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Review

The bidirectional communication between neurons and mast cells within the gastrointestinal tract

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Abstract

Normal or disordered behaviour of the gastrointestinal tract is determined by a complex interplay between the epithelial barrier, immune cells, blood vessels, smooth muscle and intramurally located nerve elements. Mucosal mast cells (MMCs), which are able to detect noxious and antigenic threats and to generate or amplify signals to the other cells, are assigned a rather central position in this complex network. Signal input from MMCs to intrinsic enteric neurons is particularly crucial, because the enteric nervous system fulfils a pivotal role in the control of gastrointestinal functions. Activated enteric neurons are able to generate an alarm program involving alterations in motility and secretion. MMC signalling to extrinsic nerve fibres takes part in pathways generating visceral pain or extrinsic reflexes contributing to the disturbed motor and secretory function. Morphological and functional studies, especially studies concerning physiological stress, have provided evidence that, apart from the interaction between the enteric nervous system and MMCs, there is also a functional communication between the central nervous system and these mast cells. Psychological factors trigger neuronal pathways, which directly or indirectly affect MMCs. Further basic and clinical research will be needed to clarify in more detail whether basic patterns of this type of interactions are conserved between species including humans.

Keywords: Mast cell; Enteric neuron; Neuroimmune interaction; Intestinal barrier; Immune response

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1. Introduction

In mammals, minute-to-minute behaviour of the gastrointestinal (GI) tract – whether it occurs under normal or pathological conditions – is mainly determined by a dynamic interplay between different cell systems, including the interstitial cells of Cajal, the enteric glial, the smooth muscle, the vascular, the immune, the neuronal and the mucosal epithelial system. Interactions between the latter three systems are mediated by a wide array of signalling molecules, including cytokines, leukotrienes, prostaglandins, neurotransmitters, neuropeptides, neurotrophic factors, proteases, nucleosides, nucleotides, immunoglobulins and free radicals. Due to their anatomically strategic position, an important role in this network is assigned to mucosal mast cells (MMCs). MMCs possess a large number and diversity of surface receptors and are known to collect information from the three abovementioned players for the detection of antigenic threats and other substances related to pathophysiological and noxious conditions (*i.e.*, parasitic infections, food allergies, inflammatory bowel diseases, irritable bowel syndrome, and stress-induced GI inflammatory responses), as well as for long-term memory for the identification of these threats and signals, including susceptibility to reinfection. Following activation, MMCs produce a plethora of stored and newly synthesized paracrine/autocrine mediators, which primarily act on vascular, epithelial, neuronal and/or immune cells. The most important interaction in this complex pattern of interplays between different cellular systems in the GI wall, is that between MMCs and the enteric nervous system (ENS). The ENS plays a pivotal role in the control of GI functions and acts largely independently of the central nervous system (CNS). MMCs signal and/or amplify pathophysiological signals to the ENS, which initiates a defense program integrating power propulsive motility and copious secretion of H_2O, electrolytes and mucus. This mechanism protects the individual, be it at the expense of symptoms including visceral pain, fecal urgency, and diarrhea (for review see: Sharkey and Mawe, 2002; He, 2004; Wood, 2004; Vliagoftis and Befus, 2005; Barbara et al., 2006).

The present review will focus on the interactions between MMCs and the intrinsic/extrinsic innervation of the GI tract, while keeping in mind that these interactions are part of a complex network of interplays between different cell systems, not only in the GI wall but also in the CNS. It is a simple biological fact that in an organism everything is connected, implying that even minor alterations in a defined cell system may lead to severe adaptations in another cell system.

2. Mast cells

Mast cells are derived from pluripotent hematopoietic progenitor cells in bone marrow. Mast cell progenitors circulate in the blood, migrate into peripheral tissues and mucosal surfaces under the influence of chemotactic factors and adhesion molecules and subsequently differentiate into mature mast cells under the influence of locally produced growth and differentiation factors. Mature mast cells in different tissues exhibit heterogeneity due to microenvironmental conditions. They can be subdivided into two predominant phenotypes, based on the expression of distinct serine proteinases. The rodent mast cell subtypes can be classified as constitutive or connective tissue mast cells (CTMCs), mainly located in connective tissues, especially around blood vessels and in the peritoneal cavity, or as T cell cytokine-dependent reactive mast cells or MMCs, particularly found in intestinal and pulmonary mucosa. In humans, mast cells are designated either as MC_{TC} for their tryptase and chymase content and – in terms of localization – correspond closely to CTMCs, or as MC_T, which only contain tryptase and correspond most closely to the rodent MMCs (Metcalfe et al., 1997; Miller and Pemberton, 2002; Vliagoftis and Befus, 2005).

In contrast to other species, mature mast cells in the murine intestine are rare (Guy-Grand et al., 1984; Miller et al., 1988). However, mast cell progenitors are abundant in the murine intestine. These progenitors ensure the capacity for a rapid expansion of mast cells in the intestinal wall during the effector response to pathophysiological or noxious conditions. Intestinal mast cell progenitors are also suspected to provide a pool of committed cells capable of redistribution to other tissues (for review see Gurish and Boyce, 2006).

Activation of mast cells mainly occurs by interaction of a multivalent antigen with its specific IgE antibody bound to the cell membrane via the high-affinity receptor FcεRI. However, mast cells can also be activated by substances like cytokines, hormones, immunoglobulins, neuropeptides, polybasic compounds, complement components, serine proteinases and certain drugs (Metcalfe et al., 1997; Stassen