LEADING ARTICLE

Stress-related changes in oesophageal permeability: filling the gaps of GORD?

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Albeit remaining a controversial issue, it has become increasingly recognised that psychological stress has a major impact on gut mucosal function and affects the course of gastrointestinal disorders. Research during the last decade has shown that stress causes barrier dysfunction of the gastrointestinal mucosa by mechanisms that mainly involve neuropeptides and mast cells. Moreover, accumulating evidence implicates increased permeability as a pathogenic factor in gastroesophageal reflux disease (GORD). Recent data demonstrating that psychological stress may induce a permeability defect in stratified epithelia, including the oesophagus, shed new light on the pathophysiological events leading to heartburn and GORD.

It has become increasingly recognised that various types of stress have a major impact on gastrointestinal physiology, thereby causing dysfunction and/or diseases. For example, stress is involved in the pathogenesis of gastric stress ulcers and peptic ulcer disease.[1] Moreover, early stressful life events and sustained stress may predispose to the development of irritable bowel syndrome (IBS)[2] and affect the course of inflammatory bowel disease.[3] In addition, a majority of patients with gastroesophageal reflux disease (GORD) report stress as an important trigger of symptom exacerbation.[4] The subject of stress-induced effects on intestinal diseases does, however, remain a controversial issue, and our understanding of the intricate neuro-immunophysiology involved in stress effects on intestinal mucosal functions is only beginning to evolve (for a comprehensive review, see Söderholm and Perdue[5]). In a recent report on psychological stress-induced effects on oesophageal permeability, Farré *et al*.[6] shed new light on the pathophysiology of GORD.

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STRESS

Although everyone has experienced life stresses of various sorts and degrees, stress is difficult to define. This is mainly due to the subjective experience of stress, with very large variations in the capacity to cope with stressful situations.[7] The most commonly used definition was put forward by Selye:[8] ''stress is any threat to the homeostasis of an organism''. This threat can be real (physical) or perceived (psychological), caused by events in the environment or from within the individual itself (for example, by inflammation).

Regardless of type of stress, the principal responses to maintain homeostasis are similar, including the behavioural response (such as anxiety), autonomic responses (such as raised heart rate), and the hypothalamic-pituitary-adrenal axis response (such as cortisol release),[2] with corticotropin-releasing hormone (CRH) being an important mediator. When the healthy individual encounters a challenge, the physiological response systems are quickly turned on and off, matching the duration and severity of the stressor, a so-called adaptive response. A harmful—that is, maladaptive (pathological stress) response—may occur through three types of reactions: stress overload, failure to shut down or inadequate responses.[7] A maladaptive response may thus be induced by a one-time life-threatening stress, but is more frequently caused by chronic daily-life stressors, such as loss, financial problems, unemployment and so on. Individuals with maladaptive responses will be predisposed to disease in multiple organ systems, including in the gastrointestinal tract (eg, exacerbations of IBS,[9] ulcerative colitis[10] or GORD).[11] One of the mechanisms connecting psychological stress and gastrointestinal diseases is stress-induced effects on mucosal barrier function.

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STRESS AND GASTROINTESTINAL BARRIER FUNCTION

From a clinical perspective, animal models of chronic stress may be more relevant than models of acute stress. Chronic stress has pronounced effects on host defence against luminal bacteria[12–14] and affects CD4+ T cells,[15 16] with consequences for the development of intestinal inflammation in animal models. On the other hand, studies in humans indicate that acute stress may influence the symptoms of gastrointestinal disorders, including GORD, by altering

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Abbreviations: CRH, corticotropin-releasing hormone; DIS, dilated intercellular spaces; GORD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; NERD, non-erosive reflux disease; RMCPII, rat mast cell protease II

mucosal function, motility or visceral perception.[4 11 17–19] Rodents exposed to acute stress show perturbed small-bowel and colonic permeability, including increased paracellular permeability to ions and molecules of various sizes,[15 20] along with altered expression of TJ proteins, ZO-2 and occludin.[21] Moreover, increased transcellular uptake of macromolecules via stimulated endocytosis is found.[22 23] Acute psychological stress may also affect the intestinal barrier to luminal bacteria.[13]

The neuro-endocrine factors that mediate intestinal mucosal function during stress have not been fully clarified, but include acetylcholine, neurotensin, substance P and CRH, with CRH being the major mediator of various stress-induced abnormalities, including those of a gastrointestinal nature. It is believed that stress impulses are transmitted from the brain to the gatrointestinal tract mainly via the vagal nerve, but sympathetic efferents may also be involved.[24–27] Stress-induced functional changes of the intestine can be inhibited by the CRH receptor antagonist, α-helical CRH9–41, given peripherally,[23] as well as centrally.[27] Moreover, both peripheral and central injections of CRH mimic stress responses in the gastrointestinal tract.[23 27–29] Two subtypes of CRH receptors—CRH-R1 and CRH-R2—have been found in the colonic mucosa.[30] CRH-R1 was shown to mediate stress effects on intestinal motor function,[28] but the relative importance of the CRH receptors regarding mucosal function is currently not known. CRH-mediated effects in the intestinal mucosa are associated with the secretion of rat mast cell protease II (RMCPII; the rodent equivalent to tryptase), activation of mast cells by microscopy, and can be inhibited by mast-cell stabilisers, which suggests that CRH acts via mucosal mast cells. Similarly, the importance of mast cells in acute stress-related changes in intestinal function has been highlighted—for example, by increased release of mast-cell proteases during stress,[18 29] inhibition of stress-induced changes by pharmacological stabilisation of mast cells,[21 23 29] and ultrastructural mast-cell activation in combination with barrier disturbances during stress.[22 31] Moreover, stress-induced barrier dysfunction does not occur in mast-cell-deficient mice (W^v/W^v) or rats (Ws/Ws).[12 32 33] Several mast-cell-released factors may be the mediators of mucosal dysfunction, for example TNFα and IFNγ with well-recognised effects on intestinal barrier function,[21 34 35] and tryptase, which could affect permeability via activation of protease-activated-receptor-2.[36 37]

Taken together, animal studies suggest that acute stress-induced intestinal barrier dysfunction, to a large extent, is mediated by CRH operating via activation of mucosal mast cells. It is also known that acute psychological stress in humans affects jejunal ion secretion,[17] and that neuro-immune regulation of intestinal ion transport does occur in humans, mainly via mast cells.[18 38] However, studies looking specifically at the effects of psychological stress on gastrointestinal permeability in humans are lacking, and the mechanisms remain to be elucidated.

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PATHOPHYSIOLOGY OF GORD

The pathophysiology of GORD has been extensively reviewed in papers by Fass and Tougas,[4] and Barlow and Orlando.[39] GORD is often divided into non-erosive reflux disease (NERD) and erosive oesophagitis; NERD is defined as GORD symptoms (mainly heartburn) with normal upper gastrointestinal endoscopy. The main theories on the pathogenesis of heartburn in NERD are oesophageal visceral hypersensitivity, sustained oesophageal contractions and abnormal tissue resistance.

Oesophageal visceral hypersensitivity—that is, increased reactivity to physiological amounts of acid—is thought to arise from peripheral sensitisation of afferents. The oesophageal mucosa receives vagal afferents, which are polymodal and under normal circumstances not consciously perceived, and mucosal spinal afferents, which are primarily nociceptors located in epithelial intercellular spaces (three cell layers from the lumen), and are likely to be involved in acid-induced oesophageal pain.[40] The sensitisation of the afferents may be caused either by inappropriately heightened perception due to neuronal dysfunction, or by appropriately heightened perception because of greater access to acid in the nociceptors. Evidence of neuronal dysfunction in NERD was found when perfusion with acid in the human oesophagus reduced the pain threshold to electrical stimulation in non-exposed mucosal areas and also increased the velocity in afferent pathways.[41] Moreover, studies have shown altered heart rate variability in GORD patients, indicative of dysfunction of the autonomic nervous system.[42] On the other hand, NERD patients are sensitive to acid exposure in the oesophagus, but are not inherently hypersensitive to mechanical stimulation,[43] suggesting that the hypersensitivity may be due to acid stimulation of the nociceptors.

Sustained oesophageal contractions represent prolonged contractions of the oesophageal longitudinal smooth-muscle layer. These contractions often correlate with spontaneous heartburn as well as a positive Bernstein test,[44] but in other studies they were associated with atypical chest pain. Sustained oesophageal contractions may thus be induced by acid exposure and contribute to the symptom of heartburn, but may also be linked with chest pain of oesophageal origin irrespective of the type of provocation.[39]

Abnormal tissue resistance, or increased permeability, can be induced by acid affecting the apical membranes and the junctional complexes of the stratum corneum, the main components of oesophageal barrier function.[45] This permeability defect, with increased ion and water flow between the epithelial cells, results in dilated intercellular spaces (DIS) seen via microscopy. There is clear evidence from animal studies that exposure to gastric acid causes increased paracellular permeability and DIS in the oesophageal epithelium. In rabbit oesophagus exposed to acid in Ussing chamers, a reduced transmucosal electrical resistance, increased mannitol flux and DIS on electron microscopy[46] were found. Moreover, altered epithelial cell expression of the tight-junction proteins, claudin-1 and claudin-4, was demonstrated in experimental oesophagitis in rats.[47] It was further shown that the combination of pepsin and acid exaggerated the barrier dysfunction and rapidly produced an irreversible lesion,[48] which may contribute to the conversion of non-erosive to erosive damage to the oesophageal epithelium. In GORD patients, DIS are found irrespective of endoscopy findings[49] or acid reflux time,[50] and NERD patients show abnormal responses in transepithelial potential difference to acid perfusion *in vivo*,[51] implicating DIS as a primary pathogenic phenomenon. On the other hand, it was recently shown that the DIS in NERD and erosive disease were reversible to 92% by omeprazole treatment for 3 months,[52] suggesting that the DIS is secondary to other pathophysiological events.

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STRESS AND GORD

Apparently, oesophageal hypersensitivity, epithelial permeability and motility all contribute to the pathogenesis of heartburn,

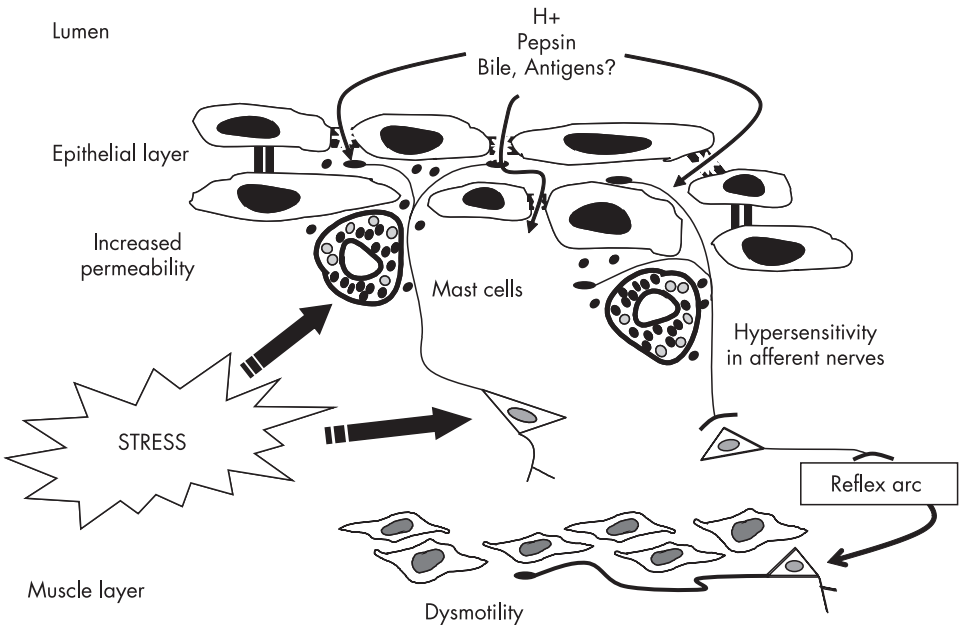

Figure 1 Stress model. Based on the current knowledge of the pathophysiology of GORD and stress mechanisms in the gastrointestinal tract, a model of stress effects on oesophageal permeability can be put forward. Stress, transmitted to the intestines via vagal and/or sympathetic efferent fibres, activates mucosal mast cells, directly or via enteric nerves, inducing release of mediators via piecemeal degranulation. This leads to increased epithelial permeability and dilatation of the intercellular spaces, as well as sensitisation of mucosal spinal afferents. Increased acid (and pepsin) exposure to the epithelium will lead to further disruption of tight junctions and activation of intraepithelial nociceptors and mast cells. The afferent nerves will convey pain signals and, via reflex arcs, oesophageal contractions, thereby inducing heartburn.

with acid reflux being a provoking factor in many instances. Stress and anxiety increase the perception of acid perfusion in humans, regardless of oesophageal mucosal injury.[4] Stress studies have, however, failed to show a higher degree of acid reflux during stress exposure.[53] On the other hand, stress affects permeability in stratified epithelia, such as skin,[54] and it was recently demonstrated that stress also affects oesophageal permeability and vulnerability to acid/pepsin exposure.[6] As intraepithelial nociceptors may be activated already by pH 5.2–6.9,[55] increased oesophageal permeability and DIS during stress may contribute to the induction of heartburn at lower luminal acid concentrations than the usual pH<4.

In skin, acute stress triggers mast-cell degranulation via activation of peptidergic nerves[56] and alters barrier function.[54] The evidence for a role of mast cells in stress-induced permeability in the oesophagus is only suggestive.[6] There is, however, clearly a role for mast cells in regulating oesophageal function, with mast-cell degranulation and release of histamine into the oesophageal lumen during acute acid-induced injury.[57] Intestinal mast cells express CRH receptors[58] and, recently, Wu *et al.* identified CRH receptor subtype 2 in the oesophageal mucosa of the rat,[59] along with expression of the cognate CRH receptor ligands urocortin 1 and 2. This suggests that the CRH signalling system and mast cells are involved in the regulation of secretomotor activity in the oesophagus.

Barlow and Orlando have put forward a hypothesis that increased permeability and DIS in NERD patients causes pH and/or osmolarity changes in the intercellular spaces, leading to activation of nociceptors, which via reflex arcs give sustained oesophageal contractions, thereby inducing heartburn.[39] This is an appealing theory; however, as the DIS normalise with omeprazole treatment, increased permeability seems to be a secondary phenomenon in NERD. A possible stress-induced increase in permeability and DIS of the oesophageal epithelium may thereby fill an important gap in the pathophysiological understanding of GORD (fig 1). The involvement of mast cells is credible from previous stress-related gastrointestinal research, and could contribute to the barrier dysfunction as well as to the sensitisation of intramucosal nociceptors and neurons. Stress probably influences the intestinal barrier through autonomic pathways acting via enteric nerves and/or directly on mucosal mast cells, but the signalling pathways involved need further elucidation. In addition, the cellular origins of CRH and CRH-related peptides in the intestinal mucosa need to be clarified.[27]

In clinical practice, the stress-induced effects on oesophageal epithelial permeability may increase the risk of developing erosive disease in patients with acid reflux. Moreover, by lowering the threshold of response to acid, increased permeability and DIS may explain heartburn during ''non-significant'' reflux in stress-exposed individuals not responding to proton pump inhibitors. Dissecting the mechanisms involved in stress-induced oesophageal permeability will give clues to additional therapeutic approaches in patients suffering from GORD.

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