PAIN MECHANISMS
IN
IRRITABLE BOWEL SYNDROME
A CLINICIAN OVERVIEW

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I AM NOT A
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I AM ONLY A CLINICIAN THAT TAKES CARE OF PATIENTS….
Recurrent abdominal pain or discomfort at least 3 days / month in the last 3 months associated with two or more of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

« Dysregulation in the complex interplay between events occurring in the gut lumen (including enteric microbiota), the gut mucosa, the enteric nervous system (ENS), and the central nervous system (CNS), leading to alterations in sensation, motility, mood, and affect, and in some circumstances in immune function. »

Mayer EA. Gut 2000;47:861-869
PATHOPHYSIOLOGY OF IBS

- Genetic susceptibility

- Early environmental exposures that include infection or family modeling of illness. Even early life events.

- Abnormal GI motility (23%-75%)

- Visceral hypersensitivity (50%-70%)

- Infection / inflammation / altered mucosal immune function (post-infectious IBS)
PATHOPHYSIOLOGY OF IBS

- Dysregulation of the brain-gut axis
- Abnormal permeability of the intestinal mucosa
- The importance of food !!!!
- The role of microbiota !!!!

The emerging evidence is that central processes, mediated by psychosocial distress, contribute to pain perception, at least as much or more than visceral signals.
PERCEPTION OF VISCERAL STIMULI

Acute tissue irritation
Inflammation
Injury

Sensitization and neuroplastic modulation of peripheral afferents, spinal circuits, and spinobulbospinal circuits

Transient or prolonged upregulation of afferent sensitivity

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PERCEPTION OF VISCERAL STIMULI

- Various stressors can regulate visceral pain
- Chronic life stressors have been associated with symptom severity in FGID
RELATIONSHIP OF IBS TO OTHER PERSISTENT PAIN CONDITIONS

- Fibromyalgia (20-50% have IBS)
- Temporomandibular joint disorder (64% have IBS)
- Chronic fatigue syndrome (51% have IBS)
- CPP in women (50% have IBS)
- Interstitial cystitis/painful bladder
- Vestibulodynia
- Tension headache

SEXUAL PAIN ??

IC ?

IBS ?

DIFFERENT ORGANS

SAME DISEASE !!!!!
WHAT IS THE LINK??

CENTRAL SENSITIZATION
Fig. 1. Three different underlying mechanisms that can be operative in chronic pain states: peripheral/nociceptive, peripheral neuropathic, and central neuropathic, or “centralized” pain.
Clinical Characteristics of Centralized Pain

- Pain in many body regions
- Higher current and lifetime history of chronic pain in several body regions
- Multiple somatic symptoms (e.g., fatigue, memory difficulties, sleep problems, mood disturbance)
- More sensitive to other sensory stimuli (e.g., bright light, loud noises, odors, other sensations in internal organs)
- 1.5 to 2 times more common in women
- Strong family history of chronic pain
- Pain triggered or exacerbated by stressors
- Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs

Fig. 4. Clinical characteristics of centralized pain.

“Central” Pain-Prone Phenotype

- Female
- Genetics
- Early life trauma
- Family history of chronic pain and mood disturbances
- Personal history of chronic centrally mediated symptoms (multifocal pain with neuropathic descriptors, fatigue, sleep disturbances, psychological distress, memory difficulties)
- Cognitions such as catastrophizing
- Lower mechanical pain threshold and descending analgesic activity

Exposure to “stressors” or acute, peripheral nociceptive input

Psychological and behavioral response to pain or stressor

New or different region of chronic pain

Fig. 2. Female sex, early life trauma, a personal or family history of chronic pain, a personal history of other centrally mediated symptoms (insomnia, fatigue, memory problems, mood disturbances), and cognitions such as catastrophizing can occur in subsets of individuals with any chronic pain state and predict which individuals are more likely to transition from acute to chronic pain.
REPORTED PERIPHERAL ALTERATIONS WITHIN THE BRAIN-GUT AXIS IN FUNCTIONAL GASTRO-INTESTINAL SYNDROMES

- Sensitization of primary afferent pathways
- Gut microbiome
- Epithelial immune activation
- Mast cells
- Epithelial permeability
- Dysmotility
SENSITIZATION OF PRIMARY AFFERENT PATHWAYS

- Acute inflammatory epithelial changes associated with infections are associated with peripheral and central sensitization, resulting in visceral hyperalgesia.

- Neuroplastic remodeling in the epithelium has been described in biopsies of IBS patients.

- Changes in afferent nerve terminals affects responsiveness of visceral stimuli and alter the release of neuropeptides, resulting in neurogenic inflammation.
- Host microbial interactions in vulnerable individuals during the early phase of the disorder may result in permanently altered immune or host cell responses, which could then continue to play a role in the persistence of symptoms, in the absence of the infectious organism

- Post-infectious IBS (10%)
INFECTION AND MICROFLORA

- The importance of small bowel overgrowth?

- Alterations in the colonic microflora in IBS patients (dysbiosis) has been shown

- There is a possible role of microflora in altered GI function, and even in pain perception in IBS patient

INFECTION AND MICROFLORA

- Gut flora can influence brain development in neonatal animals

- Dysbiosis in infancy may permanently prime the gut-brain axis for increased responsiveness in the adult
**EPITHELIAL IMMUNE ACTIVATION**

- Enhanced release of neuropeptides from primary sensory nerve endings (substance P, CGRP, serotonin, histamine, proteases) have been implicated in the sensitization of primary afferent pathways.

- The release of nerve growth factor results in neuroplastic and morphological changes in sensory and motor innervation of the colon.

**EPITHELIAL IMMUNE ACTIVATION**

- Small increase in the number of mucosal immune cells.

- In a subset of patients with IBS.
There is overlap in IBS patients with psychological symptoms and psychiatric syndromes, in particular anxiety, somatization and depression

NEUROBIOLOGY OF IBS VS DEPRESSION
Centrally acting neurotransmitters that are known to play a role in causing pain in centralized pain state (e.g. low norepinephrine, GABA, and serotonin, high glutamate and substance P) also play prominent roles in controlling sleep, mood, alertness...depression

MAST CELLS

- Increased numbers or density of mast cells, alterations in mast cell-nerve interactions and increased release of mast cell products from epithelial biopsies have all been reported in IBS studies
- Not specific to IBS
- Mast cells may be activated by immunoglobulines, neuropeptides and cytokines
They may release histamine, serotonin, CRF and proteases (implicated in pathophysiology of IBS)

Close interaction of mast cells with nonadrenergic, cholinergic, and peptidergic nerve endings...mechanism that could underly recurrent abdominal pain

The clinical relationship between an increased number of mast cells and symptoms of IBS has not been established
What may trigger increased permeability???

- Food
- Microbiota
- Bile acids
- Stress
- Genetic
- Allergic reactions
- Luminal factors (proteases)

There is solid evidence for increased epithelial permeability in some patients, even though a patho-physiological role of this abnormality by itself has not been demonstrated.
EFFICACY OF AMYTRIPTLINE IN IMPROVING INTESTINAL PERMEABILITY AND QoL IN PATIENTS WITH IBS

Amytriptiline is effective in improving QoL and intestinal permeability in patients with IBS

Giovanni Gigante et al.  # Sa1422

DYSMOTILITY AND IBS
- Literature has failed to establish that exaggerated and dysregulated contractile activity of the GI tract plays a role in the pathophysiology of chronic abdominal pain states.

- Tonic contractile activity of the sigmoid is a plausible mechanism in the etiology of chronic pain. It may cause sensitization of visceral afferent pathways, resulting in persistent sigmoid hyperalgesia, enlarged referral areas, and abnormal reflex responses.

REPORTED CENTRAL ALTERATIONS WITHIN THE BRAIN-GUT AXIS IN FUNCTIONAL GASTROINTESTINAL SYNDROMES
Enhanced stress responsiveness
Central pain amplification
Neuroimmune activation in the spinal cord
Enhanced brain responses to visceral distension
Enhance brain responses to expectation of visceral pain
Structural brain changes

ENHANCED STRESS RESPONSIVENESS

Notion of stress-induced hyperalgesia
Acute stessors have been shown to be associated with enhanced visceral perception
Importance of central and peripheral signaling system between CRF and CRF-R1
ENHANCED STRESS RESPONSIVENESS

- The central receptor signaling system involves a brain network (a stress and aroural circuit)

- This central abnormality is likely to contribute to the increased activity of the sympathetic and sacral parasympathetic nervous system in IBS patients

- Environmental factors may play a prominent role in triggering central pain states

- Environmental «stressors»:
  * Early life trauma
  * Physical trauma (especially involving the trunk)
  * Hepatitis C
  * Epstein Barr virus
  * Parvovirus
  * Lyme disease

- Emotional stress
These stessors only triggers the development of central pain states in approximately 5-10% of individuals that are exposed.
CENTRAL PAIN AMPLIFICATION

- Increased activity of endogenous pain facilitation and reduce engagement of endogenous pain inhibitory systems are mechanisms by which the CNS can modulate afferent signals from the viscera.
- Lack of descending pain analgesia is a potential mechanisms that can cause augmented central pain processing

- Reduced diffuse noxious inhibitory control (DNIC) is seen in 10-20% of controls, whereas 60-80% of individuals with conditions such as IBS demonstrate this difficulty

The baseline presence of hyperalgesia or the absence of descending analgesia have been shown to predict the subsequent intensity of an acute painful experience, analgesic requirements following surgery, and the subsequent development of chronic pain
Activation of glia (microglia and astrocytes) is a possible mechanism underlying the chronicity of pain following a psychological stressor or peripheral inflammation.
ENHANCE BRAIN RESPONSES TO VISCERAL DISTENSION IN IBS
Rectal balloon distension in patients and controls shows activation in regions associated with visceral afferent processing, emotional arousal, and attention.

IBS patients show more activations in regions associated with stress and arousal circuits.

IBS patients show activations of brain regions involved in endogenous pain modulation.

Female IBS patients show greater engagement of the emotional arousal circuit during expectation of visceral pain.
■ Changing the emotional context of subjects results in greater pain ratings, along with greater brain responses to a visceral stimulus

ENHANCED BRAIN RESPONSES TO EXPECTATION OF VISCERAL PAIN IN IBS
Increased future-oriented worry and anxiety about abdominal symptoms (anxiety sensitivity) can play a role in IBS symptom severity

Increased attention to threat, and cognitions about pain that overestimate the likelihood of worst possible outcomes (catastrophising), have been implicated as important mediators of symptom severity in IBS

Alterations in prefrontal modulation of stress and arousal circuits, along with altered engagement of endogenous pain modulation circuits, may be the neurobiological substrate underlying anxiety sensitivity and catastrophising
- IBS patients show enhanced responses to an expected, but undelivered, visceral stimulus.

- These responses are greater during expectation of an aversive stimulus

- Patients with hypersensitivity to rectal distension show greater expectation-related activation

**STRUCTURAL BRAIN CHANGES IN IRRITABLE BOWEL SYNDROME**
Patients with IBS have increased activity in the regions of the brain that code for the sensory intensity of stimuli (e.g. primary and secondary somatosensory cortices, posterior insula, and thalamus) and for the affective processing of pain such as the amygdala and anterior insula.

The core regions of the homeostatic afferent (A) and emotional arousal (B) networks.
The main components of the «pain matrix» are the primary (S1) and secondary (S2) somatosensory cortex, the insular cortex (IC), the anterior and mid-cingulate cortex (ACC), the posterior cingulate gyrus (PCC), and the thalamus.

Thus the pain system involves somatosensory, limbic, and associative brain structures.
Decreases in gray matter density in pain matrix regions in women with chronic pain disorders

GM decrease is observed in the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), lateral prefrontal cortex (LPFC), ventromedial prefrontal cortex (VMPFC), and anterior insular cortex (IC).

INCREASED GRAY MATTER DENSITY IN HYPOTHALAMUS

Hypothalamus is part of the EMS system (Emotional motor system)
Also in brain regions involved in stress and arousal circuit
CORTICAL THINNING OF THE aMCC
Reduction of 16.2% vs control

aMCC + Hypothalamus + PAG: Part of the Descending Pain Modulation System

ANTERIOR INSULA CORTEX THICKENS WITH LONG STANDING IBS

Responsible for pain perception, emotional salience, visceral integration
THE HIGHER THE PAIN CATASTROPHYSING SCORE THE THINNER THE DORSOLATERAL PRE-FRONTAL CORTEX (DLPFC) CAUSING POOR ANTINOCICETPTIVE CONTROL

Analogous structural changes have been reported in other persistent pain disorders, including vulvodynia
The biological substrate underlying these gray matter changes are unknown at the moment: they may involve changes in glial number or volume, changes in dendritic spines or synapse or less likely, neural degeneration.

Enhanced glutamate signaling and increased cytokine release have also been reported.

GENETIC FACTORS

Genetic factors are approximately 50% responsible for overall sensitivity. The same genes also make individuals more likely to develop chronic pain over the course of their lifetime:

- COMT
- A number of sodium channel mutation
- GTP cyclohydroxylase, types 2 and 3 adrenergic receptors
- Potassium channel gene (KCNS)
BIDIRECTIONAL BRAIN-VISCERAL INTERACTIONS

Gastrointestinal Tract Pain

Environmental context, stress

Functional and structural brain changes

ACTH

SNS

PSNS

Glucocorticoids

ECCs

Immune cells

Smooth muscle/ICC

Enteric neurons

Microbiota, peptidases

Interoceptive feedback (nervous, spinal)

Functional and structural spinal modulation

Intestinal target transducer cells

Luminal factors
Figure 1 Schematic representation of the pattern of bidirectional brain–gut–microbe interactions

Figure 2 Interface between the enteric microbiota, immune cells in the lamina propria and the ANS

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