

Immune-to-brain signaling and substrates of altered behavior during inflammation

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ABSTRACT

During the systemic inflammatory response to acute infection, and when in a safe environment, endothermic mammals typically display reduced activity and food intake, increased sleep, and the adoption of a curled-up position. These changes in behavior, in concert with fever, are adaptive in that they contribute to host survival. The present review addresses the immune-to-brain signaling pathways as well as possible neural substrates mediating reduced exploration and food intake during acute systemic inflammation. These involve rapid activation of peripheral nerves and glutamatergic brainstem circuits as well as slower IL-1 β action in the brain activating limbic and possibly ventral hypothalamic structures. Although mostly adaptive acutely, behavioral changes during inflammation may also reflect brain dysfunction in severe sepsis-associated delirium or become maladaptive and result in depression due to medical conditions that involve long-term inflammatory episodes with pain or discomfort. The mechanisms underlying these conditions are presently ill-understood even though neuroinflammation and neurodegeneration occur during and subsequent to sepsis-associated brain dysfunction, respectively.

INTRODUCTION

Fever and reduced activity and food intake as adaptive host responses to infection

The finding in the 1970s that peripheral administration of non-steroid anti-inflammatory drug-type antipyretics lowered survival of different species of animals after their inoculation with bacteria provided a conclusive piece of evidence in favor of the idea that fever was beneficial for survival of infected organisms.^[1-3] But

fever is an energetically costly response often requiring an increase in metabolism of 30-50%.^[4] Text books of human and veterinary medicine often have mentioned reduced activity and appetite along with the occurrence of fever during infectious disease.^[4] From an energy balance point of view on endotherms, it makes sense to reduce energy expenditure in the form of physical activity, such as exploration of one's environment, during fever. But, given the adaptive value as well as the high energy costs of increasing body temperature in



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response to infection, one may wonder how come then that the infected organism refrains from taking in more energy? In fact, reducing food intake upon infection may be an adaptive response as well since force-feeding mice during acute bacterial infection, it was indeed found to increase mortality.^[5]

Sickness behavior as motivated behavior

Benjamin Hart^[4] stated that in a “sickness behavior” perspective “the sleepy or depressed or inactive animal is less motivated to move about using energy that could fuel metabolic increases associated with fever”. To consider sickness a motivation, like fear, hunger, thirst and other motivational states, implies that its expression is flexible depending on other motivations. Thus, it is important to show that its occurrence does indeed depend on environmental conditions. Interestingly, rats that depend entirely on hoarded food for their consumption, when rendered sick by bacterial lipopolysaccharide (LPS) endotoxins, continued to hoard more food, even though they did not consume it, than did animals injected with LPS that had the possibility to hoard, but also received food in their cage.^[6] Thus, the expression of sickness behavior depends on the external conditions and, in this case, likely on the motivation to hoard food. Based on these and other observations, sickness behavior is now considered as the expression of a motivational system that reorganizes the organism’s perception and action.

Sepsis-associated encephalopathy and delirium

Septic encephalopathy or brain dysfunction occurs in up to 70% of sepsis patients.^[7] Encephalopathy was replaced by delirium due to a general medical condition in Diagnostic and Statistical Manual of Mental Disorders-IV and described as a disturbance in consciousness or perception or change in cognition characterized by reduced ability to focus or sustain attention and fluctuating changes in mental status, ranging from confusion to coma. However, functioning of the entire neuraxis and peripheral nerves can be disturbed during sepsis. Indeed, abnormal or slowed postural or protective reflexes have often been reported to occur during sepsis.^[8-10] Therefore, and notwithstanding the fact that sickness behavior can clearly be adaptive in response to an acute infection, it should also be clear that during severe sepsis important cerebral dysfunction can occur.

Why immune-to-brain signaling?

Fever can be defined as “a state of elevated core temperature” that is “due to an elevation of the set-point of body temperature, according to which the higher temperature is actively established by the operation of thermo-effectors”.^[11] Since the set-point of body

temperature is regulated by the preoptic hypothalamus, this gave rise to the question how the immune system signals the brain to bring about fever when animals are infected with bacteria.

The view of sickness behavior as being due to a motivation also implies immune-to-brain signaling. Indeed, even though the brain circuits underlying every single postulated motivational system are not known in full detail, motivations are mediated by brain circuits comprising the hypothalamus and limbic system. Thus, the occurrence of sickness behavior in response to exposure of animals to bacteria also begged the question as to how such events are signaled to the brain. In what follows the actions of the pro-inflammatory cytokine interleukin-1 (IL-1) on peripheral nerves, brain circumventricular organs and the blood-brain barrier (BBB), IL-1 transport across the BBB and IL-1 synthesis in the brain will be discussed as immune-to-brain signaling pathways.

FROM IMMUNE-TO-BRAIN SIGNALING TO NEUROINFLAMMATION?

Interleukin-1 as a mediator of immune-to-brain signaling that cannot passively cross the BBB

Once bacteria or their components have entered host tissues, they activate innate immune cells, including monocytes-macrophages and neutrophils, to generate an inflammatory response mediated by cytokines, such as interleukin-1 β (IL-1 β).^[12,13] Peripheral injection of IL-1 β mimics the symptoms of sickness and the signs of disease normally seen after infection.^[14] Conversely, systemic administration of the naturally occurring IL-1 receptor antagonist (IL-1ra) alleviates or blocks systemic bacterial LPS-induced fever in rats.^[15,16] In addition, peripheral IL-1ra also attenuates the reduction in locomotor activity and social interactions after systemic LPS injection.^[17] Thus, IL-1 mediates, at least in part, fever and sickness behavior when these occur in response to the administration of bacterial LPS. However, the fact that IL-1 is a hydrophilic large peptide of 17 kDa means that it cannot passively cross the BBB separating the brain parenchyma from blood. Consequently, proposing and testing IL-1-mediated immune-to-brain signaling pathways became a topic of intense research activity from the 1990s onwards.

Circulating IL-1 acting in brain circumventricular organs lacking a BBB

In the early 1980s, antipyretics were already known to inhibit the synthesis of prostaglandins, a family of small lipophilic mediators. IL-1 was subsequently found to induce the formation of prostaglandin E₂ (PGE₂) by stimulating the synthesis of the rate-limiting enzyme

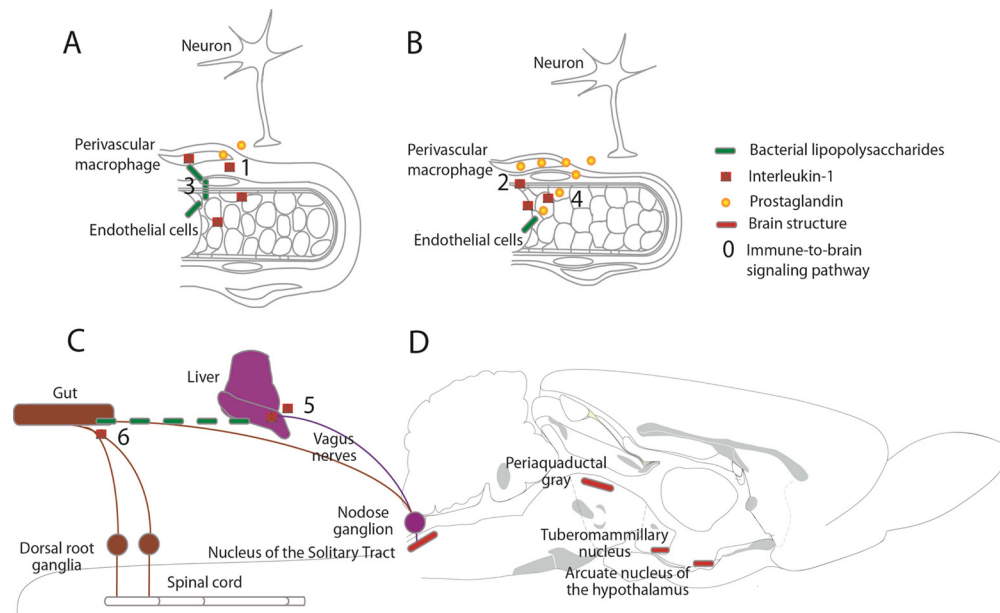


Figure 1: Immune-to-brain signaling pathways involving interleukin-1 in brain circumventricular organs (A), at the blood-brain barrier (B) and peripheral nerves (C) and substrates of altered behavior (D) during peripheral inflammation secondary to infection

cyclooxygenase in monocytes, fibroblasts, muscular and nervous tissue.^[18] Around the same time, lesions of the anteroventral wall of the third brain ventricle, which contains the organum vasculosum of the lamina terminalis (OVLT), a brain circumventricular organ where the blood-brain barrier is absent, were shown to suppress the fever response to peripheral administration of bacterial LPS or IL-1.^[19,20] In addition, local injection of PGE₂ into the OVLT resulted in higher fever than its administration in the preoptic area.^[21] This led to the first hypothesis of IL-1-mediated immune-to-brain signaling pathway according to which circulating IL-1 acts in the OVLT to induce the production of PGE, which, in turn, modulates thermosensitive neurons in the preoptic area [Figure 1A-1].^[22]

Transport of circulating IL-1 across the BBB

A more general alternative hypothesis of immune-to-brain signaling was put forward after it was shown that intravenously administered radioactive recombinant IL-1 α or β entered the brain by a saturable transport mechanism [Figure 1B-2].^[23,24] Subsequent studies provided evidence indicating that transport over the brain endothelium making up the BBB contributed more to the presence of intravenously injected IL-1 in the brain than the contained leakage from a circumventricular organ.^[25] At the same time evidence for the presence of IL-1 receptors in the brain accumulated.^[26-34] Moreover, administration of IL-1 α into the lateral brain ventricle was found to attenuate the reduction in social exploration and food-motivated behavior, but not the fever response, after systemic IL-1 β injection.^[35,36] These findings thus

clearly indicate that IL-1 can act in the brain to bring about changes in behavior after its peripheral injection.

Brain production of IL-1

As early as 1984, bioactive IL-1 had been detected in the brains of mice that were given systemic bacterial LPS endotoxin and showing signs of sickness behavior.^[37] In 1992, the presence of IL-1 β immunoreactive mononuclear cells around blood vessels of the central nervous system (CNS) was observed several hours after an intravenous injection of a high dose of bacterial LPS in rats.^[38] When using lower doses of bacterial LPS injected either intravenously or intraperitoneally, cells in the circumventricular organs and choroid plexus were found to synthesize IL-1 β [Figure 1A-3].^[39-43] Soon after this, mRNA for the LPS-recognizing receptor Toll-like Receptor 4 was found to be expressed in these organs.^[44] Interestingly, IL-1 β was also found to be synthesized by cells with microglial morphology in brain parenchyma adjacent to circumventricular organs, including in the arcuate nucleus of the hypothalamus and in the nucleus of the solitary tract, beyond 4 h after peripheral LPS injection.^[43] Bioactive IL-1 is found in plasma but not in the brain 2 h after systemic LPS administration, whereas at 6 h IL-1 is bioactive in the brain but not in plasma.^[45] When IL-1 α was given into the lateral brain ventricle at the time that brain IL-1 was bioactive, it was found to attenuate reduced social exploration without affecting the fever response after peripheral LPS injection.^[46] The subsequent finding that peripheral administration of a neutrophil-neutralizing antiserum attenuates brain IL-1 β expression as well as the reduction in locomotor activity

24 h after systemic injection of LPS suggests that neutrophil infiltration into brain provides an important source of IL-1 β at later time points.^[47] Hence, brain IL-1 production and action sustains sickness behavior after systemic LPS administration, but not necessarily fever.

Circulating IL-1 inducing prostaglandin synthesis at the BBB

In the early 1990s, a second form of the rate-limiting prostaglandin synthesizing enzyme cyclooxygenase (COX) was identified and found to be induced along brain blood vessels after peripheral administration of bacterial LPS or IL-1 β .^[48-50] Concurrently, it was shown that most IL-1 receptors in the rodent brain were expressed along blood vessels making up the BBB [Figure 1B-4].^[31-34] This led to the hypothesis according to which circulating IL-1 acts on its signaling receptor expressed by brain endothelial cells to induce COX-2-mediated prostaglandin production, which, given their lipophilic profile, can diffuse across the BBB and activate prostaglandin receptors on neurons to bring about sickness symptoms.^[48,49] Testing of this hypothesis using mice in which endothelial cells were deficient in COX-2 or PGE synthase showed that although the fever response to an intraperitoneal injection of IL-1 β was abolished in these animals, the reduction in locomotor activity was not affected.^[51,52] So, in accordance with a hypothesis put forward in 2002,^[53] BBB prostaglandin synthesis underlies IL-1 β -induced fever, but not necessarily sickness behavior.

IL-1 action on peripheral nerves

At least two of the classical symptoms of local inflammation, heat and pain, correspond to sensory modalities and thus involve neural activation. Interestingly, local IL-1 β application under the skin of a rat paw was shown in 1994 to increase the sensitivity to mechanical and heat stimuli and to augment electric activity of sensory nerve fibers.^[54] Based on these considerations, IL-1 was proposed to act on neural sensory afferents to signal the brain and bring about symptoms of sickness [Figure 1C-5]. In accordance with this hypothesis, subdiaphragmatic vagotomy was shown to attenuate the reduction in social exploration and food-motivated behavior, conditioned taste aversion, increased sleep and hyperalgesia as early as 2 h after intraperitoneal administration of IL-1 β or bacterial LPS.^[55-59] Reversible inactivation of the dorsal vagal complex, which contains the central terminals of vagal sensory fibers, by local anesthesia also restored social exploration after intraperitoneal LPS administration.^[60] Moreover, the febrile responses to systemic administration of low doses of IL-1 β or LPS were also attenuated by prior subdiaphragmatic vagotomy, whereas fevers after higher doses were

unaffected by this procedure.^[61-68] Furthermore, selective chemical lesions of C-fiber afferents after intraperitoneal injection of capsaicin in adult rodents were found to also attenuate the first phase of the fever response in response to systemic administration of LPS.^[69] This suggests that LPS-induced rapid fever responses may involve vagally-mediated immune-to-brain signaling with later fever peaks or prolonged fever depending on prostaglandin synthesis at blood-brain interfaces.

Soon after the first vagotomy studies, intravenous IL-1 β administration was found to increase afferent discharge activity of the hepatic and gastric branches of the vagus nerve in a prostaglandin-dependent way.^[70-72] Subsequently, vagal paraganglia and the nodose ganglion containing the neuronal cell bodies of the vagus nerve were observed to bind IL-1ra and to express the signaling IL-1 receptor.^[72,73] In addition, spinal sensory afferent cell bodies in dorsal root ganglia also express mRNA coding the signaling IL-1 receptor and their peripheral fibers respond to local administration of IL-1 β by increasing their activity as well as their sensitivity to heat *in vitro*.^[74,75] Interestingly, ganglia of both vagal and spinal sensory nerves express TLRs and some bacteria have been shown to directly activate sensory neurons.^[76-78] Taken together, these findings suggest that low doses of IL-1 β or bacterial fragments may act on sensory nerve fibers to signal the central nervous system to give rise to early fever, hyperalgesia and sickness behavior [Figure 1C-6].

ACTIVATION OF NEURAL SUBSTRATES OR INITIATION OF NEURODEGENERATION DURING SYSTEMIC INFLAMMATION?

Neural substrates of acute sickness behavior *Possible neural substrates of bacterial LPS-induced hypophagia*

The basomedial hypothalamus plays an important role in the long-term regulation of food intake. Interestingly, lesions of the arcuate nucleus of the hypothalamus [Figure 1D] exacerbated the anorectic effect of peripheral IL-1 β administration.^[79] However; antagonizing the action of α -melanocyte stimulating hormone, which is produced by neurons of the arcuate nucleus of the hypothalamus, on central melanocortin receptors has been found to alleviate hypophagia after the peripheral administration of either IL-1 β or LPS from 8 h onwards.^[80,81] These findings indicate that the overall role of the arcuate hypothalamus is to counter reduced food intake, even though activation of some of its composing neurons does seem to play a role in sustained inflammation-associated hypophagia.

The brainstem mediates short-term regulation of food

intake and glutamatergic projections from the nucleus of the solitary tract [Figure 1D] to the parabrachial nuclei reduce food intake.^[82] Interestingly, brainstem metabotropic glutamate receptor antagonism was found to attenuate hypophagia and to increase food intake during the first 6 h after peripheral LPS to a greater extent than in vehicle-treated animal.^[83] In parallel, intra fourth ventricle administration of this metabotropic glutamate receptor antagonist also reduced expression of the cellular transcription activation marker c-Fos in the nucleus of the solitary tract and lateral parabrachial nuclei.^[83] These findings suggest that brainstem glutamatergic circuits are part of the neuronal substrates that rapidly reduce food intake under inflammatory conditions.

Potential neural substrates of bacterial LPS-induced reduced exploration

Interestingly, all intervention strategies restoring social exploration after intraperitoneal LPS injection also reduce induction of the cellular transcription activation marker c-Fos in the central nucleus of the amygdala (CEA) and the oval bed nucleus of the stria terminalis (ovBNST).^[46,60,66] The amygdala and the bed nucleus of the stria terminalis project to the ventrolateral periaqueductal gray (vlPAG) [Figure 1D] in the pons,^[84] the stimulation of which induces immobility and reduced social interactions.^[85] Thus, c-Fos expressing neurons in the CEA and ovBNST may inhibit GABAergic neurons projection to the vlPAG resulting in immobility and reduced social interactions.^[53] In addition, reduced exploration of different environments and devices has been shown to be associated with c-Fos expression in the ventral tuberomammillary nucleus [Figure 1D] after peripheral bacterial LPS injection.^[86,87] Reduced activation of the ventral tuberomammillary nucleus may therefore be part of the neural substrates underlying reduced environmental exploration during sickness.

The realization that endogenous IL-1 β can act in the brain to bring about sickness behavior raised the question as to where in the brain it binds to the signaling IL-1 receptor to reduce social and environmental exploration. Although the hippocampus is one of the most prominent sites of neuronal IL-1 receptor expression (see transport of circulating IL-1 across the BBB), no published study to date seems to have critically addressed the involvement of hippocampal IL-1 receptors in mediating sickness behavior. It is important to point out that this is not because such approaches are not available. Indeed, several groups have employed hippocampal overexpression of the IL-1 α . These studies addressed the role of hippocampal IL-1 in mediating responses to psychological stressors, such as electrical shocks and chronic isolation, and not those occurring upon exposure

to infectious microorganisms or their components.^[88,89] However, the findings of Chaskiel *et al.*^[83] show that selective lesioning of IL-1 receptor-expressing cells in the hippocampus does not alter the reduction in social exploration after intracerebroventricular administration of IL-1 β in mice. Thus, IL-1 receptors in the hippocampus do not seem to mediate the component of sickness behavior that involves reduced exploration.

Severe sepsis may lead to neurodegeneration

Magnetic resonance imaging of septic patients with brain dysfunction has indicated the presence of vasospasms in the medial cerebral arteries and ischemic strokes in brain gray matter as well as white matter edema.^[90-92] (see for review^[93]) Post mortem examination of brains of patients who died from sepsis revealed intracerebral hemorrhage, necrotic vessels with infiltrating leukocytes, increased perivascular spaces, microglial activation, cerebral IL-1 β and TNF- α expression, neuronal apoptosis as well as perivascular dissociation of myelinated fibers and demyelination.^[91,94,95] Clinical research thus clearly indicates the occurrence of neuroinflammation that may, in turn, lead to neurodegeneration.

Recently, several groups have employed cecal ligation and puncture (CLP) in rodents to study CNS dysfunction associated with sepsis. In these models, food intake and social interactions were found to be reduced during the first days, while activity and body temperature were altered and some conditioning learning tasks impaired for several weeks after sepsis induction.^[96-99] Increased cerebral pro-inflammatory cytokine expression, impaired BBB function, cortical perivascular edema, glial cell activation, brain leukocyte adhesion and infiltration as well as neuronal death and degeneration in cortical and subcortical areas have all been observed from the first day of CLP onwards.^[96-105] Thus, relevant animal models of sepsis have been shown to result both in transient sickness behavior and in long-term learning deficits that are accompanied by neuroinflammation and neurodegeneration.

CONCLUSION

During the systemic inflammatory response to acute infection, and when in a safe environment, endothermic mammals typically display reduced activity and food intake, increased sleep, and the adoption of a curled-up position. These changes in behavior, in concert with fever, are adaptive in that they contribute to host survival. Although the precise neurobiological substrates still need to be worked out, they are brought about by immune-to-brain signaling pathways that involve rapid activation of peripheral nerves and glutamatergic brainstem circuits as well as slower IL-

1 β action in the brain activating limbic and possibly ventral hypothalamic structures. Notwithstanding the fact that they are mostly adaptive acutely, behavioral changes during inflammation may also reflect brain dysfunction in severe sepsis-associated delirium or become maladaptive and result in depression due to medical conditions that involve long-term inflammatory episodes with pain or discomfort. The mechanisms underlying these conditions are presently ill-understood even though neuroinflammation and neurodegeneration occur during and subsequent to sepsis-associated brain dysfunction, respectively.

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There are no conflicts of interest.

Patient consent

No patient involved.

Ethics approval

This article does not contain any studies with human participants or animals.

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