Neurophysiology and Neuropsychiatry of the IBS

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Neurophysiology
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On December 17, 1994, the European working team of the IBS Club [1] met once again, in Paris, for the fifth time. From the previous meetings it was becoming clear that the neurological connections were of importance in IBS, and for most of us it was still difficult to deal with the data of papers reporting works in which the neurological pathways were involved in the control of the gut. Because of (1) the potential effect of hypnosis in IBS, (2) the mechanism of action of numerous drugs potentially active in IBS, and (3) the psychological component of anismus and efficacy of biofeedback in this pathology, the connections between the nervous system and the gut appear to be important to be discussed. So, the purpose of this meeting was to describe the normal neuromuscular and neurophysiology before dealing with the neurological features potentially involved in IBS, in its anatomic and physiologic component as well as in some clinically relevant conditions. The latter attempt was based on the data presented by the speakers and discussed by all the members of the group. The participation of a French neurophysiologist to this working party made the discussion more comprehensive on the basic data regarding neurophysiology.

Intestinal Neuromuscular Connection in IBS
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During the last decade, a lot of studies were conducted on the relationship between IBS symptoms and digestive smooth muscle, which was thought to be responsible for pain (via spasms) and transit disorders [2]. Contractile state of the smooth muscle is under neural control, but the conditions of this control remain unclear for clinicians. The main functions of the neural control are efferent (to release neurotransmitters to stimulate or inhibit muscular contractions), as well as afferent (to provide pathways which integrate the information to the central nervous system).
Fig. 1. Schematic organization of the neuromuscular connection within the gut wall. The circles represent the body cells of the intrinsic neurons: the empty circle is an excitatory neuron which is stimulated by the parasympathetic system and inhibited by the sympathetic system, or influenced (stimulation or inhibition) by the interneurons; the hatched circle represents an inhibitory neuron which can be stimulated by the parasympathetic system or by the interneurons from the intrinsic system; the black circles represent the body cells of the interneurons of the intrinsic neural system.

The smooth muscle cell is under the control of neurons belonging to the enteric nervous system, which is separated in myenteric plexus (Auerbach's plexus), located between the two muscular layers, and the submucosal plexus (Meissner's plexus), located in the submucosa [3].

The relationship between both plexuses is provided through connecting nerves. The integrated function of the enteric nervous system is contraction or inhibition of the smooth muscle cells. If acetylcholine is well known and not disputed as the neurotransmitter for the smooth muscle cell contraction, the neurotransmitter for inhibition is still discussed. The putative substances for inhibition are ATP, VIP, and probably nitric oxide. Only very few fibers issued from the sympathetic nerve system can reach the smooth muscle cell and directly relax the cells. The complexity of this system can be illustrated by the peristaltic reflex. When a luminal distension occurs (arrival of the bolus in a digestive segment), an aborally propagated contraction of the circular layer of the gut wall is initiated by the intrinsic nervous system. At the same time, proximal to the bolus, the circular layer contracts while the longitudinal layer relaxes, and distal to the bolus the circular and the longitudinal layers relax. This is possible because of the very rich connections between enteric neurons within both muscular layers. This peristaltic reflex was first described by Bayliss and Starling [4] after mechanical and chemical stimulation of the small intestine. This is an example of the major role played by the intrinsic neurons which can conserve some motor function in an autotransplanted segment of small bowel. Because of that kind of independent function of the intrinsic nervous system, it is sometimes referred as the 'little brain' or the 'gut brain'. Although it is a strong structure, the normal motor function of the gut cannot be achieved only under the control of the intrinsic neurons.

The extrinsic command of the smooth muscle cell is the other major component of a normal motor function [5, 6]. The intrinsic neurons are also controlled by parasympathetic and sympathetic systems. Schematically, the parasympathetic system stimulates and the sympathetic system inhibits the smooth muscle cells. The efferent parasympathetic pathways can stimulate an intrinsic neuron which is stimulating or inhibiting a smooth muscle cell or a group of them. In the case of stimulation, the neurotransmitter is acetylcholine, and in the case of inhibition the neurotransmitter are nonadrenergic-noncholinergic substances. On the other hand, the efferent sympathetic pathway only inhibits the smooth muscle cells. Very few fibers can directly reach the muscular layers, the main contingent of adrenergic fibers is connected to the parasympathetic neurons to inhibit the release of acetylcholine and thus producing less stimulation of the intrinsic neurons (fig. 1).

Despite these data, the precise physiologic role of the extrinsic system remains unclear. One of the best examples of these discrepancies is the role of the vagus nerve on colonic motility. When cooling the vagus nerve in primates, the colonic motility is dramatically decreased [6], while there are only moderate modifications of the gut motor functions in the patients with truncal vagotomy.

Information from the gut to the brain, or from one gut segment to another go through the same anatomical structures, with an original signal arising from the parietal receptors. These afferent pathways are of importance in the pain mechanisms [7]. There are different kinds of receptors: mechanoreceptors, chemoreceptors, osmoreceptors, thermoreceptors, polymodal receptors. The body cells of these neurons can be located within the gut wall, and they have the same organization as the motor neurons in the enteric nervous system, otherwise they are located outside the gut wall, in the ganglia of the sympathetic or parasympathetic systems. The neurotransmitters for the extrinsic system are still acetylcholine and noradrenaline; in contrast, the neurotransmitters for the intrinsic system are mostly peptidergic substances such as cholecystokinin, enkephalin, VIP, and dynorphin.
One way to stimulate the receptors located in the gut wall is to use a distension of the gut. The most accessible segment is the rectum; most of the studies performed in IBS and normal subjects dealt with the subject's perceptions during rectal distension. It has been shown that IBS have a lower threshold to visceral distension commonly associated with alterations in viscerosomatic referral patterns [8]. Thus far, most of the studies dealing with visceral hyperalgesia in IBS are consistent, as altered rectal perception has been proposed as a biological marker of IBS.

From these data, we can support the hypothesis that the afferent system as well as the efferent system could be implicated in the symptoms of IBS, mainly pain and transit disorders. If an intestinal neuromuscular connection does exist in IBS, it could be located within the gut wall.

**Representation of the Small and Large Bowel at the Ganglion and the Spinal Cord Level**

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Our knowledge of the representation of the small bowel and the colon on the prevertebral ganglion and the spinal cord is based on physiological experiments that study the effect of stimulating or ablating discrete areas of the nervous system on GI motility, and on histological studies of nerve degeneration. These studies and anatomical studies have shown that the ganglia involved in control of GI motility are: celiac ganglia, superior and inferior mesenteric ganglia, aorticorenal ganglion, and the inferior hypogastric plexus. All these ganglia are devoted to the sympathetic control of GI motility. In contrast, the parasympathetic system has very long axons reaching the bowel without intermediate synapse. The nervous trunks of both systems contains efferent as well as afferent fibers.

**Morphological and Functional Organization of the Sympathetic System at the Spinal Level** [9, 10]

The sympathetic fibers originate in the lateral cornual cells in the spinal cord. This is the prevertebral or preganglionic neuron which is passing through the sympathetic trunks. Then this preganglionic neuron connects to the second neuron in the prevertebral ganglia. The postganglionic neurons have very long axons located in nervous trunks along the blood supply of the gut before entering into the bowel to project onto the intrinsic nervous system. Because of the segmental organization in the central nervous system, the splanchic nerves are projecting in different ganglion as reported in figure 2. Another segmental organization leads to innervation of the different part of the gut. The postganglionic axons issued from celiac, superior, and aorticorenal ganglia are passing along the superior mesenteric blood vessels to reach the small
Fig. 3. Schematic organization of the ganglia. Because of the different projections on the postganglionic neuron, it could be considered that the ganglion is an integrative center. The black circles represent the preganglionic neurons, the empty circles represent the postganglionic neurons.

bowel and the very proximal part of the colon. The postganglionic axons issued from the inferior mesenteric ganglion pass along the inferior mesenteric blood vessels to reach the distal part of the colon.

Morphological and Functional Organization of the Parasympathetic System [9, 10]

The organization of the parasympathetic systems is different from the sympathetic system, because the neurons do not have any relay before entering the bowel. The axons originate into the parasympathetic centers located in the dorsal vagal motor nucleus in the brain stem, and in the pelvic centers located at the sacral spinal level (S2, S3, S4). The nervous trunks are the vagus nerve and the pelvic nerves, respectively. The vagus nerve projects fibers over the entire length of the colon, and the pelvic nerves reach only the distal part of the colon.

Both systems contain afferent and efferent fibers. The afferent neurons have their body cells in the inferior vagal ganglia concerning the vagus nerve and in the dorsal root ganglia of the spinal cord concerning the splanchnic nerves. These afferent neurons have a T shape as their sensitive end is located into the gut wall (connection with receptors) and their central end is relaying into the central nervous system, directly in the nucleus tractus solitarius (vagus nerve) or at different level of the spinal cord (splanchnic nerves).

Despite the fact that the morphological and neurophysiological data are very clear and precise, a lot of questions remain to be answered especially regarding the motor or sensitive effects of sections of the nervous trunks. For instance, after truncal vagotomy, or splanchnicectomy, the consequences on the GI motility and sensitivity are not very obvious from a clinical point of view. At that time, if compensatory mechanisms are suspected they are still to be demonstrated.

Neuroregulation of Colonic Motility through Sympathetic Prevertebral Ganglia

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The last two decades have led to an important increase in our knowledge on the sympathetic ganglia. Formerly, they were thought to be only a site of connection between the preganglionic fibers issued from the spinal cord, and the postganglionic fibers. The most recent studies suggest that the sympathetic prevertebral ganglia are real nervous centers [11, 12].

A single preganglionic neuron can be connected with two or more postganglionic neurons, as the efferent information becomes divergent to different segments of the bowel. Moreover, different preganglionic neurons can be connected with a single postganglionic neuron, as different information from the central nervous system converges to the same part of the gut. The last possible connection to the ganglionic neurons is represented by the afferent fibers coming from the gut. So, the ganglionic structure, as described, responds to an integrative center receiving information from the central command and from the peripheral effectors, and dispatching information in both ways (fig. 3). As for any neuron, neurotransmitters are needed at this level. The very classical transmitters such as acetycholine and noradrenaline are present in the ganglia. However, electrophysiological studies have shown that a lot of peptidergic substances could play the role of neurotransmitters (enkephalin, dynorphin, CCK, VIP, somatostatin, neurotensin, bombesin). Some of these peptides do not respond to all the criteria of a true neuromediator, so they are called putative transmitters. One of the problems with these mediators is their neural localization, and it seems that different substances can be located in the same neuron. This colocalization could increase or decrease the effect of the liberation of the classical neurotransmitter (facilitation or inhibition).

The precise role of the prevertebral ganglion in man is still to be described, but animal experiments have definitively shown the role of the ganglion in some reflexes at a
colonic level. The experiment which demonstrated this most was performed in 1979 in an in vitro preparation with a part of the proximal and a part of the distal colon with preservation of the ganglia and nervous fiber connections. In this experiment, a mechanical distension in the distal colon induced an inhibition of colonic motility in the proximal colon and reciprocally. This colo-colonic inhibitory reflex was abolished by the section of the interganglionic neurons [13]. Although this intervention of the ganglia in reflexes at the colonic level is well known, the role of ganglia in the control of gut motility is still controversial. The removal of ganglia in dog and guinea pig only decreases the frequency of migrating motor complexes in the small bowel or increases the duration of the different phases of this complex.

Even if the role of the prevertebral ganglion is not well established in man, we should accept that it is a very important structure in the control of colonic motility and perhaps in its sensitivity. Because the same neurotransmitters as those in the central and intrinsic nervous systems are found to work in this structure, future studies involving different kinds of agonists and antagonists would give us more information on the function of the prevertebral ganglia in man.

**Afferent and Efferent Representation of the Colon and the Rectum at the Cerebral Level**

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The brain remains very difficult to explore from an experimental point of view in humans. Neurologists performed some studies in pathology, and anatomicopathologists reported the results of autopsies, but the relationship between the colonic motility and the brain were poorly studied. Yet, in dysautonomia, so-called Shy Dragger, the patients presented with transit disorders such as constipation and fecal incontinence, and with autonomic disorders such as hypotension and sweat dysregulation. In this pathological condition, despite a normal gross anatomy, cell loss exists in a few areas of the central nervous system: putamen, nucleus ambiguus, intermediolateral nuclei of the spinal cord, and autonomic ganglia. The predominant role of the putamen in fecal incontinence was highlighted by a retrospective study in which it was found that a strong correlation existed between fecal incontinence and bilateral lesions of the putamen. The more severe the lesions, the more severe the incontinence. In contrast, unilateral lesions of this area were not associated with incontinence [14]. Another way to localize the motor centers regulating colonic motility is the ascending staining of colonic nerves by horseradish peroxidase. This was performed in rats, and when the colon was injected with horseradish, the staining was found bilaterally in the nuclei of the vagus (dorsal motor nucleus, and nucleus of the solitary tract). The rectum, in contrast, projected on the spinal cord (S1 to S3). In both cases, the projection of the colon was directly on the central nervous system [15].

Other observations supported that the frontal lobe could play an important role in colorectal motility. Tumoral pathology, such as large meningiomas, traumas, or leukotomies, are frequently associated with fecal incontinence. Moreover, the patients can recover from the transit disorders after removal of the tumors. When recording the anorectal motility in patients presenting with frontal lobe damage, it was found that the rectum exhibited spontaneous contractions, and that the voluntary contraction of the anal sphincter was impaired [16]. In the same way, the electrical stimulation of the frontal lobe in cats led to strong rectal contractions [17]. The most new techniques deal with cerebral localization of the areas regulating the colonic motility, as well affereances as efferences. The cerebrally evoked potentials were first recorded in humans in 1987 [18], during a mechanical stimulation of the rectum. Even if the authors were not able to draw a proper map of the projection of the rectum on the vertex, they localized the sensory function in the postcentral gyrus. The other way to "connect" brain with gut is the central magnetic stimulation [19]. When applying a maximal magnetic stimulation on the paramedian precentral gyrus in right-handed subjects, the external anal sphincter responds to a left stimulation, and the pelvic floor musculature responds to a bilateral stimulation. In the most recently described way, differences have been shown between normal subjects and IBS by using positron emission tomography. A painful rectal sensation in healthy volunteers was associated with activity of the anterior cingulate cortex recorded by positron emission tomography, while there was no modification in this area during the same intensity stimulation in IBS patients [20].

Different cerebral areas are involved in the control of colonic and anorectal motility. The putamen and the frontal lobe play a major role in that control. But it is still impossible to separate sensory, motor, autonomic, and somatic innervation and function.
IBS Symptomatology as a Part of Neuropsychiatric Disease

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The link between IBS and psychopathology is still controversial, in part because the studies dealing with that point included different kinds of patients. Moreover, the symptoms reported by IBS patients are not specific enough to differentiate patients with a major psychological component from patients without psychological disturbance.

As well as the experience of each of us, the studies performed during the last 10 years led to conclude that IBS patients have more psychological symptoms than normal controls. When studying hospital patients, the rate of psychological disturbances can be as high as 70%. In contrast, it is well known that from the 15–18% of subjects responding to clinical criteria of IBS, only a small proportion of them is seeking health care [21]. At least two studies [22, 23], including nonconsulting patients, reported that the psychological status of the nonconsulting patients was similar to that of the normal control. IBS patients have more abnormal personality patterns and greater illness behavior than normal controls and IBS nonconsultors. The intensity of pain and the importance of bowel disorders were similar in consultants and nonconsultors, so it seems that the psychological factors are the main reason to bring the patient to the doctor. The patients seem to be unable to cope with pain and transit disorders. This approach could make the beneficial role of antidepressant therapy in IBS more understandable. The antidepressant drugs might act on a different level of neural control of GI motility, might have an analgesic role on the central nervous system, and also might have an effect on the ability of the patient to cope with symptoms. The fact that antidepressant drugs help IBS patients does not prove that IBS is a psychopathological condition. The role of psychotherapy and hypnosis is still to be discussed, even if studies reported that hypnosis can decrease colonic motility and relax smooth muscle, but it might be acting the same way as antidepressant drugs.

The patients presenting with IBS usually have a very rich symptomatology associating digestive complaints and extradigestive symptoms [24]. It is not easy to make a difference between organic and IBS on the basis of the alleged symptoms, as well as not being possible to separate IBS with and without psychopathological factors. So the personal experience of the doctor to detect the IBS patient with psychological disorders is important, but this is a very subjective method. Another way to avoid under-estimated prevalence of psychologic distress would be to use scales of psychologic evaluation such as MMPI (Minnesota Multiphasic Personality Inventory), or the Hopkins Symptom checklist. But there is no one study reporting that a subgroup of IBS patients with psychological symptoms assessed by this kind of scale have been healed by any kind of psychotherapy.

IBS seems to be a legitimate condition that does exist with or without the interaction of the mind. Psychological factors do not alter IBS conditions but modify the way the subject can cope with that, and they are the main difference between the ‘healthy’ IBS and the IBS patients.

Sites of Action of Various Drugs

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As seen before, the role of the nervous system is of importance in the pathophysiology of IBS, and some common medical therapies are relieving the symptoms through an action on the nervous system at a different level. Most of those drugs are agonists or antagonists of receptors of neurotransmitters, as they are supposed to increase or decrease the activity of neurons implicated in the control of GI motility or GI sensitivity.

In IBS patients it is not known whether the antidepressant drugs act on the associated psychological disorders, on bowel motility or on sensitivity, or on all the mechanisms together. The mechanism of action of the antidepressant drugs is different between the tricyclic drugs which are nonspecific inhibitors and paroxetine which is a very specific inhibitor of the neuronal reuptake of 5HT. When using both drugs in a short-term study, to avoid the antidepressant effect, the orocecal transit time and the whole gut transit time were delayed by imipramine in controls and diarrhea predominant IBS and in contrast paroxetine delayed only the orocecal transit time in the same subjects [25]. This suggests that antidepressant drugs could act directly on the GI motility through the nervous system before having any effect on the mood.

Somatostatin was found to decrease abdominal symptoms in IBS. Now, octreotide is available to clinical research, as a potent somatostatin analog. At least two studies reported results with octreotide in IBS, and showed that this compound could increase the threshold for visceral perception without modification of the bowel compliance or colonic tone. These results suggest that octreotide could modulate the sensory perception at a central level [26].
A new compound, fedotozine, which is a kappa agonist, has been studied in animals and it was reported that, under experimental conditions, it was able to reverse alterations of GI motility induced by stress, and to correct nociceptive responses. The mechanism of action was found to be only peripheral on the afferent sensory fibers of the enteric nervous system. In patients presenting with IBS, fedotozine was found to be more effective than placebo to relieve abdominal pain [27].

Cholecystokinin, a major neuropeptide in the brain gut axis, is involved in the transfer of message from the gut to the brain via the vagus nerve including nociception [28]. Moreover, during CCK infusion, IBS patients but not healthy controls experienced abdominal pain. CCK analogs are not available for clinical research, but loxiglumide, a CCK A antagonist, can be used in humans. In IBS patients loxiglumide slows the proximal colon transit, but not in volunteers [29]. This local action on the proximal colon support the hypothesis that CCK acts through the afferent fibers of the vagus nerve.

Because more women are suffering from IBS than men, and because the symptoms are more acute after ovulations, it has been hypothesized that female sexual hormones might interfere with normal enteric function. So leuprolide acetate was tested in female patients with IBS, and it was found that the symptoms improved after continuous administration of this GRH analog [30]. Three mechanisms of action are still under discussion: inhibition of the release of the ovarian hormones which affect gut motility through the action on the enteric nervous system, direct effect on the neurons in the brain or the spinal cord, or direct effect on the enteric nervous system [31].

These data show that there are a lot of pharmaceutical targets potentially involved in IBS physiopathology. Each target is located at a different level of integration of the information, as the whole system of control of the GI motility and the GI sensitivity is implicated.

The Spastic Pelvic Floor Syndrome: Part of the IBS?
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The spastic pelvic floor syndrome, also called anismus, paradoxical puborectalis contraction, or pelvic floor dyssynergia associates constipation with impairment to empty the rectum, mostly in young or middle-aged females, in whom spontaneous defecation is rare and use of laxatives is frequent and evacuation with digital help is common. Despite all these different names, this syndromes lacks a precise definition. In the first publication by Preston et al. [32], anismus was described as an inability to expulse a filled water balloon placed in the rectum and a paradoxical contraction of the external anal sphincter when attempting to defecate. In this study the prevalence of anismus was 100%. But over the years the prevalence dropped to 24%, suggesting that in the group of constipated patients there was a subgroup with anismus. These changes in prevalence might be due to the new procedures to explore patients with a potential anismus. The history and the physical examination of the patient should be the first step as they only make the physician suspect anismus. Afterwards, many laboratory explorations can be performed to confirm the anismus: balloon expulsion test, evacuation of an artificial stool, radiographic defecography, scintigraphic defecography, electromyography of external anal sphincter or puborectalis, anorectal manometry, dynamic integrated proctography. All these examinations are needed to show impaired defecation, decrease of the anorectal angle, paradoxical activity in external anal sphincter or puborectalis, under the conditions of the examination which are not necessarily physiological. To record these parameters under more physiological conditions, an ambulatory method was proposed, and from 11 patients with anismus in the laboratory, only 8 of them were still responding to the anismus criteria [33]. So the working party were in agreement to state that the minimal requirement for the diagnosis of anismus was: a documented impairment of ability to empty the rectum and a paradoxical recruitment of external anal sphincter and/or puborectalis electromyography at attempts to defecate, and sufficient rectal pressure increase at attempts to defecate.

Another question was: Is anismus part of IBS? The classification of the functional gastrointestinal disorders along the Rome criteria shows a clear-cut difference between anismus and IBS [34]. But, if a patient is suffering from abdominal pain or discomfort because of anismus-induced constipation he would be scoring high enough to fulfill the Rome criteria for IBS. But in contrast, anismus is supported by a demonstrably normal function of the striated muscle, whereas IBS is supposed to be related to a dysfunction of the smooth muscle, and there is no demonstrable abnormality in muscular function in IBS. The last point against anismus as a part of IBS is the improvement of the symptoms after biofeedback therapy, which leads many physicians to exclude anismus or treat it in constipated patients before diagnosing IBS.
Biofeedback in IBS and Related Conditions

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The biofeedback training is a behavioristic approach, and it is the conscious training or retraining of somatic functions which are directly or indirectly subject to the patient’s will. This supposes that only patients can benefit with biofeedback, and because the patient’s will is implicated dysfunction of striated muscle can be retrained. The voluntary conditioning needs to use a sensory signal, either acoustic or optic, reflecting the specific muscle activity. In this way, patients presenting with fecal incontinence as well as constipation due to obstructed defecation were retrained with success [35, 36].

In some studies, patients with constipation or with fecal incontinence obviously overlapped with IBS. After retraining them by biofeedback, symptoms such as abdominal pain, bloating, and disordered defecation were improved [37]. This might be an argument to suggest that biofeedback could have a positive effect in IBS. The main difficulty to accept is the lack of a controlled study. There is no published study to our knowledge comparing biofeedback versus placebo in similar groups of patients [38].

Biofeedback could be a good instrument to improve a well-defined condition, but as far as IBS and disordered defecation are still overlapping too much, and proper psychological and epidemiological investigations seem necessary for a better approach to the coincidence of both of these symptom complexes and the personalities on which they grow.

References


