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Authors

Gilbert, Miranda
Setayesh, Tahereh
Wan, Yu-Jui

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The contributions of bacteria metabolites to the development of hepatic encephalopathy

Miranda Claire Gilbert,

Tahereh Setayesh,

Yu-Jui Yvonne Wan*

Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, USA

Abstract

Over 20% of mortality during acute liver failure is associated with the development of hepatic encephalopathy (HE). Thus, HE is a complication of acute liver failure with a broad spectrum of neuropsychiatric abnormalities ranging from subclinical alterations to coma. HE is caused by the diversion of portal blood into systemic circulation through portosystemic collateral vessels. Thus, the brain is exposed to intestinal-derived toxic substances. Moreover, the strategies to prevent advancement and improve the prognosis of such a liver-brain disease rely on intestinal microbial modulation. This is supported by the findings that antibiotics such as rifaximin and laxative lactulose can alleviate hepatic cirrhosis and/or prevent HE. Together, the significance of the gut-liver-brain axis in human health warrants attention. This review paper focuses on the roles of bacteria metabolites, mainly ammonia and bile acids (BAs) as well as BA receptors in HE. The literature search conducted for this review included searches for phrases such as BA receptors, BAs, ammonia, farnesoid X receptor (FXR), G protein-coupled bile acid receptor 1 (GPBAR1 or TGR5), sphingosine-1-phosphate receptor 2 (S1PR2), and cirrhosis in conjunction with the phrase hepatic encephalopathy and portosystemic encephalopathy. PubMed, as well as Google Scholar, was the search engines used to find relevant publications.

Keywords

Liver; Gut-liver-brain axis; Bile acids (BAs); Bile acid (BA) receptors; Farnesoid X receptor (FXR); Takeda G protein-coupled receptor 5 (TGR5); Sphingosine-1-phosphate receptor 2 (S1PR2); Brain

*Corresponding author. yjywan@ucdavis.edu (Y.-J.Y. Wan).

Authors' contributions

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Declaration of competing interest

The authors declare that they have no conflict of interest.

1. Introduction of hepatic encephalopathy (HE)

HE consists of brain dysfunction caused by liver disease that leads to portosystemic shunting. HE has a broad spectrum of neurological or psychiatric abnormalities, ranging from subclinical alterations to coma.[1,2] HE is diagnosed through the observation of neuropsychiatric abnormalities with liver dysfunction after exclusion of brain disease. In HE patients, disease features include early onset of systemic inflammation, cytokine production, neuroinflammation, hyperammonemia, and subsequently brain edema, which is the cause of an alarming 70% of HE deaths.[3]

About 70% of cirrhosis patients develop HE symptoms. The development of HE has five stages ranging from minimal HE (MHE) to the most advanced comatose state grade IV HE.[4] Based on the severity, HE can also be classified into covert HE (minimalegrade I) (CHE) and overt HE (grades IIeIV) (OHE). MHE is a cognitive impairment without mental status changes. MHE can present as early as acute liver failure with no history of chronic liver disease. There may be subtle or minimal changes in concentration, memory, coordination, and intellectual function.[5] In contrast, OHE has mental status changes ranging from disorientation to lethargy and coma.[4] Disorientation in time or asterixis identifies the onset of OHE.[2,6]

It is challenging to diagnose MHE due to a lack of consensus on testing standards and threshold values.[7] The psychometric HE score (PHES) test is a gold standard to diagnose MHE; however, most patients are never tested for it.[8,9] Clinical findings are hard to reproduce or even diagnose in CHE, only discernible through abnormalities in psychometric tests. Conversely, clinical findings are semi-reproducible for detecting neurologic abnormalities in OHE. However, there has been some success with psychometric tests such as the PHES in recent studies on cirrhosis patients.[10]

The occurrence of HE ranges, with MHE presenting as less obvious impairments to central nervous system (CNS) dysfunction, such as a change in attention and delayed information processing.[11] If chronic liver diseases such as hepatitis or cirrhosis remain untreated, cognitive impairment will develop. For instance, disorientation or confusion, personality changes, and changes in consciousness are telltale signs of OHE.[12] OHE often leads to poor patient survival or a high risk of HE recurrence.[4]

The variety of clinical presentations and the difficulty in detecting MHE make it hard to quantify the exact prevalence of HE. However, it is estimated that approximately 30e40% of patients with cirrhosis develop OHE during their disease course, whereas MHE or CHE occurs in 20e80% of patients.[12–14] Patients with a previous episode of OHE have a 40% cumulative risk of recurrence at 1 year and those with recurrent OHE have a 40% cumulative risk of another episode within 6 months.[15,16]

While the exact etiology of HE still remains unclear, it is known that the buildup of ammonia plays an integral role in the progression of HE.[17] However, ammonia alone is not enough to trigger HE. Another factor that may contribute to HE development is bile acid (BA) synthesis dysregulation in chronic liver diseases, which truly exemplifies the integral interactions between the liver-gut and the brain.[18]

2. Role of ammonia in the development of HE

Increased blood ammonia is an alarming marker for the development of HE.[19–21] Ammonia is a byproduct of nitrogen metabolism and is produced mainly in the gut and kidney.[22] The small intestine and colon are also sources of ammonia due to glutaminase and urease-producing bacteria. In patients with portosystemic shunts, nitrogenous waste piles up in the circulatory system. Excess ammonia crosses the blood-brain barrier (BBB) and is subsequently absorbed and used by astrocytes to synthesize glutamine. Intracellular accumulation of excess glutamine causes osmotic and oxidative stress, mitochondrial dysfunction, and astrocyte swelling. This can lead to cerebral edema and increased gammaaminobutyric acid-ergic (GABAergic) activity.[17,23]

Chronic hyperammonemia is sufficient to induce astrocyte and microglial activation, resulting in brain-derived proinflammatory tumor necrosis factor-alpha (TNF-a), interleukin (IL)-6, and IL-1β (Fig. 1).[24–27] In an azoxymethane (AOM) induced HE mouse model, TNF-a receptor knockout (KO) mice had decreased brain swelling as opposed to the wild-type mice, further showing the impact of TNF-α on brain inflammation.[28] This inflammatory state leads to neuronal death in vitro and *in vivo*.[29]

Neuroinflammation and microglia activation are specifically implicated in the pathogenesis of HE through proinflammatory chemokine ligand 2 (CCL2). CCL2 is increased in neurons in the AOM-induced HE mouse model with concomitantly reduced anti-inflammatory chemokine and fractalkine. This thereby dysregu-lates the balance of inflammatory signals in microglia, leading to microglia activation.[30,31] IL-6 and TNF-a are known CCL2 inducers, and their upregulation is due to increased ammonia, leading to microglia activation.[32]

The activation of microglia is a delicate balance between proinflammatory and anti-inflammatory signals. Normal physiological conditions favor the dampening of microglia activation.[31] A CCL2 antagonist, INCB 3284 dimesylate, improves liver function and reduces microglia activation and neurological decline.[30] In rats with acute liver failure, the increased expression of microglia markers (OX-6 and OX-42) predicts the severity of encephalopathy (coma) due to hepatic devascularization.[33] Moreover, in cirrhosis patients with HE, microglia activation marker CD14 is elevated, leading to speculation that microglia activation could be a feature of HE.[34]

Ammonia is a product of urease-producing bacteria. Urease catalyzes the hydrolysis of urea, creating ammonia. The composition of gut microbiota impacts urease production. Gut microbiota analysis of MHE or OHE patients revealed that ammonia-associated astrocyte swelling is negatively associated with the abundance of Lachnospiraceae and Ruminococcaceae, but positively correlated with Enterobacteriaceae. Furthermore, Porphyromonadaceae is positively associated with increased diffuse white matter.[35] An additional study has also revealed that Streptococcaceae, likely via urease production, is associated with mild HE.[36]

Moreover, cirrhosis in germ-free mice is associated with hyperammonemia but is not accompanied by neuroinflammation.[37] This finding indicates the significance of gut

microbes in generating other specific chemicals that attribute to HE. It also suggests that ammonia alone is not sufficient for developing HE.[38] It is likely that altered microbiota is implicated in cognitive impairment. Nevertheless, low urease activity shows improved cognitive function after liver injury in mice colonized with altered Schaedler's flora.[39] Conversely, urease-positive taxa, including Streptococcaceae and Helicobacter, are elevated in HE patients. However, the association is inconsistent, Helicobacter pylori does not significantly increase the high blood ammonia in patients with advanced cirrhosis and subclinical HE. Likewise, eradication of Helicobacter pylori does not improve HE development.[40]

3. Role of BAs in the development of HE

3.1. Introduction of BA

BAs are no longer considered solely in the context of micelle formation and lipid absorption; they are signaling molecules with diverse effects on gut microbiota as well as on host immunity and metabolism. Free and conjugated primary and secondary BAs are generated by hepatic and microbial enzymes.[41–43] Primary BAs, i.e., chenodeoxycholic acid (CDCA) and cholic acid (CA), are endogenous ligands for farnesoid X receptor (FXR), and activation of FXR increases lipid and carbohydrate metabolism, insulin sensitivity, and immunity.[44–48] Bacterial enzyme bile salt hydrolase (BSH) deconjugates BAs. In addition, hydrophobic secondary BAs, i.e., deoxycholic acid (DCA) and lithocholic acid (LCA), are produced by the bacterial enzyme 7alpha-dehydroxylase encoded by the baiJ gene.[49,50]

Because BAs are produced by host and bacterial enzymes, dysbiosis is accompanied by dysregulated BA synthesis.[51–53] For instance, patients with metabolic syndrome, steatohepatitis, or liver cancer have dysbiosis as well as dysregulated BA synthesis.[54] Moreover, because FXR regulates BA synthesis, mice lacking BA receptor FXR have dysbiosis and spontaneously develop steatosis, progressing into steatohepatitis and liver cancer.[44,55–58] Increased serum BAs are frequently found in chronic and acute liver injury. Such an increase is a predictive value for the onset of acute decompensation and acute-on-chronic liver failure in cirrhosis patients, of which both can develop into HE.[59,60]

BA composition varies between humans, mice, and rats. In a study of species differences in BAs, humans have high plasma levels of CDCA (33% of total BAs), DCA (27%), LCA (12%), and CA (11%).[61] Mice have high plasma levels of CA (~45%), muricholic acid (MCA) (~32%), DCA (~17%), CDCA (~3%), and LCA (1.5e2.2%).[61] Rats have high plasma levels of CA (30%), MCA (22%), CDCA (18%), and LCA (~8%).[61] Additionally, in humans, primary BAs are usually conjugated with glycine, whereas rodent primary BAs are often conjugated with taurine.[62] Even with differing BA compositions, animal models of HE in mice and rats are most commonly used due to their ability to mimic human liver failure.[20]

3.2. BAs and HE

Fulminant hepatic failure patients have an increased total BA pool.[63] Increased BA concentrations are found in the cerebrospinal fluid (CSF) of cirrhotic patients with HE.[64] An increase in serum taurocholic acid (TCA), taurodeoxycholic acid (TDCA),

taurochenodeoxycholic acid (TCDCA), glycochenodeoxycholic acid (GCDCA), glycocholic acid (GCA), glycoursodeoxycholic acid (GUDCA), and CDCA, is found in patients with decompensating livers and HE.[59,65] Low levels of serum lipids are prevalent in acute-on-chronic liver failure and cirrhosis. These changes may be potential mechanisms accounting for HE development.[66,67] Among these BAs, TCA, in particular, has been identified as the main BA increased during cirrhosis and an active promotor of cirrhosis progression.[68,69] TCA is increased by ~76-folds in cirrhosis patients, promoting further liver cirrhosis through activating hepatic stellate cells.[69] Furthermore, spillover of BAs into the circulatory system occurs during acute liver failure, acute-on-chronic liver failure, non-alcoholic steatohepatitis, and even in the CSF of cirrhotic patients.[70,71] Overall, increased BAs are associated with liver disease development that leads to HE. Using animal models, galactosamine-induced acute liver failure exhibited regional cerebral edema, indicating compromised barrier function.[72] Increased BBB permeability was noted through increased Evan's Blue after injecting CDCA or DCA for 5 days.[73,74] Albumin immunoreactivity was also increased in the brain in the DCA-treated rats, further indicating increased BBB permeability.[73] Additionally, increased BBB permeability caused by BA injection may lead to excess ammonia crossing the BBB, thereby resulting in astrocyte swelling. Moreover, in AOM models, mice that were fed DCA or CA showed functional neurological decline along with increased HE development. Neurological decline was accomplished by an increase in additional BAs, including TCA.[75] In contrast, direct infusion of an FXR vivo-morpholino, 2-hydroxypropyl-β-cyclodextrin, into the frontal cortex protected neurological complications of acute liver failure in the AOM mouse model.[75,76] FXR signaling increased brain cholesterol and led to the neurologic decline. Inhibiting FXR signaling prevented the downregulation of cytochrome P450 (CYP)46A1 and the accumulation of brain cholesterol.[75,76] Additionally, reducing serum BAs via cholestyramine feeding or Cyp7A1$^{-/-}$ mice show reduced BA or AOM-induced neurological decline. In contrast, CA or DCA feeding worsened AOM-induced neurological decline.[77] Furthermore, reducing BA pool size can attenuate the reduction of CYP46A1, a key enzyme converting cholesterol into 24-hydroxycholesterol, which can freely cross the BBB and be degraded in the liver.[78]

3.3. BA receptors and HE

Several nuclear receptors and membrane-bound receptors can be bound and activated by BAs. CDCA is the main agonist of FXR followed by DCA and LCA to lesser extents.[79] Pregnane X receptor (PXR) is mainly activated by LCA and DCA.[80] LCA is additionally an agonist of vitamin D receptor (VDR).[81] Takeda G protein-coupled receptor 5 (TGR5; also known as G protein-coupled BA receptor 1 (GPBAR1)) activated by LCA and DCA increases 3',5'-cyclic adenossine monophosphate, reducing the production of proinflammatory cytokines.[82] Lastly, sphingosine-1-phosphate receptor 2 (S1PR2) can be activated by conjugated BAs, including GCA, TCA, GCDCA, and TCDCA, leading to increased inflammation.[83,84] BA receptors have just as important a role as BAs in HE.

3.3.1. FXR and HE—FXR is mainly expressed in the liver and intestine, where BAs are produced from hepatic cholesterol. FXR signaling in the digestive system regulates BA homeostasis. FXR in the brain regulates energy homeostasis. Intracerebroventricular

injection of FXR agonist GW4064 increases brown adipose tissue function and sympathetic tone in mice.[85]

In a whole-body FXR KO mouse model, mice have disrupted neurotransmitter signaling and reduced anxiety-related behavior. Measured by open-field test scores and elevated plus maze test scores, impaired cognitive and motor functions were noted as well as increased motor activity.[86] Additionally, there were alterations in glutamatergic, GABAergic, serotonergic, and norepinephrinergic neurotransmission in the hippocampus or cerebellum of the FXR KO mice. This was measured by liquid chromatography with tandem mass spectrometry of snap frozen dissection sections of mouse brains shortly after sacrifice.[86,87] Overall, whole body FXR KO contributes to mood changes and neurological degeneration similar to HE symptoms. The effect is likely due to dysregulated BAs that cross the BBB, causing neurotoxicity.

The specific role of FXR in HE remains unknown; however, AOM mouse studies have uncovered the possible impact of FXR. Expressions of apical sodium-dependent BA transporter (ASBT), FXR, and its cofactor small heterodimer partner (SHP) were significantly increased after AOM injection in the frontal cortex before the presentation of neurological symptoms compared with control tissue. Interestingly, the expression of these key BA signaling components was dramatically decreased at the time of coma.[77]

Whole body KO of FXR impairs neurological state; however, targeted brain knockdowns seem to delay neurological decline. Inflammatory cytokines (IL-6, IL-1b, IL-17, and IL-18) decrease in the brain of FXR KO mice, and it is speculated that downregulation of brain FXR signaling may be a potential treatment mechanism for HE.[88,89] Further research is warranted to shed more light on the underlying mechanism of FXR signaling in HE.[90]

3.3.2. TGR5 and HE—TGR5 is a widely expressed membrane receptor in the gall-bladder, liver, kidney, and intestine.[91] In the liver, TGR5 can be found in sinusoidal endothelial cells, Kupffer cells, and chol-angiocytes.[92] Moreover, TGR5 is found in neurons and astrocytes.[93] Natural upregulation of TGR5 has been demonstrated through an AOM acute liver failure mouse model of HE.[94] Central infusion of TGR5 agonist betulinic acid delays neurological decline and attenuates reflex impairment and presence of ataxia in AOM mouse models.[94] Additionally, betulinic acid reduces Ccl2 mRNA in isolated primary neurons of mouse pups.[94] TGR5 mRNA was also reduced in the cerebral cortex of patients dying with HE.[93] In a cell culture of rat astrocytes, Tgr5 mRNA expression is downregulated in the presence of ammonia.[93] Ammonia levels in AOM mouse models of acute liver failure do not reach significant levels until later stages of disease progression. Therefore, it is possible there is initially an increase in TGR5 expression protecting the brain during liver failure, which is then followed by a decrease in expression when ammonia levels are high.[95,96]

3.3.3. S1PR2 and HE—In early HE, elevated TCA is linked with increased Ccl2 through S1PR2 in mice.[83] Similarly, in a hyperammonemia rat model, hyperammonemia increased surface expression of S1PR2, thereby increasing CCL2 and subsequent microglia activation, leading to neuroinflammation and neurological decline.[97] Direct infusion

of S1PR2 antagonist, JTE-013, before AOM injection attenuated microglia activation, expression of proinflammatory cytokines, and subsequent neurological impairment associated with HE.[83] Together, BAs may regulate neuroinflammatory processes via the activation of S1PR2, rather than through FXR signaling. However, S1PR2 immunoreactivity is found in neurons, and TCA does not alter microglia activation status. Thus, the proinflammatory effects of BA signaling are not due to a direct action on microglia.[83]

Table 1 summarizes the importance of BA receptors regarding their neurological impact. Additional detailed information regarding BA receptors can be found in other review papers.[98–107]

3.3.4. The impact of FXR via regulating cholesterol and glucose homeostasis to affect brain function—About 25% of the body's cholesterol is in the brain, which is used to form cell membranes, as well as regulate synapse formation, action potentials, and neurotransmitter release.[108] Thus, any fluctuation in cholesterol intake may affect brain function.[109] Furthermore, intracellular cholesterol serves as a precursor for synthesizing many neurosteroids in the brain. Allopregnanolone is a neurosteroid that regulates GABA type A ($GABA_A$) receptors and is essential in mood regulation.[108,110] In neurons, a brain-specific enzyme, cholesterol 24-hydroxylase, converts excess cholesterol into 24-(S)-hydroxycholesterol.[111] Then, 24-(S)-hydroxycholesterol can exit the brain and enter the bloodstream, where it is integrated into the de novo BA synthesis pathway in the liver. Interestingly, the expression of Cyp46A1 is reduced in the frontal cortex of mice with acute liver failure progressing to HE.[76]

An FXR-mediated pathway is responsible for CYP46A1 reduction as DCA reduces CYP46A1, and guggulsterone prevents such reduction in a primary culture of neurons.[76] Furthermore, aberrant BA signaling in the brain can be reduced through cholestyramine feeding, while accumulation of brain cholesterol is reduced through a constant central infusion of cholesterol sequestrant 2-hydroxypropyl-β-cyclodextrin. These interventions prevent the reduction of brain CYP46A1 and subsequent neurological symptoms of HE, i.e., absence of reflexes and loss of muscle control.[76] Furthermore, the downregulation of Cyp46A1 in response to AOM is attenuated in Cyp7A1 KO mice, which have a reduced BA pool size.

Given the known roles for cholesterol in the brain, it is conceivable that aberrant BA signaling in the brain likely alters cholesterol clearance pathways. This may bring about alterations in neurotransmitter release and/or neurosteroid synthesis, both of which are altered in HE.[112,113]

Glucose is the main fuel for the brain, and any slight reduction can quickly cause neurological side effects such as cognitive and reflex impairments.[114] BAs and their receptors play pivotal roles in glucose homeostasis.[115] Activation of hepatic FXR leads to inhibition of hepatic gluconeogenesis accompanied by increased glycogen synthesis.[116–118] Intestinal FXR antagonists can also reduce hepatic gluconeogenesis, whereas TGR5 agonists promote glucagon-like peptide-1 (GLP-1) secretion from intestinal L cells and increase insulin sensitivity. BA signaling via FXR stimulates intestinal fibroblast growth factor

(FGF)19/FGF15 secretion, activating FGF receptor 1 (FGFR1) on hypothalamic agouti-related peptide (AGRP)/neuropeptide Y (NPY) neurons to improve glucose tolerance. Furthermore, some FGF ligands might worsen glucose handling; a study has shown that antagonizing FGF17 signaling within the hypothalamus has beneficial effects on glucose homeostasis without inducing hypoglycemia.[119] Taken together, via regulating cholesterol and glucose homeostasis, FXR likely has a profound role in regulating the function of the brain.

4. Treatments for HE

4.1. Probiotics and synbiotics

Identification and treatment of the underlying liver disease that causes HE is normally the preferred treatment method. However, additional treatments are often needed to decrease neurological decline.[120,121]

In a Meta-analysis of 14 randomized trials, probiotics reduce hospitalization and progression of HE.[122] The following probiotics were used: Bioflorin (*Enterococcus* SF68), *Pediococcus pentosaceus, Leuconostoc, Lactobacillus paracasei, Lactobacillus plantarum, Streptococcus faecalis, Clostridium butyricum, Bacillus mesentricus, lactic acid bacillus*, probiotic yogurt with Lactobacillus, 110 billion CFU, 1.25 billion Lactobacillus acidophilus, rhamnosus, Bifidobacterium longum and saccharomyces, Lactobacillus bulgaricus, Bifidobacterium bifidum, VSL#3 (4 strains of Lactobacillius, 3 strains of Bifidobacterium, and 1 strain of Streptococcus thermophilus), Balance (Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, and Streptococcus thermophilus), and Velgut (4 strains of Lactobacillus, 3 strains of Bifidobacterium, Saccharomyces boulardi, and Streptococcus thermophilus).

Synbiotic treatment of probiotics (non-urease-producing bacteria, namely Pediococcus pentoseceus 5e33:3, Leuconostoc mesenteroides 32e77:1, Lactobacillus paracasei 19, and Lactobacillus plantarum 2592) plus fermentable fiber (b-glucan, inulin, pectin, and resistant starch) can also reduce blood ammonia levels and reversal of MHE.[123]

Studies further show the positive effects of probiotics in reducing ammonia levels and MHE.[124,125] Success of these studies is mainly attributed to the reduction of endotoxins which in turn decreases ammonia levels.[126] However, the sample size of a few of the studies is small, ranging from cohorts of 25e160, and more studies should be performed to validate the findings as well as examine underlying mechanisms.

4.2. Lactulose

Lactulose is a non-absorbable sugar used to treat constipation. It is also a standard therapy for HE that reduces ammonia levels. Lactolose reduces the incidence of MHE. In hyperammonemia rats, lactulose reduces ammonia levels and attenuates motor behavior impairments, measured by open field tests.[127] However, lactulose has a notably unpleasant taste and uncomfortable side effects such as diarrhea and abdominal pain.[128] The effects of probiotics within Golden Bifid and lactulose reduce blood ammonia levels, hyper endotoxemia, and liver inflammation associated with HE in rats.[128] This promising result

only bolsters the idea that further investigation into probiotic interventions in clinical trials should be studied to validate the findings.

4.3. Rifaximin

Rifaximin is used to treat traveler's diarrhea caused by *Escherichia coli*. Rifaximin reduces ammonia levels by eliminating ammonia-producing colonic bacteria.[129] Through targeting gut microbiota and reducing the levels of the Veillonellaceae family, rifaximin has been shown to reduce liver cirrhosis-associated inflammation as well as IL-6 and TNF-a.[130,131] Together with lactulose, combination therapy has shown to be more beneficial than lactulose alone in decreasing HE mortality.[132]

4.4. Cholestyramine

Cholestyramine is used to reduce high blood cholesterol levels. It also lowers BA pool size. Cholestyramine not only treats liver failure but also delays neurological decline, scored using pinna reflex, corneal reflex, tail flexion, escape response, righting reflex, and ataxia in AOM mouse models.[75] Importantly, cholestyramine also attenuates microglia activation in AOM mouse models.[75,83] Further, reducing CCL2 and TNF-a as well as IL-6 in the cortex have been shown as possible mechanisms for cholestyramine to treat HE.[83]

5. Summary and future direction

HE is a neurological disorder brought on by severe liver disease. The connections between the liver and brain are becoming apparent, evidenced by dietary modulation. It has been shown that Western diet intake leads to systemic inflammation in the liver, brain, and adipose tissues, accompanied by microglia activation.[133,134] Furthermore, these changes are accompanied by intestinal dysbiosis and dysregulated BA synthesis. These findings stress the significance of the diet-gut-liver-brain axis.

Liver function likely affects the development of other neurological diseases, including Alzheimer's disease and dementia, which are both considered metabolic dysfunctions of the brain.[135] For example, increased oxidative stress alters brain metabolic functions, such as fatty acid peroxidation and lipid synthesis, leading to the development of Alzheimer's disease.[136] Increased oxidative stress has also been identified as a critical component in metabolic disorders; therefore, patients with metabolic disorders likely have escalated progression into Alzheimer's disease.[137] Animal studies revealed that excess amyloid-beta (Ab) in the brain is actually from the liver.[138–140] Additionally, similar pathways are implicated in HE and Alzheimer's disease, such as cholesterol metabolism and clearance dysregulation.[141,142] Taken together, the liver and the brain are closely connected, and metabolic imbalance in the liver has a major impact on brain dysfunction.

The gut-liver-brain axis is particularly significant for the development of HE. Ammonia build-up is a toxic metabolism by-product that causes increased inflammatory cytokines in the brain. The current therapy for HE focuses on decreasing ammonia build-up. However, BA concentration and receptors have also been shown in many animal models to impact the progression of HE. HE exemplifies how BA dysregulation is more than just a gut problem,

it is a systemic problem. Therefore, more studies into treating BA dysregulation would be beneficial in truly understanding the impact on HE.

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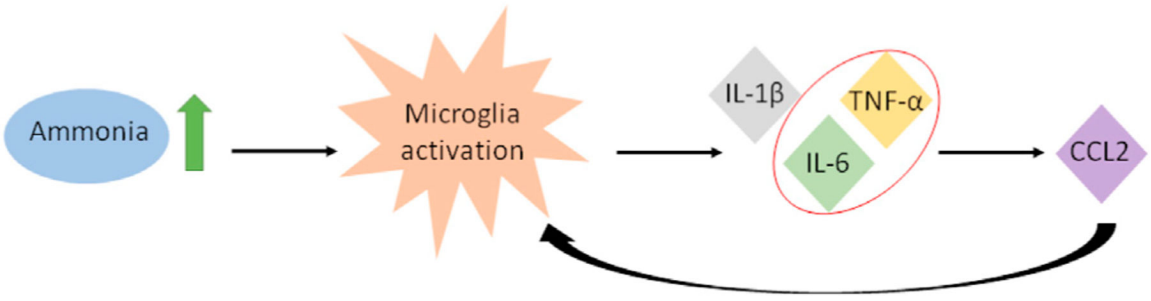

Fig. 1. Increased ammonia causes microglia activation.

Microglia activation produces TNF-α, IL-6, and IL-1β. TNF-α and IL-6 are known CCL2 inducers. Increased CCL2 is linked to microglial activation. Abbreviations: CCL2, chemokine ligand 2; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

Table 1

BA receptors implicated in the development of HE.

BA receptor	Approach	Outcomes	References
FXR	*Cyp7A1*$^{-/-}$ mice or C57Bl/6 mice pretreated with central infusion of FXR vivo morpholino, 2-hydroxypropyl-β-cyclodextrin HE induced by injection of AOM (100 mg/kg, *i.p.*)	An increase in intracellular cholesterol in the cortex of mice treated with AOM is associated with decreased Cyp46A1 expression Inhibition of FXR signaling prevents the downregulation of Cyp46A1 and the accumulation of cholesterol Reduction in the accumulation of cholesterol in the brain of *Cyp7A1*$^{-/-}$ mice (AOM compared to non-AOM treated mice) Reduction in the accumulation of cholesterol in the brain in mice infused with FXR morpholino compared to control FXR mismatched vivo morpholino sequence in AOM treated mice Delay in neurological decline (measured by a neurological score based on pinna reflex, corneal reflex, tail flexion, escape response, righting reflex, and gait) in AOM-treated mice infused with 2-hydroxypropyl-b-cyclodextrin compared to control	75
	Whole body FXR KO	A reduction in depressive-like and anxiety-related behavior Decreased attention Decreased hyperactivity to stress Impaired cognitive function Impaired motor coordination Enhanced locomotor activity compared to wild-type mice	85
TGR5	Activation of TGR5 using agonist betulinic acid via ICV injection HE induced by injection of AOM (100 mg/kg, *i.p.*)	Delay in neurological decline (measured by a neurological score based on pinna reflex, corneal reflex, tail flexion, escape response, righting reflex, and gait) Delay in time to reach coma Reduced microglia activation and proliferation Reduced proinflammatory cytokine production	93
	72-Hour incubation of cultured newborn rat astrocytes in 5 mmol/L of ammonia	Reduced TGR5 protein level in isolated rat astrocytes after incubation with ammonia Reduced *TGR5* mRNA in the cerebral cortex from cirrhotic patients dying with HE compared with brains of noncirrhotic control subjects	92
S1PR2	Infusion of S1PR2 antagonist JTE-013 into the lateral ventricle prior to AOM injection (100 mg/kg, *i.p.*)	An increase of BAs in the cortex during AOM-induced HE compared to non-AOM An increase inTCA in the serum and cortex during AOM-induced HE compared to non-AOM Infusion of JTE-013, protects against neurological decline, delay in time to reach coma Reduced microglia proliferation Reduced the number of microglia (IBA1 used as a marker) No significant increase in CCL2 mRNA expression and protein in AOM-treated mice infused with JTE-013 compared to AOM-treated mice infused with DMSO Reduced neuroinflammation through reduced IL-6 and TNF-a (mRNA and protein)	82

Abbreviations: AOM, azoxymethane; BA, bile acid; CCL2, chemokine ligand 2; Cyp, cytochrome P450; DMSO, dimethyl sulfoxide; FXR, farnesoid X receptor; HE, hepatic encephalopathy; ICV, intracerebroventricular; IL-6, interleukin-6; i.p., intraperitoneal; KO, knockout; S1PR2, sphingosine-1-phosphate receptor 2; TCA, taurocholic acid; TGR5, Takeda G protein-coupled receptor 5; TNF-α, tumor necrosis factor-alpha.