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EDITORIAL

Cellular and molecular basis of chronic constipation: Taking the functional/idiopathic label out

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Abstract

In recent years, the improvement of technology and the increase in knowledge have shifted several strongly held paradigms. This is particularly true in gastroenterology, and specifically in the field of the so-called "functional" or "idiopathic" disease, where conditions thought for decades to be based mainly on alterations of visceral perception or aberrant psychosomatic mechanisms have, in fact, be reconducted to an organic basis (or, at the very least, have shown one or more demonstrable abnormalities). This is particularly true, for instance, for irritable bowel syndrome, the prototype entity of "functional" gastrointestinal disorders, where low-grade inflammation of both mucosa and myenteric plexus has been repeatedly demonstrated. Thus, researchers have also investigated other functional/idiopathic gastrointestinal disorders, and found that some organic ground is present, such as abnormal neurotransmission and myenteric plexitis in esophageal achalasia and mucosal immune activation and mild eosinophilia in functional dyspepsia. Here we show evidence, based on our own and other authors' work, that chronic constipation has several abnormalities reconductable to alterations in the enteric nervous system, abnormalities mainly characterized by a constant decrease of enteric glial cells and interstitial cells of Cajal (and, sometimes, of enteric neurons). Thus, we feel that (at least some forms of) chronic constipation should no more be considered as a functional/idiopathic gastrointestinal disorder, but instead as a true enteric neuropathic abnormality.

Key words: Constipation; Enteric glia; Enteric nervous system; Enteric neurons; Interstitial cells of Cajap; Neurogastroenterology

Core tip: Concerning gut motility, in the last years the basic/clinical interplay between gastroenterology and neurology has become stricter, and many pathologic conditions, among which constipation, related to abnormal gastrointestinal motility are now considered and studied by a neurogastroenterological point of view. However, the fact that these conditions are still labelled as "functional" or "idiopathic" is puzzling. We examined the evidence for taking these labels out from constipation, that should be considered as a true neurenteric dysfunction.

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INTRODUCTION

The field of gastrointestinal motor activity has always attracted the researchers' interest; however, in the time course it became apparent that most gut motor disorders are attributable to disordered neural control mechanisms. Thus, by the encounter of gastroenterologists and neurologists a common branch emerged, *i.e.*, neurogastroenterology[1], in which an equal partnership had been recognized concerning gut motility. Recently, ultrastructural morphologists joined and try to bring innovative perceptions on control mechanisms of digestive motility. This had led to interesting and exciting new perspectives in the pathophysiology of some frequent disorders, such as constipation.

Chronic constipation is a frequent symptom in the general population, where is present in 2%-30% of subjects[2]. However, apart from secondary forms, associated to an underlying disease (*e.g.,* neurological[3,4]), commonly used (at least for scientific purposes) classifications still label most cases of constipation as "idiopathic" or "functional"[5-9].

It is worth noting that the concept of functional diseases has been somewhat questioned in the last years[10], since several studies conducted on prototypic functional entities, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD) have revealed that these condition may actually harbor an organic basis[11,12]. In fact, inflammation and neuronal degeneration have been reported in IBS patients[13] and duodenal mastocytosis, eosinophilia and intraepithelial lymphocytosis have been described in both IBS and FD patients[14].

Chronic constipation may be subdivided in two main subtypes, obstructed defecation (OD) and slow transit constipation (STC), that may also co-exist in the same patient[15,16], and it is generally thought (by data originating from both experimental animal models and humans) that colonic sensorimotor dysfunction and abnormal motility play a pivotal pathogenetic role[17-19]. Thus, abnormal colonic and anorectal function had been repeatedly demonstrated in these patients[20-22], and pharmacologic stimulation may help in addressing more targeted therapeutic approaches[23,24]. However, etiological factors are still poorly known[25].

This article will deal with the available evidence for neurobiological abnormalities in chronic constipation, that suggests how this symptom often underlie a true organic enteric disorder.

NEUROENTERIC ABNORMALITIES IN CONSTIPATION

To date, there is mounting evidence that colonic neuromuscular abnormalities may be of paramount importance in this setting[26,27], and there are numerous studies showing that (at least) severely constipated patients may have one or more abnormal features mainly (although not exclusively) linked to elements of the enteric nervous system (ENS)[28].

The ENS, considered as the brain of the gut, integrates secretion and motility into homeostatic patterns of behavior susceptible to disorder[29]. Thus, it is not surprising that some of the enteric circuitries responsible for these activities may be involved in the dysfunction of their basic control mechanisms. The resulting abnormalities are summarized below.

Abnormal colonic neurochemistry

This has been repeatedly shown in constipated patients: several studies showed a decreased content of vasoactive intestinal peptide (VIP) and substance P in tissues obtained from these subjects[30-34]. Moreover, *in vitro* studies confirmed that the diminished contractile response to these substances plays an important role in the impaired motility observed in the colon of constipated patients[35,36]. Of note, these abnormalities seem not to be related to chronic laxative use, since anthranoids cause a reduction in the levels of inhibitory neurotransmitters (VIP, somatostatin), but not of substance P, in the rat colon[37]. Other studies showed that excitatory nerve fibres are present in the circular muscle in STC but they are deficient in tachykinins and enkephalin[38-40]. In addition, investigations conducted on colonic strips showed that a decrease of cholinergic innervation and an increase of non-adrenergic non-cholinergic (NANC) inhibitory innervation play an important role in the impaired motility observed in the colon of patients with slow transit constipation[41]; these effects are mediated by an increase of nitric oxide and a decrease of neurotensin[42-44], as also confirmed by immunohistochemical methods in surgically resected specimens[45].

Enteric nervous system

Earlier studies addressing the ENS have shown the presence of several heterogeneous abnormalities in patients with severe constipation (especially those with STC), including reduced number of argyrophilic neurons[46] and of intraganglionic neurofilaments[47], myenteric plexus hypoganglionosis[48]. More recent studies, with the increasing use of immunohistochemical techniques[49,50], have demonstrated more consistent findings on the main elements of the ENS, such as the decrease of interstitial cells of Cajal (ICC)[51,52] (up to their complete absence in colonic inertia[53]), often associated to a reduced number of enteric neurons[54,55] and/or of enteric glial cells (EGC)[56,57]. Of interest, the expression of c-kit mRNA and c-kit protein was also found to be significantly decreased in the colon of severely constipated patients, suggesting that the c-kit signal pathway may play an important role in ICC reduction in these patients[58].

Colonic smooth muscle

Only a few studies have addressed this issue, often with

discordant findings, probably due to the heterogeneous cohorts of patients evaluated. Some authors reported that the ratio of the thickness of circular to longitudinal muscle was significantly lower in the left colon in constipated subjects[59], whereas other authors described a decreased circular muscle layer thickness in constipated patients[60], but no abnormalities of the colonic muscular layers were described in both studies. Another investigation showed the presence of amphophilic inclusion bodies in the muscularis externa of STC patients[61], even though these findings were found in about half of the patients. Normal actin expression was found in both adults and children with severe constipation[56,62], whereas the use of novel and nonconventional smooth muscle markers may reveal abnormalities linked to the smooth muscle contractile apparatus unnoticed by both routine stainings and alpha-actin, suggesting specific defects of smooth muscle cells involved in the pathogenesis of gastrointestinal motility disorders[63].

SIGNIFICANCE OF NEUROENTERIC ABNORMALITIES IN CONSTIPATION

There are few doubts that the ENS abnormalities repeatedly found in constipated patients play a pivotal role in the genesis of symptoms. In fact, the consistent finding of a significant decrease of ICC, enteric neurons, and (especially) EGC, variously associated each other, justifies the abnormal motor behavior of the large bowel in these patients.

In fact, looking at the physiological properties of these cell populations, it is obvious that the disruption of their number/connections/relationship leads to an impairment of the complex regulation of the well-coordinated colonic motor patterns[64], thus affecting the viscus' motility, due to the strict interplay between ICC, enteric neurons and EGC, with the latter acting as a physiologic bridge (not only by a simple mechanic point of view, but also by means of their neurotransmitter, immunologic, and trophic properties[65]) between the other two cell types.

Unfortunately, to date data are lacking on the possible factors causing neurenteric abnormalities in constipated patients. The current hypothesized mechanisms (often originating from experimental animal models) imply abnormalities in glial trophic factors leading to neural degeneration, and enteric localization of infective agents (bacteria, virus, prions) causing more or less selective degeneration of specific neurenteric cell populations (particularly EGC)[66], whereas genetic factors[67] or neurodegenerative changes due to aging seem to play a lesser role[68].

NEW CELLULAR PLAYERS IN NEUROMOTILITY DISORDERS

In biological sciences, interstitial tissue is seen as the connective tissue that surrounds the cells of a certain tissue while the extracellular matrix elements are known for its great capacity to retain water. However, except for a few described interstitial diseases (*e.g.,* inflammatory bowel disease, interstitial cystitis, tubulointerstitial nephropathy, interstitial lung disease) its role is easily overlooked, as well as the significance of its cellular elements. Recent studies related to biological and histological data revealed, among the known resident (fibroblasts/fibrocytes, adipose cells) and non-resident cells (mast cells, plasma cells, eosinophils, macrophages, *etc.*) of interstitial space, a novel cell type-the telocyte[69,70].

Morphologically, telocytes represent interstitial cells with telopodes-the longest cellular extensions described besides the axons of neurons[71]. This rather unique cell type, difficult to visualize by routine microscopy, displays a particular morphology by electron microscopy: (1) a small cell body (9-15 μm) with scarce cytoplasmic organelles surrounding a moderately euchromatic nucleus; and (2) telopodes are usually tortuous and organized in a 3D network by overlapping and/or by homocellular interactions[72,73]. Telopodes are very long (10-1000 μm), thin (0.1 ± 0.5 μm) and moniliform cytoplasmic extensions; the moniliform aspect is created by the alternation of thin segments-podomers with dilated segments-podoms; the latter accomodate functional units consisting of caveolae, mitocondria and endoplasmic reticulum[74] and occupy a strategic position in relation to stem cell niches, blood capillaries, and/or nerve bundles[75,76]. Telopodes also establish stromal contacts with other cells, such as mast cells, basophils, lymphocytes, eosinophils, plasma cells, or macrophages[77] and non-cellular elements (*e.g.*, collagen and elastic fibers)[78,79].

Telocytes have been described in human and mammalian cavitary and parenchymatous organs, as well as in serous membranes and other tissues (for details see www.telocytes.com). In the last two years telocytes were also described in the gut[77,80,81].

In modern times the significance of the information that could be achieved by signaling molecules found in intercellular fluids is overlooked. There is scarce information on the usefulness of the extracellular organelles (exosomes and shedding microvesicles) released in the extracellular space as mediators of cell-to-cell communication[82]. Such vesicles were recently demonstrated in the proximity of telopodes and even emerging from them in heart[83], lungs[76], skeletal muscle[76], pancreas[73], parotid gland[84] and human uterus[74].

Telocytes are supposed to be involved: (1) in intercellular signaling[72,74,77]; (2) as stem cell adjutants involved in tissue renewal[79,85]; (3) as sensors for steroid hormones[86]; (4) in the guidance of immune cells[77]; (5) as stretch sensors[87]; and (6) as contractility modulators[88]. Even though telocytes seem to be implicated in many important physiological and pathological processes[89,90], their exact functions still remain controversial. Although telocytes have not yet been described at colonic level, their possible involvement in pathophysiological mechanisms

of chronic constipation cannot be overlooked. In favor of this hypothesis there is a possible correlation between the fact that telocytes express receptors for estrogen and progesterone[91,92] and the fact that chronic constipation is linked to sex hormones[93] and is higher in women of reproductive age[94].

CONCLUSION

The improvement of scientific knowledge and the constant, increasing ability to recognize previously unknown pathophysiologic mechanisms is of paramount importance. Thus, labels such as "idiopathic" or "functional", that basically conceal the fact that too little is known of a specific pathologic entity[10], should be hopefully replaced when more knowledge is available, as pointed out several years ago[95]. As such, the recent recognition of neurenteric abnormalities in many patients complaining of constipation should point to reconsidering at least some of these forms (especially STC) as true enteric neuropathies, and to drop the "idiopathic"/"functional" label.

Besides semantic considerations, we feel that a better understanding of possible basic abnormalities in these patients is important, and may have therapeutic implications, addressing the researchers' interest for new options toward more targeted approaches[16].

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