

Selye's general adaptation syndrome: stress-induced gastro-duodenal ulceration and inflammatory bowel disease

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Abstract

Hans Selye in a note to *Nature* in 1936 initiated the field of stress research by showing that rats exposed to noxious stimuli responded by way of a 'general adaptation syndrome' (GAS). One of the main features of the GAS was the 'formation of acute erosions in the digestive tract, particularly in the stomach, small intestine and appendix'. This provided experimental evidence for the view based on clinical data that gastro-duodenal (peptic) ulcers could be caused by stress. This hypothesis was challenged by Marshall and Warren's Nobel Prize (2005)-winning discovery of a causal association between *Helicobacter pylori* and peptic ulcers. However, clinical and experimental studies suggest that stress can cause peptic ulceration in the absence of *H. pylori*. Predictably, the etiological pendulum of gastric and duodenal ulceration has swung from 'all stress' to 'all bacteria' followed by a sober realization that both factors play a role, separately as well as together. This raises the question as to whether stress and *H. pylori* interact, and if so, how? Stress has also been implicated in inflammatory bowel disease (IBD) and related disorders; however, there is no proof yet that stress is the primary etiological trigger for IBD. Central dopamine mechanisms seem to be involved in the stress induction of peptic ulceration, whereas activation of the sympathetic nervous system and central and peripheral corticotrophin-releasing factor appears to mediate stress-induced IBD.

Key Words

- ▶ peptic ulcers
- ▶ stress
- ▶ *Helicobacter pylori*
- ▶ inflammatory bowel disease
- ▶ brain-gut axis

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Introduction

Eighty years ago, *Nature* published a note from Hans Selye entitled 'A Syndrome produced by Diverse Noxious Agents' (Selye 1936). Briefly, Selye reported that if experimental rats were 'damaged by acute non-specific noxious agents such as exposure to cold, surgical injury, excessive muscular exercise, or intoxications with sub lethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical

syndrome appears'. Selye termed this the general adaptation syndrome (GAS) 'the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed and represent rather a response to damage as such.' The main features of the syndrome were a fall of body temperature and decrease in muscle tone; decrease in size of the thymus, spleen, lymph nodes and liver; acute erosions of the

digestive tract; enlargement of the adrenal glands and histological changes in the adrenal medullary chromaffin cells; increased secretion of pituitary 'thyrotropic and adrenotropic principles'. Selye's observations translate in modern terms to stress-induced immunosuppression, peptic ulceration and inflammatory bowel disease (IBD) and activation of the two main vertebrate stress response systems: the hypothalamic–pituitary–adrenal axis (HPA) and the sympathomedullary system.

Stress research has made huge advances since Selye's publication especially with respect to the fundamental neurobiology and neuroendocrinology of the stress response (McEwen 2007, Joels & Baram 2010, Henckens *et al.* 2016). However, uncertainties, irreproducible results and unresolved controversies remain (Fink 2011). These include, for example, the nature, if any, of genetic and epigenetic mechanisms that determine the susceptibility or resilience to stress; perinatal effects that might determine stress vulnerability in adults; the relative importance of the autonomic nervous versus the brain–pituitary–adrenocortical system in mental illness such as post-traumatic stress disorder, major depression and the psychoses; and whether stress and anxiety damage the human brain and if so whether the damage is reversible.

Here, attention will focus on the controversial issue of the role of stress versus *Helicobacter pylori* in the causation of gastro-duodenal ulceration. Brief mention of inflammatory bowel disease will also be made since this disorder, perhaps predicted by the GAS, might also be affected by stress.

Gastro-duodenal ulceration: stress vs *Helicobacter pylori*

The fact that emotions such as fear and anger affect acid secretions of the stomach was first documented in 1833 by US Army surgeon William Beaumont in his studies on Alexis St Martin a French Canadian fur trapper who accidentally sustained a massive gunshot wound in the stomach (Beaumont 1833). The wound resulted in a chronic gastric fistula that enabled Beaumont to make direct observations of the mucosa of the stomach and gastric secretions under different conditions. Beaumont's findings provided the basis for the subsequent experiments of Ivan Petrovich Pavlov carried out in dogs by means of a gastric pouch, which led to the discovery of the conditioned reflex and the concept of the 'cephalic phase' of gastric and pancreatic secretion (Wood 2004). However, robust evidence that stress could induce gastro-duodenal

('peptic') ulcers was first adduced by Selye's GAS findings that stress induced the 'formation of acute erosions in the digestive tract, particularly in the stomach, small intestine and appendix' (Selye 1936).

The observations of Beaumont, Pavlov and Selye and the fact that massive perforation of the stomach and other parts of the gastrointestinal tract in the human were associated with brain lesions or 'neurogenic' factors (Oppen & Zimmerman 1938, Boles & Riggs 1941, Rosenthal & Tobias 1943) led to the view that stress was the main cause of gastro-duodenal (peptic) ulceration. The first description of neurogenic ulcers was by Harvey Cushing who, perhaps ironically, in later years with failing health developed an ulcer himself (Wijdsicks 2011). Psychological studies using life events as a measure showed that chronic stress in the human is associated with peptic ulceration when the stressor comprises personal threat or goal frustration (Piper & Tennant 1993).

The assumption that peptic ulceration was caused by stress seemed to be overturned when Barry Marshall and Robin Warren in the 1980s and 90s made their 2005 Nobel Prize-winning discovery that gastric and duodenal ulcers appeared to be caused by *H. pylori* (Marshall & Warren 1984, Marshall & Windsor 2005, Cover & Blaser 2009). This suggested that antibiotics together with proton pump inhibitors could be the optimal treatment for gastro-duodenal ulcers and dyspepsia in general, a simple and apparently benign approach that is only sometimes confounded by antibiotic resistance (Tay *et al.* 2012).

There is no doubt that a substantial number of peptic ulcers are associated with the presence of *H. pylori*. However, notwithstanding the importance of *H. pylori* for peptic ulceration (and gastric cancer), several studies in the human and in rodents show that stress plays a significant role in peptic ulceration (Matsushima *et al.* 1999, Kim *et al.* 2002, Levenstein 2009, McColl 2009). The role of stress in the causation of peptic ulceration in the human is exemplified by the fact that the Hanshin-Awaji earthquake, which occurred on 17 January 1995, was followed by a significant increase in the number of people with peptic ulceration (McColl 2009, Levenstein *et al.* 2015). Among the physically injured, stomach ulcers developed independently of *H. pylori* infection. Extensive burns also lead to stress ulcers that are likely to be independent of *H. pylori* status (McColl 2009). Furthermore, most people living with *H. pylori* never develop ulcers, about 30% of patients with ulcer do not harbor *H. pylori* infection and some patients in whom *H. pylori* colonization has been cleared by antibiotics subsequently develop new ulcers (Levenstein 2009).

The above points are supported by several control-balanced clinical studies. Thus, for example, a Finnish nationwide twin cohort study of lifestyle, stress and genes in peptic ulcer disease led to the conclusions that, first, familial aggregation of the peptic ulcer disease is modest and attributable almost solely to genetic factors, and, second, that the data did not support the concept that risk factors such as *H. pylori* infection could explain familial peptic ulcer disease (Räihä *et al.* 1998). A comprehensive study in Thailand of 70 patients with perforated peptic ulcer compared with a balanced number of control subjects led to the conclusion that stress, but not *H. pylori*, is associated with peptic ulcer disease in this Thai population (Wachirawat *et al.* 2003). Finally, a recent population-based Danish cohort ($n=2410$) study showed that psychological stress increased the incidence of peptic ulcer in subjects with or without *H. pylori* infection (Levenstein *et al.* 2015).

The case for the importance of psychosocial stress factors in the causation of peptic ulcer disease has been summarized as follows (Levenstein 2000, Jones 2006, Realo *et al.* 2015). First, despite the decreasing prevalence of *H. pylori* infection in Western societies, the burden of peptic ulcer disease remains high. Second, most *H. pylori*-infected individuals never develop peptic ulcers. Third, a proportion of patients develop peptic ulceration in the absence of *H. pylori*.

The precise mechanism by which stress can cause gastro-duodenal ulcers is yet to be determined. However, in addition to the possible effects of neuroendocrine (hypothalamic–pituitary–adrenal)-induced elevation of glucocorticoid levels on the gastro-duodenal mucosa (Levenstein *et al.* 2015), central and peripheral dopaminergic mechanisms remain contenders (Szabo 1979, Glavin & Szabo 1990, Ozdemir *et al.* 2007, Rasheed & Algsham 2012). The clue to a possible role of central dopamine came from clinical observations and hypotheses regarding the etiology of Parkinson's disease and schizophrenia. Thus, as early as 1965, Strang noted an association between Parkinson's disease, characterized by central dopamine deficiency, and gastro-duodenal ulceration (Strang 1965). This was especially the case in young Parkinsonian patients compared with control subjects. *Pari-passu* duodenal ulcers are rare in patients with schizophrenia, a condition in which dopaminergic activity is thought to be increased (Glavin & Szabo 1990). Experimental evidence for a central role of dopamine deficiency as a cause of duodenal ulceration comes from the effects of N-methyl-D-aspartate lesions of the substantia nigra (Landeira-Fernandez & Grijalva 2004) and the

systemic administration of the dopaminergic neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The latter induces nigrostriatal dopamine depletion the magnitude of which correlates with the severity of the duodenal ulcers (Glavin & Szabo 1990, Sikiric *et al.* 1999). Further evidence for the role of dopamine deficiency or excess in causing or protecting against gastro-duodenal ulceration, respectively, is derived from studies of dopamine agonists and antagonists (Szabo 1979, Glavin & Szabo 1990, Ozdemir *et al.* 2007, Rasheed & Algsham 2012).

Inflammatory bowel disease

Stress, in addition to its role in peptic ulceration, is thought to play a role in IBD and related disorders such as irritable bowel syndrome, adverse reactions to food antigens and gastroesophageal reflux disease (Konturek *et al.* 2011). This effect of stress is probably mediated by the sympathomedullary system and corticotrophin-releasing factor (CRF) acting both centrally and within the gut (Bunnett 2005, Tache *et al.* 2008, Lukewich *et al.* 2014). Notwithstanding the possible role of stress in bowel disorders and the fact that CRF and its receptors are regarded by some as potentially relevant therapeutic targets (Tache *et al.* 2008), it must be stressed that the signal factors that trigger IBD and related disorders remain to be determined. The story is far from complete.

Conclusion

Hans Selye's experimental rodent observations and inferences that stress can cause the 'formation of acute erosions in the digestive tract, particularly in the stomach, small intestine and appendix' also apply to the human. Thus, stress may play a role in IBD and related disorders, but proof that stress is a main let alone sole trigger awaits further rigorous research.

With respect to the stomach and duodenum, stress and *H. pylori* are both clearly risk factors for gastro-duodenal ulceration. Whether, and if so, how stress and *H. pylori* might interact, if at all, remains to be determined. Overall, the etiology of gastric and duodenal ulceration and the causal switch in dogma from 'all stress to all bacteria' followed by a sober realization that both factors might play a role have heuristic value for our understanding of disease pathogenesis.

Declaration of interest

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