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Visceral Sensations and Brain-Gut Mechanisms

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Introduction

Over the past several years, different mechanisms located within the gut, or gut wall have been implicated as possible *pathophysiologic mechanisms* underlying the characteristic IBS symptoms of abdominal pain and discomfort. The list ranges from altered transit of intestinal gas, alterations in the colonic flora, immune cell activation in the *gut mucosa*, and alterations in *serotonin* containing enterochromaffin cells lining the gut. For those investigators with a good memory, these novel mechanisms can be added to an older list of proposed pathomechanisms, including altered gut *motility* ("spastic colitis") and alterations in mucus secretion. While the jury on any of these novel mechanisms is still out, one unique aspect about the gut and its connection to the brain are often forgotten: Our *brain-gut axis* is not designed to generate conscious perceptions of every alteration in gut *homeostasis* and internal environment, in particular when these changes are chronic, and when there is no adaptive behavioral response an affected organism could generate.

Evolution has not designed our brain-gut axis to experience abdominal pain every time the number of *mast cells* in our *ileum* goes up, or the number of our serotonin containing cells goes down. It would be counter productive for an animal with a chronic parasite infestation to experience constant *visceral* pain, and it wouldn't have any advantage for people living in third world countries with frequent enteric infections to suffer from chronic abdominal pain. It has even been suggested that visceral pain may be a secondary phenomenon of an elaborate system of signaling non-painful signals to the brain: hunger, fullness (satiety), well-being after a meal, urge to evacuate, etc. At the same time, powerful mechanisms have evolved that keep many other aversive signals out of conscious perception: contractions, luminal distension, gas volume, low-grade inflammation, etc.

The most common symptoms of IBS patients are related to altered perception of sensations arising from the GI tract, and frequently from sites outside the GI tract, such as the genitourinary system or the musculoskeletal system. Sensations of bloating, fullness, gas, incomplete rectal evacuation, and crampy abdominal pain are the most common symptoms patients experience. Numerous reports have demonstrated that a significant percentage of functional bowel disorder (FBD) patients (about 60%) rate experimental distensions of the colon as uncomfortable at lower distension volumes or pressures when compared to healthy control subjects. This finding of an increased perception of visceral signals ("*visceral hypersensitivity*") has been demonstrated during balloon distension tests of the respective part of the GI tract regardless of where their primary symptoms are – the esophagus, the stomach, or the lower abdomen.

In contrast to the current emphasis on mechanisms that may result in *sensitization* of visceral *afferent pathways* in the gut, it may well be that alterations in the way the nervous system normally suppresses the perception of the great majority of sensory activity arising from our viscera are essential for the

typical symptom constellation of IBS and other functional GI disorders to develop.

What is unique about perception of visceral events in the GI tract?

There are several features which are unique to the perception of sensory stimuli arising from the gastrointestinal tract and which differ from those coming from the rest of the body. These differences may explain many of the symptom characteristics present in functional bowel disorder patients.

Even though the events within the GI tract such as the composition of food, the concentration of acid, or the strength of contractions are continuously monitored by sensory nerve fibers, only a small fraction of this sensory information ever reaches consciousness. The majority of sensory signals play a role in reflex regulation of the digestive process and presumably in the very basic regulation of states like hunger or well-being. The only sensory signals which are consciously perceived are those which result in a beneficial behavioral response, such as: the sensation of being "full" following a big meal so that we stop eating, the sensation of rectal fullness and urgency preceding a bowel movement, and the sensation of gas which will result in an attempt to expel the gas from the upper or lower GI tract.

The situation is quite different from *somatic* stimuli. On the body surface, for instance, a heat stimulus or a minor injury to the finger causes a conscious experience of pain, leading to an immediate withdrawal of the finger to avoid further injury. In our digestive system certain potent stimuli, such as concentrated hydrochloric acid or high amplitude contractions, which occur ordinarily in the gut as a part of the digestive process, are not perceived as pain, and are for the most part not even consciously perceived.

The brain has developed mechanisms, which prevent the conscious perception of all visceral information that is not essential for the individual to respond to. However, in patients with functional bowel disorders, this inhibitory mechanism appears to be compromised. For example, people with IBS commonly experience a persistent sensation of excessive gas, even though carefully designed studies have failed to demonstrate alterations in the gas content of the bowel which correlate with symptoms of bloating. A sensation of incomplete evacuation will make a person try to go to the bathroom many times during the day, even though the rectum is virtually empty. Persons with functional heartburn experience a burning sensation in the esophagus, without abnormal amounts of refluxed acid, and persons with dyspepsia will experience a constant sensation of gastric fullness even though their stomachs are nearly empty.

An additional problem for functional bowel disorder patients is that they have no sensory "back-up" system to verify if the perceived gut sensations are appropriate. For example, if I have a sensation that my face feels swollen, I can look in the mirror, touch my face, feel the temperature, etc. If these checks

fail to confirm my sensory experience, I will likely not be concerned about the sensation in my face and forget about it. In contrast, if my belly feels full of food, gas, or stool, I have no way of verifying if this sensation actually is due to an excessive amount of food, gas, or stool. Even more so, if I experience belly pain, I have no way of verifying what may be responsible for the pain or any way of determining if it is a life threatening problem or a simple spasm. This sole reliance on our visceral sensory apparatus (without being able to use our other senses for verification) makes us highly vulnerable to even small alterations in its sensitivity and reliability. Furthermore, the system is prone to generate symptom-related anxiety and fears: if there is no easy way to verify if a particular sensation is a warning signal or an innocuous event, worries and fears about this sensation are likely to develop, in particular in an individual prone to anxiety.

What is responsible for alterations in perception of visceral events in FBD patients?

We currently do not know what factors are primarily responsible in functional bowel disorder patients for the altered perception of normal physiological events within the digestive system. Does it reflect an alteration in pathways that transmit the signals from the gut to the brain, is there an alteration in how the brain extracts stimuli, which are allowed to reach consciousness, or is there an alteration in the mechanisms by which the brain can amplify certain sensory signals?

There has been an initial enthusiasm for the concept that events which cause tissue irritation within the gut, such as mild inflammatory changes or repetitive contractions could sensitize either the peripheral nerve fibers located outside the brain and spinal cord, or the sensory pathways in the spinal cord and cause a long lasting or permanent hypersensitive state. While there is little evidence that even chronic inflammation of the gut as it occurs in inflammatory bowel disorders produces long lasting changes in the perception of visceral pain, repetitive *mechanical stimulation*, for example of the sigmoid colon, is able to induce prolonged rectal hypersensitivity in IBS patients but not in healthy control subjects or patients with inflammatory bowel disorders.

There are several plausible mechanisms that have been proposed to explain the phenomenon of visceral hypersensitivity in functional GI disorders (and related disorders such as interstitial cystitis), which can occur in the absence of specific peripheral pathologies. Several of these mechanisms may occur in the same patient, or alternatively, may be characteristic of subsets of patients.

Failure of the brain's own pain inhibition system. For example, during times of intense repeated or sustained sigmoid contractile activity, as occurs following food intake or during stressful situations, the nerve fibers into the rectosigmoid may become sensitized resulting in crampy abdominal pain or a sensation of rectal fullness. Even though further studies are needed to confirm this hypothesis, it is conceivable that IBS patients are not able to activate the pain inhibition systems, which in healthy subjects are able to suppress and prevent the development of hypersensitivity.

Generation and experience of body maps. Another concept to explain the most common symptoms of IBS patients is related to the circuits within the brain that generate *autonomic*

nervous system and hormonal responses in association with different emotional states, such as fear and anger. More than 10 years ago, it was demonstrated that IBS patients showed greater subjective anger responses to a particular laboratory stressor, and that this anger response was associated with an exaggerated contractile response of the sigmoid colon. These visceral responses associated with stress and associated emotional responses not only can cause alterations in bowel movements, but they may also play a role in the generation of sensations of abdominal pain and discomfort.

For example, the emotional response to a given situation such as sadness, fear, or joy is strongly influenced by the sensory perception of peripheral changes in the viscera (and the rest of the body) induced by the autonomic nervous system: The rapid heartbeat, sweaty palms, urge to urinate, tightness of the throat, chest pressure and a “knot in the stomach” are all part of a “body map” that our *limbic system* generates in the context of certain emotions: fear, anxiety, anger, shame etc. This body map is generated by the influence of the autonomic nervous system and various hormones (such as the stress hormones cortisol or epinephrine) on virtually every cell in the body. The body map is monitored and encoded by sensory nerves, which feed it back to the brain. It is these visceral sensations associated with certain body maps which may play an important role in the experience of fear, anxiety, and anger, as well as positive emotions, such as well being, being in love, etc.

Pain and emotional memories. Traumatic life events, such as painful childhood experiences, or sexual, verbal, or physical abuse are likely to be associated with particularly strong autonomic responses in the context of painful emotional experiences. It has recently been suggested that while initially the peripheral responses are required for the overall emotional experience, over time a visceral memory develops within the limbic system which allows a recall of the entire sensory experience, even in the absence of the full peripheral response.

Indirect evidence for such a mechanism to exist comes from several independent sources. For example, studies in patients undergoing epilepsy surgery have shown that electrical stimulation of a central part of the limbic system can trigger the experience of dyspepsia, without any associated gastric motor changes. Similarly, a survey conducted in patients with complete spinal cord lesions at the level of the cervical spinal cord demonstrated that the majority of patients continue to experience symptoms thought to arise from the upper and lower GI tract, even though the primary pathways that transmit such sensations in healthy people have been severed.

Other examples are sensations of urinary urgency following surgical removals of the bladder (cystectomies), in patients with chronic inflammation of the bladder (interstitial cystitis), and sensations of fullness in IBS patients following total surgical removals of the colon (colectomies).

From these observations it is quite conceivable that in some patients, some of the visceral sensations, including abdominal pain and discomfort, which make up the symptom complex of functional bowel disorders are recalled from memory banks within the limbic system in a way that is somehow related to emotional experience earlier in life, or linked in a nonspecific way to the general stress response.

Hypervigilance towards bodily sensations. Another mechanism, which is supported by several reports, is related to

the phenomenon of hypervigilance towards visceral sensations. An increased vigilance and associated *central amplification* of different sensory experiences is a normal response towards an anticipated potentially threatening stimulus. In order to optimize the body's response to this stimulus, once it occurs, the brain increases the gain within different sensory channels. A pathological upregulation of this mechanism, occurring even in situations without threat to the individual may play a role in the visceral hypersensitivity of functional bowel disorder patients.

Symptom related fears and anxieties. Patients may become hypervigilant towards certain bodily sensations and experience inappropriate sensations of fear and anxiety towards these sensations. This may apply to the excessive worry of not being close enough to a bathroom, whenever there is the slightest sensation of urgency, or the fear of getting sick when eating in an unfamiliar restaurant. Setting up a vicious cycle, the symptom related fears may activate pain facilitatory mechanisms within the spinal cord, thereby increasing the amount of visceral information the brain receives.

Summary

In summary, it is clear that we still have a long way to go to understand the intricate connections between our digestive system and the brain, and how alterations in this two-way communication result in functional bowel disorder symptoms. While more alterations in *peripheral mechanisms* involved in gut function are being reported, rapid progress has occurred in our understanding of the multiple mechanisms by which the brain can increase the conscious perception of visceral stimuli, which are normally rarely perceived.

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This article is in no way intended to replace the knowledge or diagnosis of your doctor. We advise seeing a physician whenever a health problem arises requiring an expert's care.

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Glossary

Afferent pathways: Nerve structures through which impulses are conducted from a peripheral sensor (e.g., within the gut or intestines) toward another nerve cell.

Autonomic nervous system: The part of the nervous system that controls involuntary actions of internal organs such as the bowel.

Brain-gut axis: The continuous bidirectional flow of information and feedback that takes place between the gastrointestinal tract, and the brain and spinal cord (which together comprise the central nervous system).

Central amplification: Sensitivity generated by changes that occur in the central nervous system (brain and spinal cord) that affect cell transmitters and receptors, thereby increasing the excitability of neurons and resulting in heightened perception of signals from the gastrointestinal tract.

Gut mucosa: The surface lining of the intestines.

Homeostasis: Maintenance of a relatively stable or balanced internal body state despite environmental fluctuations.

Ileum: The lower third of the small intestine, adjoining the colon.

Limbic system: A network of brain regions involved in the regulation of the functional of internal organs, emotions and the maintenance of homeostasis.

Mast cell: A type of immune system cell present in blood and tissue.

Mechanical stimulation: Distension or overstretching.

Motility: Spontaneous movement. A term used to describe the motor activity of smooth muscle in the gastrointestinal (GI) tract.

Noxious stimulus: Stimulus that causes or has the potential to cause pain.

Pathophysiologic mechanisms: Processes involved with a particular function.

Peripheral mechanisms: Changes that occur in body tissues outside the central nervous system that may increase responsiveness of neurons and lead to abnormal pain.

Receptor: A structure in each cell that selectively receives and binds a specific substance, such as a neurotransmitter, which initiates biochemical changes within the cell.

Serotonin (5-HT): A chemical neurotransmitter (a chemical that acts on the nervous system to help transmit messages along the nervous system).

Sensitization: Enhancement of a response by an organism that is produced by delivering a strong, generally noxious, stimulus. A neuron becomes more excitable or responsive; it may respond more intensely to naturally occurring stimuli, either peripherally (in the viscera) or centrally (in the brain).

Somatic: Skin and muscle.

Visceral: Relating to the internal organs, such as the gut/intestines or bladder.

Visceral hypersensitivity: Enhanced perception, or enhanced responsiveness within the gut – even to normal events.