Control of Inflammatory Responses: 
a New Paradigm for the Treatment of 
Chronic Neuronal Diseases

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INTRODUCTION

Inflammatory responses are defense mechanisms that protect 
the human body from microbial infection or external damage.

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The Roman physician, Celsius, is credited with providing the first 
record of the fundamental symptoms of inflammation, which are 
still recognized in modern textbooks. With recent advances in 
immunology, inflammatory responses are receiving new attention 
because of their involvement in the link between innate immunity 
and disease. Stepping forward from classical concepts of the 
immune response (i.e. the concept of self or non-self), scientists 
have accepted that immune responses are induced by danger 
or damage. Although autoimmune diseases cannot be easily 
explained by the concept of self or non-self, they can be explained 
by the danger theory of inflammatory response. This theory could 
also be applied to understanding the inflammatory responses

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in the brain, where external intrusions are rare but immune/inflammatory responses occur, sometimes to a pathogenic degree (i.e. in degenerative brain disease). Neuroglial cells, including astrocytes and microglia, are the primary tissue-resident cells responsible for immune/inflammatory responses in the brain. If such responses are improperly regulated or terminated, nerve cell dysfunction can occur as a pathophysiology of brain disease. In this review, we outline a possible approach for targeting inflammatory responses in an effort to treat chronic inflammatory brain diseases.

**ENDOGENOUS INFLAMMATORY STIMULATORS IN THE BRAIN**

Researchers studying inflammatory/immune processes in the brain must often refer to work done on peripheral inflammatory responses. Because the endogenous stimulators of inflammatory/immune responses in the brain have not yet been clarified, researchers working with glial cells have looked to studies done in peripheral macrophages. To activate neuroglial cells, these researchers have used lipopolysaccharide (LPS) and zymosan (components of the bacterial cell wall and fungal cell membrane, respectively) or inflammatory cytokines, including tumor necrosis factor (TNF)-α and interferon (IFN)-γ (well-known activators of peripheral macrophages) [1-3]. However, LPS and zymosan rarely occur in the brain, making this model unsuitable for the study of brain pathophysiology. Therefore, researchers have sought to identify endogenous substances that may be used as a model for brain disorders (Fig. 1). Two membrane components that are released from damaged nerve cells, gangliosides [4] and chromogranin [5], have been reported to cause inflammation and are currently being investigated as endogenous activating materials. Many reports have shown the presence of long-term blood-brain barrier leakage in degenerative brain disease [6,7]. Based on these reports, researchers have hypothesized that components in the blood could intrude into the brain parenchyma and cause inflammation in the brain. Efforts to identify inducers of neuroglial activation among blood components found that thrombin [8], prothrombin [9], plasminogen [10], and tissue plasminogen activator [11] can all activate neuroglial cells. Aggregations of proteins (e.g. prions, amyloid-β and α-synuclein), which are thought to be a common feature in Alzheimer’s and Parkinson’s diseases (two typical degenerative brain diseases), have been identified as the main neuroglial cell-activating substances [12,13]. In addition, intermittent hypoxia occurred in the brain is accompanied by oxidative stress and low-grade chronic inflammation, resulting in neurological deficits and disorders such as Alzheimer’s and Parkinson’s diseases [14,15]. These recent studies have shown that inducers trigger inflammatory responses that can act as a major progression factor for (if not a direct cause of) degenerative diseases. Thus, it seems reasonable to speculate

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**Fig. 1.** Endogenous inflammatory mediators in the brain. Brain inflammation can be caused by: aggregated proteins, such as prions, amyloid-β and α-synuclein; cell membrane components, including gangliosides and chromogranin (which are released from damaged nerve cells); and blood components, such as thrombin, prothrombin, plasminogen and tissue plasminogen activator (which can leak through a rupture of the blood brain barrier). In addition, oxidative stress due to intermittent hypoxia is accompanied by chronic inflammation.
that the regulation of inflammatory responses could prevent or slow disease progression.

INFLAMMATORY SIGNALING IN THE BRAIN

Given that the endogenous stimulators of brain glial cells appear to trigger inflammation, we might next question which signaling pathways are activated by endogenous inflammatory stimulators in the brain. Studies on the inflammatory signals in the brain have also drawn from work done in peripheral inflammatory cells. For example, nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), two typical inflammatory signals, are reportedly activated in neuroglial cells by substances such as LPS [2,13]. Moreover, endogenous stimulators, such as gangliosides [4] and thrombin [8], appear to cause inflammatory responses via NF-κB and MAPKs. Researchers are currently seeking to identify new inflammatory signaling molecules and pathways in the brain, in efforts to construct an activator- and cell type-specific roadmap. Because the inflammatory signals are believed to have both shared and unique pathways according to the stimulus and/or tissue, researchers expect that a synergistic effect will be obtained by controlling the inflammatory signals or modulating their interactions.

JAK-STAT as an anti-inflammatory target

We identified Janus kinase-signal transducer and activators of transcription (JAK-STAT) as a new inflammatory signal in the brain and showed that its inflammatory signal can be activated by LPS, IFN-γ, gangliosides and thrombin [4,16]. The receptor activated by these ligands or cytokines phosphorylates JAKs, leading to the phosphorylation (i.e. activation) of STAT molecules. Activated STATs form dimers and translocate to the nucleus, where they act as transcription factors; they induce the expression of inflammatory genes that have STAT-binding sites in their promoter regions, thereby activating subsequent inflammatory responses (Fig. 2) [17]. Based on the role of JAK-STAT signaling in brain inflammation, we screened anti-inflammatory substances to see if they could inhibit the JAK-STAT pathways, and if so, whether we could determine the underlying mechanism and identify a novel anti-inflammatory target. We found that curcumin (which is a main ingredient of curries and has anti-inflammatory and anticancer effects), rosiglitazone (an agonist for peroxisome proliferator-activated receptor γ; PPARγ) and 15-deoxy-delta12,14-prostaglandin J₂ (15d-PGJ₂, an anti-inflammatory prostaglandin) limit inflammation by inhibiting STAT signaling [18-20]. Because the JAK-STAT pathways mediate the actions of numerous growth factors and cytokines in vivo, their negative feedback pathways are well developed and tightly regulated. The endogenous negative feedback molecules include phosphatases and inhibitory proteins, such as the suppressor of cytokine signaling (SOCS) proteins. Curcumin activates SH2-containing phosphatase 2 (SHP2) [18], while rosiglitazone and 15d-PGJ₂...
increase the expression levels of SOCS1 and SOCS3 [19]. SHP2 and SOCS proteins are typical negative feedback molecules of the JAK-STAT pathway. Because the individual SOCS family proteins regulate different molecules of the JAK-STAT signaling pathways, we could possibly use them to specifically or synergistically control different JAK-STAT pathways. Indeed, the anti-inflammatory properties of many clinically available drugs, including aspirin, are mediated via SOCS proteins [20]. Thus, it is particularly interesting to consider the development of additional SOCS-targeting drugs.

**Nuclear receptors as anti-inflammatory targets**

Steroids are representative anti-inflammatory drugs that act specifically through glucocorticoid receptors (GRs). Despite the development of many new drugs, steroids are still broadly used to treat intractable diseases and pathological states, including inflammation, autoimmune disorders, and cancers. Although steroids have demonstrated remarkable clinical efficacy, the exact mechanisms underlying such effects have only recently been unveiled. GR is a prototype ligand-activated transcription factor that belongs to the nuclear receptor (NR) family and regulates gene expression by either transcriptional activation [21] or transcriptional repression (transrepression) [22]. In polysaccharide and lipid metabolism, steroid-activated GR forms a dimer, migrates into the nucleus and binds glucocorticoid response elements (GREs) to induce target gene transcription [23]. However, GREs are absent from the promoter regions of most inflammatory genes [24], meaning that glucocorticoid-mediated anti-inflammation acts indirectly. Indeed, the anti-inflammatory mechanism of steroids was found to act via transrepression, with ligand-activated GR indirectly suppressing the activity of inflammation-related transcription factors by inhibiting the binding of co-activators that promote transcription or by recruiting co-repressors to inhibit transcription [25].

NRs other than GR also exert anti-inflammatory effects via transrepression. PPARα and PPARγ, which are two typical NRs involved in lipid metabolism and adipocyte differentiation, are known to have anti-inflammatory actions [26,27]. An anti-inflammatory effect has been reported for liver X receptor (LXR). Our group and other researchers showed that these NRs could exert anti-inflammatory effects in the central nervous system and peripheral inflammatory cells [1,28]. Moreover, post-translational modifications of NRs contribute to this process, leading to stimulus- and/or tissue-specific regulation of the inflammatory response. We reported that oxysterols suppress IFN-γ-induced inflammatory responses via LXR in astrocytes (Fig. 3) [1]. Because most of the inflammatory mediators and cytokines that are activated by IFN-γ do not have LXR binding sites within their promoters, the inhibitory action of LXR results (as in the case of GR) from indirect action. Although we showed that SUMOylation of LXR plays a decisive role in tethering STAT1 to LXR [1], the details of the underlying mechanism are still unknown. One possibility is mediation by (i.e. interaction with) another NR. We are presently investigating whether the orphan nuclear receptor, short heterodimer partner (SHP), is involved in the LXR-dependent inhibition of STAT1 transcriptional activity. SHP lacks the conserved DNA binding domain common to other NRs [29], suggesting that it may function by binding to other NRs. Our preliminary results show that SHP appears to mediate LXR-dependent STAT1 inhibition (unpublished data).

**Post-transcriptional regulation as an anti-inflammatory target**

The anti-inflammatory chemicals and drugs described above inhibit inflammatory signaling pathways or suppress the expression of inflammation mediator-encoding genes via transrepression. When tissues are damaged or infected by microbes, however, inflammatory mediators and cytokines should be released quickly and at high levels, requiring more efficient regulatory routes, such as through post-transcriptional alterations in their RNA levels [30]. Many transcripts encoding pro-inflammatory cytokines and chemokines are present in an unstable state, undergoing rapid degradation due to the presence of AU-rich elements (AREs) in their 3′-untranslated regions (3′-UTRs). The typical inflammatory genes that undergo regulation at the post-transcriptional step include cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1) and IFN-γ. Various RNA-binding proteins and microRNAs play important roles in the post-transcriptional regulation of mRNA maturation, degradation, and translation. Thus, these regulatory elements to control RNA quality and quantity may also be viable targets for anti-inflammatory drugs. As researchers continue to study RNA metabolism and uncover the detailed mechanisms underlying the creation and destruction of RNA, other new potential anti-inflammatory drug targets may be identified. Indeed, our group has shown that 5,8,11,14-eicosatetraynoic acid (ETY A) [27], 15d-PGJ$_2$ [31,32] and 22(R)-hydroxycholesterol (22R-HC) (unpublished data) suppress inflammation by altering the expression of MAK phosphatase-1 (MKP-1), which dephosphorylates and inactivates Jun N-terminal kinase (JNK) (Fig. 4). These drugs increase the stability of the MKP-1 transcript in an HuR-dependent manner, thereby increasing the protein expression of MKP-1. Interestingly, the mechanism through which MKP-1 expression is regulated differs by drug: in contrast to ETYA and 15d-PGJ$_2$, dexamethasone (a synthetic glucocorticoid) increases MKP-1 expression by blocking
Control of Brain Inflammatory Responses

**TISSUE- AND INDUCER-SPECIFIC CONTROL OF INFLAMMATION VIA NRS**

Inflammation takes place in almost every tissue, and is designed to protect the body from microbial infection or external damage. To make use of it for therapeutic purposes while minimizing unwanted side effects, we need to uncover the exact control mechanisms. For example, clinically available COX-2 inhibitors utilize the difference between COX isotypes to reduce the side effects on the gastrointestinal system, selectively inhibiting COX-2 while having less effect on COX-1 [34]. Most NRs are important transcription factors involved in metabolism, so any strategy to target them with anti-inflammatory drugs must preserve their effects on metabolism. For example, estrogen receptor inhibitors, which are used to treat breast cancer, were developed based on tissue-specific differences in estrogen receptor complex formation [35]. These inhibitors selectively block the estrogen receptor in the mammary gland while having no effect on bone metabolism and minimizing adverse effects in tissues other than the mammary gland. The development of anti-inflammatory drugs targeting other NRs should take advantage of similar selectivity when possible. For example, the distribution of LXR isotypes differs between tissues: LXRβ is ubiquitously expressed at low levels in almost all tissues, while LXRα is abundantly expressed in tissues involved in lipid metabolism and transport (e.g., liver, intestine, lungs, and adrenal glands) [36,37]. Both LXR isoforms are expressed at significant levels in various regions of brain, with the level of LXRβ about 2- to 5-fold higher than that of LXRα [38]. Thus, differences in tissue distribution could be used for tissue-specific control in the therapeutic context. Similarly, tissue- and stimulus-specific differences in the compositions of NR complexes, which can determine the differential expression of target genes [39], could confer therapeutically relevant control. Finally, selective control could potentially be achieved through

Fig. 3. Schematic of the anti-inflammatory mechanisms of LXR ligands in IFN-γ-stimulated astrocytes (18). IFN-γ triggers an early response in which STAT1 is phosphorylated and translocated to the nucleus, thereby inducing inflammatory gene expression. Synthetic and oxysterol derivatives of LXR ligands trigger the formation of PIAS1 (or HDAC4)·pSTAT1·LXR β (or LXR α) trimers, a process mediated by the differential conjugation of SUMO (Su) to individual LXRs. This blocks the binding of STAT1 to the promoters of its target genes.
alterations in the tissue-, stimulus- and target-gene-specific post-translational regulation (e.g. SUMOylation and glycosylation [1,40]) of various signaling pathway components.

CONCLUSION

Despite years of research, inflammatory responses and the mechanisms underlying the actions of anti-inflammatory drugs remain to be clarified. Current studies in the field of immunology are expected to provide new insights into inflammation responses, inflammation-regulating drugs, and the relevant control mechanisms. Some antibodies and drugs used in clinical practice are capable of directly targeting specific signaling molecules/receptors. In the case of anti-inflammatory drugs, however, most such specific targeting therapeutics have been used only casually or experimentally. Detailed information is now being obtained regarding the pharmacological actions of typical non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and steroids. If we hope to effectively regulate inflammation for the treatment of diseases, the mechanism(s) responsible for controlling the inflammatory response need to be firmly established. We should also seek to better understand the cause-and-effect relationships between inflammatory responses and the pathogenesis/progression of related human diseases. Here, we reviewed the tissue- and stimulus-specific mechanisms believed to regulate inflammation, and discussed the need for new insights into their cause-and-effect relationships in the context of disease. Given that inflammatory/immune responses are physiological phenomena that can provide protection or cause damage, their therapeutic modulation must be precisely controlled in quantitative, qualitative and temporal terms. Improper control could compound the disease processes or cause a new disease. Thus, additional research is warranted to improve our understanding of the inflammatory response.

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REFERENCES

1. Lee JH, Park SM, Kim OS, Lee CS, Woo JH, Park SJ, Joe EH, Jou I (2009) Differential SUMOylation of LXRα and LXRβ mediates transrepression of STAT1 inflammatory signaling in IFN-γ-stimulated brain astrocytes. Mol Cell 35:806-817.
2. Qin H, Wilson CA, Lee SJ, Zhao X, Benveniste EN (2005) LPS induces CD40 gene expression through the activation of NF-kappaB and STAT-1alpha in macrophages and microglia.
3. Klegeris A, McGeer PL (1994) Rat brain microglia and peritoneal macrophages show similar responses to respiratory burst stimulants. J Neuroimmunol 53:83-90.

4. Pyo H, Joe E, Jung S, Lee SH, Jou I (1999) Gangliosides activate cultured rat brain microglia. J Biol Chem 274:34584-34589.

5. Ciesielski-Treska J, Ulrich G, Taupenot L, Chasserot-Golaz S, Corti A, Aunis D, Bader MF (1998) Chromogranin A induces a neurotoxic phenotype in brain microglial cells. J Biol Chem 273:14339-14346.

6. Erickson MA, Banks WA (2013) Blood-brain barrier dysfunction as a cause and consequence of Alzheimer’s disease. J Cereb Blood Flow Metab 33:1500-1513.

7. Sekeljic V, Bataveljic D, Stamenkovic S, Ulamek M, Jabłoński M, Radenovic L, Pluta R, Andjus PR (2012) Cellular markers of neuroinflammation and neurogenesis after ischemic brain injury in the long-term survival rat model. Brain Struct Funct 217:411-420.

8. Ryu J, Pyo H, Jou I, Joe E (2000) Thrombin induces NO release from cultured rat microglia via protein kinase C, mitogen-activated protein kinase, and NF-kappa B. J Biol Chem 275:29955-29959.

9. Ryu J, Min KJ, Rhim TY, Kim TH, Pyo H, Jin B, Kim SU, Jou I, Kim SS, Joe EH (2002) Prothrombin kringle-2 activates cultured rat brain microglia. J Immunol 168:5805-5810.

10. Min KJ, Jou I, Joe E (2003) Plasminogen-induced IL-1beta and TNF-alpha production in microglia is regulated by reactive oxygen species. Biochem Biophys Res Commun 312:969-974.

11. Vincent VA, Łowik CW, Verheijen JH, de Bart AC, Tilders FJ, Van Dam AM (1998) Role of astrocyte-derived tissue-type plasminogen activator in the regulation of endotoxin-stimulated nitric oxide production by microglial cells. Glia 22:130-137.

12. Park JI, Paik SR, Jou I, Park SM (2008) Microglial phagocytosis is enhanced by monomeric alpha-synuclein, not aggregated alpha-synuclein: implications for Parkinson’s disease. Glia 56:1215-1223.

13. Pyo H, Jou I, Jung S, Hong S, Joe EH (1998) Mitogen-activated protein kinases activated by lipopolysaccharide and beta-amyloid in cultured rat microglia. Neuroreport 9:871-874.

14. Yang Q, Wang Y, Feng J, Cao J, Chen B (2013) Intermittent hypoxia from obstructive sleep apnea may cause neuronal impairment and dysfunction in central nervous system: the potential roles played by microglia. Neuropsychiatr Dis Treat 9:1077-1086.

15. Frøyland E, Skjaeret C, Wright MS, Dalen ML, Cvancarova M, Kasi C, Rootwell T (2008) Inflammatory receptors and pathways in human NT2-N neurons during hypoxia and reoxygenation. Impact of acidosis. Brain Res 1217:37-49.

16. Kim OS, Park EJ, Joe EH, Jou I (2002) JAK-STAT signaling mediates gangliosides-induced inflammatory responses in brain microglial cells. J Biol Chem 277:40594-40601.

17. Shuai K, Liu B (2003) Regulation of JAK-STAT signalling in the immune system. Nat Rev Immunol 3:900-911.

18. Kim HY, Park EJ, Joe EH, Jou I (2003) Curcumin suppresses Janus kinase-STAT inflammatory signaling through activation of Src homology 2 domain-containing tyrosine phosphatase 2 in brain microglia. J Immunol 171:6072-6079.

19. Park EJ, Park SY, Joe EH, Jou I (2003) 15d-PGJ2 and rosiglitazone suppress Janus kinase-STAT inflammatory signaling through induction of suppressor of cytokine signaling 1 (SOCS1) and SOCS3 in glia. J Biol Chem 278:14747-14752.

20. Machado FS, Jonghord JE, Esper L, Dias A, Bafica A, Serhan CN, Aliberti J (2006) Anti-inflammatory actions of lipoxin A4 and aspirin-triggered lipoxin are SOCS-2 dependent. Nat Med 12:330-334.

21. Rozansky DJ, Wu H, Tang K, Parmer RJ, O’Connor DT (1994) Glucocorticoid activation of chromogranin A gene expression. Identification and characterization of a novel glucocorticoid response element. J Clin Invest 94:2357-2368.

22. De Bosscher K, Vanden Berghen W, Haegeman G (2003) The interplay between the glucocorticoid receptor and nuclear factor-κB or activator protein-1: molecular mechanisms for gene repression. Endocrinology 24:488-522.

23. de Kloet ER, Joëls M, Holsboer F (2005) Stress and the brain: from adaptation to disease. Nat Rev Neurosci 6:463-475.

24. Barnes PJ (1998) Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (Lond) 94:557-572.

25. Glass CK, Saijo K (2010) Nuclear receptor transrepression pathways that regulate inflammation in macrophages and T cells. Nat Rev Immunol 10:365-376.

26. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK (1998) The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 391:79-82.

27. Lee JH, Kim H, Woo JH, Joe EH, Jou I (2012) 5-8,11,14-eicosa-7,10,12-trienoic acid suppresses CCL2/MCP-1 expression in IFN-γ-stimulated astrocytes by increasing MAPK phosphorylation. J Neuroinflammation 9:34.

28. Saijo K, Crotti A, Glass CK (2010) Nuclear receptors, inflammation, and neurodegenerative diseases. Adv Immunol 106:21-59.

29. Seol W, Choi HS, Moore DD (1996) An orphan nuclear
hormone receptor that lacks a DNA binding domain and heterodimerizes with other receptors. Science 272:1336-1339.

30. Stumpo DJ, Lai WS, Blackshear PJ (2010) Inflammation: cytokines and RNA-based regulation. Wiley Interdiscip Rev RNA 1:60-80.

31. Lee JH, Woo JH, Woo SU, Kim KS, Park SM, Joe EH, Jou I (2008) The 15-deoxy-Δ12,14-prostaglandin J2 suppresses monocyte chemoattractant protein-1 expression in IFN-γ-stimulated astrocytes through induction of MAPK phosphatase-1. J Immunol 181:8442-8449.

32. Woo JH, Lee JH, Kim H, Choi Y, Park SM, Joe EH, Jou I (2015) MAP kinase phosphatase-1 expression is regulated by 15-deoxy-Δ12,14-prostaglandin J2 via a HuR-dependent post-transcriptional mechanism. Biochim Biophys Acta 1849: 612-625.

33. Kassel O, Sancomo A, Krätzschmar J, Kreff B, Stassen M, Cato AC (2001) Glucocorticoids inhibit MAP kinase via increased expression and decreased degradation of MKP-1. EMBO J 20:7108-7116.

34. Hashimoto H, Imamura K, Haruta J, Wakitani K (2002) 4-(4-cycloalkyl/aryl-oxazol-5-yl)benzenesulfonamides as selective cyclooxygenase-2 inhibitors: enhancement of the selectivity by introduction of a fluorine atom and identification of a potent, highly selective, and orally active COX-2 inhibitor JTE-522(1). J Med Chem 45:1511-1517.

35. Ramaswamy B, Shapiro CL (2003) Osteopenia and osteoporosis in women with breast cancer. Semin Oncol 30:763-775.

36. Baranowski M (2008) Biological role of liver X receptors. J Physiol Pharmacol 59 Suppl 7:31-55.

37. Wójcicka G, Jamroz-Wisniewska A, Horoszewicz K, Beltowski J (2007) Liver X receptors (LXRs). Part I: structure, function, regulation of activity, and role in lipid metabolism. Postepy Hig Med Dosw (Online) 61:736-759.

38. Whitney KD, Watson MA, Collins JL, Benson WG, Stone TM, Numerick MJ, Tippin TK, Wilson JG, Winegar DA, Kliewer SA (2002) Regulation of cholesterol homeostasis by the liver X receptors in the central nervous system. Mol Endocrinol 16:1378-1385.

39. Ogawa S, Lozach J, Benner C, Pascual G, Tangirala RK, Westin S, Hoffmann A, Subramaniam S, David M, Rosenfeld MG, Glass CK (2005) Molecular determinants of crosstalk between nuclear receptors and toll-like receptors. Cell 122:707-721.

40. Jakobsson T, Treuter E, Gustafsson JÅ, Steffensen KR (2012) Liver X receptor biology and pharmacology: new pathways, challenges and opportunities. Trends Pharmacol Sci 33:394-404.