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Review

Corticotropin-releasing factor: A possible key to gut dysfunction in the critically ill

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ABSTRACT

Critically ill patients frequently display unexplained or incompletely explained features of gastrointestinal (GI) dysfunction, including gastric stasis, ileus, and diarrhea. This makes nutrition delivery challenging, and may contribute to poor outcomes. The typical bowel dysfunction seen in severely ill patients includes retarded gastric emptying, unsynchronized intestinal motility, and intestinal hyperpermeability. These functional changes appear similar to the corticotropin-releasing factor (CRF)-mediated bowel dysfunctions associated with stress of various types and some GI disorders and diseases. CRF has been shown to be present within the GI tract and its action on CRF receptors within the gut have been shown to reduce gastric emptying, alter intestinal motility, and increase intestinal permeability. However, the precise role of CRF in the GI dysfunction in critical illness remains unclear. In this short review, we provide an update on GI dysfunction during stress and review the possible role of CRF in the aetiology of gut dysfunction. We suggest that activation of CRF signaling pathways in critical illness might be key to understanding the mechanisms underlying the gut dysfunction that impairs enteral feeding in the intensive care unit.

Introduction

Gastrointestinal (GI) dysfunction is widespread in the critically ill. Delayed gastric emptying, abnormal motility patterns, and impaired intestinal barrier integrity are commonly observed in the intensive care unit (ICU), particularly following traumatic injury and shock [1]. Impaired gut function compromises delivery of enteral nutrition, and is associated with complications and morbidities, which effect survival [2–4]. Indeed, nutritional interventions such as supplementation of pharmaconutrients [4] and micronutrients [5] have an important effect on clinical outcomes. Enteral feeding itself also might play a role in counterbalancing the effects of GI hypoperfusion associated with critical injury [4]. Gut function in the critically ill is therefore of immense clinical importance. Multiple clinical interventions could account for the disrupted GI function in the critically ill, including major abdominal trauma or surgery, use of antibiotics, acute phase hypoalbuminaemia, and the effect of many drugs [6,7]. The actions of many physiological mediators also undoubtedly affect GI functioning in a manner that is apparently extremely complex. Among such substances is corticotropin-releasing factor (CRF).

CRF is the 41-amino acid mammalian peptide neurohormone first described by Vale et al. in 1981 [8]. CRF is abundantly expressed in neurons of the paraventricular nucleus of the hypothalamus, which stimulate adrenocorticotropic hormone secretion and thereby the pituitary–adrenal axis. CRF, however, also is expressed throughout several other brain regions of mammals suggesting that there are a variety of functions of this molecule [9]. Apart from the established role of CRF in driving the hypothalamic–pituitary–adrenal (HPA) axis, more recent data has shown that CRF is of importance in peripheral tissue physiology as well as in brain function. Apart from being present in skin [10], inflammatory sites [11], and various other organs, the gut [12,13] has been demonstrated to express CRF. The presence of CRF in the GI tract is of particular interest because

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stress itself induces a typical pattern of functional changes to the gut that includes anorexia, slowed gastric emptying, colonic motile stimulation, and impairment of the intestinal epithelial barrier. Accumulated data, especially from animal studies, indicates that CRF is central to these stress-related alterations in GI physiology [14]. The similarity between the GI dysfunction associated with critical illness, and that associated with CRF activity raises the question of whether CRF is involved in the GI dysfunction of profoundly stressed critically ill patients.

Gut responses to stress and the role of CRF signaling

The gut is a vital physical, chemical, and immunologic barrier between the internal and external environments. It is composed of four tissue layers: the mucosa (which includes the epithelium), the submucosa, the muscularis externa, and the serosa. The intestinal epithelial barrier controls the passage of digested nutrients, water, electrolytes, and other molecules across the barrier, while excluding significant amounts of antigen and toxins. Critical to the intestinal barrier is the mechanical connection of the adjacent epithelial cells to each other and to the basement membrane, and the tight junction complex located apicolaterally between cells, which seals the paracellular space to maintain barrier continuity. Because tight junctions regulate the passive paracellular transport of fluids and solutes, compromise of tight junctions under stress conditions can significantly increase flux of pathogens and other undesirable foreign material into the underlying tissues. Furthermore, the secreted fluid and mucus production together with immunologic products such as immunoglobulin (Ig)A provide a defense against harmful substances including endotoxin. This ability of the mucosa to control entry of some molecules and bar entry of others is known as the intestinal barrier function. Because the physiological barrier function of the GI tract is under neurohormonal influence, it too can be affected by stress.

The GI tract has a limited portfolio of responses to stress, which can occur even when the stress is not directed at the gut. Stress may alter gut motility and transit, or may affect non-motor function. Evidence indicates that the motor response to stress is generally one of inhibition in the upper GI tract and stimulation in the lower GI tract, with the colon being more stress-responsive than the rest of the gut. The small intestine plays an important role in the non-motor manifestations of stress on the gut, with deleterious structural and functional disruptions of the epithelial barrier. A large body of data on this topic is reviewed elsewhere [15,16]. However, it was the identification of brain peptides such as CRF that affect the function of the GI system, which advanced understanding of stress-induced gut dysfunction. It is clear that this molecule exerts endocrine and motility effects quite independently of the HPA axis. This is a critical point: Whereas other releasing factors/hormones only produce effects if they act in the brain, CRF acting in the periphery has effects of physiological importance, including in the gut.

In mammals, CRF exerts its actions through G protein-coupled receptors, namely CRF type 1 [17], and CRF receptor type 2 [18], which are expressed widely within the brain and differentially in a variety of tissues, including the gut. CRF1-receptor is found in different brain regions as well as a large number of peripheral tissues inclusive of the colon and small intestine [19]. Multiple splice variants of the CRF1 receptor have been identified, but CRF1α is the main functional receptor variant, for which CRF has high affinity. Three functional variants of CRF2 receptor have been identified and designated 2a, 2b and 2c. Again, CRF2 receptors are widespread in brain neural and non-neural tissue, but also expressed in peripheral tissues, notably in the human GI tract [13]. Apart from receptor binding, CRF also binds to CRF-binding protein with high affinity. Because CRF-binding protein is highly co-localized with CRF and CRF receptor distribution, it may function to modulate the availability of CRF to receptors and limit its bio-action. The following sections will review how both central and peripheral CRF signaling is understood to affect the gut under stress and how inferences could be made about the mechanism of gut dysfunction in the critically ill.

Motility disorder in the critically ill

Impaired gastric emptying and gut motility are commonly observed in critically ill patients [1,20,21]. At least half of mechanically ventilated patients and up to 80% of head-injured patients are affected by retarded stomach emptying, which also is common in multiple trauma, burns, and sepsis. The widespread use of opioids may be foremost among the iatrogenic causes of gastric stasis [22]. Other factors include sedation, analgesics, positive pressure ventilation, inotropic support, and surgery involving manipulation of intestines, all of which are virtually inevitable causes of postoperative gastric motor stasis [23,24]. Furthermore, motility disturbances are known complications of over-resuscitation with intravenous fluid, multiple organ failure (MOF), hemodynamic instability, and intraabdominal hypertension [25,26].

In critically ill patients, the gut regions are affected differentially. Drastically reduced lower esophageal sphincter pressure and poor esophageal peristaltic activity, allow frequent gastroesophageal reflux especially in the presence of gastric stasis [27]. Delayed gastric emptying is perhaps the most common reason for enteral feeding failure in ICUs. Gastric stasis in ICU patients is characterized by a variety of active but abnormal and highly in-coordinate motility patterns in the upper gut [20]. These responses, together with abnormally high levels of motility-inhibiting gut hormones such as cholecystokinin (CCK) and peptide YY, are associated with significantly delayed gastric emptying [21].

Data indicate that CRF mimics the manner in which stress alters gut motile function as summarized in Figure 1 [14,15,28]. This occurs via both central and peripheral mechanisms involving a number of receptors for CRF, but not requiring an intact HPA because surgical removal of the pituitary or adrenals does not change the inhibitory effect of central CRF on gut motility [14,15]. The peripheral (IV or intraperitoneal) injection of CRF inhibits gastric emptying in various mammals by reducing gastric contractile motor activity and inhibiting jejunal motility [29,30]. Peripheral CRF does not appear to cross the blood–brain barrier, so the effect seems to be locally mediated. Furthermore, such effects can be replicated in isolated gastric preparations with functional enteric neurons, which supports a localized action [31].

Although the gastric inhibitory effect of stress can be replicated via either central or peripheral CRF injection, the site of action is different. For instance, pharmacologic autonomic blockade does not change the delayed gastric emptying induced by peripheral injection of CRF, but does prevent the gastric inhibition produced by cerebrospinal CRF injection [14]. Indications are that the gastric effect of peripheral CRF is via CRF2-receptors [32]. In contrast, gastric stasis following a surgical stress is via CRF1-receptors [33]. Abdominal surgery is known to activate CRF pathways and these findings suggest that peripheral CRF receptors might be important in postoperative ileus. Interestingly, CRF antagonists administered centrally also are effective in preventing postoperative ileus suggesting that both central