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A Neuro-Endocrine-Immune Symphony

SUMMARY

The inflammatory response provides a powerful means for the body to fight an infection. The neuroendocrine system plays an important role in controlling the magnitude and duration of this response and maintaining homeostasis in the inflamed state. Glucocorticoids released following activation of the hypothalamic-pituitary-adrenal axis limit the synthesis of pro-inflammatory molecules, whereas the neurohypophysial hormones vasopressin and oxytocin act both within the brain and in the periphery to maintain cardiovascular and metabolic homeostasis and to limit the rise in body temperature.

Pathogens and their hosts have been in battle for millennia, with host organisms having evolved multiple mechanisms to deal with pathogens. Foremost among these is the 'innate immune response' that consists of a variety of inflammatory responses designed to compromise the ability of pathogens to effectively colonise our bodies. These include a reduction of iron availability to inhibit bacterial replication; changes in behaviour that may limit the spread of infection and conserve body resources; alterations in body temperature usually manifested as a fever; and redirection of neuroendocrine outputs to control the inflammation. As most of these responses are orchestrated by the brain, a variety of mechanisms have evolved to enable the brain to detect and respond to infection in the body.

Detect the enemy

The 'innate' immune response is mobilised upon first exposure to a pathogen. Specific surface molecules on pathogens are recognised by special receptors called toll-like receptors on peripheral immune cells and even on endothelial cells that line brain blood vessels. Activated immune cells synthesise pro-inflammatory peptide molecules called cytokines, among which are interleukin (IL)-1β, IL-6 and tumour necrosis factor α; these cytokines bind to receptors on endothelial and perivascular cells of brain blood vessels and induce synthesis within the brain of a variety of other inflammatory molecules, including prostaglandins and additional cytokines. As a part of the repertoire of neuronal responses to immune activation, these molecules alter the activity of neuroendocrine cells to influence peripheral hormone levels and endocrine dependent behaviours.

Keeping control

The inflammatory response is powerful and important in fighting infection but, if left unchecked, could have deleterious effects on the body. Thus, concurrent with the generation of the 'pro'-inflammatory response, an 'anti'-inflammatory one occurs that includes the synthesis of anti-inflammatory cytokines and, most importantly activation of the neuroendocrine system. The hypothalamus in particular is an important structure for mediating these effects, through its ability to modulate both pituitary hormone secretion and the sympathetic nervous system. Glucocorticoids provide an important regulatory role by suppressing the generation of pro-inflammatory cytokines by cells of the immune system. Glucocorticoid release is controlled by the hypothalamic pituitary adrenal (HPA) axis and immune molecules act at multiple sites throughout this axis. Neurones in the paraventricular nucleus of the hypothalamus that synthesise corticotrophin-releasing hormone (CRH) are activated initially by prostaglandins and, subsequently, by circulating cytokines to prolong the HPA response. There are additional stimulatory effects of cytokines (especially IL-6) at both the pituitary and the adrenal to further enhance the HPA response. The neurohypophysial hormone, vasopressin, is also released both in the brain and into the circulation to counteract some of the inflammatory processes. However, vasopressin neurones appear to be somewhat less sensitive to inflammatory signals than are CRH neurones, as an immune stimulus that strongly

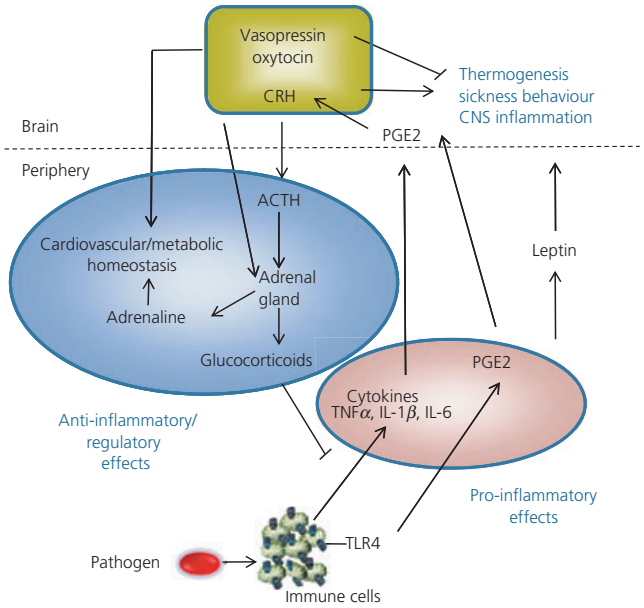

Fig. 1. Illustration of important immune neuroendocrine interactions. Cytokines and prostaglandin E that are released in response to pathogen detection by immune cells signal to the brain to activate central responses. The neuroendocrine outputs that are activated to help regulate the inflammatory response include corticosteroids, vasopressin, oxytocin and adrenaline. ACTH, adenocorticotrophic hormone; CNS, central nervous system; CRH, corticotrophin-releasing hormone; IL, interleukin; PGE2, prostaglandin E_2; TLR, toll-like receptor; TNF, tumour necrosis factor.

activates the latter is less effective with respect to inducing the early gene product, Fos, in neurohypophysial vasopressin neurones of the paraventricular nucleus. The contribution of circulating vasopressin to control the immune response is not as clear as for glucocorticoids, although there is evidence that vasopressin can down-regulate peripheral inflammatory responses; within the brain, it also has a well described action as an endogenous antipyretic to reduce the febrile response. Finally, when there is severe inflammation, leading to sepsis, the precipitous fall in blood pressure is partially countered by vasopressin-induced vasoconstriction. Oxytocin secretion also occurs during inflammation and it is considered to promote insulin and glucagon secretion and thus regulate peripheral metabolism during an infection. Other metabolic hormones may also be stimulated during inflammation. For example, leptin, a hormone important in control of food intake, mediates appetite suppression during inflammation. Some of these peripheral metabolic actions also are the result of a circulating hormone, adrenaline, as its secretion from the adrenal is also stimulated during an infection.

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It is interesting that, in concert with the activation of the HPA and neurohypophysial systems, other neuroendocrine functions may be suppressed. For example, inflammation causes suppression of the hypothalamic-pituitary-gonadal axis. This results in alterations of both reproductive endocrinology (ovarian cycle length and function) and reproductive behaviour; thus, the body's resources during an infection can be redirected away from reproduction towards controlling the infection. Interestingly, during the latter stages of pregnancy, once sufficient investment in reproduction has occurred, there are specific adaptations in the brain to circumvent these effects.

Adverse interactions

The coordinated neural, behavioural and endocrine responses to inflammation provide an important first-line defence against infection and help restore homeostasis in the body. However, in cases of where there is severe or prolonged chronic inflammation, there may be changes in brain and hormonal function that are deleterious. For example, many chronic inflammatory illnesses appear to be associated with fatigue, depression, sleep disorders and pain that can be attributed, in part, to cytokine-induced changes in glucocorticoid actions within the brain. Of particular interest is the fact that we now know that many aspects of brain function, in particular the sensitivity of the hypothalamic pituitary adrenal axis, can be permanently altered in response to stressors, including infection, experienced by a pregnant mother or newborn. It will be interesting to learn more about how the body's neuroendocrine systems are altered as a result of these early interventions.

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