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Autonomic Innervation and Regulation of the Immune System (1987-2007)

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Abstract

Since 1987, only a few neuroanatomical studies have been conducted to identify the origin of innervation for the immune system. These studies demonstrated that all primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons. Neither the thymus nor spleen receive any sensory neural innervation; however, there is evidence that lymph nodes and bone marrow may be innervated by sensory neurons located in dorsal root ganglia. There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ. Thus, the primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system (SNS) and its main neurotransmitter, norepinephrine (NE). Activation of the SNS primarily inhibits the activity of cells associated with the innate immune system, while it either enhances or inhibits the activity of cells associated with the acquired/adaptive immune system. Innate immune cells express both alpha and beta-adrenergic receptor subtypes, while T and B lymphocytes express adrenergic receptors of the beta2 subtype exclusively, except for murine Th2 cells that lack expression of any subtype. Via these adrenergic receptors, NE is able to regulate the level of immune cell activity by initiating a change in the level of cellular activity, which often involves a change in the level of gene expression for cytokines and antibodies.

INTRODUCTION

Prior to 1987, Felten and colleagues provided the initial descriptions of the catecholamine innervation of the thymus and spleen in mice, and subsequently extended their analysis to include other species, as well as lymph nodes, bone marrow and gut (Felten et al., 1985). In addition to the neurovascular innervation of all immune organs by catecholamine fibers and terminals, non-vascular innervation was demonstrated and indicated that nerves were located in juxtaposition to the cellular mediators of both innate and adaptive immunity. Identification of the neuroanatomical origin of the innervation of immune organs had also begun. For example, using retrograde neuroanatomical tract-tracing techniques, (Bulloch and Moore, 1981) reported a major parasympathetic and motor neuron input to the thymus gland that originated from both the retrofacial nucleus (compact formation of the nucleus ambiguus) in the brain stem and ventral horn motor neurons in the upper cervical spinal cord. Utilizing microdissection techniques and histochemical procedures, they subsequently identified a

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sympathetic input to the thymus from the upper cervical sympathetic chain ganglia (Bulloch and Pomerantz, 1984). However, they stated that branches of the vagus, phrenic and recurrent laryngeal nerves provided a substantial cholinergic (acetylcholinesterase, AChE) input to the thymus, which supported their earlier retrograde tracing results (Bulloch and Moore, 1981). Since it was unlikely that brainstem nuclei and spinal cord motor neurons, which were known to provide motor innervation to the esophagus, diaphragm and neck musculature, would also provide a major neural input to the thymus gland, we re-investigated the origin of the neural input to the thymus gland in rats and mice. These results were published in the first volume of Brain, Behavior and Immunity (Nance et al., 1987) and are summarized below. Figure 1 depicts the overall topic to be discussed in this article.

INNERVATION OF THE THYMUS

Utilizing small injections of wheatgerm agglutinin-horseradish peroxidase (WGA-HRP) (0.5-2.0 μl, vs 5-25 μl injections of HPR utilized by (Bulloch and Moore, 1981), the sympathetic input to the thymus was identified as originating from sympathetic chain ganglia that extended from the superior cervical chain ganglia caudal to the T3 sympathetic ganglion (Nance et al., 1987). Importantly, little or no retrogradely labeled neurons were identified in the ventral vagal complex (compact formation of the nucleus ambiguus) or upper cervical spinal cord. For the few animals in which a small number of lightly labeled neurons were identified in the brainstem or spinal cord, these results could be accounted for by spread of the retrograde tracer onto surrounding mediastinal structures (esophagus and longus coli muscle). Injections of WGA-HRP into the esophagus and longus coli muscle reproduced the identical pattern of retrogradely labeled neurons in the brainstem and spinal cord that was attributed to the thymus by (Bulloch and Moore, 1981). Furthermore, microdissections failed to identify any branches from the vagus or phrenic nerve that innervated the thymus. Finally, sectioning of the cervical vagus nerve failed to alter the acetylcholinesterase (AChE) staining in the thymus, indicating that AChE staining is associated with sympathetic nerves, and are not vagal cholinergic fibers. Afferent input to the thymus was also limited or nonexistent. Thus, the thymus gland unequivocally receives a substantial sympathetic innervation from cervical and upper thoracic sympathetic chain ganglia, and there is no neuroanatomical evidence for a parasympathetic or sensory input to the thymus gland (Nance et al., 1987).

Now twenty years later, another neuroanatomical study on the innervation of the thymus gland has been reported (Trotter et al., 2007). This study examined the innervation of the thymus gland in rats utilizing the transneuronal retrograde transport of pseudorabies virus (PRV). In addition to verifying the original observation regarding the complete absence of any vagal input to the thymus gland (Nance et al., 1987), they identified the central pathways that provide sympathetic input to the thymus. Following transneuronal transport of the virus from sympathetic post-ganglionic neurons, they identified sympathetic preganglionic neurons in the intermediolateral cell column of the T1-T7 spinal cord. At longer survival times, transneuronal transport of PRV identified additional labeled interneurons in the spinal cord, as well as sympathetic premotor neurons located in the medulla oblongata, pons and hypothalamus. We believe it is not a coincidence that the same brain areas identified by the transneuronal transport of PRV from an immune organ represent many of the same brain regions that were identified with the activity-dependent neuronal cellular marker, c-fos protein, following administration of endotoxin or stress (Wan et al., 1994). Thus, the sympathetic nervous system provides the only pathway for direct neural modulation of thymic immune function. Although neuropeptides generally associated with sensory peptides have been reported to be present in the thymus (Felten et al., 1985), at present there is no neuroanatomical or functional evidence that these fibers provide any sensory feedback from the thymus gland. Thus the presence of substance P or CGRP does not establish the existence of afferent innervation.

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INNERVATION OF THE SPLEEN

In 1989, the first neuroanatomical study on the source of innervation to the spleen was published in Brain, Behavior and Immunity (Nance and Burns, 1989). In addition to the retrograde tracer WGA-HRP, the fluorescent retrograde tracer FluoroGold was used. Utilizing small injections of tracers into the rat spleen, application of a diffusion barrier (Opsite) to the spleen post-injection, and surgical sectioning of the splenic nerve, it was found that prevertebral sympathetic ganglia associated with the celiac-mesenteric pleus provided a major sympathetic input to the spleen. In addition, many retrogradely labeled neurons were identified bilaterally in the thoracic sympathetic chain. Denervation of the spleen verified the specificity of the labeling and established that the splenic nerve is the final common pathway for neural input to the spleen. Importantly, and similar to the thymus, no evidence was found for a sensory input to the spleen from either the vagus nerve or dorsal root ganglia. We concluded that neural input to the spleen was exclusively sympathetic, with no evidence for a sensory or vagal nerve supply. Further evidence for the absence of any vagal or parasympathetic input to the spleen was subsequently published in Brain Behavior and Immunity by (Bellinger et al., 1993) who demonstrated the absence of choline acetyltransferase (ChAT) in the spleen, which is a more specific marker of cholinergic nerve fibers than AChE. Similarly, immunohistochemical studies for vesicular acetylcholine transporter, a highly specific marker for cholinergic neurons and fibers, indicated their complete absence in lymphoid tissue (Schafer et al., 1998). Finally, a transneuronal study of the innervation of the spleen with PRV has verfied this conclusion (Cano et al., 2001) and demonstrated that sympathetic preganglionic neurons that innervate the spleen arise from the T1-T12 region of the thoracic spinal cord. Longer survival times identified sympathetic premotor brain nuclei projecting either directly or indirectly to the spinal sympathetic preganglionic neurons, and again consisted of many of the same nuclei in the brainstem, pons and hypothalamus that are activated by immune stimuli (Wan et al., 1994). Thus, neuroanatomical and neurochemical evidence demonstrates that neural innervation of the spleen is entirely sympathetic in origin, and indicates further that there is no evidence for parasympathetic or sensory input to the spleen. Again, any sensory neuropeptide-positive fibers identified in the spleen are not involved in providing sensory feedback from this immune organ.

INNERVATION OF LYMPH NODES

Detailed neuroanatomical descriptions of the origin of the innervation of lymph nodes remains limited. However, the presence and distribution of sympathetic catecholamine fibers in various lymph nodes has been well documented (Felten et al., 1985), and it is likely that the ganglionic origin of this innervation would reflect the specific regions of the body where the lymph nodes reside. Consistent with this, and representing one of only two retrograde tracing studies of the innervation of lymph nodes, are the results of (Romeo et al., 1994). They focused on the superior cervical ganglion of the rat and demonstrated that injecting Fluorgold into the submaxillary lymph node retrogradely labeled sympathetic neurons in the caudal portion of the ipsilateral superior cervical ganglion. Although retrogradely labeled neurons in other sympathetic chain ganglia were not examined, this limited analysis suggests that similar to the thymus and spleen, individual lymph notes receive their sympathetic input from postganglionic neurons that are associated with supplying the sympathetic input to the particular region of the body where the immune organ is located. However, in contrast to the thymus and spleen, there is some neuroanatomical evidence that lymph nodes may receive a neural afferent supply, at least in the case of guinea pigs. (Kurkowski et al., 1990) examined the distribution of labeled neurons in dorsal root sensory ganglia following injections of FluoroGold into the tracheobronchial lymph nodes of guinea pigs. They did not examine labeling in the sympathetic chain ganglia, but did observe FluoroGold labeled neurons in cervical dorsal root ganglia that were distributed in decreasing numbers from the C3 to the C8 ganglia. Although more neuroanatomical studies are required, these results suggest there may be a sensory input to

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regional lymph nodes. Functionally, this may reflect the fact that lymph nodes collect and process immune cells from specific regions of the body, all of which receive an extensive afferent sensory innervation (skin, muscle, mucosa, etc.). Sensory fibers are important regulators of localized inflammatory responses in skin and the extension of this neural-immune interaction into the draining lymph nodes appears likely (Shepherd et al., 2005). Also, unlike the thymus and spleen, lymph nodes process immune responses that are associated with specific regions of the body and tissue compartments where the location of the immune challenge would be critical for directing the immune system to sites of injury and infection. Based upon the limited data available, it is possible that regional lymph nodes receive an afferent neural input from dorsal root ganglia. To date, there is no neuroanatomical evidence for a parasympathetic input to lymph nodes, and the failure to identify vesicular acetylcholine transporter labeled fibers in lymphoid tissue (Schafer et al., 1998) further supports this conclusion.

INNERVATION OF BONE MARROW

Same as for other immune organs, the sympathetic innervation of bone marrow is well established, and functional experiments have demonstrated that the sympathetic nervous system can regulate bone marrow function (Felten, et al, 1985). Yet, neuroanatomical studies of the origin of the innervation of bone marrow is as limited as that for lymph nodes, in part due to the intimate contact between mineralized bone that receives a sympathetic and sensory innervation, and bone marrow (Imai et al., 1997). All blood vessels receive a sympathetic nerve supply, and the same nutrient blood vessels that supply mineralizd bone, cartlige, and periosteum continue into the marrow. Likewise, presumptive sensory fibers (substance P and CGRP immunopositive) accompany noradrenergic sympathetic fibers along these same blood vessels that supply the surrounding bone and are further distributed throughout the bone morrow. Functional separation between the innervation of bone and bone morrow has yet to be established. Although application of neuroanatomical tract-tracing techniques to identifying the origin of the innervation of bone marrow versus the surrounding tissue is technically difficult, (Denes et al., 2005) recently reported the first neuroanatomical study to examine the origin for the neural innervation of bone marrow. Utilizing high concentrations of PRV, they demonstrated the transneuronal transport of the virus from femoral bone marrow to thoracolumbar paravertebral sympathetic ganglia and T8-L1 spinal sympathetic preganglion neurons. At longer survival times, virus labeling was detected in premotor sympathetic brain nuclei in the brain stem, pons and hypothalamus. While the central pattern of transneuronal labeling was comparable to what has been reported for the thymus and spleen (Cano et al., 2001;Trotter et al., 2007), the amount of central labeling of PRV infected neurons was very limited and likely was due to the high and neurotoxic doses of PRV required to initiate transneuronal transport from bone marrow. However, their results establish the origin of sympathetic neural input to bone marrow, and importantly, dual transneuronal labeling with two isogenic, but histochemically distinguishable, forms of PRV allowed a comparison between bone marrow versus the overlying skeletal muscles. Although a similar central pattern of PRV labeling was observed in many brain and spinal cord regions, there was little or no overlap (dual-labeling) throughout the neural axis. For example, labeling in the paraventricular nucleus of the hypothalamus and descending catecholamine nuclei in the brain stem and pons, produced by both muscle and bone marrow injections of PRV, were entirely separate, with no double labeling of neurons. They did not report any results regarding possible sensory input to bone marrow. Thus, the afferent innervation, as well as any possible parasympathetic input to bone marrow has yet to be established. Additional retrograde tracing studies of bone marrow and the examination of bone marrow for vesicular acetycholine transporter labeled nerves are required.

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OTHER SITES OF NEUROIMMUNE REGULATION

All regions of the body receive sympathetic input and all body surfaces that are potential sites of either microbial invasion or antigen challenge (skin, oral and gut mucosa, peritoneum, lungs) receive an extensive afferent neural innervation that is closely associated with cellular elements of the immune system. The adjuvant-like contribution of sensory fibers to the local actions of microbes and antigens at these body surfaces represent a significant modulator of the magnitude and effectiveness of the localized inflammatory (innate) immune response, as well as the subsequent adaptive immune response (Shepherd et al., 2005).

SUMMARY OF THE INNERVATION OF THE IMMUNE SYSTEM

There is a predominate sympathetic (catecholamines) input to all components of the immune system, whereas afferent innervation of the immune system may be limited to lymph nodes and bone marrow. To date, there is no neuroanatomical evidence for efferent vagal or parasympathetic innervation of the immune system, with the possible exception of the respiratory and the alimentary tracts, which have yet to be demonstrated.

RECEPTOR EXPRESSION ON IMMUNE CELLS

Findings supporting the location of sympathetic nerves and NE release within the vicinity of immune cells prompted the design of studies to determine if adrenergic receptors were expressed on the immune cell surface. The expression of such receptors would be necessary in order for neural signals to be delivered to immune cells. There are two types of receptors that bind NE, namely the alpha-adrenergic receptor (αAR) and the beta-adrenergic receptor (βAR), which are expressed in a tissue-specific manner and exhibit differing affinities for NE. The beta2-adrenergic receptor (β_2AR) subtype is the primary receptor that is expressed on immune cells in both rodents and humans [reviewed extensively in (Kin and Sanders, 2006;Sanders et al., 2001)]. The number of β_2ARs expressed on immune cells is variable and is regulated by a number of different factors, including cell activation, cytokines, hormones, and neurotransmitters. Stimulation of the β_2AR on an immune cell induces an increase in the intracellular level of cAMP and subsequent activation of protein kinase A (PKA). In addition, stimulation of the β_2AR activates other signaling intermediates, such as mitogen-activated protein kinase (MAPK).

The advent of molecular techniques to sort out specific populations of immune cell subsets allowed for the determination of which subset expressed a specific adrenergic receptor subtype at the level of protein and gene expression. Cells involved in innate immunity have been found to express the β_2AR primarily, but some cells have been reported to express other subtypes. The only review to summarize the data supporting expression of the α_1AR by primarily monocytes/macrophages was published in Brain, Behavior & Immunity, and includes a discussion of the possible pathophysiological consequences that might occur as a result of α_1AR expression (Kavelaars, 2002). In addition, most reports indicate that T and B cells involved in adaptive immunity express the β_2AR subtype exclusively. Bulk populations of CD8+ and CD4+ T cells express the β_2AR, as do naive CD4+ T cells and murine Th1 cells, while clones of murine Th2 cells do not. However, conflicting data exist when using human cells, with some suggesting the absence of a β_2AR and some suggesting the presence, primarily because it has been difficult to obtain purified populations of human IFN-γ- and IL-4-producing cells since these cytokines do not polarize in humans as well as they do in mice. However, as techniques improve to purify human CD4+ T cells that secrete only Th1- or Th2-like cytokines, it should be possible to confirm if the β_2AR is differentially expressed, and if so, for what physiological purpose.

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Upon CD4+ T cell activation, the level of β_2AR expression on most cells, except murine Th2 cells, either increased or decreased. These findings suggested that expression of the β_2AR was maintained as the naive T cell differentiated into a Th1 cell, but was repressed as it differentiated into a Th2 cell. The mechanism responsible for mediating the differential expression of the β_2AR by these two effector cell subsets remains unknown, but may involve epigenetic mechanisms (unpublished findings). The B cell expressed almost twice as many receptors as the CD4+ T cell. A few radioligand binding analyses showed expression of the αAR on B cells, but the results may be misleading since platelets, which express the αAR at a high level, were not removed from the lymphocyte samples before analysis. Also, all B cell receptor studies to date have been conducted primarily on the most common B cell type, which is also known as the B-2 cell. To date, no information is available as to whether or not the less common CD5+ B-1 B cell subset expresses the β_2AR. Taken together, adaptive immune cells are known to express primarily the β_2AR, while innate immune cells appear to express both the β_2AR, a_1AR, and a_2AR.

SYMPATHETIC REGULATION OF INNATE IMMUNITY

Innate immunity represents the first line of defense against microbes. The innate immune system reacts quickly to microbes (Toll receptors), but expresses a limited number of responses to a diverse array of organisms. Components of the innate immune system include antimicrobial chemicals (defensins) on epithelial surfaces (skin and mucosa), complement, phagocytes (macrophages and neutrophils), natural killer cells, and granulocytes, which include neutrophils, eosinophils, basophils, and mast cells, These inflammatory cells are effector cells for both innate and specific immunity. Macrophages respond to the presence of various types of bacteria, bacterial DNA (unmethylated CpG), and viruses. For example, monocytes express specific receptors (CD14, Toll-4) for lipopolysaccharide (LPS), a cell-wall constituent of gram-negative bacteria. Injections of LPS produce a cascade of inflammatory cytokines, beginning with tumor necrosis factor-alpha (TNF-α), followed by interleukin-1 beta (IL-1β) and then interleukin 6 (IL-6). Other important regulatory and effector molecules are produced by macrophages at later intervals, such as interleukin-12, interferons, and nitric oxide. These macrophage-dependent products are both effector and signal molecules. For example, TFN-α acts upon cellular death receptors to kill infected and damaged cells, and when produced in excessive amounts results in septic shock. Together with IL-1β, TNF-α produces a pyrogenic response (fever) that aids further in bacterial killing. These inflammatory cytokines also produce localized effects on vascular endothelial cells to upregulate expression of adhesion molecules, which recruit additional immune cells to sites of bacterial invasion. Concurrent changes in vascular permeability aids in the immigration of these cells from the blood stream. IL-6 mediates the acute phase response to infection and stimulates the production and release of acute phase proteins, such as CRP, from the liver. Importantly, these same cytokines set the stage for subsequent engagement and actions by the adaptive immune system. Macrophages, and their specialized associates, dendritic cells, serve as antigen-presenting cells and provide a critical first step in the full engagement of the antigen-specific adaptive immune system. Thus, modulation of the early actions of the innate immune system have significant impact on the magnitude and quality of the specific adaptive immune response. The utility of microbial adjuvants to potentiate specific immune responses to antigen is based upon this fundamental immunological process. Given the central role of macrophages in the regulation of the innate immune system, the next discussion will focus on the neural regulation of macrophages and their production of inflammatory cytokines.

Sympathetic nerves, norepinephrine, and the regulation of macrophages

Norepinephrine (NE) is the primary transmitter released from sympathetic nerve terminals. In vitro experiments with macrophage harvested from spleen and lymph nodes have shown that

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via β-adrenergic receptors, NE can dramatically inhibit the production and secretion of TNF-αin response to LPS (Ignatowski et al., 1996). Less consistent results have been observed for IL-1β production, but NE is generally regarded as inhibitory for this cytokine (Meltzer, et al, 2004). Both inhibitory and facilitatory effects of NE on IL-6 production have been noted, and the direction of the IL-6 response to NE may depend upon the concurrent presence or absence of LPS. These same in vitro studies have also shown that activation of α-adrenergic receptors with specific agonists exerts a stimulatory effect on TNF-α production by macrophages in response to LPS. However, as will be summarized below, in vivo activation of the sympathetic nervous system by either stress or central inflammatory stimuli inhibits splenic macrophage function, indicating a dominance of β-adrenergic mechanisms influencing splenic macrophage. Double-labeling immunocytochemistry has verified that splenic macrophages are the primary source of cytokine production during the first few hours after an endotoxin challenge.

Effects of central inflammatory stimuli on splenic macrophages

Two model systems have been used to test the effects of the sympathetic nervous system on macrophage function. First, we showed that intracranial injections of cytokines and related inflammatory mediators (prostaglandins) activated the sympathetic nervous system. This has been demonstrated by increased turnover rate for NE in the spleen (Vriend et al., 1993) and increased splenic nerve electrical activity (MacNeil et al., 1997). Some 15 years ago, we showed that intracranial injections of IL-1βtwo hours prior to harvesting splenic macrophage produced a suppression in the in vitro production of IL-1β in response to LPS (Brown et al., 1991). Significantly, cutting the sympathetic nerve supply to the spleen prior to the central injection of IL-1β abrogated the suppression in the in vitro IL-1β production by splenic macrophages in response to LPS. Also, intraventricular injections of prostaglandin (PGE2) produced a rapid increase in splenic sympathetic nerve activity (MacNeil et al., 1997) and produced a dramatic suppression in the in vivo production of TNF-α mRNA and protein in the spleen of animals given an i.v. injection of LPS (Nance, 2001). Same as reported for central injections of IL-1β, cutting the splenic nerve prior to central injection of PGE2 attenuated the suppressive effects of intraventricular injections of PGE2 on splenic TNF-α production.

Effects of stress on splenic macrophages

The sympathetic nervous system is activated by stressful stimuli, such as footshock, restraint, and cold water immersion. A brief (15 minute) bout of intermittent footshock was used to examine the sympathetic regulation of splenic macrophage function in rats (Meltzer et al., 2004). Both splenic and plasma levels of inflammatory cytokines were measured in response to i.v. LPS administration immediately before or following the stressor. In comparison to controls, both splenic and plasma levels of TNF-α were dramatically suppressed in the stressed animals. Subsequently, we found that the effects of stress on splenic TNF-α production was still present in animals that were adrenalectomized, indicating that the inhibitory effects of stress were independent of adrenal hormones. Finally, cutting the splenic nerve in adrenalectomized animals abrogated the immunosuppressive effects of stress on TNF-α production induced by systemic LPS. Finally, adrenal gland demedulation, combined with splenic nerve section, established that the immunosuppressive effect of stress on macrophage cytokine production was mediated entirely via the sympathetic nervous system. Concurrent measurements of IL-1βmRNA and protein in these experiments indicated that changes in IL-1βproduction followed the same pattern as found for TNF-α but the changes were much less dramatic.

In summary, activation of the sympathetic nervous system (noradrenergic nerves and adrenal medulla) exerts a potent anti-inflammatory action upon the innate immune system. Among the inflammatory cytokines produced by macrophages, the production and release of the inflammatory cytokine TNF-α is the primary cytokine that is regulated by the sympathetic

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nervous system. It is of further interest that exactly this same inflammatory cytokine has been the focus of the “cholinerigic anti-inflammatory hypothesis” (Borovikova et al., 2000;Saeed et al., 2005).

Role of the vagus nerve and parasympathetic nervous system.

Since the first report that subdiaphragmatic vagotomy attenuates the central activational effects of intraperitoneal injections of moderate doses of LPS (Wan et al., 1994), numerous studies have shown a fundamental role for the sensory vagus nerve in transmitting neuroimmune afferent information from the abdominal cavity and viscera (Maier et al., 1998). However, this immune-sensory function of vagal afferents is not unique to the vagus nerve, and all sensory fibers distributed throughout the body, such as skin, muscle, and all mucosal surfaces, can respond to immunological stimuli and transmit this information to the central nervous system. However, studies by Tracey and colleagues (Borovikova et al., 2000;Saeed et al., 2005) have suggested that the **efferent** vagus nerve, and thus the parasympathetic nervous system, plays a unique and powerful role in regulating systemic and localized inflammatory processes, primarily by inhibiting macrophage production of TNF-α. They have shown that vagal efferent stimulation can inhibit endotoxin-induced sepsis and TNF-α production, as well as localized inflammation induced in a dermal airpouch. However, as reviewed above, we have shown that the adrenal medulla and sympathetic nerves inhibit macrophage TNF-α production and systemic inflammation. Likewise, Yoon, et al (Yoon et al., 2006) have shown that inhibition of localized inflammation in the airpouch model is mediated via a sympathoadrenal pathway. Is it possible that both the parasympathetic and sympathetic nervous systems mediate the inhibition of TNF-α and inflammation?

Although it is beyond the scope of this review to fully analyze the cholinergic anti-inflammatory hypothesis, it can be stated that, thus far, there is no evidence for an anti-inflammatory role of the efferent vagus nerve that is independent of the sympathetic nervous system. The persistent, but generally ignored, lack of neuroanatomical evidence for vagal efferent input to immune organs and body regions beyond the respiratory and alimentary tracts and internal visceral organs (heart, pancreas, etc.), was reviewed in the discussions above. Also, the absence of vesicular acetylcholine transporter positive fibers in lymphoid organs (Schafer et al., 1998) indicate that there is no known parasympathetic input to the immune system. Other studies by Tracey have focused on the α7 nicotinic acetylcholine receptor as a primary mediator of the anti-inflammatory signal conveyed by the efferent vagus nerve (Wang et al., 2003). However, nicotinic receptors, including the α7 subunit, mediate the communication between the spinal 'cholinergic' sympathetic preganglionic neurons and the catecholamine-producing neurons located in sympathetic ganglia and the adrenal medulla (Skok et al., 1999). Also, nicotine administration stimulates catecholamine release by activation of nicotinic receptors localized on peripheral postganglionic sympathetic neurons and the adrenal medulla (Haass and Kubler, 1997). Finally, α7 nicotine receptor-deficient mice do not show functional deficits in parasympathetic autonomic function (Franceschini et al., 2000), as might be predicted by the cholinergic anti-inflammatory hypothesis (Wang et al., 2003). However, as predicted by the neuroanatomical and neurochemical organization of the autonomic nervous system, they found that α7-deficient mice show dysfunction in the regulation of the sympathetic nervous system (Franceschini et al., 2000). Lastly, there is electrophysiological evidence that stimulation of branches of the vagus nerve activates the adrenal nerve in the rat (Niijima, 1992), as well as elegant anterograde neuroanatomical tract-tracing studies that have traced efferent vagal fibers from the dorsal motor nucleus of the vagus to prevertebral sympathetic ganglia in the abdominal cavity, including the adrenal plexus (Berthoud and Powley, 1993). Thus, until proven otherwise, we suggest that many, if not all, of the anti-inflammatory effects associated with efferent vagal stimulation are due to the concurrent activation of the adrenal medulla and the sympathetic nervous system. It is

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surprising that no one has examined the effects of sympathectomy, adrenergic blockade, or adrenal demedulation on the inhibition of TNF-α and inflammation produced by efferent vagal stimulation.

SYMPATHETIC REGULATION OF ADAPTIVE IMMUNITY

Stimulation of the β_2AR on both a murine and human T and B cells that expressed the β_2AR increased both the intracellular concentration of cAMP and adenylate cyclase activity, suggesting the potential for modulation of cellular activity at the level of gene expression. Very early in this field of study, findings were reported both in vitro and in vivo to support the proposal that NE and β_2AR stimulation were indeed able to change cellular function [for a review of the early research, see (Sanders and Munson, 1985). The development of a β_2AR-deficient mouse was considered a breakthrough that was hoped to show convincingly that the expression of this receptor on immune cells was relevant physiologically. Brain, Behavior & Immunity published the first comprehensive immunological phenotype of this mouse in 2003 (Sanders et al., 2003). Contrary to expectations, however, the mouse phenotype was normal before and after immunization, likely due to compensation mechanisms in vivo that did not appear to involve upregulation of another adrenergic receptor subtype. However, the compensatory mechanism was lost when the β_2AR-deficient cells were removed from the mouse and assayed in vitro. The latter finding suggested that if cells from the β_2AR-deficient mouse were transferred to a normal mouse, they might provide the in vivo tool that would be necessary to study the physiological relevance of this receptor on specific immune cell subsets. Unfortunately however, these mice are on a ‘q”-haplotype that is a genetic background not yet available in an immunodeficient mouse model. Therefore, cell transfer experiments cannot be performed until the β_2AR-deficient mice are back-crossed on to a mouse strain for which an immunodeficient mouse is available. Therefore, most support for the functional relevance of the β_2AR has been obtained from functional analyses in vivo and in vitro.

T Lymphocytes

Not many studies were designed to look at T cell function in vivo, but a few studies are noteworthy [reviewed extensively in (Kohm and Sanders, 2001b). Madden and colleagues showed that the contact sensitivity response was decreased in mice that were depleted of NE either prior to or following sensitization, as compared to non-depleted mice (Madden et al., 1989). The decreased response was due to a decrease in T cell reactivity, suggesting that NE was needed for the development and/or progression of a Th1 cell-mediated immune response. However, when two different strains of mice, C57Bl/6J (Th1 cell-slanted strain) and Balb/c (Th2 cell-slanted strain), were depleted of NE and immunized 2 days later with the T cell-dependent antigen KLH, splenic cells from both strains of mice produced more Th1- and Th2-like cytokines (Callahan and Moynihan, 2002), suggesting that NE may exert a suppressive effect on Th1/Th2 cell development and/or progression. Such contradictory results demanded that another experimental approach be used. To address this need, mice that were genetically deficient for the enzyme dopamine beta-hydroxylase, which is required to synthesize NE from dopamine, were used to determine if NE regulated the magnitude of a Th1 cell-driven response (Alaniz et al., 1999). These NE-deficient mice showed that the absence of NE resulted in a diminished Th1 cell-driven response in vivo against the pathogens *Listeria monocytogenes* or *Mycobacterium tuberculosis*, suggesting that NE played a role in upregulating the magnitude of a Th1 cell-mediated immune response. Taken together, these studies are the first to indicate that NE exerted an effect on either early naïve CD4+ T cell development into a Th1 cell, the commitment to becoming a Th1 cell, and/or the amount of IFN-γ secreted by the effector Th1 cell. The role that NE played in vivo during the development and/or progression of a Th2 cell-driven response remains unclear.

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Early in vitro studies using unfractionated CD4+ T cell populations suggested that NE, β_2AR-selective agonists, or other cAMP-elevating agents either inhibited or enhanced the level of IL-2, IFN-γ, or IL-4 produced, while studies using populations of Th1 and Th2 cells suggested that these agents decreased the level of IFN-γ and increased the level of IL-4, respectively [Reviewed extensively in (Kin and Sanders, 2006;Kohm and Sanders, 2001a;Sanders and Straub, 2002). When naive T cells were isolated and activated, IL-2 secretion was decreased by exposure to NE, suggesting that NE and β_2AR stimulation affected the ability of an activated naive T cell to expand in number. However, these cultures produced an equal number of viable cells after 5 days in culture, even though they produced less IL-2, suggesting that an early decrease in IL-2 after β_2AR stimulation may affect initial cell expansion, but that this effect may dissipate over time. Also, NE stimulation of the β_2AR on a naive CD4+ T cell did not affect the number of Th1 cells that develop under defined Th1-promoting culture conditions, but did increase the level of IFN-γ secreted per cell upon reactivation. Exposure of Th1 cells to NE or a β_2AR-selective agonist before their activation decreased both IL-2 and IFN-γ production, while stimulation either at the time of, or after, cell activation appeared to be either without effect or induced an increase in IFN-γ, respectively. However, it appears that NE has no effect on murine Th2 cell activity, and this is likely because the murine Th2 cell does not express the β_2AR. In vitro exposure of human PBMC to NE or a β_2AR agonist induced a decrease in IFN-γ production, but an increase in IL-4 and IL-10 (Sanders and Straub, 2002), thus suggesting that NE caused a shift to a Th2-like cytokine environment. Although these findings are still debated, an elevation in intracellular cAMP within murine CD4+ T cell subsets appears able to affect T cell activity, but NE and β_2AR stimulation may affect only naive and Th1 cell activity, with the effect depending on the time of β_2AR stimulation in relation to T cell activation.

Exposure of murine spleen cells or human peripheral blood cells to NE increased the generation of CD8+ T cell lytic activity, perhaps by inhibiting the production of TNF-α. However, the timing of exposure to a catecholamine or agonist in relation to the stage of CD8+ T cell differentiation may be relevant to these functional outcomes. If ligands were added after the generation of CTL, i.e., during the effector stage of the response to antigen, a decrease in CTL activity occurred that may be due to a cAMP-induced decrease in the TCR-dependent release of cytotoxic granules. Thus, the role of NE and/or β_2AR stimulation in modulating CD8+ T cell activity remains uncertain in both humans and animals, but may be influenced by the time of adrenergic receptor stimulation in relation to the stage of CD8+ T cell differentiation.

B Lymphocytes

The effect of NE-depletion on the primary T cell-dependent antibody response in vivo has also been investigated [reviewed extensively in (Kin and Sanders, 2006;Kohm and Sanders, 2001b;Sanders and Munson, 1985;Sanders and Straub, 2002)]. Data have shown that either a decrease or increase in the Th cell-dependent IgM antibody response occurs after NE depletion. Taken together, the majority of results in mice suggest that NE enhances the endogenous activity of the immune cells that generate the response. NE depletion was also found to decrease serum IgG1, germinal center formation and CD86 expression on B cells after antigen exposure. Using dopamine β-hydroxylase deficient mice, the level of IgG produced by B cells in wild-type mice decreased (Alaniz et al., 1999), likely due to the effect on IFN-g production as described above for T cells. In the β_2AR-deficient mice, IgG production was the same as for wildtype mice, but this may be due to compensatory mechanisms, as discussed above. In contrast, another study reported a strain-specific enhancement in antibody production in NE-depleted C57Bl/6J and Balb/c mice, again explainable by the cytokine changes. Thus, it is difficult to conclude the effect of NE-depletion on the IgM and IgG response in vivo, although most data indicate suppression, suggesting that NE may be needed to play a positive role in an

antibody response in vivo, but the mechanisms by which this occurred are beginning to become clearer

The finding in vivo that NE-depleted mice were unable to upregulate CD86 expression on B cells when compared to NE-intact mice suggested that CD86 may be regulated by NE to help enhance the antibody response, possibly via co-stimulation of the T cell. But, when examined in vitro, β_2AR stimulation on a B cell at the time of B cell activation, in the presence or absence of a T cell, directly increased the level of CD86 expressed on, and IgG1 produced by, a B cell [reviewed extensively in (Kin and Sanders, 2006). The β_2AR- and CD86-induced increase in IgG1 occurred on a per cell basis by increasing the rate of mature IgG1 mRNA production. Class switch recombination and the number of cells producing IgG1 were unchanged, suggesting that β_2AR stimulation on a B cell affected a post-switch molecular process. The molecular mechanism responsible for mediating the increase in IgG1 involved a β_2AR-induced, CREB-mediated increase in the expression of the co-activator protein OCA-B, which interacted with the CD86-induced increase in the transcription factor Oct-2, promoting their cooperative binding at the 3'-IgH enhancer to increase enhancer activity. β_2AR stimulation was also found to increase the level of IgE produced on a per cell basis. However, in contrast to the β_2AR-induced increase in IgG1 that was found to be dependent on CREB activation, the increase in IgE was not. In the case of IgE, the findings suggested that the link between β_2AR stimulation and the increase in IgE involves the activation of p38 MAPK and formation of sCD23 (Pongratz et al., 2006). Thus, β_2AR stimulation on a B cell that is activated in the presence of IL-4 may induce the activation of two distinct signaling pathways in a B cell to regulate the level of IgG1 and IgE produced, and also appears to upregulate CD86 expression on a B cell to participate in mediating the antibody increase.

COMMENT

Taken together, these studies demonstrate the potential for NE to exert varying effects on T and B cell function in vivo. However, additional problems arise when comparing in vivo and in vitro effects of NE on T and B cell function. As previously discussed, most studies investigating the effects of NE on T and B cell function in vivo depleted normal mice of the neurotransmitter. Therefore, in vitro studies specifically examined the effects of the addition of NE on specific T and B cell cell populations and functions, while the in vivo studies were in fact studying the effects of NE-depletion on all cell populations that participated in the immune response and expressed adrenergic receptors. Also, immune responses measured in NE-depleted mice likely reflects an immune response that occurs in vitro when no NE is present, suggesting that the addition of NE to an in vitro culture might more closely reflect the real state of an immune response in vivo when NE-containing nerve fibers are intact and functional. Finally, in vivo studies may have also examined the effects of NE on cells in various states of differentiation, since NE-depletion most likely affected both naive and effector cells in these animals. Thus, future studies may be assisted by the use of additional model systems, such as adoptive transfer of specific receptor-deficient cell populations into immunodeficient mice, to investigate the role of NE in regulating the function of each cell type contributing to antibody production in vivo. Alternatively, gene disruption of NE-synthesizing enzymes or adrenergic receptor expression in specific cell populations in vivo, using conditional gene expression systems, will also be helpful.

CONCLUSIONS

Given the functional significance assigned to the neural innervation of the immune system, it is important to realize that the neuroatomical foundation for this link in the neuroimmune network continues to rest upon a handful of studies. Now twenty years after publishing the first, and seldom referenced, description of the innervation of the thymus gland (Nance et al.,

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1987), there continues to be a need for further neuroanatomical and neurochemical analyses of the neural innervation of the immune system. All conceptual models of the neuroimmune regulatory system, such as the recent “cholinerigic anti-inflammatory hypothesis” are constrained by the anatomy, and must be consistent with the neuroanatomical organization of the innervation of the immune system.

To date, a number of clinical examples support a role for a neuroimmune interrelationship in the etiology or progression of a disease state, and many of these examples are discussed thoroughly in a number of excellent reviews (Glaser, 2005;Heijnen and Cohen, 1999;Sanders and Straub, 2002). All of these reviews emphasize that an understanding of the cellular, biochemical, and molecular mechanisms by which NE regulates the level of immune cell activity will one day lead to the development of therapeutic approaches that will alter the etiology and/or progression of immune system-related diseases. Such therapeutic approaches will be important to use as one's immune system encounters the multitude of antigens in the host environment, whether they be external or internal. It will also be important to understand how one's level of immunocompetence might affect different components of the nervous system that exert an effect on immune cell activity, e.g., the level of innervation and/or locally secreted NE within lymphoid tissue and/or the level of expression for the β_2AR on immune cells.

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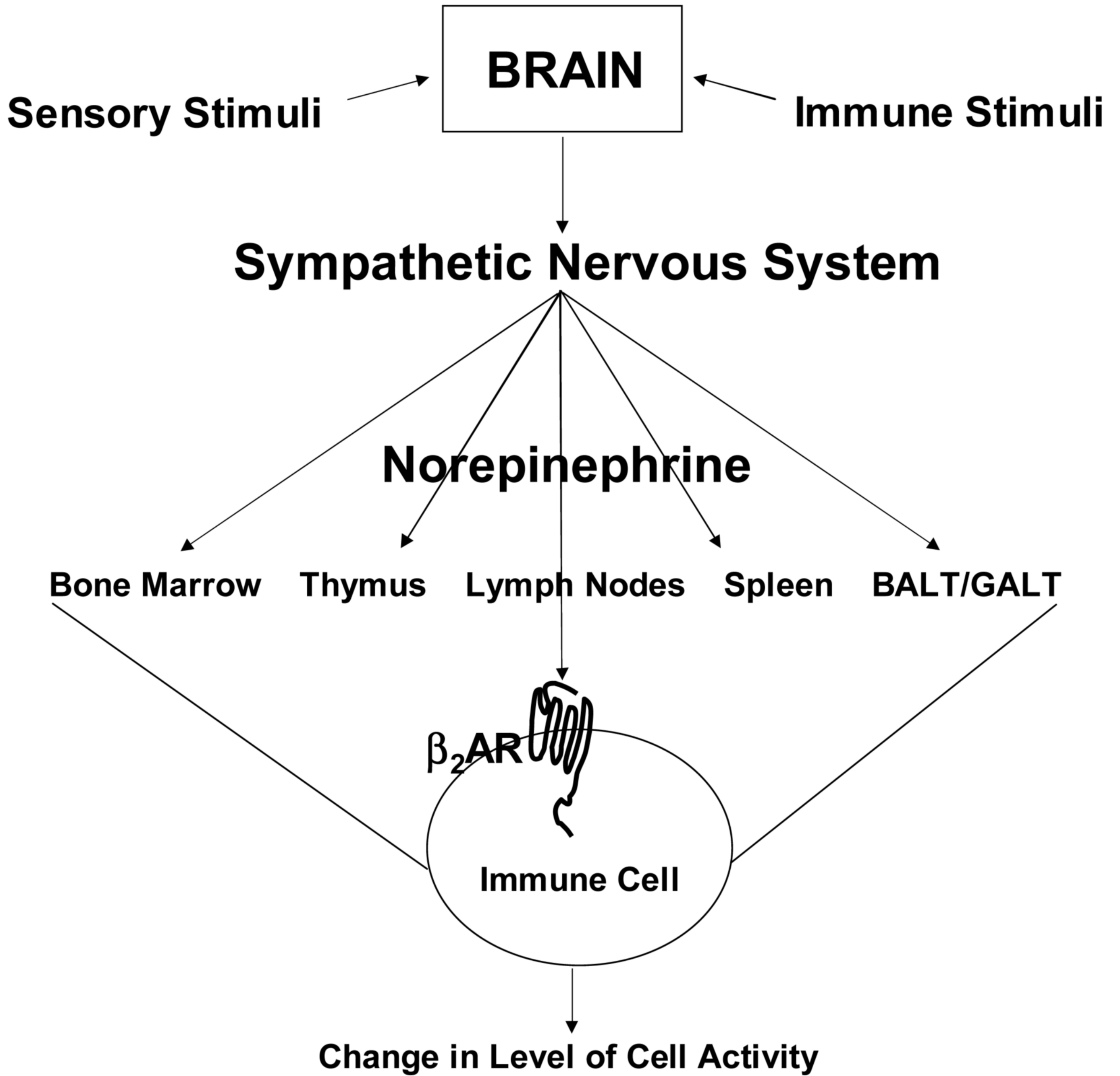

FIGURE 1.
All primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons. There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ. Input to the brain comes from sensory, e.g., dorsal root ganglia, or immune stimuli, e.g., cytokines. The primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system and its main neurotransmitter, norepinephrine. Activation of the SNS primarily inhibits the activity of cells associated with the innate immune system, while it either enhances or inhibits the activity of cells associated with the acquired/adaptive immune system. Via adrenergic receptors, which are primarily of the beta2-adrenergic receptor (β_2AR) subtype, NE is able to

regulate the level of immune cell activity by initiating a change in the level of cellular activity, which often involves a change in the level of gene expression for cytokines and antibodies.

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