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REVIEW

Stress and animal models of inflammatory bowel disease—An update on the role of the hypothalamo—pituitary—adrenal axis

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Summary Chronic psychosocial stress has been repeatedly shown in humans to be a risk factor for the development of several affective and somatic disorders, including inflammatory bowel diseases (IBD). There is also a large body of evidence from rodent studies indicating a link between stress and gastrointestinal dysfunction, resembling IBD in humans. Despite this knowledge, the detailed underlying neuroendocrine mechanisms are not sufficiently understood. This is due, in part, to a lack of appropriate animal models, as most commonly used rodent stress paradigms do not adequately resemble the human situation and/or do not cause the development of spontaneous colitis. Therefore, our knowledge regarding the link between stress and IBD is largely based on rodent models with low face and predictive validity, investigating the effects of unnatural stressors on chemically induced colitis. These studies have consistently reported that hypothalamo—pituitary—adrenal (HPA) axis activation during stressor exposure has an ameliorating effect on the severity of a chemically induced colitis. However, to show the biological importance of this finding, it needs to be replicated in animal models employing more clinically relevant stressors, themselves triggering the development of spontaneous colitis.

Important in view of this, recent studies employing chronic/repeated psychosocial stressors were able to demonstrate that such stressors indeed cause the development of spontaneous

Abbreviations: AA, acetic acid; ACTH, adrenocorticotrope hormone; ADX, adrenalectomy; ANS, autonomic nervous system; AVP, arginine vasopressin; CD, Crohn's disease; CD, cluster of differentiation; CRC, colorectal cancer; CRH, corticotrophin releasing hormone; CSC, chronic subordinate colony housing; d, day/s; DNBS, dinitrobenzene sulphonic acid; DSS, dextran sulphate sodium; ES, electric shock; GC, glucocorticoids; GR, glucocorticoid receptor; h, hour/s; HPA, hypothalamo—pituitary—adrenal axis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; ICV, intracerebroventricular; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LPMC, lamina propria mononuclear cells; min, minute/s; MPO, myeloperoxidase; MR, mineralocorticoid receptor; mRNA, messenger RNA; MS, maternal separation; n.a., not assessed; NE, norepinephrine; OC, overcrowding; PND, postnatal day; PRS, partial restraint stress; PVN, paraventricular nucleus; resp., respective; SD, social defeat; SD/OC, social defeat/overcrowding; SDR, social disruption stress; SNS, sympathetic nervous system; TGF, tumor growth factor; Th, T helper; TNBS, trinitrobenzene sulphonic acid; TNF, tumor necrosis factor; TLR, toll-like receptor; UC, ulcerative colitis; VEH, vehicle; vs., versus; WAS, water avoidance stress; wk, week/s.

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colitis and, thus, represent promising tools to uncover the mechanisms underlying stress-induced development of IBD.

Interestingly, in these models the development of spontaneous colitis was paralleled by decreased anti-inflammatory glucocorticoid (GC) signaling, whereas adrenalectomy (ADX) prior to stressor exposure prevented its development. These findings suggest a more complex role of the HPA axis in the development of spontaneous colitis.

In the present review I summarize the available human and rodent data in order to provide a comprehensive understanding of the biphasic role of the HPA axis and/or the GC signaling during stressor exposure in terms of spontaneous colitis development.

Contents

1. General introduction

Inflammatory disorders, such as Crohn's disease (CD) and ulcerative colitis (UC) represent a major health concern, particularly in Western societies, with a life-time prevalence of approximately 0.1% (for review see Singh et al., 2001). In addition to limiting quality of life due to abdominal cramps and pain, diarrhea, bloody stools, ulceration, fever, tiredness and other socially unacceptable symptoms, inflammatory bowel disorders (IBD) are further linked to an increased risk for developing inflammation-related colorectal cancer (CRC) (for review see Yang et al., 2009). Furthermore, early-onset IBD (i.e. in childhood) has been shown to cause growth problems and even to delay puberty, as an appropriate uptake of nutrients is not guarantied during periods of severe gut inflammation (for review see Mamula et al., 2008).

The pathogenesis of IBD is still not completely understood. It is generally accepted that IBD has a complex and multifactorial aetiology, involving genetic and environmental factors (for review see Andus and Gross, 2000; MacDonald and Monteleone, 2005), which are in turn associated with a dysregulation of the mucosal immune system. One environmental factor that is often discussed in this context during the last decades is the perceived level of life stress (Salem and Shubair, 1967; Duffy et al., 1991; Bernstein et al., 2010). A similar link between stress and IBD has been suggested also by a large body of rodent data (Collins et al., 1996; Gue et al., 1997; Million et al., 1999; Qiu et al., 1999; Milde and Murison, 2002; Cakir et al., 2004; Gulpinar et al., 2004; Saunders et al., 2006; Melgar et al., 2008). However, the face and predictive validity of most animal models have to be valued with caution, as they often employ unnatural- and short-term-stressors and investigate their effects on artificially (chemically)-induced colitis. In contrast relevant human stressors in modern societies that are discussed as risk factors for the development of several affective and somatic disorders are mostly chronic and psychosocial in nature (Salem and Shubair, 1967; Duffy et al., 1991; Kiecolt-Glaser and Glaser, 1995; Kiecolt-Glaser et al., 1995, 1996, 1998; Agid et al., 1999; Coker et al., 2000; Herrmann et al., 2000; Buske-Kirschbaum et al., 2001; Heim and Nemeroff, 2001; Bitton et al., 2003; Wright et al., 2004; Amat et al., 2005; Post et al., 2005; Heim et al., 2009). It is, therefore, not surprising that, except from the generally reported colitis-ameliorating role of HPA axis activation during stressor exposure, there is a paucity of detailed neuroendocrine mechanisms underlying stress-induced development/aggravation of IBD. Recent studies employing chronic psychosocial stressors to investigate the aetiology of stress-induced