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THE FEBRILE RESPONSE TO INFECTIOUS MICROORGANISMS AND NEUROLOGICAL DISORDERS

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ABSTRACT

Interleukin-1 (IL-1) is a potent pro-inflammatory cytokine which mediates cells, and organ and tissue dysfunctions. IL-1 is generated and released during infection by microorganisms, causing fever and neurological disorders. Here we report that there is a relation between the fever induced by IL-1 after infection and brain disease.

KEYWORDS: *IL-1; febrile response; fever; infection; neurological disorders; brain*

INTRODUCTION

Microbial infections can be located ubiquitously in all body tissues and are life-threatening. They cause acute-phase defensive responses that can affect homeostatic, metabolic, and immunological processes (1). Microorganisms such as bacteria are a common cause of infections that can affect all or parts of the body. The bacteria can affect the lungs, for example, in respiratory disease, but infections outside the lungs can also be present. The central nervous system (CNS) and one site may be involved with fever and systemic inflammation (2). It is known that the hypothalamus in the brain mediates the febrile phenomenon and is involved in host defense by modulating the immune system (3). Therefore, host immunity against pathogenic infections causes neuroinflammatory responses and can give rise to feverish phenomena.

Interleukin-1 induces fever and affects the CNS

Interleukin-1 (IL-1) is a very important inflammatory cytokine that mediates the acute response after microbial invasion, with biological effects on all organs and tissues (4). It is mainly responsible for fever and is mostly synthesized by macrophage cells stimulated by microorganisms and parts of them (5). IL-1 affects RNA transcription and acute phase protein synthesis by inducing C-reactive protein, serum amyloid A (SAA), complement components, and other inflammatory mediators, with decreased albumin (6). IL-1 stimulates endothelial cells in the brain, promoting angiogenesis and microorganisms cause these cells to release IL-1 and mediate inflammation (7). IL-1 produced by endothelial cells causes various pathological effects including vasculitis. Furthermore, IL-1 activates the endothelial cells

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to produce adhesion molecules, prostaglandin PGE2, and prostacyclin PGI2, the latter both involved in vasodilation and favoring edema and leakage of blood cells from the vessels (8).

IL-1 also affects fibroblasts where it stimulates mitosis and the production of PGE2 and granulocyte-monocyte colony-stimulating factor (GM-CSF), mediating fibrosis (9). IL-1 induces fever in rodents that is similar to bacterial endotoxin, with increases in adrenocorticotropic Hormone (ACTH) and various acute phase proteins with decreases in neutrophil counts and many other biological effects (5). IL-1 also acts on the mesangial cells of the kidney and on the glial cells which, together with the neurons, make up the nervous system (10).

IL-1 induces fever by involving the hypothalamus, where the body's temperature regulation center resides, and where pro-inflammatory cytokines, such as IL-1, are released (11). There are many cytokines that act at the hypothalamic level as an endogenous pyrogen, for example IL-1a, IL-b, tumor necrosis factor (TNF), Interferon-α, Interferon-β, Interferon-γ and others, although the exact mechanism of action has not yet been clarified (12).

Microbes and their products, such as endotoxin, and IL-1 induce fever with activation of hypothalamic endothelial cells and PGE2 synthesis (8). The release of neurotransmitters activates the cerebral vasomotor center, generating vasoconstriction which retains heat with an increase in the febrile temperature (13). Microorganisms cause brain infection by activating glial and neuronal cells with the production of pro-inflammatory cytokines, including IL-1, IL-6, and TNF, that produce fever when injected intravenously or into the third ventricle in rats (14). At the therapeutic level, blocking IL-1 with IL-1 receptor antagonist (IL-1Ra) or IL-37 is known to reduce fever (15) and since IL-1 induces PGE2, non-steroidal anti-inflammatory drugs blocking cyclooxygenase-2 inhibit fever (16). Therefore, IL-1 is a major pro-inflammatory molecule and is related to TNF, which has different receptors than IL-1. It is expressed by almost all human cells and organs, in the brain, and physiologically participates in the regulation of cell growth and reparative processes. This cytokine mediates a large number of pathological effects, including inflammation of organs and tissues, and plays a crucial role in the pathogenesis of disease (17). In fact, blocking this cytokine improves the pathological state of disease (18).

CONCLUSION

In the last twenty years, new members of the cytokine family have been discovered and the IL-1 genes have been found to be located on chromosome-2 (19). In the CNS, IL-1 is produced by both immune cells and non-immunocompetent cells (20). The synthesis of IL-1 in the brain leads to a series of pathology with inflammation and neurological defects. IL-1 produced by microorganisms after an infection reaches the brain through disruption or impaired permeability of the blood brain barrier (BBB). IL-1 passes the BBB through the alteration of endothelial cells and can be generated or reach the CNS via the vagus nerve, other nerve fibers, or via microglia which produce it locally upon activation. In the acute phase of ischemic stroke with cerebral hemorrhage, there is strong IL-6-mediated inflammation that can be reduced with the IL-1Ra, since IL-1 induces IL-6. In fact, stroke severity correlates with high IL-1 levels.

These results demonstrate a close relation between IL-1 secreted during microorganism infection, the brain and brain disease, stroke, and fever.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Rankin L, Artis D. Beyond Host Defense: Emerging Functions of the Immune System in Regulating Complex Tissue Physiology. *Cell*. 2018;173(3):554-567. doi:10.1016/j.cell.2018.03.013
2. Dinarello CA, Cannon JG, Wolff SM. New Concepts on the Pathogenesis of Fever. *Clinical Infectious Diseases*. 1988;10(1):168-189. doi:10.1093/clinids/10.1.168
3. Boisse L. Long-Term Alterations in Neuroimmune Responses after Neonatal Exposure to Lipopolysaccharide. *Journal of Neuroscience*. 2004;24(21):4928-4934. doi:10.1523/jneurosci.1077-04.2004
4. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews*. 2017;281(1):8-27. doi:10.1111/imr.12621
5. Dinarello CA. Infection, fever, and exogenous and endogenous pyrogens: some concepts have changed. *Journal of Endotoxin Research*. 2004;10(4):201-222. doi:10.1179/096805104225006129

6. Bauer J, Lengyel G, Thung SN, Jonas U, Gerok W, Acs G. Human fetal hepatocytes respond to inflammatory mediators and excrete bile. *Hepatology*. 1991;13(6):1131-1141. doi:10.1002/hep.1840130621
7. Salmeron K, Aihara T, Redondo-Castro E, Pinteaux E, Bix G. IL-1alpha induces angiogenesis in brain endothelial cellsin vitro: implications for brain angiogenesis after acute injury. *Journal of Neurochemistry*. 2015;136(3):573-580. doi:10.1111/jnc.13422
8. El-Radhi AS. Pathogenesis of Fever. *Clinical Manual of Fever in Children*. Published online January 2, 2019:53-68. doi:10.1007/978-3-319-92336-9_3
9. Zucali JR, Dinarello CA, Oblon DJ, Gross MA, Anderson L, Weiner RS. Interleukin 1 stimulates fibroblasts to produce granulocyte-macrophage colony-stimulating activity and prostaglandin E2. *Journal of Clinical Investigation*. 1986;77(6):1857-1863. doi:10.1172/jci112512
10. Sedor JR, Nakazato Y, Konieczkowski M. Interleukin-1 and the mesangial cell. *Kidney International*. 1992;41(3):595-599. doi:10.1038/ki.1992.89
11. Conti B, Tabarean I, Andrei C, Bartfai T. Cytokines and fever. *Frontiers in Bioscience: A Journal and Virtual Library*. 2004;9:1433-1449. doi:10.2741/1341
12. Luheshi GN. Cytokines and fever. Mechanisms and sites of action. *Annals of the New York Academy of Sciences*. 1998;856:83-89. doi:10.1111/j.1749-6632.1998.tb08316.x
13. Tan CL, Knight ZA. Regulation of Body Temperature by the Nervous System. *Neuron*. 2018;98(1):31-48. doi:10.1016/j.neuron.2018.02.022
14. Leon LR. Invited Review: Cytokine regulation of fever: studies using gene knockout mice. *Journal of Applied Physiology*. 2002;92(6):2648-2655. doi:10.1152/japplphysiol.01005.2001
15. Cartmell T, Luheshi GN, Hopkins SJ, Rothwell NJ, Poole S. Role of endogenous interleukin-1 receptor antagonist in regulating fever induced by localised inflammation in the rat. *The Journal of Physiology*. 2001;531(Pt 1):171-180. doi:10.1111/j.1469-7793.2001.0171j.x
16. Simmons DL, Wagner D, Westover K. Nonsteroidal anti-inflammatory drugs, acetaminophen, cyclooxygenase 2, and fever. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2000;31 Suppl 5:S211-218. doi:10.1086/317517
17. van de Veerdonk FL, de Graaf DM, Joosten LA, Dinarello CA. Biology of IL-38 and its role in disease. *Immunological Reviews*. 2017;281(1):191-196. doi:10.1111/imr.12612
18. Dinarello CA, Simon A, van der Meer JWM. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nature Reviews Drug Discovery*. 2012;11(8):633-652. doi:10.1038/nrd3800
19. Bensen JT, Dawson PA, Mychaleckyj JC, Bowden DW. Identification of a Novel Human Cytokine Gene in the Interleukin Gene Cluster on Chromosome 2q12-14. *Journal of Interferon & Cytokine Research*. 2001;21(11):899-904. doi:10.1089/107999001753289505
20. Roerink ME, van der Schaaf ME, Dinarello CA, Knoop H, van der Meer JWM. Interleukin-1 as a mediator of fatigue in disease: a narrative review. *Journal of Neuroinflammation*. 2017;14(1). doi:10.1186/s12974-017-0796-7