Neuroimmunity: Physiology and Pathology

Sébastien Talbot,[1,2,*] Simmie L. Foster,[1,2,*] and Clifford J. Woolf[1,2,*]

[1]F.M. Kirby Neurobiology Center, Boston Children's Hospital, Boston, Massachusetts 02115; email: Clifford.Woolf@childrens.harvard.edu

[2]Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115

Annu. Rev. Immunol. 2016. 34:421–47

First published online as a Review in Advance on February 22, 2016

The *Annual Review of Immunology* is online at immunol.annualreviews.org

This article's doi: 10.1146/annurev-immunol-041015-055340

*All authors contributed equally to this work.

Keywords

inflammation, nociceptor, pain, immunity, allergy, asthma, pathogen, TRPV1, NaV1.8

Abstract

Evolution has yielded multiple complex and complementary mechanisms to detect environmental danger and protect tissues from damage. The nervous system rapidly processes information and coordinates complex defense behaviors, and the immune system eliminates diverse threats by virtue of mobile, specialized cell populations. The two systems are tightly integrated, cooperating in local and systemic reflexes that restore homeostasis in response to tissue injury and infection. They further share a broad common language of cytokines, growth factors, and neuropeptides that enables bidirectional communication. However, this reciprocal cross talk permits amplification of maladaptive feedforward inflammatory loops that contribute to the development of allergy, autoimmunity, itch, and pain. Appreciating the immune and nervous systems as a holistic, coordinated defense system provides both new insights into inflammation and exciting opportunities for managing acute and chronic inflammatory diseases.

INTRODUCTION

The nervous and immune systems are traditionally thought of as autonomous entities, each with distinct structures and functions, and, in consequence, they are generally studied separately. However, the two systems often function in an integrated and coordinated manner in host defense (1, 2). For example, both noxious-stimulus-detecting sensory neurons that evoke pain (nociceptors) and immune cells directly detect bacteria (3); immune cells can make nociceptors more sensitive (4); nociceptors may locally alter immune function (5); and autonomic neurons can systemically suppress inflammation (6).

The driving force behind these multiple and diverse interactions is the critical evolutionary requirement for living organisms to identify and react to environmental danger (5, 7). Danger is a broad term that signifies any threat to tissue homeostasis that cannot be handled in a tissue-autonomous manner. This includes infection and exposure to toxins, as well as severe environmental conditions, such as extreme heat, cold, or mechanical force (7). The two systems share the ability to sense the external and internal environments, detect danger, and coordinate appropriate defense responses. In addition, unique features of each system are complementary, so that the two systems working together promote more effective defense than either in isolation. For example, a major outcome of the combined neuroimmune sensing of potential threats is inflammation, the body's stereotypic response to infection or injury (8).

Mechanistically, the systems communicate through a common language of cell-surface G protein and tyrosine kinase receptors that enable them to respond to the signals that each produces (1, 5). For example, cytokines produced by immune cells, such as IL-1β, can be detected by IL-1R expressed by neurons and translated into electrical impulses that cause pain (9). Conversely, neuronal impulses lead to the release of neurotransmitters that initiate neurogenic inflammation and direct various immune responses. These transmitters act on immune cells expressing receptors that recognize these neuro ligands (1, 5).

Neuroimmune coordinated interactions are phylogenetically ancient. In *Caenorhabditis elegans*, for example, specific sensory neurons detect pathogens and generate avoidance behaviors (10). The complex interaction between the two systems in mammals serves to protect tissue, however, it also opens the potential for uncontrolled amplification, leading to pathology and tissue damage (1, 3, 5, 11).

In this review, we discuss the ways in which the sensory and immune systems sense infection, tissue damage, and inflammation, and describe how immune cells communicate with neurons to change their properties (**Figure 1**). We also mention how sensory information derived about danger is processed by both systems, leading to coordinated local and systemic defense responses. Finally, we discuss how reciprocal communication between neurons and immune cells creates inflammatory feedforward loops that can cause immunopathologies and chronic inflammatory pain. These loops, we suggest, may be responsible for the flares in many autoimmune diseases triggered by sensory neuron activity, suggesting that treatment may need to target both systems.

Neuroimmune interactions occur in many situations, including in response to injury (12), infection (5), or autoimmune-mediated damage of neurons themselves (1, 13), and to microglial-related pathology (14). However, these topics will not be dealt with here. In this review, we focus only on focal interactions between peripheral sensory neurons and immune cells at the site of peripheral tissue injury or infection and on systemic inflammatory reflexes mediated by the parasympathetic arm of the autonomic nervous system, paying particular attention to the coordinated detection of, and reaction to, danger by the immune and nervous systems.

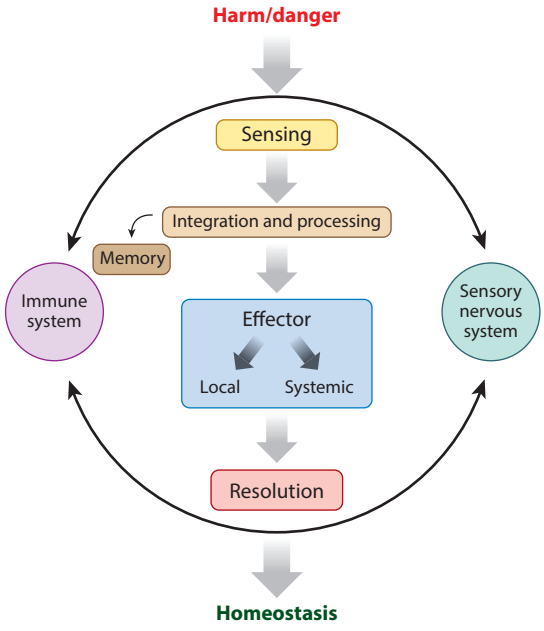


Figure 1

Schematic representation of the immune and sensory nervous systems' responses to danger. Both systems express specific receptors specialized for detecting potential environmental threats. This information is then processed and integrated to generate local and/or systemic effector responses and memory. These responses are geared toward controlling the threat and restoring tissue homeostasis. Mediators shared between the immune and nervous systems allow reciprocal integration between the two systems at each level.

ORGANIZATION

To begin, we briefly describe the structural organization of the two systems that allows for their specialized, yet integrated, functions. The vertebrate immune system is composed of the innate immune system, the body's first line of defense against pathogens (15), and the adaptive immune system, characterized by specificity and memory for particular antigens (16). The designation of an antigen as dangerous comes from coincident signals, such as tissue damage or pathogen products received by the innate immune system, which integrates the information and directs the appropriate response by antigen-specific lymphocytes of the adaptive immune system (17). Dendritic cells (DCs) seem to be the innate immune cell most responsible for signal integration (18). They communicate mainly with T helper (Th) cells in lymphoid tissues to direct four broad types of responses: type-1 responses against intracellular pathogens, including bacteria and viruses; type-2 responses, triggered by parasites and allergens; type-17 responses against extracellular pathogens, such as fungi, characterized by IL-17 involvement; and regulatory responses that limit and control inflammation (17). Other innate immune cells involved in neuroimmune interactions include mast cells (19, 20), important in type-2 immunity and itch (19); neutrophils in type-17 immunity and autoimmunity (21); and macrophages (22), which have a plasticity of function that allows them to participate in multiple types of responses, from proinflammatory to promoting tissue repair.

In contrast to the inherently mobile and dispersed cells of the immune system, the nervous system has an anatomically fixed organization. It is divided into the central nervous system (CNS),

consisting of the spinal cord and brain; and the peripheral nervous system (PNS), which carries information to and from the CNS. Nerve fibers that transmit signals from the periphery to the CNS are known as sensory or afferent neurons; those that carry information to the periphery are known as efferent or motor neurons (23). Every peripheral tissue contains both sensory and motor neurons.

Rather than depending on local movement of cells through tissue and into circulation, as in the immune system, information in the nervous system is relayed by electrical signals speeding along the relatively stable nerve fiber highways present in every tissue. Within milliseconds, diverse stimuli can be detected locally and transmitted centrally. This information can be quickly integrated with signals that come from other body compartments—and from the brain itself, in the form of memory or emotion. Within seconds, electrical impulses may be sent out to multiple tissues and coordinated motor responses initiated (24).

Typically, sensory neurons translate physical stimuli, such as touch and temperature, and exogenous or endogenous chemical stimuli into electrical signals (23). Stimuli generate graded electrical potentials in the peripheral terminals of the sensory neurons, and if these are large enough, they lead to the firing of action potentials in axons. These signals are sent to and then integrated and processed in the CNS, where they are relayed through specific neuronal circuits to motor neurons, which activate muscle contraction and glandular secretion (23). As discussed below, they can also, in certain cases, modify immune cells. The PNS may be further divided into the autonomic, or involuntary, nervous system, which monitors and regulates organ systems, and the somatic nervous system, which provides sensation from skin, muscle, and joints, and voluntary motor control. Both systems are players in various immune responses, as we will explore.

Nociceptor neurons, the population of sensory neurons that are specialized to sense intense, potentially damaging stimuli, can be divided into peptidergic neurons, which synthesize and release neuropeptides, and nonpeptidergic neurons, which do not (4, 12, 14, 24). The cell bodies of nociceptor neurons are found in dorsal root ganglia next to the spinal cord, as well as in the trigeminal ganglion and the nodose ganglion of the vagus nerve. A single neuron extends one axon into a peripheral target organ, such as the skin, where it terminates in a fine mesh of branches to form the receptive field of the neuron. A central axon extends from the cell body to enter the spinal cord or brainstem (23). Most nociceptors have unmyelinated axons (C fibers), but some are thinly myelinated (Aδ fibers; 4, 24). Because myelination increases the velocity of action potential conduction, C fiber nociceptors are characterized by a slow conduction velocity.

The nervous and immune systems together enable enhanced integrated defense, especially in regions of the body susceptible to microbial invasion, such as the skin and the mucosal surfaces of the airways and gastrointestinal tract, which are particularly densely innervated with nociceptors. Immune cells are found in close proximity to the nerve terminal processes in these tissues, both of which are then poised for interaction (25, 26).

DANGER SENSING

Both sensory neurons (**Figure 2*a***) and immune cells (**Figure 2*b***) can detect potentially damaging stimuli, as well as pathogens and injured tissue, and cooperate to induce responses to protect, defend, and repair the tissues through inflammation (2, 8). In addition, both systems can detect the products of the inflammatory response itself. Detection occurs through membrane and intracellular receptors, some of which are shared between the two systems. For example, both sensory neurons and immune cells express receptors for bacteria, acid, hypoxia, various products released by dying cells, neuropeptides, and inflammatory cytokines (1, 5, 8, 27, 28). What is unique to nociceptors is the ability to sense physical variables, such as temperature gradients (29–31) and

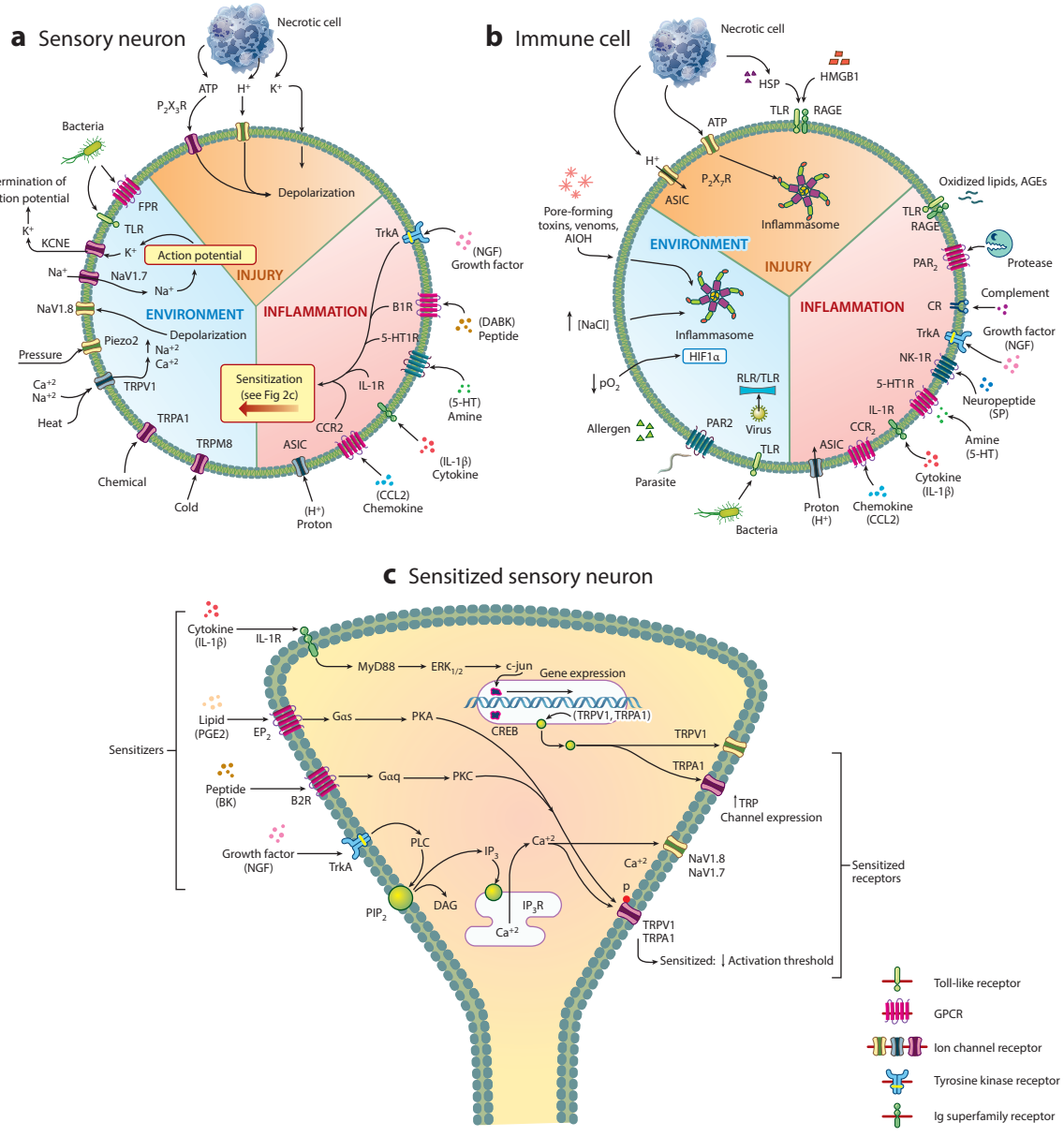


Figure 2

Danger detection. The (*a*) sensory nervous and (*b*) immune systems express arrays of specific and shared receptors that detect environment-, injury-, or inflammation-released mediators. Molecules found in the inflammatory milieu activate specific G protein–coupled or tyrosine kinase receptors expressed by sensory neurons that activate kinases to phosphorylate ion channel receptors, leading to changes in their activation properties and thresholds or increases in membrane expression. Together, these processes exacerbate or prolong the activation of nociceptors during inflammation with a reduction in threshold, leading to the phenomenon of (*c*) peripheral sensitization. Abbreviations: AGE, advanced glycation end product; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; GPCR, G protein–coupled receptor; Ig, immunoglobulin; NGF, nerve growth factor; PAR, protease-activated receptor; PGE2, prostaglandin E2; SP, substance P; RAGE, receptor for advanced glycation end products; TLR, Toll-like receptor; TRP, transient receptor potential.

mechanical forces (31, 32). The ability to recognize specific antigens is unique to immune cells (15, 33), although sensory neurons may be nonselectively activated by antigens.

Detection of Noxious Stimuli by Sensory Neurons

Potentially damaging noxious stimuli activate specific membrane receptor channels (termed transducers) that are expressed selectively by nociceptors. These transducers include transient receptor potential (TRP) (30, 34), acid-sensing ion (ASIC) (35), and piezo channels (32), among others, which have high thresholds of activation and allow cations to cross the membrane, depolarizing the terminal (4). Nociceptor function is tuned to different sensory modalities based on the expression of these channels; for example, $TRPV1^+$ sensory neurons are activated by noxious heat (30), ASICs are permeable to cations and are activated by extracellular acidosis, whereas Piezo2 is required for mechanical nociception, but not gentle touch sensation. TRP channels are rather promiscuous in their ligand recognition or activation. TRPV1, for example, apart from heat is also activated by exogenous and endogenous irritant chemicals, including capsaicin (the pungent component in chili peppers), and endocannabinoids (34). TRPA1 responds to a wide variety of chemically active irritants, such as mustard oil (the pungent ingredient in mustard and wasabi) (36), as well as endogenous fatty acid amines produced during inflammation, which all, rather unusually, form covalent bonds with the channel. This flexibility in the nociceptor recognition repertoire by the transducers allows for broad recognition of diverse environmental threats.

Itch, although less understood than pain, is also transduced by specific membrane receptors on distinct sets of nociceptors, called pruriceptors, often through specific itch-transducing G protein–coupled receptors (GPCRs), known as Mrgprs (37), and TRP channels working together (34). Interestingly, some of these two classes of receptors are also expressed on immune cells. Mast cells are important sentinels with a role in type-2 anaphylaxis to previously encountered allergens (19); however, they also sense secretagogues through MrgprB2 to release histamine (38). In addition, macrophages express TRPV2 (also expressed by some nociceptors), which may modulate their chemotaxis (39), and a population of T cells express TRPV1 which may contribute to their proliferation (40).

Recognition of Pathogens by Sensory Neurons and the Innate Immune System

Cells of the innate immune system detect infection through pattern recognition receptors (PRRs) (41). PRRs include several different classes: Toll-like receptors (TLRs), Nod-like receptors, RIG-like receptors, C-type lectin receptors, formylated peptide receptors (FPRs), and scavenger receptors (17). All of these receptors bind to conserved molecules found on or in pathogens. TLR4, for example, recognizes bacterial lipopolysaccharide; TLR9 binds to unmethylated CpGs common in prokaryotic DNA; and TLR7 recognizes viral single-stranded RNA. Nociceptors express several TLRs including TLRs 3, 4, 7, and 9, as well as FPRs (3, 42).

Although nociceptors express PRRs, for a long time it was assumed that they could not be directly activated by pathogens; however, nociceptors are activated by N-formylated peptides from *Staphylococcus aureus* through FPRs (3). The extent to which sensory neurons detect and respond to changes in the microbiome needs to be explored. Responses to viruses should also be examined, because viral infections are commonly painful.

In addition to recognizing structural features of molecules specific to pathogens, the immune and sensory systems have receptors that detect the consequences of pathogen invasion or toxin activity. For example, many bacteria secrete hemolysins that form pores in eukaryotic cell membranes (17). These pores change the balance of ions in the cells, inducing efflux of K^+ and influx

of Ca^{2+}, which generates sufficient depolarization to initiate action potentials in sensory neurons (3) and in immune cells results in activation of inflammasomes, those intracellular complexes that process IL-1β (43).

In another example, the type-2 immune response to parasites partially depends on proteolytic activity detected by special protease-activated receptors (PARs), which are expressed on epithelial cells and various immune cells (44). Many allergens, such as papain and cockroach allergens, are proteases, supporting the hypothesis that some allergy results from the triggering of pathways meant to detect parasites and toxins (17). Nociceptors express PAR2, leading to the intriguing possibility that they too may also directly sense parasites and some allergens (45).

For cells of the immune system, the detection of pathogens leads to innate effector responses, such as phagocytosis and granule release, cytokine production, antigen presentation, and induction of adaptive immunity. For nociceptors, the activation of PRRs, such as TLR7, leads to pain and itch (42). But the signaling pathways downstream of PRRs in nociceptors are only just beginning to be elucidated (46), and their full functional impact remains to be determined.

Detection of Tissue Injury

If dangerous conditions are not avoided, injury to tissue occurs. Several molecules released from the intracellular compartment during cell damage and by necrosis have dedicated receptors that are present on both immune cells and sensory neurons (5, 8). Some of these molecules are also endogenous ligands for TLRs and the inflammasome. For example, adenosine triphosphate (ATP) is released at high levels from dead or ruptured cells and binds to P2X7 receptors on macrophages (47) and P2X3 receptors on nociceptors (48). In macrophages, this leads to K^+ efflux, activation of the inflammasome, and production of IL-1β (47). In nociceptors, Na^+ and Ca^+ influx depolarizes the membrane and leads to action potentials and pain (48). HMGB1, a nuclear protein released from necrotic cells, binds RAGE (receptor for advanced glycation end products) and TLR4 (49), leading both to proinflammatory cytokine release by macrophages and nociceptor activation (50).

Detection of Inflammation

The common outcome of the detection of pathogen invasion and tissue damage is the induction of inflammation, which has evolved to eradicate pathogens and restore tissue integrity (8). The presence of inflammation is itself detected by both the sensory and immune systems. Immune cells detect signals made by other immune cells, including cytokines, chemokines, complement, amines, and lipids and prostanoids. Immune cells also both respond to and release molecules classically defined as neuropeptides, such as substance P (SP) (27, 51), neurotrophic growth factors, such as nerve growth factor (NGF) (52), and neurotransmitters, such as serotonin (5-HT) (53), indicating that these molecules are not only neural in origin. These signals tend to amplify inflammation, leading to further cytokine production and immune cell recruitment. Sensory neurons detect many signals made by immune cells: IL-1β (9), TNF (tumor necrosis factor)-α (54), histamine (55), and prostaglandin E2 (PGE2) (56, 57). The two systems may, therefore, monitor the inflammatory environment in parallel. Gene profiling of nociceptor lineages (58) and single-cell transcript analyses have revealed a broad expression of cytokine and chemokine receptors by nociceptors. The detection of inflammatory products by nociceptors, similar to the sensing of pathogen products (3), leads to pain (through IL-1β, TNF-α, and PGE2) (28, 59) and to itch (through histamine) (37), as well as to the release of neuropeptides that are locally sensed by immune cells (details below). In some contexts, the detection of sensory neuron products by immune cells can amplify inflammation and lead to tissue damage; in other contexts, it downregulates inflammation and

promotes tissue repair. The mechanisms behind these contrasting effects are complex and not fully clear. As inflammation progresses, the tissue microenvironment changes: The production of reactive oxygen species leads to lipid oxidation; glucose dysregulation leads to the production of AGEs (abnormally glycated proteins); tissues may be hypoxic and hyperosmolar; and uric acid may be released (8). This late inflammatory environment is also sensed by both systems.

Consequences of Nociceptor Sensing of Immune Stimuli: Peripheral Sensitization

What are the consequences of inflammation sensing by sensory neurons? In addition to directly activating nociceptors, enabling them to signal the presence of inflammation by producing pain, inflammatory mediators, such as IL-1β (9) or NGF (60), also sensitize the peripheral terminals of the nociceptors. This peripheral sensitization represents a particular form of stimulus-evoked functional plasticity of the nociceptor, reducing its firing threshold and increasing its responsiveness (61). As a result, low-intensity non-noxious stimuli, which normally would not activate nociceptors, can now trigger firing in these neurons; in effect, the nociceptor terminal changes in the presence of inflammation due to peripheral sensitization, from being exclusively a detector of noxious stimuli to also being a detector of non-noxious stimuli. These low-level stimuli can now begin to produce pain, a situation termed allodynia (4, 62). In addition, the sensitized state of the terminal increases the response to noxious stimuli, so that the pain experienced is increased (termed hyperalgesia). The nociceptor hypersensitivity produced by inflammation focuses conscious attention on the injured tissue (it is sore and tender) and leads to behavioral activities to protect the injury (such as avoiding bearing weight on an injured limb) until healing has occurred and the inflammation has resolved. Peripheral sensitization is a major contributor to inflammatory pain (4, 12, 14, 24).

Peripheral sensitization occurs in response to a whole set of inflammatory mediators—cytokines, chemokines, growth factors, amines, and peptides (kinins)—that bind to receptors on nociceptor terminals (**Figure 2*c***). These receptors are mostly not ion channels, but GPCRs or receptor tyrosine kinsases (5). Downstream, intracellular kinases are activated, leading to post-translational modifications in either transducer ion channels or voltage-gated sodium channels, altering threshold and ion-channel kinetics (63). There may also be increased trafficking of receptors, such as TRPV1, from intracellular stores to the membrane (24, 63). The net result is to increase transduction sensitivity and lower the threshold for action potential initiation (63). Although PGE2 produced by COX2 is the most well-known sensitizer (57), and this explains why nonsteroidal anti-inflammatory drugs have an analgesic action in inflammatory conditions (64), NGF is also a major sensitizer (65), and this understanding has led to the development of neutralizing monoclonal anti-NGF antibodies as a therapeutic for chronic inflammatory pain conditions (66). IL-1β (57), IL-5 (11), IL-6 (67), activin (a transforming growth factor-β member) (68), TNF-α (69), CCL3 (70), and GDNF (71) have been shown to have similar actions. Much of nociceptor sensitization is related to a decrease in the activation threshold of TRPV1 or TRPA1 (72–75) and of the sodium channels NaV1.7, NaV1.8, and NaV1.9 (76–79). These changes are limited to anatomical sites where inflammation produces the necessary sensitizing mediators (called the zone of primary hyperalgesia). Pain hypersensitivity outside the zones of inflammation reflects changes in the CNS—known as central sensitization triggered by sensory input—and is reviewed elsewhere (4, 12, 62). During inflammation, many sensitizing mediators are likely to be released simultaneously, thus pharmacologically targeting only one of these agents might have limited effects. Targeting the sensitized nerve or a downstream convergent signaling enzyme might have broader, larger, and more durable effects on inflammatory pain.

Itch, as well as pain, may have a component of sensitization. Th2 cell–derived IL-31 activates human and mouse sensory neurons expressing IL-31Ra to produce itch (80), and epithelial cells release thymic stromal lymphopoietin (TSLP) during atopic dermatitis, which sensitizes $TRPA1^+$ sensory neurons to trigger itch (81). Indeed, it is fair to say that itch is largely an expression of neuroimmune interactions.

The chemical phenotype of the neuron is also modified by inflammation. When the peripheral terminal of the nerve is exposed to growth factors such as NGF, retrograde signals are sent to the soma to promote increased proinflammatory neuropeptide transcription, as well as TRP and voltage-gated sodium channel expression (65, 82, 83). These changes may further enhance the sensitivity of nociceptors and their peptide-mediated actions, especially in conditions of non-resolving or chronic inflammation, such as rheumatoid arthritis.

Peripheral sensitization is one of the major and most investigated forms of sensory neuron–immune cell interaction—which heightens pain sensitivity in the presence of active inflammation—but it represents only one part of this complex interaction, and only one direction, from immune cell to neuron (4, 12, 14, 24, 28). There is, as we discuss below, substantial signaling in the reciprocal direction, from sensory neuron to immune cell.

Detection of Antigens by the Adaptive Immune System

A unique part in the recognition of novel antigenic stimuli is played by the somatically recombined receptors of the adaptive immune system (16). Somatic recombination allows for the generation of an array of diverse receptors that can theoretically detect any antigen, self or non-self. Cells bearing a receptor that is specific for a particular antigen previously encountered during the lifetime of the organism are retained as memory cells, which can rapidly expand to eliminate repeat pathogen invasions. The recognition of antigen in sensitized animals initiates immune changes that, in some cases, include the participation of sensory neurons (84).

EFFECTOR MECHANISMS

What are the outputs of the immune and sensory nervous systems generated in response to sensing dangerous environments, infection, injury, or inflammation? Which of these processes are localized and which are systemic, and how do they protect the host and regulate inflammation?

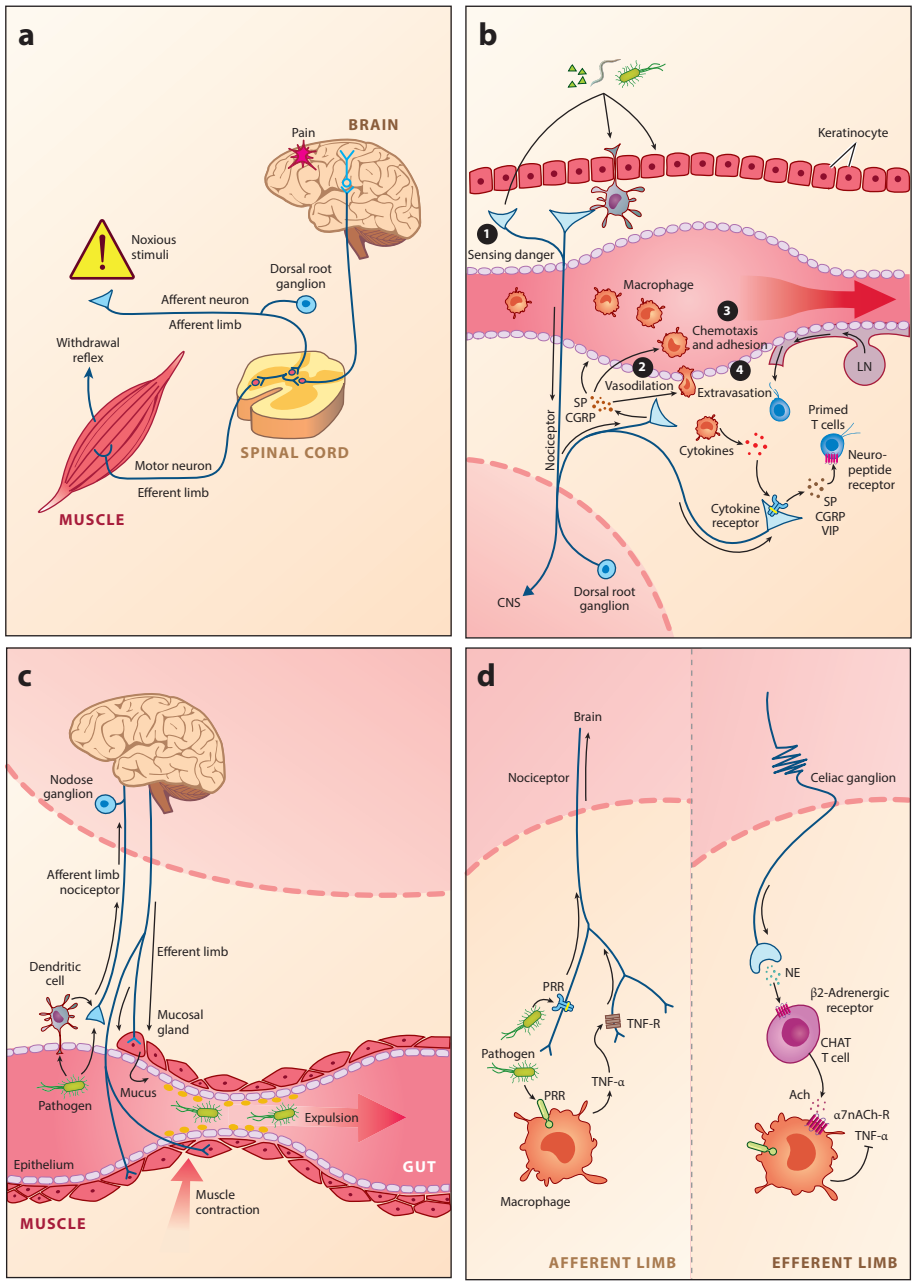
Spinal Withdrawal Reflexes

The flexion withdrawal reflex is a critical part of our defense mechanisms; noxious stimuli activate the peripheral terminals of nociceptors, sending an input to the spinal cord that activates a neural circuit that excites those motor neurons innervating the flexor muscles, resulting in the rapid removal of the affected limb from the noxious stimulus (**Figure 3*a***). This reflex is faster than the actual perception of pain, and it functions to immediately avoid or minimize harm, a major defense mechanism in a hostile environment. Slightly later (a few seconds), the brain receives and integrates this same information, leading to the experience of pain, and can form a memory of the experience that helps teach us to avoid a particular danger.

Axon Reflex and Neurogenic Inflammation

Apart from initiating reflex withdrawal and pain, nociceptors also generate neurogenic inflammation via local reflexes that operate at a tissue level and do not involve the CNS. Inflammation was first characterized by Celsus as having four cardinal signs: dolor (pain), calor (heat), rubor (redness), and tumor (swelling) (5). Sensory neurons clearly initiate inflammatory pain. Less obvious,

perhaps, is the recognition that sensory neurons also contribute to the heat, redness, and swelling of inflammation through the axon reflex (85, 86). In this reflex, when action potentials originating from a peripheral terminal reach a branch point in the peripheral receptive field, they are transmitted back down to the periphery. Both the local, direct activation of peripheral terminals and the axon reflex lead to depolarization of terminals and an influx of calcium through voltage-gated calcium channels, which trigger the rapid and local release of amino acid and neuropeptide



neurotransmitters (1, 3, 27) (**Figure 3*b***). Neuropeptides, such as calcitonin gene-related peptide (CGRP) and SP, act on vascular endothelial and smooth muscle cells to produce redness and heat (secondary to vasodilation) and edema (secondary to plasma extravasation), as well as the margination of immune cells in blood vessels by promoting adherence to the endothelium (1, 5, 87). The vascular leakage may contribute to the influx of immune cells from capillaries to the site of injury, dilute pathogens, and expose them to plasma proteins. The local action of nociceptors on endothelial and vascular smooth muscle cells together constitute neurogenic inflammation (88, 89). However, we are beginning to appreciate that the actions of sensory neurons on blood flow and capillary permeability are not the major proinflammatory effects of local neuropeptide release: Neuropeptides can act directly on immune cells, providing an opportunity for sensory neurons to modify immune cell recruitment and activation in ways that extend well beyond the original understanding of neurogenic inflammation (1, 3, 5, 11, 14, 26, 81).

Reflex Responses to Parasites

It is difficult for immune cells to deal by themselves with multicellular pathogens; typical defense mechanisms, such as phagocytosis or lysing individual infected cells, are not especially effective. Nociceptors, however, are ideally positioned in the skin, airways, and gastrointestinal tract to recognize multicellular parasites and initiate effective motor responses—such as scratching (90), coughing (85), vomiting, and peristalsis (91)—to physically expel the invader. Scratching is a repetitive motor function, partly reflex, partly driven by a voluntary urge in response to the sensation of itch, but the other functions are mediated by autonomic reflexes (37). For scratching, pruritogens, such as histamine, activate itch transducers that are present on sensory neurons and some immune cells, which release further pruritogens (14, 37, 42, 55, 81, 86, 90, 92–95). Scratching may be a protective response to try physically to remove the pruritogenic agent (e.g., migrating parasitic worms) from the skin. Although in many cases the itch occurs too late to deal with the specific attack (as with mosquito bites), it will drive behaviors to reduce overall exposure. A feature of both pain and itch that reflects their alarm function is that the sensation is sufficiently unpleasant that it cannot be ignored or a response delayed until later (90).

Figure 3

Neuron reflexes. (*a*) Withdrawal reflex. Noxious stimuli are sensed by nociceptors that signal to the spinal cord; there, the afferent neurons synapse with interneurons, which activate flexor motor neurons to elicit withdrawal of the affected limb, and with projection neurons, which send signals where pain is perceived in the brain. (*b*) Axon reflex. ❶ Noxious stimuli activate local nociceptors and generate action potentials that travel orthodromically, toward the central nervous system; concomitantly, local depolarization of the afferent fibers and antidromic action potentials that travel toward the periphery result in the local release of neuropeptides (axon reflex). ❷ The peptides cause vasodilation and endothelial gaps in capillaries, resulting in plasma leakage. ❸ The neuropeptides also drive blood leukocyte adhesion and extravasation and ❹ directly activate infiltrating immune cells. (*c*) Mucosal reflex. Gastrointestinal tract pathogens activate epithelial and dendritic cells, and these activate vagal afferent nociceptors. These fibers signal to the brain and activate efferent fibers to stimulate mucus secretion and gastrointestinal muscle contraction to expel the pathogen. (*d*) Invading pathogens activate pattern recognition receptors expressed by macrophages, thus triggering the release of TNF-α. The latter activates TNF-R expressed by nociceptors in the vagus nerve, which travel to the brainstem. Efferent vagal fibers send signals via the celiac ganglion to the spleen, releasing norepinephrine, which activates $CHAT^+$ T cells expressing β2-adrenergic receptors. These T cells then release acetylcholine, which acts on the macrophage α7nACh receptor to inhibit the release of TNF-α. Abbreviations: α7nACh-R, α-7 nicotinic receptor; Ach, acetylcholine; CGRP, calcitonin gene-related peptide; CNS, central nervous system; LN, lymph node; NE, norepinephrine; PRR, pattern recognition receptor; SP, substance P; TNF, tumor necrosis factor; VIP, vasoactive intestinal peptide.

Autonomic reflexes control smooth muscle contraction and mucus production. Nociceptors traveling in the vagus nerve innervate the gut and airways, and sense pathogens, toxins, or allergens in these organs (96, 97). They elicit in the brainstem a reflex motor arc that sends electrical impulses to mucosal glands and muscles in the vicinity of the threatened area, leading to the production of mucus—which inhibits the migration of pathogens—and triggering muscle contraction to expel the pathogen—through coughing, diarrhea, or vomiting—and, through bronchoconstriction, reduce the exposure of the airways to an irritant (**Figure 3*c***) (29, 85, 91, 96, 98).

Systemic Inflammatory Reflexes

The autonomic nervous system not only controls smooth muscle, it also regulates the homeostasis of the cardiovascular, pulmonary, and gastrointestinal systems, and plays an important part in systemic responses to infection and inflammation (23). When infection spreads to the blood, systemic responses are activated that generate fever. Macrophages in the liver and spleen sense systemically infiltrating pathogens and make IL-1β (99, 100). This cytokine acts on nuclei in the brain to induce COX-2 to make PGE2, which changes the body temperature set point. In addition, the fever response activates sympathetic neurons, leading to elevations in heart rate and blood pressure, increasing blood flow to tissues, and enhancing delivery of immune cells. The increased body temperature may then aid pathogen clearance.

Although the systemic inflammatory response is necessary for clearing pathogens from the blood, excessive systemic inflammation causes septic shock and death; endothelial barriers become hyperpermeable, leading to loss of intravascular volume and resulting in hypotension; and clotting factors are activated systemically, blocking blood flow to organs and causing multiorgan dysfunction. Therefore, the systemic inflammatory response must be tightly regulated.

The parasympathetic nervous system plays an important role in preventing excessive inflammation through an inflammatory reflex, a circuit that starts with peripheral innate immune stimuli and terminates on splenic macrophages, attenuating inflammation (6, 101) (**Figure 3*d***). The efferent arc of the reflex involves action potentials traveling along the vagus nerve in preganglionic motor fibers to the celiac ganglion to activate postganglionic norepinephrine-expressing neurons with fibers in the splenic nerve; this leads to the production of acetylcholine in the spleen (102). Acetylcholine binds to the α7nACh-R expressed by splenic macrophages and inhibits their production of TNF-α (103). As the postganglionic splenic nerve fibers are adrenergic, mainly sympathetics, for a long time the source of the acetylcholine in the spleen remained a mystery (6). This mystery was solved by the discovery of a subset of T cells in the spleen that produce acetylcholine and respond to norepinephrine, a case, once again, where immune cells and neurons share common signaling molecules (102). Interestingly, these T cells are found in multiple immune tissues, including lymph nodes and Peyer's patches, but their role and interaction with the PNS is still being explored (6).

The afferent arm of the inflammatory reflex remains much less well understood, but there are some clues; innate immune activators, which include pathogen- and immune-cell-derived signals, such as cytokines, stimulate vagal nerve afferents that transmit information to the nucleus tractus solitarius in the brainstem to trigger the efferent limb of the inflammatory reflex (97). Populations of capsaicin-sensitive nociceptors in the gut, with cell bodies in the dorsal root ganglion and nodose ganglion, sense pathogenic bacteria and signal to the brainstem, as well as activating local axon reflexes and the release of neuropeptides (104).

Although the axon reflex—activated by tissue damage, pathogens, or inflammation—contributes to changes locally in a tissue, systemic reflexes act globally on the immune system to suppress its activity (6, 101, 102). It is not yet clear what exactly triggers the escalation from

local to systemic responses. There is some suggestion that the location of the stimulus (inside the gut lumen versus inside the abdominal cavity or blood) and its magnitude may determine when a systemic response is generated. Nevertheless, the discovery of the inflammatory reflex has added a whole new dimension to neuroimmune interactions, one where output from the nervous system limits excessive immune activity.

Role of Sensory Neurons in Physiological Immune Responses

The extent and precise nature of the physiological, biologically adaptive roles of sensory neuron–immune interactions in the response to infection and sterile tissue damage remains incompletely understood. The emerging picture is complicated, with sensory neurons having different effects on distinct aspects of the inflammatory response to pathogens and in models of sepsis. Nevertheless, the sensing of pathogens by sensory neurons appears to contribute importantly to host defense (3), as in parasite expulsion (91). In addition, sensory neurons may have a direct role in eradicating bacterial pathogens, via the axon reflex and peripheral neuropeptide release (3), because some neuropeptides have antimicrobial activity (105). Similar to canonical antimicrobial peptides, many neuropeptides have a small size, a cationic charge, and are amphipathic. In particular, vasoactive intestinal peptide (VIP) is present constitutively at mucosal surfaces and induced during infection. It is potent against gram-negative and gram-positive bacteria, as well as trypanosoids, and stable VIP analogs are in development as new antimicrobials (106). Many small peptides may serve double duty as both signaling and effector molecules (51, 105).

NGFb, produced by many immune cells, is, interestingly, highly homologous to the *Drosophila* Toll ligand Spaetzle, which is essential for *Drosophila* immunity to *S. aureus*, and patients with hereditary deficiency in NGF have both severe sensory and autonomic neuropathy, due to a failure to form nociceptors and sympathetic neurons, and frequent, severe *S. aureus* infections (52). *S. aureus* ligands, including autolysins (pore-forming hemolysin), activate the inflammasome in macrophages and neutrophils, leading to the release of NGF (52). NGF, in turn, acts in an autocrine manner on the macrophages to stimulate Ca^{2+} flux, phagocytosis, and superoxide production, culminating in increased intracellular killing of bacteria (52). NGF causes peripheral sensitization of nociceptors and inflammatory pain by binding to its receptor, TrkA (65, 66, 77), but it may also be necessary for efficient bacterial clearance (52). Although reducing sensitization with anti-NGF antibodies is desirable (66), this may cause problems with infection in some patients.

Sensory neuron denervation in various animal models increases infection severity, including the severity of *Mycoplasma pulmonis* infection in rats (107) and fungal candidiasis in mice (108), and polymicrobial septicemia (109) in TRPV1-deficient mice (1). In septic rats, small systemic doses of capsaicin increase the release of anti-inflammatory cytokines (IL-10) and attenuate the rise of proinflammatory cytokines (110). In these situations, it seems that sensory neurons may promote aspects of local inflammation necessary or helpful for microbial defense, while limiting systemic production of proinflammatory cytokines. However, it is possible that some pathogens exploit sensory neuron activation. *Helicobacter pylori*, the main cause of gastritis, activates sensory neurons to secrete CGRP, leading to the release of somatostatin and the inhibition of histamine, which reduces acidity in the stomach, thus providing a more favorable environment for the bacterium to survive (111). *M. ulcerans*, which causes painless ulcers, produces a polyketide that binds to angiotensin-II receptors on sensory neurons and hyperpolarizes them, leading to analgesia (112). This analgesic effect appears to promote the survival of the pathogen (112). *S. aureus* infection can directly activate nociceptors, and this appears, unexpectedly, to lead to an inhibition of immune cell infiltration by the production of neuropeptides, including CGRP (3). Genetic ablation of sensory neurons in this model led to increased lymphadenopathy and local infiltration of immune

cells in response to live bacterial infection (3). This mirrors the process in *C. elegans*, where a neural circuit negatively regulates immunity to pathogenic bacteria (113).

Sensory neuron activation appears, then, to have different effects on distinct aspects of infection and inflammation, depending on the timing, tissue compartment, and type of response, and may act to promote active pathogen defense while modulating excessive inflammation. However, some pathogens may exploit the anti-inflammatory effects of sensory neurons to aid their invasion and infection (3, 111, 112).

Involvement of Sensory Neurons in Inflammatory Disease

Although the capacity of sensory neurons to drive the vascular responses that constitute neurogenic inflammation and to recruit immune cells to sites of infection and damage may aid the protection of tissue (5), in certain circumstances sensory neurons may exacerbate inflammatory disease. This inference arises largely from clinical observations indicating that patients with denervation of various tissues may be less susceptible to inflammatory disease in those tissues; patients who have nerve damage to a limb appear to be protected, for example, from developing rheumatoid arthritis (114) or psoriasis (94) in that limb.

Sensory neurons seem to contribute to inflammatory disease in a variety of tissues where nerves and immune cells are found in close proximity: the skin, joints, lung, pancreas, and gastrointestinal tract. Studies have used surgical denervation, chemical or genetic ablation of defined populations of sensory nerves, or genetic deletion or pharmacological inhibition or activation of particular channels. In addition, neuropeptides have been administered to mimic the effector actions of the nerve. Each of these approaches has possible limitations. Surgical denervation eliminates not just sensory neurons but also somatic and autonomic motor neurons. Chemical ablation may be incomplete; genetic ablation may lead to compensatory effects; and pharmacological manipulations may have partial actions or off-target effects. A newer method with promise to deliver more specific spatiotemporal control is optogenetic activation or silencing of particular sensory fibers (115).

In the 1960s, a surgical lesion to the sciatic nerve was shown to protect rats from the subsequent development of adjuvant-induced arthritis (114), a finding that was replicated in 2014 (116). The arthritic joints were also found to be more densely innervated by SP-containing nerves, and SP infusion increased the severity of adjuvant-induced arthritis (117). In models of psoriasis, denervated skin was spared from inflammatory lesions (94), characterized by reduced immune cell infiltration (92). Skin is innervated both by sympathetic efferents and nociceptor afferents, but the denervation produced by the ablation of nociceptors alone has been sufficient to reverse imiquimod-mediated psoriasis (26). Eliminating capsaicin-sensitive ($TRPV1^+$) sensory fibers also abolishes contact-sensitivity responses (95).

Nociceptor interaction with immune cells has been intensively studied in murine models of allergic airway inflammation (11, 85, 98). In a model of airway sensitization, C-fiber denervation in rats (produced by neonatal exposure to high-dose capsaicin) decreased the number of DCs in the lung and also decreased pulmonary lymphatic immune cell influx (118); consistent with this finding, stimulating lung nociceptors in adult mice with nonablative doses of capsaicin increased neuropeptide release and immune cell infiltration (11). Ablating nociceptors or pharmacologically silencing them with a charged sodium-channel blocker reduced ovalbumin- and house-dust-mite-induced airway inflammation as measured by a decreased influx of immune cells into bronchoalveolar lavage fluid (11). Stimulation of capsaicin-sensitive sensory neurons in subjects with active allergic rhinitis produced a dose-dependent leukocyte influx (119), and capsaicin desensitization reduced allergen-challenge symptoms (118). In the gut, surgical denervation of vagal afferents suppressed inflammation in 2,4,6-trinitrobenzenesulfonic acid–induced colitis (120),

resiniferatoxin-desensitized mice (with reduced TRPV1 activity) showed amelioration of a dextran sodium sulfate–induced colonic inflammation (121), and capsaicin-induced nociceptor denervation prevented induction of colitis in a model mediated by the adoptive transfer of T cells (122).

Mucosal mast cell mediators from patients with inflammatory bowel disease excite nociceptive visceral sensory nerves, an effect inhibited by histamine-receptor blockade and serine-protease inactivation (20), and signaling between mast cells and the enteric nervous system contributes to food allergies (123).

Although ablating sensory nerves reduces inflammation in diverse models of inflammatory disease, in some cases, the reverse is seen. For example, in a serum transfer model of arthritis, pharmacological ablation of nociceptor sensory neurons led to worse arthritis (124). This particular study suggests that in the effector stages of arthritis modeled by serum transfer, nociceptors secrete neuropeptides, such as somatostatin, that inhibit inflammation. Other neuropeptides, such as CGRP and VIP, have been implicated in protection from autoimmunity (106).

NEUROPEPTIDES AND IMMUNE RESPONSES

How are the diverse effects of sensory neurons on physiological and pathological immune responses mediated? Beyond neurogenic inflammation, sensory neurons can alter many immune effector functions, such as phagocytosis, DC maturation and trafficking, $CD4^+$ T cell differentiation, and B cell antibody production (1, 2, 5, 11, 26) (**Figure 4**). Activated sensory neurons release neuropeptides from their peripheral terminals, and immune cells express receptors for almost all known neuropeptides. Many immune cells express transcripts for neuropeptides and neurotrophic factors, such as NGF, indicating that immune cells produce what are commonly thought of as purely neuro signals. Below, we highlight examples of how specific neuropeptides may contribute to distinct types of immune responses, keeping in mind that this is a nascent field and, in many instances, there is conflicting evidence on the role of any particular neuropeptide.

Neuropeptides and Innate Immunity

Sensory neurons and tissue-resident innate immune cells, including macrophages (125), DCs (26), and mast cells (126), are in close contact in skin and mucosal tissues (**Figure 4*a***). During early inflammation, neuropeptides released by nociceptors promote some innate immune functions, particularly antimicrobial activity. CGRP and other peptides activate, in vitro at least, the phagocytosis of *Leishmania* and bacteria (51, 127), and VIP can be directly antimicrobial (106). Neuropeptides cause immune cells to upregulate adhesion molecules (87), adhere to vasculature, and move toward sites of inflammation by chemotaxis. However, CGRP, as well as galanin and somatostatin, can suppress the release of TNF-α from macrophages (3) and inhibit DC cytokine production and maturation, as discussed in the next section.

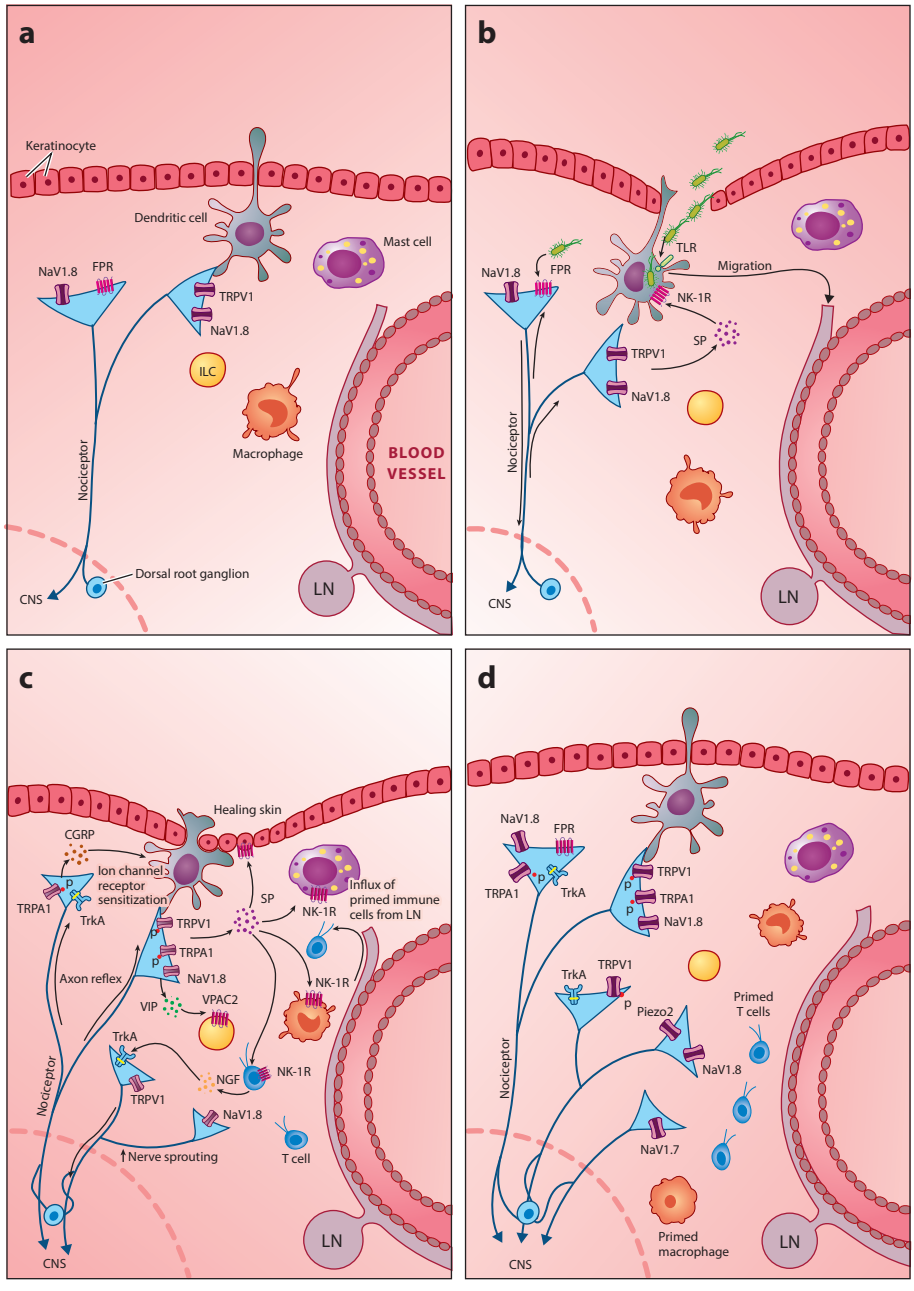
Neuropeptides, Dendritic Cells, and Regulation of Adaptive Immunity

DCs transmit information about pathogens and tissue damage to lymph tissue to direct the differentiation of naive T cells into appropriate effector types. Immature DCs are highly phagocytic and motile, but after being activated through PRRs, DCs mature. Mature DCs express high levels of major histocompatibility complex and costimulatory molecules, and produce T cell–skewing cytokines (17).

Neuropeptides influence DC maturation, migration, antigen presentation, and cytokine production, and, therefore, can influence different types of adaptive immunity, although the exact functions of specific neuropeptides remains unclear (**Figure 4*b*,*c***). In type-1 immunity (exemplified

by defense against intracellular pathogens and various autoimmune disorders), SP seems to amplify the type-1 cytokine milieu. For example, SP increases DC production of type-1-skewing cytokines, such as IL-12 (128). SP also induces IL-1β and TNF-α from macrophages and has effectively been used as an adjuvant to induce Th1 and CD8 lymphocytes in vivo (129).

In type-2 immunity, including allergy and specialized tissue repair, SP again may amplify the response, for example by inducing histamine release from mast cells (93). CGRP and VIP,



however, seem to have dualistic effects. For example, CGRP promotes Th2 skewing in naive T helper cells (130), but in established type-2 responses, the adoptive transfer of CGRP-pretreated DCs diminished allergic airway inflammation in vivo (131). VIP, similarly to CGRP, tends to bias toward a Th2-skewing profile (132). For example, treating naive macrophages with VIP leads to upregulation of major histocompatibility complex and costimulatory molecules (133) and increased Th2-skewing cytokines, but once macrophages have been activated by lipopolysaccharide and IFN-γ, VIP inhibits their function (134). Innate lymphoid cells (ILCs) are an intermediate effector cell between antigen-presenting cells and lymphocytes; ILC2 are involved in allergies and asthma. VIP, through VPAC2, activates ILC2 in naive (135) and asthmatic mice (11). VIP also has direct effects on T cells, augmenting naive T cell skewing toward Th2 subtypes and amplifying Th2 responses during established inflammation (134).

Not as much is known about neuropeptide involvement in type-17 responses to extracellular pathogens and autoimmunity. But, sensory neurons do communicate with DCs to drive production of IL-23 and direct type-17 immunity in psoriasis, and although the specific mediator has not yet been identified, it is likely to be a neuropeptide (26). The ablation of capsaicin-sensitive nociceptors, which are in close contact with dermal dendritic cells, reduces dermal DCs' release of IL-23 and activation of $\gamma\delta$T17 cells (hallmarks of psoriatic lesions), offering another sensory neuron target for reducing an inflammatory condition (6). In fungal candidiasis, CGRP may be important in DC production of IL-23 (108). Another potential candidate is SP, which in some cases may skew toward Th17 differentiation (84).

Along with their roles in amplifying inflammation, there is evidence that implicates CGRP and VIP, along with somatostatin and other neuropeptides, in limiting inflammation and maintaining immune tolerance. CGRP acts as a negative regulator of DC maturation and antigen presentation after pretreatment in vitro (136), and CGRP-pretreated DCs are less able to activate antigen-specific T cells to proliferate (131). In a model of dextran sodium sulfate–induced colitis, $CD11c^+$ DCs were hyperinflammatory in CGRP-deficient mice (137). Additionally, VIP may promote the generation of regulatory T cells in several models (106).

Given the multiple studies implicating neuropeptides in both amplifying and limiting various types of immune responses, more work is needed to tease out the full repertoire of sensory neuron–immune cell interactions mediated by neuropeptides and the extent to which this is context-, tissue- and timing-dependent. Adding to the complexity, neuropeptide receptor subtypes often transduce opposing outcomes (134).

Figure 4

Neuroimmune interplay. (*a*) Healthy skin harbors innate immune cells, such as dendritic cells, macrophages, and ILC2s, and is innervated by nociceptors. (*b*) Pathogen invasion activates pattern recognition receptors expressed by dendritic cells, macrophages, and nociceptors. Nociceptors both signal to the central nervous system and trigger a local axon reflex to release neuropeptides. In turn, the peptides activate ILC2s and macrophages to modify the inflammatory response and the dendritic cells that migrate to the lymph node. (*c*) Dendritic cell–primed lymphocytes then migrate from the lymph node to the affected tissue. Neuropeptides activate immune cells to release cytokines, thus enhancing other immune cell activation, as well as sensitizing nociceptors. Activated immune cells also release NGF, which acts on the TrkA to drive local nerve terminal sensitization and sprouting. (*d*) Following the resolution of inflammation, the tissue harbors phenotypically altered nociceptors with a denser innervation, as well as primed and memory immune cells, ready for recall responses. Abbreviations: CGRP, calcitonin gene-related peptide; CNS, central nervous system; FPR, formylated peptide receptor; ILC2, group 2 innate lymphoid cell; LN, lymph node; NGF, nerve growth factor; NK-1R, neurokinin 1 receptor; SP, substance P; TLR, Toll-like receptor; TrkA, tropomyosin receptor kinase A; TRP, transient receptor potential; VIP, vasoactive intestinal peptide.

FEEDFORWARD NEUROINFLAMMATORY LOOPS

In physiological situations, the local and systemic reflexes mediated by neuroimmune interactions can help bring the system back to homeostasis: Pathogens are eradicated; tissue is repaired; innate effector cells die or become quiescent; and memory is generated by both systems (2) (**Figure 4*d***). The memory allows for a quicker, more efficient response to repeated insults. There is, however, a cost: The bidirectional communication between the two systems and their memory paves the way for the generation of feedforward loops that can lead to immunopathologies and chronic inflammatory pain, particularly when persistent insults overwhelm the normal mechanisms that resolve inflammation (**Figure 5**).

Feedforward Loops in Allergy and Itch

What is the evidence for feedforward loops driving pathology? In the lungs, asthmatic patients have a reduced threshold for exacerbations in response to airborne irritants (138), reflecting excess sensitivity and activity of sensory fibers (139). Eosinophils cluster around airway nerves in asthmatic patients (85) and release basic proteins, which enhance sensory neuron activity (140). Allergen challenges lead to phenotypic switches in the nodose ganglion low-threshold mechanosensitive neurons, which begin to express TRPV1, an effect mimicked by exogenous exposure to GDNF or BDNF (141). Ablation of NaV1.8$^+$ nociceptor fibers reduces immune cell infiltration in ovalbumin and house-dust-mite models of asthma (11). A neuroimmune loop is established for type-2 allergic inflammation in the lung by the proasthmatic cytokine IL-5, released by activated CD4$^+$ and ILC2s, which directly stimulate nociceptors, promoting the release of neuropeptides, such as CGRP and VIP. VIP, in turn, directly activates CD4$^+$ T cells and ILC2s to produce IL-5, closing the proinflammatory feedforward loop between T cells and ILC2s and nociceptors. Silencing sensory neurons with a permanently charged sodium-channel blocker (QX-314) reverses this maladaptive neuroimmune interplay, indicating how targeting sensory neurons alone can have a profound immunosuppressive action (11).

Another example is itch, in which mast cell–nerve interactions are an important driver. Sensory neurons are in close contact with mast cells, particularly in the skin and airways (93, 126). When activated, mast cells release mediators that engage a foreign agent, recruit leukocytes, and initiate activity in itch sensory fibers, thus generating scratching and itch (93). Mast cells release histamine to act on H_1R expressed by sensory neurons, inducing lipoxygenase production, phospholipase A2 activation, and TRPV1 sensitization (55). The products of activated mast cells also cause long-lasting changes in neuronal excitability, and changed gene expression in nerves, resulting in phenotypically altered neurons (142). Neuropeptides, including SP, released by sensory neurons promote mast cell degranulation, contributing to the establishment of another proinflammatory loop between neurons and mast cells. Blocking this, by targeting either cell type (or both), could have beneficial actions on allergic inflammation.

Increased Innervation of Inflamed Tissue

The feedforward loops not only sensitize neurons and recruit immune cells, they also lead to significant remodeling of peripheral innervation (**Figure 4*d***). This contributes to the primed state, so that flares can be easily triggered. Immune cells are a rich source of neurotrophins, which increase the innervation of inflamed tissue through sensory neurons expressing relevant cognate receptors. In asthma, for example, patients have a denser network of nociceptors around small airways (85), and NGF levels in asthmatic patients positively correlate with disease severity (143). In human participants with allergic rhinitis, nasal provocation with an allergen increased NGF in

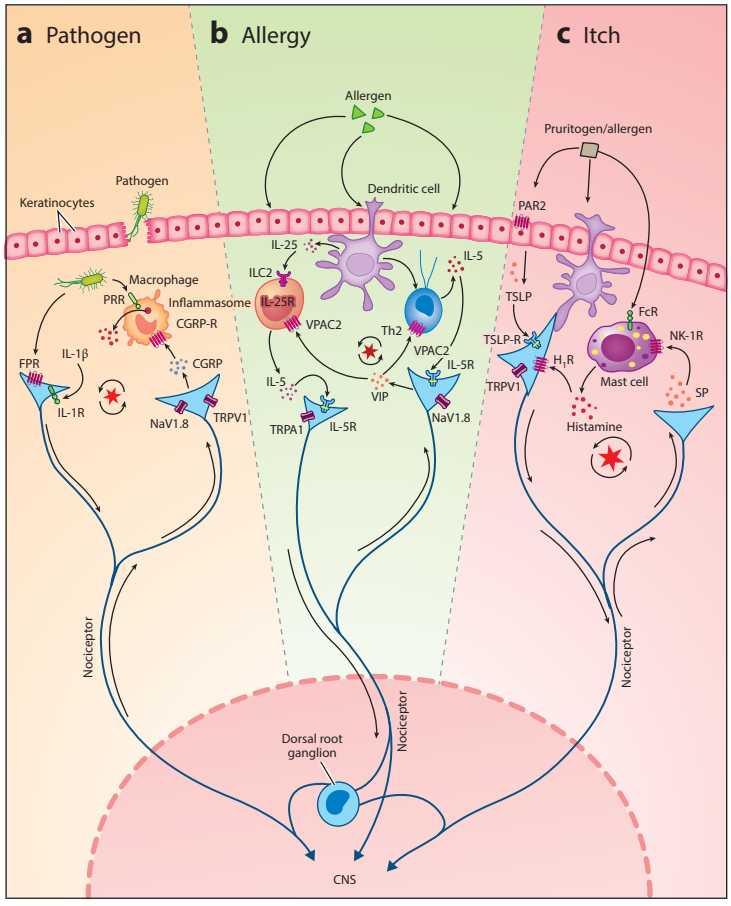


Figure 5

Inflammatory loops. (*a*) Skin-colonizing pathogens activate pattern recognition receptors on macrophages, leading to release of IL-1β, which stimulates IL-1R expressed on nociceptors, thus triggering the generation of action potentials. Antidromic depolarization promotes the local release of CGRP, which, in turn, activates macrophages to further release IL-1β. (*b*) Airway allergens activate dendritic and epithelial cells to release IL-25 and IL-4, activating ILC2s and T helper cells. These cells release IL-5 to stimulate IL-5R expressed on nociceptors, which, through axon reflexes, release VIP. VIP, in turn, further enhances ILC2 and Th2 cell release of IL-5. (*c*) Pruritogens activate dermal dendritic cells or epithelium-expressed protease receptors, or both, triggering nociceptor activation by direct contact or through TSLP signaling. Concomitantly, pruritogens activate mast cell Fc receptors to release histamine, which subsequently activates H_1R-expressed nociceptors. The local release of substance P by nociceptors enhances mast cell activity and degranulation. Abbreviations: CGRP, calcitonin gene-related peptide; CNS, central nervous system; FcR, Fc receptor; FPR, formylated peptide receptor; H_1R, histamine H1 receptor; ILC2, group 2 innate lymphoid cell; NK-1R, neurokinin 1 receptor; PRR, pattern recognition receptor; SP, substance P; Th, T helper; TRP, transient receptor potential; TSLP, thymic stromal lymphopoietin; VIP, vasoactive intestinal peptide.

nasal lavage fluids (144). Mice with inflammatory bowel disease have increased SP^+ and $TRPV1^+$ fiber innervation (122), and NGF promotes increased SP^+ fiber innervation in psoriatic lesions (145). Surprisingly, mast cell–derived TNF-α contributes to the elongation of epidermal and dermal nerve fibers, as well as to the inflammation observed at sites of contact hypersensitivity (146).

Therefore, inflammation includes neuroimmune amplification loops, in which immune cells secrete cytokines that activate neurons, and neurons secrete peptides that activate immune cells. The contribution of these to disease is just beginning to be unraveled and much more remains to be discovered. Nevertheless, the presence of such feedforward loops has been demonstrated in allergic airway inflammation (11), psoriasis (26), contact dermatitis (81), and inflammatory bowel disease (122), and they may offer a new therapeutic target for these immune diseases: the nervous system.

Conversely, there is evidence that neuroimmune communication can form negative feedback loops, as in bacterial infection in which sensory neurons suppress aspects of innate immune responses by releasing the neuropeptides CGRP, galanin, and somatostatin (3). This process might be something that bacteria exploit to proliferate and spread more readily, or it could be a brake, a means of preventing the local inflammation activated by the pathogens from producing excessive tissue damage. This remains to be teased out.

SUMMARY AND CONCLUSIONS

In this review, we have discussed the coordinated actions of the sensory and immune systems in host defense. The two systems detect environmental danger, infection, or tissue injury, using both shared and unique sensing mechanisms, and together they initiate inflammation to terminate the danger and allow a return to homeostasis (6). The defensive roles of the two systems are, we argue, deeply intertwined: One system can communicate with the other to amplify, stabilize, or dampen particular functions (1, 5). The two systems also detect inflammation itself. Inflammatory cytokines produced by immune cells change the threshold and activation properties of sensory neurons (peripheral sensitization), and neuropeptides released by sensory neurons can control the trafficking and activation state of immune cells.

The two systems have a similar general organization for responding to potentially damaging stimuli. Sensory neurons transduce environmental stimuli into electrical activity to generate the sensations of pain and itch, and they initiate motor and glandular responses to eliminate or minimize the danger, as well as memory, so that the insult may be avoided in the future. Immune responses parallel this process, with the innate immune system transmitting information about pathogens, toxins, or tissue damage to lymphoid tissues, where cells of the adaptive immune system integrate multiple signals to initiate effector responses to deal with the threat and create an immune memory.

Communication between the sensory and nervous systems is organized into both local and systemic reflex arcs. At the tissue level, local axon reflexes involving the somatic nervous system initiate vasodilatation and plasma leakage to allow immune cells to reach the infected or injured area of the body, and they also have a direct action on immune cells. Autonomic reflex responses, such as diarrhea and vomiting, act to expel pathogens or parasites, and somatic withdrawal reflexes remove contact from noxious stimuli. Finally, a vagal reflex activated by inflammation limits systemic inflammation.

Although there are clear data showing that the interaction of the two systems has important consequences for disease, the specifics are only just beginning to be understood, with some contradictory data on the actions of neuropeptides in various disease models and on immune cells that need to be more fully understood and resolved. Part of the problem may arise from focusing on single mediators and isolated cell types; the actual biological meaning of neuropeptide action in vivo is more likely to depend on the integration of multiple, coordinated signals, reflecting the context of the perceived danger, the tissue type and compartment, and the chronicity of inflammation.

Nevertheless, feedforward loops between sensory neurons and immune cells appear to be a common feature of chronic pain, itch, allergy, and aspects of some autoimmune diseases. These

loops can lead to disproportionate immune responses and chronic pain. Shared sensing mechanisms and reciprocal communication may lead to a primed state of interaction, characterized by hyperinnervation, sensitized neurons with increased or altered neuropeptide levels, and the presence of poised innate and adaptive effector cells in areas of chronic inflammation.

This is an exciting time for the study of neuroimmune interactions, and novel experimental approaches will help develop a more definitive picture of these, including targeted ablation in the adult of sensory neuron subsets (3, 11, 26), optogenetic (115, 147) or DREADD (designer receptor exclusively activated by designer drug) technology–based activation or silencing of sensory neurons (148), genome editing to control specific genes in sensory neurons and immune cells (149), and the exploitation of human stem cell–derived nociceptors to model phenotypic changes in chronic disease (150) and their impact on a specific population of immune cells. In addition to the specific efforts needed to identify mediators and mechanisms, the logic and language behind how sensory neurons direct immune responses in different inflammatory diseases need to be unraveled to address issues such as their involvement in the generation of inflammation and its resolution, biologically adaptive versus maladaptive interactions, and opportunities for novel treatment strategies.

One way of interrupting an ongoing neuroimmune loop in a type-2 inflammatory setting is by using charged sodium-channel blockers to specifically silence nociceptors in areas of inflammation (11). Alternatively, adaptive responses can be mimicked or enhanced by, for example, stimulating the vagus nerve to activate the immune-suppressing inflammatory reflex (6, 101, 102).

In conclusion, the somatosensory pain and immune systems fundamentally share the same basic function: danger detection. As such, the two systems have a similar modus operandi through their complementary sensing, effector, and memory mechanisms, all of which are geared toward a return to homeostasis but that have the potential to cause disease. The systems share a remarkable range of common GPCR and tyrosine kinase receptors for sensing similar sets of peptides, cytokines, and chemokines, and can, thereby, directly modulate each other's response. The adoption of a more unified portrait of inflammation, in which the sensory nervous and immune systems are seen to act as one integrated system, might be more appropriate, both because it could lead to a better understanding of inflammation and because it may present new therapeutic opportunities.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by the Hood Foundation (C.J.W.) and the National Institutes of Health (grants PO1NS072040, R37NS039518, and P30HD018665). S.T. holds a postdoctoral fellowship from the Canadian Institutes of Health and Research, and S.L.F. is supported by the National Institute of Neurological Disorders and Stroke (grant R37NS039518-14S1). We thank Stan Mikov Art for preparation of the figures.

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