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CXCL1/CXCR2 is involved in white matter injury in neonatal rats via the gut–brain axis

Can Yang†, Zhiyuan Feng†, Hong Deng, Lu Dai, Ling He, Linlin Yin and Jing Zhao*

Abstract

Background: This study aimed to investigate whether CXCL1/CXCR2 mediates intestinal injury or white matter injury by delivering inflammatory mediators through the gut–brain regulation axis.

Methods: Neonatal SD rats, regardless of sex, were administered 3% dextran sulfate sodium via intragastric administration at different time points to construct necrotizing enterocolitis (NEC) models. Meanwhile, hypoxia and ischemia were induced in 3 day-old SD rats to construct hypoxic–ischemic brain injury (HIBI) and NEC + HIBI models, without gender discrimination. Hematoxylin–eosin staining was used to observe pathological changes in neonatal rat intestinal and brain tissues. Western blotting detected CXCL1 and CXCR2 expression in NEC, HIBI, and NEC + HIBI rat intestinal and brain tissues.

Results: Compared with normal rats, pathological damage to periventricular white matter was observed in the NEC group. In addition to the increased mortality, the histopathological scores also indicated significant increases in brain and intestinal tissue damage in both HIBI and NEC + HIBI rats. Western blotting results suggested that CXCL1 and CXCR2 expression levels were upregulated to varying degrees in the intestinal and brain tissues of NEC, HIBI, and NEC + HIBI neonatal rats compared to that in the normal group. Compared with the HIBI group, the expression of CXCL1 and CXCR2 continued to increase in NEC + HIBI rats at different time points.

Conclusions: CXCL1/CXCR2 may be involved in white matter injury in neonatal rats by delivering intestinal inflammatory mediators through the gut–brain axis.

Highlights

1. Pathologically impaired periventricular white matter was observed in NEC neonatal rats.
2. Hypoxic-ischemic brain injury can also lead to intestinal inflammation.
3. CXCL1 and CXCR2 were significantly upregulated in intestinal and brain tissues in NEC, HIBI, and NEC+HIBI rats compared to the normal group.
4. Compared with the HIBI group, CXCL1 and CXCR2 expression continued to increase in NEC+HIBI rats.

Keywords: White matter injury, Necrotizing enterocolitis, Gut–Brain axis, CXCL1, CXCR2

Background

Statistically, approximately 15 million premature babies are born worldwide each year. With an 11% probability of occurrence, there is an inevitable risk of brain damage in these preterm births, despite breakthroughs in

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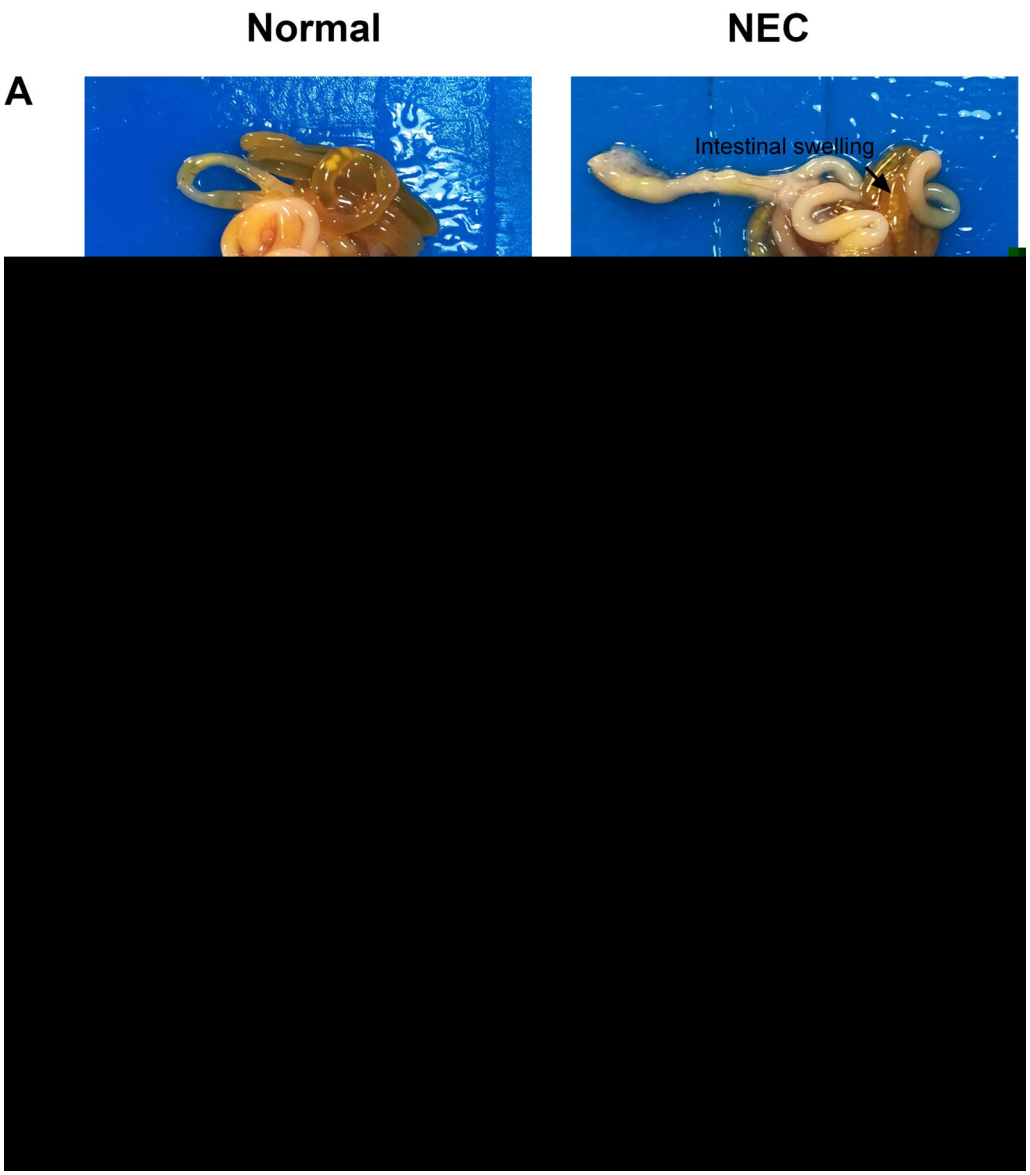

Fig. 1 Pathological intestine and brain changes in NEC neonatal rats 72 h after intragastric administration (3 rats for each group). **A** Pathological intestinal tissue features in the control group and NEC neonatal rats. **B** H&E staining results suggest that NEC neonatal rats displayed pathological intestinal tissue changes, with pathological scores greater than 2, accompanied by inflammatory cell infiltration. **C** Pathological changes in the periventricular white matter of NEC neonatal rats observed using H&E staining. The arrow points at the nerve cells

Table 1 Comparisons of intestinal and brain injury scores between normal and NEC groups

Group	Intestinal injury score	Brain injury score
Normal (n = 3)	0 ± 0	0 ± 0
NEC (n = 3)	2.33 ± 0.58	1.17 ± 0.29
F	16	16
P	0.016*	0.016*

NEC necrotizing enterocolitis

* $P < 0.05$ indicates statistical significance

induction ($P < 0.05$), and CXCR2 expression was significantly upregulated at 72 h (1.80 ± 0.40 vs. 0.88 ± 0.24, $P < 0.05$) in HIBI rats' intestinal tissues compared to the control group (Fig. 4A). Similarly, CXCL1 and CXCR2 expression in the NEC + HIBI group was significantly elevated 12 h after hypoxic–ischemic induction compared to the control groups ($P < 0.05$). Compared with the HIBI group, the relative CXCL1 expression in the NEC + HIBI group increased significantly at 3 (1.82 ± 0.29 vs. 1.16 ± 0.17), 24 (3.17 ± 0.07

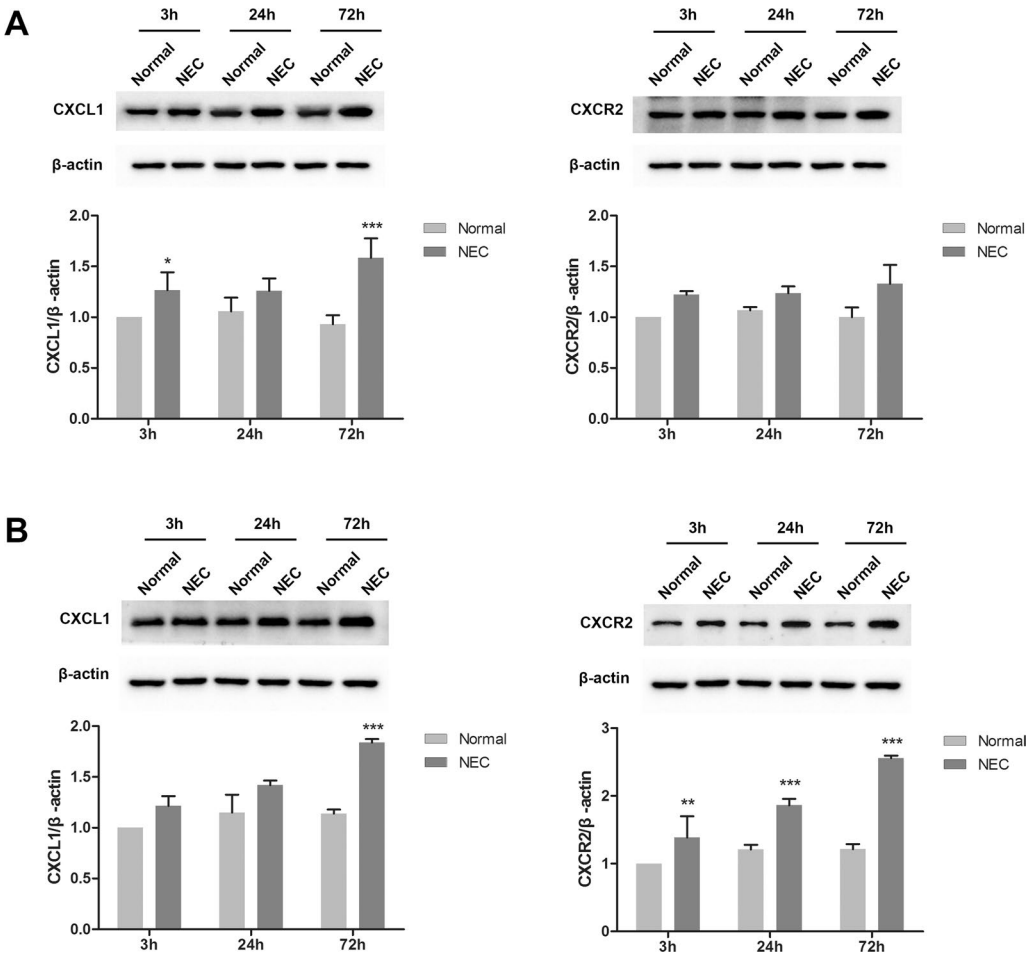

Fig. 2 CXCL1 and CXCR2 expression is upregulated in the intestine (**A**) and brain (**B**) tissues of NEC rats compared with the control group 3, 24, and 72 h after intragastric administration (six rats in each group at each time point). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared with the normal group

vs. 1.97 ± 0.31), and 72 (4.26 ± 0.25 vs. 2.70 ± 0.17) h ($P < 0.01$), while CXCR2 expression was notably upregulated only at 24 h (2.21 ± 0.14 vs. 1.09 ± 0.13, $P < 0.001$). Furthermore, in the brain tissues (Fig. 4B), CXCL1 levels in HIBI neonatal rats increased significantly 12 (3.13 ± 0.54 vs. 0.94 ± 0.14), 24 (4.35 ± 1.14 vs. 1.15 ± 0.39), and 72 (6.43 ± 1.06 vs. 1.01 ± 0.40) h after hypoxic–ischemic induction, and CXCR2 levels increased after 24 (1.63 ± 0.31 vs. 0.94 ± 0.33) and 72 (2.43 ± 0.58 vs. 1.19 ± 0.10) h ($P < 0.05$). CXCL1 and CXCR2 expression levels were also significantly higher in NEC + HIBI rats than in normal rats at all time points ($P < 0.05$). Compared with the HIBI group, CXCL1 expression in the NEC + HIBI group was significantly upregulated at all time points ($P < 0.05$), while that of CXCR2 was significantly increased 3 (1.52 ± 0.17 vs. 1.21 ± 0.10), 12 (2.36 ± 0.34 vs. 1.43 ± 0.24) and 24 (2.30 ± 0.11 vs. 1.63 ± 0.31) h after hypoxic–ischemic induction ($P < 0.05$). These results showed that CXCL1 and CXCR2 expression was upregulated to varying degrees in the intestinal and brain tissues of HIBI and NEC + HIBI neonatal rats, and that they may be involved in white matter injury via the gut-brain axis. Raw data of Fig. 4 including three replications are shown in Additional file 3: Figure S3 and Additional file 4: Figure S4.

Discussion

With histopathological observation and protein level detection, this study observed brain tissue injury and increased CXCL1/CXCR2 expression levels in intestinal and brain tissues of NEC rats. After the successful construction of HIBI model, we found that from

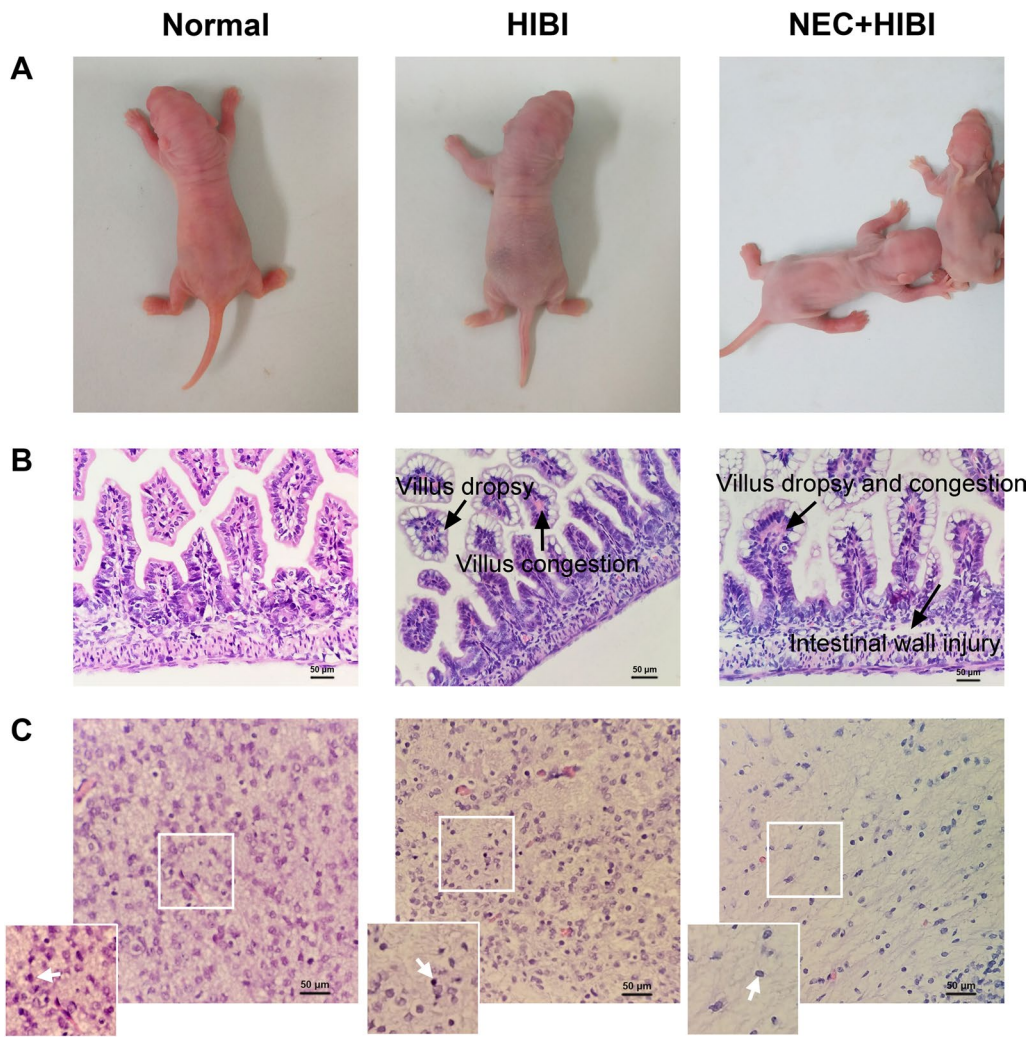

Fig. 3 Pathological intestine and brain tissue changes in HIBI and NEC + HIBI rats. **A** Behavioral manifestations of HIBI (20 rats in total with five deaths) and NEC + HIBI in neonatal rats (23 rats in total with eight deaths) compared to the normal group (17 rats in total with two deaths). (**B**, **C**): Pathological changes in the intestinal (**B**) and brain (**C**) tissues observed under a 400 × microscope 72 h after intragastric administration (3 rats in each group). The arrow points at the nerve cells

Table 2 Comparisons of intestinal and brain injury scores between normal, HIBI, NEC + HIBI groups

Group	Intestinal injury score	Brain injury score
Normal (n = 3)	0 ± 0	0.17 ± 0.29
HIBI (n = 3)	1.17 ± 0.29*	1.17 ± 0.29*
NEC + HIBI (n = 3)	3.33 ± 0.58##	1.83 ± 0.29#
F	61.8	25.33
P	< 0.001	0.001

HIBI hypoxic-ischemic brain injury, *NEC* necrotizing enterocolitis

* Compared with normal; # compared with HIBI

* $P < 0.05$, # $P < 0.05$, ## $P < 0.01$ indicate statistical significances

normal rats to HIBI rats and then to NEC + HIBI rats, the mortality of animals increased, accompanied by worsening brain and intestinal tissue damage, as well as increased CXCL1/CXCR2 expression levels, suggesting the occurrence of inflammation in intestinal and brain tissues.

NEC is a common complication in preterm infants. About 10% of preterm infants develop NEC, of which only 50% survive, and of those who survive, nearly half suffer from long-term neurological sequelae [26]. Biouss et al. experimentally showed that NEC severity in newborn rats is related to brain injury severity [27]. Martin et al. found that 24 month-old preterm infants

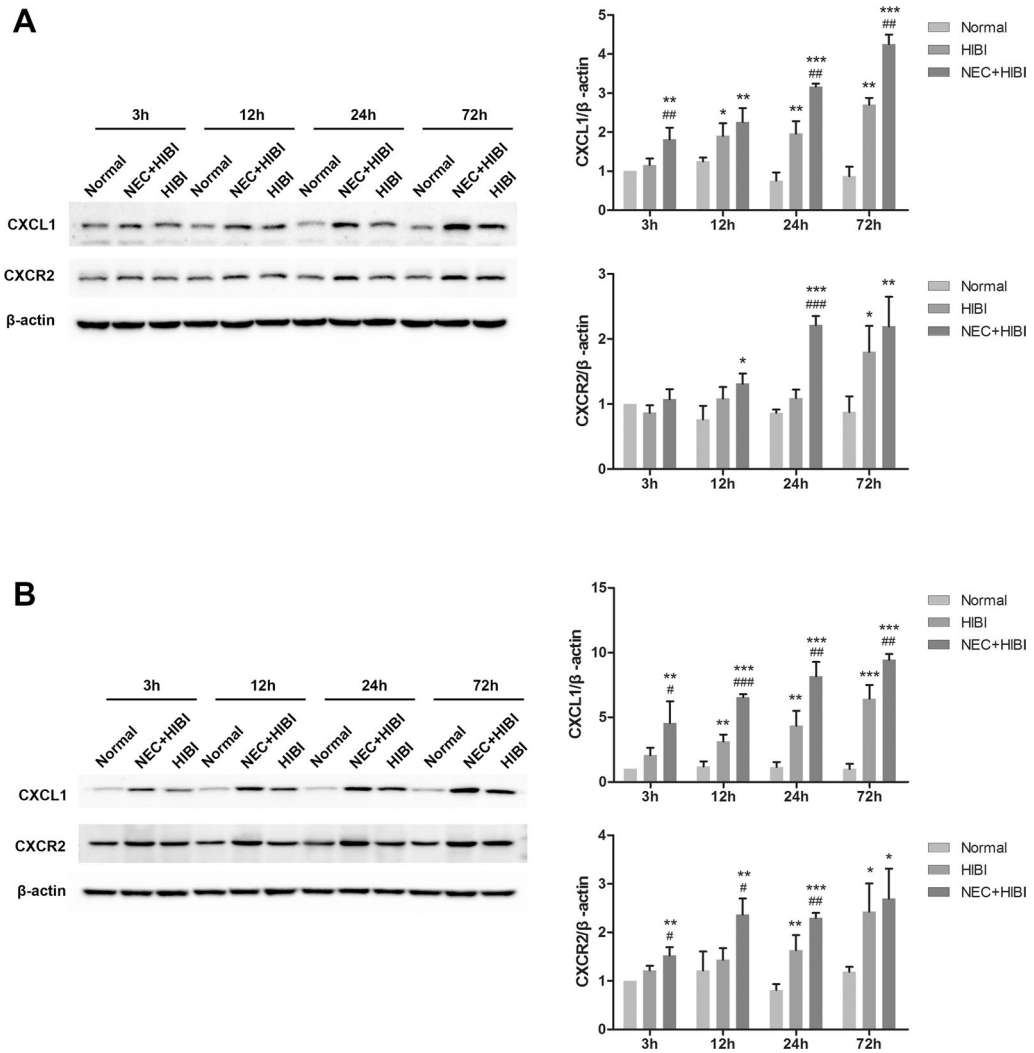

Fig. 4 CXCL1 and CXCR2 expression changes in intestinal (**A**) and brain (**B**) tissues of HIBI and NEC + HIBI neonatal rats (3 rats in each group at each time point of 3, 12, 24 and 72 h). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared with the normal group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ compared with the HIBI group

with a history of NEC had an increased risk of neurodevelopmental dysfunction and microcephaly [28]. The present study also confirmed the increased possibility of periventricular white matter injury and decreased number of glial cells in neonates with NEC. As a potential regulatory mechanism of premature brain injury, the relationship between intestinal and nervous system diseases has been widely discussed in recent years, and the concept of the gut-brain axis has been derived.

The gut-brain axis is a communication system consisting of interactive and bidirectional neural, hormonal, and immune signals between the gut and brain, of which gut microbes are major contributors [29]. Ma et al. found changes in colon morphology and increased intestinal permeability in mice with traumatic brain injury [30]. Metagenomic sequencing has revealed that brain injury can affect the composition of the intestinal flora [31]. Studies have also shown that patients with central nervous system disorders, such as Parkinson's disease, may experience gastrointestinal dysfunction before diagnosis [32]. These studies suggest that brain injury may affect intestinal injury through reverse signal transmission via the gut-brain axis. Our findings confirmed the above viewpoints and found that the intestinal tissues of neonatal rats were also damaged after HIBI. Likewise, intestinal and brain injuries were more severe in NEC + HIBI rats, suggesting that there may be a mechanism of gut–brain axis regulation in neonatal rats with hypoxic-ischemic

brain injury. However, the molecular mechanisms that mediate the gut-brain axis have not been clearly studied. In addition to histopathological assessment, the present study also found increased mortality in HIBI and NEC + HIBI rats, suggesting that intestinal and brain injury may be one of the causes of mortality in neonatal rats. This finding is consistent with the conclusions of many studies based on humans. It is known that HIBI is a significant cause of mortality in the adults as well as in the neonates [33]. The mortality rate among neonates with severe NEC requiring surgery is estimated at 20–30% [34]. These studies further confirmed that we have been relatively successful in mimicking the disease environment of human NEC and HIBI in neonatal SD rats. However, the mortality of NEC combined with HIBI in neonates is not clear, and it was only reported that NEC occurs in 40% of hypoxic–ischemic neonates [35]. The results of this study suggested that the risk of death was about 1.4 times higher in NEC + HIBI rats than in HIBI rats, but epidemiological studies with a larger sample size based on human demographic statistics are still necessary to confirm the extrapolation of our results.

The gut is an important immune organ in the human body; gut epithelial cells, immune cells, and microorganisms maintain intestinal immune homeostasis through cytokine interaction [31]. When the intestinal immune system is imbalanced, pro-inflammatory cytokines may participate in brain inflammation through the gut-brain axis, thereby leading to brain damage [36]. CXCL1 is a pro-inflammatory chemokine that mediates immune cell migration after binding to CXCR2 and participates in biological effects, such as inflammation and immune responses. Previous reports have found that NEC disrupts intestinal immune homeostasis and increases CXCL1 expression in pathological intestinal tissue [37]. Meanwhile, CXCL1 induces peripheral neutrophil migration to the central nervous system by binding to CXCR2 [38]. Our study found that CXCL1 and CXCR2 expression was upregulated to varying degrees in the brain and intestinal tissues of NEC, HIBI, and NEC + HIBI neonatal rats, suggesting that CXCL1/CXCR2 may affect brain injury by delivering intestinal inflammatory mediators through the gut-brain axis. An intestinal flora-based study can explain our findings and indicate that changes in intestinal flora can induce NEC, allowing intestinal pro-inflammatory cytokines to penetrate the intestinal and blood–brain barriers, leading to systemic inflammatory responses and inflammatory brain injury [36]. Activated intestinal immune cells can also migrate to the site of brain injury and secrete pro-inflammatory cytokines to participate in the inflammatory response and aggravate brain injury [39]. Combined with our results, we conclude that intestinal immunity, inflammatory responses, and brain injury are interrelated, and that CXCL1/CXCR2 may play an important role in inflammatory transmission. These findings also give us some hints that the development of CXCL1 and CXCR2 inhibitors based on gut microbiota is expected to alleviate NEC symptoms, and reduce the risk of HIBI complication in infants with NEC, by blocking inflammatory mediators and inhibiting the migration of peripheral neutrophils to the central nervous system, but human-based in vitro and in vivo experiments are still urgently needed.

There are a few limitations associated with our study. First, the animal gender was not recorded in this study, resulting in the fact that the effect of sex variables on the results could not be assessed. Second, we could not analyze CXCL1 and CXCR2 expression in intestinal and brain tissues at the transcriptional level—doing so could have improved our study overall. Finally, the current study lacks an understanding of the immune response mechanisms involved in the CXCL1/CXCR2 pathway. In a follow-up study, we will conduct a blocking experiment on CXCR2, detect peripheral and central immune cell enrichment, and identify glial cell activation in rats to further explore CXCL1 regulatory mechanisms in the gut–brain axis.

Conclusions

Through the construction of animal models, white matter injury was found in NEC rats, while intestinal inflammation was observed in HIBI rats, potentiating a bidirectional regulation mechanism of the gut–brain axis in intestinal and brain injuries. Furthermore, upregulation of CXCL1 and CXCR2 expression was detected in the intestinal and brain tissues of NEC, HIBI, and NEC + HIBI neonates, further indicating that CXCL1/CXCR2 may transmit inflammatory mediators through the gut-brain axis to influence brain injury.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12868-022-00749-1.

Additional file 1: Figure S1. WB raw data of Figure 2A.

Additional file 2: Figure S2. WB raw data of Figure 2B.

Additional file 3: Figure S3. WB raw data of Figure 4A.

Additional file 4: Figure S4. WB raw data of Figure 4B.

Additional file 5: Table S1. Pathological scoring criteria for intestinal tissue injury. **Table S2** Pathological scoring criteria for brain tissue injury.

Acknowledgements
Not applicable.

Author contributions
JZ and CY designed the research and drafted the manuscript. ZF and LH acquired data and analyzed data. LY, HD and L D acquired data and performed statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article (and its Additional files). The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The animal use protocol listed below has been reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of North Shichuan Medical College (Approval No. AEWC-2020ER038-3). All methods were carried out in accordance with relevant guidelines and regulations. The study was carried out in compliance with the ARRIVE guidelines. Consent to participate as Not Applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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