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Original Article

Lactate dehydrogenase-1 may play a key role in the brain energy disturbance caused by cryptococcal meningitis

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KEYWORDS
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Abstract *Background:* Cryptococcal meningitis (CM) may affect the conversion of lactate to pyruvate in the brain, resulting in abnormal levels of adenosine triphosphate (ATP) throughout the brain. Lactate conversion to pyruvate is mainly caused by lactic dehydrogenase 1 (LDH1), which is composed of four LDHB subunits. However, the underlying mechanism of LDH1 in CM remains unclear.
Methods: Cerebrospinal fluid (CSF) from 17 patients was collected, including eight patients with non-infectious diseases of the central nervous system and nine patients with CM. Based on clinical data and laboratory reports, data regarding intracranial pressure, CSF white cell counts, lactate dehydrogenase (LDH), adenosine deaminase, glucose, protein, and chloridion were collected. Meanwhile, LDH1, LDH5, lactate, pyruvate, and ATP levels were detected in CSF. Whereafter, the levels of lactate, pyruvate, ATP, and the amplitude and frequency of

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action potentials in the neurons with low expression of LDHB were explored.
Results: Intracranial pressure and white cell count in CSF were significantly increased in patients with CM. In patients with CM, the LDH1, pyruvate, and ATP levels in the CSF were significantly decreased, and the levels of lactate were found to be increased. Furthermore, pyruvate and ATP levels were decreased, while lactate was increased in the neurons with low expression of LDHB. The amplitude and frequency of APs in the neurons with low expression of LDHB were significantly decreased.
Conclusion: Reduced levels of LDH1 in the brain of patients with CM may lead to increased lactate levels, decreased pyruvate and ATP levels, and negatively affect neuronal activity.

Introduction

Cryptococcal meningitis (CM) is an infectious disease of the central nervous system (CNS) caused by the *Cryptococcus neoformans* (Cn), with a mortality rate of 80%—90%.[1—4] In addition to high mortality rates, CM can result in neurological deficits, including headaches, seizures, disturbance of consciousness, and limb paralysis, which affect patient quality of life and bring a burden to families and society.[5,6] Cn first encroaches on the pia mater and gradually encroaches on the brain parenchyma, affecting the ventricular system and cerebral vessels.[7] As the disease progresses, structural damage to the brain could be observed, which is often irreversible and has serious consequences.[8,9]

In CNS injury, neuronal dysfunction is accompanied by energy metabolism disorders,[10] and timely correction of these metabolic disorders can effectively protect neurons.[11,12] Adenosine triphosphate (ATP), mainly from glucose, is the brain's primary energy source.[13] A previous study suggested that patients with CM especially were accompanied by decreased cerebral glucose concentration, a risk factor for a poor prognosis.[14] A low glucose level in the brain leads to a decrease in the amount of glucose available to the cells, an insufficient energy supply to the cells, and eventually damage to neurons.[15] At present, abnormal glucose metabolism has attracted much attention. Monitoring glucose concentration changes in the cerebrospinal fluid (CSF) of patients with CM and timely correction of glucose abnormalities have become necessary to treat CM, but the therapeutic effect is unsatisfactory.[14] Because the conversion of glucose into ATP in the brain needs to go through a series of complex metabolic pathways, of which the lactate metabolism pathway plays a critical role, elevating the glucose level in the brain alone may not necessarily improve the brain's energy metabolism disorder.[16]

The conversion of lactate to pyruvate is considered as a key step in the tricarboxylic acid cycle.[17] The conversion between pyruvate and lactic acid is mainly regulated by lactate dehydrogenase (LDH) which contains 5 isoenzymes: LDH1, LDH2, LDH3, LDH4 and LDH5.[18] LDH is a homologous or heterotetrametric enzyme composed of two subunits, LDHA and LDHB.[19] LDHA promotes the conversion of pyruvate to lactate, while LDHB promotes the conversion of lactate to pyruvate.[19] LDH1 is made up of four subunits of LDHB, while LDH5 is made up of four subunits of LDHA.[20] Previous research has shown that lactate level in CSF was altered in an animal model of intracranial infection, demonstrating that abnormalities in lactate metabolism can also lead to neuronal dysfunction.[21] After glucose in the blood enters the brain, it is first converted into essential metabolic substrate pyruvate in astrocytes.[22] Part of the pyruvate enters the tricarboxylic acid cycle to produce ATP, which maintains the energy requirements of astrocytes.[22] The other part of pyruvate is catalyzed by lactate dehydrogenase 5 (LDH5) into lactate, which is excreted from astrocytes and forms the "lactate pool".[23] Neurons can absorb lactate from the "lactate pool".[23] The lactate is converted into pyruvate under the catalyzing of LDH1, thereby carrying out the tricarboxylic acid cycle and producing ATP, which provides energy for neurons.[23] However, the changes in energy metabolism in the brains of patients with CM, especially lactate, pyruvate, LDH1, LDH5, and ATP, remain unclear.

To investigate the changes in energy metabolism in CM further and provide theoretical guidance for neuroprotective mechanisms, CSF from patients with CM was collected to analyze lactate, pyruvate, LDH1, LDH5, and ATP levels. Based on the characteristics of CSF, the *in vitro* model of neurons was then constructed to detect the energy metabolism and activity of neurons.

Materials and methods

CSF and clinical data collection

This study was approved by the Fourth People's Hospital of Nanning and registered under project number [2021] 25. Clinical and CSF data were collected from hospitalized patients in the Fourth People's Hospital of Nanning from June 2021 to December 2023. The cases were divided into control (Ctrl) and CM groups. The inclusion criteria comprised of the following: 1) Cases included in the Ctrl group who were diagnosed with non-CNS infectious diseases; 2) cases in the CM group diagnosed as CM, and the final diagnosis was based on positive CSF test results, including Cn isolation in CSF culture, positive cryptococcal antigen in CSF, or positive CSF ink staining; 3) the patient or their client signs the informed consent. Exclusion criteria included the following: 1) Metabolic diseases (such as

diabetes, hyperthyroidism, Cushing's syndrome, and primary hyperaldosteronism); 2) no signed consent was obtained from the patient or client. According to the above criteria, CSF samples and clinical data from 17 individuals were collected, including eight individuals with ischemic stroke (IS) in the Ctrl group and nine individuals with CM in the CM group. The intracranial pressure (reference value, 80—180 mm H_2O) and the laboratory data of CSF were collected, including white cell counts (reference value, 0—5 $\times$ 10^6/L), glucose (reference value, 2.5—4.5 mmol/L), lactate dehydrogenase (LDH) (reference value, 0—40 U/L), adenosine dehydrogenase (ADA) (reference value, 0—8 U/L), proteins (reference value, 150—450 mmol L^{-1}), and chloridion (Cl) (reference value, 120—130 mmol L^{-1}).

Detection of CSF

Human lactate ELISA Kit (BOSHEN BIOTECHNOLOGY BS-E4820H1), Human pyruvate ELISA Kit (BOSHEN BIOTECHNOLOGY BS-E5562H1), Human ATP ELISA Kit (BOSHEN BIOTECHNOLOGY BS-E4820H1), Human LDH5 ELISA Kit (BOSHEN BIOTECHNOLOGY BS-E7114H1), and Human LDH1 ELISA Kit (BOSHEN BIOTECHNOLOGY BS-E7110H1) were applied to detect the lactate, pyruvate, ATP, LDH5, and LDH1 levels. The microplate reader (infinite F50) was employed to obtain the data on lactate, pyruvate, ATP, LDH5, and LDH1.

Primary neuron culture and transfection

Newborn rats (24 h old) were used for primary neuron culture, which was carried out according to the method of Li et al.[24] All the animals were obtained from the Animal Laboratory Center of Guangxi Medical University. The animal study was carried out at Guangxi Medical University. The animal experiments were performed under a project license (NO. 202101023). Lentiviruses (LV) with green fluorescence were purchased from Sangon Biotechnology (Shanghai) Co., Ltd., including a negative control (NC, titer: 5.13 $\times$ 10^8TU/ml) and RNA interference expressing LDHB (RNAi-LDHB; titer: 6.94 $\times$ 10^8 TU/mL). Neurons cultured for three days were transfected with NC or RNAi-LDHB (multiplicity of infection = 5). After 72 h, the cell morphology was examined using a Nikon microscope. After 15 days of culture, the neurons were utilized to perform the next step of the experiments.

Immunofluorescence (IF) analysis

The fixation, penetration, and blocking of the neurons were based on the methods described by Li et al.[12,24] The neurons were incubated with anti-neuron specific enolase (anti-NSE) antibody (1:50, BOSTER, BM4495) at 4 °C overnight. The neurons were incubated with a red fluorescent secondary antibody (CST, #8889) at 37 °C for 45 min. Lastly, 4′,6-diamidino-2-phenylindole (DAPI) staining solution was added, and the cells were incubated at room temperature for 3 min. Neuron-specific enolase (NSE) is considered a neuron-specific marker that can be used to identify neurons. The fluorescence signals of transfected cells (green) and neurons (red) were observed with Olympus BX53 fluoroscope.

Western blot

Protein extraction, protein concentration detection, sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE), membrane transfer, antibody incubation, and visualization of immunoreactive bands were performed as described by Li et al.[12] The primary antibodies were anti-LDHB antibody 1:1000 (Sangon Biotech, D164590), anti-LDHA antibody 1:1000 (Sangon Biotech, D164055), and anti-alpha-Tubulin antibody 1:10000 (Abcam, ab7291). The NC membranes were incubated with secondary antibody 1:8000 (Proteintech, SA00001-2) at room temperature for 1 h. The ImageJ software was applied to quantify immunoreactive bands. Protein levels were determined by normalizing to Tubulin loading controls.

Detection of the neuronal lactate, pyruvate, and ATP

The lactate Content Assay Kit (Solarbio, BC2235) was utilized to detect neuronal lactate. Pyruvate Content Assay Kit (Solarbio, BC2205) was used to detect neuronal pyruvate. The ATP Content Assay Kit (Solarbio, BC0305) was utilized to detect neuronal ATP. The microplate reader (infinite F50) was employed to obtain data on neuronal lactate, pyruvate, and ATP.

Neuronal electrophysiology

The Digidata 1550 B patch-clamp amplifier and the Axon Digidata 1550 B 16-bit data acquisition system were utilized to record the neuronal action potentials (APs). P 97 SUTTER INSTRUMENT was used to make patch electrodes (resistance of 3—6 MΩ). The neurons were immersed in an extracellular fluid. The patch electrodes were filled with intracellular fluid. The configuration of extracellular and intracellular fluids was refer to Li et al.[12,24] Whole-cell recordings were used to record the neuronal APs (clamping voltage, −70 mV) at room temperature. Five cells were detected in each group. pClamp 10.7 data acquisition software was employed to analyze the amplitude and frequency of neuronal APs.

Statistical analyses

Continuous variables were presented as means±standard deviations (SD). An independent sample t-test was used for the comparison between the means of two independent groups. The statistical analysis software used was SPSS version 25.0. A p-value <0.05 was statistically significant.

Results

Characteristics of population and CSF

Clinical and laboratory baseline data are exhibited in Table 1. The weight and BMI were higher in CM group, which may be related to the higher proportion of male in the CM group. The intracranial pressure and CSF data between the control group and the CM group are displayed in Fig. 1. It was found that intracranial pressures were increased in the CM group

Table 1 Clinical and laboratory baseline data.

	All	Ctrl	CM
Total, number	17	8	9
Male, number (%)	13 (76.47)	5 (62.50)	8 (88.89)
Female, number (%)	4 (23.53)	3 (37.50)	1 (11.11)
Age (years), mean ± SD	59.59 ± 11.71	51.75 ± 20.96	46.78 ± 14.05
Height(m), mean ± SD	1.64 ± 0.06	1.63 ± 0.07	1.65 ± 0.02
Weight (Kg), mean ± SD	58.71 ± 9.00	53.71 ± 8.98	63.16 ± 6.65*
BMI(kg/m^2)', mean ± SD	21.64 ± 2.51	20.13 ± 2.33	22.98 ± 1.87*
intracranial pressure (mmH_2O), mean ± SD	192.18 ± 77.29	136.88 ± 39.36	241.33 ± 74.57#
CSF-Cell (× 106/L), mean ± SD	60.12 ± 99.69	1.50 ± 2.39	112.22 ± 120.93*
CSF-LDH (U/L), mean ± SD	27.5 ± 13.07	25.88 ± 4.52	28.94 ± 18.45
CSF-ADA (U/L), mean ± SD	0.84 ± 1.11	0.50 ± 0.533	1.14 ± 1.47
CSF-glucose (mmol/L), mean ± SD	3.13 ± 0.74	3.38 ± 0.68	2.90 ± 0.80
CSF-protein (mg/L), mean ± SD	560.86 ± 525.31	332.68 ± 145.41	763.69 ± 685.23
CSF-Cl (mmol/L), mean ± SD	120.36 ± 9.79	120.78 ± 13.84	120.00 ± 5.97

(*.vs Ctrl, $p < 0.05$; #.vs Ctrl, $p < 0.01$).

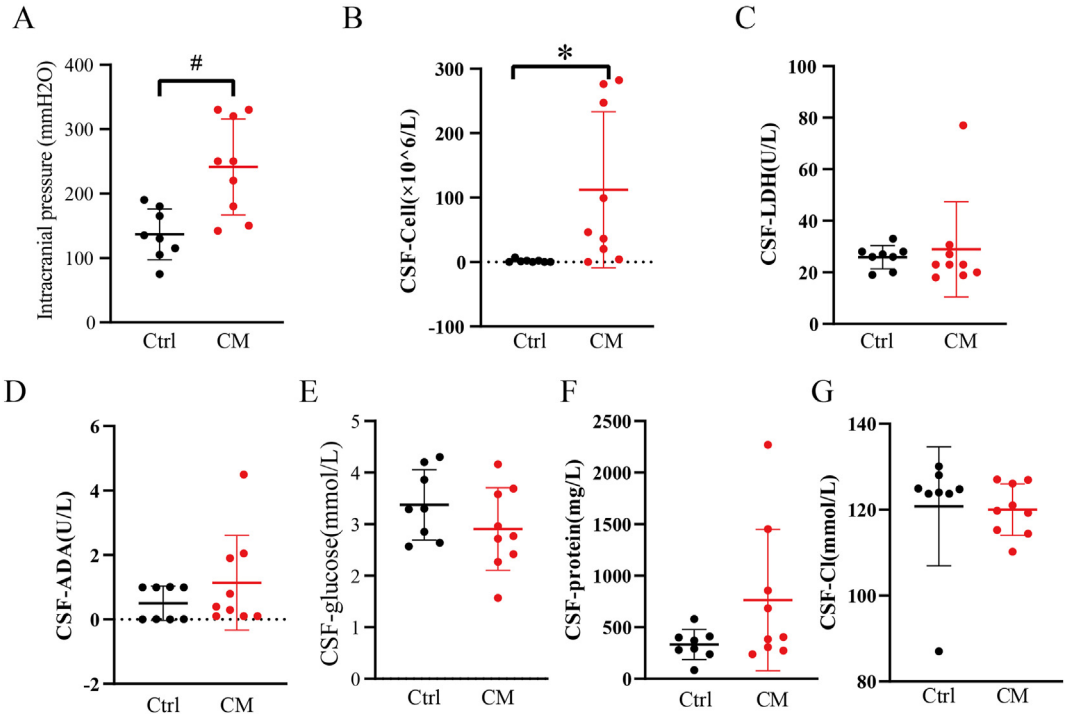

Figure 1. The intracranial pressure and CSF data between the control group and the CM group. (**A**) The intracranial pressure: intracranial pressures were increased in the CM group (*, $p < 0.05$). (**B**) The white cell counts in CSF: The white cell counts in CSF were increased in the CM gourp (#, $p < 0.01$). **(C-G)** The levels of LDH, ADA, glucose, protein and Cl in CSF: The levels of LDH, ADA, glucose, protein and Cl in CSF were not not significantly changed in the CM group.

(vs. Ctrl, $p < 0.01$; Fig. 1A), and white cell counts in CSF were increased in the CM group (vs. Ctrl, $p < 0.05$; Fig. 1B). After further analysis of the CSF, the levels of lactate were significantly increased in the CM group (vs. Ctrl, $p < 0.01$; Fig. 2A), while pyruvate, ATP, and LDH1 levels were decreased considerably in the CM group (vs. Ctrl, $p < 0.01$; Fig. 2B–D). However, the levels of LDH5 showed no significant change (vs. Ctrl, $p > 0.05$; Fig. 2E).

Construction of *in vitro* model of neuron

To further explore the effect of LDH1 on CNS energy metabolism, an *in vitro* model of neurons was constructed. LDH1 is made up of four subunits of LDHB, while LDH5 is made up of four subunits of LDHA.[20] Therefore, LV was used to interfere with the LDHB expression of neurons, and the results showed that the neurons displayed both green and

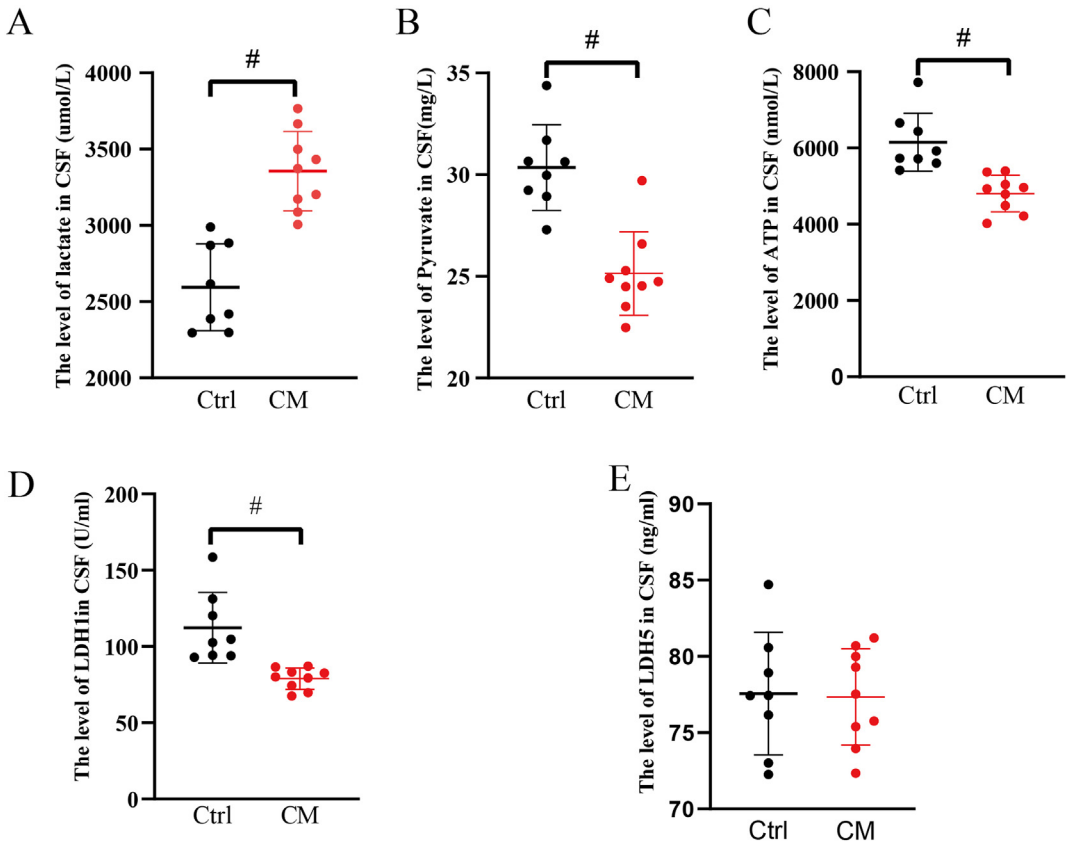

Figure 2. The lactate, pyruvate, ATP, LDH1, and LDH5 levels between the control group and the CM group. **(A)** The level of lactate in CSF: the level of lactate was significantly increased in the CM group (#, $p < 0.01$). **(B)** The level of pyruvate in CSF: the level of pyruvate was significantly decreased in the CM group (#, $p < 0.01$). **(C)** The level of ATP in CSF: the level of ATP was significantly decreased in the CM group (#, $p < 0.01$). **(D)** The level of LDH1 in CSF: the level of LDH1 was significantly decreased in the CM group (#, $p < 0.01$). **(E)** The level of LDH5 in CSF: the level of LDH5 was not significantly changed in the CM group.

red fluorescence, indicating their successful transfection (Fig. 3A). The result of the western blotting indicated that the expression of LDHB was significantly decreased (vs. NC, $p < 0.01$, Fig. 3B). The expression of LDHA was not considerably changed (vs. NC, $p > 0.05$, Fig. 3B). Subsequently, the lactate, pyruvate, and ATP levels in the *in vitro* model was detected. The results showed that the neuronal lactate levels were significantly increased while that of neuronal pyruvate and ATP were significantly decreased in the RNAi-LDHB group (vs. NC, $p < 0.01$, Fig. 3C).

Neuronal activity

The APs of neurons were detected by a patch clamp. The electrophysiological results showed that the amplitude and frequency of neuronal APs were significantly decreased in the RNAi-LDHB group (vs. NC, $p < 0.01$, Fig. 4).

Discussion

Elevated intracranial pressure is considered the most common symptom of CM and an important factor affecting the prognosis of patients.[25,26] Junyan Qu et al. confirmed that the white blood cell counts in CSF may be an important indicator of the prognosis of the disease.[27] These indicators reflect the degree of brain injury. The results showed that intracranial pressure and cerebrospinal fluid white blood cell counts were increased in patients with CM, suggesting that Cn caused damage to the brain. The damage caused by pathogenic microorganisms to CNS is mainly divided into two stages: the disturbance of energy metabolism in the early stage and the development of structural changes in the late stage.[22] Previous study demonstrated that timely correction of energy metabolism disorders in the CNS can protect neurons.[11,12] The results reported no significant difference in CSF glucose between the control group and the CM group, which further indicates that CSF glucose does not fully reflect brain energy metabolism. The brain's energy source is ATP, which is converted from glucose.[13] However, the conversion of glucose into ATP in the brain needs to go through a series of complex metabolic pathways. Among these pathways, the lactate metabolism pathway plays a key role. Therefore, monitoring and correcting CSF glucose levels alone does not necessarily fix the brain's energy metabolism disorders.[16] Subsequently, the level of ATP in CSF was analyzed. The results ATP levels in CSF was significantly reduced in the CM group, suggesting that ATP in CSF may be a more appropriate indicator of brain energy metabolism.

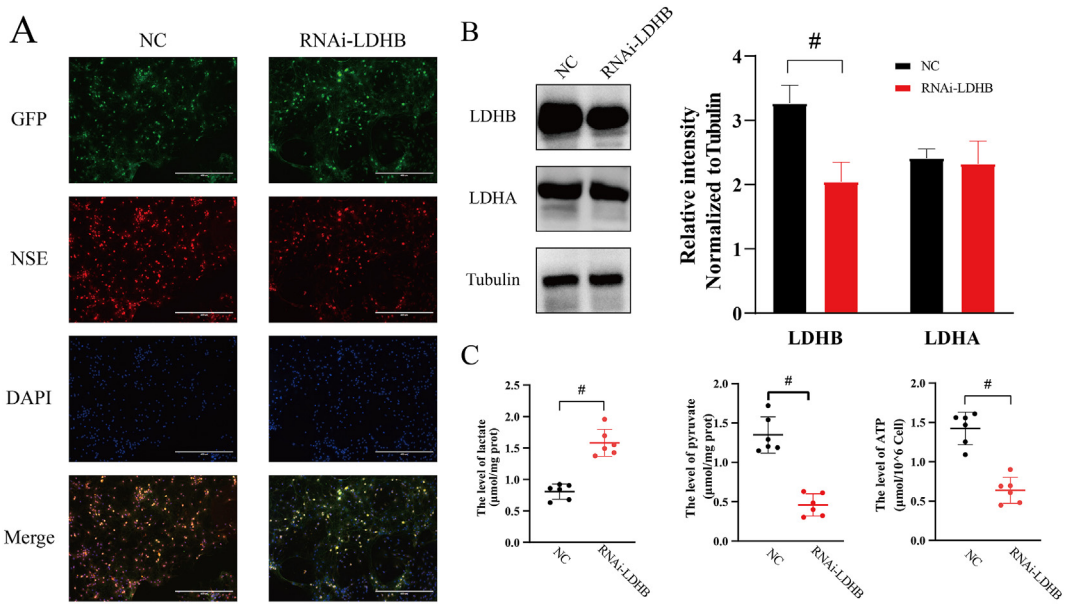

Figure 3. The *in vitro* model of neurons with low expression of LDHB. **(A)** Neuronal fluorescence (× 200): green fluorescence, LV; red fluorescence, NSE (Scale bar: 50 μm). **(B) The expression of LDHB and LDHA:** LDHB expression was significantly decreased, and LDHA expression was not significantly changed in RNAi-LDHB (#, $p < 0.01$). **(C)** The levels of lactate, pyruvate and ATP in neurons: The neuronal lactate levels were significantly increased, and neuronal pyruvate and ATP levels were significantly decreased in RNAi-LDHB group (#, $p < 0.01$).

Abassi et al. indicated that individuals with elevated baseline lactate levels in CSF were more likely to have altered mental status, seizures, and elevated intracranial pressure, increasing their risk of death.[28] When glucose and lactate are present at the same time, neurons are more inclined to use lactate for aerobic metabolism and produce energy.[16] However, due to the lack of 6-phosphofructokinase-2, the glycolytic capacity of neurons is low, and the amount of lactate synthesis is small.[29] Astrocyte-neuron metabolic coupling is the main pathway for neurons to obtain lactate.[16] Through LDH5, astrocytes convert glucose from peripheral blood into lactate and discharge it out of the cell, forming a "lactate pool".[30] The lactate in the neuron, taken up from the lactate pool, was converted by LDH1 to pyruvate and goes through the tricarboxylic acid cycle to produce ATP.[23] In this study, it was found that the level of CSF lactate was increased in patients with CM while the CSF pyruvate level was decreased, indicating that the conversion of lactate to pyruvate was disturbed in the brains of the individuals with CM. Subsequently, the LDH5 and LDH1 in CSF levels were detected. The results showed that the LDH1 levels were significantly reduced, suggesting that Cn invaded the CNS and was more inclined to reduce the level of LDH1, thus disturbing the conversion of lactate to pyruvate. In addition, *C. n* can cause host cells to produce lower levels of IL-6, affecting the energy metabolism reprogramming.[31,32] The elevated metabolism during infection may lead to decreased production or increased consumption of LDH1. As a result, the level of ATP was decreased, ultimately leading to energy metabolism disorder in the brain. Huang et al. found that the level of LDH in CSF was higher in CM patients with poor prognosis than in CM patients with good prognosis.[33] In our study, we did not observe significant differences in LDH levels in the CSF, which may stem from the fact that the prognosis of patients with CM was not factored into the analysis. In addition, even though the level of LDH1 was decreased and the level of LDH5 did not change significantly, the level of total LDH did not change significantly, which may be related to the alteration of other isoenzymes.

Skeletal muscle has a higher content of LDHA, which preferentially converts pyruvate to lactate. The brain has higher levels of LDHB, which ensures the conversion of lactate to pyruvate.[20,34,35] To further investigate the effect of LDH1 on the energy metabolism of neurons, an *in vitro* model of neurons with low expression of LDHB was constructed. By detecting the lactate, pyruvate, and ATP levels in the neurons in the RNAi-LDHB group, lactate was significantly increased while pyruvate and ATP were significantly decreased, consistent with the trend of clinical specimens. Neurons are the most important cells in the CNS to perform basic physiological functions and are responsible for the reception and transmission of signals.[36] The level of ATP is closely related to the activity of neurons, in which Na^+/K^+ ATPase (NKA) plays a key role.[37,38] NKA, which uses the energy of ATP hydrolysis to introduce Na^+ into the cell and expel K^+ out of the cell, consumes up to a lot of ATP.[39] The transport of Na^+ and K^+ by NKA is a key factor in the formation of APs.[39] To clarify the functional characteristics of neurons with low expression of LDHB, neuronal APs, which are considered a basic indicator of neuronal activity, were evaluated.[40] The results showed that low expression of

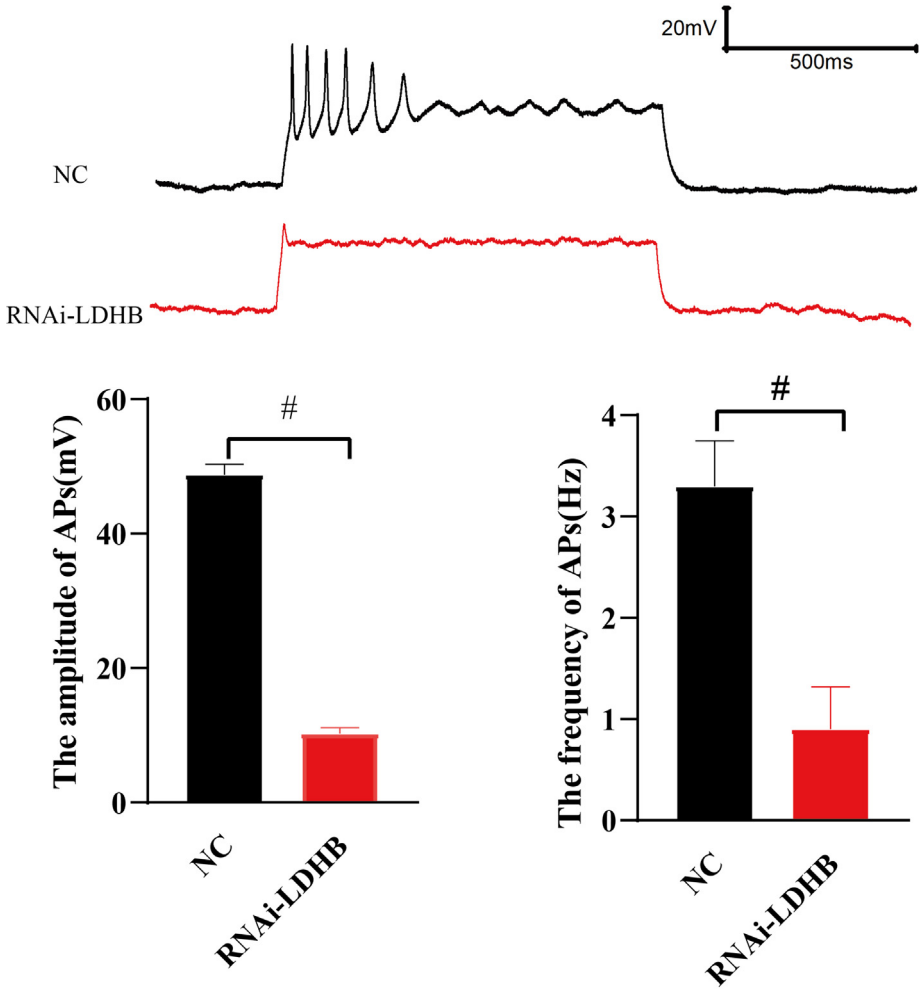

Figure 4. The neuronal electrophysiology: the amplitude and frequency of neuronal APs were significantly decreased in the RNAi-LDHB group (#, $p < 0.01$).

LDHB could result in a significant decrease in both the amplitude and frequency of neuronal APs, which also suggested a decrease in neuronal activity. However, some limitations of the study should be acknowledged. The insufficient number of clinical samples is one major limitation. In addition, *in vitro* and *in vivo* models of CM were not constructed to investigate the potential mechanisms of Cn's effect on CNS energy metabolism. In future studies, these deficiencies can be addressed.

In summary, reduced levels of LDH1 in the brain of individuals with CM may lead to increased lactate levels, decreased pyruvate and ATP levels, and negatively impact neuronal activity.

Ethics statement

All patient protocols were authorized by the Ethics Committee of Fourth People's Hospital of Nanning (approval number [2021] 25) and conformed to the Declaration of Helsinki's ethical principles. Written informed consent was acquired from all human subjects. All experimental procedures were approved by the Ethics Committee of Guangxi Medical University (ethical batch number: (NO. 202101023)) and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Animals.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Qingdong Zhu: Writing — original draft, Methodology, Investigation, Data curation, Conceptualization. **Qian Long:** Formal analysis, Data curation, Conceptualization. **Cailing Wei:** Visualization, Validation, Resources. **Jieling Chen:** Visualization, Validation, Software, Investigation. **Lanwei Nong:** Writing — original draft, Validation.

Jianglong Qin: Visualization, Validation, Investigation. **Zhizhong Huang:** Visualization, Validation. **Yanqing Zheng:** Funding acquisition, Formal analysis. **Sijun Li:** Writing — review & editing, Software, Project administration.

Declaration of competing interest

The authors state that they have no conflicts of interest. The authors declare that they have no competing interests.

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