Stress and the Gut

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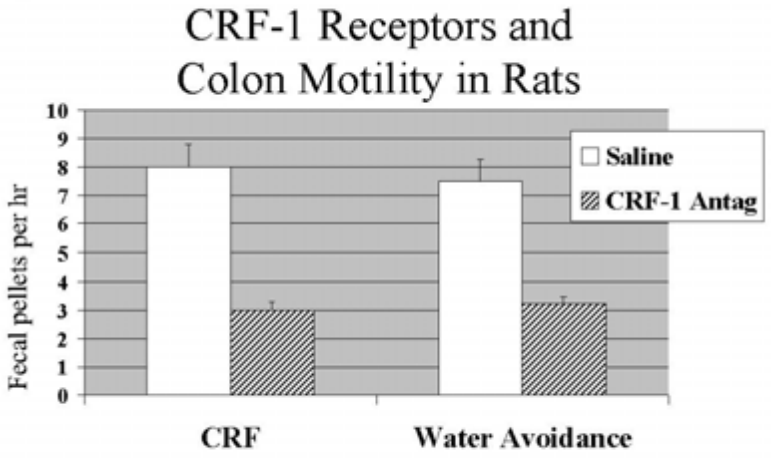
Stress is a ubiquitous condition that affects all people. Stress can be mental or physical, although in the context of this article the focus will be mental stress. Mental stress involves challenge, threat or worry about future adverse events. Such stress activates the brain's stress response systems, which in turn affect the body. Many of the body's major systems are altered by stress (cardiovascular, muscular, urinary, gastrointestinal, sweat glands, etc) often with adverse consequences.

Gastrointestinal function is particularly influenced by stress. Common gastrointestinal symptoms due to stress are heartburn, indigestion, nausea and vomiting, diarrhea, constipation and associated lower abdominal pain. These symptoms and the alterations in intestinal function that cause them are becoming understood.

Gastrointestinal Stress Reactions in Animals and CRF

In animals such as rats, stress can be induced in experimental situations. When rats are wrap restrained, or placed on a small platform surrounded by water they become stressed. During these situations, alterations in motility of the gut occur. The upper gut, including the stomach and small intestine, exhibits markedly reduced transit. This may be a defense mechanism to promote vomiting and reduce oral intake. Conversely the large bowel motility increases with increased stool output and transit speed. This may be a defense mechanism to eliminate toxins. We have learned that a hormone called corticotropin releasing factor (CRF) influences these changes. CRF is released from nerve cells in the hypothalamus of the brain. These nerve cells release the hormone via long processes into other parts of the brain such as the locus ceruleus, where arousal and autonomic nervous system changes are mediated. In rats, injection of CRF blockers into the brain fluid diminishes the stress induced motility changes in the gut. CRF directly injected into the brain fluid mimics the stress

Figure 1



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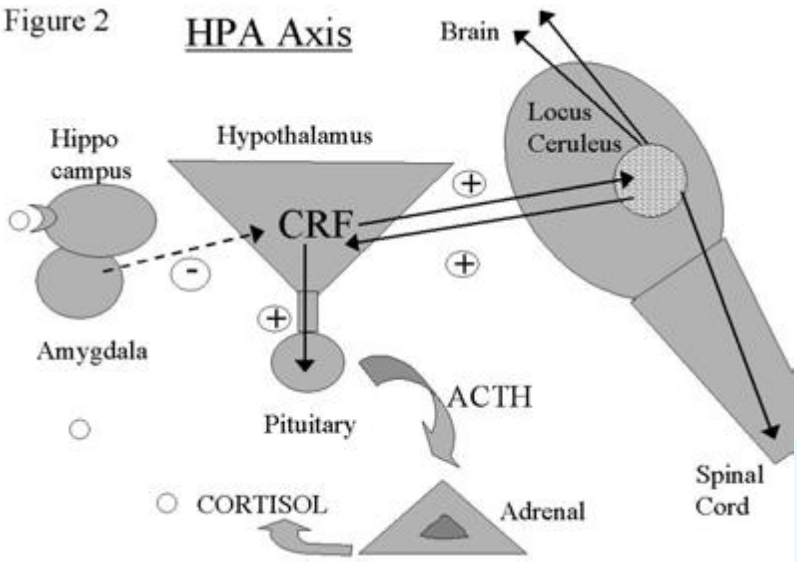
response closely (**Figure 1**). CRF also stimulates the gut directly via CRF-1 and CRF-2 receptors. CRF-1 receptors stimulate colonic contractions, while CRF-2 receptors reduce upper gut activity. Antagonists to CRF-1 receptors are currently being tested for treatment of depression, and may become available for testing in functional bowel disorders as well.

Brain Areas Involved in Stress Reaction

Two of the primary brain regions involved in stress reactivity are the hypothalamus and the locus ceruleus. Activation of the hypothalamus by stress is likely to be mediated in part by the limbic brain (particularly the amygdala and hippocampus) and partly by the locus ceruleus in the brainstem. The locus ceruleus and the hypothalamus actually stimulate each other, creating the potential for a vicious cycle, where a stress reaction in one region stimulates the other, which in turn stimulates the first to react even more. The limbic system is a group of connected and related brain regions that mediate emotions and flight or fight attitudes. The limbic or "emotional brain" is more primitive by evolutionary standards, and is not necessarily under control by the higher intellectual cortex. This system receives sensory and higher cortical inputs, calls upon memories and determines the threat level imposed by a stimulus. The amygdala for instance is a limbic structure in the base of the brain that is important in anger and rage. In cats, electrical stimulation of the amygdala causes hissing, back arching and the hair to stand on end, typical of anger and defense postures in cats. In animals that have damage to the amygdala a placid state results in which anger cannot be induced. Inputs to the amygdala are thought to originate from the hippocampus, the cingulate cortex and other parts of the limbic system. The locus ceruleus is located in the pontine portion of the brainstem. The locus ceruleus is the source of most of the stimulant neurotransmitter norepinephrine in the nervous system. Cells here project to other brain areas, releasing norepinephrine to activate other systems and increase arousal and alertness. Release of norepinephrine increases heart rate, blood pressure and primes the muscles and nervous system for fight or flight. This reaction is not helpful in routine stress of daily activities. If the stress reaction is excessive or the perceived threat too frequent, tachycardia (racing heart), hypertension, muscle tension, bowel spasms, and dyspepsia can result.

Hypothalamic-Pituitary-Adrenal Axis

CRF release is the first step in activation of the hypothalamic-pituitary-adrenal axis (HPA axis) involved in stress response. This is the major endocrine (hormonal) response system to stress. Release of CRF by the hypothalamus stimulates the pituitary gland immediately underneath it. The pituitary gland responds to CRF by release of adreno-corticotropic hormone (ACTH) to stimulate adrenal gland secretion of the stress hormone cortisol. Cortisol promotes fluid and salt retention and impairs inflammation, functions helpful in the short term during flight or fight situations or injury. Again, if the HPA system is activated too frequently adverse health outcomes such as hypertension (from salt retention) and impaired immune function (from excess cortisol)



may result. The CRF system and the norepinephrine systems work together to respond to stress with resultant changes in bodily functions that prepare for flight or fight. (**Figure 2**)

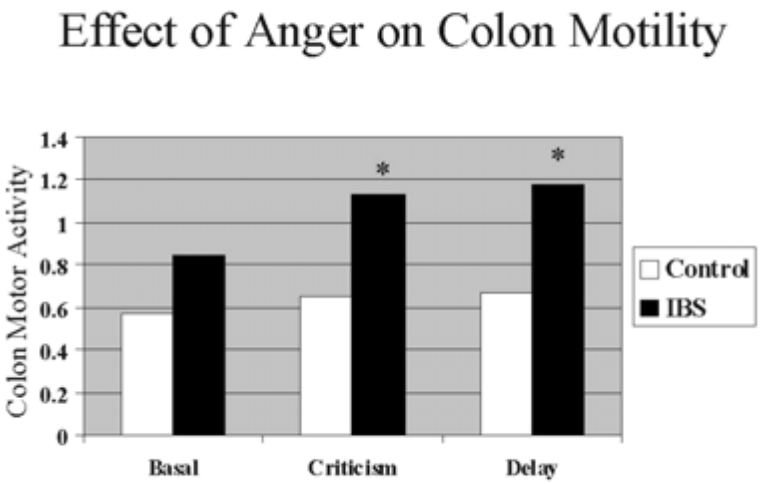
Gastrointestinal Stress Response in Humans

Humans respond to stress in similar ways to animals. A variety of human studies indicate stress promotes decreased gastric emptying and accelerated colonic transit in normal volunteers. A pioneering study by Almy measured colonic contractions during flexible sigmoidoscopy. The volunteers were told that a cancer was found, leading to abrupt increases in colonic contractions, which resolved after the hoax was explained. Other stressors such as ball-sorting, driving in city traffic and mentally challenging listening tasks similarly increase colonic contractions and reduce gastric motility. Recent data also indicates that intestinal sensitivity increases with stress compared to relaxation. This effect may lower the threshold for sensing intestinal events. In gastroesophageal reflux for example, psychological stressors can increase heartburn symptoms. Analysis of the esophageal pH (measurement of acid) indicates that the amount of reflux doesn't increase during stress, but the probability of feeling a reflux as heartburn does increase. In one small study of normal controls, intravenous infusion of CRF induced greater rectal sensitivity to balloon distension. It may be that the sensitizing effects of stress on the gut are partly mediated by the stress hormone CRF.

Irritable Bowel Syndrome and Functional Dyspepsia

Two of the major causes of uncomfortable or painful intestinal symptoms are irritable bowel syndrome (IBS) and functional dyspepsia. IBS occurs in approximately 12% of people worldwide. Dyspepsia (indigestion/upper abdominal discomfort) is also very common. The majority of dyspepsia is functional, that is not associated with ulcers, gallstones, reflux esophagitis or cancer. In both of these common disorders, motility and sensory changes are present which mimic the stress state. Both disorders demonstrate hypersensitivity of the gut (either stomach or intestine). Both disorders demonstrate alterations in motor function of the gut typical of stress and CRFinduced changes. In functional dyspepsia the stomach generally has mildly reduced emptying and reduced accommodation of meals. In IBS, colonic contractions are generally increased.

Figure 3



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Furthermore, IBS subjects appear to have increased stress responsiveness in the gut. In one study, IBS patients and healthy controls both underwent ambulatory motility recordings in the colon. Both groups were confronted on return to the lab ("you're late", "you came to the wrong window", "now the study may need to be repeated"). Colonic motility jumped up in the IBS patients during confrontation, but not in healthy volunteer (**Figure 3**). IBS patients may also have greater sensitivity to the stress hormone CRF. Infusion of CRF intravenously to IBS patients and controls in one study caused significantly greater colonic motor responses in IBS patients. Another study indicates that listening stress increases rectal sensitivity to balloon distension in IBS patients but not controls. It appears both intestinal motility and sensory responses to stress are heightened in IBS patients. These alterations are likely to cause symptoms such as diarrhea and intestinal cramps due to increased contractions of the gut and increased sensitivity of the gut during stress.

The chemical mediators of these changes are not yet established, although alterations in CRF release or CRF receptors may be implicated to some extent in functional bowel diseases. IBS (and other functional bowel symptoms) are generally worsened by stress. In fact recent research has indicated that IBS symptoms tend to resolve in those without major psychosocial stressors. Conversely, symptoms are persistent in subjects with ongoing "threatening" psychosocial stressors. The onset of IBS and functional dyspepsia often begin with bereavement, abuse or other major negative life events. Emotional distress is very common in IBS patients, particularly those who seek medical treatment for the condition. **Anxiety and depression are significantly increased in IBS patient populations, present in nearly 40%.** Psychosocial distress appears much less common in IBS sufferers who do not seek medical care. Population based surveys, however, do still suggest tendencies toward emotional reactivity in people with IBS. Accordingly, stress modification, psychotherapy and hypnosis appear helpful for IBS and functional dyspeptic symptoms. Tricyclic antidepressants also appear effective for IBS and other functional bowel symptoms, even in low doses. Recent evidence indicates the drugs may work by reducing the brain's response to intestinal pain during stress. Sedatives such as the

benzodiazepine Librium can reduce the effect of stress on the gut. During ball sorting challenge, Librium blunts the colonic motor response to mental stress in IBS patients. This effect may explain the benefits of combined sedative-anti-spasmodic drugs for IBS.

Summary

There is much yet to learn about the effects of stress on the gastrointestinal tract. The exact neural and hormonal pathways that mediate excess gut sensitivity and altered contractility during stress are not defined. Where these pathways are excessive or dysfunctional in IBS, functional dyspepsia and other GI disorders is unclear. Specific neurotransmitters are likely to underlie the gastrointestinal stress reaction, and may be amenable to pharmacologic blockade. Psychological therapies are likely to blunt the stress response as well. New tools such as brain imaging to study brain responses to stressors and drugs, and molecular biology to study function of neurotransmitters and their receptors are likely to lead to better understanding of the stress response and its role in disease states. Based on this knowledge, advances in pharmacology may lead to better drug therapies to address these important health problems.

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