NEUROIMMUNOMODULATION IN VISCERA

INTRODUCTION

The notion that mental stress or “depressed” emotional states exacerbate or even trigger inflammatory disease is widely accepted on both intuitive and empirical grounds. However, significant advances in experimental biomedicine have been made over the past few years which provide a more and more solid basis for understanding these phenomena. At the cornerstone are anatomical and functional discoveries on the close and reciprocal relationships between the nervous and immune systems (1-6). The many facets of this “crosstalk” have been displayed in a large number of studies which, in some fortunate cases, are on the doorstep for clinical application (7). The anatomical basis for neuro-immunocrosstalk is provided by innervation of immune organs by the autonomic nervous system and direct apposition of sympathetic, parasympathetic, enteric and sensory nerve fibers to immune cells in all organs investigated thus far (4, 6, 8, 9). Another equally important channel for influences by central nervous system onto inflammatory processes in the periphery is represented by the hypothalamo-pituitary-adrenocortical (HPA) axis (10). Functionally, production of a vast array of signaling molecules by cells of both immune and nervous systems, and presence of the respective receptors on both cell populations enable for reciprocal communication (1). In peripheral organs, neuroimmune interactions in rheumatoid arthritis (10), allergic skin and airway conditions (9, 11), inflammatory bowel disease (12, 13), postoperative ileus (7, 14), experimental liver injury (15, 16) and diabetes (17) were studied in more detail. This editorial will focus on selected aspects of neuroimmunomodulation in abdominal organs. Some salient findings are summarized in figure 1. The vast field of neuroimmune interaction in central nervous system will not be considered here.

Figure 1. Summary diagram of some pro- (+) and anti- (-) inflammatory effects of parasympathetic vagal, sympathetic and peptidergic afferent neurons. These neuronal influences take place on the background of circulating cytokines regulated by the hypothalamus via ACTH from the pituitary.

VAGUS NERVE

The vagus nerve is of key importance for regulation of gastrointestinal motor and secretory functions. However, several studies over the past decade indicated that both vagal efferent parasympathetic and afferent neurons play a significant role in orchestration of inflammatory and immune processes.

Vagal afferents: In the mid-nineties of the past century, several experimental animal studies suggested that subdiaphragmatic vagal afferents play a pivotal role in signalling inflammatory processes to the brain where a variety of reactions were initiated. These reactions included fever and various endocrine and behavioral changes summarized as “sickness behavior” (18-20). These experiments were mostly done in rats where intraperitoneal or i.v. injections of bacterial toxins, e.g., lipopolysaccharide (LPS) resulted in elevation of body temperature and sickness behavior that was blocked by vagotomy. The concept of fast vagal afferent signaling in these paradigms seemingly resolved the riddle that humoral transfer of inflammatory mediators to circunventricular organs and thence signaling to the ventromedial preoptic hypothalamus (VMPO) was considered too slow as to be able to trigger fast fever and endocrine reactions. However, studies by other groups quickly followed who questioned the proposed neural pathway, i.e., the hepatic versus other branches of the abdominal vagus (18, 21), as well as the general validity of vagal afferents as inflammation messengers (22-25). It became apparent that involvement of vagal afferents took place only if small doses of inflammatory mediators were injected and with higher doses a humoral pathway via the blood circulation was more and more important (26-28). Nevertheless, current concepts still maintain a role for vagal afferents in concert with humoral signals in triggering and controlling fever and sickness behaviour (29-31).

Vagal efferents: Meanwhile, a series of experiments yielded results indicating a significant role of vagal parasympathetic efferents in intraabdominal inflammation. Electrical stimulation of the cervical vagus in rats pretreated with LPS i.p. reduced the levels of TNFα in both serum and liver (32). This was thought to be mediated via the α7 subunit of the nAChR on macrophages, in particular Kupffer cells in the liver as this anti-inflammatory effect of vagal stimulation was blocked by the respective antagonists (33). As a critical remark, there is no immunohistochemical evidence for cholinergic innervation of the rat liver (despite of a wealth of functional data). Thus, a sound basis for understanding this effect is still lacking. Nevertheless, together with evidence for sensing peripheral inflammation by vagal afferents, TNFα reduction through vagus nerve stimulation was readily incorporated into the concept of an “inflammatory reflex” (34). Recently, vagus stimulation was shown to ameliorate experimental postoperative ileus by reducing infiltration of the gut wall by leukocytes. Again, some
insight into the molecular processes has been gained by demonstrating involvement of nAChR α7 and the Jak2/STAT3 pathway (14). In a similar vein, vagotomy led to exacerbation of experimental colitis in mouse (35). As vagus nerve stimulation is an established therapeutic tool in epilepsy, clinical trials using this method in gastrointestinal inflammatory disorders may come up in the next few years.

**SYMPATHETIC SYSTEM**

The sympathetic nervous system exerts both anti- and pro-inflammatory effects in the intestines (12). On one hand, this depends on noradrenalin concentration. At low concentrations, this transmitter binds to α-adrenoceptors, thereby decreasing cAMP levels while binding preferentially to β-adrenoceptors, thereby increasing cAMP levels, takes place at high concentrations. Further, levels of circulating cortisol come into play by its cooperating effect on β-adrenergic signaling. On the other hand, β-adrenergic signaling stimulates aspects of T helper cell type 2 (TH2) immune responses which are characteristics, e.g., of colitis ulcerosa, while TH1 immune responses are suppressed. The density of sympathetic innervation is differently changed in Crohn’s disease and colitis ulcerosa where a marked loss or increase of adrenergic nerve fibers, respectively, was observed. These changes in nerve fiber density are probably brought about by different levels of attracting and repelling factors. Animal studies indicated that there is a shift from β- to α-adrenoceptor expression during chronic gut inflammation. Thus, influence of the sympathetic system on severity and course of these diseases strongly depends on the temporal pattern of sympathetic activation. Again, circulating cortisol and thus the HPA axis play an important role for the balance of α- and β-adrenergic responses. These factors may determine the stress induced exacerbation of IBD well known to clinicians (13).

In the liver, sympathetic adrenergic neurons are protective in experimental hepatitis via β2 adrenoceptors on immune cells (16). On the other hand, sympathetic activity aggravates liver injury by carbon tetrachloride and promotes liver fibrosis by stimulating hepatic stellate cells (36, 37).

**PEPTIDERIC PRIMARY AFFERENT NEURONS**

Primary sensory neurons containing peptides like substance P (SP), calcitonin gene-related peptide (CGRP) and somatostatin are abundant in dorsal root, trigeminal and jugular ganglia while they are rare in the nodose ganglion. They typically issue unmyelinated C and thinly myelinated A delta fibers and can release their peptides from both central and peripheral endings, the latter providing a basis for the so-called local effector function. They are sensitive to capsaicin via the TRPV1 receptor. Thus, experiments using capsaicin-pretreated rats and mice were instrumental in elucidating the role of these neurons in inflammatory processes.

Stomach and intestine: Capsaicin-sensitive afferents releasing CGRP at their peripheral endings are protective in rat models of alcohol and salicylate induced damage of the gastric mucosa. This effect is most likely mediated by the vasodilatory function of CGRP (38). In experimental colitis CGRP released from primary afferents exerts a similar protective effect (39). On the other hand, CGRP recruits mucosal mast cells and CGRP containing nerve fibers are more abundant in murine intestines infected with Schistosoma mansoni (40). Substance P is able to degranulate mast cells and acts pro-inflammatory through stimulation of cytokine production in various immune cells (40, 41). Somatostatin appears to counteract these processes (42, 43).

Liver: In experimental mouse models of liver injury, neonatal capsaicin treatment leading to degeneration of peptidergic primary afferent neurons effectively protects the animals (16). In these models which mimic many aspects of immune hepatitis in humans, liver injury as indicated by elevated plasma levels of transaminases, e.g., ALT and AST, and signs of apoptosis and necrosis, is induced by stimulating CD4 T cells with concanavalin A (ConA) or galactosamine/staphylococcus enterotoxin B (GalN/SEB) which triggers a cascade from T cells via macrophages, by application of GalN/LPS which directly stimulates macrophages to produce TNFα, by GalN/TNFα that works through TNF receptors on hepatocytes or by inducing hepatocyte apoptosis with antibodies to the death receptor CD-95 (15). In all models except the latter, TNFα is a central mediator of liver injury. Protection against liver injury by neonatal capsacin treatment as indicated by low ALT, AST and TNF (in models with endogenous TNF production) levels was ascribed to lack of peptide release from sensory neurons innervating the liver. Thus, peptides released from primary afferent neurons in untreated animals may interfere with immune and inflammatory processes at various levels of that cascade. Significantly, the effect of capsacin can be mimicked though not completely by pre-treatment with NK-1 receptor antagonists (44, 45). This indicates that SP is of pivotal role in initiating and maintaining liver injury although other mediators, in particular CGRP, may be also involved. However, CGRP appears to have rather a protective effect in ConA induced liver injury, probably by suppressing the TLR response (46, 47). Ongoing work suggests that these processes are more complex. Considering the damping effect of vagus nerve stimulation on TNF production in the liver (32), one may predict a protective effect of parasympathetic cholinergic neurons also in experimental hepatitis yet this has still to be tested. Thus, there is still a lot of experimental work ahead before these insights can be translated into clinical practice.

Pancreas: Capsaicin sensitive primary afferent neurons expressing the TRPV1 receptor may play even more sophisticated roles in immune processes. A recent study suggested that in non-obese diabetic (NOD) mice (a model for type I diabetes) with polymorphism of the trpv1 gene, reduced release of peptides, e.g., SP and CGRP from sensory nerve fibers within the pancreas favoured proliferation of, and islet infiltration by au-
toreactive T cells (17). Thus, peptidergic primary afferent neurons may be pivotal in pathogenesis of type 1 diabetes.

**CONCLUSION**

These examples demonstrate that the autonomic nervous system exerts significant modulatory effects on major disorders in virtually every abdominal organ. What adds more to the complexity is induction of plasticity in neurons innervating inflamed tissue (12). This is indicated also by results from both experimental and clinical studies showing changes in expression of peptides or receptors in these neurons (48-50). Although many questions still have to be answered, future therapeutic strategies have to consider the innervation of affected organs in order to take advantage of neuroimmunomodulatory effects.

**REFERENCES**


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