Published in final edited form as:

Neuroimage. 2009 September ; 47(3): 908–910. doi:10.1016/j.neuroimage.2009.05.058.

Neural concomitants of immunity—Focus on the vagus nerve

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Inflammation and immunity have been implicated in a wide variety of diseases and disorders ranging from Alzheimer's disease to cardiovascular disease to hemorrhagic shock. As such any Special Issue devoted to Brain–Body Medicine must consider the neural concomitants of inflammation and immunity. In this editorial we will briefly consider the evidence for the neural concomitants of immunomodulation. First, we will briefly review the anatomy and physiology of neural–immune communication. Evidence for the somatotopic organization of the vagus nerve and for pain processes suggests that such an organization may be relevant for the investigation of the neural concomitants of immunity. Then we will provide an overview of what is known from both animal and human studies including neuroimaging studies. Finally, we will discuss some of the challenges and opportunities in this exciting area of investigation.

The anatomy and physiology of neural–immune communication

Whereas there is still some lingering controversy surrounding the idea of neural–immune communication, the evidence provides strong support for numerous interactions among the central nervous system (CNS), peripheral nervous system (both sympathetic and parasympathetic branches), the endocrine system, and the immune system (Felton, 2000; Sternberg, 2006; Watkins and Maier, 1999). Neurohormonal pathways involving circulating hormones such as cortisol (in humans) and catecholamines, such as norepinephrine, have been described in some detail (Sternberg, 1997, 2006). In addition to, and perhaps at least as important as the humoral pathway, are neural pathways, including the peripheral nervous system (reviewed in Sternberg (2006)), the sympathetic nervous system (SNS: reviewed in Nance and Sanders (2007)), and the parasympathetic nervous system, which is the focus of this editorial (reviewed in Tracey (2002, 2007), and van der Zanden et al. (2009)).

While release of neurohormones into the circulation provides a mechanism for regulation of immunity at a systemic level, through neurohormonal binding to receptors in immune cells, neural pathway regulation of immunity confers an added dimension to immune regulation—that of anatomical location (Sternberg, 2006; Tracey, 2002). Thus, neural pathways regulate immunity at a local and regional level. This level of anatomical organization is important because immune organs are specialized to regulate different aspects of immune function (e.g. thymus and lymph nodes regulate cellular immunity; bone marrow and spleen regulate humoral immunity; skin and mucosa contain the first line defense cells of innate immunity). Specific regions within immune organs are further specialized to regulate different immune cells at different stages of development (Felton, 2000). Thus within the thymus and lymph

nodes there are regions where developing and maturing T lymphocytes are exposed to antigen and either die through apoptosis or go on to mature to become specific immune activated cells, each with a specialized function, for example capable of killing viruses or cancer cells. Within the spleen and bone marrow, B lymphocytes mature to the stage where they can produce specific antibodies.

Superimposed on this anatomical structure of functional specificity of immune cells and organs, is the structure and specificity of the neural pathways that innervate these organs. The sympathetic nervous system regulates immunity at a regional level, through innervation of immune organs including the spleen, thymus and lymph nodes (Nance and Sanders, 2007; Sternberg, 2006). Sympathetic influences can be both pro- and anti-inflammatory (Elenkov et al., 2000; Thayer and Fischer, 2009). The SNS plays a role in the redistribution of immune cell populations acutely, and also can be immunosuppressive, affecting immune cell function during conditions of massive norepinephrine release within these organs, such as occurs during stress (reviewed in Kennedy et al. (2005); Nance and Sanders, 2007). The peripheral nervous system regulates immunity at sites of inflammation, wherever in the body this might occur. Neuropeptides released from peripheral nerves tend to be pro-inflammatory and are largely responsible for the characteristic features of “calor, rubor and dolor” (heat, redness and pain) at inflammatory sites (Sternberg, 2006).

Of particular relevance for this editorial, the parasympathetic nervous system has been shown to play a crucial role in immunomodulation. Both afferent and efferent parasympathetic activities are thought to play roles in immunomodulation (Sternberg, 2006; Tracey, 2007; Van der Zanden et al., 2009). By the nature of its “wandering” route through the body the vagus nerve may be uniquely structured to provide an effective early warning system for the detection of pathogens as well as a source of negative feedback to the immune system after the pathogens have been cleared (Berthoud and Neuhuber, 2000). The vast majority of vagal fibers (upwards of 80%) are sensory in nature and thus provide an effective coverage of the body for the detection of invaders (Berthoud and Neuhuber, 2000). The anatomy of the afferent vagus has been described in detail by Berthoud and Neuhuber (2000) and in many species including humans has been shown to have connections to the heart, lungs, esophagus, and liver among other organs. Moreover, the afferent vagus has interleukin (IL)-1 receptors expressed by paraganglia cells situated in parasympathetic ganglia (Sternberg, 2006; Watkins and Maier, 1999). The presence of cytokines such as IL-1 in the periphery is relayed via the vagus nerve to CNS structures, one of the most important being the nucleus of the solitary tract (NTS). At the NTS, the afferent and efferent aspects of the parasympathetic nervous system meet. Therefore the NTS is a major relay station for neural-immune communication (Sternberg, 2006). On the afferent side, vagal afferents terminate in the NTS in a somatotopic manner resulting in functional divisions of the NTS (Maier et al., 1998). This somatotopic organization may allow for a high degree of localization and specificity of immune-to-brain communication. This is important as the anatomical location of the pathogens conveys information necessary to mount a location specific and thereby more effective response. Moreover, the NTS has direct and indirect connections to a wide range of neural structures thus giving the vagus nerve the capacity to influence a broad array of processes (Groves and Brown, 2005). On the efferent side, the NTS provides input to the dorsal motor nucleus of the vagus (DMV) and the nucleus ambiguus (NA). These are the sources of the efferent signals which innervate many of the organs associated with the immune system including the heart, liver, and gastrointestinal system. Acetylcholine release from the vagus nerve modulates immune responses at least in part via alpha 7 nicotinic receptors that inhibit NF kappa B and thus cytokine synthesis and release. It should be noted that the source of the regulatory acetylcholine is not unambiguous and it has been suggested that it may be immune-cell derived instead of being released from nerve endings (Kawashima and Fujii, 2004). Taken together these parasympathetic

pathways form what has been termed “the cholinergic anti-inflammatory pathway” (Tracey, 2007). This mechanism of immunomodulation is particularly relevant to this Special Issue as several neuroimaging studies in humans have identified CNS structures associated with (cardio)vagal modulation.

The evidence for anatomic specialization of immune regulation in both efferent and afferent directions suggests that different regions of the immune response may indeed be reflected centrally in an anatomical representation within the brain, which reflects the anatomical organization of the immune system. Such organization could, if proven to exist, potentially confer differential and specialized control of immune responses through efferent neural routes.

Neural concomitants of immune function

Both animal and human studies have implicated CNS structures in immunomodulation (Goehler et al., 2000; Ohira et al., 2006). Ascending from the NTS, the vagus reaches the parabrachial nucleus, the thalamus, the paraventricular nucleus, the central nucleus of the amygdala, the insula cortex, and in animals the infralimbic cortex including the homologous sites in humans of the anterior cingulate cortex (ACC) and the medial prefrontal cortex (MPFC), (Ter Horst and Postema, 1997; Thayer and Lane, 2009). In humans, a few neuroimaging studies have investigated the neural concomitants of immune function and have generally confirmed the importance of the insula, the ACC, and the MPFC (Ohira et al., 2006; Rosenkranz et al., 2005). Ohira et al. (2006), using positron emission tomography (PET) reported that increasing natural killer (NK) cell counts were associated with increasing activity in the orbitofrontal cortex and left insula cortex whereas decreases in T helper cell counts were associated with decreases in activity in the medial orbitofrontal cortex and the right insula. Rosenkranz et al. (2005) using fMRI showed associations between tumor necrosis factor (TNF)-alpha measured in the periphery in response to immunological challenge and activity in the anterior cingulate cortex (ACC) as well as between eosinophils and activity in the insula. These data suggest that specific brain regions may be associated with regulation of specific immune functions. Relatedly, neuroimaging studies of cardiovagal function have identified a similar set of structures (e.g., Critchley et al. 2003; Gianaros et al., 2004; Lane et al. 2009). For example, Lane et al. (2009) found positive associations between vagally mediated heart rate variability and activity in the ACC and insula among other structures. Thus, evidence from both animal and human studies provide support for the idea that forebrain structures may be involved in immunomodulation at least partially via the neural concomitants of the cholinergic anti-inflammatory pathway. However, systematic studies are needed in which specific immune processes from specific locations are mapped onto specific brain regions. Thus whereas there is evidence that the NTS has a somatotopic organization there is as yet no evidence that this extends into the forebrain regions that have been linked to immune processes.

Challenges and opportunities

Tracey (2007) has suggested that future research on the connections between the brain and the immune system may reveal an immunological homunculus. Analogous to the classical maps of the brain that somatotopically relate specific neural structures to specific action in the periphery, an immunological homunculus may reveal that there may be specific brain regions associated with the modulation of specific immune functions. Whereas the evidence for the somatotopic organization of immune functions is sparse as of yet, it has been demonstrated for the related phenomenon of pain (Henderson et al., 2007; Weiss et al., 2008). Henderson et al. (2007) using high-resolution functional magnetic resonance imaging (fMRI) showed that pain from different locations as well as from different tissues was

represented somatotopically in the insula cortex. Weiss et al. (2008) using event-related fMRI showed that different afferent vagal nerve fibers (i.e., A δ versus C) were represented differentially in the cortex of humans. Advances in neuroimaging and other related technologies such as transcranial magnetic stimulation (TMS) may allow for the mapping of the neural concomitants of a range of immune functions such that for example, one brain region might be associated with the control of cytokine responses in the liver whereas another brain region may be associated with NK cell distribution. However to take advantage of the opportunities afforded by these advances in technology several challenges have to be met. For example, the coordination of the timing of the various immune responses, which can span from seconds to hours, with the timing of various neuroimaging paradigms such as PET or fMRI is an important hurdle to overcome if the association of specific brain regions with specific immune functions is to be physiologically meaningful. Another challenge involves the fact that many of the neural functions associated with immunomodulation may be inhibitory in nature. It is an underappreciated fact of neuroimaging that the tight link between observed signal and the underlying metabolic activity is only monotonic for glutamate and excitatory neural activity (Magistretti and Pellerin, 1999). On the other hand it has been shown that the association between the observed signal and the underlying metabolic activity for inhibitory processes is certainly not monotonic (Aron, 2007, p.220; Chatton et al., 2003; Thayer, 2006). Given that inhibitory interneurons may be critical to the modulation of large scale excitatory neural networks, this lack of ability to clearly observe inhibitory activity represents a significant challenge to the study of the inhibitory cholinergic anti-inflammatory pathway and may impact the ability to study neural-immune communication more generally. Other paradigms from neuroscience as well as appropriately designed animal studies may be a necessary complement to human neuroimaging studies in the search for the immunological homunculus.

In conclusion, converging evidence provides clear support for neuroimmunomodulation. The identification of the cholinergic anti-inflammatory pathway and the explication of its basic anatomy and physiology may provide the initial groundwork for the future development of an immunological homunculus much as is being revealed for pain and nociception. However, this is not the only pathway that may be illuminated by neuroimaging studies of immune processes and research is needed that investigates all aspects of neuroimmunomodulation. Several important challenges, as outlined above, need to be met before such work will bear fruit. The papers contained in this Special Issue represent a promising start as they have faced some of these challenges and surmounted them with innovative and creative paradigms from which others might learn.

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