Visceral sensitivity in explaining functional bowel disorders : from concepts to clinical practice

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Functional digestive disorders (FDD) consist of several syndromes characterized by the absence of any organic or biochemical abnormality and mainly defined by a cluster of symptoms more or less related to one segment of the gut (1). The most frequent and most studied of them are Non-Ulcer Dyspepsia (NUD) and Irritable Bowel Syndrome (IBS). Abdominal pain is the most f equent complaint of these patients. It may result from organic or functional disorders and may be related to different neurophysiological mechanisms.

Classical aetiological theories have implicated psycho-social factors and abnormalities in gastrointestinal motility. Consequently to this hypothesis, most of the prevailing therapeutic approaches to resolve pain in patients with FDD have focused on motility patterns, using antispasmodics, bulk-forming agents and more recently prokinetic compounds. These drugs are mainly acting on the efferent nerve pathways controlling the function of digestive muscle.

Over the last decade, a large attention has been paid to the role of visceral sensitivity in the pathophysiology of FDD and especially the Irritable Bowel Syndrome (IBS) (see Rev. Mayer Raybould) (2). These studies have enlightened the role of nerve afferent pathways arising from the gut and processing information to the peripheral and central nervous systems and thereby triggering a number of reflexes. The afferent nerve pathways have thus been recognized as a possible target for new treatments aimed to relief pain in patients with FDD.

Visceral afferents : their nature and anatomical background

Digestive nerve pathways are organized in 2 levels : the enteric nervous system (ENS) which is also named "intrinsic innervation" and located in the wall of the digestive tract and the "extrinsic nerves" which connect ENS to the spinal cord and the CNS, via sympathetic ganglia or the parasympathetic pathways, including the vague. Both the ENS and the extrinsic nerves contain afferent (sensitive) and efferent (excitatory or inhibitory) neurons.

The informations, used by the CNS to modify the various digestive functions (motility, secretion, absorption) are produced by receptors located in the different layers of the gut wall and connected to sensitive enteric neurons. Their activity has been characterized by electrophysiological studies (3). Their activation induces clusters of spikes in these sensitive nerve fibers. Mechanical events like contraction, relaxation or luminal distension of a part of the gut trigger mechanichal receptors which have been shown to be of 2 types : some adapt slowly and are triggered in physiological conditions ; some adapt rapidly and are triggered by supraphysiological (e.g. intense phasic contractions) or pathological conditions. The digestive wall also contains "polymodal" receptors triggered by various stimuli (mechanichal, chemical, osmotic stimuli), which are always intense and constitute an aggression of the gut (4). Since these receptors are triggered by very intense stimuli, some authors have proposed to call them «nociceptors». Moreover, these nociceptors display similar function and spinal projections as nociceptors mediating somatic noxious perception.

Neurons of the myenteric plexus are organized as a network that really constitute an independent "enteric nervous system" (ENS), also named intrinsic plexus because of its location inside the gut wall. The ENS contains as much neurons as the spinal cord does, and most of these fibers are afferents. Inside the ENS, interneurons allow connections between afferent and efferent neurons as well as between neurons of different levels. This integrated network deals primarily with gut sensations by recognizing the size, the speed and the direction of the movements of food particles. Extrinsic afferents from the digestive tract are part of the "neuro-vegetative" nervous system and proceed along sympathetic and parasympathetic nerves (5). Vagal afferents proceed outside the upper gut through the vagus nerve to the nodose ganglion where is located the neuronal cell body. This neuron then projects to the nucleus tractus solitarius (NTS). Vagal afferents arise from the oesophagus, stomach, small intestine and the proximal part of the colon. At the level of the intestine, afferent neurons of the sympathetic nerves proceed along splanchnic nerves (upper gut) or hypogastric nerves (lower gut) to (i) the mesenteric or hypogastric ganglia respectively ; (ii) the prevertebral ganglia. Then they reach the dorsal root of the spinal cord, from where secondary neurons project

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to the NTS (Fig. 1). Nerve pathways responsible for proprioceptive sensations of the rectum and anus proceed along the parasympathetic nerves innervating the pelvic floor to the dorsal root ganglion and then, the spinal cord and the lemniscal pathway and are responsible for the control of defecation and the perception of rectal contents (Fig. 1).

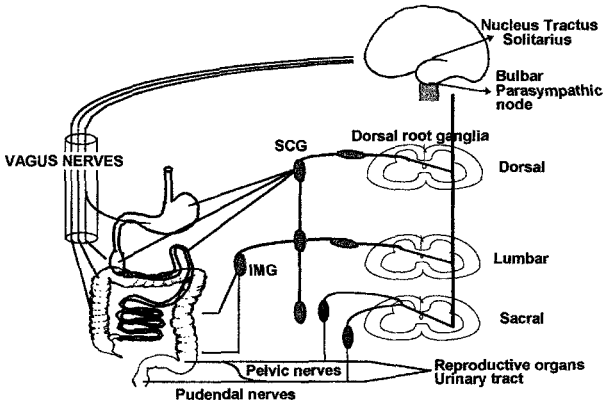

Fig. 1. — Afferent innervation of the gastrointestinal tract. Anatomical distribution to sympathetic and parasympathetic areas. SCG = Sympathic Chain of Ganglions ; IMG = Inferior Mesenteric Ganglion.

To reach the cortex, afferents raising from the gut proceed along parasympathetic nerves to a complex integrative structure of the bulb, the dorsal vagal nucleus (DVN), and the nucleus of the tractus solitarius. Some afferent pathways project on different nuclei of the cerebral stem, the central and lateral hypothalamus, the lymbic area and the neocortex.

Recently, several studies have determined the areas of the cortex that are involved in the perception of visceral sensations. Using positron emission tomography (PET scanner), it has possible to demonstrate that in patients with irritable bowel syndrome (IBS), areas stimulated by rectal distension could be different from those stimulated in healthy controls (6).

Neuromediators

Neuromediators of the myenteric plexus are rather numerous and may be classified in view of their biochemical structure : (i) amines (acetylcholine and norepinephrine), peptides, purines (ATP, ADP, adenosine) and recently NO (Nitric Oxide). The latest participates in the non-adrenergic non-cholinergic neurotransmission (NANC) (7). The length of this review precludes a detailed description of these neuromediators with their respective role in the processing of visceral sensations. We have published elsewhere a detailed review on this subject (8).

Physiology and pathophysiology of visceral afferents

Integration of the functions of digestive afferents

Intrinsic afferents are the basis for a nervous system organizing peristaltic movements. Some afferent neurons have efferent axon(s) directly projecting on smooth muscle cells or acting indirectly via synapses with motoneurons of the ENS. These neurons are responsible for "axonal reflexes". Local reflexes are triggered in intrinsic nerve afferents of the ENS, particularly by distension of the intestinal lumen and by chemical stimuli from the intraluminal content. These reflexes may induce motor responses, i.e. a contraction or a relaxation of the gut segment, mainly resulting in a peristaltic movement, or secretory responses, either exocrine, i.e. increase in gastric acid secretion, or endocrine, i.e. gastrin release from the antrum. Local reflexes involve usually short segments of the gut, although they sometimes proceed information between two adjacent organs.

A viscero-visceral reflex is aimed to coordinate the activity between two organs. Such a reflex may be observed at all the levels of the gut. These reflexes regulate the flow of digesta along the gut and control emptying of the stomach into the duodenum. In man, the distension of the gastric fundus induces a reflex antral contraction. On the other hand, the antral relaxation following duodenal distension regulates gastric emptying, as shown by studies using the barostat technique. In the lower gut, many authors have reported the observation of a rectocolonic inhibitory reflex. In patients with rectal outlet obstruction, rectal distension also inhibits colonic motility in both fasted and post-prandial states. Chemical irritation of the rectal wall enhances this inhibitory reflex in animals and in man, an intrarectal injection of glycerol induces a recto-colonic reflex with colonic relaxation and giant superimposed colonic contractions. Viscero-visceral refle. es may also be observed between non-adjacent organs, e.g. the gastro-colonic reflex which may at least in part be responsible for the colonic response to eating. In human healthy volunteers, a delayed gastric emptying is observed after voluntary suppression of defecation. Some reflexes have also been observed between exocrine or endocrine secretory processes and motility events. Indeed, the stimulation of splanchnic afferents triggers a release of epinephrine by adrenal glands and a release of opioid peptides which in turn are regulating factors of digestive functions.

Finally, the central nervous system receives continuously inputs from digestive afferents, containing information about the intaluminal content of the various segments and plays an important role to integrate external or extra-digestive informations and to trigger adaptative responses of the digestive tract. In physiological conditions, a lot of informations from the digestive tract are not transmitted beyond the hypothalamic nuclei and do thus not reach the cortex. In pathological conditions, the

Table 1. — **List of substances tested exhibiting inhibitory influence on perception of graded rectal distension in awake rats and humans. Note that some substances are active only after inflammation**

Pharmacological Class	Drugs tested			
		Animals		Humans
Antagonists NK1	N	CP 96345, RP 67580		
Antagonists NK2	N	SR 48968, MEN 10376		
Antagonists NK3	N	SR 142801		
Neuropeptides	N	Octreotide, lanrec tide	IBS/H	Octreotide, Oxytocin
Antagonist B2	I	H0 140		
δ agonist	N	IO 1784		
Antagonists SHT1A	N	DU 1255, SV 15931		
Antagonists 5HT3	N, I	Ondansetron, Granisetron	IBS	Granisetron
	N	Cilansetron	IBS	Alosetron
Agonist ω I	N	Alpidem		
Opioid agonists μ	N	Damgo		
Opioid agonists κ	N, I	U 50488, Fedotozine	IBS	Fedotozine
Opioid Mixed	N, I	Trimebutine		
Agonist β3 adrenergic			H	SR 58611A
NOS inhibitors	I	Amino-guanidine		

N : normal ; I : inflamed rectum.
IBS : irritable bowel syndrome ; H : healthy.

stimulation of parietal nociceptors induces painful or unconfortable sensations.

Abnormalities of processing of visceral sensations, possibly involved in the pathophysiology of functional bowel disorders

Hypersensitivity of the gut to distension in patients with irritable bowel syndrome (IBS) has been suggested twenty years ago by Ritchie who showed that IBS patients experienced pain at lower distending volumes during rectal distension than controls. The role of colonic distension in the pathophysiology of IBS has also been suggested by the observation that abdominal pain was reported by IBS patients at the time food arrives in the colon as determined by the measure of oro-caecal transit time. The pathophysiology of visceral hypersensitivity in patients with IBS remains controversial. Some authors have claimed that it could be related to a default in relaxation of the colonic wall resulting in an increase in parietal tension when a contraction occurs, with the subsequent stimulation of parietal mechanoreceptors. However, studies performed with the barostat concluded that colonic compliance, i.e. the elastic properties of the colon, was not different in IBS patients and in controls. These results suggest that the primary disorder responsible for the visceral hypersensitivity in patients with functional bowel disorders could be located on visceral afferents. However the exact level of this abnormality has not yet been defined. There are some experimental data supporting the involvement of peripheral afferents in the pathophysiology of visceral hypersensitivity in IBS. The primary disorder could be located at the level of parietal mechanoreceptors themselves.

The daily clinical experience suggests that psychological factors may influence abdominal symptoms in IBS patients. Some authors have suggested that psychological factors could account for hyperalgesia observed in these patients. More recently, it has been shown that stress may influence the sensitivity of healthy volunteers to luminal distension of the colon or rectum. In IBS patients, studies have evaluated visceral perception firom other digestive organs than the intestines. Balloon distension of the oesophagus induces pain at a lower pressure threshold in IBS patients than in controls, while oesophageal motility is normal. A gastric hypersensitivity has also been observed in IBS patients. In a recent study, hypersensivity was obviously diffuse in IBS patients who underwent a set of distensions at the level of the oesophagus, various parts of the small intestine, colon and rectum. These observations suggest that there is a diffuse abnormality of visceral perception, involving the whole gut in IBS patients. Comparisons have also been made between visceral and somatic pain in IBS patients. These studies have shown that somatic perception was almost not modifyied in IBS patients or even that these patients tolerate well more intense painful stimuli than controls, e.g. during electrical stimulation of the skin.

Pharmacological approach for new treatments of functional bowel disorders

Based on the experimental evidences presented here above and on the results of studies conducted with the barostat for evaluating visceral sensations in humans and the influence of drugs on them (9), a number of pharmacological targets have been identified for the development of new treatments aimed to relieve abdominal pain in patients with FDD. In Table 1, are listed the drugs that have shown a potential effect on sensory thresholds elicited by luminal distension, either in animals or in humans. For some of them, a clinical benefit has been shown in phase II studies (10). However, it is

not possible at the moment to consider the effect of drugs on sensory thresholds as a key indicator of their clinical efficiency.

Conclusion

The role of visceral afferents has been recognized over the last years as one of the main components of the control of digestive functions. In physiological conditions, the informations processed by afferents trigger a number of reflexes. In pathological conditions, like FDD, an abnormal processing of these informations appears to be an important feature for the pathophysiology of abdominal pain that characterizes these syndromes. Therefore a modulation of this «hypersensitivity» by drugs is a new challenge in the treatment of FDD. The receptors and the neuromediators involved are numerous. FDD could thus be splitted in several pathological entities which might benefit in the future from these new and more specific treatments.

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