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ORIGINAL ARTICLE

Neuroendocrine markers and psychological features in patients with irritable bowel syndrome

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Abstract
Background and aims The key role of the brain-gut axis in the pathophysiology of irritable bowel syndrome (IBS) has been recognized. The aim of this study was to assess the possible association between IBS, neuroendocrine markers, and psychological features.
Methods One hundred and twenty-five consecutive IBS patients and 105 healthy subjects were enrolled. Plasma serotonin, plasma and urinary cortisol, and plasma neuropeptide Y levels were evaluated. All patients were given a questionnaire to assess IBS symptom severity. In 66 patients, a psychodiagnostic assessment was carried out.
Results A high incidence of specific psychological features, including state anxiety (69.69 %), trait anxiety (54.54 %), obsessions and compulsions (28.78 %), was observed in IBS patients. A positive correlation between neuropeptide Y and state anxiety (r=0.287, p=0.024) and simulation/social ingenuity (r=0.269, p=0.039) was found in these patients. In diarrhea-predominant IBS, plasma cortisol was linearly related to plasma serotonin (r=0.5663, p<0.001).
Conclusions In IBS patients, a significant correlation was found between specific psychological features and neuroendocrine markers, especially plasma cortisol and neuropeptide Y; in diarrhea-predominant IBS, a correlation between plasma cortisol and serotonin was found, although it needs to be confirmed in more extensive cohorts.

Keywords Neuroendocrine markers · Psychological features · Irritable bowel syndrome

Abbreviations

NPY	Neuropeptide Y
IBS	Irritable bowel syndrome
HS	Healthy subjects

Introduction

Patients with irritable bowel syndrome (IBS) have an increased reactivity to psychosocial stressors, which is characterized by hypersensitivity to distension of the rectum, colon, and small intestine and an abnormal motor pattern in the small intestine and colon [1, 2].

Approximately 60 % of IBS patients have comorbid mood and anxiety disorders; conversely, 75 % of patients

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with major depression and panic disorders are affected by IBS [3]. The presence of psychological and/or psychiatric disorders likely exacerbates IBS symptoms [2, 4], and many of these patients benefit from appropriate psychotherapy [5].

IBS patients show an increased severity of symptoms associated with acute psychosocial stress. A decrease or complete remission of symptoms often follows the resolution of psychosocial stress [6]. In fact, the central nervous system may influence the function of the enteric nervous system through the autonomic nervous system, and the gut can influence the function of the central nervous system through extrinsic sensory neurons, the cell bodies of which are located in the dorsal and cranial ganglia [7]. This two-way communication alters visceral perception and motor function through both the enteric nervous system and the autonomic nervous system (sympathetic and parasympathetic).

Recent studies have emphasized the importance of the body's response to stress, which is among the main factors that can modulate motility and visceral perception through the interaction between the brain and gut (brain–gut axis) [5, 8, 9].

Corticotropin-releasing hormone (CRH) is a neuropeptide that is produced by the central nervous system, immune system, and some peripheral tissues, including enterochromaffin cells [10]. CRH plays a key role in the body's response to stress, activating the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–autonomic nervous system (HANS) axes.

Neuropeptide Y (NPY) is a polypeptide found in the brain, spinal cord, peripheral noradrenergic neurons, and gastrointestinal tract. The activation of the HANS axis in response to stress induces the release of NPY. This peptide may lead to an increase in intestinal permeability and visceral sensitivity by activating mast cells. Similarly, the activation of HPA in response to stress induces the release of plasma cortisol [8].

In healthy subjects, a positive correlation has been found between serum cortisol and NPY, which are used as activation markers of the HPA axis and sympathetic fibers of HANS [11], respectively. In recent years, researchers have focused on the possible role played by the serotonergic system in the pathophysiology of IBS.

Serotonin (5-HT) is an active mediator in both the central nervous system and peripheral tissues, and it acts through interaction with specific receptors [7]. It regulates the sensory, secretory, and motor functions of the digestive tract through the intrinsic and extrinsic nervous systems. In particular, some authors observed that patients with diarrhea had higher postprandial plasma levels of 5-HT than healthy volunteers [12], while other authors reported that the density and affinity of the 5-HT transporter (SERT) is different in patients with IBS than in controls [13]. The intestinal and extraintestinal disorders observed in patients with IBS may be associated with the abnormal activation of central stress circuits, which alters the neuroendocrine (HPA axis and 5-HT) and autonomic output (HANS axis) and changes in central processing of peripheral symptoms.

The aim of this study was to assess:

- Specific psychological features in IBS patients
- Neuroendocrine markers in controls and in IBS patients with different clinical expressions of IBS: diarrhea-predominant IBS (D-IBS), constipation-predominant IBS (C-IBS), or alternating IBS (A-IBS)
- The possible correlation of cortisol, NPY, and 5-HT levels with IBS symptom severity in patients with stress-related psychological features
- The possible correlation between specific psychological features and cortisol, NPY, 5-HT levels, and symptom severity in different clinical forms of IBS

Materials and methods

A total of 125 consecutive patients (38 M, 97 F; average age 42.69±13.94 years; age range 19–70 years) affected with IBS according to Rome II criteria [3, 14] who were referred to the Gastroenterology Unit of the University of Pisa from 2005 to 2009 were enrolled. In total, 43 patients had D-IBS, 53 had C-IBS, and 39 had A-IBS. A total of 105 healthy volunteers were also enrolled (39 M, 66 F; mean age 46.17± 15.34 years; age range 19–70 years); these volunteers were recruited from the hospital staff and their relatives who had no gastrointestinal symptoms.

The nature of the study was explained to both the patients and the healthy volunteers, each of whom provided written informed consent before beginning the study, in accordance with the principles of the Declaration of Helsinki (revision of Edinburgh, 2000).

Inclusion criteria:

- Age range 18–70 years
- None of the patients or volunteers had taken any medication that could alter the autonomic response (e.g., anticholinergic drugs or beta blockers), had psychotropic activity (e.g., tricyclic antidepressants, 5-HT reuptake inhibitors, or benzodiazepines), and/or otherwise potentially interfered with gastro-intestinal motility within the 15 days preceding the study

Exclusion criteria:

- Severe organic diseases
- Significant changes in serum chemistry
- History of abdominal surgery (except appendectomy)
- Lactose intolerance (demonstrated by lactose breath test)
- Pregnancy

Patients and controls fasted overnight, and venous blood samples were taken. The 5-HT (serotonin RIA, DRG Instruments GmbH, Marburg, Germany), cortisol (Access Cortisol, Beckman Coulter, Milan, Italy), and NPY (EURIA-NPY, Euro-Diagnostica AB, Malmö, Sweden) levels were determined in venous blood samples. The cortisol levels (Access Cortisol, Beckman Coulter, Milan, Italy) were measured in one sample of 24-h urine excretion in all eligible patients and controls.

In female patients and controls, neither blood nor urine sampling was performed during ovulation or in the terminal phase of the menstrual cycle.

The severity of IBS symptoms was estimated with the IBS-SSS questionnaire [15], which takes into account the following items: (a) presence and severity of abdominal pain or discomfort, (b) frequency of abdominal pain or discomfort, (c) presence and severity of abdominal distension, (d) degree of satisfaction of defecation behavior, and (e) degree of interference of IBS symptoms with daily lifestyle. Each of the above items generates a maximum score of 100, leading to a maximum possible score of 500.

The following questionnaires were administered to 66 patients (26 D-IBS, 25 C-IBS, and 15 A-IBS) who agreed to participate in a psychodiagnostic interview [16–18]:

- The State-Trait Anxiety Inventory X-1, the State-Trait Anxiety Inventory X-2, and State-Trait Anxiety Inventory X-3, which assess anxiety
- The Eysenck Personality Questionnaire, which assesses stable personality dimensions, such as introversion–extroversion, emotional stability, antisocial tendencies, simulation, and social ingenuity
- The Psychophysiological Questionnaire, which evaluates stress and specific psychophysiological features
- The Fear Survey Schedule, which assesses the fears of the subject and clarifies the relationships between the problem situations and emotional, cognitive, and behavioral reactions.
- The D Questionnaire, which assesses possible symptoms of depression
- The Maudsley Obsessional-Compulsive Questionnaire, which examines the obsessions and compulsions of the subject

All of these tests are part of the CBA (Cognitive Behavioral Assessment 2.0.) [18].

Statistical analysis

All of the results are expressed as the mean ± standard deviation. The numerical comparison of continuous data was performed using the *t* test for paired samples. ANOVA with Bonferroni correction was used for the analysis of variance between groups. Statistical significance was assumed at a p value <0.05.

In the linear regression analysis, the dependent variables were emotional stability, state anxiety, simulation/social ingenuity, and specific psychophysiological features, and the independent variables were 5-HT, NPY, and plasma cortisol levels. We chose these neuroendocrine markers as independent variables because they could potentially affect the emotional state

Pearson and/or Spearman rank correlation coefficient were used when appropriate. Statistical analyses were carried out with STATA 10 software (Stata Statistical Software, College Station, TX, USA).

Results

Psychological features in IBS patients

IBS patients showed state anxiety (69.69 %), trait anxiety (54.54 %), and obsessions and compulsions (28.78 %), particularly "checking" (27.27 %).

Comparison of neuroendocrine markers between IBS patients and controls and among patients with different clinical expressions of IBS

Significant differences were observed in the plasma levels of neuroendocrine markers between IBS patients and controls. In particular, basal plasma levels of NPY (54.89± 43.98 pmol/l) were higher in IBS patients than in controls (30.26±21.47 pmol/l; $p<0.001$; Fig. 1); significant differences were also detected in NPY between D-IBS, C-IBS, A-IBS, and controls (54.71±46.58, 54.02±33.37, 55.95± 51.99, and 30.26±21.47 pmol/l, respectively; $p<0.001$). The mean levels of plasma cortisol were not statistically significant in patients with IBS (18.74±8.13 μg/dl) compared

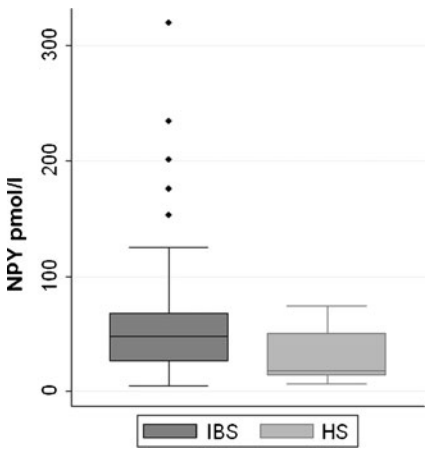

Fig. 1 Box plot showing the distribution of NPY plasma levels in IBS patients and HS. NPY levels were significantly different between IBS and HS ($p<0.001$)

with controls (17.00±4.02; p=0.058; Fig. 2). Normal plasma cortisol levels were also found in IBS subgroups (D-IBS= 19.04±9.75 μg/dl; C-IBS=16.99±6.97; A-IBS=20.68±6.81; p=0.05). A statistical analysis was performed to evaluate the possible correlation between cortisol and NPY levels. No correlation was found (r=0.0019; p=0.553), confirming the general uncoupling of the HPA and HANS axes. IBS patients showed a weak correlation between plasma 5-HT and cortisol levels (r=0.033, p=0.015), while D-IBS patients showed a substantial correlation between plasma 5-HT and cortisol levels (r=0.5663, p<0.001). No correlation was found in healthy subjects.

Univariate linear regression analysis demonstrated associations between state anxiety and NPY (Coef.=17.88; p= 0.024; 95 % C.I.=2.467–33.30), simulation/social ingenuity and NPY (Coef.=10.07; p=0.039, 95 % C.I.=0.54–19.60), plasma cortisol and psychophysiological features (Coef.=−2.32; p=0.047; 95 % C.I.=−4.59–−0.035), and 5-HT and plasma cortisol (Coef.=0.01; p=0.015; 95 % C.I.=0.00–0.01).

Correlation of cortisol, neuropeptide Y, and 5-HT plasma levels with symptom severity in IBS patients with specific psychological features

In patients with IBS we found weak correlations between NPY and state anxiety (r=0.287, p=0.024) and simulation/-social ingenuity (r=0.269, p=0.039), whereas fears and NPY (r=−0.676, p <0.001) were negatively correlated. Correlations between urinary cortisol and fears (social rejection; r= 0.327, p=0.023) and fears (effective and relevant; r=0.328, p= 0.024) were also detected.

No correlation was found between IBS-SSS and cortisol (r=0.0051, p=0.532) or NPY (r=0.0008; p=0.786) in IBS patients with psychological disorders.

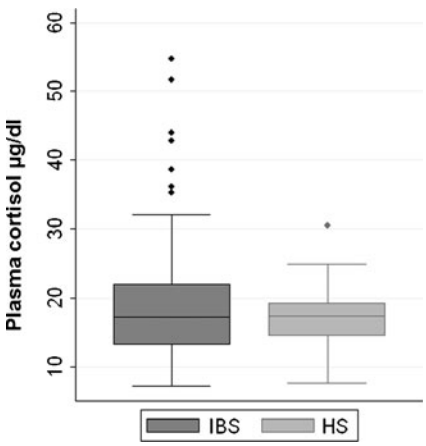

Fig. 2 Box plot showing the distribution of plasma cortisol levels in IBS patients and HS. Plasma cortisol levels were not significantly different between IBS and HS (p=0.058). *IBS* irritable bowel syndrome, *HS* healthy subjects

Correlation of specific psychological features and cortisol, NPY, 5-HT plasma levels, and severity of symptoms in the different clinical subgroups of IBS

In the D-IBS group, NPY was correlated with state anxiety (r=0.442, p=0.039) and simulation/social ingenuity (r= 0.608, p=0.003). Within the same D-IBS group, plasma 5-HT was correlated with trait anxiety (r=0.476, p=0.029), and doubting/ruminating (r=0.469, p=0.032), whereas IBS-SSS (r=0.613, p=0.026) was correlated with state anxiety (r= 0.574, p=0.040) and simulation and social ingenuity (r= 0.613, p=0.026). No significant correlations were found between neuroendocrine markers, psychological disorders and IBS-SSS. In the A-IBS subgroup, the following significant correlation was found: plasma 5-HT and obsessions and compulsions (r=0.577, p=0.039). In particular, we found a correlation between "checking" and plasma 5-HT (r=0.643, p= 0.018). In the group with C-IBS, no significant correlations were found between neuroendocrine markers, psychological disorders, and IBS-SSS.

Discussion

Consistent with previous studies [2–4, 19], we found a higher prevalence of psychiatric/psychological disorders in IBS patients, particularly state anxiety, trait anxiety, and obsessions and compulsions.

In the present study, the mean levels of plasma cortisol were not significantly different between IBS patients and controls.

In a study of 73 women with IBS, Heitkemper et al. [20] reported increased levels of urinary cortisol compared with healthy subjects, with no difference in patients with and without psychiatric/psychological disorders. HPA response was attenuated in patients with greater symptom severity and specific psychiatric disorders (e.g., depression, post-traumatic stress disorder, and chronic fatigue syndrome) [21]. Bohmlet and colleagues [22] found reduced levels of salivary cortisol in patients with functional disorders of the digestive system, with high rates of psychiatric comorbidity. However, Chang et al. [23] found reduced basal levels of ACTH associated with mildly elevated plasma cortisol levels, suggesting that IBS is associated with a dysregulation of the HPA axis. Furthermore, Elsenbruch and Orr [24] found increased levels of postprandial salivary cortisol in patients with D-IBS but not in patients with C-IBS compared with controls. In contrast, in this study, we found normal plasma cortisol levels in IBS and IBS subgroups.

Fukudo et al. [25] found increased plasma levels of ACTH but normal levels of cortisol in response to CRH injection in IBS patients, while Bohmelt et al. [22] showed blunted ACTH and cortisol responses. Dinan et al. [26]

showed increased ACTH and cortisol responses to the infusion of CRH.

In summary, the majority of studies support increased HPA activity under basal conditions and a higher response under stimulation in patients with IBS without psychiatric comorbidity. Blunted HPA response has been detected in patients with psychiatric disorders associated with chronic and severe depression, such as PTSD and chronic fatigue syndrome.

In the present study, no correlation was found between cortisol (considered a marker of HPA) and NPY (considered a marker of the HANS axis).

Furthermore, basal plasma levels of NPY were higher in IBS patients than in controls. It is possible that NPY levels may vary under laboratory conditions (cold pressor test, mathematical calculations, changes in body position, etc.). In fact, in our study, 69.69 % of patients showed situational and transient state anxiety. Moreover, the NPY is negatively correlated with fear, but positively correlated with anxiety. Anxiety and fears are different emotional states. Anxiety is a warning sign: it warns about imminent danger and it enables the person to take the right measures to face a threat. Fear occurs in response to a known threat which is external, defined, or otherwise non-conflictual in origin; anxiety occurs as a response to a threat that is unknown, internal, vague, or conflictual in origin [27]. There are conflicting results about the activation of the sympathetic nervous system in IBS. Some evidence suggests that individuals with IBS have increased sympathetic nervous system activation [28]. Cardiovascular autonomic function was altered in patients with IBS [29, 30]; however, levels of urinary catecholamines were found to be increased in IBS patients in a study [20] while not significantly different in patients with chronic abdominal pain and controls in another study [31].

All of the patients with IBS showed a weak correlation between 5-HT and cortisol plasma levels, and the correlation within the group of patients with D-IBS was more significant.

According to Levi [32], psychosocial stimuli can act on the "psychobiological heritage" of the individual (genetic factors and childhood experiences), causing long periods of somatic illness through a series of specific changes.

The correlation of plasma 5-HT and cortisol levels in D-IBS patients can be explained by the concomitant activation of the HPA axis to limit local inflammatory processes in response to both exteroceptive and interoceptive stress (with the consequent activation of EC, production of 5-HT, activation of mast cells, and secretion of cytokines), which in turn amplifies the activation of central stress circuits (interoceptive stress). This explanation also justifies the positive correlation between trait anxiety and 5-HT plasma levels. 5-HT therefore serves a dual function as a neurotransmitter; peripherally, it is an index of inflammation (increased density of EC cells with subsequent release of 5-HT), while centrally, it is related to the perception of discomfort/pain and symptoms (increased levels indicate well-being).

The communication between the brain and the gut as a pathophysiological mechanism of IBS has been recognized [8]. In fact, the alteration in the central processes [33, 34] and/or in the neuro-endocrine-immune activation [35–37] may play a key role in the pathogenesis and course of the syndrome. However, in most cases the neuro-endocrine and immune response has only a paracrine effect. The local release of some neuropeptides [8] into the enteric nervous system plays a role in the pathophysiology of IBS, but these neuropeptides cannot be assayed in the serum because they spread in a paracrine way when they get closer to mucosal innervation. For example the histamine release from mast cells located 5 μm of nerve fibers may perturb nerve function and contribute to abdominal pain perception in IBS patients [38], but cannot be assayed in peripheral blood. However, in some IBS subgroup the chance to find an alteration of serum neuro-endocrine markers could be higher, because the low-grade inflammation [39] involves cytokines and hormone with endocrine effects. Evaluation of these markers, that can only partially clarify the pathogenesis of IBS, could instead provide an additional diagnostic discriminator for patient selection and treatment.

Conclusions

The significant correlation between plasma 5-HT and cortisol levels in D-IBS is consistent with the hypothesis that the activation of the HPA axis is associated with 5-HT activity and the therapeutic efficacy of selective 5-HT3 receptor antagonists. The results of this study demonstrate the association between the increase in 5-HT, the activation of the HANS by extero-/interoceptive stress, and the presence of specific psychological features, particularly in certain clinical forms of IBS. The present results could justify the use of both psychotherapy and drugs acting on 5-HT receptors or on the reuptake of 5-HT in some IBS patients.

Conflict of interest The authors have no conflicts of interest to disclose.

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