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Irritable bowel syndrome (IBS): could we decide what is behind?

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Abstract
Functional visceral problems are frequently present nowadays in the medical practice probably due to the significant mental and emotional load on people. Although physicians and psychophysiologists are active on the field, still we are far from a complete knowledge, despite the fact that scientists like the Hungarian Professor György Ádám already had initiated a new approach called visceral psychophysiology already a long time ago. In this article, we commemorate Professor Ádám by analyzing one of the most frequent functional disorders, irritable bowel syndrome (IBS), calling psychophysiology for help. First, we try to give a definition, then show the general descriptions and characteristics of IBS. Factors like stress, gender, and gastrointestinal pain are followed by the potential role of the immune system and the neuronal factors as well as the supposed brain mechanisms. We hope that this overview of the IBS-history would show how significant scientists can be decisive in certain fields of the science and practice.

Keywords Visceral problems · Visceral psychophysiology · Irritable bowel syndrome · IBS · Main factors behind

Abbreviations

ACC	Anterior cingulate cortex
CNS	Central nervous system
CRF	Corticotropin releasing factor
ENS	Enteral nervous system
FGIDs	Functional gastrointestinal disorders
GI	Gastrointestinal
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
HRQL	Health-related quality of life
NES	Neuroendocrine system
QOL	Quality of life
RH	Rectal hypersensitivity
WGO	World Gastroenterology Organisation

Introduction

Today, probably due to the frequently extra mental and emotional load on the people, visceral functional problems have become frequent (Carvalho and Damasio 2021; Yan et al. 2023). But still, the medical and psychological knowledge about these conditions is far from satisfying despite the effort of psychophysiologists and physicians active on the field (Vasant and Ford 2020) The Hungarian Professor György Ádám was among the first scientists who established the new area of visceral psychophysiology and laid down the bases of it (Ádám 1967, 1978, 1980, 1998, 1999). This article is dedicated to his memory and commemorates his 100th birthday.

From among the many functional gastrointestinal disorders (FGIDs), I have selected the irritable bowel syndrome (IBS), a frequent condition still having some unsolved problems with the diagnosis and characteristic features. To show the complexity of this disease, below I summarize definitions of IBS.

Definition

There have been papers which declared there was not enough knowledge about this disease to have a clear picture about reasons and processes (Hubbard et al. 2016; Alonso et al. 2011). The next-generation of the definitions lists the main symptoms (Khan and Chang 2010; O'Malley et al. 2011; Sinagra et al. 2017). Finally, there are definitions which try to refer to the mechanisms (Drossman et al. 2002; Surdea-Blaga et al. 2012). The most generally accepted descriptions and definitions are the Rome II-III-IV-V criteria (Drossman

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1999; Oka et al. 2020; Sperber et al. 2007; Hellström and Benno 2019; Black and Ford 2022, Keefer et al. 2022; Shin and Chang 2022).

Characteristic features are that IBS patients differ from the normal individuals in several psychological factors, like anxiety, interpersonal sensitivity, depression, hostility, and somatization tendency, although these factors are not different in the subtypes (Ádám 1983; Whitehead et al. 1980). In addition, the severity of psychopathology is not correlated either with colonic motility or with the seriousness of symptoms of IBS patients (Drossman et al. 2002).

In 1988, Professor Ádám and myself organized a symposium dealing with FGIDs with the aim to resolve the discrepancy among the different approaches ("Gastrointestinal Psychophysiology", Budapest, 1989). It turned out that the western (mainly American) and eastern (mainly Russian) schools differed significantly. Whereas the western schools basically had built on Skinner's and Thorndike's basic research (Jenkins 1984), the eastern schools relied on Pavlov's groups, represented by Bykov, Aiarapetyantz, and his colleagues (Airapetyantz and Bykov, 1966; Bykov 1933, 1957;). Whereas the former published in English, the latter in Russian (much later translated into English) thus seldom had read each-other's publications.

The central concept of the Russian Pavlovian school was based on the term "analyzer", according to which basic function of the analyzer is "insulation" of important parts of the environment for detailed analysis. Bykov and Airapetantz, applying this principle, stated that functionally, there is no difference between the somatic and visceral neuronal systems, respectively, that is, the two systems are identical (Airapetantz and Bykov 1966; Bykov 1957). They had used stimuli strong enough during the conditioning experiments and avoided those not evoking visible reactions.

The American research groups, on the other hand, denied or neglected the specific perception, instead supposed affective or uncertain feelings of the visceral stimuli. As they stated: interoception significantly differs from both exteroception and proprioception, respectively (Brener 1977). Another similar conception was based on the symptom-report (Pennebaker 1983), stating that one cannot feel even the states but only their changes. Still another approach is based on the principle that the subjective feelings of the internal signals only reflect to the emotional excitement arousal (Blascovich and Katkin 1985). Finally, an even less specific hypothesis states that visceral afferentation only provides diffuse information and evokes "mass" reactions that are absolutely non-specific (Cervero and Sharkey 1985).

The two sets of conceptions seem to be contradictory: According to the Russian school, visceral perception is a special existing phenomenon, whereas according to the American groups, these processes do not exist or are non-significant. Professor Ádám and the Central-European researchers, however, acting as a kind of connective agent, stated that this contradiction can be resolved if we imagine the sensory procedure along to a continuum and suppose that there exist crucial levels (thresholds). He came up with the dual nature (Janus-face) theory, based on the existence of two basic areas: protopathic (protocritic) versus epicritic sensory processes. This means that there exists a special critical perception level (or perception threshold) below which there is no perception as opposed to the stimuli above this threshold. What made this conception more specific was the statement that most of the visceral stimuli are below the critical level hence remain undetected (Ádám 1967, 1983, 1998, 1999), and only in special cases exceed the sensory threshold and show the other side of the Janus-face.

This symposium resulted in the formation of a unified picture of the FGIDs from the medical and functional approach to the psychological and reflexive theories with the psychophysiological resolutions in between. The overview of one of the FGIDs, the irritable bowel syndrome (IBS) in this article, uses this complex approach and is defined (by combining the main features of the above descriptions) as follows:

Irritable bowel syndrome (IBS) is one of the functional psychosomatic gastrointestinal disorders (FGIDs) that, despite differences in location and symptom patterns, share common features with regard to their motor and sensory physiology, central nervous system (CNS) relationships, and the approach to patient care. It is a multifactorial disease that implies visceral hypersensitivity, alterations at the level of nervous and humoral communications between the enteric nervous system and the central nervous system, alteration of the gut microflora, an increased intestinal permeability, and light intestinal inflammation. IBS involves the dysfunctional activation of specific brain regions crucial for interoception and disgust processing and is regarded chronic, recurring, remitting, and debilitating. This functional gut disorder is characterized by episodic exacerbations of a cluster of symptoms including abdominal pain, bloating and altered bowel habit, diarrhea, and/or constipation with a worldwide prevalence between 10 and 20%.

IBS and its features

Traditionally, IBS had been classified into three different subtypes based on colonic motility and/or on psychological test scores: diarrhea predominant, constipation predominant, and mixed (Whitehead et al. 1980). Intensity of bowel symptoms is correlated with the so-called "motility index", but no single or dominant feature helped to distinguish the subtypes. Severity of psychopathology is not correlated either with colonic motility or with seriousness of symptoms of IBS patients.

Based on these and similar data, in the early phases, it has been supposed that IBS (and other FGIDs) was sensory phenomena, that is, no organic changes are behind but changes of the activity of the viscerosensory system. This means that activity of this system is generally out of our consciousness, and we only feel it if some unusual (i.e., possibly pathological) changes happen in the visceral organs. As Ádám pointed out: "the main function of the visceral afferent nerves reaching the central nervous system at the level of the spinal cord, the medulla, and the midbrain is the protection of homeostasis". However, continues Ádám, it does not mean that this system cannot change the behavior quasi directly, called once "extrahomeostatic" function. According to this view, the viscerosensory system functions like a sense organ, which, in addition to regulating visceral organs, carries information to the higher brain centers and affects behavior (Ádám 1983). Later, the "extrahomeostatic" view and terminology have been eliminated, and the "homeostasis" has become a general term including internal (physiological) and external (behavioral) processes (Ádám et al. 1990a, b, Ádám 1998, Porcelli and Sonino (eds), 2007). Significant contribution to the literature was presented as early as 1988 (Klein 1988) in which the topic had been critically analyzed.

One of the main research approaches has been introduced by Drossman and Whitehead, respectively (for overview, see Drossman et al. 2002). IBS–as described by them–is highly frequent and has essential characteristics, like impaired health-related quality of life (HRQL), emotional distress, high healthcare costs, and disability. It has become clear that understanding and improving the IBS phenomenon require integrated multicomponent pharmacological and behavioral strategies.

There are evidences that psychological factors, in which IBS patients differ from the normal individuals, have a role in the severity and duration of IBS, but it is not clear which of them are important and how they interact. To find it out, a multiple test battery was applied in a model study, including somatization, catastrophizing, abuse, life events, anxiety, interpersonal sensitivity, hostility, and neuroticism. It was found that catastrophizing and somatization are the most effective factors (van Tilburg et al. 2013), although these factors are not different in the subtypes.

Regarding the regulation of psychological factors, especially of depression, one candidate is the autonomic nervous system (ANS), which acts as the principal interface of the gut–brain axis. Other candidates are some gastrointestinal hormones, like cholecystokinin (CCK), which affects mechanosensitivity of the rectum, and is a factor mediating effects of mood disorder.

Depression and anxiety favor bad gut feelings even if there are no painful stimuli (Farista 2022). In a representative study, a total of 1,256,325 hospitalized IBS patients were studied. 344,165 (27.4%) of them had depression, 478,515 (38.1%) had anxiety, much more compared to general adults. IBS patients with a co-diagnosis of anxiety or depression stayed much longer in the hospital (Tarar et al. 2023).

Soon some challenges had appeared stating that the gut neuroendocrine system (NES), modulated by the CNS, may be a factor in the formation of the IBS (El-Salhy et al. 2014). The anatomical defect in the gastrointestinal endocrine cells that have specialized microvilli projecting into the lumen and, by releasing hormones into the lamina propria, reacting to luminal stimuli, initiates a chain reaction that progresses affecting the entire NES.

Convergence of the neuronal, endocrine, and immune pathways represented a new frame for the research (Buckley et al. 2014). Evidences indicate that a maladaptive stress response activated by the stress hormone corticotropin-releasing factor (CRF) may be responsible to the activation, persistence and intensity of symptom flares. Other factors are childhood trauma, a positive family history, prior gastrointestinal infection, and dietary behavior. Finally, immune system was regarded as another factor affecting bowel function and consequently IBS.

It has become evident that IBS is a condition with a multifactorial and heterogeneous etiology and pathogenesis and is characterized by psychiatric comorbidity. IBS is now regarded as a disorder of brain-gut axis; altered central processing and modulation of visceral sensory signals may contribute to the increased postprandial symptom generation found in IBS.

Another condition that favors the formation of IBS is alexithymia (difficulties identifying and describing one's own emotions), which is associated with impaired interoceptive sensitivity thus is one probable factor contributing to IBS (Murphy et al. 2018). The affected component is interoceptive awareness, dependent from emotional experience, from emotional stimulus processing, and from activation of brain structures monitoring internal emotional and visceral state. A study in a healthy population shows that interoceptive awareness is a negative factor thus a predictor for alexithymia, hence also for FGIDs. (Herbert et al. 2011).

Hypersensitivity and associated factors

Rectal pain associated with distension of the rectum is termed rectal hypersensitivity (RH) (Roberts et al. 2022). Whereas rectal pain threshold differs in IBS patients from that of healthy controls, there are no differences in subtype, gender, or diagnostic criteria of IBS. Research now focuses on pathological and therapeutic significance of rectal hypersensitivity in therapy and prognosis. Rectal hypersensitivity is defined as follows:

"Rectal hypersensitivity is defined as increased sensitivity to experimental stimuli applied to the gastrointestinal (GI) tract. It can arise due to a combination of either heightened sensitivity to noxious stimuli (hyperalgesia) and/or non-noxious stimuli (allodynia) due to factors such as peripheral and central sensitization. Additional mechanisms include alterations in central factors such as aberrant brain processing and abnormal descending inhibitory control of pain pathways" (Roberts et al. 2021).

Hypersensitivity, in general, seems to be present in several—so-called functional–disorders as one of the main etiological factors causing FGIDs, among others in IBS, functional dyspepsia, and non-cardiac chest pain, associated with significant healthcare and socioeconomic costs of repeated visits to consultants, hospitalization, and work absenteeism. Factors behind may be peripheral sensitization (that is ability of an organism or part of an organism to react to stimuli; irritability, degree of susceptibility to stimulation) of afferent neurons, both of the enteric and the (afferent) autonomic nervous system, central sensitization of spinal cord dorsal horn neurons, and psychiatric comorbidity accompanying psychosocial factors that influence processing of afferent signals by the brain. Possibly, all or more than one of them play a role in forming IBS (Anand et al. 2007).

Interestingly, although not with this term, the suspicion of the role of changed sensitivity of the gut system has been raised early by Ádám (1983, 1998, 1999) and his colleagues (Bárdos and Ádám 1978, 1980). Genetic and inflammatory disorders associated with central and peripheral functional alterations may exist behind (Azpiroz et al. 2007). Associated with these, changes of the intraluminal milieu and genetic factors, motor disturbances, and consequent altered transport of intestinal gas seemed to play a role.

New techniques for assessing intestinal perception, like computerized barostat to evoke rectal distension, recording cerebral evoked potentials, as well as brain imaging modalities such as functional magnetic resonance imaging and positron emission tomography, have helped to identify mechanisms of intestinal hypersensitivity. However, according to some researchers, visceral perception following rectal distension in IBS is still assessed the best with the help of subjective verbal reporting (Keszthelyi 2012). Other researchers, at the same time, had combined structural magnetic resonance imaging (MRI) with questionnaires to assess somatic symptoms and identified several brain regions associated with multiple somatic symptoms (Grinvall et al. 2018). These affected brain regions have a role in emotional regulation as well as in sensory processing but are not affected by IBS symptoms severity.

Another approach to uncover mechanisms behind IBS and other FGIDs supposed the role of the hormonal system. One candidate was the altered serotonergic (5-HT) metabolism (Keszthelyi et al. 2015) accompanied by increased perception of intestinal pain both in healthy and hypersensitive, but not in non-hypersensitive IBS patients (since not all IBS patients are also hypersensitive). This calls the attention to the role of socially relevant personality traits in forming and managing IBS.

Regulatory role of gut sensitivity and gut-brain interactions in IBS

IBS is a very complex and multifactorial phenomenon which is therefore not easy to study. In addition, results are different depending on the study methods, region of research, clinical practice, and availability of the resources since none of these factors are uniform. This is why World Gastroenterology Organisation (WGO) Global Guidelines contain "cascades" of context- and resource-sensitive approach, respectively, for diagnosing and managing of IBS (Quigley et al. 2015).

One possible approach is using animal models (rats, cats, and sometimes dogs), which allow repetitions, provide homogeneous samples and many options (Ádám 1967; Bárdos and Ádám 1980). IBS models usually apply intestinal preparations (fistulas, implanted stimulators, or isolated open-ended intestinal loops), and record animal behavior and brain functions (including first of all pain) as results of intestinal stimulation. Animal models of intestinal functions, their effects on behavior, and their brain relationships have been studied intensively in Professor Ádám's laboratory.

To study the effects of different small intestinal distention on the behavior, "isovolemic" versus volumetric distention was applied in rats. The results suggest that instead of aversivity, discomfort is a steady, inherent concomitant factor of physiological mechanoceptive gut stimuli (Bárdos 1989). Results also suggest that unpleasant feelings frequently may accompany stronger food processing activity even when the person cannot detect the exact place and source.

The most important contributions to the FGID literature were those experiments which applied stimulation of isolated intestinal preparations and detected/measured behavior and brain functions, first of all pain and consummatory activity. As it turned out, small and medium intestinal distension affected fluid intake (Ádám 1967, 1983; Bárdos 1997; Bárdos and Ádám 1980; Gyetvai and Bárdos 1999), whereas stronger distension elicited pain and behavioral changes (Bárdos and Ádám 1978, 1980). A quite new finding has helped to understand the frequently hidden behavioral changes, since effects elicited by milder stimuli were weaker than pain but still unpleasant; thus, we have introduced the new term to characterize this reaction as "discomfort" (Bárdos 1989; Bárdos et al. 2002). We used special preparations to test the sensitivity of different parts of the gut system (Bárdos and Nagy 1995) and the possible role of visceral nociceptors in generating pain or discomfort (Bárdos 1993).

The animal studies have been paralleled by human experiments that tested discomfort and pain of visceral origin in humans. Brain activity as well as verbal reactions has been recorded while visceral activity was measured and changed if possible (Ádám 1983; Ádám et al. 1966; Ádám and Mészáros 1962; Ádám et al. 1965, 1990a, b; Fent et al 1999). Special methodological studies tested the best stimulator conditions (Ádám et al. 1999), and a new direction of stimulating humans has utilized the experiences obtained from the animal studies (Ádám et al. 1990a, b). Altogether, the models applied in our laboratories contributed significantly to the understanding the function of the visceral sensory system in regulating behavior but also raised more new questions than they have answered.

Main mechanisms underlying IBS and its symptoms and basic features.

The role of pain

One of the leading complaints of IBS patients is pain (frequently associated with defecation), being part of almost all definitions and descriptions of the disease (and actually of almost all FGIDs). Pain–actually evoked by a balloon inflation in the colon–has been detected already early (e.g., Ritchie 1973). Frequently affected areas are hypogastrum (40%), iliac fossae (31%), and rectum (21%), with no significant differences between clinical groups. Pain threshold was much lower in IBS patients than in healthy controls. The threshold is frequently modulated by psychological factors and also by stress. Selective attention to gastrointestinal sensations and disease attribution may lie behind pain sensitivity (Whitehead and Palsson 1998).

Abnormal pain processing seems to be the main factor of intestinal pain, but biomechanical abnormalities may also contribute (Drewes et al. 2001). Abnormal features of rectal sensation in IBS patients were unpleasantness of pain sensation, longer persistence of pain sensation after termination of stimulation, and higher pain scores in the case of tonic painful distension (Kwan et al. 2005). A thorough literature search had shown that, in addition to central mechanisms, probably sensitization of high-threshold nociceptive afferents might be the decisive factor of visceral hypersensitivity (Keszthelyi et al. 2012a, b). Altered rectal perception seems to be one important pathophysiological mechanism of developing GI symptoms in general and particularly in pain and bloating (Posserud et al. 2007).

Stress, as an important factor

Pain processing is related to the fact that IBS is a bio-psycho-social disorder caused by dysregulation of either the central or the enteric nervous system through operations associated with psychosocial factors (psychopathology, healthcare seeking, life events, and somatosensory amplification) the best. One of the factors identified relatively early is stress. Psychological and physical stressors affect gut function and brain-gut interactions mediated by the emotional motor system, by modulatory responses of autonomic, neuroendocrine, attentional, and pain factors (Sapkota et al. 2014). It seems that DSM-IV had not contained all and enough psychosocial components and also contained less psychosomatic diseases and cases than found lately. New data regarding prevalent factors (alexithymia, persistent somatization, functional somatic symptoms secondary to a psychiatric disorder, and demoralization) effectively improved diagnoses and treatment thus have been included into the new DSM-V (Porcelli and Sonino, 2007).

The mediator of stress-effects seems to be the corticotropin-releasing factor (CRF1), which affects colonic motility, defecation, gut hypersensitivity, and mast-cell activation, hence generating a maladaptive gut response (O'Malley et al. 2011, Sapkota et al. 2014). This is probably an important component of changes of the gut-associated immune responses (see below) that seems to be a primary factor in forming IBS.

The low-grade inflammation and immune activation of the intestinal mucosa challenge the traditional opinion of IBS as a prototypic gut functional disorder and raise a hypothesis that links stress and infections to IBS development. These stress-induced changes result in the breakdown of intestinal epithelial barrier's functions and visceral pain and hypersensitivity (Alonso et al. 2011). The affected mucosal barrier thus facilitates penetration of food and bacterial antigens initiating immunological responses and inflammation of the mucosa. A rat model has shown that stress may play an important role in patients with IgA-associated IBS-D disturbing intestinal microbial functions and GI functions (Rengarajan et al. 2020).

The effect of stress can be modified by gender, immune functioning, and gut microbiota alterations (Moloney et al. 2015). There are several factors regarded as therapeutic tools controlling stress-induced changes, like glutamate, GABA, and epigenetic mechanisms. It is now apparent that stress-induced visceral pain and its psychiatric comorbidities have a multifaceted etiology. It has been shown that–among others—early life stress and maladaptive coping strategies negatively affect gut-brain communication and may significantly worsen IBS severity. This is why behavioral therapies (e.g., gut-directed hypnosis

and mindfulness-based treatments) have recently gained a significant role in treating IBS (Jagielski and Riehl 2021).

Psychological and psychosocial factors

An important finding found already at 1982 has been the role of learning in the formation of IBS (but not in gastric ulcer). It was shown that multiple somatic complaints are present in people with IBS who consult a physician frequently for minor illnesses. Social learning could be one of the crucial factors in the formation of FGIDs. Later, Whitehead and colleagues have shown that neither the tolerance to stepwise distention of the rectosigmoid area nor contractions elicited by balloon distention are factors in IBS patients; thus, peripheral mechanism, for example changing receptor sensitivity, might be a possible causal factor.

One of the main results of these approaches is the role of psychosocial factors, like abuse history and stressful life events, in FGIDs. Clustering of IBS in families can be explained by genetic factors and social learning mechanisms, together with depression, anxiety, comorbid psychiatric disorders, health beliefs, and coping of the patients (Surdea-Blaga et al. 2012). In addition to alexithymia, the defectiveness/shame schema and four coping dimensions (active coping, instrumental support, self-blame, and positive reframing) are also supposed to be affective factors. Other predictors of the two subscales of alexithymia (difficulty identifying feelings and difficulty describing feelings) are gender, the schemas of defectiveness/shame and entitlement, and global psychological distress (Phillips et al. 2013).

Another factor is sex (gender). In Western countries, twice as many women as men get IBS suggesting a role of sex hormones interacting with other risk factors. Ovarian hormones clearly are related to the onset of IBS, still–according to the respective studies—not as a causal factor because they arguably only modulate IBS onset and symptomatology. Since the sickness ratio is different in women and men, male hormones should be studied as well (Mayer et al. 2004; Meleine and Matricon 2014).

Immune functions in IBS

Factors affecting IBS described so far have turned out to be insufficient to explain all features of this disease. The search for other factors directed the attention to one of the main protective mechanisms, the immune system. One of the findings that helped to look for immune effects was achieved by using placebo-treatment in IBS patients (Kokkotou et al. 2010). They found higher rates of some immune components in patients treated with placebos than in non-treated controls. The changes of two measurable immune components helped to call the attention toward these mechanisms.

Initial findings have been supported by examining post-infectious changes in IBS patients. Some risk factors identified were illness severity, female gender, and together with adverse psychological condition, whereas genetic predispositions were uncertain. Animal studies, supported by some human findings, have shown mast-cell activation, accretion, and impairment of the serotonin transporter by inflammation, as well as changes of the microbiota. Mast cell and lymphocyte production and an alteration in cytokine level and intestinal permeability seem also to be important (Matricon et al. 2012). Mediators produced by immune cells may affect activity of the GI nerves through interaction of the immune system with the nervous system (Hughes et. al. 2013; Ringel and Maharshak 2013).

Recognition of the role of low-grade inflammation in IBS favors clinical trials to test the drugs affecting pathophysiologic mechanisms, such as impaired hormonal regulation and bile acid metabolism, immune dysfunction, the epithelial barrier, and the secretory properties of the gut (Sinagra et al. 2016, 2017).

Neuro-gastroenterology and brain functions

Interactions among the brain, spinal cord, and gut are in the focus regarding abdominal pain and disordered gastrointestinal functions. It is supposed that visceral sensation can be modulated by inflammation and stress through the changing relationship of the enteral nervous system (ENS) and the brain functions, that is the brain-gut axis is a central topic for understanding etiology of these diseases (Grundy et al. 2006).

Although we knew that psychological processes influence gastrointestinal sensorimotor functions, the exact mechanisms remained unknown for long. It has significantly changed when brain imaging techniques had been introduced and applied about 10 years ago, which made it possible to understand the function and operation of the brain-gut axis (Van Oudenhove et al. 2007). Now, it is generally accepted that the brain-gut axis is a bidirectional pathway between the gastrointestinal system and the brain. Any functional disturbances of this system may cause changes of the GI functions and may lead to FGID symptoms (Van Oudenhove et al. 2004; Smith et al. 2011).

Several studies have tried to identify brain areas and sites associated with certain GI parts. For example, primary sensory and motor cortices and the midsection of the medial surface are affected by esophageal distension, whereas bilateral prefrontal and orbitofrontal cortices and anterior and ventral parts of the medial surface by lower intestinal stimuli (Derbyshire 2003a, 2003b). Developing neuroimaging has made it possible to study structure and function of the brain and also the signaling system affecting it (Mayer et al. 2009).

The new techniques have helped to better understand and detect the functional differences between somatic and visceral pain, respectively. Studying the dysfunction of the brain-gut axis caused by visceral stimuli but not by somatic stimulation helped to clearly differentiate the two subsystems, as suggested much earlier by Professor Ádám and myself (Ádám 1967, 1998, 1999; Bárdos and Ádám 1980; Bárdos 1989, 1993, 2021). Recently, it has been found that noxious lower gastrointestinal distension activates areas processing unpleasant affects and autonomic responses, whereas noxious somatic sensation affects areas associated with cognition and skeleto-motor responses (Derbyshire 2003b).

Some challenges

This seemingly clear and logic relationship regarding effects of internal signals has been challenged by the studies of Köteles and his colleagues (Köteles 2021, Köteles and Doering 2016, Witthöft et al. 2020), who have shown that internal proprioceptive/somatosensory and viscероceptive signals are integrated on multiple levels by the brain; thus, it is difficult–regarding awareness impossible–to separate them. These findings have opened a new era for both the theory and practice as well as for new therapeutical approaches. Similar result was obtained while testing the relationship of different interoceptive dimensions and their association with IBS-related functional gastrointestinal symptoms using a multimethod approach. It has shown that strong functional gastrointestinal symptoms were characterized by an increased perception of different somatic sensations together with a reduced trust in bodily signals (Gajdos et al. 2021).

Although there is a significant knowledge about IBS mechanisms, far not all IBS patients show increased perception of non-painful rectal distension, suggesting possible differences of visceral afferent signals. There were three subgroups identified: healthy controls and normosensitive versus hypersensitive IBS patients. Normosensitive patients and healthy controls show normal brain responses to distension, whereas hypersensitive patients are characterized by increased activation of insula and reduced deactivation in pregenual anterior cingulate cortex during noxious rectal distensions. It looks important to determine the type of interoceptive sensitivity to select the correct therapeutic intervention (Larsson et al 2012).

Processing of the internal signals affects alexithymia and increased interoceptive awareness generating affective disorders and altered insula and anterior cingulate cortex (ACC) function and interoceptive awareness. In addition to the nervous pathways, chemical communication, namely hormonal changes, may have a role in the generation of functional disorders. Alexithymia and awareness of autonomic nervous system reactivity are associated with glutamate levels in the left insula, whereas GABA concentration in ACC is associated only with alexithymia, together resulting in increased interoceptive awareness in alexithymia and an unspecific emotional arousal (Ernst et al. 2013).

Communication between the brain cortex and the gut system via the brain-gut axis formulates a reflex circuit. Disturbances of the circuit may generate functional gastrointestinal disorders (FGIDs) characterized by pain and motility dysfunctions. Therapies of FGIDS currently focus on neuromodulatory interventions using different pharmacological methods to influence peripheral intestinal receptors. A new approach, however, direct electrical stimulation of the muscular layers of the bowels, is a promising method that has gained preferences (Gaman and Kuo 2008). It is worth to note, however, that nowadays complex, multiple treatment approach is preferred and popular.

Finally, it is worth to mention that FGIDs in children and adolescents require specific attention since development of the brain-gut axis and the visceral-brain functions may be strongly affected by early visceral dysfunctions. As it was found in a special study, pediatric IBS group is characterized by cortical thickening in the posterior cingulate cortex, whereas cortical thinning in posterior parietal and prefrontal areas, including the dorsolateral prefrontal cortex. Abdominal pain severity was related to cortical thickening in the intra-abdominal area of the primary somatosensory cortex, whereas quality of life was associated with insular cortical thinning. Such changes may be responsive to therapeutic interventions and may characterize disease progression or reversal (Hubbard et al. 2016).

Summary

If one have read this paper carefully, could realize that the changes initiated by Professor Ádám many years ago in the field of psychophysiology (e.g., Ádám 1967, 1983, 1998, 1999) have helped significantly to understand the essence of IBS and other FGIDs and promised an advancement of handling and treating these diseases. His disciples and once students have continued his work and have spread his ideas for the present time researchers and practitioners (Bárdos 1989, 1993, 2021; Köteles and Doering 2016; Köteles 2021).

Since the several essential advancements have been made on the field improving significantly our understanding of IBS and other FGIDS (e.g., Drossman 1999; Grinswall et al. 2018; Köteles 2021; Madva et al. 2023; Moloney et al 2015; Oka et al. 2020; Rengarajan et al 2020; Roberts et al. 2022; Shin and Chang 2022; van Tilburg et al. 2013; Witthöft et al 2020). The result is a complex and multifactorial view of these diseases proving that contribution of significant scientists, like Professor Ádám, may initiate a serious development of a scientific field.

Conclusions

IBS is now regarded as a multifactorial disease that implies visceral hypersensitivity, alterations in communication between the enteric and the central nervous system, changing gut microflora, increased intestinal permeability, and minimum intestinal inflammation (Surdea-Blaga et al. 2012). A biopsychosocial model integrates gut functions with psychosocial assessment and helps to select diagnosis and treatment as well. Antidepressants could be used to eliminate comorbid anxiety and depressive disorders and to improve the symptoms of FGID. (Jones et al. 2006; Jones et al. 2007).

Frequently unconsciously, functional disorders can be due to behavioral, mental, or psycho-social dysfunctions. IBS is one of those with characteristic symptoms like abdominal pain and irregular intestinal motility and defecation. These diseases are multifactorial and multilevel as well, associated with malfunction of a complicated neuronal network including several brain sites. Negative side effects of interventions without a real impact produce nocebo effects that affect visceral functions, in the case of IBS, visceral pain, or discomfort without a plausible reason. IBS is characterized by stimuli that from the GI tract pass through the spinal cord and reach several cortical and subcortical brain sites. As a result, some cortical areas become thicker while others thinner which changes the effect of them on the visceral organs. This complicated relationship is further modified by several hormones (Bárdos 2021).

Although research suggests that positive psychological well-being may be protective, present brain-gut therapies primarily focus on negative psychological factors. Patients described opposing relationships between positive and negative psychological constructs, IBS symptoms, health behavior engagement, and health-related quality of life (HRQoL), respectively (Madva et al. 2023). An intervention to improve well-being may be a novel way to treat IBS symptoms, increase health behavior participation, and improve HRQoL in IBS.

It is clear now that managing of FGIDs requires complex methodology, provided by a team including physicians, psychologist/psychiatrist, associates, and even the patient himself/herself. They may not only suggest medical or pharmacological treatment, but also physiotherapy, modifications of the lifestyle, alimentary changes or physical activity, etc. Placebo-analgesia is also an option used effectively in the therapeutic practice because may affect brain feelings, pain processing, and hormone release (including opioids) which all may affect the top-down pain modifying systems and improve condition of the IBS patients (Bárdos 2021).

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Declarations

Conflict of interest I hereby state that there is no conflict of interest regarding this paper.

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