Stress and the colon: central-vagal or direct peripheral effect of CRF?

Richard C. Rogers, Gerlinda E. Hermann, and R. Alberto Travagli

Department of Neuroscience, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana

Stress, defined as the perception of threatening stimuli and the emotion and mental activity expended contemplating the threat, has been associated medically with the derangement of normal bowel function since ancient times (Nature of Man, Hippocrates, circa 630 BC). More recently, Bockus (2) provided a cogent description of “motor neuroses of the colon” and noted particularly that the stress and strains of civilization are often reflected in a spastic, hypermotile colon. Bockus (2) speculated that the effect of stress on the colon was probably the result of hyperactivation of vagal projections to the colon. Not long after Bockus, Almy et al. (1) reported experimental observations on the effects of acute mental anxiety in medical students that left no doubt that stressful events can lead immediately to drastic increases in colonic motility.

While these earlier efforts established a strong connection between stress, anxiety, and debilitating increases in colonic motility, the responsible physiological mechanisms were not well understood.

The discovery and physiological characterization of corticotropin releasing factor (CRF) in the late 70s and early 80s strongly suggested that this brain peptide regulates more functions in response to stress than just the release of adrenocorticotropic hormone from the anterior pituitary (3, 26). CRF, which is released in response to physiological or psychological threat (17), evokes widespread autonomic changes, including depression of gastric motility and decreased colonic transit (reviewed in Ref. 22).

The first suggestion of a link between stress, CRF, and the hypermotile colon was made by Williams et al. (28). These investigators observed that the colonic hypermotility induced by restraint stress in rats could be mimicked by either intravenous or intraventricular CRF injections, and the effect was antagonized by intravenous or intraventricular application of the CRF antagonist, α-helical CRF. While Williams et al. (28) established the role of CRF in provoking colonic hypermotility, they did not discriminate the site of action for CRF. Subsequent efforts by several investigators focused on, as Bockus predicted (2), a mechanism in which CRF acts on selected vagal efferent pathways to either inhibit gastric (6, 7, 10, 27) or activate colonic (9, 25) motility.

CRF gastrointestinal inhibition is primarily via a direct activation of nonadrenergic, noncholinergic (NANC) inhibitory vagal projections (10). Additional evidence suggests that CRF can also induce gastric relaxation by inhibiting gastroexcitatory vagal efferent responses to excitatory TRHergic inputs and to thyrotropin-releasing hormone (TRH) itself (6, 7, 27). The mechanism of action of CRF for this latter effect, however, is not clear, because CRF only produces excitatory responses within identified vagal efferent neurons both via a direct effect on their membrane and, indirectly, via an increase of the excitatory inputs impinging on them (10). Perhaps CRF produces its effects to withdraw excitatory input to the stomach by modulating yet-to-be-discovered transduction mechanisms within gastroexcitatory vagal efferents.

In the present issue of Am J Physiol Regul Integr Comp Physiol, a study by Tsukamoto et al. (25) suggests that the stress effects that increase colonic motility are produced exclusively as a consequence of a central action of CRF on vagal excitatory inputs to the colon. These authors recorded colonic motility with a strain gauge to show that restraint stress, as well as intraventricular injections of CRF, produce significant increases in colonic motility. The colonic contractions induced by CRF were eliminated by intracerebroventricular, but not peripheral, pretreatment with the nonselective CRF receptor antagonist astressin, by hexamethonium, atropine, or truncal vagotomy. In vitro, muscle strip preparations of the colon, instead, were insensitive to CRF (25).

The data of Tsukamoto et al. (25) are clear enough; there is, however, compelling evidence suggesting that the central-CRF-vagal efferent mechanism may also be paralleled by the direct action of CRF on the colon itself. Several observations support this possibility, including the demonstration of the equal effectiveness of CRF to augment colonic motility, whether the peptide is delivered centrally or peripherally (13, 14, 25, 28). CRF has also been reported to increase colonic electrical activity when delivered to the splanchnic arterial circulation (15). Recent work of Liu and colleagues (11, 12) and Chatzaki et al. (4) have clearly demonstrated the presence of CRF type 1 receptors in the myenteric and submucosal plexus of the gut, including the colon.

There is clearly a mismatch between the bodies of work suggesting that CRF operates exclusively on vagal efferent fibers to drive colonic motility (25) or that CRF action is directly on the colon (4, 9, 11–14, 16). It should be noted that subtle variations in the experimental approaches between investigators are, at times, sufficient to explain differences in results. For example, studies showing a direct colonic action of CRF demonstrate increased electrical activity (13) and colonic enteric neuron activation (12, 16) but not changes in colonic motility (25). Strain gauge studies of CRF involvement in stress-related increases in colonic motility only detect the central nervous system-vagal mechanism (25). It is possible that CRF can act peripherally to activate the enteric plexus and to produce changes in smooth muscle electrical activity, but these changes fail to translate into significant motility events. Conversely, it is possible that the narrow muscle strip preparations (3 mm) used by Tsukamoto et al. (25) may not possess sufficient intact myenteric or submucosal plexus to generate a response to CRF.

Something else to consider is that while vagotomy eliminates any central effects of CRF (25), this procedure also
deprives the gut of a substantial source of tonic excitatory input (reviewed recently in Ref. 18), potentially rendering the colon less sensitive to the effects of agonists, such as CRF.

This situation is similar to the controversy concerning the relative significance of vagal inhibitory vs. vagal excitatory control over gastric motility (reviewed recently in Ref. 24). There is a mismatch in neurophysiological vs. pharmacological data regarding the pathway(s) responsible for the vagal efferent effects on the stomach. For example, the following stimuli all produce a significant vagovagal mediated reduction in proximal gastric motility and tone: esophageal distension, antral mucosal contact and distension, intestinal distension or nutrients, intestinal acid and irritant stimulation, as well as the action of CCK (reviewed recently in Ref. 18). All of these reflex effects are eliminated by vagotomy. Pharmacological evidence suggests that a major component of these reflexes depends on activation of a vagal inhibitory NANC pathway, whereas neurophysiological evidence suggests that the withdrawal of cholinergic excitatory inputs to the stomach may be, instead, the primarily responsible mechanism for gastric relaxation (5, 15, 19, 21). This disparity may be explained by a peculiarity in the organization of gastric-projecting medullary vagal circuits. Vagal motoneurons are tonically active (23), and the vast majority is likely “gastroexcitatory”, i.e., impinging on cholinergic postganglionic neurons (reviewed in Ref. 18). Neurophysiological methods favor the probability of finding vagal motoneurons involved in descending (cholinergic) excitation of the stomach (5, 15). The relatively smaller number of vagal motoneurons neurons coupled to the NANC pathway, however, produces a disproportionately large reduction in gastric motility and tone (8, 19). The end result is that it is easier, due to sampling bias, to demonstrate gastric relaxation as induced by cholinergic withdrawal (i.e., reduction in excitation) using neurophysiological tools. In contrast, it is easier to demonstrate the activation of a NANC (i.e., inhibitory) pathway with pharmacological tools, since its effects on a tonically activated gut are more readily observable than the withdrawal of an excitatory tone. Recent studies suggest, not surprisingly, that the overall reflex control of gastric motility is mediated by both vagal efferent mechanisms (19, 20).

Similar to the dual innervation to the stomach, it seems just as likely that the mechanism of action of CRF to drive colonic motility is a combination of vagal and enteric activities. These actions, however, may be expressed at different times and under different circumstances yet to be determined. It is incumbent upon investigators to use complementary techniques to establish the details.

REFERENCES