

Pathophysiology of Irritable bowel syndrome: The role of brain-gut axis and serotonergic receptors

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SUMMARY

The last decade has been marked by substantial progress in the understanding of the pathophysiology of Irritable Bowel Syndrome (IBS). Considerable advances contributing to this progress include the decryption of the secrets of the enteric nervous system (ENS) and the neuronal pathways involved in the transmission of visceral nociception as well as the localisation of potential processing centres in the central nervous system (CNS). Serotonin is sequestered in the neterochromaffin cells and is an essential mediator in the ENS. It manifests its actions mainly by 5-HT₃ and 5-HT₄ receptors and plays a key role in intestinal motility and secretion. The “central processing unit” of serotonergic actions in the ENS is the AH/Dogiel morphologic type II neuron which was formerly considered to be the primary afferent neuron. It remains unknown whether the neurologic disorder in IBS consists of an exaggerated response to noxious stimuli in the gut, or misinterpretation by the CNS of otherwise accurate information. The exact locus of projection of visceral information in the brain is not known, but there is increasing evidence for areas such as the thalamus, the prefrontal cortex and the amygdaloid nucleus in the limbic system. Anxiogenic colonic response is probably mediated by CRF-1 receptors. Autonomic pathways from the brain stem may also play a role by regulating the intensity of perception during visceral stimulation. More accurate localisation of the neurologic derangement along the brain-gut axis is required, thus permitting a more targeted therapeutic intervention.

Key words: Serotonin, visceral nociception, affered neuron presynaptic inhibition

Irritable bowel syndrome (IBS) is a fairly common disorder, although not completely understood. Despite intensive research in this particular field of gastroenterology there is, as yet, no effective treatment. A number of pharmacological agents have been used with varying, even poor, results. The inability to produce an effective drug for IBS mainly reflects our poor understanding of the pathophysiology of this syndrome which was largely considered a “psychosomatic” disorder. The considerable advances in neuro-gastroenterology have contributed to a different approach to IBS and deciphered many of its secrets, such as the brain-gut axis and the key role of the enteric nervous system (ENS) and serotonin in the pathogenesis of the syndrome.

Nowadays we consider IBS to be not a “psychosomatic” but a neurologic disorder. Most IBS patients share the common characteristic of visceral hypersensitivity, expressed as lowered perception thresholds to colorectal distension (CRD) which is not due to altered compliance.¹ Peripheral neural pathways responsible for the transmission of noxious or innocuous visceral stimuli have been elucidated. A disturbed processing of the visceros-

Abbreviations used in the text:

IBS: Irritable Bowel Syndrome,
ENS: Enteric Nervous System,
CNS: Central Nervous System,
CRD: Colorectal distension,
CRF (Corticotropin Releasing Factor),
5-HT: 5-hydroxytryptamine

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ensory information by the brain of IBS patients has been postulated, but the mechanism remains unclear.

PHYSIOLOGY OF VISCERAL SENSATION - THE "BRAIN-GUT" AXIS

The knowledge of the neuroanatomy and the physiology of sensation are essential prerequisites for the understanding of what we call "visceral hypersensitivity" in IBS. The initial stimulus seems to originate from the enteroendocrine cells which serve as chemical or mechanical transducers for noxious stimuli.² Degranulation of these cells releases serotonin, the key neurotransmitter of the ENS. The pathway for the transmission of the signal to the central nervous system consists of three neurons³: The first neuron lies in the dorsal root ganglion and terminates in the dorsal column laminae of the spinal cord. Some fibers project to noradrenergic neurons in the prevertebral ganglia and contribute to the modulation of intestinal motility. The second neuron lies in the dorsal horn of the spinal horn and projects to the thalamus and reticular formation of the brain stem through the spinothalamic and spinoreticular tracts respectively. These neurons synapse with autonomic centres and with the third neuron which projects to the limbic system (emotional responses) and to the sensory cortex leading to the conscious perception of the stimulus. Efferent autonomic pathways (serotonergic, adrenergic) from the brain stem centres, such as the periaqueductal grey, alter the sensitivity of the dorsal horn neurons, thus modulating the intensity of perception during visceral stimulation.³

The exact locus of the projection in the sensory cortex is not yet known. Studies of cerebral blood flow using PET scan in patients with IBS showed evidence of activation of the right prefrontal cortex and rostral anterior cingulate cortex and posterior cingulate cortex during CRD.⁴ Reduced activation was noticed in the perigenual cortex, temporal lobe and brain stem.⁴ It is possible that such changes are due to altered central noradrenergic modulation as IBS patients show a reduced activation of circuits involved in the integrated affective autonomic and antinociceptive response to an average stimulus.⁴ Additionally, there is evidence of selective activation of brain regions responsible for processing negatively charged emotional information.⁴

The role of anxiety in the exacerbation of symptoms of patients with IBS has been the focus of many studies investigating the role of the limbic system and mainly that of the amygdaloid nucleus in visceral responses to

stress. Parasympathetic action stimulates distal colonic motility whilst sympathetic stimulation regulates intestinal secretion and permeability.⁵ Stereotaxic delivery of corticosterone to the central amygdaloid nucleus increases anxiety and demonstrates an exaggerated visceromotor response to CRD in rats.⁶ Descending neuronal pathways from the area of the amygdala seem to be involved in the modulation of the visceromotor response.⁶ This effect is probably mediated by CRF-1 receptors which are responsible for colonic and anxiogenic responses to stress.^{7,8} Endogenous serotonin peripherally released in response to stress is probably involved in central CRF-induced stimulation of colonic motility by acting on 5HT₃ receptors.⁸ CRF receptors are also located peripherally on enteric smooth muscle and can be stimulated by locally produced CRF, by enteric neurons, enterochromaffinic and immune cells.⁹

Recent data suggest a dysregulation of adrenal activity in IBS patients.¹⁰ Compared with controls IBS patients showed increased salivary cortisol levels in the morning, while they maintained the physiological circadian fluctuation.⁸

ENTERIC NERVOUS SYSTEM: THE ROLE OF SEROTONINERGIC ACTIONS

The digestive tract comprises the main reservoir of the body's 5-hydroxytryptamine. More specifically, serotonin is sequestered in neurons, enterochromaffin cells and enteric mast cells and is released by signalling functions to the enteric nervous system.¹¹ There is evidence of enhanced postprandial serotonin release from IBS patients.¹² There are seven subtypes of serotonin receptors but two (5-HT₃ and 5-HT₄) predominate in the gut.¹³ 5-HT₃ receptors are scattered throughout the ENS but 5-HT₃ can also be found in the brain, spinal cord and dorsal root ganglion neurons.¹⁴⁻¹⁶ A large proportion of spinal receptors are located on the central terminals of afferent neurons many of which are capsaicin sensitive.¹⁷ 5-HT₃ receptor excitation results either in contraction via acetylcholine or relaxation of the smooth muscle via nitric oxide release.¹⁸ 5-HT₄ receptors are mainly located on neurons of the ENS but can also be found on smooth muscle and enterochromaffin cells.¹⁸ In a similar way as 5-HT₃ receptors, they stimulate colonic motility by releasing acetylcholine, substance P and calcitonin-gene related peptide, but also regulate colonic secretion.¹⁹ Nevertheless, the cascade of 5-HT₄ activation may also lead to colonic relaxation.²⁰ Alosetron is a 5-HT₃ inhibitor, whilst tegaserod and prucalopride are potent 5-HT₄ agonists.²¹⁻²²

Serotonin serves for both neurotransmission and paracrine signalling by being released and diffused in the extracellular space to interact with its receptors and sensory afferents.²³ Mechanical (brushing of luminal contents), chemical (chemotherapy) and other injurious stimuli (irradiation) can lead to serotonin release.²⁶ Whether the powerful bowel contractions in IBS can lead to degranulation of enterochromaffin cells remains unknown.

The ENS, although regulated by the central nervous system, can act in an independent fashion and control digestive functions and gut motility. Serotonin has four important actions on the neural elements of ENS.²⁵ Two of them occur in the neuronal cell bodies, one mediates presynaptic inhibition and the last occurs in terminal projections of AH/Dogiel morphologic type II enteric neurons.

1) Neuronal bodies

Two excitatory actions take place at this level, the rapidly and the slowly activating response.²⁵ The former is produced by the opening of ligand-gated ionic channels and is mediated by the 5-HT₃ receptor subtype. Binding of serotonin to the receptor leads to the opening of ionic channels and depolarisation of electrical potential across the membrane to action potential threshold. Various pharmacologic agents act on these receptors either as agonists (phenylbiguanide, 2-methyl-5-hydroxytryptamine) or selective antagonists (granisetron, tropisetron and alosetron). Alosetron is a potent 5-HT₃ inhibitor that has proved to be effective in the treatment of IBS.²⁶

The slowly activating response is mediated by the 5-HT_{1P} receptors.²⁵ These are metabotropic receptors and their binding with serotonin involves changes in neuronal metabolism. The protein complex of 5-HT_{1P} receptor includes G-protein and enzyme. The activation of the latter after serotonin binding leads to second messages (cyclic adenosine monophosphate) in the cytoplasm. This cascade of metabolic events leads to the slow excitatory response.

2) Presynaptic inhibition

This is an important action of serotonin as it prevents runaway excitation of neural circuits and takes place in neurons that are excited by exposure to mediators (serotonin, histamine) released in paracrine manner from enterochromaffin, immune or inflammatory cells.²⁵ Serotonin-mediated presynaptic inhibition also occurs at the sites of nicotinic synapses of cholinergic neurons in the ENS.²⁵ When serotonin binds to these receptors, it

suppresses the release of acetylcholine and other neurotransmitters.²⁵ The type of such receptors has not been identified.

3) AH/Dogiel morphologic type II neurons

These neurons are multipolar and present highly specialised electrophysiologic behavior.²⁵ They constitute the fundamental element of the microcircuits of the ENS.²⁵ One of their neurites projects out of the myenteric plexus into the lamina propria and the mucosa.²⁵ Serotonergic excitatory receptors belonging to the 5-HT₃ subtype are located on the terminals of these neurites.²⁵ When mechanical or chemical stimuli lead to degranulation of the enterochromaffin cells scattered in the epithelium the released serotonin binds to these receptors leading to excitatory response.²⁵ Because of this responsiveness to serotonin, AH/type II neuronal projections were initially regarded as the “primary afferent neurons” of the ENS. As their properties are unique and different from the classic neurophysiologic behavior of primary sensory afferent neurons, it has been suggested that they should be called “AH/Dogiel type II.”²⁵

SEROTONIN IN THE PATHOPHYSIOLOGY OF IBS: INCREASED INTESTINAL MOTILITY OR ALTERED VISCERAL NOCISEPTION?

Despite the recent advances in the understanding of the pathophysiology of IBS there are gaps in current knowledge. Serotonin increases intestinal motility and secretion by increasing the firing rate of secretomotor neurons.²⁷ The latter evokes secretion from the crypts of Lieberkuhn and induce vasodilation of arterioles to increase blood flow in support to stimulated secretion.²⁷ The efficacy of 5-HT₃ receptor blockade in women with diarrhea predominant IBS²⁸ suggests an overstimulation of secretomotor neurons by serotonin. The reason for this selective efficacy of alosetron in women is not understood but may be due to a different metabolism or higher levels of serotonin in female patients.²⁹ A recent study showed increased serotonin concentration in colonic mucosa of patients with constipation-predominant IBS when compared with individuals with diarrhea predominant IBS, although this may reflect impaired released of serotonin.³⁰ Undoubtedly there are many other candidate mediators/transmitters involved either in the regulation of colonic motility or in visceral perception, such as calcitonin gene related peptide, substance P, norepinephrine and opiates,^{31,32} but the full characterisation of their role in IBS has yet to be elucidated.

IBS is clinically characterised by abdominal pain, ur-

gency, bloating and alteration of stool consistency.³³ Visceral hypersensitivity¹ is a common characteristic of these patients, although the exact site of the disordered neurophysiology is not known. Mechanosensitive primary afferents may be hypersensitive to noxious stimuli and transmit erroneous information to the central nervous system. On the other hand information may be accurate but misinterpreted by central processing circuits responsible for visceral nociception. In some patients, derangement may exist in both brain and periphery. 5-HT₃ receptor stimulation by serotonin seems to be directly related to visceral nociception in rodents: Colorectal distension in the anaesthetised rat is associated with induction of the proto-oncogene *c-fos* and subsequent *c*-fiber afferent activation.³⁴ 5-HT₃ blockade by alosetron significantly reduced numbers of Fos-L1 neurons in the spinal cord.³⁴ Further evidence to support the role of 5-HT₃ receptors in visceral perception includes the inhibition by granisetron of colorectal distension-induced *c-fos* immunoreactivity in the nucleus of the solitary tract³⁵ as well as a similar reduction of *c-fos* immunoreactivity by 5-HT₃ receptor blockade in the trigeminal nucleus following chemical stimulation of the rat nasal mucosa.³⁶ Humans with IBS demonstrate an exaggerated gastrocolonic postprandial response and lowered colonic perception thresholds following intraduodenal lipid infusion.³⁷ This finding, in combination with the higher serotonin levels found postprandially in IBS,¹² indicates that serotonin may also modulate visceral nociception. Nevertheless recent evidence suggests that therapeutic 5-HT₃ receptor blockade by alosetron has an indirect anti-nociceptive effect by reducing colorectal tone and consequently abdominal pain.³⁸

The question whether therapeutic blockade of 5-HT₃ receptor occurs centrally or in the periphery remains unanswered. 5-HT₃ receptor protein and mRNA are widely distributed in the enteric nervous system, dorsal root ganglion neurons, spinal cord and brain.¹³⁻¹⁶ 5-HT₃ inhibitors are thought to act almost exclusively in the periphery. Alosetron has been reported to inhibit the vasomotor response to CRD in dogs when injected intracerebrally, suggesting a central site of action.³⁹ Although this may not be the case in man, a simultaneous action in the CNS cannot be precluded.

CONCLUSIONS

The last decade contributed to a tremendous evolution in our knowledge of a formerly "mysterious" entity called IBS. Serotonin is an important substance involved in the neurophysiologic control of intestinal function, ei-

ther as a neurotransmitter or as a paracrine mediator. Serotonergic 5-HT₃ receptors seem to be the cause for diarrhea and abdominal discomfort in IBS, although this evidence is mostly based on the efficacy of 5-HT₃ receptor antagonists in the diarrhea-predominant IBS in women. Alosetron and tegaserod have been major advances, as they constitute the first pharmacological agents for the etiological treatment of IBS. The initial enthusiasm was followed by doubts pertaining to the safety of the alosetron, as it was associated with ischaemic colitis. On the other hand, the therapeutic advantage of tegaserod when compared to placebo remains controversial and further studies in humans with prucalopride may prove unethical because of the carcinogenic effect of the latter in animals.

More extensive research is required for the exact localisation of the neurologic derangement along the brain-gut axis which may be different for every type of IBS (diarrhea, constipation-prone or alternating IBS). Other potential candidate receptors (5-HT_{2B}) for serotonergic modulation must be sought. This, in combination with the elucidation of the exact role of other neurotransmitters/mediators involved in gut function, will allow an alternative and targeted therapeutic intervention.

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