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Is small intestinal bacterial overgrowth involved in the pathogenesis of functional dyspepsia?

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ABSTRACT

Functional dyspepsia is a highly prevalent disease, with significant impacts on patients' quality of life and economic robustness of health care systems worldwide. It constitutes a constellation of symptoms located in the gastro duodenal region while its pathogenesis remains poorly understood. Accumulating evidence suggest that small intestinal bacterial overgrowth is associated with the etiology of functional gastrointestinal disorders. We herein present the hypothesis that a causal link between small intestinal bacterial overgrowth and functional dyspepsia might exist. Development of functional dyspepsia symptoms may derive from abnormal fermentation of carbohydrates due to increased proliferation of coliform bacteria, resulting in luminal distension, increased intestinal permeability and immune response perpetuation in predisposed hosts, secondary to an episode of infectious gastroenteritis. Moreover, the treatment of functional dyspepsia remains challenging and we explore the feasibility of innovative therapeutic modalities based on our hypothesis.

Introduction

Functional dyspepsia (FD) is one of the most common functional gastrointestinal disorders (FGID). Its prevalence in the community reaches up to 20%, and it has detrimental impacts on patients' quality of life, work performance and family relationships [1]. FD is characterized by the presence of symptoms thought to originate in the gastro duodenal region, including sensation of epigastric pain or burning, early satiety (inability to finish a normal-sized meal), fullness during or after a meal, or a combination of the above, in the absence of organic, metabolic or systematic disease that could explain them [2]. According to the recently published Rome IV consensus, FD comprises two major subtypes: epigastric pain syndrome (EPS), referring to patients with epigastric pain or burning, and postprandial distress syndrome (PDS) in patients complaining about meal-related symptoms, notably early satiety and postprandial fullness [3]. FD is a multifactorial disorder whose pathogenesis remains elusive. A number of putative pathophysiological mechanisms (Fig. 1) including altered gastrointestinal (GI) motility, visceral hypersensitivity, dysregulation of the gut-brain axis, psychological disturbances, low-grade inflammation and immune system dysfunction have been proposed [4]. To date, gastrointestinal sensorimotor function has been thought to be primarily responsible for the pathogenesis of FD since disturbances in gastric physiology (impaired accommodation, delayed emptying and visceral hypersensitivity to gastric distension) have long been thought to contribute to symptom generation. These observations prompted various therapeutic measures including the use of prokinetics and acid suppression agents, with suboptimal efficacy [5]. In this context, a growing body of scientific literature provides new insights into the role of gastric physiological disturbances. More precisely, they seem to correlate poorly or not at all with symptoms and they are identical in the different FD subtypes [6]. Additionally, profound immune activation with increased cytokine release, small bowel T cells homing associated with symptom manifestations and delayed gastric emptying is present in FD [7]. These findings imply that gastric disturbances in FD are subordinate and the stomach may not be the ultimate cause of symptoms, as previously thought. At the same time, it is

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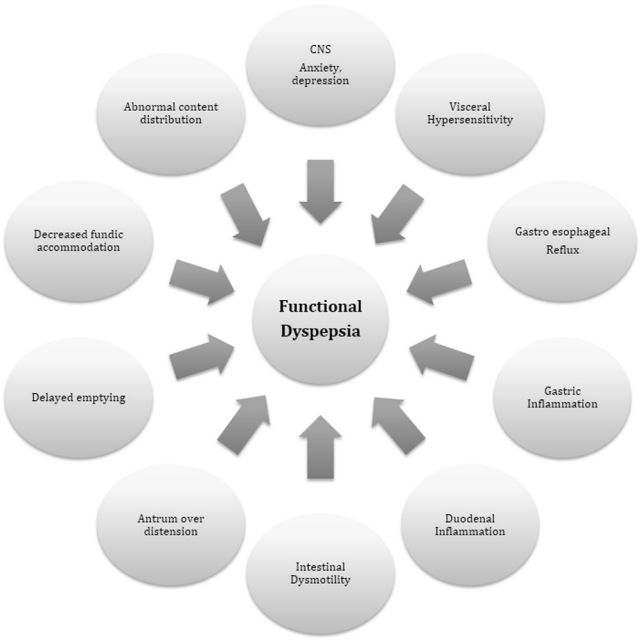

Fig. 1. Mechanisms potentially contributing to functional dyspepsia pathogenesis; CNS: Central Nervous System.

increasingly recognized that complex duodenal perturbations, particularly subtle inflammation, may play a role in the pathophysiology of FD [7–10]. These new data suggest that we may have been looking at the wrong organ, and perhaps the time has come to focus our attention elsewhere [11].

The hypothesis

We hypothesize that small intestinal bacterial overgrowth (SIBO) may be a distinct pathogenic mechanism underlying the development of FD, while the precise role of the intestinal microbiome as yet remains largely unknown.

Intestinal microbiota

The human gastrointestinal tract constitutes a microbial ecosystem in which trillions of microbial cells including bacteria, viruses, protozoa, archaea, yeasts and parasites collectively reside [12]. At present, more than 50 bacterial phyla have been described, with *Firmicutes and Bacteroidetes* being the two most prominent, followed by *Actinobacteria and Proteobacteria*. Despite similarities in terms of abundance and distribution among healthy individuals, the evidence supports the concept that each human possesses a unique microbiological "fingerprint" [13]. This diverse and dynamic microbial community interacts with the host in myriad ways. The beneficial microbes, termed commensal flora, not only contribute to the proper maintenance of gastrointestinal homeostasis but also play a pivotal role in several metabolic and physiological pathways, creating a bidirectional useful relationship, termed symbiosis [14]. Under certain circumstances, the composition and function of commensal flora in the intestinal tract may undergo alterations (qualitative and/or quantitative) resulting in disturbance of the fragile equilibrium of gut microbial communities, a situation known as dysbiosis. Dysbiosis has been inextricably linked not only to several gastroenterological disorders but also to a wide spectrum of systemic chronic disorders (e.g. atherosclerosis, cancer) and diseases with inflammatory, metabolic or autoimmune aspects [12,15]. Our knowledge of the gut microbiota and of the small intestinal microbiota in particular, is limited: the small intestine remains inaccessible and the majority of bacteria (around 80%) remain uncultured because they require particular growth conditions [16]. Therefore, standard culture studies are unable to evaluate their complex diversity, individual differences and fluctuations over time. The number of bacteria inhabiting the small bowel lumen is considerably lower compared to that of the colon, with their numbers increasing from 10^1–10^3 bacteria per gram in the duodenum to 10^{11}–10^{12} cells per gram as we move towards the distal ileum [17]. The majority are Gram-positive and anaerobes from the oral cavity; while in the terminal ileum Gram-negative with Gram-positive anaerobes and facultative anaerobes dominate [18]. More detailed information has been provided by pioneering culture-independent approaches. In addition to quantitative polymerase chain reaction (q-PCR) techniques, the advent of bacterial sequencing based on the 16S ribosomal RNA (16S rRNA) gene approach revolutionized the scene. Nowadays, bacterial species can be identified through amplification of a region of the 16S rRNA gene and subsequent comparison of the results with known sequences. Moreover, partial 16S rRNA sequencing (pyrosequencing) provides an in depth analysis of the number, nature and abundance of the bacterial species, omitting "classical" bacterial culture or DNA cloning methods [16]. Recently, emerging techniques the "-omics" studies based on DNA sequencing appeared, enhancing our ability to analyze the microbiome. Similar technologies have been developed to study the bacterial genome (metagenomics), expressed mRNA in GI tract samples (metatranscriptomics), produced proteins (metaproteomics) and the metabolite profiles (metabolomics). Consequently, these culture independent techniques are expected to maximize our understanding of different bacterial phyla as well as potential host-microbiome interactions [18].

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is a heterogeneous syndrome characterized by large numbers of colonic-type flora in the small intestine [19]. A large variety of gastrointestinal symptoms including bloating, flatulence, abdominal discomfort, diarrhea or constipation can be present, and malabsorption, anemia and deficiency of vitamins may also be clinical manifestations of the syndrome. SIBO usually arises when colonic-type bacteria are allowed to proliferate due to intestinal stasis [17]. The latter takes place when certain predisposing factors are present, namely advanced age, anatomical GI tract alterations with stagnation of contents, intestinal motility disorders and low gastric acid production. In addition, pancreatic enzymes insufficiency and innate immunity disorders may also contribute. Associations between SIBO and multiple other medical conditions have been established, including irritable bowel syndrome (IBS), obesity and inflammatory bowel disease (IBD). The "gold standard" for the diagnosis has been considered the aspiration of the proximal small intestine content for quantitative culture and determination of bacterial counts. Bacterial counts of $\geq 10^5$ colony forming units (CFU)/Ml are strongly indicative of SIBO presence [20]. A lower threshold at $\geq 10^3$ colony forming units (CFU)/Ml in a suitable clinical context has been also proposed. Although favored, small bowel aspiration carries some major methodological drawbacks since it is a time-consuming, costly invasive procedure. Moreover, the potential for sample contamination with oral and esophageal flora, inability to culture a large proportion of bacteria and false negative results due to missing overgrowth in the distal small bowel should not be underestimated. To overcome these limitations, alternative approaches to diagnose SIBO have been implemented. Noninvasive hydrogen breath testing using lactulose or glucose as substrates