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# Does stress induce bowel dysfunction?

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## Abstract

Psychological stress is known to induce somatic symptoms. Classically, many gut physiological responses to stress are mediated by the hypothalamus-pituitary-adrenal axis. There is, however, a growing body of evidence of stress-induced corticotrophin-releasing factor (CRF) release causing bowel dysfunction through multiple pathways, either through the HPA axis, the autonomic nervous systems, or directly on the bowel itself. In addition, recent findings of CRF influencing the composition of gut microbiota lend support for the use of probiotics, antibiotics, and other microbiota-altering agents as potential therapeutic measures in stress-induced bowel dysfunction.

### Keywords

bowel dysfunction; irritable bowel syndrome; microbiota; NLRP6; stress

Psychological stress is known to cause bowel dysfunction. Psychological stress-associated gastrointestinal symptoms include, but are not limited to nausea, vomiting, abdominal pain and alteration in bowel habits [1]. Classically, many physiological responses to stress are mediated by the hypothalamus–pituitary–adrenal axis. In addition to the hypothalamus–pituitary–adrenal axis, stress-induced corticotrophin-releasing factor (CRF) release can also lead to bowel dysfunction by acting directly on the bowel itself and also through the CNS. More recently, there is a growing body of evidence of yet another pathway by which CRF can induce bowel dysfunction: that of alteration of the composition of gut microbiota. We



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will briefly discuss the mechanisms by which members of the CRF family (e.g., CRF, urocortin 1, urocortin 2 and urocortin 3) are known to affect gastrointestinal tract function: motility, permeability and inflammation.

An important aspect of bowel function is the regulation of its motility and thus its ability to transit nutrients and waste. During stress, the release and subsequent binding of CRF family members to its receptors (e.g., CRF1, CRF2) affect gastrointestinal motility. The direct physiological effects of CRF family members are in part dependent on the type of CRF family receptor expressed on the target organ. For example, CRF2 is the predominant CRF family receptor expressed in the stomach of rats and appears to mediate decreased gastric motility as intraperitoneal injections of CRF2-specific ligands urocortins 2 and 3 in rats resulted in delayed gastric emptying [2]. Activation of the CRF1 receptor on colonic tissue on the other hand increased motility. While the type of CRF receptor expressed on a particular gastrointestinal organ appears to dictate the type of dysmotility involved, CRF receptors within the CNS do not regulate motility in the same manner. For example, urocortin 1 is predominantly a CRF1 ligand, and urocortin 2 is mainly a CRF2 ligand but injection of either urocortin into the CNS resulted in delayed gastric emptying [3,4]. Currently, generalizable mechanisms governing the effects of CRF family members within the CNS on gastrointestinal motility remain elusive and are subjects of ongoing investigation.

Stress can also increase intestinal permeability and thus bowel dysfunction. In the laboratory, short-term stress has been shown to disrupt intestinal barrier integrity in rats [5]. This is mediated by CRF in a peripheral manner as intraperitoneal injection of CRF and CRF receptor antagonists both abolished the increased intestinal permeability seen in rats that underwent water-avoidance stress (WAS). At the molecular level, stress-induced CRF release appears to downregulate zona occludens-1 expression at the cell–cell tight junction, leading to increased intestinal permeability [6]. Of interest is that patients with irritable bowel syndrome (IBS), a chronic gastrointestinal disorder in which patients can experience acute exacerbations in symptoms following stressful events, also have increased gut permeability [7]. This may be in part secondary to CRF as exogenous intravenous administration of CRF was found to induce intestinal barrier permeability in healthy human volunteers [8]. Though CRF induces increased intestinal permeability in an acute setting based on human and laboratory data, there are likely other mechanisms by which increased intestinal permeability is maintained in patients with IBS; one such possible mechanism is stress-induced immunological changes of the gastrointestinal tract.

In patients with IBS, there is evidence of chronic low-grade inflammation with IBS patients having higher number of mast cells and other inflammatory cell counts compared with normal controls [9]. Consistent with the findings of increased number of immune cells in IBS patients, stress is also known to induce upregulation of cytokine expression. Patients with IBS have been found to have elevated levels of circulating IL-1β, IL-6, IL-8 and TNF-α [10,11]. Evidence of stress-associated inflammation is not limited to patients with IBS. Patients suffering from post-traumatic stress disorder also have higher circulating levels of IL-1β, IL-6 and TNF-α in the peripheral blood [12–15]. Even in otherwise healthy volunteers, army medical response troops during combat training had significantly higher

levels of circulating proinflammatory cytokines such as IL-6 and TNF-α compared with levels measured during a rest period [16]. As inflammation and its associated release of cytokines are known to result in the increase of intestinal cell membrane permeability via alteration of the cell–cell tight junctions [17], it is likely that inflammation also contributes to increased gut permeability. It is not surprising then, that the aforementioned army medical response troops also had increased intestinal permeability during combat training [16]. Furthermore, increased gut permeability has been positively associated with visceral hypersensitivity in patients with diarrhea-predominant IBS [7]. One possible explanation is that both increased bowel permeability and visceral hypersensitivity are attributable to the direct effects of intestinal inflammation as bowel inflammation is known to cause pain. Alternatively, another possibility is that the passage of yet-to-be-defined factors from the bowel lumen through the mucosal layer of the intestines leads to the sensitization of efferent pain signaling pathways from within the gastrointestinal tract [18].

The mechanism by which stress can induce gut inflammation, however, has yet to be clearly defined. Our investigative efforts indicate that the disturbance of gut microbiota may be a novel pathway by which stress causes bowel inflammation. Using WAS mouse model, we demonstrated that WAS-related increase in CRF in mice induced enteritis and downregulated nucleotide-binding oligomerization domain protein-like receptors, pyrindomain containing (NLRP)-6 inflammasomes in the small bowel [19]. WAS-associated enteritis was reduced with probiotic administration. Given that NLRP6 was previously shown to be important in maintenance of gut microbiota homeostasis [20], these findings are consistent with stress-induced enteritis via a putative CRF–NLRP6–dysbiosis–enteritis pathway. As rosiglitazone, a PPAR-γ agonist known to induce NLRP6 expression was able to ameliorate WAS-induced enteritis, this indicates that NLRP6 may be a central host factor in stress-induced bowel dysfunction.

There is evidence that stress induces gut microbial dysbiosis and the resultant bowel dysmotility, inflammation and increased permeability. In animal models, stress lead to changes in gut microbiota in rodents [19]. Investigators using a mouse model of depression found that these mice have altered gut microbiota and also increased colonic motility [21]. In a model of WAS-induced visceral hypersensitivity, treatment of rats with rifaximin, an oral antibiotic, resulted in a relative increase of Lactobacilli and also reversed stress-induced mucosal inflammation, visceral hypersensitivity and intestinal permeability [22]. The abrogation of stress-induced pathology by rifaximin may be secondary to increased Lactobacilli population as stressed rats gavaged with *Lactobacillus farciminis* and *paracasei* have also be shown to have attenuated mucosal permeability and reduced visceral hypersensitivity compared with controls [23,24].

Disturbance of gut microbiota has also been associated with stress in humans. In a study examining the fecal contents of three astronauts, *Bacteroides fragilis* subspecies thetaiotaomicron was found to be increased in all of the astronauts when they were housed in presumably stressful isolated Skylab conditions [25]. Another study found decreased lactic acid bacterial counts in the feces of healthy college students during times of stress [26]. Furthermore, patients with IBS also have altered gut microbiota [27], and treatment of IBS patients with rifaximin led to improvement in patient symptoms [28]. To further lend

credence to gut microbiota playing a role in bowel function, a recent meta-analysis also concluded that probiotic therapy in IBS patients was efficacious, though the most beneficial probiotic strains and the magnitude of symptom improvement were less clear [29].

In summary, psychological stress has long been known, both clinically and experimentally, to cause bowel dysmotility. Much of CRF-dependent mechanisms of stress-induced bowel dysmotility have been explored. Other aspects of CRF-medicated bowel function, such as intestinal barrier permeability homeostasis and neurosensing, are not clearly defined. Most recently, with the advent of newly available deep sequencing techniques, studies on gut microbiota have been garnering interest. Given the available evidence of the association between stress and IBS, the clinical improvement of IBS patients with alteration of their gut microbiota, and laboratory experiments in animal models, it is likely that stress-induced bowel dysfunction is at least in part mediated by the gut microbiota. Pharmacotherapeutics, including gut microbial composition-altering therapies such as agents that act along the NLRP6 pathway, antibiotics, probiotics and intestinal microbiota transplantation hold great promise in the restoration of normal bowel function but will require further studies, both preclinical and clinical, to realize their potential.

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