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Keywords Prostaglandin E synthase · Cyclooxygenase 2 · Interleukin-1 · Prostaglandin E\(_2\) · Central nervous system

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**Abbreviations**

- **CFA**: Complete Freund’s adjuvant
- **COX**: Cyclooxygenase
- **CVO**: Circumventricular organ
- **IL-1β**: Interleukin-1β
- **IL-6**: Interleukin-6
- **i.c.v.**: Intracerebroventricular
- **i.p.**: Intraperitoneal
- **i.v.**: Intravenous
- **LPS**: Lipopolysaccharide
- **PGD\(_2\)**: Prostaglandin D\(_2\)
- **PGE\(_2\)**: Prostaglandin E\(_2\)
- **PGF\(_{2\alpha}\)**: Prostaglandin F\(_{2\alpha}\)
- **PGI\(_2\)**: Prostacyclin
- **PGH\(_2\)**: Prostaglandin H\(_2\)
- **mPGES**: Microsomal prostaglandin E synthase
- **TNF-α**: Tumor necrosis factor-alpha
- **TXA\(_2\)**: Thromboxane A\(_2\)
Introduction

Higher organisms are constantly exposed to potentially harmful microorganisms. While the skin and the mucosal linings of the body provide a barrier against such microorganisms, the mobile immune system serves to identify and kill those pathogens that have managed to enter the body. In addition to these defense mechanisms for the maintenance of tissue integrity, several reactions elicited by brain come into play during the immune challenge in order to redress homeostasis [1, 2, 3, 4]. Thus, in response to the signals emitted by the immune cells, the brain launches a complex array of reactions known as illness responses. These include fever, inactivity, anorexia, hyperalgesia, and alterations in hormone secretion, such as activation of the hypothalamus-pituitary-adrenal axis [2, 3, 4]. Although some of these responses were interpreted as favorable for the organism by the ancient Greeks, their value for survival was not experimentally verified until the last decades [1]. It is now recognized that, for example, the febrile response is evolutionarily well conserved, and it has been demonstrated that the blocking of fever production is accompanied by an increase in mortality during bacteremia [1, 5].

However, while the illness responses seem to be adaptive during acute infections, the same responses may be destructive during sustained inflammatory conditions. Among such deleterious effects of the brain-mediated illness response are the hyperalgesia and anorexia that are associated with rheumatoid arthritis, HIV, cancers, and other chronic diseases [6, 7]. Because presently available anti-inflammatory drugs carry several serious side effects, there is a clear need for more knowledge on the mechanisms through which the brain monitors and reacts to peripheral inflammation in the body in order to identify new drug targets that could alleviate the illness responses in a more-specific way. Here we will briefly review these questions with focus on recent data revealing the importance of cerebrovascular prostaglandins in the central nervous responses to peripheral inflammation.

Pathways for immune-to-brain communication

At the site of inflammation, leukocytes produce compounds known as cytokines. These exert local actions as signaling molecules between immune cells, but they may also reach the bloodstream and target remote structures such as the brain [2, 3, 4]. The cytokines that have received most attention as important for immune-to-brain communication are interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). How the signal from inflammation in the periphery can alert the brain has, however, been a matter of debate. The cerebrovascular endothelial cells are joined by tight junctions that constitute an effective barrier between the blood and the brain parenchyma. Thus, with the exception of conditions when pathological processes in the brain or its linings result in infiltration of inflammatory cells and/or production of inflammatory messengers, molecules as large as cytokines normally cannot reach deep neural structures [8]. This has fostered many different hypotheses on how cytokines can signal to the brain. While these different hypotheses are not mutually exclusive, their respective importance is still controversial and may vary not only with the location [9] and severity [10, 11] of the inflammation, but also with its time course [12] and the type of illness response [13]. So far, at least four different possible mechanisms for immune-to-brain signaling have been identified (Fig. 1).

![Fig. 1 Putative pathways for cytokine signaling across the blood-brain barrier (BBB). 1. Cytokine transport over the BBB by carrier-mediated mechanisms; 2. binding of cytokines to circumventricular organs lacking BBB; 3. cytokine binding to peripheral vessels such as the vagus nerve; 4. cytokine-mediated prostaglandin production in cells associated with the BBB](image)

Direct transport of cytokines over the blood-brain barrier via specific carrier-mediated mechanisms

While direct transport mechanisms have been demonstrated for IL-1β, IL-6, and TNF-α [14], they have low capacity and are rapidly saturated. Thus, it is unlikely that they play a major role during the acute phase of inflammation.

Passage of cytokines into the brain through the circumventricular organs

The circumventricular organs (CVOs) are specialized brain regions that lack a blood-brain barrier. CVOs can bind cytokines [15], and they express CD14 and toll-like receptors 2 and 4 [16], suggesting that they can bind and respond directly to bacterial fragments [17]. CVO neurons are activated during immune challenge [18, 19], but their role in immune-to-brain signaling is controversial. Thus, although lesions of CVOs have been shown to block aspects of the illness response [20], this has been reported to occur only when underlying structures are also severed, but not when the lesions are restricted to the CVOs [21].