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The Neuroprotective Role of Lipoxin A4 in Reinstating Blood Brain Barrier Integrity in Neuroinflammatory Disease Processes

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Abstract

Background: The blood-brain barrier (**BBB**), formed by the vascular endothelium, astrocytic foot processes, pericytes, is a highly selective barrier that is responsible for maintaining brain homeostasis and ultimately proper neuronal function. Disruption of the BBB, leading to increased BBB permeability, has been reported in several neurodegenerative diseases, including Alzheimer's disease (**AD**) and traumatic brain injury (**TBI**).[1] Loss of BBB integrity leads to the proliferation of pro-inflammatory cytokines, including TNFα, IL-1β, and IL-6.[2] Moderate inflammation has a beneficial response in the system following an acute injury. However, prolonged inflammation has been known to perturb homeostasis and have devastating neurodegenerative effects.[4-7] Therefore, anti-inflammatory compounds are extensively tested for their potential therapeutic role in lowering these inflammatory changes. Lipoxins (**LXs**) are a class of arachidonate-derived eicosanoids, which are a class of specialized pro-resolving lipid mediators (**SPMs**).[8] Hence, lipoxins are recognized as "breaking signals" in the inflammatory process. One form of lipoxin, Lipoxin A4 (**LXA4**), has been found to decreased production of proinflammatory mediators, inhibit neutrophils chemotaxis and infiltration to the site of injury, and promote the phagocytic clearance of debris by macrophages.[4,12,13,14] This literature review aims at understanding the neuroprotective role of LXA4 in reducing BBB breakdown and reinstating BBB integrity.

Hypothesis: LXA4 treatment attenuates acute inflammation and reinstates the BBB integrity in acute BBB breakdown and inflammation.

Methods: A comprehensive literature search was performed using PubMed and EMBASE databases.

Conclusion: LXA4 serves a critical role in resolution of inflammatory process by regulating the activation of monocytes and modulating the generation of reactive oxygen species (**ROS**). LXA4 treatment has shown to reinstate the BBB integrity in acute BBB breakdown models.

Acknowledgement and References

- We acknowledge the contribution of Medical Scholarship team in knowledge as well as in support in creating this poster.

Background

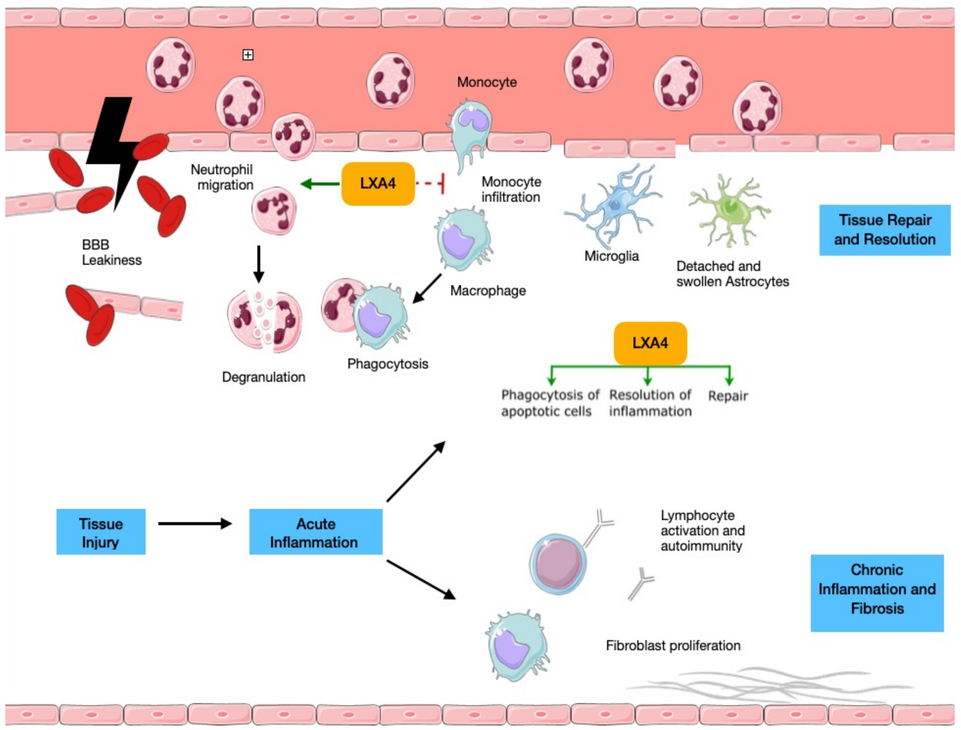

Fig 1. Potential mechanism of LXA4 in the resolution of inflammation. The schema was adapted from Fu et al. (2020) and Jaén et al. (2021). The schema was created by Minjal Patel using images provided by Servier Medical Art (https://smart.servier.com/image-set-download/), licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licences/by/3.0/).

Methods

Study Strategy

Database Searched	Date of Search	Key Word String	Number of Results
PubMed	07/05/23	blood brain barrier integrity	5252
	07/05/23	lipoxin a4 AND blood brain barrier	14
	07/05/23	lipoxin a4 neuroprotective role	13
	07/05/23	blood brain barrier integrity AND lipoxin A4	3
	07/05/23	lipoxin a4 AND reinstating blood brain barrier	0
EMBASE	07/05/23	lipoxin A4 AND neuroprotective role	16

Study Selection: A varied selection of primary resources where researchers developed an *in vitro* and *in vivo* model of the blood brain barrier leak were evaluated during this study. These articles also focused on determining the role of LXA4 in mitigating neuroinflammation through various biomarkers. In particular, there was a focus on surface endothelial markers (GFAP) and pro-inflammatory markers (TNFα, IL-1β, IL-6). Peer-reviewed systematic reviews were also used to gain a broad perspective of the current research on the topic, with particular emphasis on more recent trends, with a focus on findings published between 2000 and 2023.

Data Analyses: This study did not involve further analysis of the findings. The studies included in this literature review utilized immunohistochemistry (**IHC**), **Western blot, qt-RT PCR** and **ELISA** experiments to measure the effects of LXA treatment on hippocampal tissue samples exposed to acute injury.
Data Analyses in Citations: The studies then analyzed the data using one-way analysis of variance (**ANOVA**) to determine the statistical significance of these changes.[3, 15-19]

Results

LXA4 Attenuates Inflammation

- LXA4 has been shown to downregulate the mRNA and protein expression of pro-inflammatory cytokine markers (TNFα, IL-1β, IL-6) and increases secretion of anti-inflammatory cytokine markers (IL-10).[14-17]
- It has shown to attenuate TBI-induced damage through Evans blue (EB) extravasation in mice models.[17]
- Aspirin-triggered LXA4 exhibited significant decrease in GFAP positive astrocytes as well as CD11b, CD45 and Iba1 positive microglia immunoreactivity.[3]
- LXA4 diminished the inflammation caused by LPS injection.[15,16]

LXA4 Upregulates LXA4 Receptor (ALXR)

- When immunostaining for ALXR, there was significantly greater colocalization with GFAP 24 hours post-TBI injury.[17]
- Luo et al. found increased immunoreactivity when staining for the LXA4 receptor through various brain layers, including the injured cortex, compared to the control group.[17]
- ALXR upregulation was also triggered by the reperfusion of the cerebral cortex in neonatal rat astrocytes exposed to a protocol for ischemic injury.[18]
- Futokoro et al. found an upregulation of LXA4 receptor in the brain of mice 24 hours after an ICH injury when compared with the control group.[19]

LXA4 Reinstates BBB Integrity

- LXA4 treatment has shown to significantly inhibit neutrophil infiltration, in male Sprague-Dawley rats 24 hours post-SAH when compared to the vehicle group using the neutrophil marker (MPO).[15]
- ICH induction significantly increased expression of TNFα mRNA at 72 hours after insult. BML-111 significantly suppressed the increase in TNFα mRNA.[19]

Conclusions and Future Directions

- LXs present with therapeutic potential for neurodegenerative diseases due to their pro-resolving properties. There needs to be further research on the pharmacodynamics and drug delivery of LXs.
- While they have shown promise with smaller administrations in animal models, there is limited understanding of its delivery. As an endogenous SPM, the short half, life and rapid inactivation limit the development of this drug.[4,5]