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Lactate alleviates trigeminal neuralgia symptoms in mice by suppressing neuroinflammation

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Abstract

Objectives: Trigeminal neuralgia is a neuropathic pain syndrome that undesirably affects patient's quality of life. Lactate exerts extensive pathophysiological effects on the brain; however, it remains unclear whether lactate improves trigeminal neuralgia symptoms as well as the underlying mechanisms.

Methods: In our study, unilateral constriction of the infraorbital nerve was performed to establish a mouse model of trigeminal neuralgia. Conditional knockout of the astrocyte-specific lactate dehydrogenase gene was performed to decrease brain exposure to lactate. The behavioral changes were observed and the pain thresholds were detected via von Frey tests at 1, 5, 10, 15, and 30 days after surgery to evaluate the impact of lactate on trigeminal neuralgia. Intracerebroventricular injection of L-lactate was administered to evaluate the biological function of lactate in our model.

Results: We revealed that lactate levels in the spinal trigeminal nucleus were elevated by approximately 2.5-fold (3.63 vs. 1.43 μmol/g) after surgery, which remained elevated for at least 30 days. This shift in lactate levels appeared to be independent of peripheral circulation, as plasma lactate levels remained unaltered until 30 days after surgery. Increased lactate exposure alleviated trigeminal neuralgia symptoms after the surgery. Mechanistically, lactate suppressed reactive oxygen species production and neuroinflammation.

Conclusions: Lactate may alleviate trigeminal neuralgia symptoms in mice by suppressing neuroinflammation.

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Introduction

Trigeminal neuralgia (TN) is a common craniofacial neuralgia characterized by severe and recurrent pain in the distribution of the trigeminal nerve. It is an undesirable condition that discourages patients from daily activities, such as washing the face, brushing teeth, and even eating food.[1,2] Epidemiological studies have suggested that TN affects >4 per 100,000 people annually and contributes to depressive mood, highlighting the burden on these patient's mental health.[3–6] Despite the unremitting efforts by health personnel, optimal methods for TN management are yet to be established.

In recent years, lactate has received renewed attention because it might be beneficial for various neurological disorders and neuroprotection by improving functional recovery after nerve injury via the promotion of protein lactylation, reduction of neuroinflammation, activation of neuronal metabotropic receptors, and boosting of the cyclic adenosine monophosphate (cAMP) signaling pathway.[7–10] Trigeminal nerve injury, caused by neurovascular compression of the trigeminal nerve root, has long been hypothesized to be the primary trigger for TN; the cascade of reactions that follows and the underlying mechanisms via which they cause TN remain unclear.[11,12] In addition, it remains unknown whether the accumulation of lactate in the central nervous system is beneficial for the prevention and treatment of TN.

In this study, using a mouse model of TN, we observed lactate accumulation in the caudal part of the spinal trigeminal nucleus (Sp5C), which is believed to play an important role in regulating nociceptive information processing in the trigeminal nervous system.[13] Previous studies have reported that the attenuation of astrocyte activation contributed to alleviation of TN symptoms, suggesting an important role of astrocytes in TN.[14] Additionally, lactate is primarily produced by astrocytes in the central nervous system.[15] Therefore, we subsequently confirmed the beneficial effect of lactate in alleviating TN symptoms by constructing lactate dehydrogenase (*Ldh*) conditional knockout (cKO) mice. Moreover, we revealed that *Ldh* cKO-dependent lactate elevation in the Sp5C zone reduced reactive oxygen species (ROS) production and neuroinflammation in our model.

Materials and methods

Animals

This study is reported in accordance with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.[16] All animal experiments were conducted in compliance with the protocols approved by the Institutional Animal Care and Use Committee (IACUC) of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (No.2019KI-030). All animals were handled as per the National Institute of Health Guidelines for the Care and Use of Laboratory Animals.[17] m-Glial fibrillary acidic protein (mGFAP)-Cre mice (B6.Cg-Tg (*Gfap-Cre*)77.6Mvs/2J,

JAX Stock) were mated with *Ldh*$^{flox/flox}$ (Cyagen, C57BL/6N-*Acss1*em1.1cyagen) mice. Breeding colonies were maintained by mating *Ldh*$^{flox/flox}$ with *mGfap-Cre* to generate experimental cKO animals.[18] The mice were housed under standard bedding in colonies at 22°C–24°C under a 12-h light/dark cycle. Animals had ad libitum access to water, and food was only withdrawn if required for an experiment. No samples or animals were intentionally excluded from the analyses. The investigators were blinded to group allocation.

Mouse model of TN

The mouse model of TN was established via chronic constriction injury of the unilateral infraorbital nerve (CION), as described in a previous study.[19] Mice were anesthetized via intraperitoneal injection of 2.5% avertin (T48402, Sigma, St. Louis, MO, USA) at a dose of 0.15 mL/g and then placed in the supine position on the surgical pad; the oral cavity was exposed. Then, an incision (0.5 cm long) was made in the left palatal–buccal mucosa, and the tissue was separated via blunt dissection to identify the infraorbital nerve branch of the trigeminal nerve. The infraorbital nerve was ligated with 4.0 catgut (BD171001, Boda, Shandong, China), and the distal nerve was cut at a length of approximately 1 mm.

Face-grooming times

Face-grooming times, defined as an uninterrupted sequence of face-grooming actions, were counted over a period of 10 min, as previously described.[20]

Mechanical allodynia

Mechanical allodynia tests were performed according to a previous study.[21] In general, 3 days before testing, mice were habituated to the testing environment for 1 h. The tests were performed before the surgery (baseline) and on postoperative days 1, 5, 10, 15, and 30. A series of calibrated von Frey filaments (2, 4, 6, 8, 10, and 15 g) were applied to the skin within the infraorbital territory. To avoid interference, the hair in the measurement area was ipsilaterally shaved. Each filament was executed five times at 10-s intervals. The force of the von Frey filament with three-fifths positive reactions was recorded as the mechanical pain threshold.

Tissue preparation

For tissue treatment for the lactate assay, the mice were decapitated at predefined time points, and the tissue was frozen in liquid nitrogen until the experiments were performed. During tissue treatment for dihydroethidium (DHE) staining, the mice were perfused with 0.9% normal saline and then with 4% paraformaldehyde (PFA). The brains were extracted, fixed in 4% PFA for 24 h, and dehydrated in 30% sucrose (wt/vol) in PBS for 48 h at 4°C; they were then embedded in Tissue-Tek OCT compound (4583, Sakura Finetek) and frozen on dry ice. Finally, 4-μm brain sections were used.

DHE staining

A DHE probe was used to detect intracellular ROS in brain tissues (S0033S, Beyotime Institute of Biotechnology, China). Fluorescence was detected using a SpectraMax Microplate Reader (Molecular Devices, San Jose, CA, USA) at 488 nm excitation and 525 nm emission wavelengths.

Quantitative reverse transcription–polymerase chain reaction (qRT–PCR)

Total RNA was extracted from the Sp5C zone of mouse brain tissue using TRIzol reagent (15596018, Thermo Fisher Scientific); this was followed by reverse transcription using a cDNA synthesis kit

(1725035, Bio-Rad, China). The Qubit Assay Kit (Q32854, Life Technologies) and Nano 6000 Assay Kit (5067-1511, Agilent Technologies) were used to measure the concentration of total RNA and assess RNA integrity, respectively. qRT–PCR was performed using a Realplex 2 system (Eppendorf North America); 18S mRNA was used as a reference. Primer sequences are listed in Table 1.

Lactate measurement

Lactate levels in the plasma and brain tissues were determined using the lactate assay kit (MAK329, Millipore Sigma) as per the manufacturer's instructions. Lactate in the sample was converted into an intermediate in the presence of a lactate enzyme mixture and lactate substrate mix with the strongest optical density (OD) value at 450 nm; the OD value was proportional to the level of lactate in the sample.

Intracerebroventricular (ICV) injection

We administered an ICV injection according to a published protocol;[22] mice were administered with sodium L-lactate continuously for 2 weeks at a rate of 0.5 μL/h using a mini-osmotic pump (ALZET, #2002). Overall, 0.5 mol/L L-lactate was dissolved in sterile artificial cerebrospinal fluid (aCSF, 124 mM NaCl, 26 mM $NaCO_3$, 2.5 mM KCl, 2.0 mM $CaCl_2$, 1.0 mM $MgCl_2$, 1.25 mM Na_2PO_4, and 10.0 mM D-glucose; pH 7.4) in a total volume of 200 μL. Sodium L-lactate was delivered to the third ventricle of the brain using appropriate coordinates: (anteroposterior: −1.8 mm, dorsoventral: −5.0 mm). After the experiments, stereotaxic implants were anatomically verified.

Table 1. Primer sequences used in this study.

Target	Sequence
qPCR	
Acss1	5′-CAAAGACTACTGTGTAACTGCGA-3′
	5′-TGGACTGTACTTGACAATGTTGG-3′
IL-1β	5′-TGCCACCTTTTGACAGTGATG-3′
	5′-CACGATGGAGGGGCCGGACTCGTC-3′
IL-6	5′-TGAGAAAAGAGTTGTGCAATGG-3′
	5′-GGAGAGCATTGGAAATTGGGG-3′
Cxcl1	5′-GCACCCAAACCGAAGTCA-3′
	5′-AAGCCAGCGTTCACCAGA-3′
18S	5′-TTGACTCAACACGGGAAACC-3′
	5′-AGACAAATCGCTCCACCAAC-3′

Statistical analyses

Statistical analyses were performed using GraphPad Prism 9.0 (GraphPad Software, USA). All data were subjected to Shapiro–Wilk normality tests before the analyses. Survival was estimated using the Kaplan–Meier method and compared between the different groups using log-rank test. For data that were distributed normally, two-tailed Student tests or two-way analysis of variance were selected to compare two groups. For data that were not distributed normally, values were presented as medians and interquartile ranges. Kruskal–Wallis with Dunn multiple comparisons test was performed for comparison between more than two groups, and Mann–Whitney test was used for comparison between two groups. All data, unless otherwise indicated, were described as means ± standard error of mean. p-values <0.05 were considered to indicate statistical significance.

Results

Lactate levels were increased in the Sp5C zone in a mouse model of TN

Previous studies have shown that lactate rapidly accumulates in specific sites upon nerve injury in mice.[7] Additionally, the Sp5C zone may play a critical role in regulating nociceptive information processing in the trigeminal nervous system.[23] To determine whether lactate will accumulate in the Sp5C zone, unilateral CION was performed

to establish a mouse model of TN (Figure 1(a)). The results showed no significant difference in the basal pain level between the study groups before CION; however, the face-grooming time increased and mechanical pain thresholds in the ipsilateral zones decreased among CION mice until 30 days after surgery (Figure 1(b) and (c)). Subsequently, we assessed the lactate levels in the Sp5C zone, which increased up to 2.8-fold in the ipsilateral Sp5C zone after CION (Figure 1(d)). This shift in lactate levels appeared to be independent of peripheral circulation, as plasma

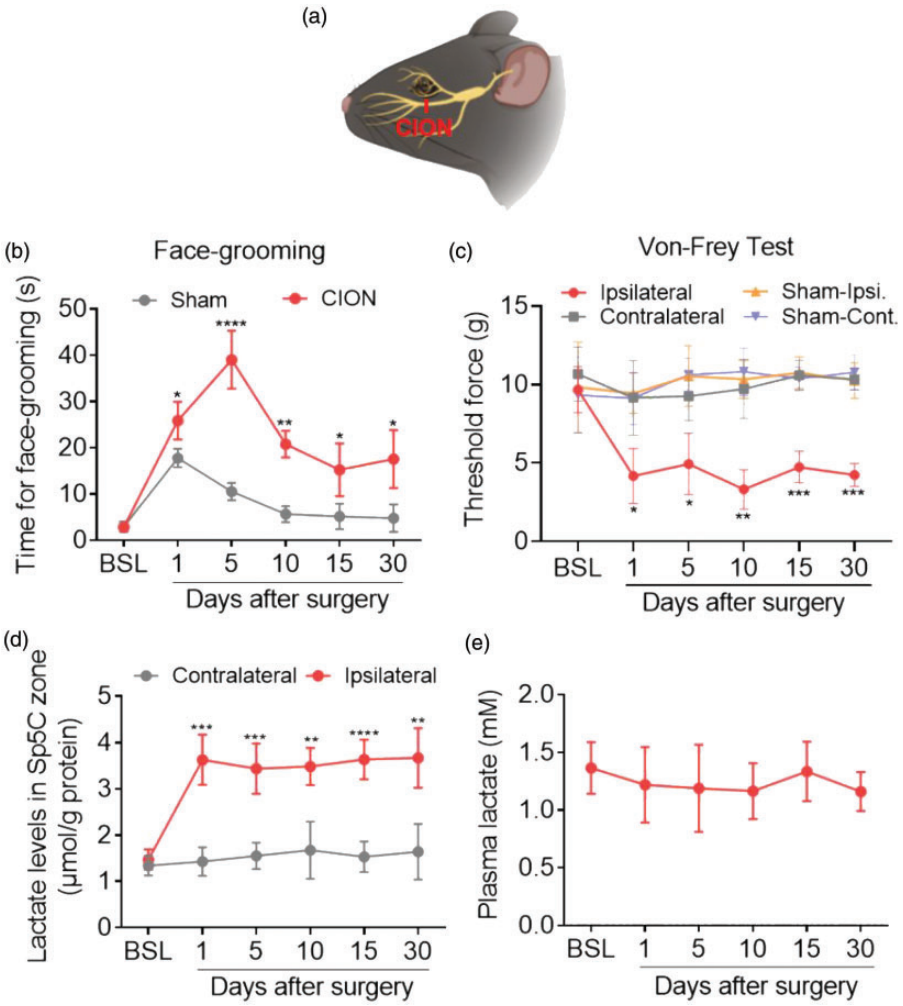

Figure 1. Lactate levels were increased in the Sp5C zone in a mouse model of TN. (a) Schematic representation of the mouse model of TN. (b) Face-grooming times at different time points before and after surgery (n = 12). (c) Mechanical hyperalgia at different time points before and after surgery (n = 12). (d) Lactate levels in the Sp5C zone at different time points before and after surgery (n = 12) and (e) plasma lactate levels at different time points before and after surgery (n = 12). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Sp5C: spinal subnucleus caudalis; TN: trigeminal neuralgia; CION: chronic constriction injury of infraorbital nerve.

lactate levels remained unaltered after CION (Figure 1(e)). These findings indicate that lactate levels were increased in the Sp5C zone in our mouse model of TN. We also explored whether the accumulation of lactate in the Sp5C zone is beneficial for TN management.

Ldh deletion in the brain exacerbates TN symptoms

We inhibited lactate utilization via cKO of *Ldh*, which is responsible for conversion of glucose to lactate. The immunofluorescence double-staining results for the cellular localization of Ldh expression in the Sp5C zone showed that Ldh was expressed mainly in the astrocytes. Therefore, we crossed $Ldh^{flox/flox}$ mice with *Gfap*-Cre mice to generate experimental *Ldh* cKO mice (Figure 2(a)). *Ldh* cKO efficiency was confirmed using qPCR (Figure 2(b)). We found that lactate levels were decreased in the Sp5C zone of the cKO mouse brain (Figure 2(c)). We assessed TN symptoms in *Ldh* cKO mice and wild-type mice; the results showed that *Ldh* cKO exacerbates TN symptoms after CION (Figure 2(d) and (e)). Collectively, these results suggest that inhibition of lactate production in the brain can exacerbate TN symptoms.

Lactate attenuates TN by suppressing neuroinflammation in the Sp5C zone

Accumulating evidence has revealed the crucial role of lactate in regulating various pathological processes and neuroprotection;

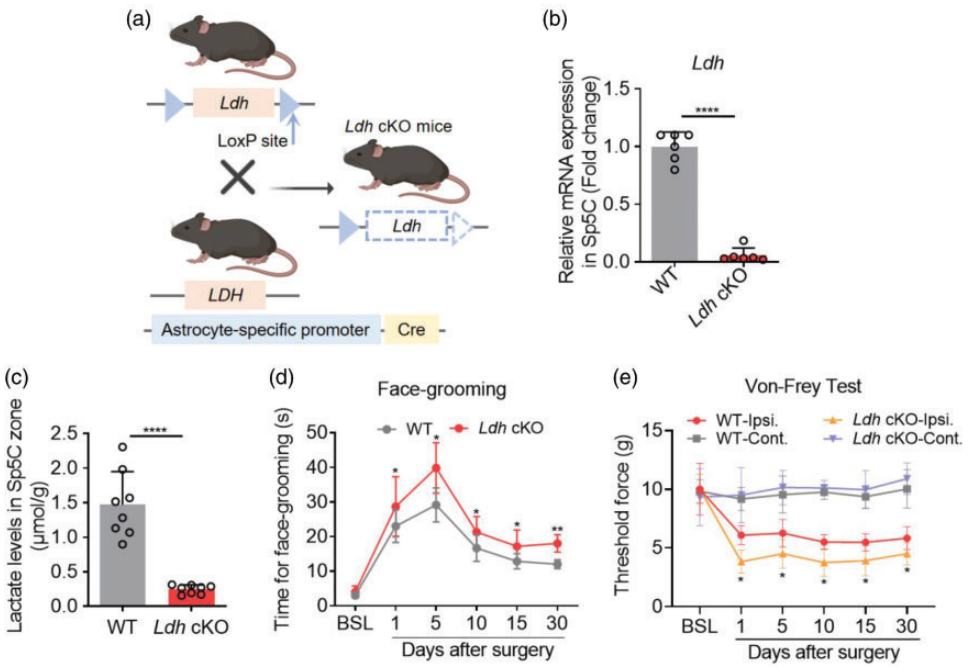

Figure 2. *Ldh* deletion in the brain alleviates TN symptoms. (a) Schematic representation of genome editing using the Cre-loxP recombination system. (b) The levels of *Ldh* mRNA in the brain tissue (n = 6). (c) Lactate levels in the Sp5C zone (n = 6). (d) Face-grooming times at different time points before and after surgery (n = 10) and (e) mechanical hyperalgia at different time points before and after surgery (n = 10). *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$. *Ldh*: lactate dehydrogenase; TN: trigeminal neuralgia; mRNA: messenger ribonucleic acid; Ipsi: ipsilateral; count: contralateral.

therefore, we next focused on the biological functions of lactate in our model. We administered an ICV injection of L-lactate to *Ldh* cKO mice using a mini-osmotic pump. Lactate levels in the Sp5C zone were significantly elevated after an ICV injection of L-lactate (Figure 3(a)). The results showed that lactate administration alleviated TN symptoms among *Ldh* cKO mice (Figures 3(b) and 4(c)). Additionally, the *Ldh* cKO-induced upregulation of ROS production and neuroinflammation in the Sp5C zone were reversed by ICV injection of L-lactate (Figure 3(d) to (h)). Taken together, these data indicate that lactate attenuates TN by suppressing neuroinflammation in the Sp5C zone.

Discussion

In this study, we demonstrated that lactate levels were elevated in the Sp5C zone in a mouse model of TN, which suppressed ROS production and neuroinflammation as well as alleviated TN symptoms (Figure 4). Thus, our results suggest that increasing brain lactate levels can yield optimal outcomes in TN management.

The central nervous system (CNS) environment has been demonstrated as inhibitory to axon regrowth after nerve impairment. Neuropathic pain arises concomitantly to nerve impairment.[24] Therefore, neuropathic pain may be relieved by promoting axonal regeneration. By approaching a specific status of glial cells, the inhibitory CNS environment can be reversed to support axon regeneration.[25] Previous studies have indicated that elevated lactate levels, through a metabolic switch to aerobic glycolysis in the glia, act on neuronal γ-aminobutyric acid receptors in an unexpected inverse activation manner and increase cAMP signaling for neuronal regrowth.[7] Thus, we hypothesized that lactate can help relieve TN symptoms. Lactate, as a metabolic end-product, can exhibit signaling functions in addition to its cognate roles.[26] Prior studies have reported the neuroprotective roles of lactate involving promotion of axon regeneration and functional recovery after nerve injury,[7] prevention of ischemic neuronal death,[8] protection against the brain injury resulting from ischemic stroke,[9] and protection of neural tissue from excitotoxicity.[10] Therefore, lactate could be another promising therapeutic option for nerve injury. Therefore, after observing an increase in the lactate levels in the Sp5C zone of TN mice, we further investigated the impact of lactate accumulation in the Sp5C zone on TN and discovered a lactate-dependent improvement of TN symptoms. In our study, we focused on the biological functions of lactate in our model through the deletion of *Ldh* and ICV injection of L-lactate. Our results indicated that lactate can suppress ROS production and neuroinflammation in the Sp5C zone. Therefore, it is reasonable to conclude that the exacerbation of TN symptoms among *Ldh* cKO mice was correlated with a decrease in the lactate levels in the Sp5C zone. Our findings support the current understanding that lactate plays a neuroprotective role in several neurological disorders. Additionally, this is the first study to report the effect of lactate on attenuation of ROS production and neuroinflammation in a mouse model of TN, which expands our knowledge about the biological functions of lactate.

Existing studies also suggest that lactate is associated with pain induction rather than pain relief, but none of these achievements have translated to clinical work.[27–29] Thus, there is an urgent need to further explore the impact of lactate on TN symptoms. There are several reasons for the discrepancies between our findings and those of the existing studies: (a) we focused on the Sp5C zone, which may play an important role in regulating nociceptive information processing in the trigeminal nervous system; however, other studies focused on

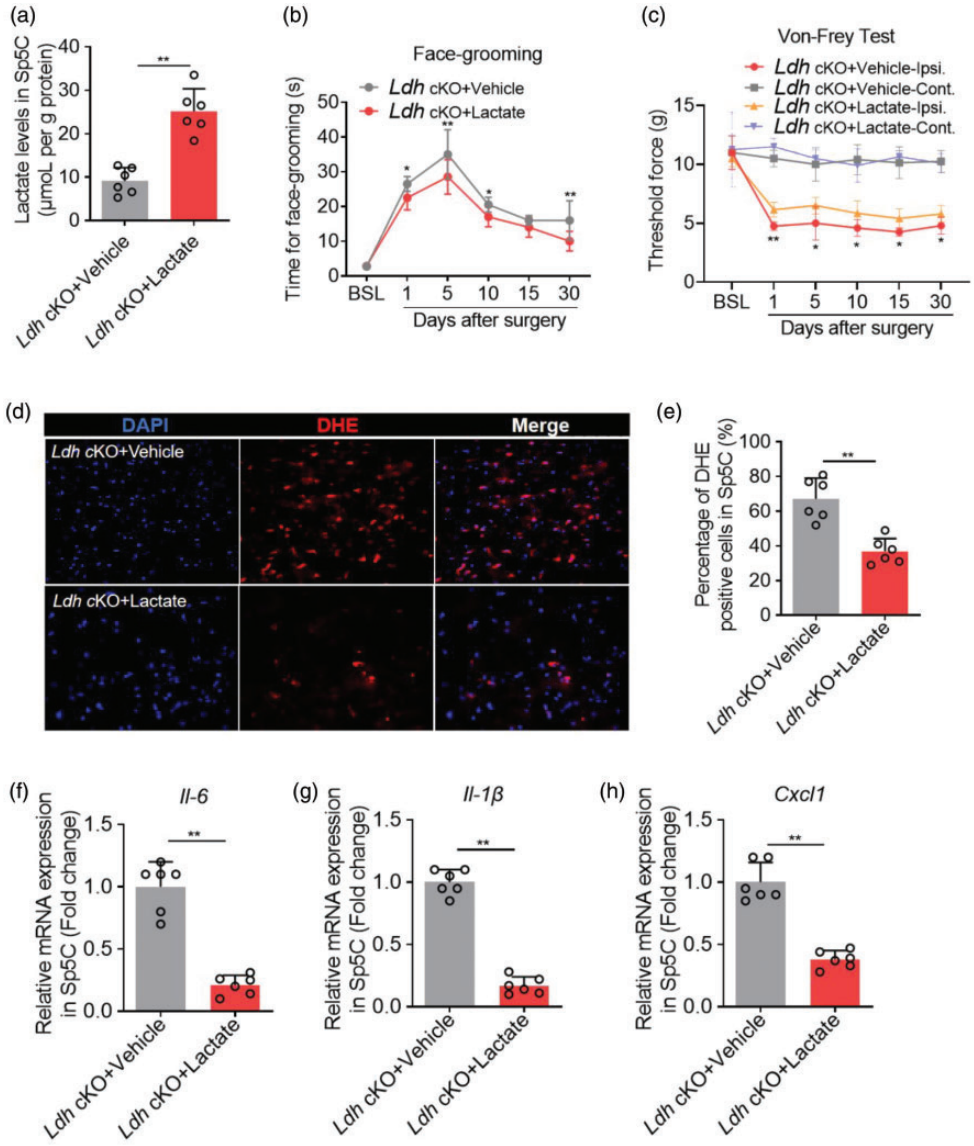

Figure 3. Lactate suppresses neuroinflammation and alleviates TN symptoms. (a) Lactate levels in the Sp5C zone of different mice (n = 6). (b) Face-grooming times at different time points before and after surgery (n = 10). (c) Mechanical hyperalgia at different time points before and after surgery (n = 10). (d) Detection of ROS in the Sp5C zone of different mice using DHE staining (n = 6). (e) Percentage of DHE-positive cells were calculated (n = 6). (f–h) The levels of *IL-6* mRNA (G), *IL-1β* mRNA (H), and *Cxcl1* mRNA (I) in the Sp5C zone of mice among different groups (n = 6). *$p < 0.05$, **$p < 0.01$. TN: trigeminal neuralgia; Sp5C: spinal subnucleus caudalis; ROS: reactive oxygen species; DHE: dihydroethidium; mRNA: messenger ribonucleic acid.

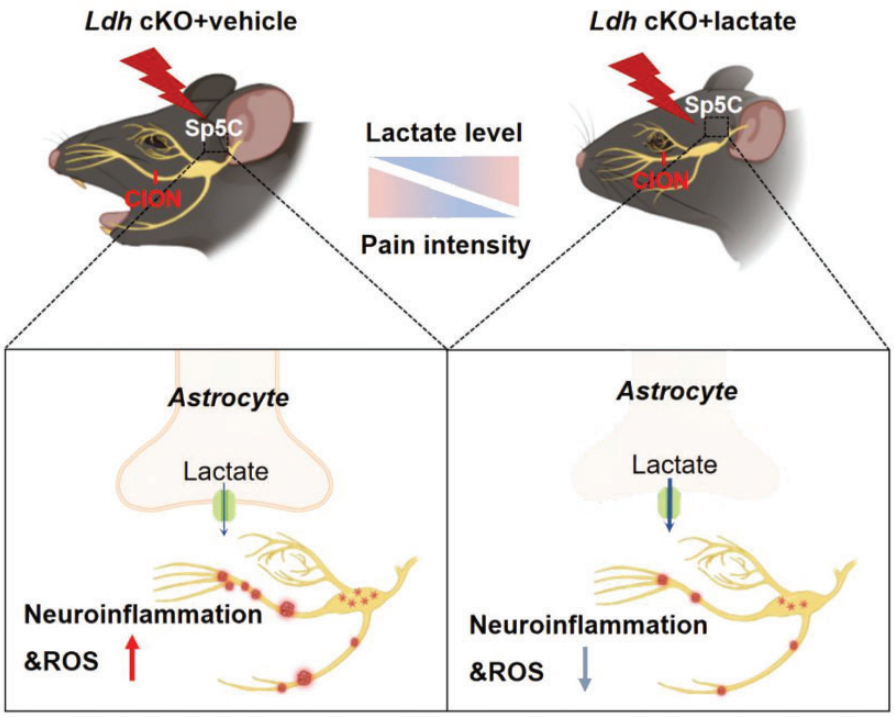

Figure 4. Lactate alleviates TN symptoms by suppressing neuroinflammation in the Sp5C zone. TN: trigeminal neuralgia; Sp5C: spinal subnucleus caudalis.

the dorsal root ganglia, microglia, or astrocyte–neuron lactate shuttle; 2) the dosages for treatment in our study were different from those in previous studies; and 3) the genetic tools used in our study were different from those used in other studies.

The current findings have clinical significance and translational potential. On the one hand, it is clear that elevation of lactate levels in the Sp5C zone might be considered as a clinically beneficial strategy for alleviating TN symptoms. No such therapy related to lactate has yet achieved regulatory approval for clinical application, and further evidence is still required.

Certain limitations in this study should be acknowledged. First, as female transgenic mice were used for breeding, the experiments described in this study were conducted exclusively on male transgenic mice. Therefore, there may be sex bias regarding the results. Second, we observed that the *Ldh* cKO-induced upregulation of ROS production and neuroinflammation in the Sp5C zone was reversed by ICV injection of L-lactate, but the duration of these effects has not been investigated in this study.

Conclusion

The results from the present study demonstrate that lactate may alleviate TN symptoms in mice by suppressing neuroinflammation in the Sp5C zone. The results highlighted lactate as a promising alternative for prevention and treatment of TN.

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Author contributions

X.L., F.L., and T.Q. conceived the original idea and performed the experiments and data analysis. X.L., F.L., and W.Z. wrote the manuscript. T.Q. polished the manuscript and prepared the figures. All authors have read and approved the final version of the manuscript.

Data and material availability

The data that support the findings of this study are available from the corresponding author upon request.

Declaration of conflicting interests

The authors report there are no competing interests to declare.

Ethics declaration

All animal experiments were conducted in compliance with protocols approved by the Institutional Animal Care and Use Committee (IACUC) of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (No.2019KI-030).

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