
Review

Trauma and the gut: interactions between stressful experience and intestinal function

Functional gastrointestinal disorders form an important health care burden in Western societies. In one of their most common manifestations, the irritable bowel syndrome (IBS), there is evidence for altered visceral sensory and motor responses to stimuli. Psychiatric disturbances may determine the degree to which symptoms are experienced as stressful or debilitating. Traumatic experiences could have a role in the aetiology or perception of IBS, and there are indications that functional gastrointestinal disorders are a common occurrence in patients with post-traumatic stress disorder (PTSD). Acknowledging that enteric infections could be important precipitating factors in subgroups of patients, this review will focus mainly on the possible role of stressful life events in the development and expression of disordered gastrointestinal function in IBS. After a concise summary of acute effects of experimental stressors on intestinal motility in laboratory animals, the growing body of evidence from animal studies pointing to lasting changes in behavioural and autonomic responsivity following brief exposure to stress will be reviewed. We argue that more attention in animal research to the long term effects of stressful experience on basal and stimulated intestinal motility and the neural mechanisms involved, as well as to individual differences in responsivity, may improve our understanding of stress related disturbances of human gastrointestinal function.

Human studies

THE IRRITABLE BOWEL SYNDROME

Motility, sensitivity and psychology

Functional gastrointestinal disorders represent a combination of chronic or recurrent gastrointestinal symptoms that cannot be explained by structural or biochemical abnormalities. These comprise oesophageal disorders, including functional ('non-cardiac') chest pain, gastro-duodenal disorders, including functional dyspepsia, bowel disorders, including IBS, and functional biliary and anorectal disorders.¹ Current diagnostic criteria for the IBS are restricted to a combination of abdominal pain (associated with defaecation or changed bowel habit), disordered defaecation and abdominal distention.² Prevalence in Western populations ranges between 10 and 20%,^{3, 4} although overlap with functional upper abdominal disorders may be considerable.⁵ Although only 50% of people with IBS seem to consult a physician,⁶ and there is a large individual turnover in onset and disappearance of abdominal symptoms,⁷ costs related to absence from work and health care use are considerable.⁸

Despite the large body of literature, the presence and nature of disturbed intestinal motility in IBS remain controversial (for a general review, see McKee and

Quigley⁹). One important limitation remains that studies of intestinal contractility or myoelectric activity have only been performed in clinical samples. Interest in small bowel dysfunction in IBS has developed relatively recently, but it seems clear that both basal and stimulated motility are altered. In the fasted state, increased daytime frequencies of the migrating motility complex (MMC) and of discrete clustered contractions have been reported.^{10, 11} The absence of differences in basal MMC frequency between controls and patients with IBS during sleep¹¹ seems to indicate heightened reactivity to behavioural arousal. During brief psychological stress, inhibition of clustered contractions is seen in some patients,¹² and the reduction in MMC frequency during a 24 hour period of intermittent stressful stimuli is greater than that in controls.¹³ The picture that has emerged from studies of basal and stimulated colonic motility in IBS over the past 20 years is far from clear. Practical considerations usually limit measurements in humans to descending or sigmoid colon, and experimental conditions (bowel preparation, luminal content, patient mobility) vary considerably. Both normal¹⁴ and increased¹⁵ basal spike burst and contractile activity have been reported, though within-group variance is usually high. When measurements are performed on the unprepared colon, patients with IBS do show an exaggerated motility response to a meal.¹⁶ Studies of the colonic effects of well-defined laboratory stressors in IBS are relatively scarce. Motor and electric responses to frustrating mental arithmetic^{17, 18} or the cold pressor test¹⁷ do not differ significantly from controls. Provocation of anger by performance criticism and lack of observer attention causes significantly greater increases in colonic spike activity in patients with IBS than in controls,¹⁹ although patients also seemed to be angrier and more hostile after the experiment. Clearly, more information on intestinal motility responses in IBS is needed, and use of 24 hour ambulant recording techniques²⁰ may help to assess the effects of more relevant daily life stressors.

There are strong indications for altered visceral sensitivity in IBS, and this factor may have a role in motility responses to stressful stimuli. Both sensory perception²¹ and the motility response to²² intraluminal balloon distention of the rectosigmoid are increased in IBS. As increased sensory perception is most prominent in diarrhoea predominant patients,²³ it has been suggested that abnormal sensation may be secondary to the occurrence of diarrhoea.²⁴ Heightened visceral perception in IBS, however, is not restricted to the distal colon, but is also found in the small intestine²⁵ and oesophagus.²⁶ Indeed, increased perception of physiological duodenal contractions may contribute to symptoms.²⁷ In contrast, somatic sensation elicited by ice-cold water²¹ and transcutaneous electrical stimulation²⁸ is normal or even

reduced²⁹ in IBS. The evidence available at present indicates that specifically altered visceral perception has an important role in the bowel hyperalgesia seen in IBS, and may involve increased central nervous system excitability or changes in descending pain modulatory systems.³⁰

Psychiatric illnesses are frequently associated with intestinal dysfunction in IBS, anxiety and affective disorders being most often diagnosed.³¹ As psychological disturbances usually precede onset of gastrointestinal complaints in IBS,^{31,32} but not organic disorders,³² they are not thought to be simply a reaction to the chronic presence of physical disease. Higher levels of anxiety and depression are found in patients with IBS compared with those with inflammatory bowel disease,³³ and also compared with those with functional chest pain.³⁴ The IBS patient group may therefore occupy a special position in the functional disorders on the basis of psychiatric as well as gastrointestinal symptoms. High levels of anxiety may mean patients present more readily to the clinician, and not always purely for gastrointestinal dysfunction. People with IBS who consult a physician are consistently found to be more psychologically distressed than those with similar abdominal symptoms who do not consult.³⁵ However, in a large-scale population survey IBS non-patients still showed higher lifetime rates of anxiety and affective disorders than subjects without gastrointestinal symptoms.³⁶ When recruited by the same strategy and inclusion criteria, IBS patients and non-patients seem not to differ in actual levels of psychological distress, but merely in whether they feel the need to consult a physician.³⁷ This concept is underlined by more recent experimental findings indicating that a subgroup of patients with IBS with jejunal hypersensitivity and postprandial dysmotility is characterised by an incapacity to cope effectively with stress.³⁸

Role of stressful life events

In assessing the role of stressful life events in the origin and manifestation of gastrointestinal symptoms in IBS, one can distinguish relatively recent events that either trigger onset or affect symptom severity, and stressful experiences earlier in life that may affect propensity to develop IBS. Studies in broader groups of functional gastrointestinal disorders seem to indicate a positive correlation between stressful life events in the preceding year and current severity of abdominal symptoms.³⁹ When using restrictive criteria for IBS, retrospective studies ranging from six months to one year failed to find significantly increased overall prevalence of stressful life events compared with organic illness³² or controls,³³ although stressful events preceded onset of bowel symptoms more often in IBS than in the organic group.³² Where IBS is clearly precipitated by an infectious episode, however, stressful life events in the preceding year are more frequent than in patients who do not develop symptoms of IBS, indicating pronounced synergy between stress and activation of the digestive immune system.⁴⁰ As recall of stressful events longer than three months ago is not likely to be very reliable⁴¹ and could be confounded by selective affective bias in patients with IBS,⁴² prospective studies of bowel symptoms after stress levels have been established are perhaps better suited to clarify their relation. Using time-lagged correlation, stress levels in a three month period were correlated significantly with bowel symptoms in the following three months, even when adjusted for individual differences in somatisation (tendency to exaggerate both physical and psychological symptoms).^{41,43} The slope of the regression line of stress on symptoms was significantly steeper for the IBS group than for controls or patients who did not meet diagnostic criteria, indicating greater reactivity to stress.⁴³ The

absence of increased influence of daily life stress on symptoms in functional dyspepsia⁴⁴ or organic bowel disease⁴³ indicates that the relation is relatively specific for IBS.

At the beginning of the 1990s, information began to emerge on a strong association, mainly in women, between functional gastrointestinal disorders and a history of childhood and adult sexual abuse and childhood physical abuse, although the latter was usually found in combination with sexual abuse.⁴⁵ By using structured interviews rather than self-report questionnaires, prevalence of severe sexual trauma in patients with IBS was considerably higher than in those with inflammatory bowel disease.⁴⁶ Population based studies have found a significant association between a history of sexual, physical or emotional abuse and IBS symptoms.^{3,47} Abused patients with symptoms of IBS are more likely than non-abused patients to seek health care for gastrointestinal symptoms⁴⁸ and to report somatic stimuli as painful.⁴⁹ The latter finding seems odd considering the normal somatic but increased visceral sensation in IBS, as discussed earlier. Measurement of sensitivity to bowel distention in abused patients is needed to clarify these findings. At present, it is too early to conclude whether abuse leads to actual changes in motility or in sensation thresholds, or whether the association between abuse and IBS symptoms can simply be explained by increased psychological distress and associated illness behaviour.⁴⁵ The need for consideration of traumatic life events in patients presenting with functional gastrointestinal disorders nevertheless seems clear.

POST-TRAUMATIC STRESS DISORDER

Gastrointestinal correlates

The most recent diagnostic criteria for PTSD state that it must follow experiencing or witnessing events that involve actual or threatened death or serious injury, or a threat to the physical integrity of self or others.⁵⁰ It is followed by spontaneous or conditioned re-experiencing of the traumatic event, avoidance of related stimuli, general numbing of responsiveness, and increased arousal. Prevalence in the general population is in the order of 1%. PTSD is associated with a number of other psychiatric disorders including generalised anxiety, panic disorder, major depression, and somatisation disorder.⁵¹ The presence of PTSD is usually coupled with poor physical health and cardiovascular morbidity that cannot be explained by biased self-reporting resulting from 'negative affectivity'.⁵² Reports on gastrointestinal symptoms in PTSD are relatively rare. Increased prevalence of disturbances of gastrointestinal function, including functional bowel disorders, in World War II and Korean prisoners of war^{53,54} may at least partially relate to the malnutrition and infectious disease experienced. Gastrointestinal symptoms have, however, also been found in combat veterans⁵⁵ and former hostages⁵⁶ with PTSD. Recently, the first systematic prospective study of functional gastrointestinal disorders in Vietnam combat veterans with PTSD found that 61% met diagnostic criteria for IBS or functional dyspepsia, but there was no difference in perceived severity of PTSD between patients with and without bowel symptoms.⁵⁷ The results seem to indicate that presentation with IBS-type symptoms may co-vary with a broader range of traumatic experiences than sexual or physical abuse.⁴⁵ Continued attention to visceral responses in PTSD is particularly important as there is evidence that physiological symptoms after trauma may persist in patients who no longer meet formal psychiatric criteria for PTSD.⁵⁸

Conditioning versus generalised sensitisation

Initially, laboratory measurements of autonomic reactivity in patients with PTSD concentrated on responses to conditioned stimuli related to the original traumatic experience. Psychophysiological (heart rate, skin conductance) responses to combat sounds and imagery were significantly greater in Vietnam veterans with PTSD than in veterans without the diagnosis.⁵⁹ Similarly increased responses to recall of traumatic imagery have been reported for civilian patients,⁶⁰ and the specificity of such conditioned responses forms part of current diagnostic criteria.⁵⁰ More recently, however, evidence has emerged that simple conditioning cannot account fully for symptoms of irritability, hypervigilance and increased startle responses to neutral stimuli.⁶¹ Combat veterans with PTSD⁶² and an undefined PTSD patient group⁶³ also display increased heart rate, skin conductance and eye-movement responses to random presentations of loud tones. Mean cardiovascular and respiratory responses to mental stimuli in IBS patient groups are similar to controls.^{12 17 18} The stimuli used are, however, relatively mild, and the experimental groups studied are probably heterogeneous in the amount and intensity of life stress experienced. Acute gastrointestinal motility responses to neutral stressors will have to be assessed in order to determine the nature of the correlation between combat related PTSD and symptoms of IBS and dyspepsia.⁵⁷ It is still unclear why traumatic experiences would lead to specific visceral sensitisation in some individuals, but not in others. The interplay between stress induced central nervous system (CNS) changes and intestinal motility and sensitivity are likely to be complex. If traumatic experiences have a role in the initiation of altered perception of motility in IBS, it is quite possible that abdominal discomfort, in turn, acts to reinforce CNS abnormalities in a vicious circle of mutual aggravation.⁶⁴ As it is evidently difficult to follow prospectively consequences of severe stressful experiences for psychological and intestinal responsiveness in humans, use of existing animal models for stress induced sensitisation could help to clarify neural or hormonal mechanisms relevant for the gut.

Animal models

STRESS AND INTESTINAL MOTILITY

Attempts have been made to investigate the effects of acute stress on intestinal motility in human volunteers, but such studies have a number of drawbacks.⁶⁵ It is unclear what relation the stimuli used (cold or pain stimuli to the skin, mental arithmetic) have to daily life stressors. The use of invasive techniques to measure transit or motility in the various divisions of the gastrointestinal tract has its limitations, and study of the nervous system mediators involved is difficult. Animal studies have therefore been used from the mid-1980s to study the relation between stress and motility. Some of the earlier studies on small intestinal motility were performed in dogs, fitted either with electrodes or force transducers directly on the intestinal wall. One to two hours of acoustic stress (broad frequency noise) has no effect on the dog fasting jejunal MMC,⁶⁶ but prolongs the pattern of irregular contractions seen after a meal.⁶⁷ Most studies investigating mechanisms of stress induced changes in intestinal motility, however, have been performed in the laboratory rat. The clearest effects are found when rats are partially or completely immobilised (restraint stress). In the fasted state, the MMC is immediately replaced by a pattern of irregular spiking, and spike burst frequency in the colon is

increased.⁶⁸ Small intestinal transit of a meal is delayed and colonic transit accelerated by wrap restraint.⁶⁹

Although a distinction between purely 'physical' and purely 'psychological' stress is often artificial,⁷⁰ models have also been used in which fear is the predominant component. In rats forced to remain on a small platform in a flooded cage, small intestinal transit of a labelled meal is delayed, and colonic transit accelerated.^{71 72} In fasting rats, classically conditioned fear of a cage in which foot shocks have been experienced the previous day causes an increase in proximal colonic spike burst frequency^{73 74} but, in contrast to restraint, does not affect jejunal MMC frequency.⁷⁴ One problem in the interpretation of stress effects has been that it is difficult to judge the emotional impact of the various stressors on the animals in question. Analysis of the different behavioural components displayed during stress has shown that the size of increased colonic spike burst activity is determined by the amount of fear experienced in the shock apparatus, previously shocked rats showing a greater increase than non-shocked controls.⁷⁴ Autonomic pathways, primarily the vagus nerve, rather than hormones of the hypothalamic-pituitary-adrenal axis are thought to mediate stress effects on intestinal transit and motility.^{69 75} Intra-cerebroventricular injection of antagonists or antisera against a number of neurotransmitters and neuromodulators, most notably corticotropin releasing factor, can reduce or prevent stress effects on intestinal transit and motility.⁷⁶⁻⁷⁸ It is often unclear, however, whether their effects are due to general alterations in pathways involved in the stress response, or apply more specifically to gastrointestinal reactivity. Comparison with the effects of such blockers on behavioural responses to stress, but also more site specific, local injection,⁷⁹ may shed more light on the mechanisms mediating changes in intestinal motility.

STRESS INDUCED SENSITISATION

Rats exposed to a series of 80–135 inescapable tail shocks, approximately within a one hour period, fail to learn to escape from a compartment in which foot shocks are administered to one that is 'safe' on the following days.^{80 81} Initially, this phenomenon was termed 'learned helplessness' (LH) as it was assumed that animals learned that escape from shocks was impossible, resulting in 'behavioural despair'. Further studies, however, indicated that inescapably shocked rats also subsequently showed increased immobility in a large open space⁸² and reduced social interaction,⁸³ indicating that increased anxiety may be the main determinant of immobility responses after LH shocks (see Maier⁸⁴ for a review). It has been observed that the escape deficit alluded to only occurs after administering a relatively large number of shocks.⁸⁰ When, however, rats are exposed to a single foot shock on five consecutive days,⁸⁵ or to 10 foot shocks in a 15 minute period,⁸⁶ the behavioural immobility and corticosterone responses after exposure to a novel, large open space are increased for at least two weeks. Moreover, the magnitude of the change in behavioural responsiveness seems to increase gradually in the first week following foot shock stress.⁸⁶ Sensitised behavioural reactivity and activation of the hypothalamic-pituitary-adrenal axis to a number of novel challenges from two to four weeks after foot shock have since been reported.^{87 88} The effects of a short session of foot shocks seem compatible with increased behavioural defensiveness akin to anxiety, and there are indications that they may be reversed by chronic treatment with classic anxiolytics, but not antidepressants.⁸⁹ The sensitising effects of stressful experience seems to be interchangeable with that of a variety of psychoactive drugs, probably by way of their

non-specific stressful character rather than specific pharmacological actions.⁹⁰ Interestingly, social deprivation for two weeks in young rats increases later stress and drug induced behavioural sensitisation.⁹¹ It is tempting to relate such results to the finding that early adversity (abuse) in humans increases the risk for development of PTSD after combat experience later in life.⁹²

When rats from an inbred strain are confronted with an aggressive conspecific, resulting in defeat and submission and followed by a short period in the presence of the aggressor in an enclosed compartment,^{93 94} the amplitude of circadian body temperature rhythms is reduced for several days following the defeat experience.⁹⁵ Unlike a single session of foot shocks,⁹⁶ a single social defeat also results in loss of body weight that recovers within two weeks.⁹³ Less transient changes after social defeat, however, seem to have more in common with those observed after inescapable shocks. As in foot shocked rats,⁸⁶ the immobility response to a sudden drop in background noise is increased for at least three weeks after a single defeat experience.⁹³ Similarly, exposure to a foot shock session reduces the analgesic effects of a single tail shock,⁹⁷ and defeat those of morphine⁹⁸ 10 days later. Although the mechanisms by which long term effects of foot shocks and social defeat develop may differ, evidence that they result in fundamentally different states of behavioural reactivity is, at present, lacking. Thus, it has become clear that short exposure to stress (foot shocks, drug administration, restraint, social stress) can result in persistent changes in behavioural, hormonal, and analgesic responses to similar or novel stressors that grow stronger over time. Such animal models may be helpful in our understanding of the pervasive consequences of traumatic stress in humans, although autonomic and visceral responses after stressful experiences have as yet received little attention.

TOWARDS MORE USEFUL MODELS

Reports on long term effects of stress on intestinal motility in laboratory animals are relatively scarce. A reduction in the duration of MMC activity fronts was noted for two days after 12 hours of 'travel stress' in the rat,⁹⁹ and increased colonic spike burst frequency was still seen three days after six hours of restraint stress.⁶⁸ Both seem to represent immediate after-effects of moderate duration stress on basal motility. It was recently reported that the introduction of a novel stressful stimulus in the home cage, an electrified prod, causes a clear increase in colonic spike burst frequency in rats that had received a short session of foot shocks two weeks earlier, but not in the control group.⁹⁶ As this particular stimulus, applied under resting conditions, did not induce clearly differential behavioural responses in rats with and without a previous foot shock experience, it is possible that more specific changes in the control of colonic motility occur in parallel with the behavioural sensitisation found with different challenges. It is too early to speculate to what extent central or peripheral mechanisms may contribute to sensitisation of colonic responses after a stressful experience. Altered in vitro contractile responses of colonic and jejunal tissue to electrical or cholinergic stimulation after stress have been reported,^{100 101} but these were only measured in the days immediately following the stress experience. Future assessment of activation of specific brain centres by novel stressors in 'traumatised' rats using stains for immediate early gene products¹⁰² could complement recent advances in the use of functional imaging techniques to assess CNS responsivity to stimuli in patients with IBS.¹⁰³ Methods have also been developed to assess visceral sensitivity in the laboratory rat, and with their help altered visceromotor

responses to distention have been found after intraluminal pretreatment with acetic acid or the experimental colitis induced after treatment with trinitrobenzene sulphonic acid.^{104 105} It would be interesting to examine whether previous stressful experiences can potentiate experimental colitis induced hyper-responsivity. Although disentanglement of central and peripheral components will be no mean task, parallel lines of investigation examining changes in brain areas important for the control and perception of intestinal motility, and of changes in local regulatory and effector mechanisms in the gut, may improve our understanding of the relation between behavioural and colonic sensitisation after stressful experience.

As evidence is beginning to emerge that IBS patient and non-patient groups show clear differences in coping capabilities,^{35 106} and that higher scores for anxiety, depression, somatisation, and neurotic trait increase the likelihood for development of post-infectious IBS,⁴⁰ the need for relevant animal models addressing individual vulnerability seems clear. In all likelihood, not only behavioural and neuroendocrine, but also intestinal responses to stress in laboratory rats will depend to some degree on genetically and developmentally determined individual reactivity and coping styles.¹⁰⁷ Locomotor activity in a large, novel arena, the so called open field, is a partly hereditary, partly environmentally determined predictor of individual differences in rodent reactivity to other novel stressful challenges, low locomotor activity generally being associated with high levels of defaecation.¹⁰⁸ Rats selected for either high or low activity in the open field seem to show fundamental differences in behavioural, hormonal and cardiovascular response patterns to novel challenges.^{109 110} Recent evidence indicates that rats in the 'low activity' cluster show a greater colonic motility response than those in the 'high activity' cluster to a novel stressor that does not induce defaecation (Stam *et al*, unpublished observations). The challenge for the future is to determine whether, and via which mechanisms, such selected groups with different coping styles also show differential vulnerability to stress or infection induced intestinal sensitisation. In the long run, biobehavioural studies in the laboratory rat may help to explain why functional bowel disorders in humans result in such extreme discomfort and disability in some patients, whereas others with similarly disordered motility simply get on with their lives.

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