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Original Article

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Lipocalin-2 Secreted by the Liver Regulates Neuronal Cell Function Through AKT-Dependent Signaling in Hepatic Encephalopathy Mouse Model

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ABSTRACT

Hepatic encephalopathy (HE) associated with liver failure is accompanied by hyperammonemia, severe inflammation, depression, anxiety, and memory deficits as well as liver injury. Recent studies have focused on the liver-brain-inflammation axis to identify a therapeutic solution for patients with HE. Lipocalin-2 is an inflammation-related glycoprotein that is secreted by various organs and is involved in cellular mechanisms including iron homeostasis, glucose metabolism, cell death, neurite outgrowth, and neurogenesis. In this study, we investigated that the roles of lipocalin-2 both in the brain cortex of mice with HE and in Neuro-2a (N2A) cells. We detected elevated levels of lipocalin-2 both in the plasma and liver in a bile duct ligation mouse model of HE. We confirmed changes in cytokine expression, such as interleukin-1β, cyclooxygenase 2 expression, and iron metabolism related to gene expression through AKT-mediated signaling both in the brain cortex of mice with HE and N2A cells. Our data showed negative effects of hepatic lipocalin-2 on cell survival, iron homeostasis, and neurite outgrowth in N2A cells. Thus, we suggest that regulation of lipocalin-2 in the brain in HE may be a critical therapeutic approach to alleviate neuropathological problems focused on the liver-brain axis.

Keywords: Hepatic encephalopathy (HE); Lipocalin-2; Hyperammonemia; Neuron; Brain inflammation

INTRODUCTION

Hepatic encephalopathy (HE), which is caused by liver failure and portosystemic shunting, is accompanied by neurological or psychiatric dysfunction as well as hyperammonemia, severe inflammation, and cholinergic neuronal dysfunction [1,2]. In addition, patients with HE exhibit various neurological features such as cognitive impairment, personality changes, sleep disturbances, motor abnormalities, depressive symptoms, brain edema, and brain atrophy [3-6]. In the central nervous system (CNS), hyperammonemia leads to astrocyte swelling [7], an impaired glutamate system [8], and mitochondrial dysfunction [9] and ultimately contributes to glial and neuronal dysfunction. A bile duct ligation (BDL) model is commonly used as a mouse model of HE; this model exhibits memory impairment, decreased brain cholinergic activity, hyperammonemia, increased blood-brain barrier

Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Jo D, Jung YS, Song J; Data curation: Jo D, Jung YS, Song J; Formal analysis: Jo D, Jung YS, Song J; Funding acquisition: Song J; Investigation: Jo D, Jung YS, Song J; Project administration: Jo D, Jung YS, Song J; Writing - original draft: Jo D, Song J; Writing - review & editing: Song J.

permeability, and motor dysfunction [10-14]. In this study, we used a BDL mouse model to evaluate for neurological changes in HE.

Recent studies have highlighted the liver-brain-inflammation axis to elucidate the neurological alterations caused by liver failure [15,16]. Several studies have mentioned that increased levels of endotoxin and pro-inflammatory cytokines in blood plasma cause depressive-like behavior and memory loss [17-20]. Liver failure with liver inflammation is associated with Kupffer cell activation and high secretion of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 [21-23]. Some studies have reported that TNF-α is a crucial factor related to sleep disturbances, fatigue, and depressive symptoms [24,25]. The liver is innervated by vagal nerve afferents, and cytokines secreted by the liver can activate these [26,27]. Inflammatory mediators such as cytokines and chemokines in the blood regulate immune cell infiltration and induce behavioral changes in the brains of BDL model mice [28,29].

Lipocalin-2, which is also known as neutrophil gelatinase-associated lipocalin (NGAL), is an approximately 25-kDa glycoprotein [30] that is expressed in human neutrophils [31]. Lipocalin-2 also modulates complex cellular mechanisms including innate immune responses [32], cell proliferation [33], cellular apoptosis [34], pathogen clearance [35], metabolism homeostasis [36], tumor metastasis [37], and iron metabolism [32]. In addition, lipocalin-2 modulates metabolic responses such as hyperglycemia, dyslipidemia, and glucose metabolism through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [38].

In the CNS, the lipocalin-2 receptor is highly expressed in neurons, microglia, and astrocytes [39], and lipocalin-2 has been shown to control iron accumulation, amyloid beta (Aβ) accumulation, and astrocyte function in Alzheimer's disease (AD) model brains [40,41]. A current study reports that lipocalin-2 is a critical inflammatory mediator that controls the interaction between neurons and microglia and is involved in cognitive function [42].

Lipocalin-2 is known to regulate inflammatory responses through TNF receptor 2-mediated phosphoinositide 3-kinase (PI3K)/AKT, NF-κB [43], and CCAAT/enhancer-binding protein (C/EBP) activation [44]. High levels of hepatic lipocalin-2 are found in liver failure models and promote liver fibrosis by mediating by pro-inflammatory cytokines and chemokines [45,46]. One study mentions that hepatic lipocalin-2 is considered a prognostic factor in patients with liver failure and alcoholic hepatitis [47].

Thus, we investigated the function and specific pathway of lipocalin-2 in the brains of mice in a BDL mouse model of HE. We also confirmed alterations in several inflammatory mediators in neuronal cells by lipocalin-2 treatment. In this study, we emphasized the importance of hepatic lipocalin-2 for neuronal cell function in the brain in HE, focusing on the liver-brain axis.

MATERIALS AND METHODS

BDL surgery

Twelve-week-old wild-type C57BL/6J male mice (Koatech, Pyeongtaek, Korea) were housed in the Laboratory Animal Research Center, Chonnam National University (CNU), under a 16-hour light/8-hour dark cycle at 23°C with 60% humidity and given ad libitum access

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to water and food. Mice underwent BDL or a sham operation. BDL was performed using 5-0 black silk suture under 2% isoflurane anesthesia. Experiments were conducted two weeks postoperatively. The experiments were conducted following the recommendations of "96 Guidance for Animal Experiments" by the Animal Committee at CNU. The animal experimental protocol was approved by the Animal Ethics Committee at CNU (CNU IACUC-H-2022-8).

Cell cultures and treatment conditions

The Neuro-2a (N2A) cell line was cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum (FBS), 1 mM sodium pyruvate, and 100 U/mL penicillin-streptomycin. Cells were cultured at 5% CO_2 at 37°C. The culture media was changed once every 2 days. We induced differentiation of N2A cells by adding 20 μM *all-trans* retinoic acid (Sigma-Aldrich, St. Louis, MO, USA) to DMEM containing 2% FBS, 1 mM sodium pyruvate, and 100 U/mL penicillin-streptomycin culture media. N2A cells were treated with or without 1 μg/mL mouse recombinant lipocalin-2 (50060-M08H; Sino Biological, Chesterbrook,PA, USA) and 30 mM NH_4Cl (A9434; Sigma-Aldrich) for 24 hours.

RNA isolation and analysis

Total RNA was isolated using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), in accordance with the manufacturer's instructions, and used as template to synthesize cDNA with TOPscript RT DryMix (dT18 plus; Enzynomics, Daejeon, Korea). The cDNAs were analyzed using the Applied Biosystems StepOnePlus real-time PCR system (Applied Biosystems, Foster City, CA, USA) and Power SYBR Green PCR Master Mix (Applied Biosystems). Based on the obtained cycle threshold values, the mRNA expression was calculated using the $2^{-\Delta\Delta CT}$ method. All primers are listed in **Supplementary Table 1**. Data were normalized to L32 (mouse) expression, which was determined using 5′-TCTGGTGAAGCCCAAGATGG-3′ (forward) and 5′-CTCTGGGTTTCCGCCAGT-3′ (reverse) primers.

Western blot analysis

The N2A cells and brain tissue were lysed in ice-cold radioimmunoprecipitation assay buffer (Translab, Carpentersville, IL, USA) for 15 minutes on ice. The protein concentration of protein extract was quantified using a bicinchoninic acid protein assay kit (Thermo Fisher Scientific, Waltham, MA, USA). Protein (50–70 μg) was separated on 10%–12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and the protein was transferred onto polyvinylidene fluoride (PVDF; Millipore, Burlington, MA, USA) membranes activated with absolute methanol. The PVDF membranes were incubated with 5% bovine albumin (GenDEPOT, Katy, TX, USA) and 5% skim milk (BD Bioscience, San Jose, CA, USA) in 1× Tris buffered saline with Tween 20 buffer for 1 hour and 30 minutes at room temperature. After incubation, the membranes were incubated with the following primary antibodies (1:1,000 dilution) overnight at 4°C: anti-p AKT (9271s; Cell Signaling Technology, Danvers, MA, USA), anti-AKT (UST4691p; Cell Signaling Technology), and anti-β-actin (MAB8929; AbFrontier, Seoul, Korea).

After the primary antibody incubation, the membranes were incubated with horseradish peroxidase (HRP)-labeled secondary antibody (1:5,000 dilution) for 2 hours at room temperature. The membranes were visualized using an enhanced chemiluminescence solution (Thermo Fisher Scientific) with Fusion Solo software (Vilber, Collégien, France). Protein expression was analyzed using ImageJ (provided from National Institutes of Health), the protein level was normalized to the β-actin protein level, and the phosphorylation of protein was normalized to the total form of the protein.

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Lipocalin-2 enzyme-linked immunosorbent assay (ELISA)

Mouse plasma samples were analyzed using a sandwich ELISA to measure lipocalin-2 levels (MLCN20; R&D Systems, Minneapolis, MN, USA). All assays were performed as recommended by the manufacturers. Mouse plasma was mixed with 1X assay diluent and incubated for 2.5 hours at room temperature. After incubation, biotin conjugate was added to each sample, and the mixture was incubated for one hour at room temperature with gentle shaking. After incubation, 1X streptavidin-HRP solution was added to each sample, and they were incubated 45 minutes at room temperature with gentle shaking. After incubation, 3,3′,5,5′-tetramethylbenzidine substrate was added to each well, and they were incubated for 30 minutes at room temperature in the dark. After incubation, stop solution was added to each well, and lipocalin-2 was measured at 450 nm using an Epoch microplate reader.

Statistical analysis

All data are presented as the group mean ± standard error of the mean. Statistical analysis was conducted using unpaired 2-tailed t-test with Welch's correction in Prism 8 (GraphPad Software Inc, La Jolla, CA, USA). Data were considered significant at $p < 0.05$, $p < 0.01$, and $p < 0.005$.

RESULTS

Lipocalin-2 levels are increased in the livers of BDL model mice

Changes in the concentration of plasma lipocalin-2 after BDL surgery were evaluated using ELISA (**Figure 1A**). BDL surgery significantly increased the concentration of lipocalin in the blood of model mice compared with sham-operated mice. We examined whether BDL surgery regulated the gene and protein expression of lipocalin-2 in the impaired liver (**Figure 1B** and **1C**). BDL surgery increased the expression of lipocalin-2 mRNA and protein in liver tissue from model mice compared with sham-operated mice.

Lipocalin-2 signaling is activated in the brain cortices of BDL model mice.

We next examined the expression of genes and proteins related to inflammation, insulin resistance, and iron metabolism, which are known target genes of lipocalin-2, in the brain cortices of model mice. We measured the expression of inflammation-related genes in the brain cortices of BDL model mice (**Figure 2A**). The gene expression of *IL-1β* and cyclooxygenase-2 (*Cox-2*) was confirmed to be increased by BDL surgery. This result indicates that inflammation is increased in the brain cortices of BDL model mice. BDL surgery decreased the expression of hepcidin antimicrobial peptide 1 (*Hamp1*), a gene related to insulin resistance, and significantly increased the expression of transferrin receptor 1 (*Tfr1*), which is related to iron metabolism (**Figure 2B**). We measured the phosphorylation of AKT using western blot (**Figure 2C**, **Supplementary Figure 1**). BDL surgery induced insulin resistance through dephosphorylation of AKT (serine 473) in the cortex. Therefore, an increased concentration of lipocalin-2 induced by BDL surgery was confirmed to regulate the expression of the target genes of lipocalin-2.

Lipocalin-2 regulates neuronal cell function through the AKT pathway

To induce an in vitro model of BDL surgery, neurons were treated with lipocalin-2. To determine whether lipocalin-2 regulates the intracellular metabolism of neuronal cells, we measured the mRNA and protein expression of factors related to inflammation, insulin resistance, and iron metabolism. The mRNA expression of *IL-1β* and *Cox-2* in neuronal cells was increased by lipocalin-2 treatment (**Figure 3A**). The mRNA expression of bone

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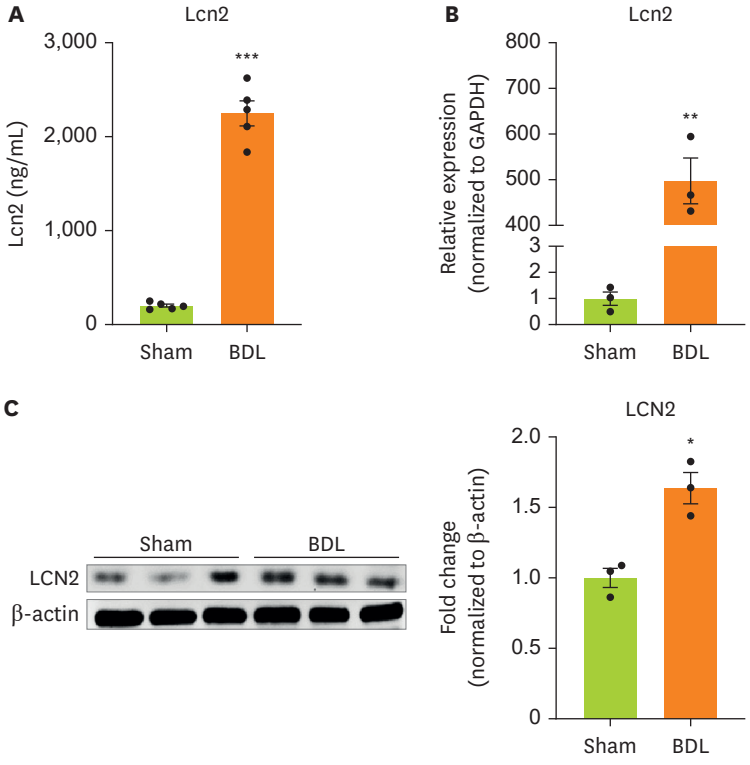

Figure 1. Lipocalin-2 gene expression is increased in the livers of BDL model mice.
(A) Lipocalin-2 levels measured by ELISA in sham-operated or BDL-treated mice. (B) RT-qPCR analysis of the total RNA isolated from liver tissues from sham-operated or BDL-treated mice. (C) Western blot analyses showing the expression of lipocalin-2 in liver tissues from sham-operated or BDL-treated mice. Data are reported as the mean ± standard deviation. All data were analyzed by 2-tailed Student's t-test.
BDL, bile duct ligation; ELISA, enzyme-linked immunosorbent assay; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; Lcn2, lipocalin-2.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

morphogenetic protein 6 (*Bmp6*), which is related to insulin resistance, and *Tfr1*, which is related to iron metabolism, in neuronal cells was increased by lipocalin-2 (**Figure 3B**). We also confirmed dephosphorylation of AKT in neuronal cells by lipocalin-2 (**Figure 3C**). These results indicate that lipocalin-2 regulates intracellular metabolism such as inflammation, insulin resistance, and iron metabolism in neuronal cells.

DISCUSSION

Herein, we investigated the roles of lipocalin-2 secreted by the liver in the brain HE using a BDL mouse model. First, we found elevated expression of lipocalin-2 both in the blood plasma and liver in BDL model mice compared with normal mice. According to a recent study, liver fibrosis caused by BDL causes inflammation, severe oxidative stress, and cellular apoptosis related to lipocalin-2 [48]. One study reported that lipocalin-2 induced the secretion of pro-inflammatory cytokines such as IL-1β through NF-κB activation in hepatocytes in liver disease [49]. Another study mentioned that elevated serum levels of lipocalin-2 were due to increased secretion by the liver and led to IL-6 secretory signaling [50]. Furthermore, increased levels of lipocalin-2 in plasma are linked to chronic liver failure and nonalcoholic steatohepatitis and have the potential to predict liver recovery [51,52]. Elevated levels of lipocalin-2 in blood plasma are associated with some neurological diseases

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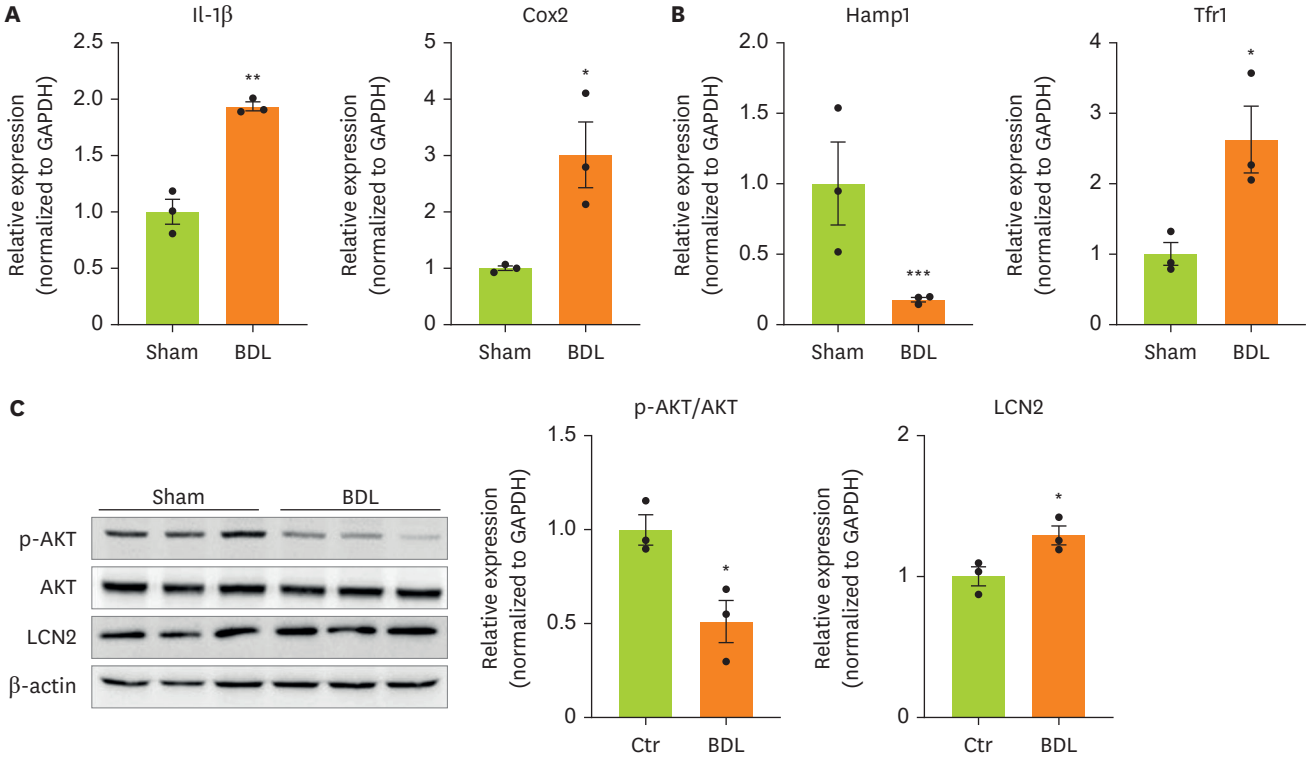

Figure 2. Cytokine and iron metabolism gene expression and AKT phosphorylation are increased in the brain cortices in BDL model mice.
(A, B) RT-qPCR analysis of total RNA isolated from cortex tissues from sham-operated or BDL-treated mice. (C) Western blot analyses showing the expression of AKT and p-AKT in cortex tissues from sham-operated or BDL-treated mice. Data are reported as the mean ± standard deviation. All data were analyzed by 2-tailed Student's t-test.
BDL, bile duct ligation; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; Il, interleukin; Cox2, cyclooxygenase 2; Hamp1, hepcidin antimicrobial peptide 1; Tfr1, transferrin receptor 1; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; LCN2, lipocalin-2; Ctr, control.
*p < 0.05, **p < 0.01, ***p < 0.001.

such as Parkinson's disease [53]. Furthermore, hepatic lipocalin-2 is increased in liver damage models and promotes inflammatory cytokines [45,46]. Given this evidence, elevated levels of lipocalin-2 both in the blood and liver may be related to liver dysfunction, increased inflammatory responses mediated by cytokines, and neurological changes.

Next, we observed significantly increased expression of *IL-1β, Cox2,* and *Tfr1*, reduced expression of *Tfr1*, and reduced phosphorylation of AKT in the brain cortices of BDL model mice. One current study found elevated mRNA levels of lipocalin-2 in the brain cortex accompanied by hyperammonemia in HE [54]. In the CNS, IL-1β is a major pro-inflammatory cytokine that aggravates inflammatory and immune responses [55]. Increased levels of IL-1β disturb neuronal differentiation [56], cell proliferation, neurite outgrowth, and apoptosis [57,58] in the brain [59]. In addition, IL-1β can stimulate Cox2 activation in CNS cells and is involved in pain hypersensitivity [60-63]. Cox-2 is a major regulator of increased prostaglandin E2 (PGE_2) synthesis after an inflammatory response in cells [60] through G protein-coupled receptors [64,65]. Increased expression of Cox2 in the CNS accelerates inflammation [60] and is related to the neuropathogenesis of AD through the NF-κB pathway [66,67].

Based on our data, we assume that there is an increased inflammatory response, immune response, apoptosis, and pain hypersensitivity as well as reduced neuronal differentiation and suppressed neurite outgrowth in the brain cortices of BDL model mice. In the CNS, the PI3K/

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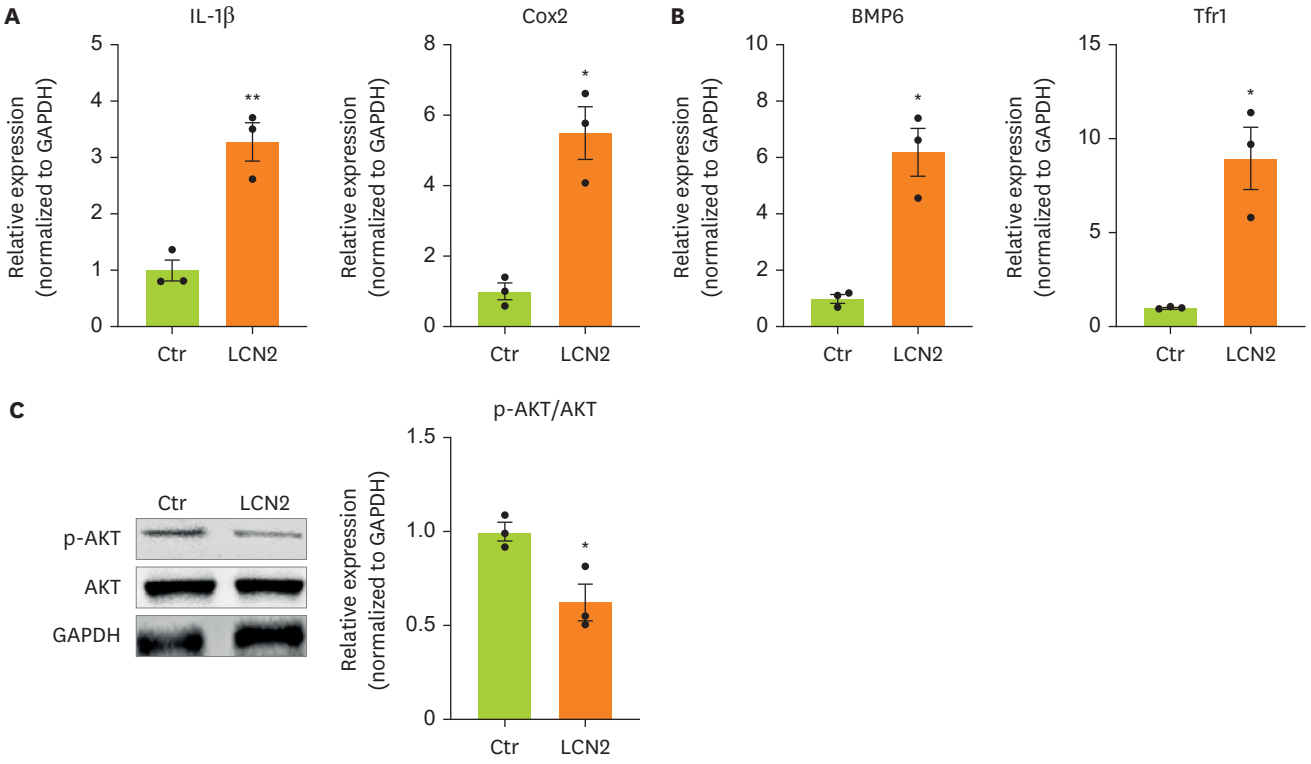

Figure 3. Cytokine and iron metabolism gene expression and AKT phosphorylation are increased by lipocalin-2 treatment in N2A cells.
(A, B) RT-qPCR analysis of the total RNA isolated from N2A cells. (C) Western blot analyses showing the expression of AKT and p-AKT in N2A cells. Data are reported as the mean ± standard deviation. All data were analyzed by 2-tailed Student's t-test.
N2A, Neuro-2a; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; Il, interleukin; Cox2, cyclooxygenase 2; Bmp6, bone morphogenetic protein 6; Tfr1, transferrin receptor 1; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; LCN2, lipocalin-2; Ctr, control.
*$p < 0.05$, **$p < 0.01$.

AKT pathway is a crucial signaling pathway that regulates inflammatory responses in CNS cells [68] and is involved in neuronal differentiation [69]. In addition, NF-κB signaling is induced by PI3K/AKT [70,71]. The PI3K/AKT pathway regulates the secretion of pro-inflammatory cytokines such as IL-6 and IL-1β in dendritic cells [72], microglia [73], and neurons [74], production of anti-inflammatory cytokines [75], and neuronal cell survival [76].

Some studies have reported that lipocalin-2 promotes activation of PI3K/AKT signaling and induces cell proliferation [77], and its promoter has a binding site for NF-κB [78]. One study reported that lipocalin-2 attenuated the activation of the PI3K/AKT pathway and subsequently led to inhibition of cell proliferation [79]. Based on this evidence, we speculate that lipocalin-2 may attenuate neuronal differentiation and increase neuroinflammation through increased secretion of inflammatory cytokines in the brain by suppression of AKT-mediated signaling.

Hamp1 is a small hormone peptide that is produced by hepatocytes and regulates iron metabolism [80]. Hepcidin modulates iron absorption through iron homeostasis [74]. Furthermore, the level of hepcidin has been correlated with liver dysfunction [81]. One recent study showed that the overexpression of hepcidin in astrocytes inhibited brain damage due to Aβ toxicity [80]. Aβ is a major pathological factor in AD [82], and excessive accumulation and aggregation of Aβ cause memory impairment and cognitive dysfunction [83]. Another study reported that hepcidin was strongly related to iron accumulation in the brain in AD and affected the progression of its neuropathogenesis [84]. Our data showed that reduced levels

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of the *Hamp1* gene in the brain cortices of BDL model mice might be linked to a reduced cell protective effect and impaired iron metabolism in the brain in HE.

Finally, we confirmed increased levels of Il-1β, Cox-2, Bmp6, and Tfr1, reduced activation of AKT phosphorylation, and attenuation of the *Hamp1* gene in N2A cells after lipocalin-2 treatment. To mimic hepatic lipocalin-2 from passing from the blood circulation into the brain, we treated N2A cells with lipocalin synthesized protein. The increased levels of IL-1β and Cox-2 observed in N2A cells are similar to the expression patterns of these factors in the brain cortex. Bmp6 is considered a neurotrophic factor [85] and negative regulator of neurogenesis in the brains of patients with AD [86]. One study observed high levels of Bmp6 in the dentate gyrus accompanied by reduced neurogenesis and excessive Aβ plaque accumulation [87], which are involved in memory formation and synaptic failure in patients with AD [88]. Moreover, the *Tfr1* gene regulates iron overload and ferroptosis [89-91]. Some studies have illustrated that increased expression of Tfr1 attenuates neurite outgrowth [92], impairs iron homeostasis [93], disrupts the dopamine system [94], and contributes to poor motor coordination [95]. Another study reported that Tfr1 could modulate iron-mediated immune responses through the NF-κB pathway [96]. Considering our data and previous reports, lipocalin-2 may reduce neurite outgrowth and dysregulate iron-dependent mechanisms, inflammatory responses, and cell death in neurons by increasing the expression of *Bmp6* and *Tfr1* genes.

Although there are many limitations to fully elucidating the roles of lipocalin-2 in the brain in HE, we can conclude several points in this study. First, HE causes elevated levels of lipocalin-2 both in the blood circulation and in the liver. Second, hepatic lipocalin-2 may control inflammatory responses by regulating IL-1β secretion, pain hyperactivity by regulating Cox-2 expression, and iron metabolism by controlling Trf1 expression through AKT-mediated signaling in the brain cortex. Third, hepatic lipocalin-2 may accelerate inflammatory responses and cell death and dysregulate neurite outgrowth through iron-dependent mechanisms through AKT-mediated signaling in neurons.

Thus, the modulation of lipocalin-2 signaling in the brain may be a key target for treating neuropathological and neuropsychiatric issues in the brain in HE. Further studies on the roles of lipocalin-2 both in the brain and liver in liver failure are needed to identify the critical mechanisms of action of lipocalin-2. We also highlighted that lipocalin-2 is a cardinal protein to illustrate the mechanism of the liver-brain axis in patients with HE.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
List of RT-PCR primers

Click here to view

Supplementary Figure 1
The protein level of lipocalin-2 is increased in BDL model mice cortex.

Click here to view

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