Review on the Influence of Stress on Immune Mediators, Neuropeptides and Hormones with Relevance for Inflammatory Bowel Disease

J an H. Niessa a,c, Hubert Mönnikes b,c, Axel U. Dignass b, Burghard F. Klapp c, Petra C. Arck a,c

a Biomedizinisches Forschungszentrum, Campus Virchow-Klinikum; b Department of Medicine, Division of Hepatology, Gastroenterology and Endocrinology, Campus Virchow-Klinikum, and c Department of Medicine, Division of Psychosomatic and Psychotherapy, Charité, Humboldt University, Berlin, Germany

Key Words
Stress · Immune and neuroendocrine system · Corticotropin-releasing factor · Neuropeptides · Substance P · Neurokinin · Inflammatory bowel disease

Abstract
Stress has long been postulated to influence the progression of inflammatory bowel disease (IBD). Our current understanding of the relationship between stress and IBD is still limited, and hence explanation for the occurrence of relapses has remained largely speculative. Stress affects the immune system, the neuroendocrine system and the intestinal epithelium. Stress induces the release of pro-inflammatory Th1 cytokines and neuropeptides, such as tachykinins. Thereby, stress may induce alterations of the intestinal epithelium via the interaction of the neuroendocrine and immune system and may induce relapses of IBD. The present review focuses on this network and highlights the role of distinct mediators and mechanisms, i.e. neurotransmitters, hormones and immune cells, which are involved in the response to stress on the one hand, and contribute to the onset, progression or relapses of IBD on the other.

Introduction
In their daily work, many physicians and patients are implicating that stress may affect clinical symptoms of idiopathic inflammatory bowel diseases (IBD), i.e. ulcerative colitis and Crohn’s disease. Ulcerative colitis and Crohn’s disease are relapsing-remitting diseases often characterized by striking swings between intestinal inflammation and quiescence. Putative predisposition for these diseases are environmental [1], immunological [2] and genetic factors [3, 4].

Recently, various studies revealed that the risk of relapses may be related to stress. In an animal model, exacerbation of hapten-induced colitis was triggered by exposing mice to a stress source in addition to a subthreshold dose of dinitrobenzensulfonic acid (DNBS) [5]. In humans, long-term perceived stress was shown to be related to relapses of ulcerative colitis [6].

The present review will focus on associations between stress and immune mediators known to be involved in IBD to highlight the importance of a psychoneuroimmunological (PNI) approach in order to understand the pathogenesis of IBD. Therefore, the effects of stress on the immune and the neuroendocrine system will be discussed. In addition, the release of neuropeptides in re-
response to stress, and the epithelial function in response to stress will be discussed with respect to implications for IBD.

**Definition of Stress**

Stress is an important part of our daily life, and yet there is still a considerable controversy about the meaning of stress. Stress is defined as a real or perceived threat that causes an individual response. The aim of the physiological stress response is the maintenance of homeostasis. Events which initiate the stress response are stressors [7]. The potency of the stressor to induce physiological responses is dependent upon the perception of the situation by the individual. Further, the capacity of an individual to develop certain coping strategies are of great importance, especially in respect to the physiological long-term stress response [8].

Although stress is often thought about as harmful, one has to distinguish between positive stress, called eustress and negative stress, which is referred to as distress [7]. Interoceptive stress is defined as physical stress, whereas exteroceptive stress is defined as psychological stress. An adequate stress response is important in our interaction with the environment, e.g. everyday challenges of either physical or psychological nature.

Diseases could result from an altered stress response or a heightened responsiveness to stress. Dysregulation of the stress response could be the consequence of an extraordinarily intense or prolonged stress, or particularly conditions that impair the normal capacity to regulate stress, e.g. early life events [9].

**Stress and the Immune System**

A wealth of published data is available relating stress to immunological alterations, such as natural killer (NK) cell activity, distribution of lymphocytes and synthesis of cytokines. A close relationship between psychological factors and the immune system was shown by Pavlovian conditioning of immune function, such as the degranulation of mast cells in the gut [10]. CD4+ lymphocytes are responsible for the occurrence of stress-triggered relapses of colitis in an animal model [5].

Many studies in humans are focused on the relation between single immunological parameters and stress without discussing the complex alterations of the immunological network. Nevertheless, some key observations can be made besides the great variety of the viewed studies. Acute stress stimulates the immune system as shown by an increase of NK cells and CD8+ lymphocytes [11]. Dhabbar et al. [12] showed that a delayed-type hypersensitivity reaction in the skin was enhanced by an acute stressor. In contrast, chronic stress suppresses the immune system as shown by a decrease of macrophages, NK cells and CD8+ lymphocytes [13].

In animals, stressors such as ultrasonic stress [14], restraint stress [15] or water avoidance stress are used for such experiments. Although experimental animal models give insights into the importance of stress for the induction of alterations of the immune system, experimental stress models are very likely not comparable to daily stress in humans and may not be representative of the human stress.

T-helper lymphocytes can be divided into two subclasses, the Th1 and Th2 lymphocytes. Th2 lymphocytes are characterized by the secretion of pro-inflammatory cytokines, such as TNF-α, IFN-γ, IL-12 and IL-18 [21]. Studies in humans and animals indicate that stress skews the Th1/Th2 balance to a Th1 immune response [22]. A short synopsis of current studies, which have investigated the association between stress and cytokines imbalances, is given in table 1. Stress typically induces an increase of pro-inflammatory Th1 cytokines.

These observations are supported by the fact that lymphoid structures, such as the thymus, spleen and lymph nodes, are in close contact to the nervous system [23]. It is of considerable interest that immune cells on the one hand express various receptors for neurotransmitters – peptides and hormones, and on the other hand release such molecules; e.g. lymphocytes are able to synthesize catecholamines [24]. It is evident that these mediators orchestrate a multidirectional cross-talk [25]. Furthermore, treatment with norepinephrine leads to differential expression of cytokine genes in spleen cells in vitro [26]. It was even demonstrated that the activity of NK cells can be directly modulated by the sympathetic nervous system independent from glucocorticoid levels [for detailed review, see 28]. Damage to innervation can occur during inflammatory responses and the extent to which this disruption in the innervation initiates or perpetuates inflammatory responses in conditions such as IBD is still unknown [reviewed in 29]. A striking example for the multidirectional cross-talk between the neuronal and immune system is facilitated by the same molecule, corticotropin-releasing factor (CRF). Immunoreactive CRF (irCRF) has been localized in local immune accessory cells in various experimental models of inflammation. In
Table 1. A short synopsis of current studies which investigate the association between stress and cytokines

<table>
<thead>
<tr>
<th>Stressor</th>
<th>Individuals included</th>
<th>Follow-up period</th>
<th>Alteration of cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological stress</td>
<td>27 university students</td>
<td>1 day prior examination</td>
<td>IFN-γ ↑, TNF-α ↑, IL-10 ↑, IFN-γ/IL-5 ↑ [16]</td>
</tr>
<tr>
<td>Videotaped speech task</td>
<td>56 healthy volunteers</td>
<td>Immediately after task</td>
<td>IFN-γ ↑ [17]</td>
</tr>
<tr>
<td>Acute psychological stress</td>
<td>Lupus erythematosus/rheumatoid arthritis/healthy controls</td>
<td>Acute stress</td>
<td>IFN-γ ↑ in all groups [18]</td>
</tr>
<tr>
<td>Laboratory stress model</td>
<td>15 allergic patients/15 healthy controls</td>
<td>1 h after mental stress</td>
<td>IFN-γ ↑, IL-4 ↑, IL-5 ↑ in comparison to controls [19]</td>
</tr>
<tr>
<td>Academic examination</td>
<td>16 first-year medical students</td>
<td>24 or 48 h after examination</td>
<td>IFN-γ ↓, IL-2 ↓, IL-1α ↓, IL-1β ↓ [20]</td>
</tr>
</tbody>
</table>

Th1 cytokines, such as IFN-γ and TNF-α and the Th2 cytokines, such as IL-4 and IL-10, are given. Stress typically induces an increase of pro-inflammatory Th1 cytokines. Thereby, stress skews the Th1/Th2 balance to a Th1 immune response.

↑ = Increase; ↓ = decrease.

humans, CRF has been localized in tissues undergoing inflammatory processes, such as thyroid glands of patients with Hashimoto thyroiditis or the colonic mucosa of patients with ulcerative colitis. CRF was also detected in sympathetic nerve cell bodies and sympathetic ganglia after IL-2 administration, which supports the hypothesis that the majority of immune CRF in early inflammation is of peripheral nerve rather than immune cell origin [for review, see 27].

Stress and the Neuroendocrine System

An integrative network of brain structures, involving hypothalamic subnuclei (in particular the paraventricular nucleus), the periaqueductal gray, and the amygdala mediate the stress response by providing output to pontomedullary areas and to the pituitary gland, which in turn modulate efferent autonomic and neuroendocrine control mechanisms of the organism. This central network receives input from cortical structures, like the medial prefrontal and the anterior cingulate cortex, as well as information from the periphery by ascending projections from the brainstem, which relay information transmitted to the brain via afferent neuronal projections and circulating substances, like glucocorticoids. Major outputs of this brain circuitry – which is named ‘emotional motor system (EMS)’ – to the periphery involve autonomic (autonomic nervous system), neuroendocrine (hypothalamic-pituitary-adrenal (HPA) axis) and pain modulatory systems [for detailed review, see 30].

CRF is one of the principal mediators of the stress response of the organism in the brain. Among other brain areas, CRF neurons are located in the paraventricular nucleus of hypothalamus, the amygdala and the locus coeruleus complex, which are part of the EMS [31–33]. Several convergent findings suggest that the stress-induced modulation of gastrointestinal function is mediated by activation of brain CRF receptors in brain nuclei which are part of the EMS [32, 34–36]. Peripheral autonomic pathways convey acute stress and central CRF-induced alteration of gastrointestinal function, like inhibition of gastric emptying and stimulation of colonic motor function, whereas associated activation of the pituitary-adrenal axis does not seem to play a role [32].

Medullary CRF-2 receptors play a role in stress-induced modulation of upper gastrointestinal function, e.g. inhibiting of gastric emptying. In contrast, the experimental data point to a role of cerebral CRF-1 receptors in the altered lower gastrointestinal function, e.g. stimulation of colonic transit by psychological stress or centrally injected CRF [37]. Novel findings that anxiogenic behavioral responses to stress or central administration of CRF are also mediated by cerebral CRF-1 receptors [38] could be of significant relevance for the understanding of brain pathways involved in the central nervous system (CNS) mediation of stress-related symptoms in gastrointestinal disorders, especially in patients with primarily or reactively associated psychological symptoms [for detailed review, see 30]. In addition, Gue et al. [39] have questioned the role of CRF in the ability of stress to induce an exacerbation of colitis. On the other hand, it was shown...
Fig. 1. Complex interactions between CNS, the neuroendocrine and immune system in response to stressor with possible importance for pathophysiology of IBD.

Fig. 2. Inflammation-prone Lewis rats possess a defect of the CRF synthesis. A ↑↑ response is higher than a ↑ response. Thereby, immunosuppressive glucocorticoids are reduced in the periphery, indicated by ↓. If Lewis and Fischer rats are exposed to stress, an experimental induced colitis of Lewis rats will be enhanced compared to Fischer rats [43].

Stress and Tachykinins

In response to acute and chronic stress, the activity of substance P (SP) is increased in the CNS. Increased systemic SP activity inhibits stress-induced ACTH, CRF and noradrenaline concentrations [44, 45]. One might speculate that SP may have a pro-inflammatory effect via decreasing central CRF levels.

However, most studies on the interaction between stress and tachykinins focused on the relationship between the stress response and tachykinin-mediated inflammatory activity in the periphery. In mice, ultrasonic stress-induced abortion is associated with SP-dependent alterations of decidual cytokine concentrations [46]. Also, there is evidence that stress affects physiologic intestinal function via the release of SP. Theoretically, the source of SP release could be afferent nerve fibers acting with the sympathetic nervous system, intrinsic enteric neurons, or immune competent cells within the intestine [for detailed review, see 47]. It has been observed that a NK1 receptor antagonist decreased the restraint stress-induced defecation in the rat [48]. Further, stress induces alterations of peritoneal macrophages, such as the increased release of IL-1, IL-6 and TNF-α [49], as well as the enhanced expression of NK receptors [50].

Tachykinins and IBD

Within the enteric plexus of the lamina propria, immunological effector cells are in intimate contact with nerve fibers, called the 'hardwired enteric immunity' [51]. Intestinal immune cells are expressing receptors for neuropeptides, and thereby the release of neurotransmitter in response to stress may trigger intestinal inflammation [52]. Studies in humans and experimental animal models indicate the great importance of tachykinins and their receptors for the pathogenesis of inflammatory processes.
within the gut. Interestingly, it was observed that the expression of NK1 receptors is dramatically increased in patients with IBD [53], and that the local intestinal environment induces this expression of NK receptors by immune competent cells [54].

In animal models it has been shown that tachykinins and/or preprotachykinin (PPT) mRNA levels are elevated in response to distinct inflammatory conditions of the gut. The infection of rats with Clostridium difficile toxin A leads to an elevated release of SP from macrophages of the lamina propria [55]. The expression of ß- and γ-PPT mRNA of intestinal rat macrophages was increased in response to lipopolysaccharide (LPS) or Salmonella dublin [56]. After induction of experimental colitis with dextran sulfate the concentration of SP was elevated in the peripheral blood plasma of rats [57] and it was observed that the induction of colitis with TNBS leads to an increased ß-PPT mRNA expression in colonic tissues of rats [58]. Further, the application of NK1 antagonists reduces the intestinal infiltration of granulocytes and lymphocytes in response to various inflammatory stimuli, such as parasites or TNBS [59–61].

Stress, the Epithelium and IBD

Intestinal epithelial cells (IEC) form a barrier between the lumen of the intestine and the lamina propria. This barrier regulates the passage of microorganism and restricts the passage of macromolecules into the lamina propria, where antigens might be taken up by antigen-presenting cells. IEC are involved in the modulation of intestinal inflammation by the release of cytokines and chemokines [62].

There is evidence that both acute and chronic stress affects the physiologic function of the epithelium. Abnormalities of epithelial ion secretion and passage of macromolecules into the lamina propria were found in response to an acute stressor [63, 64]. In response to chronic stress, an increased ion secretion, increased ionic permeability, and an increased macromolecule passage through the epithelium were observed. Comparison of mast cell-deficient rats with wild-type rats revealed that alterations of epithelial permeability in response to stress are dependent on the presence of mucosal mast cells [65].

In humans and mice it was shown that the occurrence of mucosal inflammation is associated with disturbances of epithelial function. In mice characterized by an expression of a dominant negative N-cadherin gene, the function of N-cadherin is defective. A defect of the N-cadherin function leads to disturbed tight junctions of the epithelial barrier, and thereby the risk of ulcerative colitis like mucosal inflammation is enhanced [66]. In humans, increased permeability of the epithelium in response to stress could induce an increased transepithelial migration of intestinal microbes. Thereby, the mucosal immune system might be activated and thus the intestinal inflammatory process maintained.

Stress and IBD in Humans and Other Primates

The idea that psychological factors can affect the outcome of idiopathic IBD has a long history. In the 1950s, ulcerative colitis and Crohn’s disease were considered as a prototype of psychosomatic diseases [67]. Several observations in man and animal experiments have indicated a link between stress in consequence of physiologically distressing living conditions and the clinical manifestation of IBD. Ulcerative colitis was described in Bedouin Arabs after they have moved to government housing [68]. An exacerbation of colitis was observed in captive Siamese gibbons, indicating the idea that the stress of captivity is involved in the pathogenesis of colitis in these animals [69]. Further, cotton-top tamarins develop colitis in captivity. Remission of the disease will be entered by transferring affected tamarins to natural living conditions [70].

When viewing the literature about the effects of stress on IBD, it is important to notice that both the design and results of these studies are highly divergent. Some published observations are case reports [71], retrospective studies and nonprospective controlled studies. Others were only focused on a short-term and not on a long-term association between life events and IBD [72]. Some studies failed to show an association between stressful life events and the occurrence of relapses [73, 74]. In a meta-analysis, 138 studies conducted before 1990 were reviewed on the possible association between psychiatric factors and ulcerative colitis. Most of the studies contain serious flaws in their study design, such as lack of control subjects, unspecified manner of data collection, and absence of diagnostic criteria. Most importantly, the seven established observations are case reports [71], retrospective studies and nonprospective controlled studies. Others were only focused on a short-term and not on a long-term association between life events and IBD [72]. Some studies failed to show an association between stressful life events and the occurrence of relapses [73, 74]. In a meta-analysis, 138 studies conducted before 1990 were reviewed on the possible association between psychiatric factors and ulcerative colitis. Most of the studies contain serious flaws in their study design, such as lack of control subjects, unspecified manner of data collection, and absence of diagnostic criteria. Most importantly, the seven studies with a systemic and proper study design failed to show such an association [75].

However, other studies showed a positive correlation between psychosocial life events and disease activity, but only in patients with Crohn’s disease and not in patients with ulcerative colitis [76]. In a prospective study, 124 individuals with IBD were followed up for 6 months.
Stress-exposed individuals demonstrated an increased risk of clinical disease episodes compared to nonexposed individuals. By performing a multiple regression analysis, major stress events were shown to be the most significant indicator of disease activity in the presence of considered co-variables. But only 7% of the alterations in the disease activity was uniquely attributed to stress [77]. An independent team of physicians and psychologists examined 122 patients with ulcerative colitis and a matched hospital control population. Patients with ulcerative colitis had a significantly higher anxiety trait and state compared to the control population. In the 12 months prior to the investigation more stressful life events were assessed in patients with ulcerative colitis [78]. Also, it was observed that stress management is of importance in the treatment of IBD and may help to prevent exacerbation of IBD [79].

More advanced methodological approaches for the investigation of the role of stress in the pathophysiology of IBD focused on the relationship between daily hassles and self-rated disease activity [72]. It became obvious that the former concept of counting critical life events was too broad for such studies, since life events may not be perceived as a stressor as implicated by psychological theories [6]. In a prospective study, colitis symptoms as well as everyday stress was assessed by a diary given to the patients. A significant correlation between daily hassles and disease activity was revealed [80]. Levenstein et al. [6] implemented a questionnaire for the measurement of perceived stress for such studies. In contrast to most of the previous studies, they focused on long-term and not on a temporal short-term association between stress and ulcerative colitis. They found that long-term and not short term perceived stress is related to the risk of relapses (table 2).

Further, IBS might result from post-infectious states which occur in up to 31% of patients with gastroenteritis [81, 82]. It is of great interest that patients in remission from IBD develop IBS-like symptoms in a higher frequency than expected [83]. It is postulated that the development of IBS is the result of the interaction between genetic predisposition, behavioral factors, enteric infection or recent exacerbation of IBD and a persistent sensory motor dysfunction following inflammation [84]. However, it is not the aim of the review to discuss in detail the effects of low-grade intestinal inflammation on the development of IBS. Nevertheless, we would like to point out that the development of IBS-like symptoms in IBD patients with remission, particularly ulcerative colitis, could be the result of a persistent sensory motor dysfunction following inflammation [84, 85].

**Stress and Crohn’s Disease**

Crohn’s disease is characterized by a Th1 immune response in contrast to ulcerative colitis [86]. Th1 lymphocytes are a subset of CD4+ lymphocytes which secrete...
pro-inflammatory cytokines, such as TNF-α, IFN-γ, IL-12 and IL-18 [21]. As it was shown previously, the Th1 cytokines IL-12 and IL-18 are upregulated in human IBD [87, 88]. Elevated IFN-γ and TNF-α concentrations induce a further IL-12 production, and the production of several macrophage-derived cytokines, such as IL-1β, IL-6 and TNF-α [89].

One may ask what the underlying reasons for an excessive Th1 activity or an overproduction of IL-12 might be. Increased Th1 activity could be due to a genetically determined increased intrinsic Th1 activity or due to a disturbance of the counter-regulation of a Th1 response. Disturbance of the counter-regulation of an increased Th1 activity could be due to an inadequate cytokine suppressor response, to an abnormal response of Th1 cells to suppressor cytokines, such as IL-10 and TGF-β, or an intrinsic or extrinsic overproduction of Th1 cytokines, such as TNF-α.

Stress is able to augment the synthesis of pro-inflammatory Th1 cytokines (table 1). In an animal model it was proved that the pro-inflammatory cytokine TNF-α is increased and the suppressor cytokine TGF-β is decreased in response to stress [22]. The result may be the activation of cytotoxic T cells, which contribute to the immunopathology of IBD.

### Stress and Ulcerative Colitis

In contradiction to Crohn’s disease, ulcerative colitis is a Th2-mediated inflammatory process of the colon [90]. Th2 cells are characterized by the secretion of Th2 cytokines, such as IL-4, IL-5, IL-10 and IL-13 [88]. IL-4 and IL-13 mRNA expression are elevated in rectal biopsy specimens of patients with ulcerative colitis [91]. Although ulcerative colitis resembles more a Th2-mediated disease, there is some intriguing data that TNF-α is involved in the immune pathophysiology of ulcerative colitis [92]. It has been suggested that the increased TNF-α levels are causing the ‘final cell death’ of the inflamed mucosa. In an animal model, mucosal inflammation and damage at an infection with Trichinella spiralis, a nematode, depends on the signaling along the TNF receptor (TNFR), as was shown in studies with TNFR-deficient mice. Nevertheless, parasitism is a Th2-mediated disease [93]. Stress augments the release of pro-inflammatory cytokines and may thereby enhance the mucosal damage of the Th2-mediated ulcerative colitis.

<table>
<thead>
<tr>
<th>Th1</th>
<th>Th2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5</td>
<td>CXCR4</td>
</tr>
<tr>
<td>CXCR3</td>
<td>CCR3</td>
</tr>
<tr>
<td>LAG-3</td>
<td>CCR4</td>
</tr>
<tr>
<td>CD26</td>
<td>CCR8</td>
</tr>
<tr>
<td>Membrane IFN-γ</td>
<td>CD30</td>
</tr>
<tr>
<td>IL-12 β2 chain</td>
<td>CD62L</td>
</tr>
<tr>
<td>CRTH2</td>
<td></td>
</tr>
</tbody>
</table>

### Implications for the Clinic/Further Perspectives

In the last few years, some T-cell surface molecules were identified which are preferentially involved in a Th1 or Th2 immune response. CCR5, LAG-3, CXCR3, membrane IFN-γ and LAG-3 are related to a Th1 response, whereas CXCR4, CCR8, CCR4, CD30 and CD62L are related to a Th2 response [94] (table 3). First results in patients suffering from Crohn’s disease indicate a strong positive correlation between CCR5+ Th1 cells and increasing stress perception in peripheral blood, as well as locally in the intestinal mucosa [Arck, unpubl. data]. The expression of the above-mentioned surface molecules characterize a specific immune response. Instead of detecting a panel of intracellular Th1 or Th2 cytokines, it is easily possible to detect one of these surface molecules and to diagnose a specific immune response. In further studies it should be revealed if these surface markers are related to individual perceived stress and if alterations of these molecules are indicators for relapses of IBD.

Stress could augment the severity of IBD. Psychological intervention, such as Jacobson’s muscle relaxation, influences stress-mediated alterations of the immune system, e.g. TNF-α levels in the peripheral blood can be downregulated by Jacobson’s muscle relaxation [95]. Thereby, the symptoms of IBD could be influenced.

One may speculate whether further PNI therapeutic approaches may result from the understanding of IBD as a stress-immunological disease. Possible mediators, which could be manipulated for the treatment of IBD, are neuropeptides, such as SP, and mediators, which are released by immune competent cells. The application of NK1 receptor antagonists allows to reduce tachykinin-
mediated activation of immune competent cells and possibly associated pathophysiologic disturbances of the gastrointestinal function, like motility, secretion and sensitivity [96].

Theoretically, two different strategies for the therapy of stress-induced alterations of the immune system could be proposed. Either the effect of pro-inflammatory mediators could be neutralized by application of neutralizing antibodies, such as anti-TNF-α or anti-IL-12, or the activated immune system can be suppressed by application of suppressor cytokines, such as TGF-β or IL-10. Immune active cytokines do not only influence immune competent cells, they also mediate epithelial wound healing [97].

In humans the treatment of Crohn’s disease with neutralizing anti-TNF-α antibodies, such as infliximab, has a beneficial effect [98, 99]. However, the treatment of Crohn’s disease with IL-10 showed only a tendency to clinical improvement as contradiction to most of the experimental data [100].

With the present review article we provide detailed information on putative mediators involved in the progression of IBD. It was our aim to discuss critically the possible role of stress on the onset, progression or occurrence of relapses in IBD. However, we would like to point out that the pathophysiology of IBD is a complex interaction of environmental factors, the epithelium, the immune and neuroendocrine system. Thus, we put our emphasis on PNI mechanisms, which are based on distinct measurable and reproducible experiments.

Acknowledgements

This work was supported by grants from the Charité, Humboldt University, Berlin, Germany to J.H.N, H.M. and P.A., a grant from the Fritz Bender Foundation to P.A. and A.D., and a grant from the Deutsche Forschungsgemeinschaft to H.M. (DFG, Mo458/4-1) and to J.H.N. (DFG, Ni575/2-1).

References


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