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Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens

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Abstract

The central nervous system (CNS) regulates innate immune responses through hormonal and neuronal routes. The neuroendocrine stress response and the sympathetic and parasympathetic nervous systems generally inhibit innate immune responses at systemic and regional levels, whereas the peripheral nervous system tends to amplify local innate immune responses. These systems work together to first activate and amplify local inflammatory responses that contain or eliminate invading pathogens, and subsequently to terminate inflammation and restore host homeostasis. Here, I review these regulatory mechanisms and discuss the evidence indicating that the CNS can be considered as integral to acute-phase inflammatory responses to pathogens as the innate immune system.

The local acute-phase inflammatory response is characterized by *rubor* (redness), *dolor* (pain) and *calor* (heat). Although these are all cardinal clinical features of inflammation, their proximal triggers are neural in origin. Similarly, the systemic acute-phase response also involves key neural elements — fever and activation of the central hormonal-stress response — mediated by the effects of immune factors on the hypothalamus. The cellular and molecular components of the innate immune system provide the first line of defence against invading pathogens¹, through recognition of pathogen-associated molecular patterns (PAMPs), and initial nonspecific cellular and humoral responses². However, immune mediators and cytokines that are subsequently released by the innate immune system rapidly activate neural responses that both amplify local immune responses to clear pathogens and trigger systemic neuroendocrine and regional neural responses that eventually return the system to a resting state. Although this interplay constitutes an important feedback loop that optimizes innate inflammatory responses to invading pathogens, prolonged or inappropriate central nervous system (CNS) counter-regulatory responses might also predispose the host to excess inflammation (in the context of inadequate hormonal suppression) or uncontrolled infection (in the context of excess or prolonged anti-inflammatory hormonal responses). These can lead to pathological and lethal effects, including toxic shock, tissue damage and death.

Competing interests statement

The author declares no competing financial interests.

DATABASES

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AP1 | CCL2 | CRH | CXCL8 | IFN γ | IL-1 β | IL-10 | IL-12 | JNK | α -MSH | MyD88 | NF- κ B | NPY | TLR2 | TLR4 | TNF

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In this Review, I describe how specific elements of the CNS and innate immune system interact, present evidence indicating that these two systems form a cohesive and integrated early host response to pathogens, and identify areas for future research efforts to fully elucidate this interaction.

General principles and areas of controversy

The nervous system has several characteristics that make it an ideal partner with the innate immune system in immediate nonspecific host defence. It reacts rapidly (in the order of milliseconds to minutes) to many types of nonspecific environmental stimuli. Neurotransmitters and neuropeptides often bind to G-protein-coupled receptors that activate the same secondary signalling pathways (such as those including protein kinase A, cyclic AMP and protein kinase C) as signals triggered by immune mediators. Immune mediators often interact with neuro-transmitter receptors³ and also modulate neural pathways that are integral to the acute-phase response, such as pain^{4,5}. In turn, neuropeptides (such as substance P) trigger the release of pro-inflammatory mediators (such as histamine) that might amplify or facilitate inflammation by enhancing vasodilation, blood flow, vascular leakiness and leukocyte trafficking to sites of inflammation.

G-protein-coupled receptors

Cell-surface receptors that are coupled to G-proteins, and have seven transmembrane-spanning domains. The acetylcholine, adrenergic and neuropeptide receptors are all members of this family. Typically, activation of the G-protein-coupled receptor produces a diffusible second messenger that, in turn, triggers various biochemical cascades.

The effects of neural factors on inflammatory responses, while rapid in onset, might vary over time, enhancing or dampening these responses^{6,7}. Such variations in effects, coupled with the lower magnitude of neural compared to immune stimuli (2–3 fold compared to more than 1,000 fold, respectively) might be considered by some as evidence that neural regulation of inflammatory responses are of little biological relevance. In fact, this pattern and scale of neural effects are well suited for physiological modulators, because normal endogenous systems are characterized by tempered oscillations over time, rather than by large changes⁸. The nervous system is therefore ideally positioned to modulate the immediate nonspecific inflammatory response to immune stimuli and partner with it in a unified response to pathogens.

CNS-mediated regulation of immunity occurs through systemic, regional and local routes (FIG. 1). The peripheral nervous system provides a first line defence at local sites of inflammation through the release of neuropeptides that generally increase local inflammatory responses. The sympathetic (or adrenergic) nervous system (SNS), and the parasympathetic (or cholinergic) nervous system generally inhibit inflammation at a regional level, through innervation of immune organs. Neuroendocrine responses control inflammation at a systemic level by the hypothalamic–pituitary–adrenal (HPA) axis through the anti-inflammatory effects of glucocorticoids released from the adrenal cortex; by the hypothalamic–pituitary–gonadal (HPG) axis through sex hormones released from the ovaries and testes; and by the hypothalamic–pituitary–thyroid hormone axis through thyroid hormones released from the thyroid gland.

Sympathetic nervous system

(SNS). A division of the autonomic nervous system that consists of fibres projecting from the central nervous system, through ganglia near the spinal cord, to innervate organs such as the heart, lungs, intestine, blood vessels and sweat glands. In general, sympathetic nerves dilate the pupils, constrict peripheral blood vessels and increase heart rate.

Parasympathetic nervous system

A division of the autonomic nervous system that consists of nerve fibres projecting from the central nervous system and sacral portion of the spinal cord, which extend to nerve-cell clusters (ganglia) at specific sites, from which fibres are distributed to blood vessels, glands and other internal organs. Functions of parasympathetic nerves include slowing the heart rate; inducing the secretion of bile, insulin and digestive juices; dilating peripheral blood vessels; and contracting the bronchioles, pupils and oesophagus.

Extensive literature has shown that many immune cells contain the molecular machinery required to respond to neural factors, including receptors for neurotransmitters, neuropeptides and neurohormones, and the components of their signalling pathways. However, some debate still exists regarding the specific immune-cell types that express neural receptors⁹ and the biological significance of neural modulation of immune responses. This is, in part, because the effects of neural factors on some elements of innate immunity, such as macrophages and cytokine production, have been more extensively studied than others, such as dendritic cells (DCs) and Toll-like receptor (TLR) expression, which have been only superficially addressed. In addition, the mechanisms of the effects of neural factors on many immune responses have not been fully investigated. Also, neural factors might have varying effects over the time course of an immune response, or at different stages of immune-cell maturation^{10,11}.

Similarly, although the effects of pathogen products, such as bacterial lipopolysaccharide (LPS), on CNS responses have been long established, detailed analyses of the mechanisms of these effects have only recently begun to be addressed. Therefore, issues such as the potential differences of various PAMPs on patterns of CNS activation have not been studied. It has only recently been shown that LPS can trigger CNS inflammation directly through TLR4, without the involvement of peripheral cytokines¹²; that microglia in the CNS express TLRs after exposure to various pathogens or pathogen products, such as LPS, peptidoglycans and CpG DNA; and that mice deficient in the TLR adaptor protein MyD88 (myeloid differentiation primary-response gene 88) show a decreased CNS-mediated inflammatory response to *Streptococcus pneumoniae*^{2,13,14}.

HPA-axis-mediated regulation of immunity

The HPA axis provides an important physiological feedback loop of inflammation through the anti-inflammatory effects of glucocorticoids (BOX 1). Although the Nobel Prize was awarded for the use of glucocorticoids in the treatment of rheumatoid arthritis in 1950 (REF. 15), it was not until recently that the important physiological role of glucocorticoids in regulating multiple aspects of immune-cell function was recognized. For example, glucocorticoids can cause a shift in adaptive immune responses from a T helper 1 (T_H1) type to a T_H2 type, largely through inhibiting the production of the T_H1-cell-inducing cytokine interleukin-12 (IL-12) by DCs and macrophages¹⁶, and in physiological concentrations, glucocorticoids can increase delayed-type hypersensitivity⁶. Moreover, as highlighted in this Review, they also regulate the innate immune response to bacterial and viral infection.

Delayed-type hypersensitivity

A cellular immune response to antigen that develops over 24–72 hours with the infiltration of T cells and monocytes, and depends on the production of T helper 1-cell-specific cytokines.

Box 1 Components of the hypothalamic–pituitary–adrenal axis

The physiological feedback loop through which glucocorticoid release is regulated consists of a set of brain regions (the hypothalamus) and endocrine organs (the pituitary and cortex of the adrenal glands) known as the hypothalamic–pituitary–adrenal (HPA) axis (FIG. 1). Systemic exposure of the host to pro-inflammatory stimuli (such as bacterial lipopolysaccharide) as well as to physical or psychological stimuli, results in secretion of corticotropin-releasing hormone from cells of the paraventricular nucleus of the hypothalamus into the hypophyseal blood supply around the pituitary gland. This stimulates the release of adrenocorticotrophic hormone from the anterior pituitary into the blood, which in turn stimulates the synthesis and release of endogenous glucocorticoids from the adrenal cortex (FIG. 1). This bi-directional communication between the immune system and the central nervous system (CNS)^{136,137}, in which cytokines, including interleukin-1 (IL-1), IL-6 and tumour-necrosis factor (TNF), signal to the brain, and the brain responds by regulating the immune system, in part, through the anti-inflammatory effects of glucocorticoids, constitutes the main hormonal negative-feedback loop for CNS regulation of immunity. In addition to their role in regulating the immune system, glucocorticoids also downregulate the HPA axis itself, and are essential for the maintenance of several homeostatic mechanisms in the body, including the CNS and cardiovascular system, as well as for metabolic homeostasis.

Impaired HPA-axis function and disease

A blunted HPA axis is seen in a wide range of autoimmune and inflammatory diseases across several species, such as thyroiditis and scleroderma in chickens¹⁷; systemic lupus erythematosus (SLE) in some mouse models (such as MRL mice); inflammatory arthritis, experimental allergic encephalomyelitis and other autoimmune and inflammatory diseases in certain susceptible rat strains¹⁸; and rheumatoid arthritis, Sjogren's syndrome, SLE, irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia in humans^{19,20}. Furthermore, interruptions of the HPA axis, through surgical interventions (adrenalectomy or hypophysectomy) or through pharmacological intervention with glucocorticoid antagonists (such as RU486), renders otherwise relatively inflammation-resistant animals highly susceptible to inflammation and increases mortality from septic shock following exposure to infectious or pro-inflammatory triggers, such as streptococcal cell walls²¹, *Salmonella typhimurium*²², cytomegalovirus²³ and Shiga toxin²⁴. Conversely, reconstitution of the HPA axis by treatment with exogenous glucocorticoids or by hypothalamic transplantation²¹ reverses this effect and prevents mortality in these animal models^{21–25}.

Glucocorticoid resistance

Impaired glucocorticoid control of inflammation might also result from lack of glucocorticoid responsiveness, or glucocorticoid resistance, of target cells or tissues, and might contribute to autoimmune, inflammatory and allergic diseases^{26–31} (TABLE 1). Glucocorticoid receptors are members of a superfamily of nuclear hormone receptors (which includes the receptors for progesterone, oestrogen, androgen, mineralocorticoid and thyroid hormone) that reside in the cytoplasm or nucleus of almost all cells and, once bound to hormone, move to the nucleus and function as transcription factors³². Glucocorticoid resistance might result from mutations or polymorphisms of glucocorticoid receptors^{26,33,34} or impaired interactions of the receptor with one of the >200 cofactors, such as corticosterone-binding globulin³⁵ and multidrug resistance-1 (REF. 36), that are required for glucocorticoid-receptor function. In addition, expression of glucocorticoid receptor- β , an inactive form that does not bind ligand or activate gene transcription^{37,38}, is induced during chronic inflammation³⁹, and might result in relative glucocorticoid resistance in such states.

Finally, pathogens might themselves induce gluco-corticoid resistance. We have recently shown that *Bacillus anthracis* lethal toxin selectively and potently represses the activity of glucocorticoid receptor and other nuclear hormone receptors in a non-competitive fashion⁴⁰, by preventing glucocorticoid-receptor binding to DNA through interactions with one or more of its cofactors or accessory proteins⁴⁰. Should other bacterial products behave similarly, it could provide a mechanism by which invading pathogens might interfere with the host's glucocorticoid-mediated negative-feedback control of inflammation, potentially predisposing the host to toxic shock. Indeed, although the precise mechanisms of this effect are unclear, we have shown that interference with glucocorticoid production, such as by adrenalectomy, render otherwise anthraxlethal-toxin-resistant mouse strains highly susceptible to rapid death from this toxin⁴¹.

Excess HPA-axis activity and illness

An excess of circulating glucocorticoids, which can occur as a result of chronic stress, is associated with increased susceptibility to viral infections, prolonged wound healing or decreased antibody production after vaccination^{42,43}. Fluctuations in the levels of circulating glucocorticoids, such as circadian variations or fluctuations that occur during exercise, also suppress IL-1 β and tumour-necrosis factor (TNF) production by leukocytes^{44,45}.

Taken together, these studies indicate that a fine balance of glucocorticoids is required for the maintenance of immune homeostasis and to avoid excessive immunosuppression and death from overwhelming infection, or death from shock resulting from excessive cytokine and pro-inflammatory responses (FIG. 2).

Glucocorticoid effects on innate immune-cell function

In general, glucocorticoids suppress maturation, differentiation and proliferation of all immune cells, including DCs and macrophages (FIG. 2). Glucocorticoids inhibit DC differentiation depending on the stage of maturation⁴⁶ and the DC subtype¹¹. Glucocorticoids also reduce the capacity of DCs to promote allostimulatory responses and efficient activation of naive T cells *in vitro*, possibly owing to downregulation of expression of MHC class II and co-stimulatory molecules^{46,47}. *In vivo*, dexamethasone (a synthetic glucocorticoid) impairs the ability of rat thymic DCs to produce IL-1 β and TNF, but not IL-10 (REF. 48). Dexamethasone also inhibits IL-12p40 production by LPS-stimulated human monocytes by downregulation of activation of JUN N-terminal kinase (JNK), mitogen-activated protein kinase (MAPK), activator protein 1 (AP1) and nuclear factor- κ B (NF- κ B)⁴⁹. In addition, in both mice that are transgenic for corticotropin-releasing hormone (CRH) (which chronically overproduce glucocorticoids) and in wild-type mice that are treated chronically with corticosterone⁵⁰, splenic germinal centres fail to form, owing to impaired development of mature follicular DC networks.

Glucocorticoids regulate gene transcription by binding to hormone-response elements in the promoters of various genes, but they can also regulate gene expression through interaction with other transcription factors, such as NF- κ B or AP1 (REF. 32). For example, NF- κ B normally exists in an inactive state, bound to inhibitor of NF- κ B (I κ B). Upon cell activation, NF- κ B is released from I κ B and translocates to the nucleus, where it can bind to specific promoter sites and upregulate the expression of pro-inflammatory cytokines⁵¹ (FIG. 3). Glucocorticoids inhibit NF- κ B by interacting with RelA (also known as p65, a subunit of NF- κ B) and by inducing the expression of I κ B⁵¹. Consistent with this inhibition of NF- κ B, physiological doses and preparations of glucocorticoids (such as corticosterone and hydrocortisone) lead to decreased production of pro-inflammatory cytokines (such as IL-1, IL-6 and TNF)⁵².

Glucocorticoid effects on immune-cell trafficking

Both endogenous and synthetic (dexamethasone) glucocorticoids inhibit the expression of many cell-adhesion molecules that are involved in cell trafficking, including intracellular adhesion molecule 1 (ICAM1), endothelial-leukocyte adhesion molecule 1 (ELAM1; also known as E-selectin)⁵³ and vascular adhesion molecule 1 (VCAM1)^{54,55}. Glucocorticoids also inhibit the production and secretion of chemokines, such as CC-chemokine ligand 2 (CCL2; also known as MCP1) and CXC-chemokine ligand 8 (CXCL8; also known as IL-8) by eosinophils⁵⁶, as well as expression of the mRNA encoding the eosinophil chemoattractant IL-5 by mast cells and T cells^{57,58}. Finally, dexamethasone downregulates T-cell expression of CCL8 (also known as MCP2) and CCL7 (also known as MCP3), which are chemotactic for many cell types including monocytes, DCs, and natural killer (NK) cells⁵⁹.

Glucocorticoid effects on TLR expression

Although the effects of glucocorticoids on TLR expression by immune cells have not been addressed, recent studies indicate that glucocorticoids might alter TLR expression levels of non-immune cells. For example, in respiratory epithelial cells, dexamethasone upregulates TLR2 mRNA levels⁶⁰, and might function synergistically with TNF and interferon- γ (IFN γ)^{60,61}. Glucocorticoids can also upregulate expression of TLR2 mRNA by human epithelial cells *in vitro*, through upregulation of MAPK phosphatase 1 (MKP1)⁶². Interestingly, TLR2-deficient mice have an impaired corticosterone response to LPS, which is related to decreased amounts of IL-1, IL-6 and TNF in the blood and adrenal glands (REF. 63). These mice also have increased mortality rates when exposed to *Mycobacterium tuberculosis* and *Staphylococcus aureus*^{64,65}. TLR2 and TLR4 have also been found to be expressed in cells of the human adrenal cortex⁶³. Although their function in this location has not been defined, further clarification of interactions between immune cells, pathogens and TLRs expressed in the adrenal cortex could elucidate the role of this gland in pathogen defence. Indeed, recent studies indicate that during viral infection an increased IL-6 response might directly induce adrenal glucocorticoid responses that are independent of hypothalamic CRH⁶⁶, indicating more of a direct role for the adrenal glands in host defence.

Together, these effects of glucocorticoids on innate immune responses tend to prevent immune-cell trafficking from immune organs to sites of inflammation, reduce activation of innate immune cells and cytokine production at sites of inflammation, and dampen the inflammatory response (TABLE 2).

Regional SNS control of immunity

The SNS includes a neuronal component that regulates immunity at a regional level through the innervation of immune organs and the release of noradrenaline, and a hormonal component that regulates immunity systemically through the release of adrenaline from the medulla of the adrenal glands (BOX 2).

Noradrenaline

The primary neurotransmitter of the sympathetic nervous system. It is a biogenic amine derived from tyrosine and its metabolite dopamine, which is converted to noradrenaline by the enzyme β -hydroxylase.

Adrenaline

A neurotransmitter of the sympathetic nervous system. It is a biogenic amine derived from tyrosine and its metabolite dopamine, which is converted to adrenaline from noradrenaline by the enzyme phenylethanolamine-*N*-methyl transferase.

Box 2 Components of the sympathetic nervous system

The neuronal component of the sympathetic nervous system consists of brain regions and noradrenergic sympathetic nerve fibres that release the neurotransmitter noradrenaline and connect central nervous system (CNS) adrenergic brainstem regions to primary and secondary lymphoid organs. Noradrenaline and related ligands bind to two forms of the adrenergic receptor, α and β , which are both classic seven-transmembrane domain G-protein-coupled receptors composed of two different subunits that assemble as heterodimers to form multiple subtypes¹³⁸. Binding of noradrenaline to β_2 -adrenergic receptors on dendritic cells and macrophages leads to upregulation of cyclic AMP and activation of protein kinase A, which in turn leads to suppression of pro-inflammatory cytokine production, such as tumour-necrosis factor (TNF), interleukin-1 (IL-1), IL-6 and IL-12 through inhibition of nuclear factor- κ B¹³⁹.

Noradrenaline effects on innate immunity

Most studies addressing the direct effects of catecholamines, such as noradrenaline, and the SNS on immunity have examined their effects on adaptive immunity and antibody production⁶⁷, and less is known about adrenergic effects on innate immunity. *In vivo* studies in which the SNS is ablated by chemical sympathectomy or interrupted surgically by cutting sympathetic nerve innervation of lymphoid organs, indicate that the SNS has an important role in regulating immunity at a regional level. Although some studies show that catecholamines and SNS activation increase immune and pro-inflammatory responses^{68,69}, most studies indicate that SNS effects are inhibitory¹⁰. Activation of the SNS that occurs following stressful stimuli, such as exercise and psychological stress, is associated with decreased NK-cell activity⁷⁰, which can be prevented by pretreatment with adrenergic receptor antagonists. Furthermore, excessive SNS-mediated signalling to the immune system caused by a large release of noradrenaline (for example, soon after chemical sympathectomy) can be immunosuppressive^{7,71}.

In vitro, noradrenaline mediates its immunosuppressive effects on DCs and monocytes by inhibiting the production of pro-inflammatory cytokines, including TNF, IL-1, IL-6 and IL-12, while upregulating the production of anti-inflammatory cytokines, such as IL-10, from these cells^{10,72}. Pharmacological blockade of adrenergic receptors has been shown to potentiate IL-6 secretion and inhibit IL-10 secretion *in vivo*^{73,74}. Noradrenaline also increases secretion of the chemotactic chemokine CXCL8 by fibroblasts isolated from patients with rheumatoid arthritis and increases the migration of NK cells, monocytes and macrophages, but inhibits DC migration *in vitro*^{10,75,76}. Noradrenaline inhibits the *in vitro* DC-chemotactic response to the chemokines CCL19 and CCL21 (which are important for DC migration from the site of antigen to regional lymph nodes), through upregulation of anti-inflammatory IL-10 production¹⁰. Taken together, it has been proposed that the effects of the SNS on DCs might not only have an anti-inflammatory role but might also contribute to the clearance of pathogens and modulation of the type and strength of the adaptive response¹⁰. However, as depletion of noradrenaline has been shown to reduce resistance to some bacterial infections⁷⁶, the role of SNS responses in bacterial host defence remains to be determined.

Neuropeptide Y effects on immune cells

Neuropeptide Y (NPY) is synthesized and released simultaneously with noradrenaline from sympathetic neurons and other cells throughout the body, including cells in the adrenal medulla and possibly immune cells⁷⁷.

NPY binds to any of five G-protein-coupled NPY receptors (Y_{1-5}), which are differentially expressed in tissues⁷⁸. The Y_1 receptor is expressed widely throughout the body, including by leukocytes, whereas the Y_2 and Y_5 receptors are mainly expressed in the CNS. Exposure of macrophages to NPY inhibits IL-6 secretion, and when co-cultured with noradrenaline, its secretion is further inhibited^{76,79}.

These studies indicate that the anatomical and molecular machinery exists to allow bi-directional signalling between the SNS and immune system. Activation of the innate inflammatory response by pathogens leads to the rapid release of innate cytokines (IL-1 and TNF) that, in turn, stimulate the SNS to release noradrenaline and related transmitters from sympathetic nerve endings in immune organs. This inhibits NK cells and macrophage pro-inflammatory cytokine production, providing negative-feedback inhibition to dampen the inflammatory response and restore homeostasis. By contrast, the noradrenaline-mediated stimulation of immune-cell migration and CXCL8 production indicates that, in some circumstances, local or regional release of noradrenaline might serve to perpetuate some aspects of local innate immune responses and inflammation, and could contribute to resolution of the response by promoting wound healing.

Adrenal medulla factor effects on immunity

Whereas noradrenaline and NPY released by sympathetic nerve endings provide regional regulation within immune organs, adrenaline and NPY released from the adrenal medulla regulate immunity systemically. Direct administration of adrenaline decreases circulating numbers of monocytes, B and T cells, and NK cells *in vivo*, by signalling through β -adrenergic receptors expressed by immune cells^{80,81}. In animal studies, although adrenaline infusion has no effect on mortality from toxic shock, β -adrenergic-receptor blockade increases mortality, highlighting the role of the SNS in this syndrome⁸¹.

In addition to adrenaline, the adrenal medulla contains and releases large amounts of IL-6 and TNF in response to inflammatory stimuli, such as LPS, IL-1 α and IL-1 β ⁸². The discovery of antimicrobial chromogranin peptides that are released simultaneously with adrenaline from chromaffin cells of the adrenal medulla⁸³ coupled with the presence of TLRs on cells of the adrenal cortex raise the interesting possibility that the adrenal glands might have a more direct role in the response to pathogens, activation of innate immune responses and clearing of infectious agents than previously thought.

In summary, most of the systemic effects of the SNS are anti-inflammatory, although some effects increase inflammation, such as the induction of chemotaxis and chemotactic chemokines such as CXCL8 (TABLE 2).

Regional parasympathetic control of immunity

The parasympathetic nervous system modulates immune responses at a regional level through both the efferent and afferent fibres of the vagus nerve. The afferent fibres of the vagus nerve can signal the presence of peripheral inflammation to the brain, through IL-1 receptors expressed by paraganglia cells located in parasympathetic ganglia⁵. Therefore, during inflammation in the gut or peritoneum, IL-1 released by activated innate immune cells binds to paraganglia cells, activates afferent fibres of the vagus nerve and induces rapid activation of parasympathetic brainstem regions. This is the first step in the 'inflammatory reflex', which leads to the release of acetylcholine from efferent vagus nerve fibres and resultant negative-feedback control of inflammation⁸⁴. Cutting the vagus nerve both prevents immune signalling to the brain with its concomitant activation of cholinergic brainstem regions and removes vagal control of inflammation and toxic shock^{5,84,85}. There is some controversy in the literature regarding the cellular source of acetylcholine that regulates inflammation⁹. It has been

suggested that the source of acetylcholine acting on macrophages is more likely to be immune-cell derived than released from nerve endings⁹.

Vagus nerve

The main nerve trunk of the parasympathetic nervous system. It contains both afferent fibres that carry signals from the periphery to the brain, and efferent fibres that carry signals from the brain to the peripheral organs that it innervates.

Cholinergic effects on innate immunity

The primary parasympathetic neurotransmitter is acetylcholine, which binds to two general receptor subtypes, nicotinic and muscarinic cholinergic receptors, each of which consist of many different subunits that heterodimerize and provide cell and tissue specificity for cholinergic effects. Both of these receptors are found in immune cells, but nicotinic receptors specifically mediate cholinergic anti-inflammatory effects in macrophages.

The main cholinergic receptor expressed on macrophages is the $\alpha 7$ subunit of the nicotinic acetylcholine receptor⁸⁶. Activation of this receptor on macrophages inhibits NF- κ B signalling, thereby inhibiting pro-inflammatory cytokine production⁸⁶ (FIG. 3). A recent report indicates that nicotine, a cholinergic agonist for the $\alpha 7$ subunit, inhibits macrophage cytokine production by recruiting JAK2 (Janus kinase 2) to the $\alpha 7$ subunit. This initiates the anti-inflammatory STAT3 (signal transducer and activator of transcription 3) and SOCS3 (suppressor of cytokine signalling 3) signalling cascade⁸⁷. Interestingly, administration of nicotine promotes the survival of animals that are exposed to various inflammatory stimuli^{88,89}, indicating that acetylcholine receptor $\alpha 7$ -subunit agonists might be useful for treatment of inflammatory disease.

The cholinergic neuronal inflammatory reflex pathway also prevents increased serum concentrations of TNF during toxic shock, through the release of acetylcholine from the vagus nerve, indicating that this pathway has an important role in preventing excessive inflammatory responses. Accordingly, vagotomy exacerbates the TNF response to inflammatory stimuli and sensitizes animals to the lethal effects of endotoxin, whereas cholinergic agonists and vagus-nerve stimulation prevent these effects⁸⁴. Acetylcholine also inhibits endotoxin-induced release of pro-inflammatory cytokines (IL-1, IL-6 and TNF) but not anti-inflammatory cytokines (IL-10) from macrophages^{86,90}.

Additional support for a role for the parasympathetic nervous system in dampening inflammatory responses is provided by acetylcholine-mediated inhibition of high mobility group box 1 (HMGB1), a protein released by necrotic cells, and activated macrophages and somatic cells during severe sepsis. HMGB1, which is secreted later than the 'classic' pro-inflammatory cytokines (12–18 hours after administration of LPS *in vivo* compared with TNF and IL-1, which peak at 2 hours and 4–6 hours, respectively)⁹¹, might signal through TLR2 and TLR4 to stimulate the production of TNF and IL-1. In turn, expression of HMGB1 is induced by activated macrophages, NK cells and mature DCs in response to IL-1, TNF and IFN γ . Consistent with a role for HMGB1 in sepsis, HMGB1-specific antibodies have been shown to prevent the lethal effects of endotoxin in animal models^{92,93}.

The effects of the parasympathetic nervous system on leukocyte trafficking are less clear, as acetylcholine has been shown to increase the production of CCL2 by monocytes⁹⁴, but both vagus-nerve stimulation and an acetylcholine agonist, acting through the $\alpha 7$ subunit, have been shown to inhibit leukocyte recruitment to endothelial cells by suppressing the expression of VCAM1 (REF. 95).

Therefore, as for glucocorticoid and SNS regulation of innate immunity, the parasympathetic nervous system is activated by cytokines released during activation of the innate immune system, and in turn provides a negative-feedback control of innate immune responses to restore homeostasis.

Local peripheral nervous system control

The peripheral nervous system regulates inflammation locally at inflammatory sites through the release of neuropeptides from sensory peripheral nerves that are involved in pain, touch and temperature perception. Peripheral neuropeptides that are known to regulate inflammation include CRH, substance P and calcitonin gene-related peptide (CGRP)⁹⁶. Numerous studies have shown that these neuropeptides are expressed at sites of inflammation and are generally pro-inflammatory^{97,98}, thereby favouring pathogen clearance (FIG. 4). The stimulation of peripheral nerves by innate immune mediators results in the characteristic features of local inflammation, including vasodilation, vascular leakiness, oedema and pain. Antagonists to these neuropeptides generally reduce inflammation at inflamed sites, and cutting peripheral nerves reduces inflammation that is distal to the site of the nerve lesion⁹⁹.

Corticotropin-releasing hormone

Although hypothalamic CRH has an anti-inflammatory effect through the induction of glucocorticoid release from the adrenal glands, it is pro-inflammatory when released locally from nerve endings at sites of inflammation⁹⁷. Macrophages and B and T cells all express CRH receptors, and B and T cells also express CRH mRNA and release CRH protein¹⁰⁰. Highlighting the biological significance of these effects are studies showing that the CRH receptor 1 antagonist, antalarmin, suppresses macrophage TNF, IL-1 and IL-6 production and secretion *in vitro*⁹⁷ and reduces inflammation *in vivo* in a rat model of inflammatory arthritis¹⁰¹.

Calcitonin gene-related peptide

CGRP, which is a 37-amino-acid neuropeptide that mediates its effects through G-protein-coupled receptors¹⁰², is mainly expressed by sensory nerve fibres that innervate most organs in the body. CGRP has been reported to increase or suppress cytokine production by T cells and peripheral blood mononuclear cells (PBMCs)^{98,103}, suppressing IL-2 production from T cells *in vitro*, but stimulating IL-6 and TNF release from human PBMCs after LPS administration *in vitro*⁹⁸. Given these contradictory findings, more research is needed to elucidate the effects of CGRP on the innate immune system. CGRP increases the synthesis of CXCL8 by human epithelial cells, but has no effect on CCL2 (REF. 104), whereas in explants from human dental pulp, CGRP administration moderately increased CCL2 production while CXCL8 secretion remained unchanged¹⁰⁵. CGRP has direct effects on DCs, inhibiting their activation, resulting in reduced expression of MHC class II and co-stimulatory molecules, and reduced production of IL-12, thereby impairing their ability to activate T cells¹⁰³. In the thymus⁹⁶, CGRP might be involved in inducing thymocyte apoptosis, possibly through the inhibition of NF- κ B signalling pathways¹⁰⁶. Upregulation of CGRP expression in certain brain regions after injury (such as induced by ischaemia) indicates that it might also have a role in the nervous system response to injury⁹⁶.

Substance P

Substance P, which is a neuropeptide released by peripheral nerves that mediate pain perception, interacts with immune cells through two receptors, neurokinin-1 and neurokinin-2 (REF. 107). Substance P stimulates macrophage and eosinophil secretion of the pro-inflammatory cytokines TNF, IL-1 β , IL-2 and IL-6 *in vitro*^{98,108}; increases NK-cell activity and migration *in vitro*^{109,110}; and stimulates the release of CXCL8 and CCL2 from

leukocytes^{105,111}. Furthermore, substance P induces the release of vaso-active mediators from mast cells, including histamine and serotonin^{112,113}, and therefore contributes to vascular leakiness and oedema at sites of inflammation. Immune cells, including lymphocytes, monocytes and DCs, can also produce substance P⁷⁵. Neonatal rats in which substance-P-containing primary afferent nerves are destroyed by capsaicin administration show a reduced capacity to mount a neurogenic inflammatory response¹¹⁴. This has led some researchers to suggest that substance P might have an important role in regulating the inflammatory response. Indeed, substance P antagonists have been shown to be effective as anti-inflammatory agents¹¹⁵.

Both glucocorticoids and catecholamines regulate CGRP and substance P. Glucocorticoids upregulate the expression and release of CGRP in dorsal root ganglion sensory neurons *in vitro* and noradrenaline inhibits the production and release of CGRP and substance P through α_2 -adrenoreceptors in dorsal root ganglion sensory neurons¹¹⁶. These interactions between the hormones and neurotransmitters of the HPA axis, and the sympathetic, parasympathetic and peripheral nervous systems indicate that modulation of immune responses by peripheral neuropeptides might occur not only through direct effects on immune cells but also indirectly through interactions of multiple neuronal and neuroendocrine pathways.

α -Melanocyte-stimulating hormone

The neuropeptide α -melanocyte-stimulating hormone (α -MSH) is a 13-amino-acid peptide derived from cleavage of the pro-opiomelanocortin gene product from which adrenocorticotrophic hormone (ACTH) is also derived. α -MSH is released by pituitary cells¹¹⁷, neurons of the arcuate nucleus and the paraventricular nucleus in the hypothalamus¹¹⁸, and from peripheral nerves. It suppresses cytokine-mediated inflammation through induction of IL-10 production by monocytes, and reduces physiological markers of shock when injected systemically¹¹⁹. Furthermore, α -MSH inhibits LPS-induced stimulation of macrophages by blocking TLR4 signalling through an intracellular inhibitor IRAK-M (IL-1-receptor-associated kinase M)¹²⁰. α -MSH inhibits the activation of transcription factors, such as NF- κ B¹²¹, and inhibits the production of IL-1, IL-2, TNF and IFN γ ¹¹⁹, but promotes CXCL8 mRNA expression and secretion by fibroblasts¹²².

Pro-opiomelanocortin

(POMC). A 241-amino-acid precursor polypeptide that is synthesized in corticotrophin cells of the pituitary gland. Biologically active peptides derived from POMC include adrenocorticotrophic hormone, enkephalins and α -melanocyte-stimulating hormone.

Arcuate nucleus

A collection of neurons in the hypothalamus. It regulates the secretion of hormones through afferent dopaminergic projections to the pituitary.

Paraventricular nucleus

(PVN). A collection of neurons in the hypothalamus that are adjacent to the third ventricle. It contains mainly neurosecretory neurons that secrete corticotrophin-releasing hormone, which stimulates pituitary corticotrophs. In addition, PVN neurons project to the sympathetic brainstem nuclei, parasympathetic brainstem pre-ganglionic neurons and spinal cord.

Opioids—Both synthetic opiates (morphine) and endogenous opioids (endorphins and enkephalins), which are pro-opiomelanocortin gene products that are released by pituitary cells together with ACTH, have been shown to be anti-inflammatory *in vitro* and *in vivo*³. Although endogenous opioids have previously been reported to stimulate chemotaxis of PBMCs¹²³,

more recent studies indicate that they inhibit chemokine-induced chemotaxis of human neutrophils and monocytes³. In addition, the endogenous opioid methionine-enkephalin desensitizes monocyte chemokine receptors by phosphorylating them¹²⁴. Endogenous and exogenous opioids mediate their effects through three main membrane-bound opioid receptor subtypes, μ , δ and κ , which are expressed in the CNS, in dorsal root ganglia, by central and peripheral nerve terminals, and by lymphocytes and monocytes¹²⁵. In addition to direct receptor-mediated effects on immune cells, opioids might mediate some of their anti-inflammatory effects indirectly, through glucocorticoids, as opioids are known to stimulate the HPA axis and induce glucocorticoid release¹²⁶.

Endorphins

Endogenous opioid peptides that are produced by the pituitary gland and the hypothalamus. They regulate feelings of pain and hunger.

Enkephalins

Short five-amino-acid polypeptides that are members of endogenous opioid family and that bind to opiate receptors.

Vasoactive intestinal peptide

In contrast to the pro-inflammatory effects of neuropeptides described earlier, vasoactive intestinal peptide (VIP) released by peripheral nerves or microglia¹²⁷, acting through its two G-protein-coupled receptors, VPAC1 and VPAC2, has been reported to inhibit inflammation. VIP inhibits the production of pro-inflammatory cytokines, such as IL-2, IL-6, IL-12 and TNF, by PBMCs, monocytes and T cells^{128–131}; inhibits the expression of CXCL8 by monocytes in response to endotoxin¹³²; inhibits NK-cell activity; prevents macrophage activation; promotes DC maturation¹³³; stimulates macrophage production of the anti-inflammatory cytokine IL-10 (REF. 130); and decreases TLR2 and TLR4 mRNA expression by intestinal epithelial cells *in vitro*¹³⁴. In addition to production by neurons, VIP is also produced by mast cells, leukocytes and neutrophils, and by lymphocytes in response to immune stimuli¹³⁵. Therefore, the neuropeptide VIP can be considered as both a neuroeffector and a lymphocyte effector.

Taken together, these studies indicate that most neuropeptides, with the exception of VIP released from peripheral nerves, are pro-inflammatory (TABLE 2), and either directly or indirectly contribute to the vascular leakiness, leukocyte accumulation and immune activation at sites of inflammation.

Concluding remarks

Activation of the innate immune system in response to pathogen recognition provides both initial signals for the induction of inflammatory responses as well as signals for the activation of counter-regulatory CNS responses that terminate inflammation. Activation of the peripheral nervous system at local inflammatory sites serves to enhance innate immune responses and stimulate the release of vasoactive mediators that increase immune-cell recruitment and amplify local clearance of the pathogen. After pathogen clearance, activation of the HPA axis, SNS and parasympathetic nervous systems dampen inflammatory responses and restore host homeostasis. Removal of these inhibitory CNS pathways would allow uncontrolled activation of innate immune responses to the extent that they could become deleterious to the host.

For many years, the concept that the central and peripheral nervous system regulate immunity was considered to be highly controversial. However, as described in this Review, a wealth of data has now accumulated, indicating that the molecular machinery required to respond to neurotransmitters, neuropeptides and neurohormones are indeed present in immune cells. In

addition, in some cases, immune cells produce and secrete neural mediators, supporting the importance of such mechanisms of immune regulation. However, the precise cellular source and maturation phase at which immune cells either produce such molecules or respond to them still requires clarification. In addition, the signalling mechanisms and physiological circumstances under which such regulation occurs largely remain unaddressed. And with most studies so far focusing on the effects of glucocorticoids on innate immune responses, evidence for a role of other neuropeptides and neurotransmitters in innate recognition systems, such as TLRs on immune cells, is scarce.

Research that focuses on these issues should provide further important insights into the molecular mechanisms and physiological role of the links between the immune system and the CNS that occur at systemic, regional and local levels, and will provide further evidence that these interactions have important physiological roles in health and disease.

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Figure 1. Schematic illustration of connections between the nervous and immune systems
 Signalling between the immune system and the central nervous system (CNS) through systemic routes, the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system (SNS) and the peripheral nervous system (PNS) are shown. Figure modified with permission from Molecular Psychiatry REF. ¹⁴⁰ © (2005) Macmillan Magazines Ltd.

Figure 2. Effects of glucocorticoids on immune-cell populations

Glucocorticoids act on immune cells both directly and indirectly to suppress the induction of pro-inflammatory responses. They inhibit the production of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β) and tumour-necrosis factor (TNF), while promoting the production of anti-inflammatory cytokines, such as IL-10, by macrophages and dendritic cells. They also promote apoptosis of macrophages, dendritic cells and T cells, leading to inhibition of immune responses. IFN γ , interferon- γ ; NK cell, natural killer cell; T_C, cytotoxic T cell; T_H, T helper cell.

Figure 3. Molecular mechanisms of neurotransmitter and glucocorticoid regulation of cytokine production

Glucocorticoids bind to glucocorticoid receptors in the cytosol, which displaces heat-shock protein 90 (HSP90) and allows receptor dimerization, movement into the nucleus and binding of the glucocorticoid–glucocorticoid-receptor complex to DNA. This leads to transcription and translation of proteins, including inhibitor of nuclear factor- κ B (I κ B). I κ B then sequesters NF- κ B, preventing it from activating transcription of pro-inflammatory cytokines. In addition, the glucocorticoid–glucocorticoid-receptor complex can interact with NF- κ B directly to suppress cytokine production¹³⁶. Noradrenaline binding to β -adrenergic receptors at the cell surface induces cyclic AMP (cAMP) and protein kinase A (PKA) activation, which inhibits cytokine production through inhibition of NF- κ B. Acetylcholine binds to nicotinic cholinergic cell-surface receptors and inhibits cytokine production again through inhibition of NF- κ B⁹⁵. TLR, Toll-like receptor.

Figure 4. Effects of the peripheral nervous system on immune-cell populations in lymphoid organs Neurotransmitters released through nerve terminals can both directly and indirectly affect immune responses. With the exception of vasoactive intestinal peptide (VIP), these neuropeptides stimulate the production of pro-inflammatory cytokines. In addition, some neuropeptides and their receptors are expressed by immune cells, including acetylcholine; VIP; calcitonin gene-related peptide (CGRP); substance P; muscarinic and nicotinic acetylcholine receptors; and serotonin receptors, such as 5HTT (5-hydroxytryptamine transporter), 5HT1A, 5HT2 and 5HT7. CRH, corticotropin-releasing hormone.

Table 1
Mechanisms of glucocorticoid resistance in autoimmune and inflammatory diseases

Disease	Glucocorticoid receptor mutations and polymorphisms	Glucocorticoid receptor expression	Associated protein expression levels	Glucocorticoid sensitivity	Refs
Rheumatoid arthritis	Glucocorticoid receptor-β polymorphism: (A/G) TTTA	Increased stability of glucocorticoid receptor-β mRNA	ND	ND	26
Systemic lupus erythematosus	Glucocorticoid receptor polymorphism: (T/C) GGA	ND	Increased multidrug resistance-I	ND	33,36
Systemic lupus erythematosus-associated nephritis	Glucocorticoid receptor mutation (frameshift mutation, resulting in early stop signal)	Decreased	ND	ND	34
Crohn's disease	ND	Increased glucocorticoid receptor-β mRNA	Increased binding of cortisol to serum albumin	ND	31,35
Asthma	ND	Increased glucocorticoid receptor-β mRNA	ND	Decreased binding to glucocorticoid-response elements	27,28
Multiple sclerosis	ND	ND	ND	Decreased	29,30

ND, not determined.

Table 2
Interaction of neural and neuroendocrine factors with components of the innate immune system

	Toll-like receptors	Dendritic cells	Macrophages	Natural killer cells	Innate cytokines (IL-1, IL-6, IL-12 and TNF)	Chemokines (CCL2 and CXCL8)	Chemokine receptors
Glucocorticoid	+	–	–	–	–	–	ND
Noradrenaline	ND	ND	–	–	–	+	ND
Neuropeptide Y	ND	ND	–	ND	–	ND	ND
Acetylcholine	ND	ND	–	ND	–	+	ND
CRH	ND	ND	ND	+	+	ND	ND
CGRP	ND	–	ND	+	+	+	ND
Substance P	ND	ND	ND	ND	+	+	ND
α-MSH	–	ND	ND	ND	–	+	ND
Opioids	ND	ND	ND	ND	–	+	ND
VIP	–	ND	–	–	–	–	–
Oestrogen	ND	–	ND	ND	–	–	ND
Progesterone	ND	+	ND	ND	ND	–	ND

Inhibitory effect denoted by '–'; stimulatory effect denoted by '+'; α-MSH, α-melanocyte-stimulating hormone; CCL, CC-chemokine ligand; CGRP, calcitonin gene-related peptide; CRH, corticotropin-releasing hormone; CXCL, CXC-chemokine ligand; IL, interleukin; ND, not determined; TNF, tumour-necrosis factor; VIP, vasoactive intestinal peptide.