

Neuroimmune alterations of ENS functioning

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Introduction

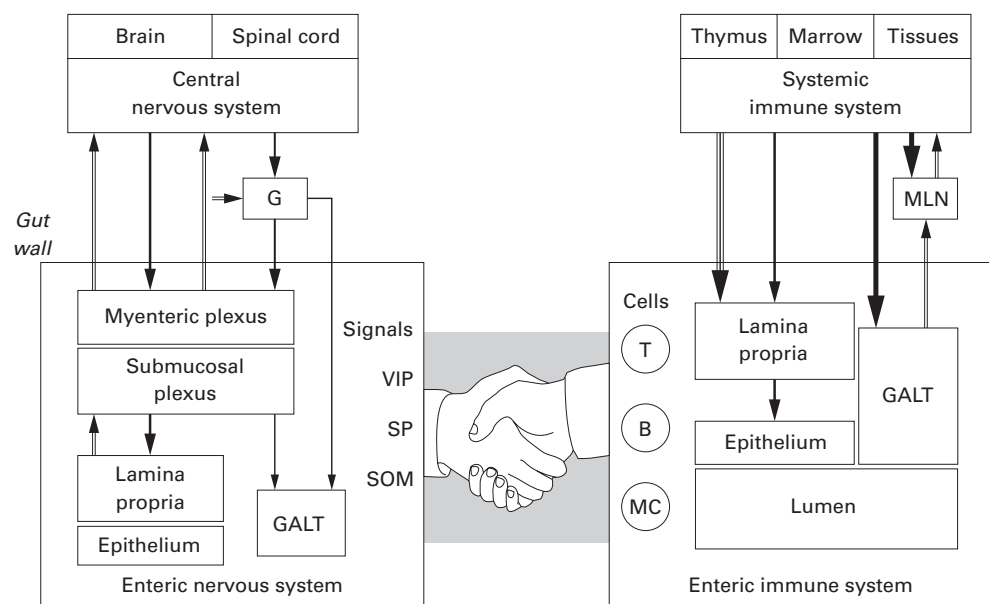
Only recently has it been considered that numerous interactions between the enteric nervous system and local immunocytes are responsible for adaptive functional changes, including motility and secretion (fig 1). Several neuropeptides such as tachykinins, vasoactive intestinal peptide, somatostatin, and opioids are involved in both intrinsic and extrinsic innervation but can also affect immune reactions directly. They exert a dual role in the regulation of local and peripheral motor and secretory reflexes and affect the release of cytokines and proinflammatory mediators. On the other hand, proinflammatory mediators such as eicosanoids and cytokines may activate intrinsic neurones directly or stimulate extrinsic neurones indirectly, releasing neuropeptides which act on intrinsic neurones, smooth muscle cells, or enterocytes. These acute immediate neuroimmune reactions are often followed by long term changes in the number of receptors at the presynaptic or postsynaptic level as well as phenotypic changes of the effector cells, as evidenced for smooth muscle cells and enteric neurones which can synthesise cytokines.

Major gut targets in inflammation

There are at least three major target cells affected by the presence of inflammatory mediators: smooth muscle cells, glial cells, and neurones. Both intrinsic enteric neurones and terminals of extrinsic afferent and efferent nerves are affected (fig 2). Indeed, phenotypic

changes in smooth muscle cells under the influence of proinflammatory mediators consist mainly of expression and release of cytokines.¹ Up and downregulation of a number of receptors for neuromediators² and neuropeptides³ have also been demonstrated. Indeed, the number of alpha and beta adrenoceptors is inversely altered in the acute phase of inflammation in the guinea pig ileum. Mast cells, leukotrienes, and prostaglandins are involved in this up and downregulation of receptors, and changes in the physical properties of smooth muscle have also been demonstrated both in vitro and in vivo.

Inflammation induces neuronal phenotypic changes and affects the release of mediators in the gut intrinsic nervous system (fig 3). The myenteric plexus may secrete cytokines such as interleukin (IL) 1 and tumour necrosis factor α (TNF- α),⁴ but also interferon γ ⁵ and transforming growth factor β ,⁶ although the physiological role of such secretions remains unknown. The presence of cytokines in the proximity of the myenteric plexus during inflammation may affect the release of classical neurotransmitters and the number of receptors for them and for neuropeptides, as well as altering electrophysiological properties. For example, it has been shown that IL-1 β , through release of leukaemia inhibitory factor, de-



Abbreviations used in this paper: ACh, acetylcholine; IL, interleukin; TNF- α , tumour necrosis factor α ; NAd, noradrenaline; 5-HT, 5-hydroxytryptamine.

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Figure 1 Interaction between the central nervous system and the immune system. VIP, vasoactive intestinal peptide; SP, substance P; SOM, somatostatin; G, ganglion; GALT, gut associated lymphoid tissue; MLN, mesenteric lymph node. (From Ottaway.²⁰)

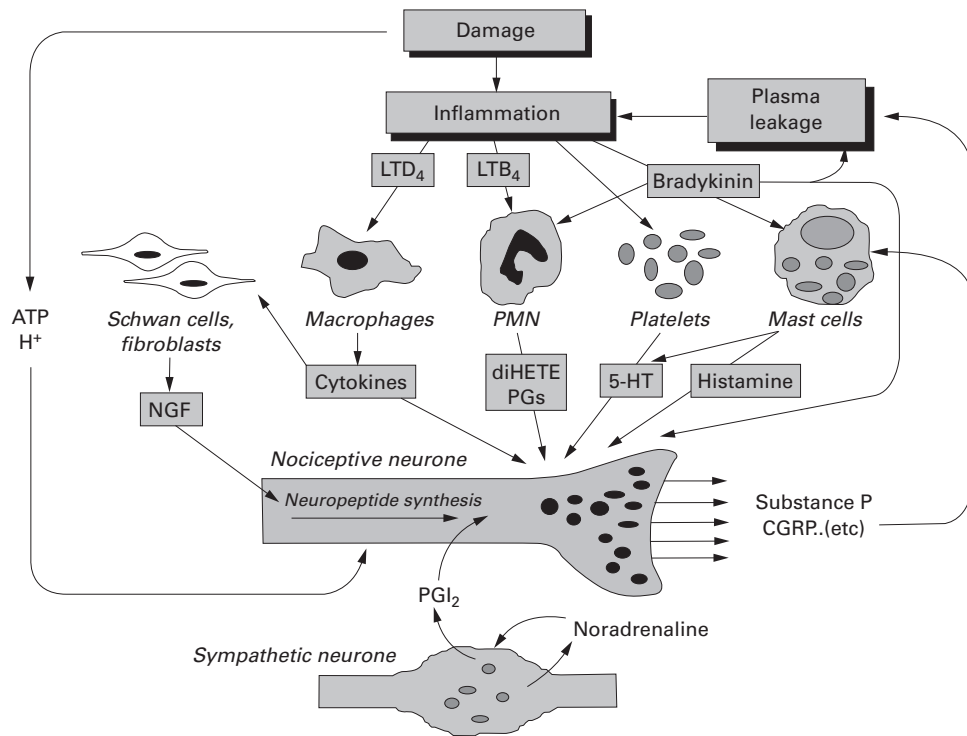


Figure 2 Influence of inflammatory mediators on extrinsic afferent and efferent nerves. *LT*, leukotriene; *PGs*, prostaglandins; *NGF*, nerve growth factor; *CGRP*, calcitonin gene related peptide; *5-HT*, 5-hydroxytryptamine; *diHETE*, dihydroxyeicosatetraenoic acid.

increases the release of acetylcholine (ACh)⁷ and increases the activity or expression of inducible nitric acid synthase.⁸ *TNF-α* may also selectively affect noradrenergic function by reducing the release of noradrenaline (NAd)⁹ from myenteric plexus, while *IL-6* may decrease or increase this NAd release, depending of its concentration.¹⁰ Release of other mediators may also be influenced by inflammatory mediators as altered responsiveness to histamine and 5-hydroxytryptamine (5-HT), as well as to carbachol, was observed in inflamed guinea pig ileal strips.¹¹ Electrophysiological measurements have recently permitted the characterisation of changes in resting potential or in spontaneous firing, as well as in the dura-

tion and amplitude of fast excitatory postsynaptic potentials in the guinea pig jejunal myenteric plexus during *T. spiralis* infection.¹² From a functional point of view, the time course of inflammation development in trinitrobenzene sulphonic acid induced colitis in rats is associated with typical alterations in electrical spike activity, corresponding to a progressive increase in the duration of electrical spike bursts. These alterations are transiently suppressed by systemic administration of *IL-1* receptor antagonist, suggesting that the activity of myenteric neurones controlling colonic motility during inflammation are permanently modulated by cytokines.¹³ In addition, some neuroimmune connections may ini-

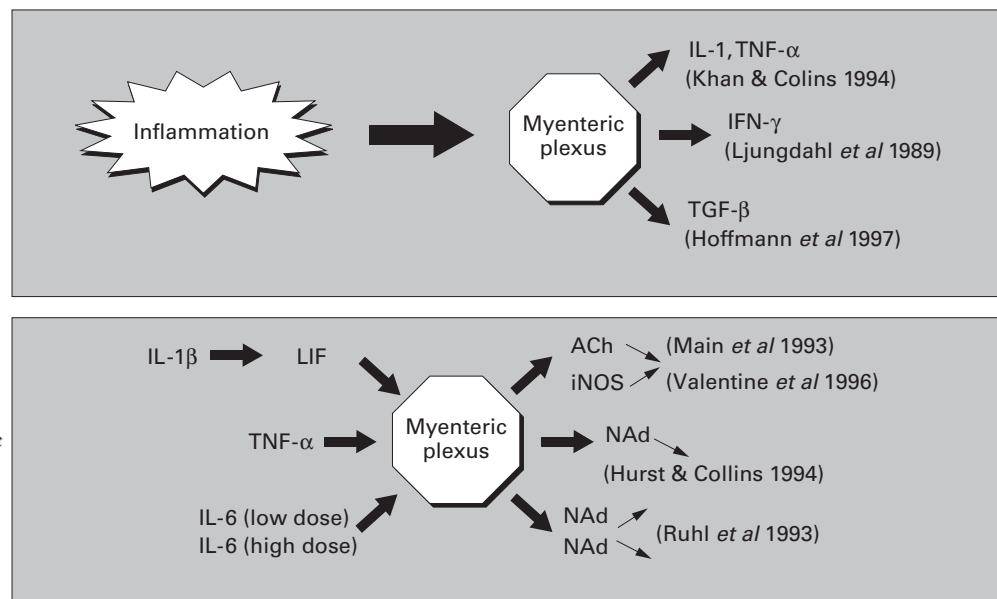


Figure 3 Inflammation induced phenotypic changes and mediator release in the gut intrinsic nervous system. *IL*, interleukin; *TNF-α*, tumour necrosis factor α ; *TGF-β*, transforming growth factor β ; *LIF*, leukaemia inhibitory factor; *ACh*, acetylcholine; *iNOS*, inducible nitric acid synthase; *NAd*, noradrenaline.

Table 1 Pathological motility disorders and the enteric nervous system

Type	Inflammatory mediators	Cytokines	Neurotransmitters	Neuropeptides
Inflammation (acute)	LTB ₄	IL-1	5-HT (5-HT _{1A} /5-HT ₃) NO	BK (B ₂) SP (NK ₁)
Anaphylaxis	PGE ₂	IL-1	5-HT (5-HT ₃) Histamine (H ₁)	SP (NK ₁)
Parasitism			5-HT (5-HT ₃) ACh (M ₁)	SP (NK ₁) NKA (NK ₂)
Septic shock	PGE ₂ (EP ₂) PAF	IL-1 TNF- α	NAd (α_1/α_2) NO	CRF

LTB₄, leukotriene B₄; IL, interleukin; PGE₂, prostaglandin E₂; PAF, platelet activating factor; TNF- α , tumour necrosis factor α ; 5-HT, 5-hydroxytryptamine; NO, nitric oxide; NAd, noradrenaline; BK, bradykinin; ACh, acetylcholine; SP, substance P; NK, neurokinin; CRF, corticotrophin releasing factor.

tiate neuroplasticity through the release of substances such as nerve growth factor with a new distribution of neuronal endings affecting both intrinsic and extrinsic neurones and consequently ascending and descending pathways participating in peristaltic reflexes.

Role of ENS in altered gut secretory and motor patterns

There is increasing evidence that substance P, mast cells, and nitric oxide are strongly involved in local activation of intrinsic neurones in motor and secretory effects of enterotoxins such as cholera toxin, *Clostridium difficile*, and *Escherichia coli* toxins. For example, cholera toxin activates receptors located on *Escherichia coli* cells, releasing IL-1 and activating mast cell degranulation, which in turn releases substance P. This sensory neuropeptide is activated indirectly via vasoactive intestinal peptidergic neurones in close proximity to enterocytes. Local immune reactions are also involved in gastrointestinal motor disturbances induced by sepsis and anaphylactic reactions. In this context, cytokines such as IL-1 and TNF- α , as well as platelet activating factor, participate locally in the genesis of these motor alterations through modulation of the enteric nervous system.

In vitro, it has also been shown that inflammation affects the responsiveness of both the myenteric and submucosal plexus to chemical or physical stimuli. In the peristaltic reflex elicited by field stimulation, both ascending and descending contractile reflex pathways are inhibited by exogenous IL-1. This effect seems not to be mediated by prostaglandins or via histamine receptors. Moreover, in the inflamed ileum, phosphatidylinositol hydrolysis may be essential to stimulate phasic contractions, and inflammation may down-regulate the protein kinase C pathway.¹⁴

Recent results have established that intrinsic and extrinsic enteric neurones are involved in the regulation of inflammatory processes and may indirectly affect local neuroimmune reactions. In several models of experimental inflammation, intrinsic denervation as well as destruction of sensory C fibres affect the local immune reactions, with a cytoprotective role of these neuronal components.^{15,16} Alterations in motility related to anaphylactic challenge in sensitised rats involve extrinsic innervation and

particularly afferent vagal fibres. During challenge, degranulation of mast cells is associated with local release of IL-1 which in turn activates vagal afferent fibres directly or indirectly through release of 5-HT and activation of the 5-HT₃ receptor subtype.^{17,18} Similarly, alterations of the intestinal motor pattern associated with septic shock also involve both intrinsic and extrinsic innervation, with an important role for vagal afferents and local activation of the nitrergic component¹⁹ (table 1).

Finally, our present knowledge supports the concept that activation of the gut immune system triggers immediate and persistent alterations of the enteric nervous system, which could be responsible for chronic dysfunctioning such as that observed in functional bowel disorders such as irritable bowel syndrome.

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