Editorial

Risk factors for anxiety and depression in patients with gastrointestinal disorders—the role of the gut-brain axis

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In the past decade the acknowledgement of the importance of the gut-brain axis for the etiology of diverse pathologies such as mental illnesses has increased significantly (1). The association of changes in the dynamic bi-directional connection between gut and brain with the development of mental and gastrointestinal diseases has become more evident in the last years (2). The gut-brain axis with its diverse neural, endocrine and immune signaling pathways (3) might explain the numerous observations of high prevalence of mood disorders, such as anxiety and depression, in the presence of gastrointestinal abnormalities, which gave rise to the examinations that were very recently published by Wu *et al.* under the title "*The status and risk factors for anxiety/depression in patients with atrophic chronic gastritis*: *a cross-sectional study*" (4).

Interestingly, mood disorders do not only pose a risk factor for gastrointestinal disturbances of a functional type, e.g., irritable bowel syndrome, but also somatic gastrointestinal disorders with more 'somatic' pathogenesis such as inflammatory bowel disease (5). Conversely, pathologies of the gut, such as ulcerative colitis or advanced gastrointestinal cancer increase the risk for psychological distress and depressive mood (6) as well as manifest psychiatric diseases such as anxiety and depression (5,7). This double-sided association between mood and gastrointestinal disorders are in line with the observations of Wu *et al.* reporting a high prevalence of anxiety and depression in patients suffering from chronic gastritis (4). In detail, using the Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 36.4% of the study's population had anxiety, 25.4% had depression, and 21.2% had both anxiety and depression.

Although the understanding of the gut-brain axis has enormously advanced in the recent years, gaps in knowledge still remain (2), e.g., why certain patients with gastrointestinal diseases suffer from mood disorders and others do not. This question about risk factors for the development of anxiety and depression in the setting of gut disorders was addressed by Wu *et al.* in a population of 66 male and 52 female patients with a mean age of 52 years ranging from 25 to 77 with atrophic chronic gastritis (4). This work was able to identify, among others, poor sleep quality, high salt diet and abdominal pain as risk and exercise as protective factors for the presence of mood disorders in these patients (*Figure 1*) (4). It is to note that underlying mechanisms responsible for these associations were not identified; however, the involvement of the gut-brain axis in their mediation is highly probable.

In the most recent years the microbiota and its metabolites, as an integral component of the connection

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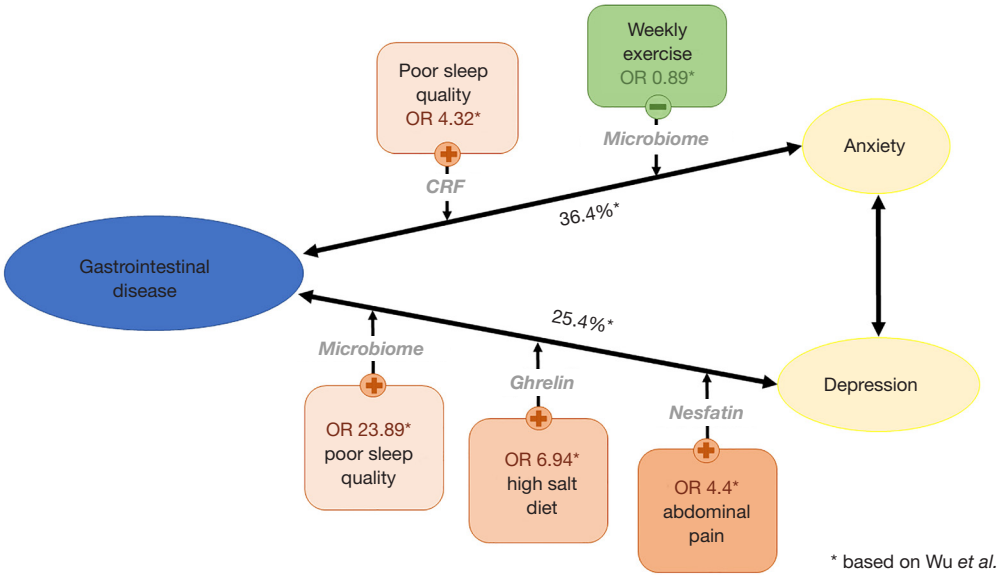

Figure 1 Risk and protective factors for depression and anxiety in patients with gastrointestinal disorders. Data presented with a * symbol are based on Wu *et al.* (4); +/red color indicates an OR >1.0/positive association with anxiety or depression; –/green color indicates an OR <1.0/negative association with anxiety/depression; text presented in grey is based on hypothetical considerations and needs confirmation from future research. OR, odds ratio; CRF, corticotropin-releasing factor.

between gut and brain, have deservedly earned enormous attention as they are implicated in the modulation of intestinal motility and permeability, mucosal immune functions and enteric nervous system activity (8). Gut microbiota composition is greatly impacted by diet, consequently it is not surprising that high salt diet induces modifications of gut permeability and immune homeostasis associated with increased vulnerability to inflammatory stress by microbiome alteration (9). Noteworthy, changes in microbiota, e.g., induced by probiotics, antibiotics or pathogens are associated with anxiety and depression (8), possibly explaining why Wu *et al.* observed an odds ratio of 6.94 for depression and 6.81 for both depression and anxiety in patients consuming excess salt with their diet (4). In contrast, weekly exercise time was negatively associated with the risk of anxiety (4). Here again, the microbiota could pose the underlying basis for this interaction, since moderate exercise has been associated with changes in microbiota resulting in increased intestinal permeability, preservation of mucous thickness, reduced bacterial translocation and anti-inflammatory effects (10), possibly affecting signaling to central behavior-regulating areas. Alterations or even dysfunctions of the gut microbiota, representing a direct link between gastrointestinal and brain functions, may be responsible for pathologies connecting gut and behaviour; this interaction should be further elucidated.

Wu *et al.* also found abdominal pain to be a risk factor for depressive symptoms in gastritis associated with an odds ratio of 4.44 (4). Visceral pain is mediated via the enteric nervous system, which is greatly modulated by intestinal peptides, representing a crucial component of the gut-brain axis (11). In detail, several peptides, including ghrelin, nesfatin-1, peptide YY, cholecystokinin, secreted from specialized enteroendocrine cells along the gastrointestinal tract e.g., in response to food intake, not only signal locally but their receptors are additionally found in regions of the central nervous system, enabling a direct mediation of the state of the gastrointestinal tract to the brain (11). Since many of those peptides such as ghrelin and nesfatin-1 are implicated also in mood regulation, the direct peptidergic communication between the gastrointestinal tract and brain represents an additional pathway linking the gut and mental functions (12), thus possibly gastrointestinal and mood disorders. Noteworthy, an increase of circulating nesfatin-1 was associated with heightened visceral hypersensitivity (13), giving rise to the hypothesis that intestinal peptides may be involved in the correlations observed by Wu *et al.* between abdominal pain and depression (4). Additionally, the increased risk of depression with high salt intake could be

linked, besides microbial changes, also to altered peptidergic signaling, since high salt intake is associated with increased circulating ghrelin (14) and ghrelin was shown to exert both, anxiogenic and anxiolytic effects (15). Elucidating the peptide-dependent mechanisms responsible for alterations in mental health due to gut disorders and vice versa requires more investigations in the future.

Corticotropin-releasing factor (CRF), a major mediator in the hypothalamic-pituitary-adrenal (HPA) axis mainly secreted from the hypothalamus, is greatly implicated in gastrointestinal functions (16). In addition to its central expression, both CRF and its receptors are also expressed in the gastrointestinal tract (16) and involved in gastrointestinal secreto-motor functions, intestinal permeability and visceral hypersensitivity (16), besides being a crucial mediator in the body's stress reaction and therefore being strongly involved in the pathogenesis of depression and anxiety (17). CRF may be involved in the association between abdominal pain and both depression and anxiety (odds ratio of 5.42) identified by Wu *et al.* (4) as CRF elevations are related to mood abnormalities and CRF receptor 1 activation is involved in the induction of visceral hypersensitivity (16,17). CRF has pleotropic actions and is additionally, besides its role in mood disturbances, implicated in sleep regulation (18). Briefly, poor sleep causes overdrive of CRF signaling (18), which may be the reason why poor sleep quality in the study by Wu *et al.* was associated with both anxiety and depression in patients with gastritis (4); however, this hypothesis needs to be examined in further investigations.

As commonly known, novel insights, as presented by Wu *et al.* in their recent publications, raise new questions, particularly on the underlying mechanisms responsible for the associations between gastrointestinal and mood disorders and the involvement of the gut-brain axis herein. These gaps in knowledge should be addressed in the future and the above-mentioned hypothetical considerations of the importance of microbial and peptidergic gut-brain signaling connecting gut and mental (dys)functions need further prove. A better understanding of these interrelations may pave the way for future therapeutic approaches in the treatment of not only gastrointestinal but also mental disorders.

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