Stress and the Gastrointestinal Tract
V. Stress and irritable bowel syndrome

EMERAN A. MAYER, BRUCE D. NALIBOFF, LIN CHANG, AND SANTOSH V. COUTINHO
UCLA/CURE Neuroenteric Disease Program, Departments of Medicine, Physiology, and
Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, California 90024

A variety of stressor types play a role in the development of irritable bowel syndrome (IBS). Stress, defined as an acute threat to the homeostasis of an organism, real (physical) or perceived (psychological) and posed by events in the outside world or from within, evokes adaptive responses that serve to defend the stability of the internal environment and to ensure the survival of the organism. Numerous reports in the literature provide evidence for a prominent role of stress in the pathophysiology (38) and clinical presentation of IBS symptoms (Refs. 23, 24, 27 and detailed references therein). A model that summarizes the possible role of different types of stressors in the development and modulation of IBS symptoms is shown in Fig. 1. According to this model, different types of stressors play a role in 1) permanent enhancement of stress responsiveness (pathological stress), 2) transient symptom exacerbation, and 3) symptom perpetuation (symptom-generated stress). Early life stress and trauma, in the form of abuse, neglect, or loss of the primary caregiver, play a major role in the vulnerability of individuals to develop functional gastrointestinal (GI) disorders later in life. Acute, life-threatening stress episodes in adult life (rape, posttraumatic stress syndrome) are also important risk factors in the development of functional GI disorders. In the genetically predisposed individual, both early life stress and severe life-threatening stress (referred in this article as “pathological stressors”) can result in permanent, irreversible enhancement of the responsiveness of central stress circuits and therefore vulnerability to development of functional (as well as affective) disorders later in life. Other types of stressors occurring throughout the life of an individual, which may result only in transient changes in stress responsiveness, clearly play a role in symptom exacerbation. For example, psychosocial stressors in the form of sustained, threatening life events have been associated with onset and symptom exacerbation in IBS. “Physical” or interoceptive stressors of the digestive system, such as enteric infections, trauma, and surgery, may play a similar role in symptom exacerbation in the predisposed individual. Finally, in the affected patient, fear conditioning and interoceptive conditioning are likely to play important roles in triggering stress responses to situations and contexts that by themselves are not threatening or stressful (14). For a large number of IBS patients, the positive-feedback loop of conditioned fear responses to interoceptive stimuli or contextually conditioned stimuli of symptom-generated stressors may play a primary role in symptom chronicity.

How are stressors translated into integrative physiological responses relevant for GI function?

The traditional concept of stress has focused on the subjective conscious feelings, thoughts, beliefs, and memories reported by some individuals in association with stressful life events. However, the major breakthroughs in this area have occurred through an under-
standing of the biological mechanisms that are responsible for the detrimental effects of certain stressful life events on health (25). The organism’s response to stress is generated by a network comprised of integrative brain structures, in particular, subregions of the hypothalamus (paraventricular nucleus, PVN), amygdala, and periaqueductal gray. These structures receive input from visceral and somatic afferents and from cortical structures, in particular, the ventral subdivision of the anterior cingulate and the medial prefrontal (ventromedial and orbitofrontal) cortex (3, 42). This integrative network provides outputs to the pituitary and to pontomedullary nuclei, which in turn mediate the neuroendocrine and autonomic output to the body, respectively. This central stress circuitry is under feedback control via ascending monoaminergic projections from these brain stem nuclei, in particular, serotonergic (raphe nuclei) and noradrenergic (NA) (including locus ceruleus) nuclei, and via circulating glucocorticoids, which exert an inhibitory control via central glucocorticoid receptors located in the medial prefrontal cortex and hippocampus (37). The parallel outputs of this central circuitry (“emotional motor system,” EMS), which is activated in response to various stressors, include responses of the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, endogenous pain modulatory systems, and ascending aminergic pathways. These pathways are summarized in Fig. 2.

One important chemical mediator of the central stress response is corticotropin-releasing factor (CRF) (and probably related currently unknown molecules) located in certain effector neurons of the PVN, the amygdala, and the locus ceruleus complex (41). CRF secretion by PVN neurons is under positive-feedback regulation by central NA pathways (including those originating from locus ceruleus), thereby forming a bidirectional positive-feedback loop between the CRF and NA systems. Central injection of CRF can reproduce behavioral and physiological responses similar to those seen in response to acute psychological stress (30, 39), and inhibition of CRF-mediated responses by antagonists (38, 39) or in knockout animals results in a decrease in the animals’ response to stress (32, 40).

**Fig. 1.** Role of stress in development and modulation of irritable bowel syndrome (IBS) symptoms. Different types of stressors may play a role in the permanent biasing of stress responsiveness, in transient activation of the stress response, and in the persistence of symptoms.

**Fig. 2.** Inputs and outputs of the emotional motor system (EMS). Output pathways of the EMS are activated by psychosocial (exteroceptive) and physical (interoceptive) stressors. Major outputs to the periphery are autonomic, pain modulatory, and neuroendocrine responses. An important output to the forebrain occurs in terms of attentional and emotional modulation. Feedback from the gut to the EMS occurs in form of neuroendocrine (epinephrine, cortisol) as well as visceral afferent mechanisms.
ENHANCED RESPONSIVENESS OF CENTRAL STRESS CIRCUITS

The responsiveness of the EMS is likely to be under partial genetic control, and it shows considerable plasticity in response to early life events (22) and to certain types of pathological stress (15). For example, studies in animals and humans clearly demonstrated that certain types of pathological stress can alter the responsiveness of feedback systems by downregulation of pre- and/or postsynaptic receptors [adrenergic, serotonergic, glucocorticoid receptors (GC)] and, in the most severe forms, by structural changes in certain brain regions (reviewed in Ref. 23). Thus pathological stress can not only activate but also fundamentally change the responsiveness and output of the central stress circuits. These alterations could affect the individual output pathways of the EMS differentially and in different directions, for example, an increase or decrease in target-specific sympathetic and vagal outputs, up- or downregulation of the HPA axis, and up- or downregulation of pain perception. Some of the best-characterized alterations in this central adaptation to pathological stress are an increase in CRF synthesis and secretion (30), an increase in the activity and sensitivity of central NA systems (22, 33), and downregulation of GC (31) suggestive of an enhanced HPA response to stress. In contrast, an upregulation of GC has been found in animals exposed to “early handling” stress and in patients with posttraumatic stress disorder (PTSD), which supports an enhanced negative-feedback control of cortisol and a blunted HPA response to stress (44). As a consequence of these alterations in the central stress circuitry, secondary changes in receptor systems can occur in spinal or peripheral target cells of the output systems. Thus, in cases of pathological stress resulting in permanent changes in the central stress circuitry, lifelong changes in peripheral receptor systems may also be expected. In the following paragraphs, we discuss evidence for alterations in the three output systems of the EMS in IBS patients.

Changes in autonomic nervous system responses. In the most common functional GI disorders, IBS and functional dyspepsia (FD), persistent alterations of autonomic responsiveness are likely to play a role in altered bowel habits and alterations in gastric emptying, respectively. Evidence for such enhanced responsiveness of autonomic responses in IBS (reviewed in Ref. 23) includes increased responses of distal colonic motility in response to laboratory stress and possibly food intake and delayed gastric emptying in a subset of patients.

A model of IBS, taking into account altered autonomic regulation of gastric and distal colonic function and based on an upregulation of CRF-containing neurons in Barrington’s nucleus (part of the locus ceruleus complex), was recently reported by Valentino and co-workers (41). Although descending CRF-containing projections from this pontine nucleus to the distal colon may mediate increased stress- and food-induced motor responses of the distal colon, ascending projections to the locus ceruleus and to the forebrain may be responsible for mediating arousal and shifting attention to visceral afferent stimuli. Increased expression of CRF message and release of CRF in IBS patients, or a subset of patients, is also consistent with the reported evidence for certain increased sympathetic responses (12, 21).

Changes in the frequency of high-amplitude propagated contraction (HAPC) in the colon, presumably via alteration in vagal colonic regulation, may play an important role in diarrhea and slow-transit constipation, thereby determining the predominant bowel habit pattern in IBS (reviewed in Ref. 23). There is evidence that decreased cardiovagal tone is present in a subset of patients with IBS, in particular in female patients with constipation-predominant bowel habit and more severe symptoms (1, 19). The correlation of changes in cardiovagal tone and vagal regulation of the intestine is emphasized by the recent demonstration in patients with functional constipation of parallel changes in cardiovagal tone and autonomic regulation of whole gut transit and distal colonic mucosal blood flow (11).

Thus, although enhanced sacral parasympathetic modulation of the distal colon, reflecting enhanced responsiveness of neurons within the locus ceruleus complex, may be shared by all IBS patients, alterations in vagal output to the small intestine and proximal colon may be variable, depending on severity and the predominant bowel habit.

Neuroendocrine changes. Preliminary evidence for alterations in HPA axis function was demonstrated in diarrhea-predominant IBS patients who showed decreased 24 h plasma cortisols, blunted cortisol responses, and normal ACTH responses to noxious rectosigmoid distention (26). In contrast, Heitkemper et al. (20) reported that urine cortisol levels obtained immediately on rising were significantly higher in a subgroup of IBS women compared with control women. Even though a thorough characterization of HPA axis responses in patients with functional gastrointestinal disorders has not been reported, these preliminary findings suggest the pattern of sensitized GC feedback also reported in patients with PTSD, fibromyalgia, and chronic fatigue syndrome. However, HPA responses at baseline and in response to provocations in these patients have been conflicting, which may be caused in part by methodological differences and the presence of comorbid depression in some patients. There is significant overlap in the epidemiology of all these conditions with IBS. Other evidence for central alterations in neuroendocrine responses in IBS comes from reports of abnormal neuroendocrine challenge tests in this patient population (8, 17). Existing data support neuroendocrine alterations in IBS and other overlapping syndromes, but further well-designed studies are needed to fully characterize these alterations.

Possible relevance of autonomic and neuroendocrine changes for intestinal immune modulation. Although it is not known currently whether these HPA axis changes are an epiphenomenon or play a role in symptom generation and pathophysiology of these syn-
dromes, one may speculate about their possible role (in conjunction with alterations in autonomic gut regulation) in the observed findings in postinfectious IBS patients. The reported persistence of chronic inflammatory mucosal changes after eradication of the infectious organism (18) and increased intestinal permeability and hyperplasia of enterochromaffin cells (34) are consistent with an inadequate physiological response to acute gut inflammation, in particular an inadequate cortisol (and possibly an altered sympathetic) response. Stress-related alterations in cytokine networks, in particular a suppression of cellular immunity and a shift toward humoral immunity [alteration in T helper (Th)1/Th2 balance], have been reported (10). Multiple reports in the literature on increased intestinal mast cell numbers in IBS patients (29) are consistent with such a Th2 shift.

Changes in pain modulation. Evidence suggestive of alterations in stress-induced modulation of viscerosomatic sensitivity comes from human and animal studies. IBS patients show cutaneous normo- or hypoalgesia combined with visceral hypersensitivity (27). A similar pattern was also seen in a recently described rat IBS model in response to an acute psychological stressor (5). Preliminary results from the use of psychological laboratory stressors in healthy volunteers suggest a stress-induced increase in colonic or rectosigmoid sensitivity to distension (6). Even though all published human studies are open to methodological criticism, they are consistent with reported findings in animals of a differential viscerosomatic pain modulation. It is of interest to note that patients with bulimia (who, in contrast to IBS patients, have a hyperactive HPA axis) show cutaneous hypoalgesia as well, which precedes symptom exacerbations (13).

Changes in regional brain activation. Functional brain imaging studies of IBS patients have shown decreased activation of ventral subdivisions of the anterior cingulate cortex (ACC) and increased activation of the dorsal subdivision (28). Because dorsal ACC is inhibited by intense visceral stimuli in healthy control subjects (unpublished observations), increased dorsal ACC activation may be related to alterations in attentional processes in IBS in regard to visceral sensory events. Decreased ventral cingulate/medial prefrontal cortex activity was also reported in patients with depression (9) and PTSD (33), both affective disorders commonly associated with IBS. Southwick et al. (33) reported a decrease in prefrontal and orbitofrontal cortical metabolism in patients with PTSD in response to the α2-antagonist yohimbine. Together with results from preclinical studies showing decreased metabolism in cortical regions with high NA release (33), these results are consistent with enhanced NA release in these brain regions in PTSD patients. One may speculate that the decreased activation in ventral anterior cingulate, ventromedial frontal cortex, and hippocampus seen in IBS patients may also be related to enhanced NA release from locus ceruleus projections in response to stress, consistent with the Valentino model (41). Recent evidence suggests that regional brain activation in response to visceral stimulation may differ between male and female IBS patients (4, 7). Although most brain regions showed similar activity patterns in male and female patients, differences were seen primarily in the insular and anterior cingulate cortices.

ANIMAL MODELS OF IBS

Although early attempts to model different aspects of IBS in nonhuman animals have met with only limited success, several animal models utilizing different pathological interoceptive and exteroceptive stressors (2) that mimic at least some of the pathophysiological features of IBS are now available. For example, Al-Chaer et al. (2) recently demonstrated that colonic irritation in neonatal rats results in chronic visceral hypersensitivity that persists into adulthood even after the inflammation has resolved. More recently, a single experience of foot shocks in the adult rat has been shown to cause long-term sensitization of the cardiovascular response to colonic distension (36). In the rat, neonatal stress in the form of moderate periods of maternal separation of newborn rats results in permanent changes in the central nervous system accompanied by a compromised ability to restrain the synthesis and release of CRF in response to acute laboratory stressors. These neurochemical changes are associated with enhanced fearfulness, increased HPA responsiveness to stressors, and an increased risk of developing depression-like behaviors. It was demonstrated recently (5) that maternally separated rats also exhibit permanent alterations in their stress responsiveness that predispose the adult animals to the development of visceral hyperalgesia and somatic hypoalgesia in response to psychological stress. Additionally, colonic motor function in response to stress is also enhanced in these animals, thereby mimicking all the main features of IBS. Together with knockout technology, these and other animal models (16, 22, 35, 43) will help to determine which components of the altered stress response are epiphenomena and which play a primary role in pathophysiology.

SUMMARY AND CONCLUSIONS

In summary, an extensive literature is consistent with an enhanced stress responsiveness in IBS patients, manifested by predicted autonomic, pain modulatory, and attentional responses and a sensitized GC feedback. This response pattern is associated with changes in brain activity in limbic regions. The blunting of the HPA axis together with alterations in sympathetic modulation of immune function may predispose individuals to develop postinfectious IBS. The fact that up to 40% of IBS patients show evidence for increased anxiety and the fact that the changes are similar to those reported in a variety of other so-called “functional” disorders (e.g., fibromyalgia, chronic fatigue syndrome, and interstitial cystitis) suggest a model in which alterations in the central stress circuits in predisposed individuals are triggered by pathological stressors and play a primary role in pathophysiology.
REFERENCES


