Vagal immune-to-brain communication: a visceral chemosensory pathway

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Abstract

The immune system operates as a diffuse sensory system, detecting the presence of specific chemical constituents associated with dangerous micro-organisms, and then signalling the brain. In this way, immunosensation constitutes a chemosensory system. Several submodalities of this sensory system function as pathways conveying immune-related information, and can be classified as either primarily brain barrier associated or neural. The vagus nerve provides the major neural pathway identified to date. The initial chemosensory transduction events occur in immune cells, which respond to specific chemical components expressed by dangerous micro-organisms. These immune chemosensory cells release mediators, such as cytokines, to activate neural elements, including primary afferent neurons of the vagal sensory ganglia. Primary afferent activation initiates local reflexes (e.g. cardiovascular and gastrointestinal) that support host defense. In addition, at least three parallel pathways of ascending immune-related information activate specific components of the illness response. In this way, immunosensory systems represent highly organized and coherent pathways for activating host defense against infection.

Keywords: Cytokines; Immunosensory; Acute phase; Primary afferents; Vagus

1. Introduction

The brain is an important player in host defense against infection. In addition to coordinating metabolic, endocrine and behavioral changes that support the immune response, the brain modulates the immune system via neuroendocrine and direct neural regulation of immune cell functioning. But first, the immune system must alert the brain to the presence of an infection. This requirement implies the existence of an immunosensory system (Besedovsky and del Rey, 1992), in which immune-derived cells detect infections and signal the appropriate neural substrates. In this way, immune-nervous system interactions are characterized by bi-directional communication, aimed at the achievement of precise and effective host defense.

Immunosensory mechanisms can be classified into two general types of pathways: via specialized cells residing in brain barrier regions such as cerebrovascular endothelium (Van Dam et al., 1992; Ericsson et al., 1997) or choroid plexus (Herkenham et al., 1998) and circumventricular organs (Saper and Breder, 1994), or via peripheral sensory nerves associated with the vagus (Watkins et al., 1995a,b). Collectively, these ‘immune-to-brain mechanisms’ function as an immune chemosensory system organized to detect both pathogen and immune cell generated chemical stimuli.

Chemosensory systems, like other sensory systems, detect a wide range of stimuli, to which they must respond by rapidly activating the appropriate behavioral and physiological responses. For example, detection of olfactory stimuli associated with a predator requires behavioral responses such as hiding or escape, as well as endocrine and metabolic support for responses (e.g. stress hormones and glucose mobilization). In a similar way, immune chemosensory systems involve detection of a pathogen, followed by the induction of behavioral responses such as social isolation and reduced food intake. Concomitantly, physiological responses such as fever, increased sleep, and the mobilization of energy substrates support the peripheral immune responses. These responses are collectively re-
ferred to as ‘sickness symptoms’ or as the ‘acute phase’ of host defense.

Theoretically, any peripheral nerve may be capable of immunosensation. For instance, trigeminal ganglion cells respond to cytokines (Kobierski et al., 2000) which are immune-derived hormone-like mediators, and spinal visceral nerves respond to inflammation. However, the concept of immunosensation implies that responses to, for instance, cytokines lead to the initiation of brain-mediated acute phase responses, as such as fever. Of peripheral nerves that have been investigated so far (which haven’t been many), support exists only for the vagus as an immunosensory nerve. Sectioning of the abdominal vagus nerve inhibits acute phase responses such as fever in some experimental paradigms (Watkins et al., 1995a,b; Sehic and Blatteis, 1996; Romanovsky et al., 1997; Fleshner et al., 1998). Concordantly, immune stimuli activate vagal sensory neurons (Niijima, 1996; Ek et al., 1998; Gaykema et al., 1998; Goehler et al., 1998a,b). Based on anatomical and functional considerations, the vagus nerve is particularly well suited for an immunosensory function. This nerve conveys a variety of chemosensory signals, such as signals arising from meal-related stimuli. The broad distribution of vagal afferents to most visceral structures, including those most frequently in contact with pathogens, such as the lung and gastrointestinal tract, ensures that vagal afferents are ideally positioned to detect immune activation early on in an infection. This review focuses on immune-activated vagal pathways, but because the existence of parallel pathways is a hallmark of sensory system organization (Ulinski, 1984) the importance of other immunosensory pathways (e.g. brain barrier cells) must also be recognized. It is not within the scope of this paper to include all relevant contributions to the field, but rather to provide sufficient information to convey the general structure and function of this novel chemosensory system.

2. Immune chemosensory mechanisms

Immune cells are capable of detecting dangerous microorganisms and distinguishing them from benign and beneficial ones (Matzinger, 1994). The effectiveness of immune responses relies upon vigilant chemosensory surveillance rapidly responding to replicating bacteria and viruses. Two rather different mechanisms operate that lead to the activation of acute phase responses.

1. T-cell independent. Specific pathogen products can bind to receptors expressed on the plasma membranes of certain immune cells (see below), provoking them to release chemical mediators such as cytokines and chemokines, that serve to recruit other immune cells to fight the infection. These mediators also serve to signal the nervous system, activating acute phase responses.

2. T-cell dependent. Alternatively, certain immune cells take up either whole microorganisms, or particles released by micro-organisms, such as toxins, and process them for presentation to T-cells. Once activated by this ‘antigen’, T-cells release cytokines that activate other immune cells to fight the infection. In addition, T cell derived cytokines likely signal the brain, as above. For example, treatment with the Staphylococcus enterotoxin B (SEB), a product of Gram positive bacteria, elicits brain-mediated acute phase responses (Shurin et al., 1997; Goehler et al., 1999a) via activation of T-cells (Shurin et al., 1997) possibly via the release of cytokines.

2.1. Immune receptor molecules

The details of T-cell independent immune chemoreceptive mechanisms are of great current interest, and a few patterns are now emerging. Cell wall constituents seem to be particularly salient features for the recognition of bacteria. Several cell wall components signal the presence of Gram-positive bacteria, including lipoteichoic acid and proteoglycan products such as muramyl dipeptide. For Gram-negative bacteria, lipopolysaccharides (LPS) are the single most salient cell wall constituent. LPS first binds to a plasma protein, LPS-binding protein (Ulevitch and Tobias, 1999), before it is able to bind to the ‘LPS receptor’ (CD14). This mechanism finds an analogy in the binding of odorants to the olfactory binding protein before binding to odorant receptors on primary olfactory neurons (Steinbrecht, 1998) suggesting that certain features of stimulus presentation may be similar among different chemoreceptive systems.

Although CD14 is the best characterized LPS receptor, there is evidence of other proteins that also serve that function. Of special interest are the TOLL-like receptors (TLRs). These are mammalian homologs of Drosophila proteins that in adult flies participate in pathogen recognition (Kopp and Medzhitov, 1999). Each member of the TOLL family in flies induces defense responses to specific types of pathogens. For instance, drosophila TOLL activates antifungal defense mechanisms, whereas one of its homologs, ‘18-wheeler’, induces antibacterial peptides.

The specific functions of mammalian TOLL proteins have yet to be sorted out. However, like the drosophila TOLL proteins, mammalian TOLL-like receptors may transduce somewhat different signals. For example, TLR-2 appears to mediate activation to the Gram-positive bacterial cell wall components proteoglycan and lipoteichoic acid (Schwandner et al., 1999; Yoshimura et al., 1999), whereas TLR-4 may be important for the response to Gram-negative LPS. This apparent receptor selectivity may provide one mechanism by which the innate immune system tailors its responses to specific types of pathogens (Medzhitov and Janeway, 1997).
2.2. Immune sentinels are chemoreceptors

The initial recognition of a previously unencountered pathogen is carried out by a specialized subset of immune cells, referred to as ‘sentinels’ (Steinman, 1991). The most important of these cells, (also termed ‘professional antigen-presenting cells’, Matzinger, 1994), is the dendritic cell (Banchereau and Steinman, 1998). Dendritic cells are members of the monocyte lineage, which also includes macrophages and microglia (Goerdt et al., 1996; Banchereau and Steinman, 1998). Dendritic cells can be identified by their high and constitutive expression of MHC molecules (necessary for antigen presentation to T cells) and their many long, dendrite-like processes (Cella et al., 1997). They possess a number of attributes that qualify them to function particularly well as an ‘immune sentinel’. Dendritic cells are found in all tissues of the body, including skin, lung, gastrointestinal tract, and nerve (especially the vagus nerve, see below). They express receptors for a wide variety of pathogen-associated chemicals, including TOLL-like receptors, and are capable of internalizing pathogens or pathogen-associated particles as well (Reis e Sousa et al., 1999). Thus, dendritic cells are capable of utilizing both types of the above-mentioned chemosensory mechanisms to activate brain-mediated acute phase responses, and thus potentially signal the presence of any type of pathogen, including parasites or tumour cells as well as bacteria and viruses (Cella et al., 1997; Reis e Sousa et al., 1999). When activated by the detection of pathogen associated chemical stimuli, dendritic cells release proinflammatory molecular signals (Banchereau and Steinman, 1998), such as cytokines and chemokines capable of signaling the brain. Thus, dendritic cells likely serve as immunosensory sentinels for the nervous system, as well as the immune system.

A particularly interesting feature of dendritic cell distribution, likely relevant to a role in vagally-mediated immunosensation, is their prominent location within the vagus nerve and associated paraganglia (Goehler et al., 1999b; Fig. 1). Numerous dendritic cells intersperse themselves between vagal fibers within the nerve, and within the paraganglia their processes appear to embrace adjacent glomus cells. These dendritic cells, as well as other immune cells associated with the vagus, express interleukin-1 (an important pro-inflammatory cytokine) immunoreactivity rapidly following intraperitoneal injections of LPS. Thus these immune cells provide a potential source of cytokine mediators available to activate vagal afferents.

As immunosensory sentinels, dendritic cells (and other possible sentinels, such as mast cells and macrophages) can also be considered analogous to accessory cell chemoreceptors, such as taste cells. Dendritic and taste cells experience first contact with the chemical stimulus, and respond by generating a second signal capable of activating neural elements. An obvious difference, however, between immunosensory chemoreceptors and other types is their mobility. Taste cells, for instance, are located in fixed buds along the tongue, palate and throat. These are logical places for taste cells to be, given that taste stimuli arrive there before being swallowed. Most tastants themselves are not highly mobile, thus the muscles of, for example, the tongue are sufficient to maintain control of the chemosensory stimulus. These attributes are not typically found in immune stimuli (i.e. pathogens) which tend to be highly mobile and may actively avoid detection. Consequently receptor cells must also be mobile. Similarly, pathogens may enter the body by a number of different means, or they may even be generated within the body (as are tumour cells), and therefore the receptors must be

Fig. 1. Dendritic immune cells associated with the abdominal vagus nerve visualized with immunohistochemistry for MHC class II (using the MHC OX6 monoclonal antibody). Darkly stained dendritiform cells intersperse with abdominal vagal nerve fibers (in A) and also among glomus cells in vagal paraganglia (in B). The vagal paraganglion in B is counterstained with cresyl violet to provide light background staining. Scale bars=50 μm.
widely distributed throughout the body, as are dendritic cells. Thus, characteristics of immune receptor cells reflect features of the pathogenic stimuli.

3. How do immune receptor cells signal the vagus?

Upon detection of pathogens, immune receptor cells release a variety of chemical substances capable of activating the nervous system. Important mediators include cytokines such as interleukin-1 (IL-1), tumour necrosis factor (TNF), interleukin-6 (IL-6) and interferon-gamma (IFN). Other likely mediators include prostaglandins, which are ubiquitous inflammatory mediators implicated in local inflammatory processes, and notably, in the initiation of brain mediated host defense responses, especially fever (Saper and Breder, 1994; Blatteis and Sehic, 1997). Pro-inflammatory fragments of complement proteins, notably C3a and C5a, are also likely to function as neurally relevant immune signals (Blatteis and Sehic, 1997).

Two potential kinds of mechanisms likely lead to immune signaling to the vagus. Either vagal sensory neurons themselves respond to immune cell-derived signals (as olfactory neurons respond to odors), or vagally innervated accessory-type cells (analogous to taste cells) may initially respond to these signals.

3.1. Potential mechanisms of neuronal immunosensation

Vagal sensory neurons express receptors for some of the immune-derived mediators mentioned above. Evidence that vagal neurons themselves may directly respond to immune mediators is provided by the observations of Ek et al. (1998), that some vagal sensory neurons express IL-1 receptor type I messenger RNA. In addition, many vagal sensory neurons express receptors for prostaglandin (EP3 receptors; Ek et al., 1998).

Vagal afferents respond to a variety of mast cell products (Greene et al., 1988; Undem et al., 1993) and express immune/inflammatory peptides and their receptors, including those of the proinflammatory peptide tachykinin/neurokinin receptor family (Fischer et al., 1996). Tachykinins, notably substance P, are released upon tissue injury or in allergy or asthma from mast cells or nerve fibers. Interestingly, neurokinin-2 receptor activity in vagal afferents is upregulated dramatically (from about 20% of vagal afferents responding, to greater than 85% responding) after immunization and re-exposure of a foreign protein (antigenic challenge; Weinreich et al., 1997), indicating that vagal afferents become sensitized to immune-related stimuli. In addition, tachykinin receptors become ‘unmasked’ following treatment with serotonin (5HT) or 5HT3 receptor agonists (Moore et al., 1999). This functional increase in tachykinin responsivity was long-lasting. The observation that such a large proportion of vagal afferents can be induced to respond to inflammatory mediators suggests that a major function of the vagus may involve signaling immune and inflammatory situations.

If vagal afferents are themselves capable of responding to chemical stimuli derived from activated immune cells, what tissues are their targets? Abundant immune type tissue and cells are found throughout the gastrointestinal tract, not surprisingly as this is a barrier site for infectious agents. Specialized lymphoid tissue, the Peyers patches, lie at the base of the crypts of the small intestine. In addition, macrophages and dendritic cells line the epithelium of the villi, and overlie the Peyers patches (Nagura et al., 1991). Anterograde tracing of vagal afferents innervating the duodenum have demonstrated vagal fibers coursing through the epithelium, within the lamina propria and the crypts (Berthoud et al., 1995a). Thus vagal afferents occupy a position in which they might be sensitive to locally produced cytokines. Berthoud et al. (1995a) also reported a close association of vagal afferent fibers with a cell type described as possessing several long dendrite-like processes. Given this morphology and location, these uncharacterized cells may in fact be a type of dendritic immune cell (Nagura et al., 1991; Reudl et al., 1996). Such an arrangement could allow a rapid signaling of mucosal immune activation.

Lymph nodes also provide a site of early immune activation, as these are the major locations in which antigen presenting cells interface with the T cells that serve to co-ordinate immune responses. The lymphatic system comprises an interconnecting network of conducting vessels that carry immune cells and antigens, including microorganisms, from lymph node to node, progressively to the heart. In addition, lymph nodes are innervated by both sympathetic and sensory neuropeptide containing nerve fibers (Feltone et al., 1984; Fink and Weihe, 1988; Popper et al., 1988). Given that much of the lymphatic system, notably the pelvic, mesenteric, deep cervical, and mediastinal ducts and nodes, lies well within the range of vagal afferent peripheral terminal fields, we investigated whether vagal afferents might also innervate lymph nodes. Using injections of the retrograde tracer fluorogold into cervical and pelvic lymph nodes, we found retrogradely labeled neurons in the nodose and jugular ganglia (Fig. 2). These observations indicate that vagal afferents are clearly well situated to monitor early stage activation in immune-related tissues.

3.2. Chemosensory accessory cells may also serve as immune receptors

In addition to activating vagal afferents directly, immune cell derived mediators may activate vagal immunosensitive pathways via the chemoreceptive cells located in the vagal paraganglia, or via neuroepithelial bodies found in lung airways. Goehler et al. (1997), using a biotinylated interleukin-1 receptor ligand, demonstrated binding sites
on glomus-like cells within paraganglia. Vagal paraganglia are comprised of glomus cells, which have been demonstrated to be chemoreceptive when located in other structures, such as the aortic and carotid bodies (Matsuura, 1973). At least one other type of cell is also present, that may function similarly to glia or immune cells (Goehler et al., 1999b). Many glomus cells are innervated by vagal afferents (Berthoud et al., 1995b). Vagal paraganglia are penetrated by blood and lymph vessels, suggesting that these structures are likely monitoring substances circulating in body fluids. Given the induction of IL-1 immunoreactivity after immune challenge with bacterial endotoxin within dendritic-like cells (Goehler et al., 1999b) and the co-distribution of IL-1 IR with cells expressing IL-1 binding sites, it seems likely that vagal paraganglia constitute a mechanism by which the vagus may monitor immune-related stimuli circulating in blood or lymph.

Structures similar to paraganglia, the neuroepithelial bodies, are found in the airways of the lung. These structures contain cells that are morphologically highly similar to the glomus cells of the carotid and aortic bodies and vagal paraganglia; they apparently serve chemosensory functions. Interestingly, the cells of the neuroepithelial bodies seem to provide the only target for vagal afferent fibers in the lung epithelium (Adriaensen et al., 1998). Given the important role of the lung as a barrier and clearance site for airborne, as well as circulating pathogens, the neuroepithelial bodies would be fortuitously located as immune-vagal interfaces.

4. Primary afferent activation

Like other chemosensory pathways, vagal immunosensation involves the activation of primary afferent neurons as the initial stimulus-to-nervous system interface. Primary afferent neurons associated with the vagus nerve reside in a fused ganglion complex: the vagal–glossopharyngeal ganglion, which consists of the nodose (inferior vagal), the petrosal (glossopharyngeal) and jugular (superior vagal) ganglia. Both pathogen-derived chemical constituents and immune cell-derived cytokines have been shown to induce the expression of the immediate–early gene product c-Fos, a marker for activation in many cell types including many neurons, in vagal sensory neurons.

4.1. Pathogen-derived signals

Both intraperitoneal and intravenous injections of the bacterial endotoxin LPS induce the expression of c-Fos protein in vagal afferent neurons (Gaykema et al., 1998). In addition, Staphylococcus enterotoxin B (SEB), a product of gram positive bacteria, induces c-Fos protein and c-fos mRNA (Goehler et al., 1998a,b; Fig. 3) in vagal afferent neurons located in both the jugular (superior) and nodose (inferior) vagal ganglia. The detection of SEB is a T-cell mediated process that likely takes place in lymph nodes. The finding that both LPS (T-cell independent) and SEB (T-cell dependent) induce activation in vagal sensory neurons demonstrate that this immunosensitive pathway likely carries information regarding immune activation to a wide variety of pathogens. In addition, because vagal sensory neurons located in the jugular ganglia primarily innervate structures located above the diaphragm (Altschuler et al., 1989), including deep cervical lymph nodes (see above), these findings show that immunosensitive vagal afferents are situated to signal the presence of immune activation or mediators in both the thoracic and abdominal cavities. Consequently, experiments using subdiaphragmatic vagotomy to determine whether vagal afferents transduce specific immune signals may be compromised by sparing immunosensitive vagal afferents that
5. Ascending immunosensitive pathways

Bacteria-derived immune stimuli including LPS and SEB, as well as cytokines including IL-1, activate interconnected nuclei in the brainstem, midbrain and forebrain that also relay and process both gustatory and other visceral sensory information (Wan et al., 1994; Day and Akil, 1996; Elmquist et al., 1996). From studies assessing c-Fos expression and separate studies employing neuronal tract tracing techniques, it is possible to tentatively identify three parallel pathways conveying immunosensory information. These pathways likely activate discrete components of the sickness experience, from the initiation of fever and neuroendocrine responses, to the alterations in behavior and hedonics that are associated with illness and inflammation. It is important to note that immune activation also initiates protective local reflexes, such as gastric retention (Hermann et al., 1999) and emesis, that serve to isolate and expel pathogenic organisms. (Andrews and Lawes, 1992)

Vagal afferents terminate in the dorsal vagal complex of the caudal medulla. The dorsal vagal complex consists of the area postrema (a circumventricular organ), the nucleus of the solitary tract (nTS), and the dorsal motor nucleus of the vagus. Together these nuclei integrate sensory signals with descending neural inputs to control visceral reflexes, whereas no such expression was found after saline injection (shown in B). The expression of c-fos mRNA was visualized by hybridization of digoxigenin-labeled RNA antisense probes (Courtesy Dr. N. Quan, Ohio State University), followed by alkaline phosphatase-conjugated antiserum against digoxigenin. Scale bars=50 μm.

innervate important supradiaphragmatic structures such as lung and lymph nodes.

4.2. Immune cell-derived signals

As mentioned above, immune cells release a variety of chemical mediators, that are likely to actually activate vagal afferent neurons. IL-1 is one of the major cytokine mediators functioning to activate brain-mediated acute phase responses (Dunn, 1993; Maier et al., 1993). IL-1 administration mimics the effects of immune activation on host defense responses, and blocking its actions using the interleukin-1 receptor antagonist prevents defense responses, such as fever, normally resulting from certain illness or inflammatory conditions (Leon et al., 1996). Vagal primary afferents express IL-1 receptors (Ek et al., 1998). Peripheral administration of IL-1 also induces c-fos mRNA (Ek et al., 1998) and c-Fos protein (Goehler et al., 1998a,b) in vagal afferent neurons, and induces increases in electrically recorded neural firing (Niijima, 1996). These findings indicate that one pathway by which IL-1 exerts its effects on acute phase responses is likely via vagal afferents.

5.1. nTS-VLM-paraventricular and preoptic hypothalamus (Fig. 4A)

Treatment with immune stimulants such as LPS or interleukin-1 activate catecholaminergic neurons in the

5.2. nTS-PB-central extended amygdala (Fig. 4B)

Immune stimuli activate specific subnuclei associated with the central extended amygdala (Tkacs et al., 1997; Day et al., 1999): the lateral central nucleus of the amygdala proper (CeA), and the dorsolateral, or oval, subdivision of the bed nucleus of the stria terminalis (BST). This activation is likely driven by immunosensitive neurons in the external lateral PB (Ericsson et al., 1994; Elmquist et al., 1996; Tkacs and Li, 1999), a region heavily innervating these central extended amygdala regions (Fulwiler and Saper, 1984; Bernard et al., 1994; Alden et al., 1994). In addition, ascending catecholaminergic neurons in the nTS/VLM project directly to these structures (Riche et al., 1990; Terenzi and Ingram, 1995) and may also contribute to immunosensitive responses of the central extended amygdala. This structure is believed to integrate emotional context with ongoing sensory processing, and to initiate or regulate the appropriate autonomic output, e.g. elevated heart rate in response to fear (Roozendaal et al., 1990; LeDoux, 1995).

5.3. nTS-PB-midline thalamus-infralimbic and insular cortex (Fig. 4C)

Nuclei of the midline thalamus (paraventricular, central medial, and subparafascicular) express increased levels of c-Fos protein following treatment with LPS, as do the pre- and infralimbic, and insular cortices (Gaykema et al., in preparation; Elmquist et al., 1996). These thalamic and cortical structures are interconnected (Freedman and Cas-Sell, 1991) and process visceral sensory information that arise from the nTS directly (Ruggiero et al., 1998) and from the PB (Bester et al., 1999). Thus, this ascending pathway integrating visceral sensory information at the thalamic and cortical levels likely carries an immunosensory component. As such, this pathway further integrates immune activation into a complex of autonomic, gustatory, and behavioral adjustments, leading for instance to changes in emotional and hedonic states, and could influence changes in taste perception during illness (e.g. conditioned taste aversion).

5.4. Differential activation of ascending pathways by different immune stimuli: do parallel pathways carry pathogen specific information?

A hallmark of chemosensory systems is the segregation of information based on modality of stimulus conveyed, on

VLM and nTS that project directly to the paraventricular nucleus of the hypothalamus (PVN; Ericsson et al., 1994; Sagar et al., 1995; Elmquist et al., 1996). These projections appear to be critically involved in the activation of this central component of the hypothalamus–pituitary–adrenal (HPA) axis (Ericsson et al., 1994) that ultimately leads to elevations in plasma corticosteroids during immune stimulation. Subdiaphragmatic vagotomy inhibits activation of PVN neurons, and subsequent secretion of adrenocorticotropic hormone (Wan et al., 1994; Gaykema et al., 1995; Kapcala et al., 1996) following treatment with LPS or IL-1. These findings imply that, in the context of immune stimuli, vagal input drives this ascending pathway. Components of this medullary projection also target neurons in the preoptic area (Saper and Levisohn, 1983; Tucker et al., 1987), a region associated with the integration of sensory signals leading to the induction of fever (Scammell et al., 1996; Elmquist et al., 1997). Part of the ascending pathway from the nTS to the hypothalamus and preoptic area runs via the secondary viscerosensory relay in the lateral parabrachial nucleus (Fulwiler and Saper, 1984; Moga et al., 1990). This relay may also contribute to the immunosensory effects on neurons in, e.g. the PVN (Elmquist and Saper, 1996).

Fig. 4. Three central immunosensory pathways can be distinguished that convey and process information about immune activation. These pathways originate in the dorsal vagal complex, and reach the hypothalamic and preoptic area (A), the central extended amygdala (B), and the visceral thalamo-cortical system (C). Abbreviations: BST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; cc, corpus callosum; HIP, hippocampus; IL, infralimbic cortex; INSC, insular cortex; MIT, midline and intralaminar thalamus; NTS, nucleus of the solitary tract; PBL, lateral parabrachial nucleus; POA, preoptic area; PVN, paraventricular nucleus of the hypothalamus; VLM, ventrolateral medulla.


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the output system driven. Therefore, different pathogenic stimuli will likely activate specific patterns of brain activation based on the particular acute phase responses most appropriate to that pathogen. So far, this issue has not yet been explored systematically. However, preliminary data comparing c-Fos expression patterns in the brains of animals treated with LPS (T-cell independent) with SEB (T-cell dependent) suggests that such an organizational pattern may obtain.

Comparison of SEB- and LPS-induced expression of c-Fos protein in the rat brain reveals differential patterns of activation. LPS induces c-Fos in all three of the above-mentioned pathways, with an especially strong hypothalamic response. In contrast, SEB appears to activate the nTS-PB-central extended amygdala pathway preferentially, with only weak to modest response in the PVH (Gaykema et al., 1999). In the lower brainstem, SEB treatment activates more rostrally located neurons in the nTS and VLM than does LPS. These observations may reflect differential coding based on signal transduction (e.g. T-cell dependency).

6. Perspectives: organizing features of immunosensory systems

From the foregoing, it is evident that vagal viserosensory neurons respond to immune-related stimuli, and that this information is processed via a similar, but ultimately unique, pattern of neural activation as other chemosensory systems. Immune cells respond to variety of pathogen-associated chemicals by releasing mediators, such as cytokines that further activate immunosensory pathways serving to generate appropriate responses to the stimulus (i.e. acute phase responses). A pictorial representation of the model is shown in Fig. 5. Although many details of this system remain to be clarified, some patterns, or organizing features, can be identified.

6.1. Characteristics of receptors and their distribution is driven by characteristics of the sensory stimulus

Sensory receptors must respond to relevant features of a particular physical stimulus, and the receptor sheet must be...
located in tissues exposed to the stimulus. For example, olfactory receptors are located in the nasal cavity, where they are exposed to airborne odorants. Similarly, vagal afferents responding to gut-derived ‘satiety’ signals during normal feeding supply the gut specifically (Schwartz et al., 1999). In contrast, infection or inflammation can occur anywhere in the body. This fact demands that immunosensory receptors be distributed in a diverse array of tissues, including lung, G-I tract, and lymph nodes. Correspondingly, vagal afferent lesions that spare some supradiaphragmatic fibers do not block acute phase responses to immune-related stimuli (Porter et al., 1998).

6.2. The brain substrates responding to a sensory stimulus support appropriate neuroendocrine, autonomic or behavioral responses to that stimulus

The acute phase response consists of a co-ordinated set of functional changes that enhance and support host defense. Mapping of immunosensitive neurons in the brain demonstrates that the pattern of activation is consistent with what is currently known of the central autonomic network nuclei that control at least the neuroendocrine and autonomic responses to illness.

6.3. Parallel pathways likely code for different features of the sensory stimulus

Vertebrate sensory systems are characterized by parallel pathways (Ulinski, 1984). In addition to the several types of brain barrier pathways, it is possible that vagal pathways for immunosensation may also consist of separate submodalities, perhaps coding for different types of pathogens, or the location of infection within the body. Such an organization can allow for a tailoring of responses depending on the requirements for effective defense against a specific kind of pathogen. It also allows for redundancy in a system that is critical to survival.

6.4. Sensitization

The mammalian immune system has evolved secondary immune responses (e.g. antibody-mediated) to enable rapid immune activation when re-exposed to a pathogen. Part of this rapid activation is reflected, and perhaps supported, by the sensitized recruitment of vagal afferent responses upon re-exposure to immune stimuli. Interestingly, this sensitization may explain pathology associated with conditions such as allergy or asthma.

Characterizing immune-to-brain communication as a chemosensory system provides a conceptual structure from which to analyze and interpret current findings. Immunosensory pathways are not simply ‘immune-to-brain mechanisms’. Rather, they constitute modalities of a coherent sensory system that has evolved to rapidly and efficiently detect pathogenic microorganisms, and to activate brain-mediated responses directed toward effective support of host defense. Whereas much detail is lacking from our understanding of the structure of these pathways, as well as the specific circumstances under which each pathway is most important, future research will undoubtedly shed light upon these issues.

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