Stress and visceral perception

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MM Delvaux. Stress and visceral perception. Can J Gastroenterol 1999;13(Suppl A):32A-36A. Functional bowel disorders are characterized by the presence of a visceral hyperalgesia in most patients. This visceral hyperalgesia is related to an enhanced perception of sensations originating from the gut. Stressful events can dramatically influence the course of functional bowel disorders, and patients suffering from these syndromes appear to be more susceptible to the stressful events of daily life. However, until now, few studies have evaluated the relationship between stress and visceral perception. Some studies of healthy volunteers indicated contradictory results, but the studies used different methodologies. During stress conditions, either physical or mental, thresholds of perception of rectal distension were increased, suggesting a 'distraction effect', or were decreased, supporting a sensitizing effect of stress. In most studies, rectal compliance was not affected, but stress has been shown to alter the rectal tone, as measured by a barostat. One study comparing irritable bowel syndrome patients with controls demonstrated the importance of cognitive processes in the modulation of visceral perception by stress. Animal studies have also demonstrated the sensitizing effect of stress on the perception of rectal distension. Mediators involved may be numerous, but corticotropin-releasing factor has been demonstrated to play a major role at the central level. Mast cells and histamine release may play a role at the peripheral level. Stress can thus be included in an integrative model explaining the pathophysiology of functional bowel disorders. Advances in the understanding of the relationship between stress and visceral perception may constitute a basis for a therapeutic approach of functional bowel disorders targeted on the central nervous system.

Key Words: *Functional bowel disorders, Irritable bowel syndrome, Stress, Visceral perception*

Stress et perception viscérale

RÉSUMÉ: Les troubles intestinaux fonctionnels se caractérisent par la présence d'une hyperalgésie viscérale chez la plupart des patients. Cette hyperalgésie viscérale est liée à une perception plus aiguë des sensations émanant de l'intestin. Les événements stressants peuvent influer de façon dramatique sur l'évolution des troubles intestinaux et les patients qui en souffrent semblent plus sujets aux événements stressants dans la vie de tous les jours. Par contre, jusqu'à présent, peu d'études ont porté sur le lien entre le stress et la perception viscérale. Certaines, menées auprès de volontaires en bonne santé, ont fait état de résultats contradictoires, mais elles ont utilisé des méthodologies différentes. En présence de stress physique ou mental, les seuils de perception de la distension rectale s'élèvent, ce qui suggère un ‹‹ effet de distraction ››, ou s'abaissent et appuient alors l'hypothèse d'un effet sensibilisant du stress. Dans la plupart des études, la compliance rectale n'a pas été affectée mais le stress s'est révélé apte à modifier le tonus rectal mesuré à l'aide d'un appareil barostatique. Une étude qui comparait les patients atteints d'un syndrome du côlon irritable à des témoins a démontré l'importance du processus cognitif dans la modulation de la perception viscérale par le stress. Des études animales ont également démontré l'effet sensibilisant du stress sur la perception de la distension rectale. Les médiateurs en jeu sont peut-être nombreux, mais on a démontré l'important rôle de la corticolibérine au niveau central. La libération de mastocytes et d'histamine peut jouer un rôle au niveau périphérique. Le stress peut donc être inclus dans un modèle d'intégration expliquant la physiopathologie des troubles intestinaux fonctionnels. L'approfondissement de nos connaissances sur les liens entre stress et perception viscérale pourrait devenir la base d'une approche thérapeutique des troubles intestinaux fonctionnels axée davantage sur le système nerveux central.

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Visceral sensory function and its disturbances have been demonstrated to play a major role in the pathophysiology of functional bowel disorders (FBD). Studies published during the past five years have confirmed and further assessed the initial demonstration by Ritchie (1) and by Lasser et al (2) that patients with FBD frequently present with a visceral hypersensitivity that is best shown by distension studies. The development of the barostat, which enables precise, repetitive distensions of the gut and simultaneous recording of the distending pressure and volume, has led to a number of studies on visceral hyperalgesia in both healthy volunteers and patients with FBD (3). The increasing knowledge about visceral afferent nerve pathways has allowed the description of a number of transmitters that constitute the target for the development of new drugs aimed to relieve abdominal pain in FBD patients (4).

The role of stress and stressful events is recognized in patients with FBD. Psychological stress is widely believed to play a major role in the irritable bowel syndrome (IBS) by precipitating exacerbations of symptoms. Subjects with IBS show a greater reactivity to stress, and stress scores are significantly correlated with the number of disability days and the number of clinical visits for bowel symptoms (5). The role of stress in inducing changes in gut motility has been recognized in both animals and humans (6,7).

It is, thus, worthy to assume that visceral perception and particularly visceral hypersensitivity are influenced by stress in patients with FBD. However, very few studies have investigated this field.

STUDIES IN ANIMALS

One recent study evaluated the effects of stress on visceral perception in animals (8). In this study, the perception of rectal distension was characterized by the rectocolonic inhibitory reflex that is triggered by distension and by the number of contractions of striated abdominal muscles, as previously demonstrated (9). These reflexes, either viscerovisceral or viscerosomatic, are triggered by painful distensions. We obtained an obvious viscerosomatic reflex in humans (increase in the number of abdominal contractions) only for distensions far above the usual pain or discomfort threshold measured in human distension studies (unpublished data).

In rats, when a restraint stress was applied for 2 h before the distension was performed, the response to rectal distension was sensitized (8). The number of abdominal cramps evoked by rectal distension was significantly higher in stressed animals compared with the number in controls (Figure 1). In this study, stress did not affect the compliance of the rectum because the pressure-volume relationship did not change after stress (Figure 2). One may, therefore, conclude from this study that stress modulates the perception of painful rectal distension in animals and sensitizes the animals to distension, thereby inducing stress hypersensitivity.

STUDIES IN HUMANS

The first study was published by Erckenbrecht (10) in 1989. The author demonstrated that psychological (dichotomous listening) and physical stresses (cold pressor test) showed

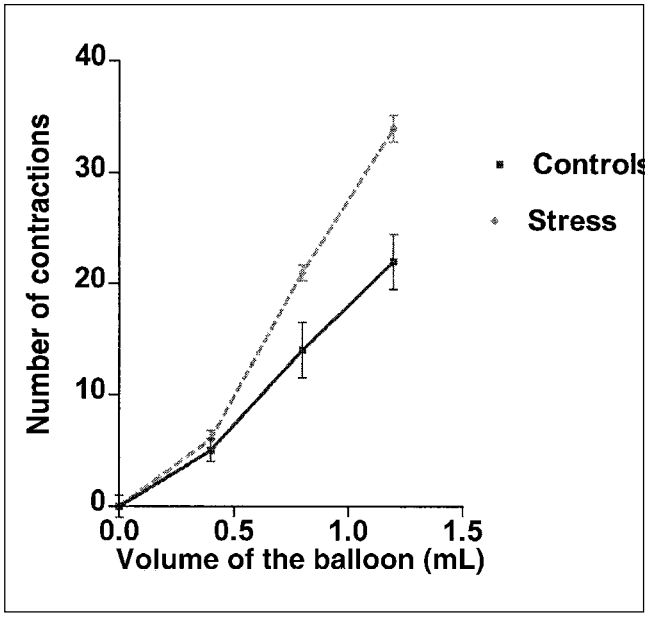

Figure 1) *Response of the abdominal striated muscles expressed in number of contractions per 5 mins, to increasing volume of rectal distension after sham stress (controls) or partial restraint stress. Effect of stress is significant for the highest volumes of distension tested. Data from reference 8*

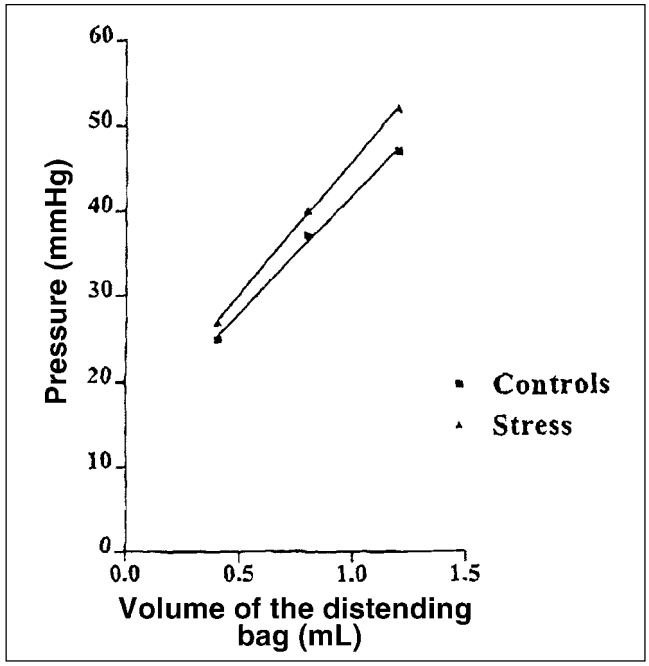

Figure 2) *Pressure-volume relationship during rectal distension in stressed and control animals. No change was observed in the compliance of the rectum. Data from reference 8*

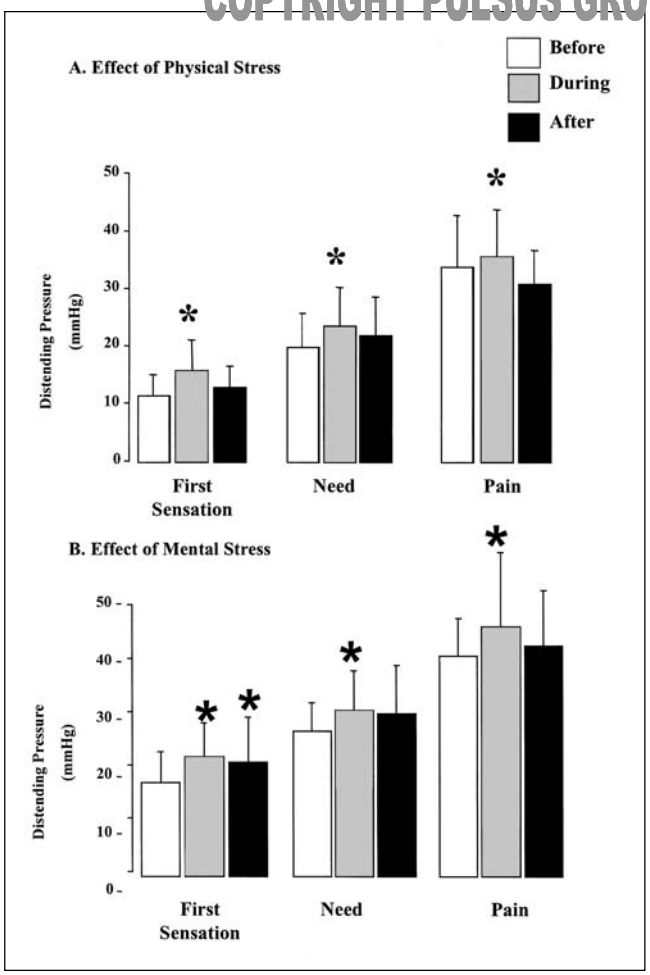

Figure 3) *Thresholds of pressure inducing rectal sensations in healthy volunteers submitted to mental (dichotomous listening) and physical stress (cold pressor stress). *P<0.05*

differential effects on perception of rectal distension. During the psychological stress, volume thresholds inducing a sensation of urge to defecate were lower than those during the basal condition, while during physical stress, the thresholds were higher than those during baseline conditions. This effect was even long lasting in the case of mental stress because thresholds detected 1 h after the end of the stressful period were still significantly lower than the baseline measurements. From these results, it was concluded that stimulation of the central nervous system (CNS) by psychological stress sensitizes the perception of a 'painful' peripheral visceral stimulus, while the hyperstimulation of peripheral somatic perception by a physical stress triggers distraction mechanisms that lead to decreased perception. The latter effect may result from a competition of sensory messages from somatic and visceral origin in triggering sensations at the level of the CNS, or it may result from peripheral reflexes inducing mutual influence of visceral and somatic afferent pathways on each other. The latter assumption was demonstrated by Bouhassira et al (11) and Sabaté et al (12), who showed that the electrical stimulation of a peripheral somatic nerve influences the perception of gastric or rectal distension.

More recent studies have had contradictory results. In a preliminary study published as an abstract, Mönnikes et al (13) showed that a short psychological stress (5 mins) had nearly no measurable effect on pressures triggering rectal sensations in IBS patients with rectal hypersensitivity or in healthy volunteers. However, in this study, the 'distraction' effect was much more marked in healthy controls than in patients. In the latter group, the pressure triggering rectal discomfort increased by only 15% compared with baseline measurements, while it increased by 60% in controls. One may conclude from these results that a short lasting stress did not influence the thresholds of perception triggered by rectal distension in terms of pressure applied. However, during stress itself, a distraction effect was observed that was much more pronounced in patients with IBS than in controls. This may be related to the more important susceptibility of IBS patients to stressful events (14).

Other studies in the field have included healthy volunteers. Ford et al (15) published very interesting results of a study where they compared the effects of stress (dichotomous listening) with the effects of active relaxation in 22 volunteers. These authors evaluated the effects of these stressful and relaxing periods on imposed distensions. They did not track thresholds of perception but characterized the intensity of response to three defined distensions of the rectum, at increasing pressures. They observed that stress provokes a moderate increase in the intensity of sensations recorded by subjects for a given painful stimulus at the level of the sigmoid but not of the transverse colon. The sensation of gas (bloating) also increased during the period when the psychological stress was applied. Active relaxation had no effect on the intensity of pain and had few effects on gas sensation, which was less intense at the highest distension step in both the transverse and the sigmoid colon. The authors concluded that stress and relaxation did not affect compliance of the colon.

In a recent study, we evaluated the effects of physical (cold pressor stress) and mental (dichotomous listening) stress on the perception of rectal distension and on the tone of the rectal wall in healthy volunteers (16). We observed a clear distraction effect for both mental and physical stress during the time the stress was applied but did not observe any increase in the perception of rectal distension characterized by lowered thresholds for the following sensations: first sensation, urge to defecate and pain (Figure 3). However, when we considered the responses of the subjects to a given stimulus, we observed an increase in the intensity of reported symptoms, at least for the painful sensations (Figure 4). In addition to these changes in the distending pressure at the various thesholds, we observed a significant increase in the volumes measured in the bag at the various thresholds. These changes in volume indicated that stress may have modified the compliance of the rectum. Indeed, it has been shown previously in humans that stress stimulates colonic motility (17).

Although these studies sometimes showed contradictory results, they clearly indicate that stressful situations, either

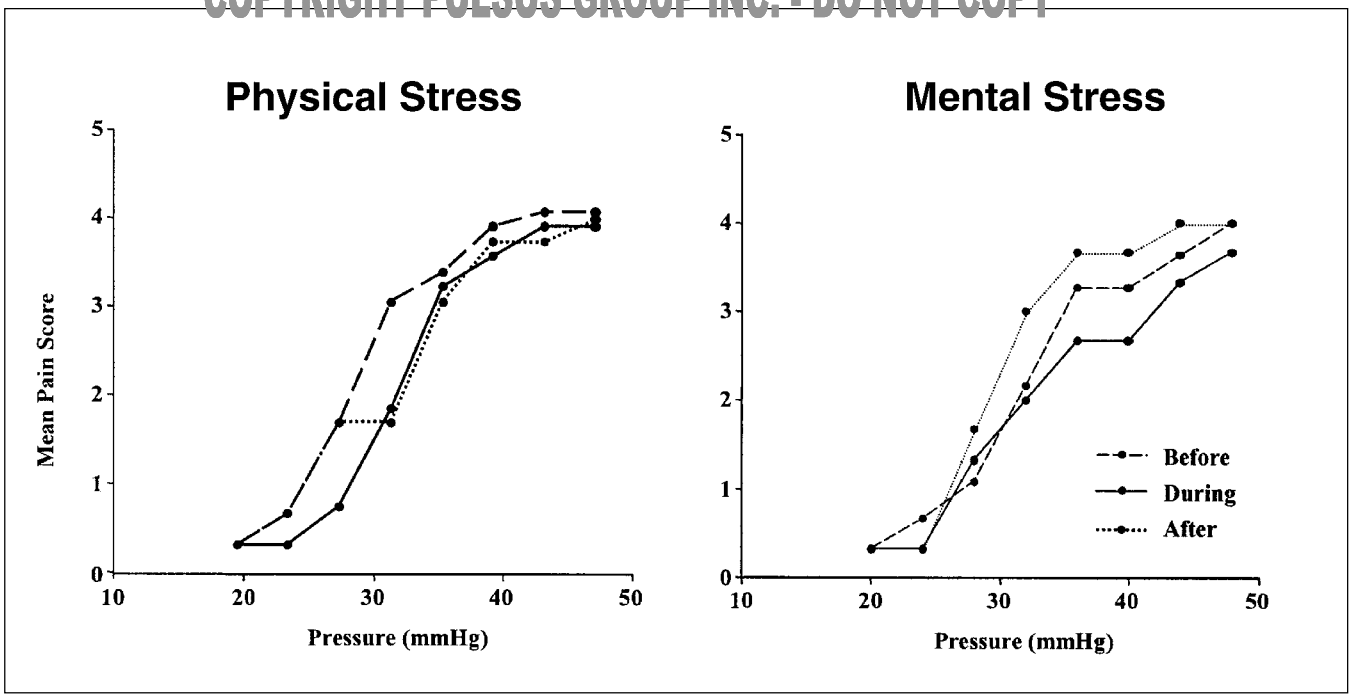

Figure 4) *Intensity of the response to painful rectal distension applied during and after mental (dichotomous listening) and physical stress (cold pressor stress) in healthy volunteers*

physically or mentally stressful, influence perception of visceral sensations in humans. However, the mechanisms involved may be rather complex, and one must keep in mind that stress also influences the motility of the gut. Effects may even be contradictory, more intense sensations being reported by the subjects but higher thresholds of perception, measured with barostat. The complexity of the changes in perception observed during stress conditions may be explained by the number of peripheral and central factors that influence them.

PATHWAYS INVOLVED AND NEUROTRANSMITTERS

Studies on visceral hypersensitivity in patients with IBS have proposed that hyperexcitability of the dorsal horn of the spinal cord is central for the development of this hyperalgesia (18,19). However, others have reported that the primary disorder may be located at the level of the mechanoreceptors within the gut wall itself (20). Changes induced by stress may be generated by the alterations in gut motility that stress provokes (17) or by the interaction among various afferent pathways as suggested by studies using the RIII reflex, presented above. Changes in motility may also result in alteration of gut compliance and in tone changes. Both are known to influence the perception of luminal distension (21). Thus, a peripheral action of stress may be responsible, at least partly, for its sensitizing action on visceral afferents and receptors. This hypothesis is reinforced by the observation in animals that stress increases the release of mediators by mast cells and that doxantrazole, a mast cell stabilizer, prevents the sensitizing effect of stress on rectal distension in rats (8).

Besides this local or peripheral effect of stress, one must also consider that stress mainly affects the mental status of the individual. Visceral hypersensitivity may result from differences in cerebral processing of standard peripheral afferent signals. This observation reinforces the role of psychosocial factors in the pathogenesis of FBD that are frequently characterized by visceral hyperalgesia. These psychosocial factors, previous illness and illness behaviour may influence the perception of pain in patients with IBS (22). From the experimental results described above, many observations support the role of cognitive processes in the modulation of visceral pain perception. Studies in healthy volunteers have revealed both a distraction effect during the stress period, which is clearly related to cognitive processes, and a sensitizing effect of stress, which may result from a more complex mechanism. Recent studies with positron emission tomography scans showed that distinct areas of the brain can be stimulated by rectal distension in IBS patients and in controls (23). There are multiple candidates for integration of stress and visceral perception processes at the CNS level. One main nucleus is the locus coeruleus, where projecting noradrenaline-containing neurons can be activated by nonnoxious stimuli through sympathetic pathways (24) and are also able to enhance signal processing during stress by means of corticotropin-releasing factor (CRF) action (25).

Several neurotransmitters play a role in the process of visceral sensations by afferent nerves. The purpose of the present report is not to describe the neurotransmitters in detail; we have recently published a review on this topic (4). Among these neurotransmitters, somatostatin, serotonin and calcitonin gene-related peptide play a significant role at

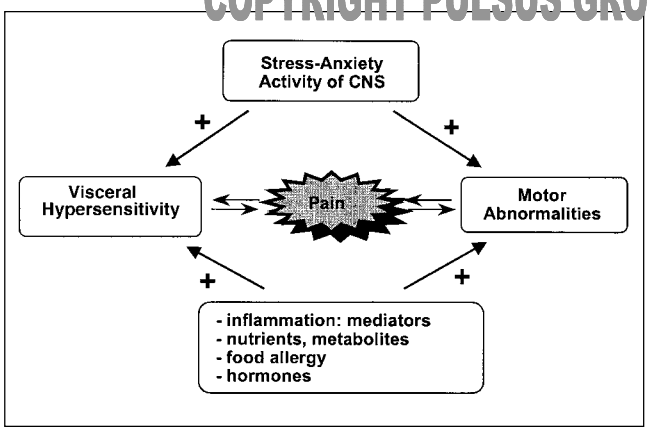

Figure 5) *Integrative view of multiple factors involved in the pathogenesis of abdominal pain in patients with functional bowel disorders. Respective role of these factors in the activity of afferent and efferent nerve pathways. CNS Central nervous system*

the peripheral level. A number of neuropeptides and transmitters may be involved at the central level. Somatostatin may play a role, but some studies have shown that CRF was also able to modulate visceral reflexes and even was involved in the modulation of perception of rectal distension in humans (26). On the other hand, CRF is known to play a major role in mediating the effects of stress on the gut (reviewed in 27). Therefore, one of the neurotransmitters may mediate the effect of stress on visceral perception. A recent study in animals included experiments with an antagonist of CRF (8). Interestingly, this CRF antagonist suppressed the sensitizing effect of stress when administered centrally in rats. Moreover, in the same experiments, the intracerebroventricular injection of CRF mimicked the effects of stress and increased the perception of rectal distension (8). One may, thus, conclude that the role of CRF may be important in the interaction between stressful events and abnormal visceral perception.

CONCLUSIONS

Stress is commonly considered to be one of the factors involved in the pathophysiology of FBD. These disorders are frequently characterized by visceral hyperalgesia. It is, therefore, worthy to propose an integrative scheme of the multiple factors responsible for abdominal pain in patients with FBD (Figure 5). These factors act on either the afferent or the efferent nerve pathways, or both and they play a role not only at the central level but also at the peripheral level. This integrated view of the pathophysiology of FBD may have concrete implications for the therapeutic management of such patients, including an approach to the CNS.

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