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REVIEW

Stress and the gastrointestinal tract

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Abstract Stress, defined as an acute threat to homeostasis, evokes an adaptive or allostatic response and can have both a short- and long-term influence on the function of the gastrointestinal tract. The enteric nervous system is connected bidirectionally to the brain by parasympathetic and sympathetic pathways forming the brain–gut axis. The neural network of the brain, which generates the stress response, is called the central stress circuitry and includes the paraventricular nucleus of the hypothalamus, amygdala and periaqueductal gray. It receives input from the somatic and visceral afferent pathways and also from the visceral motor cortex including the medial prefrontal, anterior cingulate and insular cortex. The output of this central stress circuit is called the emotional motor system and includes automatic efferents, the hypothalamus–pituitary–adrenal axis and pain modulatory systems. Severe or long-term stress can induce long-term alteration in the stress response (plasticity). Corticotropin releasing factor (CRF) is a key mediator of the central stress response. Two CRF receptor subtypes, R1 and R2, have been described. They mediate increased colonic motor activity and slowed gastric emptying, respectively, in response to stress. Specific CRF receptor antagonists injected into the 0 block these visceral manifestations of stress. Circulating glucocorticoids exert an inhibitory effect on the stress response by receptors located in the medial prefrontal cortex and hippocampus. Many other neurotransmitters and neuroimmunomodulators are being evaluated. Stress increases the intestinal permeability to large antigenic molecules. It can lead to mast cell activation, degranulation and colonic mucin depletion. A reversal of small bowel water and electrolyte absorption occurs in response to stress and is mediated cholinergically. Stress also leads to increased susceptibility to colonic inflammation, which can be adaptively transferred among rats by sensitized $CD4^+$ lymphocytes. The association between stress and various gastrointestinal diseases, including functional bowel disorders, inflammatory bowel disease, peptic ulcer disease and gastroesophageal reflux disease, is being actively investigated. Attention to the close relation between the brain and gut has opened many therapeutic avenues for the future.

Key words: corticotropin-releasing factor, emotional motor system, glucocorticoids, mast cells, stress.

INTRODUCTION

> As it is not proper today to cure the eyes without the head nor the head without the body, so neither is it proper to cure the body without the soul, and this is the reason why so many diseases escape Greek physicians who are ignorant of the whole. (Socrates)[1]

Stress is an acute threat to the homeostasis of an organism, be it real (physical) or perceived (psychological). It evokes adaptive responses that serve to defend the stability of the internal environment and to ensure the survival of the organism.[2] However, activation of these adaptive or allostatic systems can become maladaptive because of frequent, chronic or excessive stress and lead to a predisposition to disease.

The idea that mental state can affect the function of the human body is not new. According to Hippocrates[1] (460–377 BC), psychosomatic disorders are abnormal physical reactions to stressful emotions, incidents and situations. Galen (AD 129–199) maintained that fear, anger, grief and other emotions were 'diseases of the soul'.[1] The writings of Rene Descartes[3] in 1637 led to a major 'paradigm shift' in the Western world by propos-

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ing the separation of the thinking mind (res cognitans) from the machine-like body (res extensa). Over the next 300 years, the clinical distinction between 'medical' and psychiatric disorders held ground with disorders of the mind being relegated to asylums. The modulation of gut function by the brain began to be critically explored in the nineteenth and the early twentieth centuries by William Beaumont, Ivan Pavlov, Walter Cannon and later by Stewart Wolf.[4]

Beaumont's classic monograph, published in 1833, described his studies of Alexis St Martin, a man who had sustained a gun shot wound in the abdomen that left him with a permanent gastric fistula. He recorded more than 200 observations over a period of 8 years. He wrote:

> In febrile diathesis, or predisposition from whatever cause . . . fear, anger or whatever disturbs the nervous system . . . the villous coat becomes sometimes red and dry, and at other times pale and moist, and looses it [sic] smooth and healthy appearance.[2]

Pavlov, who examined visceral conditional or anticipatory responses in dogs, was on one occasion preparing to demonstrate the conditioned salivary response of a dog to a representative of the Tsar. Pavlov sounded his bell, but not a drop of saliva emerged from the cannula in the dog's salivary duct because the dog was transfixed by a commotion below. This experience demonstrated that conditioned reflexes could be inhibited during emotionally charged situations.[2]

In 1905, Cade and Latarjet reported similar findings in a human subject who, after incarceration, had a spontaneous gastric fistula of the stomach in an epigastric hernia.[2] Walter Cannon reported an inhibition of gastric emptying and acid secretion in cats who were made to face a dog, and attributed it to the activation of the sympathetic nervous system for 'fight or flight' response.[3]

In the late 1970s, George Engel advanced his biopsychosocial model of disease causation, and provided the framework for the integration of the body, mind and social environment.[5] The past three decades have seen a rapid advancement in our knowledge of how stress affects the gastrointestinal (GI) tract, with the focus now on the concept of the brain–gut axis, central stress circuitry, emotional motor system, modulation of visceral sensitivity, changes in hypothalamic–pituitary–adrenal responses, brain mapping and the role of stress in both organic and functional bowel disorders. These concepts are discussed briefly in this review.

THE ENTERIC NERVOUS SYSTEM: 'BRAIN OF THE GUT'

The enteric nervous system (ENS) contains approximately 100 million neurons, which is close to the same number found in the spinal cord.[5] These include sensory, motor and interneurons. It makes sense to distribute this vast neural network along the digestive tract, close to the effector systems, rather than concentrate it in the central nervous system (CNS). The ENS and CNS are linked bidirectionally by the sympathetic and the parasympathetic pathways forming the brain–gut axis.[6]

CENTRAL STRESS CIRCUITRY

The central stress circuitry refers to a neural network, composed of integrative brain structures, that generates the response to stress. It includes the lateral prefrontal cortex and medial prefrontal structures (ventromedial cortex, perigenual and infragenual cingulate cortex). Output from the medial prefrontal cortex projects to the amygdala and hypothalamus, mainly the paraventricular nucleus (PVN) in the forebrain and periaqueductal gray in the hindbrain. These regions further project to the pontomedullary nuclei and the pituitary gland. The final output of this central stress circuitry is called the emotional motor system and includes the autonomic neurotransmitters norepinephrine and epinephrine, neuroendocrine (hypothalamus–pituitary–adrenal axis [HPA]) and pain modulatory systems. This circuit is under feedback control by serotonergic neurons from the raphe nuclei and noradrenergic neurons from the locus coeruleus.

Corticotropin-releasing factor (CRF) is an important mediator of the central stress response and is located in certain neurons of the PVN, amygdala and locus coeruleus complex.[8] Injection of CRF in the CNS of experimental animals produces behavioral and physiological responses similar to those seen in response to acute psychological stress.[8–11] Circulating glucocorticoids (GC) exert an inhibitory effect on the central stress circuitry by receptors located in the medial prefrontal cortex and hippocampus.[12]

PLASTICITY OF CENTRAL STRESS RESPONSE: 'STRESS MEMORY'

Chronic or excessive stress can alter the central stress circuitry, leading to increased CRF synthesis, an increase in the activity and sensitivity in the central noradrenergic drive, down regulation of central glucocorticoid receptors and reduced inhibitory gamma-aminobutyric acid activity.[8,13] In addition, secondary changes in the spinal cord dorsal horn neurons, gut immune cells and ENS can also occur.

The hippocampus is the area of the brain involved in the encoding and retrieval of memory. Recent magnetic resonance imaging (MRI) studies have demonstrated decreased hippocampal volume in patients with post-traumatic stress disorder as a result of prior sexual abuse.[14] The flashbacks and intrusive memories in abuse victims can be caused by hippocampal alterations. The present study demonstrates that neurotransmitter systems, as well as cerebral structure, can be altered by stress. Severe life stressors frequently antedate the onset of functional GI disorders. Life stressors can also exacerbate symptoms and influence health-care behavior and outcome. One useful measure of stressful life events is an interview-based instrument called the Life Events and Difficulties Schedule. At least five

studies on GI disorders have used this tool to show a strong association between stress and GI disorders.[15]

STRESS AND GASTROESOPHAGEAL REFLUX DISEASE

There is a weak relationship between the symptoms of heartburn and the demonstrated degree of acid reflux. Up to 64% of the patients with stress and gastroesophageal reflux disease (GERD) reported aggravation of their symptoms by stress, and stress reduction measures often resulted in a subjective improvement.[16,17] In a study carried out by Bradley *et al.*, patients with GERD were divided into two groups: those with a tendency to report GI symptoms during psychological distress (high GI susceptibility) and those who did not have a tendency to report GI symptoms during psychological distress (low GI susceptibility). The former group reported more heartburn associated with experimental stressful tasks despite an equal measured acid exposure in both of the groups.[18] It is not known how stress can aggravate the symptomatic expression of GERD, particularly heartburn, but a change in the diaphragmatic pinch function as a result of altered breathing pattern,[8] an increase in esophageal chemosensitivity,[8,19] and a slowing of gastric emptying because of stress might contribute. Mittal *et al.* in a study of 20 healthy subjects found that short-term psychological stress inhibited the lower esophageal sphincter and increased tonic and phasic crural diaphragmatic contractions.[20] Intra-esophageal pH measurements in both normal subjects and patients with GERD have failed to demonstrate an increase in acid reflux during psychologically induced stress.[16,18] However, compared with other mechanisms, the role of stress is relatively minor and anxiolytic drugs are not useful in the treatment of reflux disease. It is more likely that stress leads to an abnormal perception of the acid refluxate rather than an increase in its volume. Hence, it might play a role in a subgroup of patients with nonerosive disease.

STRESS AND FUNCTIONAL DYSPEPSIA

No unique personality profile has been found in patients with functional dyspepsia, although anxiety, neuroticism and depression are more prevalent compared with healthy subjects. Contrary to common belief, most environmental factors such as smoking, alcohol, coffee or use of non-steroidal anti-inflammatory drugs (NSAIDs) are not important contributors.[21]

In the DIGEST study, which investigated the prevalence of upper GI symptoms over 3 months among 5581 healthy subjects from the general population, the major risk factors were psychological stressors, particularly recent life events.[22] Hui *et al.* found that the number of positive and negative life events were similar in both subjects with dyspepsia and control subjects, but the former had a higher negative perception of major life events and daily stresses.[23]

Subjects with functional dyspepsia have a lower vagal tone and a higher sympathetic tone than healthy control subjects.[24,25] Impaired proximal gastric accommodation response to meals, causing postprandial distress, has been described in these patients, possibly related to stress-induced chronic vagal suppression.[24] Other investigators have found evidence of altered gastric perception in subjects with dyspepsia, leading to upper abdominal discomfort on isobaric gastric distention compared with control subjects.[27]

In healthy subjects, fear, anger, painful stimuli, preoperative anxiety, or intense exercise results in a slowing of gastric emptying[9,10] and an increase in intestinal contractile activity. These effects might have evolved as a response to prevent digestion during a stressful period when energy is better spent on defense. CRF is the likely mediator of these central responses, acting at specific type 2 receptors (CRF-R2) in the PVN and dorsal vagal nucleus, leading to a decrease in the gastric vagal outflow. Injection of CRF into the cerebrospinal fluid inhibits gastric emptying in animals and this effect can be blocked by astressin, which is a specific CRF-R2 antagonist.[9,28]

STRESS AND PEPTIC ULCER DISEASE

The first description of an association between stress and peptic ulcer disease was in men with supervisory jobs, who had a higher ulcer prevalence than executives or craftsmen.[29] Cobb and Rose found that air traffic controllers were almost twice as likely as civilian copilots to have ulcers, particularly those with higher stress levels in their workplace.[30] Duodenal ulcers have been found more frequently in prisoners of war during follow up than in non-captured veterans of the Vietnam War.[31] In a study of 30 children with peptic ulcers who were compared with 30 matched controls, the ulcer group was found to have more frequent emotional disturbances and traumatic life events preceding the onset of illness.[32] Feldman *et al.* observed that patients with peptic ulcer disease perceived their life events more negatively than others.[33] Alp *et al.* and Ellard *et al.* found that chronic stressors and acute events of high personal threat were significantly associated with the onset and relapse of duodenal ulcers.[34,35]

Societal stress provides a unique, indirect way of determining the relationship between stress and ulcer disease. Societal stress derives from an event that affects the whole society or a large part thereof, and if stress plays a role then such an event should increase the ulcer rates in the affected population. Incidence of ulcer disease has been found to increase during periods of mass population movements, during early urbanization of society and during military training. There were reports of an increased number of perforated peptic ulcers during the London air raids of World War II.[36] Hui *et al.* studied the relationship between negative social events and stress with the incidence of perforated peptic ulcers in Hong Kong residents over a period of 24 years and found a positive correlation with societal stress.[23] More recently, an increased incidence of bleeding ulcers was

observed after the devastating Hanshin-Awaji earthquake in the southern part of Hyogo, Japan, which killed more than 6000 people.[37] A comparison was made between a group of 10 831 patients who underwent an endoscopy within 2 months of the earthquake and 16 100 patients who did so at the same 61 hospitals during the same period the previous year. In the most devastated area, despite a significant decline in the total number of endoscopies performed, there was an increase in patients with gastric ulcers (GU). In particular, a marked increase in bleeding GU was seen. Hence, the earthquake-induced life event stress not only triggered but exacerbated GU.[37]

Stress as an etiologic factor might help explain the rising trend of ulcer disease and its complications seen at the turn of the nineteenth century, seasonal variation of ulcers and the large proportion of patients with non-NSAID, non-Helicobacter pylori-related ulcers.

STRESS AND INFLAMMATORY BOWEL DISEASE

Many clinicians have observed that emotional conflicts appear to provoke exacerbation of colitis. Altered mother–child relationships have been emphasized, with the mother representing a dominant figure.[38,39] Recent work has focused on the cotton-topped tamarin, a Colombian monkey that develops ulcerative colitis (UC) and colonic carcinoma in captivity. These animals live in fixed social units in the jungle, with one breeding female, several non-breeding females and one to three reproductively active males who care for the offspring. Capturing these animals and caging them in male–female pairs produces severe social disruption leading to the development of colitis.[40]

The first reports of UC developing in Bedouin Arabs occurred in those who had moved from their nomadic life into government housing. Salem and Shubair suggest that the stress of modern living or the change of lifestyle influenced the development of the colitis.[41] In recent years, efforts have been made to confirm these observations through more rigorous study designs. North *et al.* studied the effect of major life events and mood on bowel symptoms and pain in 32 patients with inflammatory bowel disease (IBD) and found no association at 1 or 2 months.[42] In a more rigorous study using a larger sample of 124 IBD patients, Duffy *et al.* evaluated monthly major life events with symptoms of pain, bowel dysfunction and bleeding. At baseline, patients with a history of major stressful life events had a greater risk of active disease and there was a persisting twofold increased risk at 6 months follow up.[43] Another study of 10 patients with Crohn disease found a significant association between acute daily stressors and bowel symptoms, even after controlling for major life events.[44] Levenstein *et al.* enrolled 62 patients with UC in remission and followed them for up to 45 months for perceived stress, depressive symptoms and stressful life events. Exacerbation status was monitored for up to 68 months. It was found that short-term stress did not trigger exacerbation in UC, but long-term perceived stress tripled the risk of exacerbation during the following 8 months.[45]

Hence, it may be likely that major stressors are important in influencing disease activity in IBD. These stressors are not unique and include illness, death in the family, divorce or separation, interpersonal conflict and major loss. The role of daily minor stressors is, however, controversial.

STRESS AND THE INTESTINAL BARRIER FUNCTION

The continuous epithelial cell layer in the small and large bowel, interconnected by tight junctions, restricts both transcellular and paracellular permeation of molecules. This is known as the intestinal barrier function.

Saunders *et al.* reported increased jejunal permeability to mannitol and 51Cr-ethylenediamine tetraacetic acid in stressed rats, despite a normal light microscopic structure of the mucosa.[46] Kiliaan *et al.* demonstrated the transepithelial flux of horseradish peroxidase, which is a large antigenic molecule, in rats after stressful stimuli, showing that stress can significantly increase intestinal permeability.[47]

Barclay and Turnberg measured the effect of psychological stress on jejunal electrolyte and water transport in healthy subjects using a triple-lumen perfusion technique. They found that stress caused a reduction in water absorption and reversal of net Na^+ and Cl^- absorption. This effect was abolished by atropine, showing that cholinergic parasympathetic pathways are important in mediating these stress-induced intestinal permeability changes.[48] Santos *et al.* found that the cold-pressor test in healthy volunteers and patients with food allergies increased jejunal water secretion along with luminal release of mast cell mediators, tryptase and histamine.[49] These stress-induced changes are caused by CRF secreted locally by immune cells, postganglionic sympathetic neurons and colonic enterochromaffin cells.[50] The effects of CRF are mediated by peripherally located receptors (possibly on enteric neurons) and can be blocked by the CRF antagonist α-helical CRF.[50,51]

In contrast to glucocorticoids having no role in CRF-induced permeability changes in the above studies, Meddings and Swain found that a stress-induced increase in epithelial permeability disappeared after adrenalectomy or glucocorticoid receptor blockade in rats. Dexamethasone treatment increases GI permeability, mimicking the effects of stress.[52]

The role of mast cells was studied by Santos *et al.*[53] who found a significant increase in colonic permeability and mucosal mast cell numbers after chronic stress in rats. Mast cell degranulation in the gut occurs in response to psychological stress and can even result from Pavlovian conditioning. Enteric mast cells are innervated by projections from the CNS and can be activated by neurons releasing CRFand/or acetylcholine.[51,53,54] Mast cell degranulation products initiate polymorphonuclear cell influx, increased secretion and propulsive motility leading to pain and diarrhea. Increased mast cell numbers are found in the mucosa and muscularis externa of the colon in patients with irri-

table bowel syndrome (IBS). A brain–mast cell connection is the most likely mechanism of symptom exacerbation by psychogenic stress in patients with IBS.

MODULATION OF INTESTINAL INFLAMMATION BY STRESS

The rat model of colitis induced by intrarectal administration of trinitrobenzene sulfonic acid (TNBS) or dinitrobenzenesulfonic acid (DNBS) has been extensively used to study the relation between stress and colonic inflammation.

Colonic inflammatory response to TNBS and DNBS is enhanced by preceding stress and, conversely, previous colonic inflammation increases colonic susceptibility to stress.[55,56] Qiu *et al*. showed that in mice who had recovered from DNBS-induced colitis, stress, together with a subthreshold dose of DNBS, could reactivate the colitis, whereas the latter alone was ineffective.[57] Furthermore, this susceptibility to stress-induced reactivation of colitis could be adoptively transferred to other rats by $CD4^+$ lymphocytes. It is likely that stress can reactivate quiescent colitis by increasing the colonic permeability to luminal antigens, which then activate previously sensitized $CD4^+$ cells. Hence, stress not only increases intestinal permeability, it can also modulate intestinal inflammation by the interrelated cholinergic pathways, CRF release and mast cell activation.

STRESS AND IRRITABLE BOWEL SYNDROME

Major stressful life events are more common in patients with IBS compared with healthy subjects and patients with UC. Several studies have shown that up to 66% of patients with IBS (and more with chronic functional abdominal pain) have a current Axis I psychiatric diagnosis, and this is much higher than organic medical disease controls or normals.[4,58,59] Rates of childhood sexual abuse and any lifetime sexual victimization are reported in 32–44% of patients with IBS in the developed world.[58,59] Contradictory evidence was reported by Talley *et al*. in a study of 997 patients and Kiloski *et al*. who reviewed 44 publications on the subject. They found a similar frequency of abuse history in patients with functional bowel disease and patients with organic disease.[60,61] However, patients with a history of abuse are more likely to report their symptoms and seek medical help. For the patient, a history of abuse translates into 65% greater pain scores, threefold more days spent in bed, significantly greater psychological distress and poorer daily function, and 30% more physician visits and lifetime surgeries.[62] In referral centers, there is a higher frequency of abuse history seen among patients with persistent or refractory symptoms and a lower frequency among patients seen in primary care settings.[4]

An increased prevalence of functional GI complaints is also found in prisoners of war and former hostages. Recently, military personnel who returned from the Persian Gulf War with GI complaints were found to exhibit similar visceral hyperalgesia to patients with IBS.[63]

Post-infectious IBS can develop after enteric infection and inflammation. IBS-like symptoms are reported by 7–30% of patients who have recovered from bacterial gastroenteritis 3–12 months previously. The presence of a stressful life-event at the time of infection (in addition to being a female and having a longer diarrheal episode) has been found to predict a higher risk of developing IBS after an otherwise uncomplicated episode of infectious diarrhea.

Gut sensitivity seems to be increased by stress and decreased by relaxation. In patients with functional GI symptoms, psychosocial stress seems to have an even greater physiologic response and worsened symptoms.[64,65] Acute stress induces differential motor effects in the upper and lower GI tract. Unlike delayed gastric emptying, colonic motility is stimulated by various stressors.[65–68] This stress-related increase in colonic motility is mediated by CRF acting at the PVN and locus coeruleus and can be blocked by CRF antagonists and reproduced by CRF administered intraventricularly.[69,70]

Recently, a model of IBS was proposed by Valentino *et al*. based on up-regulation of CRF containing neurons and CRF receptor subtype 1 (CRF-R1) in Barrington's nucleus (part of the locus coeruleus complex). Projections from this nucleus innervate the sacral parasympathetic preganglionic neurons that increase distal colonic motility in response to food and stress. The ascending aminergic projections from this nucleus to the forebrain could mediate the visceral hyperalgesia and hypervigilance seen in patients with IBS.[71] After stressful events, colonic sensitization can occur by the up-regulation of CRF-R1 receptors in the PVN and locus coeruleus. CRF-R1 antagonists could have potential therapeutic value in the treatment of patients with IBS in the future.[64]

Alterations in HPA have been reported in patients with IBS, although the results have not been consistent. Higher morning urine and salivary cortisol levels have been reported in subjects with IBS compared with control subjects, thus indicating chronic stress.[72,73] In contrast, decreased 24-h cortisol and blunted cortisol responses to rectosigmoid distension were observed by Munakata *et al*. in patients with diarrhea-predominant IBS.[74]

STRESS AND FUNCTIONAL BRAIN IMAGING

More recently, powerful tools to explore brain function, namely positron emission tomography (PET) and functional (f)-MRI, have become available. PET scanning measures positrons emitted during the decay of 2-(^{18}F) fluoro-2-deoxy-D-glucose, which is taken up by cells competitively with 2-deoxyglucose, reflecting regional cerebral activity. f-MRI localizes regions of activity in the brain following task activation, which alters the balance of oxyhaemoglobin and deoxyhaemoglobin within specific regions of the activated cortex. In response to visceral painful stimuli, control subjects show activation

of the anterior cingulate gyrus (ACG), whereas patients with IBS do not. The ACG is an area of dense opiate binding and is likely to attenuate the incoming sensory input. Failure to activate the ACG in patients with IBS in response to actual and anticipated painful stimuli represents a failure of a central pain modulation system. Prefrontal cortex activation is seen preferentially in patients with IBS. This area is associated with hypervigilance, emotional vocalization and recall of negatively charged memories.[4,75] Using f-MRI, Mertz *et al*. found increased ACG activation,[76] and Verne *et al*. reported increased somatosensory processing at all cortical levels, not just limbic and frontal cortical areas.[77] These interesting new findings raise a number of questions: (i) Are patients with IBS less protected from ascending visceral stimuli?; (ii) Are IBS and other functional GI disorders actually a form of cerebral dysfunction?; and (iii) Does the lack of consistent functional and structural alterations in the GI tract simply reflect the fact that we have been looking in the wrong place all the time?

MIND-DIRECTED THERAPIES FOR THE GUT

Non-pharmacologic therapy to allay stress can play an important role in the management of some patients with functional GI disorders and, perhaps, a subgroup with 'organic diseases', particularly when the symptoms seem out of proportion to the physiologic aberrations evident. Research suggests that no particular form of treatment is superior. The available options are cognitive behavioral therapy (CBT), dynamic psychotherapy, hypnotherapy and relaxation therapy.[78]

Cognitive behavioral therapy involves helping patients recognize that stress and their belief in their illness are causing or aggravating their symptoms, and learning how to control their thinking and perception of the situation.

Dynamic psychotherapy is based on the idea that a significant proportion of the distress experienced by the patient is a reflection of their problems in interpersonal relationships. Guthrie *et al*. studied the efficacy of psychotherapy for patients with severe refractory IBS who had failed a wide spectrum of medical interventions. One hundred and one patients were randomized to 12 h of interpersonal psychotherapy or supportive listening. The evaluating gastroenterologist was blinded to each patient's treatment. There was a significant improvement in the interpersonal psychotherapy group, which persisted over a 1-year follow up.[79]

The rationale for using hypnotherapy is that while the patient is in a highly suggestive state, the hypnotherapist can use relaxation techniques and guided imagery to induce relaxation of the GI smooth muscles. Patients are also instructed to practise at home with instructions on autohypnosis. There is some evidence that hypnosis can reduce colonic contractile activity and normalize thresholds for pain during rectal balloon distention.[80,81]

Relaxation therapy involves a variety of techniques to teach patients how to counteract the physiologic effects of stress and anxiety. Relaxation therapy is often combined with CBT.

CONCLUSION

The pieces of the jigsaw puzzle linking the mind to the gut are being put together at a rapid pace in research centers worldwide. As seemingly unrelated observations are linked together, a clear picture is emerging of the profound influence that our thoughts and emotions have on our GI function. In the future, therapies that target the ENS and CNS will assume greater roles and the chasm between 'functional' and 'organic' disorders will disappear.

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