Journal of Inflammation Research

Dovepress
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REVIEW

The Modulation of Neuroimmune Responses in Peripheral Inflammation

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Abstract: The brain, as the "commander-in-chief" of the human body, is known to pick up the peripheral situation and dictate orders to the periphery on time, and the immune system makes no exception. Inflammation is a defensive reaction of the body, which can be beneficial, however, unrestricted inflammation can result in life-threatening injuries and multi-organ dysfunction. The intricate interaction between the nervous and the immune system would prevent inflammation from spreading indefinitely. The onset of life-threatening bursts of inflammation may indicate neurological dysregulation, at which point additional interventions are necessary to establish a new balance. However, these interventions must be predicated on an understanding of the neuroimmune communication. Consequently, we provide a comprehensive pathway that illustrates how the central nervous system detects peripheral inflammatory signals that are transmitted by nerves or related substances and subsequently regulates peripheral inflammation through the autonomic nervous system and neuroendocrine system, intending to discover new methods of treating peripheral inflammation by intervening the nervous system.

Keywords: central nervous system, peripheral inflammation, vagus nerve, neuroimmune

Introduction

Peripheral inflammation is a kind of defense mechanism, and the body uses it to combat the invasion and attack of external harmful substances. In the inflammatory reflex, whether it is pro-inflammatory or anti-inflammatory, the secretion of cytokines is essential.[1] Because the pro-inflammatory cytokine storm may lead to systemic inflammatory response syndrome (SIRS), which brings more serious injuries than the initial stimulus, it is extremely important to accurately assess the extent of its increase.[2] Compensatory reactive anti-inflammatory syndrome (CRAS) may be due to the excessive production of anti-inflammatory cytokines, and anti-inflammatory cytokines will suppress the immune system and increase the risk of infection.[3] Previous studies have proved that the degree of inflammation can be controlled through neuroimmune interaction, to achieve local damage control and prevent further damage.[1,4] The onset of peripheral inflammation can be regarded as the result of the synergistic action of the nervous system and the immune system. This process can be summarized into three main steps: the perception and transmission of peripheral inflammatory signals, the synthesis and coordination of the received inflammatory signals by the central nervous system (CNS), and the transmission of the synthesized information from the CNS to the periphery to regulate the immune system. These steps involve extremely complex molecular mechanisms and procedures. Of course, there is local neuroimmune regulation in the periphery.[5]

Both animal studies and clinical studies have shown that peripheral inflammation can be alleviated by interfering with the nervous system.[6–8] However, due to the current lack of sufficient understanding of the underlying mechanisms, our ability to target the nervous system for intervention in the treatment of peripheral inflammation has been greatly limited. This review aims to describe the progress of research into the mechanisms of bidirectional regulation between the CNS and peripheral inflammation, with the goal of achieving an in-depth understanding based on current studies. It explores

Received: 9 April 2025
Accepted: 1 July 2025
Published: 10 July 2025

therapeutic approaches to enhance the effectiveness of CNS interventions in the clinical management of peripheral inflammation and improve patient prognoses.

Inflammatory Signals: Perception and Input

Nerve Conduction

A wide range of substances in the peripheral circulation can transmit peripheral inflammatory signals to the CNS in multiple ways, thereby triggering a variety of responses in the CNS. These substances are produced during inflammation, including a wide range of inflammatory and anti-inflammatory cytokines, chemokines, and other related molecules. In addition to serving as agents in the transmission of signals, they also induce a variety of co-occurring changes in illness behaviors (as detailed below). This inflammatory signaling is partially mediated by vagal sensory fibers. Cytokines, pathogen products, and other inflammatory molecules secreted by peripheral immune cells can act on the tumor necrosis factor (TNF) receptors, IL-1β receptors, Fc receptors, Toll-like receptors, or pattern recognition receptors (PRR) on the vagus nerve afferent nerves to transmit these signals to the CNS.[9–11] These signals are specific because different clusters of nerves within the afferent vagus nerve are responsible for encoding information about identified cytokines.[12] This explains how the brain generates distinct responses to different inflammatory cytokines. Elucidating the specific markers of neural clusters that respond to different inflammatory mediators could enable the precise neuroimmune control of peripheral inflammation and reduce the side effects of neurological interventions.

The vagus nerve afferent nerve is activated by peripheral inflammatory cytokines and projects to the nucleus tractus solitarius (NTS) in the medulla oblongata of the brainstem.[13] There, it continues to stimulate the release of glutamate by excitatory glutamatergic neurons in the NTS, thereby transmitting inflammatory information to the CNS.[14,15] In addition to the excitotoxic effect of glutamate on CNS neurons, glutamate can also stimulate the NR2B receptor on mast cells, resulting in the secretion of lots of neuropeptides and inflammatory mediators.[16] These mediators directly cause neuronal destruction or indirectly through the activation of glial cells. Subsequently, impaired neurons and activated glial cells will release a diverse array of neuropeptides and inflammatory mediators, which will continue to activate the brain mast cells. This persistent malignant positive feedback process results in a consistent rise in inflammatory mediators, which in turn triggers neuroinflammation.[17,18] It seems that activating vagal afferent nerves due to peripheral inflammation increases the levels of glutamate in the CNS, leading to a certain degree of neurotoxicity.

Nociceptors found on the free nerve endings of primary sensory neurons in the dorsal root ganglia play a role in inflammatory signaling. For example, TRPA1 and TRPV1, which are part of the transient receptor potential ion channel family, are present throughout the peripheral and CNS.[19] When these receptors are activated, they have a specific anti-inflammatory effect.[20,21] Furthermore, their simultaneous activation results in a synergistic effect.[22]

BBB Destruction and Peripheral Immune Cell Infiltration

Aside from relaying inflammatory signals to the CNS through the stimulation of peripheral sensory nerves, it is probable that there exist alternative routes for the CNS to respond and regulate peripheral inflammation.[23] The BBB is a crucial physiological structure that maintains homeostasis in the intracerebral environment by separating the CNS from the peripheral circulation. It is composed of vascular endothelial cells, pericytes, basement membrane, and astrocytes.[24] The effects of peripheral inflammation on the CNS require investigation of this crucial physiological structure because these structures cooperate to block the penetration of peripheral hazards, and any abnormality in one of them can disrupt CNS homeostasis (Figure 1).

Under normal physiological conditions, the peripheral circulatory system exchanges substances with the brain bilaterally by BBB.[25] And leukocytes are typically found within the blood vessels and do not enter healthy brain tissue.[26] However, under pathological conditions where there is peripheral inflammation, the damage to the endothelial cell caused by various inflammatory cytokines, the changes in tight junctions between endothelial cells, the activation of astrocytes and microglia, the enhancement of oxidative stress, and the alterations of transport pathways and receptors can disrupt the BBB integrity and increase the transportation of certain hazardous substances.[27,28] Thereby peripheral immune cells and cytokines can cross the BBB and infiltrate into the brain.[26,28,29] The BBB demonstrates a heightened sensitivity to the presence of TNFα in the

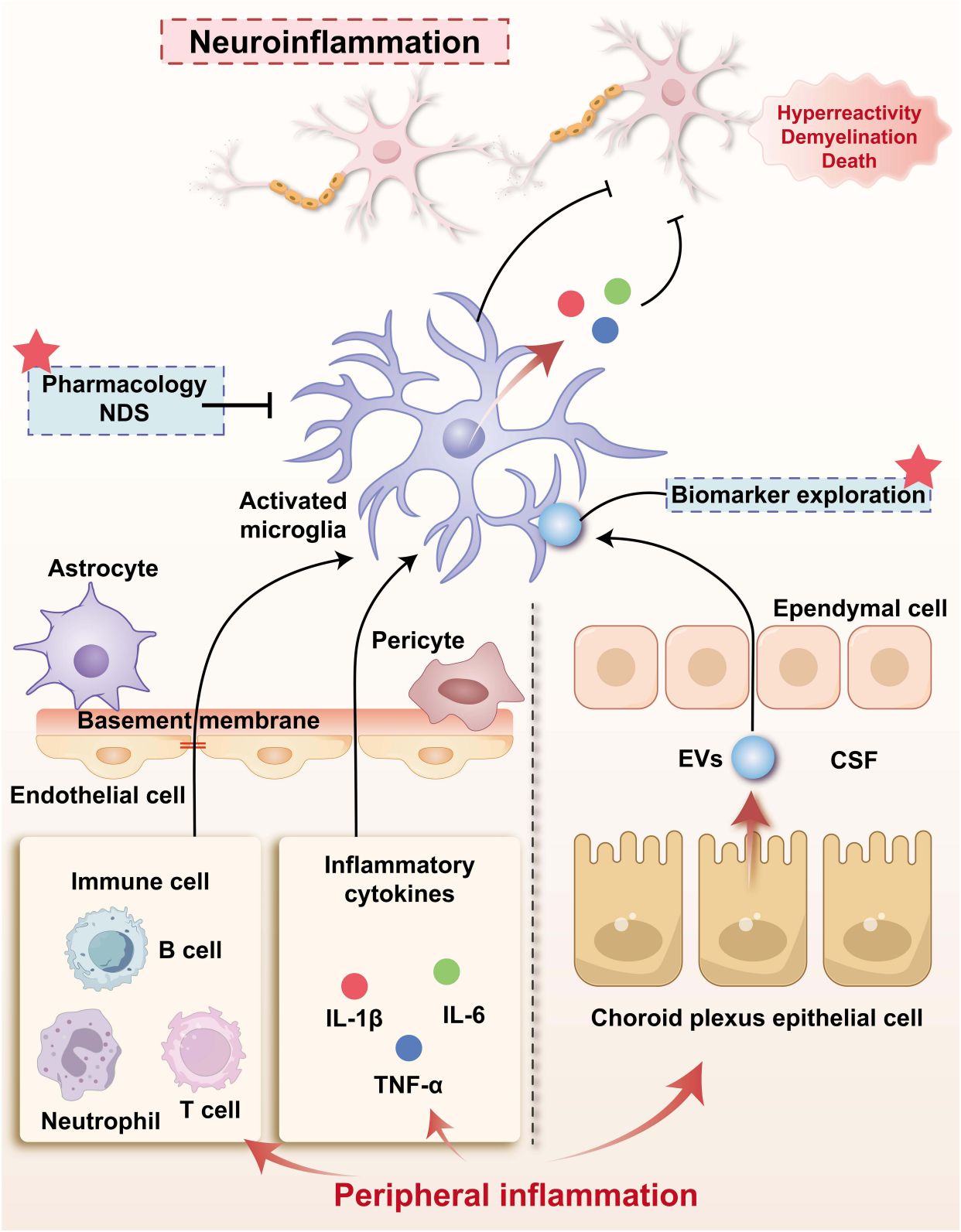

Figure 1 Transmission of peripheral inflammatory signals via the BBB or CSF. The red stars indicate directions that merit further exploration.
Abbreviations: NDS, nanoparticle delivery systems; EVs, extracellular vesicles; CSF, cerebrospinal fluid.

https://doi.org/10.2147/JIR.S533106

peripheral blood, leading to increased permeability of the BBB and the migration of monocytes.[30] The infiltration of peripheral blood monocytes into the hippocampus is a means of transmitting peripheral inflammatory signals to the CNS through cell-cell contact between monocytes and hippocampal tissue, and this process involves the release of pro-inflammatory cytokine by monocytes.[31] Furthermore, the infiltrating monocytes interact with glial cells and neurons, resulting in neuroinflammation and hyperreactivity.[31,32] The neuroinflammation that was induced by peripheral LPS injection was inhibited following the depletion of monocytes.[33]

Research by the team of Vanessa Y. Ruiz, employing single-cell RNA sequencing analysis of in vitro matured human $CD14^{+}CD16^{+}$ monocytes, revealed a distinct subset exhibiting a gene expression signature associated with CNS inflammatory diseases. This subset demonstrated a preferential capacity for migration across an in vitro human BBB model.[34] Concurrently, researchers explore cell-mediated nanoparticle delivery systems conjugated to monocytes for brain tumour therapy.[35,36] Consequently, beyond pharmacological strategies reducing monocyte infiltration to mitigate neuroinflammation, the intrinsic capacity of specific monocyte subsets to penetrate the BBB and infiltrate brain tissue could be leveraged. Combining this with nanoparticle delivery systems offers the potential for more precise therapeutic interventions.

Additionally, peripheral T and B cell infiltration into the brain via the compromised BBB not only causes neuronal demyelination but also participates in central immune surveillance.[37,38] Peripheral inflammatory signals take time to cross the BBB and reach the CNS, but perivascular cells (PDGFRβ+ cells), key BBB and neurovascular unit components, can detect them within two hours of infection. By releasing the chemokine CCL2, these cells rapidly boost glutamatergic neuron firing and excitatory synaptic transmission in various brain regions for an initial response.[39]

Other Pathways

There are other additional paths for the transfer of messages at the periphery-central interface, but the two pathways mentioned above are the primary routes for the transmission of peripheral inflammatory messages to CNS. The choroid plexus is a component of the blood-cerebrospinal fluid barrier and is responsible for the production of cerebrospinal fluid (CSF). CSF also functions as a medium for peripheral inflammatory signal transmission, as evidenced by the observation that, in the stimulation of peripheral inflammation, choroid plexus-secreted extracellular vesicles or proinflammatory extracellular vesicles originating from other tissue transmit inflammatory signals to the brain via CSF.[40,41] These vesicles can be taken up by astrocytes and microglia, resulting in the inhibition of miRNA target inhibition and the upregulation of inflammatory genes.[41,42] However, further exploration is required to elucidate the specific mechanism by which peripheral inflammation leads to the secretion of these extracellular vesicles. Moreover, the identification of a clear biomarker for these extracellular vesicles could pave the way for the development of novel treatment targets for peripheral inflammation (Figure 1). Periventricular organs, which are regions of the brain that lack the BBB, such as the area postrema (AP), are composed of ependymal cells and non-neuronal Cox2+ cells that can respond to inflammatory cytokines in the peripheral circulation and secrete prostaglandins to transmit inflammatory signals to neurons.[43,44]

Overall, although this signal transmission can potentially cause some adverse effects on CNS, the next response of the brain is dependent on the central perception of peripheral inflammation signals.

Brain Responses to Peripheral Inflammation

Microglia Activation

Microglia are a type of immune cell that are distributed throughout the whole brain and conduct complex and close two-way communication with other brain tissues, such as neurons and astroglia. Consequently, microglia are not only responsible for immune function, but also exhibit heightened sensitivity to alterations in the brain microenvironment, thereby contributing to the maintenance of brain stability.[45,46] Microglia have a role in the pathological processes of many different CNS disorders. As the disease progresses, its phenotype expression, morphology, and function are extremely dynamic, and this is also the case in pathological scenarios involving peripheral inflammation.[47,48] The inflammatory information transmitted peripherally can stimulate microglia through the influence on synaptic connections and neuronal networks in the brain, or the secretion of inflammatory substances and other cytokines.[49,50]

The activation of microglia in the brain is induced by peripheral inflammation in both the early and late stages of the disease, and this effect can persist for an extended period.[51–53] The activation of microglia induces the disruption of the BBB, the raised expression of pro-inflammatory cytokines in the brain, the reduction of hippocampal synaptic plasticity, the onset of oxidative stress, and neuronal death in the brain.[54–56] The reduction of cell death and the amelioration of the impairment of synaptic plasticity in the hippocampus were achieved by inhibiting microglia activation, which also resulted in the reversal of the decline in the expression of anti-apoptotic proteins and the reduction of central and peripheral inflammatory cytokines.[57,58] To address this abnormal activation of microglia upon peripheral inflammation, it is crucial to promptly restore him to a state of equilibrium. The IL-10 anti-inflammatory cytokines, which are produced by central natural killer cells and neutrophils, can interact with the IL-10 receptor on microglia, thereby inhibiting the dysfunction of neurons caused by the over-activation of microglia. It can also inhibit the secretion of TNF by microglia, thereby facilitating the restoration of microglia homeostasis and forming a benign circuit to prevent the further progression of the pathological process.[59]

Brain Region-Specific Regulation

A variety of inflammatory signals from peripheral inflammation are transmitted to the CNS and subsequently increase neuronal activity in specific regions of the brain. After consolidating across multiple cerebral nuclei, the information is transmitted to the periphery, where it elicits a variety of responses, including anti-inflammatory effects. The hypothalamic-pituitary-adrenal (HPA) axis can be activated by inflammatory signals through a brainstem-hypothalamic pathway of the dorsal vagal complex (DVC)-parabrachial nucleus (PB)-paraventricular nucleus of the hypothalamus(PVN). This pathway leads to the adrenal cortex producing glucocorticoids (GCs) that enter the circulation and produce the immune suppressive effect.[44] This effect prevents the persistent elevation of peripheral pro-inflammatory cytokines, which in turn acts on the hypothalamus and pituitary via a feedback effect.[60,61] Furthermore, the activation of PVN is accompanied by cognition and illness behaviors, which are the result of the integration of signals from other brain regions.[62] Not all pro-inflammatory cytokines cause illness behaviors after signaling to the CNS and the release of IL-17a during inflammation can help improve impairments in social behavior by influencing CNS neuronal activity.[63] Furthermore, the information about peripheral inflammation can be retained in the central processing. It has been discovered that certain neurons in the insular cortex are responsible for encoding information related to the beginning of peripheral inflammation, and the reactivation of these neurons can trigger peripheral inflammation through the autonomic nervous system.[64]

As previously stated, peripheral vagal afferent nerves can transmit peripheral inflammatory signals to the NTS. The NTS, along with the dorsal motor nucleus of the vagus (DMV) and the area postrema (AP), make up the dorsal vagal complex (DVC) (Figure 2). The NTS has direct connections to the rostral ventrolateral medulla (RVLM), where the majority of preganglionic sympathetic neurons are situated.[65,66] Neurons that release glutamate in the NTS project to preganglionic sympathetic neurons in the RVLM, leading to the activation of the sympathetic nervous system, which helps counteract inflammation generated by TNFα.[67] The AP plays a crucial role in regulating various bodily functions such as the vomit reflex, feeding, metabolism, inflammatory response, stress response, and taste aversions.[68] It is capable of receiving vagal input signals and owns the distinct advantage of being located outside the BBB, which allows it to detect and transmit peripheral information. Consequently, when the AP is activated during peripheral inflammation, it may lead to a broad spectrum of sickness behaviors.[68,69] The peripheral cholinergic anti-inflammatory pathway can be activated to produce anti-inflammatory effects by stimulating the DMN, which is the source of vagal efferent fibers.[70,71] In this way, the DVC functions as an adapter interface, as it simultaneously activates the peripheral anti-inflammatory pathway and upstream brain regions (eg the central amygdala nucleus, striatal bed nucleus of the stria terminalis, paraventricular nucleus of the hypothalamus, and ventral preoptic area) to produce relevant anti-inflammatory effects and immune behaviors.[72,73] The excitatory glutamatergic neurons are key members in the adapter action of the DVC.[74]

In addition, peripheral inflammation induced changes in the rats' hippocampal glutamate receptors, leading to impaired cognitive function.[75] The elevated levels of glutamate in the nucleus ambiguus of mice with sepsis have been shown to exert a neurotoxic effect on cholinergic neurons, ultimately resulting in the inhibition of peripheral cholinergic anti-inflammatory effects.[76] This is coupled with the fact that the previously described peripheral inflammatory signals transmitted to the CNS via vagal afferent nerves result in elevated glutamate levels in the CNS.

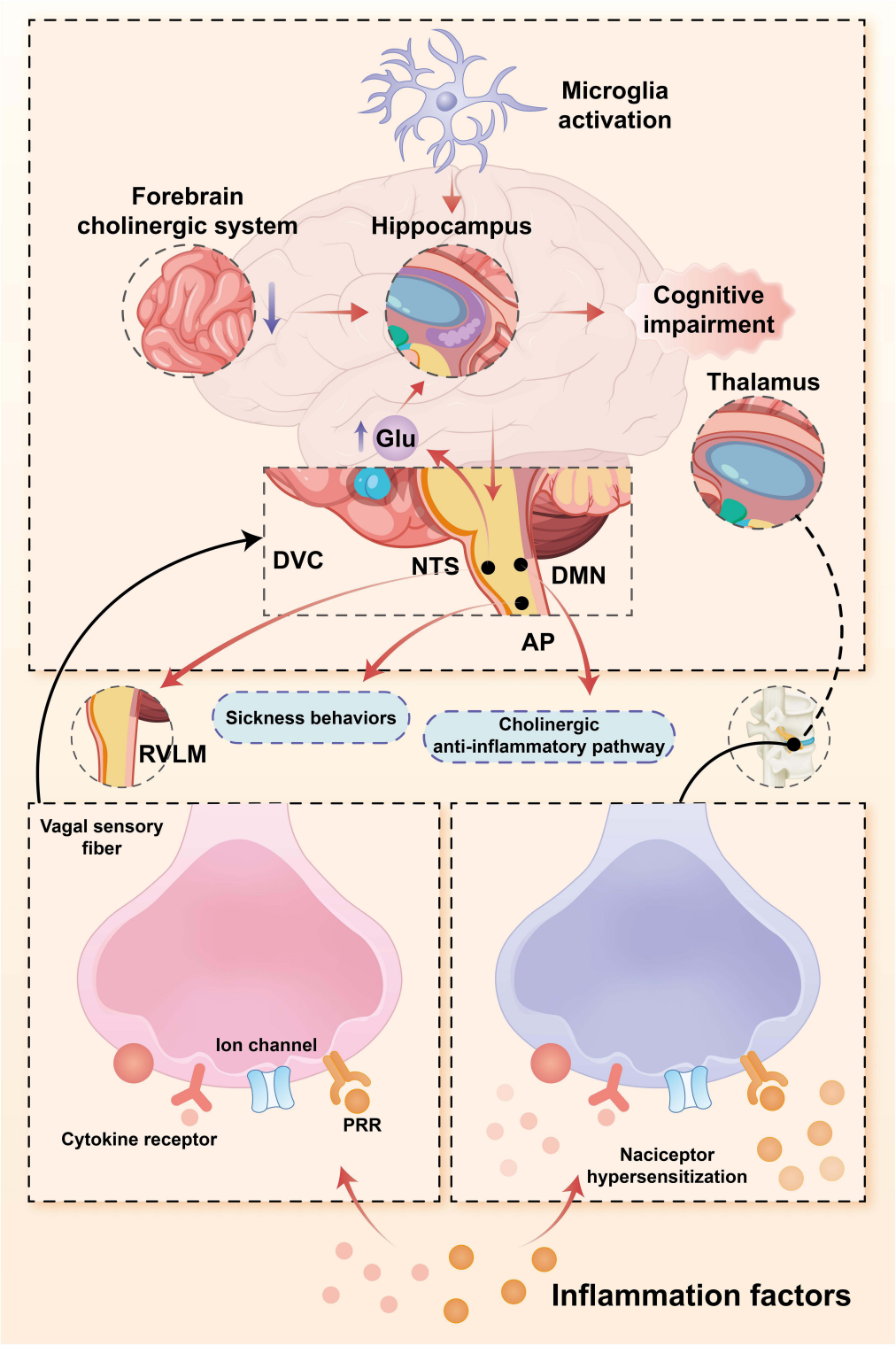

Figure 2 The brain's responses to peripherally derived inflammatory signalling via neural transmission.
Abbreviations: Glu, glutamate; DVC, dorsal vagal complex; DRG, dorsal root ganglia; NTS, the nucleus tractus solitarius; DMV, the dorsal motor nucleus of the vagus; AP, area postrema; DRG, dorsal root ganglia; RVLM, rostral ventrolateral medulla.

Consequently, these findings underscore the imperative to acknowledge the neurotoxicity associated with the glutamatergic system within the CNS. This phenomenon may also be associated with inflammatory encephalopathies resulting from multiple peripheral inflammatory conditions.[77] However, the current study did not explore the changes in extracellular glutamate concentration in different brain regions upon peripheral inflammation. In vivo real-time monitoring of glutamate concentrations is required for a more accurate understanding of their spatiotemporal dynamics.

Central Cholinergic Inhibition and Alterations in Immune Plasticity

Peripheral inflammation not only activates central-associated nerve anti-inflammatory systems but also triggers competing inhibitory effects to achieve a state of balance. The central cholinergic nerves, projecting to the forebrain which contains a high density of M1 muscarinic acetylcholine receptor (M1 mAChR), play an important role in the regulation of peripheral inflammation.[78] The selective optogenetic modulation of these forebrain cholinergic neurons has been shown to exert anti-inflammatory effects in the periphery by relying on the structural integrity of the vagus nerve.[79,80] This central cholinergic anti-inflammatory modulation would then be relatively weak in diseases associated with cholinergic dysfunction, such as Alzheimer's disease. Inhibitory effects on the central cholinergic nervous system are induced by peripheral inflammation, which includes the decrease of M1 mAChR and acetylcholine transferase expression and the increase of cholinesterase expression.[51,81] However, the selective activation of central cholinergic neurons can alleviate the peripheral inflammation in sepsis mice,[79] indicating that its peripheral anti-inflammatory benefits are probably being discounted by these Inhibitory effects.

Cholinergic neurons are primarily located in the basal forebrain and brainstem of the brain. They release acetylcholine through their widely spread axonal fibers, which control neural activity in various nuclei and play a crucial role in functions like locomotion, sleep, emotion, and memory.[82,83] In the presence of peripheral inflammation, the population of central cholinergic neurons decreases, as well as the number of cholinergic neurons projecting from the basal forebrain to the hippocampus.[84] The hippocampus is a brain region involved in the regulation of cognition and learning. Thus, some researchers have proposed that this reduction of cholinergic neurons in the hippocampus may be the underlying mechanism of neuropsychiatric symptoms caused by peripheral inflammation, and enhancing cholinergic neuron signaling to the hippocampus or increasing hippocampal acetylcholine levels using cholinesterase inhibitors can improve cognitive impairments in mice with sepsis.[85–87] Peripheral inflammation has a suppressive impact on the central cholinergic nerves, impairing both cognitive performance and its ability to regulate peripheral anti-inflammatory responses. However, whether these two effects are separate or combined is unclear and requires further attention and investigation.

Moreover, it was discovered that there was an increasing level of chemokine CCL17 produced by the specific group of neurons in the hippocampal CA1 region when mice were injected with LPS.[88] The aforementioned implies that the hippocampus is also involved in the entire regulatory chain that contributes to the formation of peripheral inflammation. Interestingly, a study discovered that long-term activation of innate immunity brought on by peripheral inflammation did not alter hippocampal neurological plasticity or cause depressive-like behaviors; rather, hippocampus structure and function could remain intact.[89] Perhaps, the innate immunity undergoes remodeling and strengthening throughout chronic activation to adapt to external changes, which is a result of its plasticity,[90] this process also serves as a protective mechanism for the CNS. Likewise, the adaptive immune system exhibits plasticity. The CNS becomes desensitized and tolerant to neuroinflammation due to repeated peripheral inflammation, that may persist over time. This tolerance may attenuate neurological hyperreactivity, the activation of microglia, and the expression of inflammatory cytokines in the brain as a result of peripheral inflammation.[91,92]

Peripheral inflammation leads to an increase in pro-inflammatory cytokine expression in both peripheral and specific regions of the brain.[52,53] This is accompanied by immune cell infiltration, degenerative demyelination of neurons, activation of microglia, and destruction of the BBB, all of which contribute to the emergence of central neuroinflammation. In neurodegenerative diseases, such as multiple sclerosis and Parkinson's disease, if peripheral inflammation persists, it will worsen the primary lesion and further exacerbate cognitive dysfunction and anxiety-like symptoms.[93,94] So it is crucial to promptly control peripheral inflammation in these patients.

Overall, it is crucial not to overlook the safeguarding of the CNS in the presence of peripheral inflammation. While previous studies have identified brain regions involved in controlling peripheral inflammation, it is important to note that

this does not necessarily indicate a direct connection between these brain regions. There may be additional nuclei or neural pathways responsible for regulating peripheral inflammation or more neural pathways within the highly intricate CNS. The brain's reaction to peripheral inflammatory signals can be characterized as extensive since it decodes and analyzes the signals sent by the peripheral afferent nerves system, as well as activates other relevant brain regions to allow the body to execute responses other than anti-inflammatory ones, which necessitate a high level of accuracy and promptness.

Peripheral Anti-Inflammatory Pathways

The autonomic nervous system and the neuroendocrine system are the primary mechanisms by which the brain regulates the immune system. The parasympathetic and sympathetic nervous systems are involved in the autonomic response; instead, the HPA axis is mainly involved in the neuroendocrine response (Figure 3).

Cholinergic Anti-Inflammatory Pathway

The neuroendocrine HPA axis and autonomic nerves should be relatively independent in their involvement in inflammatory regulation, as the activation of the HPA is not significantly impacted by subphrenic vagotomy.[23] In contrast to the vagal anti-inflammatory reflex, which responds swiftly to inflammation, the HPA axis induces a long-lasting anti-inflammatory response throughout the body, though at a slower pace.[95] Inflammatory signals are transmitted to the brain through vagal afferent nerves, which immediately activate vagal efferent nerves. These nerves complete neurotransformation at the celiac ganglion and subsequently activate parasympathetic noradrenergic neurons that innervate the

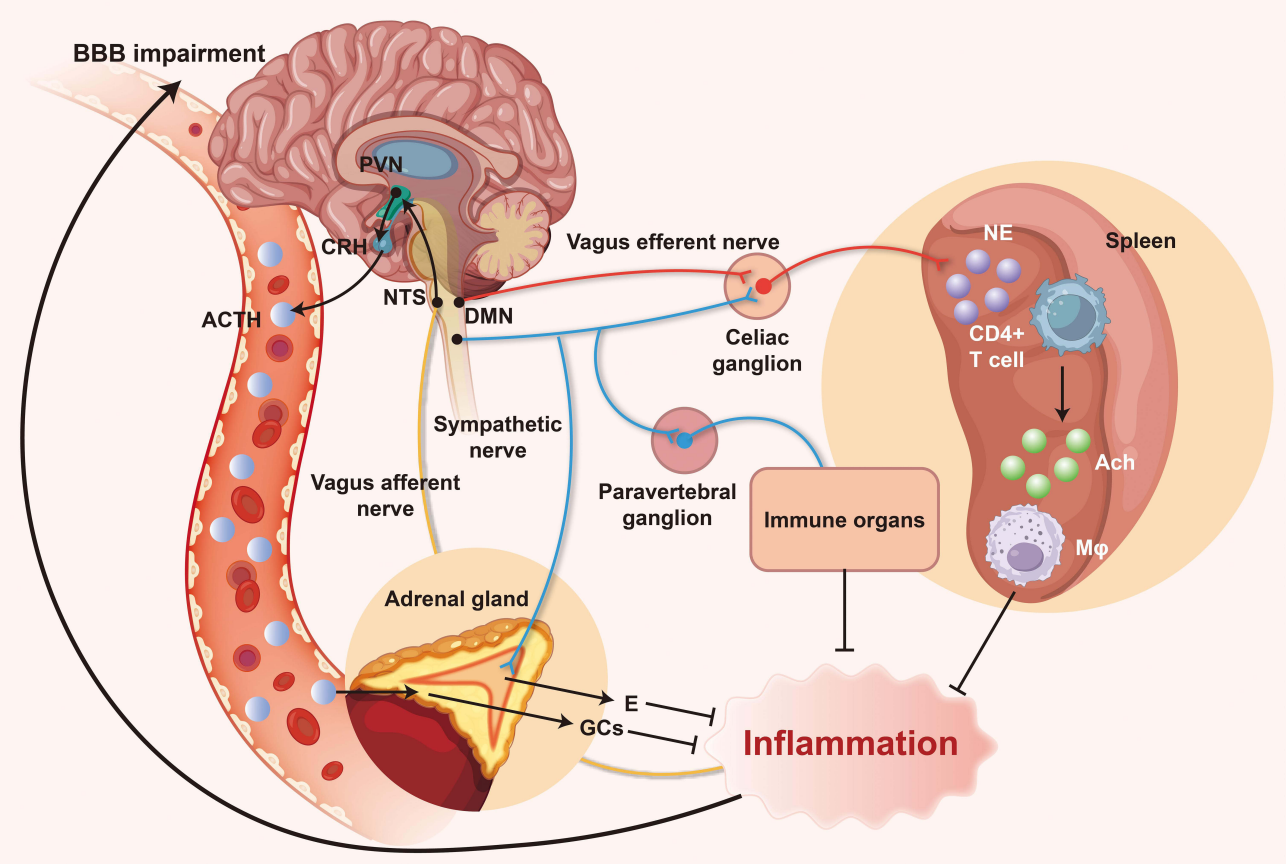

Figure 3 The neuroimmune circuits in peripheral inflammation.

Abbreviations: BBB, blood-brain barrier; PVN, paraventricular nucleus of the hypothalamus; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; GCs, glucocorticoids; DMV, the dorsal motor nucleus of the vagus; NTS, the nucleus tractus solitarius; Ach, acetylcholine; NE, norepinephrine; E, epinephrine; Mφ, macrophage.

spleen to release norepinephrine (NE), which continues to act on the β2 adrenergic receptor on the CD4+ T-cells, leading to the secretion of acetylcholine.[96,97] Acetylcholine then acts on the α7nACh receptor on the macrophage, inhibiting the secretion of pro-inflammatory cytokine and exerting an anti-inflammatory effect.[98,99] This is a classic peripheral vagal cholinergic anti-inflammatory pathway. Furthermore, activated α7nACh receptors can enhance the contacts between macrophages in the spleen, hence further amplifying the results of the anti-inflammatory effect.[100]

The spleen is an essential component in this pathway. Spleens that are isolated have the ability to generate acetylcholine on their own, and the cholinergic effect of the spleen is amplified in an adverse environment of inflammation.[101] The vagus nerve innervates many tissues or organs, and its anti-inflammatory effects should theoretically be widespread. Thus it's vital to consider whether other tissues are engaged in this system, even though the spleen plays a major role in the cholinergic anti-inflammatory pathway. Within various organs, vagus efferent nerves have the potential to perform anti-inflammatory effects through the application of certain pathways. For example, it was found that in mice with denervated spleens and deficient T-cells, activated vagal efferent nerves interacted with cholinergic enteric myenteric neurons. These activated cholinergic enteric neurons subsequently inhibited the activity of resident enteric myenteric macrophages expressing α7nACh receptors, thereby attenuating intestinal inflammation and improving postoperative intestinal obstruction.[102,103] Conversely, it has been discovered that neither bone marrow nor lymph node cells significantly contribute to the vagus nerve stimulation's protective impact against renal ischemia.[104] Importantly, the study of cholinergic anti-inflammatory pathways that specifically target organs or tissues can enable precise modulation of potential neuroimmune therapeutic targets for treating specific diseases. The protective role of this pathway has already been partially demonstrated in experimental disease models, such as acute kidney injury,[104] ARDS,[105] pancreatitis,[106] and sepsis.[107]

Sympathetic Nervous System

The immune system is regulated by the sympathetic nervous system(SNS) and peripheral cholinergic anti-inflammatory pathways in a synergistic manner during peripheral inflammation.[108] The SNS is composed of two distinct groups of neurons: the preganglionic cholinergic neurons, which secrete acetylcholine, and the postganglionic adrenergic neurons, which primarily secrete NE. These neurons are connected by synaptic contact at the paravertebral nerve nodes. The adrenal medulla is distinguished by the fact that it is the sole recipient of preganglionic sympathetic innervation and secretes NE or epinephrine (E) into the bloodstream to modulate peripheral inflammation.[109] In contrast to the parasympathetic nervous system, the majority of immune organs (such as the spleen, lymph nodes, and thymus) receive a significant number of innervations from sympathetic postganglionic neurons.[110] There are also adrenergic receptors on innate and adaptive immune cells that possess the ability to bind NE, particularly β2-adrenergic receptors, which enable them to interact directly with the SNS.[111,112]

The primary mechanism by which the SNS induces an immunosuppressive response is the secretion of the neurotransmitter NE. NE inhibits excessive inflammation in LPS-stimulated mice by dose-dependently reducing the production of pro-inflammatory cytokines in immune cells, simultaneously increasing the production of the anti-inflammatory IL-10 and inhibiting the migration of lymphocytes from lymph nodes to peripheral tissues.[113–115] The depletion of peripheral adrenergic nerves by injection of 6-hydroxydopamine hydrochloride (6-OHD) in mice with LPS-induced inflammation reduces the efficacy of inflammation resolution and contributes to a hyperinflammatory state.[116] In the same vein, the immunosuppressive impacts of sympathetic activation have been manifested in human clinical trials, and it probably serves as an important driver of immunosuppression in sepsis.[117,118] The IL-10 and TNF cytokine responses in mice with intravenous LPS-induced inflammation were unaffected by the combined excision of cervical and lumbar sympathetic nerves, indicating that the endogenous anti-inflammatory effects of sympathetic nerves are primarily derived from the thoracic sympathetic nerves that innervate the abdominal viscera.[119]

Nevertheless, it is hard to ignore the possibility that the current discoveries about the respective anti-inflammatory effects of the two routes are the consequence of a combination of their actions since NE and β2 adrenergic receptors also contribute to the cholinergic anti-inflammatory pathway. The SNS may be more advantageous for immune regulation considering the immune system's innervation and receptor distribution. However, its activation as the basis for the body's "fight-or-flight" response is nonspecific and spontaneous (especially in disease). And pain, stress, or physiological

changes in the body can increase its tone.[120,121] There is a significant risk of sympatho-vagal imbalance with continuous sympathetic activation and vagal inhibition, resulting in irreversible immunosuppression, if the nerve tone of the SNS is continuously increased to achieve immunomodulation. This autonomic dysfunction will exacerbate the severity of the disease and result in an unfavorable prognosis.[117,122,123] Controlling the hypertonic SNS to achieve sympatho-vagal rebalance can thus have a therapeutic effect. Dextromethorphan can prevent sympathetic hyperactivation and cause a relative rise in peripheral cholinergic vagal anti-inflammatory nerve tone in a mouse model of experimental severe acute pancreatitis, which in turn, lowers systemic inflammation and pancreatic damage.[124] In clinical trials, thoracic epidural analgesia decreases mortality, enhances patient prognosis, and controls sympatho-vagal imbalance caused by acute pancreatitis.[125,126] As a systemic inflammatory treatment, it is not a bad notion to stabilize autonomic homeostasis by controlling over-activated sympathetic nerves, in addition to treating peripheral inflammation by stimulating the vagus nerve (Table 1).

Table 1 Inflammation Treatment by Intervening Nerve System in Humans

Diagnosis	Number	Type of Study	Intervention	Effect on Nervous System		Results	Reference
				Sympathetic Nervous Tone	Vagus Nervous Tone		
Cardiac surgery	14	Prospective randomized study	High spinal anesthesia	Down	–	IL-10 levels were markedly elevated in both intensity and duration.	[127]
Postesophagectomy	30	Randomized controlled study	TEA	Down	–	Serum IL-6 and IL-8 levels were significantly reduced. TEA reduced the systemic pro-inflammatory response and provided optimal post-operative pain relief.	[128]
Sepsis	20	Open double-blind, sham-controlled, pilot study	Transcutaneous auricular VNS	–	Up	Serum TNF-α and IL-1β levels were reduced. IL-4 and IL-10 levels were elevated.	[8]
Cardiac surgery	54	Randomized study	Low-level VNS	–	Up	Serum TNF-α and IL-6 levels were significantly lower.	[129]
Rheumatoid arthritis	17	Prospective study	VNS	–	Up	VNS inhibits TNF production and attenuates disease severity.	[130]
Crohn's disease	9	A 12-month pilot study	VNS	–	Up	Pro-inflammatory cytokines (IL-6,IL-12,IL-23,TNF-α) were reduced. Restored a homeostatic vagus tone.	[131]
Surgical colectomy	18	Pilot study	Abdominal VNS	–	Up	IL-8 and IL-6 production was reduced.	[132]

(*Continued*)

Table 1 (Continued).

Diagnosis	Number	Type of Study	Intervention	Effect on Nervous System		Results	Reference
				Sympathetic Nervous Tone	Vagus Nervous Tone		
Lobectomy via thoracotomy	100	Prospective study	Intermittent stimulation of the auricular branch of vagus nerve	–	Up	Serum concentrations of CRP and IL-6 were reduced but IL-10 was elevated. Reduced incidence of pneumonia and shorter hospitalization time.	[133]

Abbreviations: VNS, Vagus nerve stimulation; TEA, Thoracic epidural analgesia; CRP, C-reactive protein.

Vagal-Adrenal Anti-Inflammatory Pathway

In addition to the two anti-inflammatory pathways previously mentioned, a vagal-adrenal anti-inflammatory pathway has been recently identified which induces a protective neurological response in rodents by electrically stimulating vagal efferent fibers in the absence of afferent vagal signals.[104,134] Specific peripheral somatosensory receptors may be present in this pathway. In contrast to the electrical stimulation of spinal sympathetic reflexes which are not dependent on the presence of the PROKR2ADV neurons, Shenbin Liu and Zhifu Wang discovered that selectively stimulating sensory neurons expressing Prokr2 protein, which is distributed somatosensory-specifically (innervating deep fascial tissues such as periosteum, articular ligaments, and myofascia in the limbs, but not the epidermal tissues of the skin and major fascial tissues such as the peritoneum), would activate a vagal-adrenal anti-inflammatory pathway to inhibit inflammatory storms caused by the LPS treatment.[134,135]

In response to systemic inflammation, each of these anti-inflammatory pathways can be activated to carry out immunomodulatory functions. While they may appear to be independent, the immune system can be influenced by various interactions between them. In general, the activation of these pathways can be identified as a synergistic effect of immunosuppression. However, each pathway will achieve an overall balance through its feedback or regulation. If the balance among anti-inflammatory pathways is abnormal, it may result in a poor prognosis owing to irremediable immunosuppression in the later stages of the disease. Therefore, neurological interventions can be used in the early stages to control the dysregulated neurological balance.

Conclusion

This review offers a macroscopic perspective on the neuroimmune communication that occurs during peripheral inflammation. Peripheral inflammation initiates this reflex by transmitting sensory information to the spinal cord and brain via multiple pathways. This process subsequently stimulates the peripheral autonomic nervous system or the release of hormones, resulting in the modulation of various immune system functions. The altered peripheral inflammatory signals continue to be transmitted upwards, forming a closed loop. Inflammation is accompanied by a series of disagreeable sensations and disease behaviors due to the presence of numerous branches of central regulation in a closed-loop regulation process. Even though a growing body of research is gradually extending our understanding of neuroimmune and increasing the number of neuroimmune junctions that can be investigated as potential therapeutic targets (eg, interventions for increased BBB permeability, microglia activation, neural pathway imbalances), more animal and clinical studies are needed to develop definitive neuroimmune therapies for peripheral inflammation that are less harmful to the patient, early, and short-cycle.

Funding

This study was supported by grants from the National Natural Science Foundation (No. 8236031060).

Disclosure

No author has financial or other contractual agreements that might cause conflicts of interest.

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