeting CysLT₁R such as montelukast, pranlukast, and zafirlukast are also in use for asthma and allergic rhinitis and are well tolerated with low therapeutic-to-toxic ratio [33,59,60]. These drugs mediate their effect by selective antagonism of CysLT₁R and have no effect

on CysLT₂R. Although there are no clinically available CysLT₂R antagonists, development of such agents is deemed necessary as some patients fail to respond to CysLT₁R antagonists [33,61]. An agent was developed as a dual antagonist of CysLT₁R and CysLT₂R, named BAYu9773, but it showed poor potency and selectivity for these receptors in human tissues [62]. More dual antagonists are also under development [63].

5-LOX/Cys-LT/CysLTRs in CNS Diseases

Although 5-LOX, Cys-LT, and CysLTRs are traditionally known targets in asthma and other allergic diseases, their role also has been shown to be associated with other human diseases such as cancer, atherosclerosis, and several CNS diseases. Among the CNS diseases, they are related to brain injury, Multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, epilepsy, and depression and they also facilitate viral entry into the brain (Figure 3). Although normal physiological role of 5-LOX in the brain remains elusive, its pathophysiological role is more extensively studied [8]. 5-LOX is expressed on neurons and regulates synaptic plasticity, and brain aging [64,65]. Age-dependent higher expression of 5-LOX is seen in aged mouse, rat, and human hippocampus [65,66], and glucocorticoid receptor-dependent mechanism might be one of the regulatory mechanisms involved in neuronal expression of 5-LOX [67]. Age-related increased expression of CysLT₁R has been also shown in aged rat brain, localized in glial cells and several types of neuronal cells [66]. While the basal expression of the CysLTRs, especially CysLT₁R [43], is very weak in the normal brain, it remains unclear how the receptor is upregulated in the inflamed brain. Although acute inflammation relative of the CysLT₁R signaling is important in reparative responses in injured brain [68], chronic inflammation, however, is considered harmful in such scenario [69]. Whereas glial cells, namely microglia and astrocytes, are regarded as the

key players in neuroinflammation, their activity has been shown to be regulated by Cys-LT and CysLT₁R. For instance, LTD4 activates mouse microglial cells *in vitro*, which is mediated by CysLT₁R [70]. Microglia are the resident immune cells in the brain, which are activated following brain injury, and their activation can either be harmful (M1 pathway) or be beneficial (M2 pathway) [71]. Our recent study also indicates the role of CysLT₁R in bacterial lipopolysaccharide-induced neuroinflammation in mice; we downregulated the activity of the receptor using its shRNA-mediated knockdown and pharmacological inhibition by pranlukast to study the role of the receptor in microglial activation, and we found that such activation of microglia was normalized in CysLT₁R-shRNA- or pranlukast-treated animal groups along with the downregulation of the M1 pathway molecules such as IL-1 β , and TNF- α (F. Chen, A. Ghosh, F. Wu, S. Tang, M. Hu, H. Sun, L. Kong and H. Hong, unpublished data). Another study has depicted the role of 5-LOX, and LTD4 in TGF- β 1-induced astrocyte migration through the activation of CysLT₁R [72]. Administration of zileuton or montelukast attenuated such migration of astrocytes, suggesting a role of these molecules in astrocyte-mediated neuroinflammation. However, in the same study, administration of a CysLT₂R-specific antagonist had no effect on such phenomenon, suggesting a greater role of the CysLT₁R rather than the CysLT₂R in neuroinflammation.

Brain Injury

Association of Cys-LT/their receptors has been shown in different types of brain injury, including traumatic brain injury [73,74], ischemia-related brain injury [75–77], and brain cryoinjury [78,79].

However, the concentration of free arachidonic acid is usually very low in the brain, but it can increase greatly following different stimuli such as ischemia [80]. Cerebral ischemia is clinically

Figure 3 Contribution of 5-LOX/Cys-LT/CysLTRs in CNS and other diseases. They are traditionally known for mediation of asthma and the CysLT₁R antagonists or 5-LOX inhibitors are used for clinical management of the disease; montelukast is also approved by the Food and Drug Administration of the USA for the management of other allergic diseases. However, the importance of these inflammatory molecules is emerging in other fields and has been shown to be associated with cancer, atherosclerosis, and several brain diseases as displayed in the Figure. (Figure illustrations were created using MOTIFOLIO Biomedical PowerPoint Toolkits for Presentations and Microsoft Office PowerPoint).

characterized by reduced cerebral hypoperfusion, which causes reduced blood circulation, wholly or partly, to the parts of the brain and accompanied by neuroinflammation and neuronal death. In global ischemic models, an augmented formation of Cys-LT has been demonstrated following reperfusion [81–83]. Moreover, higher level of these lipid mediators is also seen in cerebrospinal fluid (CSF) of patients with acute cerebral ischemia [84]. Although the role of LTs in the developmental process of trauma-associated ischemia is not well known, interestingly, cPLA2-deficient mice are less susceptible to cerebral ischemia/reperfusion injury [85,86]. The first evidence of neuroprotection, through postischemic modulation of LT levels, was obtained by the use of MK-886, an LT synthesis inhibitor, in an *in vivo* model of pMCAO (permanent occlusion of the middle cerebral artery) in rats [87]. Whereas neuroinflammation is a critical component following brain injury, it is accompanied by an aggravated level of Cys-LT receptors [88]. Despite the fact that CysLT₂R is the main isoform of CysLTRs in the normal brain, the first line of data, from experiments carried out with CysLTR antagonists, suggested that selective CysLT₁R antagonists, including pranlukast and montelukast, might have a protective effect in focal cerebral ischemia [89,90]; protective effect of montelukast against global ischemia was also shown [91]. However, recent studies showed spatiotemporal expression of CysLT₂R in cerebral ischemia [75] and that using HAMI 3379, a CysLT₂ receptor antagonist, is neuroprotective against ischemic injury and neuroinflammation [76,92]. Association of GPR17 in ischemia-related neuroinflammation has also been shown [93]. The neuroprotective effect of the FLAP inhibitor zileuton and genetic disruption of ALOX5AP has also been shown to ameliorate ischemic stroke and reduce infarct size and neuroinflammation following cerebral ischemia [94–96]. Moreover, genetic association studies have linked the risk of ischemic stroke with the leukotrienes biosynthesis pathway [97–99].

Multiple Sclerosis/Experimental Autoimmune Encephalomyelitis

Multiple sclerosis (MS) is a severe neurological disease characterized by autoimmunity-mediated demyelination, oligodendrocyte damage, and, ultimately, axonal loss [100]. Despite an increasing appreciation of the importance of remyelination, most therapeutic approaches for MS are immunomodulatory drugs that target the inflammatory component of the disease [49]. Increased expression of 5-LOX in lesions [101,102] and of 5-LOX-derived LT products in the cerebrospinal fluid [103,104] is found in patients with MS. Yoshikawa and colleagues showed that pharmacological inhibition of 5-LOX could attenuate axonal damage and motor deficits related to MS pathology [105]. Demyelination of the CNS relative of arachidonic acid cascade was also suggested by studies in models of experimental autoimmune encephalomyelitis (EAE) [106,107]. Moreover, the effector phase of EAE can be ameliorated by targeting cPLA(2) α , which is the precursor of the LTs [108]. Infiltration of Th17 cells in the inflamed area of the brain, which is a characteristic of EAE, can be blocked by inhibiting LTs [109], and inhibition of Th1/Th17 by the FLAP inhibitor zileuton and Cys-LT antagonists is fruitful in a model of EAE [110,111]. The role of GPR17

and purinergic signaling has also been strongly suggested as a reparative approach in MS [49,112].

Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent form of dementia, pathologically characterized by extracellular senile plaques consisting of β -amyloid ($A\beta$) plaques and intracellular neurofibrillary tangles (NFTs) of tau protein owing to a progressive loss of memory and cognition. Using different *in vivo* and *in vitro* studies, it has been shown that LTD4-induced upregulation of CysLT₁R is correlated with increased $A\beta$, and amyloid precursor protein (APP) and is associated with cognitive dysfunctions in mice [113–115]; such pathological symptoms are attenuated through administration of selective CysLT₁R antagonists such as pranlukast and montelukast [116,117]. Moreover, the CysLT₁R antagonists mediate structural and functional rejuvenation of the aged brain through several mechanisms such as by downregulating GPR17 and CysLT₁R, reducing microglial reactivity, and by maintaining blood–brain barrier integrity [66]. 5-LOX and FLAP have also long been recognized to be associated with different forms of AD [118–121] with several mechanisms [122–124]. 5-LOX is elevated in AD brain and is immunoreactive that might be involved in posttranslational modifications of the $A\beta$ senile plaques and NFTs [125]. It is an endogenous modulator of $A\beta$ formation *in vivo* [126] and participates in corticosteroid-dependent $A\beta$ generation [127]. In line with the fact that $A\beta$ aggregation is dependent of 5-LOX, agents as dual inhibitors of $A\beta$ and 5-LOX have been developed [128]. Pharmacological studies using zileuton also exist showing ameliorative effect of the drug on AD phenotypes in different animal models [129–131]. Genetic knockout study on the 5-LOX gene has also evidenced similar beneficial effects against AD pathology supporting the pharmacological findings [127].

While the aforementioned studies mainly focused on the familial form of AD, the sporadic form of AD is also important to consider. Whereas the incidence of sporadic AD is largely characterized by oxidative stress, neuroinflammation and a great load of proinflammatory cytokines, the 5-LOX pathway regulates the proinflammatory mediators in the cerebral cortex [132]. COX/5-LOX are mediators of such inflammation-related neurotoxicity [133] and licoferone, a novel dual inhibitor of COX/5-LOX, reduces oxidative stress and increased burden of proinflammatory cytokines in a rat model of sporadic AD [134].

Mild cognitive impairment (MCI), which serves as a prodrome to AD, is also associated with 5-LOX upregulation in the early development of the disease [135], and montelukast shows protective effect in an animal model of MCI [136].

Parkinson's Disease

Parkinson's disease (PD) is pathologically characterized by degeneration of the dopaminergic neurons in the substantia nigra of the brain and manifested by the movement disorders in elderly populations. The LOX isozymes, including 5-LOX, are involved in the maintenance of normal dopaminergic function in the striatum and the differentially contribute to striatal vulnerability in response to neurotoxicity [137]. Another study

highlighted the participation of the 5-LOX system in MPTP-induced PD model [138]; however, the activity of LTB₄ mainly was shown in such mediation of the disease rather than the Cys-LT. Wang et al. [139] studied the expression pattern of the CysLT₁R, CysLT₂R, and GPR17 in PD mouse model. Although the expression of CysLT₁R and GPR17 was found to be decreasing, CysLT₂R was shown to be increasing and expressed mainly in the proliferating astrocytes. Interestingly, CysLT₂R is the mediator of inflammation and consequent neurotoxicity *in vitro* PD model [140].

Epilepsy

Epilepsy-related BBB (blood–brain barrier) disruption has been shown to be mediated by Cys-LT [141], and modulation of Cys-LT by montelukast suppresses the development and frequency of seizures *in vivo* [142,143]. Clinical evidence also exists highlighting the efficacy of pranlukast in epileptic patients [144].

Viral Entry into the Brain

Cys-LT and other AA metabolites have been shown to facilitate pathogen entry into the brain through disruption of the BBB. Bertin et al. [145] have shown that Cys-LT can facilitate the entry of HIV-1 into the brain, which contributes to HIV-1-mediated CNS dysfunctions through the CX3CL1/fractalkine-mediated transmigration of the virus through infected CD4⁺ T cells. Another study has depicted the relevance of these inflammatory molecules in *Escherichia coli*-mediated meningitis [146]. PKC α , which controls the activity of the Cys-LT in many pathophysiological processes, is also a regulator of the activity of the Cys-LT during such viral invasion across the BBB, according to the mechanisms reported in this study [146]. In the same study, blockade of the activity of cPLA₂ α and 5-LOX, the precursors of arachidonic acid and Cys-LT synthesis, respectively, recovered the incidence of viral entry into the brain suggesting a greater role of the Cys-LT and arachidonic acid metabolism pathways in facilitating viral entry into the brain. Higher expression of 5-LOX was also found in dolphin brains with encephalitis [147].

Others

Limited evidence has shown the efficacy of montelukast in an animal model of Huntington's disease (HD) [148]. Montelukast, given orally, ameliorated mitochondrial dysfunction and TNF- α level relative of the disease pathology; however, the study did not show whether montelukast mediated such effect by down-regulation of Cys-LT/their receptors. Another study exists depicting the role of CysLT₁R in depressive behavior and neuroinflammation in a mouse model of chronic mild stress (CMS) [149]. The study showed that hippocampal expression of CysLT₁R is increased in the CMS-exposed mice in a time-dependent manner and lentivirus-mediated knockdown of the receptor in the mouse hippocampus prevents such CMS-induced depressive behaviors.

Conclusive Remarks and Future Outlook

The inflammatory milieu relative of Cys-LT has been implicated in a range of pathological conditions such as in asthma, allergic rhinitis, cardiovascular disease, cancer, and neurological dysfunctions. Although many aspects of the roles of the Cys-LT and their receptors, as mediators of inflammation, in asthma and other allergic diseases are well established, their pathophysiological role in the brain is very little known and much more attention should be given to gain the utmost understanding of their role in CNS diseases.

Acknowledgments

The work is supported by grants from the Natural Science Foundation of China (81273497 and 81573413 to HH) and the Natural Science Foundation of Jiangsu Province (SBK201320969 to HH). AG is a recipient of China Govt. Scholarship-Chinese University Program (China Scholarship Council) for foreign students at CPU. FC is a recipient of PhD Research Assistantship at CPU. AT is a recipient of Postgraduate Scholarship at CityU HK.

Conflict of Interest

The authors declare no conflict of interest.

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