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Progress in Animals with Diarrhea Irritable Bowel Syndromes

Yizhuo Gao[1], Shiyu Liu[2], Tao Yu[3,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Francesco Cilea Music Conservatory Reggio Calabria, Reggio Calabria, Calabria 89100, Italy
[3]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
**Correspondence Author*

Abstract: ***As a common clinical functional bowel disease, diarrhea type irritable bowel syndrome is easy to repeat, and its symptoms are unpredictable, which adversely affects the patients' quality of life, mental health and even career. Therefore, it will be of great use to use the pathophysiology to guide the personalized treatment options of IBS-D to improve the patients' symptoms and improve their quality of life. This paper will review the progress of IBS-D animal research to provide a high quality basis for basic research in IBS.***

Keywords: Diarrhea, An animal model of irritable bowel syndrome**.**

1. Introduction

Irritable bowel syndrome [1] (irritable bowel syndrome, IBS) is a functional bowel disease with repeated stool characteristics, defecation frequency changes, abdominal distension and abdominal discomfort related to defecation. The prevalence of IBS in different regions of the world is between 1.1% and 45%, and that of IBS in China is 5% – 6% [2]. At present, according to the Roman diagnostic criteria, IBS is mainly divided into four types, namely constipation type (IBS with predominant constipation, IBS-C), diarrheal type (IBS with predominant diarrhea, IBS-D), mixed type (IBS with mixed bowel habits, IBS-M), and untaped type (IBS unclassified, IBS-U) [1]. The epidemiological survey in China showed that the prevalence of IBS-D (23.3%) was greater than that of IBS-C (19.0%) (P=0.019), and the prevalence of IBS in women was higher than that of male people, while there was no significant difference in the prevalence of IBS in urban and rural areas [3][4]. IBS-D has no obvious effect on the health of patients. At present, the treatment of IBS-D mainly depends on spasmolysis, antidiarrheal, regulation of intestinal flora and the application of intestinal non-absorption of antibiotics [5]. As a functional bowel disease, IBS-D is not only intestinal symptoms, but also associated with other somatic symptoms such as sexual dysfunction, migraine, chronic pelvic pain, and its symptoms are unpredictable, which adversely affects the patients' quality of life, mental health and even career [6][7]. Therefore, it is necessary to develop pathophysiology models related to IBS-D symptoms and use pathophysiology to guide personalized treatment options of IBS-D to improve patients' symptoms and improve their quality of life[8].Animal experiments rely on a wide range of sources from animals , easy to obtain, short formation time and small pathological score error, become a "living reagent" that is difficult to replace in clinical research, and play an important role in medical research. This paper will review the progress of IBS-D animal research [9].

2. The Occurrence Mechanism and Pathophysiology of IBS-D

It is currently believed that changes in gastrointestinal motility and visceral nerve function are the core mechanism of IBS-D, but IBS-D as a functional disease cannot be explained by inflammation, metabolic abnormalities, as well as organic changes. Research believes that [10], previous intestinal infection or chronic intestinal infection makes the intestine in a state of low-grade mucosal inflammation, and inflammation-activated intestinal immunity causes changes in intestinal permeability, and then leads to visceral nerve allergy. This process is related to the decline of intestinal flora diversity and intestinal flora disorder. Cui Xiao et al [11] Targeting the capsaicin receptor illustrates a possible mechanism of the gut flora alteration with IBS-D, suggesting that beneficial bacteria can inhibit capsaicin receptors at the incoming nerve terminals or cell membranes, and activation of these receptors leads to increased visceral sensitivity. Hu Jiayan [12]et al believes that the use of antibiotics can reduce intestinal biodiversity, damage intestinal epithelial mucosal barrier function and alter cytokine production, which may also lead to the occurrence of IBS-D. Animal experiments have shown that the severity of intestinal inflammation is positively correlated with visceral hypersensitivity responses [13]. Moreover, a cross-sectional study found elevated fecal bile acid concentrations in IBS-D patients compared with the normal population, which may also be related to intestinal microecology changes [14].

3. IBS-D

Based on the clinical presentation of IBS-D, the pathophysiology findings were mainly divided into peripheral and central parts. Peripheral part mainly includes gastrointestinal symptoms such as diarrhea and abdominal pain, and the central part includes psychological changes. At present, the animal species selected in studying IBS-D at home and abroad include mouse, rat, guinea pig, hamster, pig, cat and dog, ferret, ape and other animals, among which rodents are the most widely used in IBS-D model.

3.1 Progress of IBS-D

Abdominal pain is an important complaint in IBS-D patients and an important manifestation of gut-brain axis dysfunction. At present, it is believed that abdominal pain is mainly related to the decline of neuralgia threshold, and childhood trauma,

previous systemic inflammation, and psychological trauma may lead to visceral sensory hypersensitivity. Since the hallmark feature of IBS is visceral pain, a key requirement for model evaluation is that they exhibit visceral hypersensitivity and exhibit pain-like behavior for lumen expansion [15].

In the absence of observable colonic damage, stress and negative emotions can greatly increase visceral pain. Studies have shown that when stress is repeated daily (usually 1 hour a day for 7-10 days) for restraint and water avoidance, to address this problem, a heterogeneous stress paradigm has been introduced in which animals were randomly exposed to different stressors (cold, restraint, water avoidance) to elicit sustained stress response while increasing colonic sensitivity [16][17][18]. Early life stress, including mother-child separation (simulation neglect), limited nesting (simulating poor care), and odor attachment learning (simulating abusive caregivers' attachment), can develop visceral allergies later in life, thus enhancing visceral pain [19].

Colorectal dilatation causes high visceral sensitivity in rat through continuous mechanical stimulation factors, and no obvious colorectal pathological changes, which is a common method in IBS-D. Select rat 8-21d, using angioplasty by the balloon (20mm long, 3mm diameter), surface coated with medical paraffin oil, insert from the anus to the colorectal, and the balloon was expanded by water injection (0.3 mL), the balloon was removed slowly decompression within 1min, 30min within 1h. The colorectal dilation method is simple to operate, no anesthesia, good repetitive, and stable after molding [20].

3.2 Progress of IBS-D

At present, it is considered that the intestinal microbiota disorder is closely related to the occurrence of IBS-D, but the causal relationship is not clear. Studies have suggested that the mechanism of IBS-D may be related to affecting low-grade mucosal inflammation and immunohistochemistry, visceral hypersensitivity, intestinal barrier function, and bile acid metabolism [21]. The intestinal flora disorder in IBS-D patients mainly showed reduction and even absence of L. lactic and bacillus bifidus. Microorganisms with excessive proliferation of small intestinal bacteria produce excessive gas in the process of food fermentation, causing abdominal distension, diarrhea and diarrhea [22]. The intestinal flora interacts with contents from diet or other luminal contents, and with endogenous chemicals that alter intestinal function, interfering with intestinal epithelial cells and having an impact on the gut-brain axis [23]. Bacterial lipopolysaccharide activates receptors on the intestinal mucosal barrier, stimulates the brain by affecting the immune system activation, cytokine synthesis, and stimulating the vagus nerve, and leads to low-grade inflammation and intestinal barrier function damage by directly affecting nociceptive receptors and activating mast cells [24]. Gut microbiota also regulates endocrine cell activity by regulating the opioid receptors and cannabinoid receptors in the terminal colon [25][26]. However, the diversity of microflora increases the complexity of experimental models, which is difficult to apply to the basic research of most IBS.

Faecal microbiota of patients with diarrhea IBS was colonized into germ-free mice on sterilized and ventilated shelves for 3 weeks on a 12h light / 12h dark cycle without water and food restriction, which were operated by professional technicians in a level 2 hood to minimize bacterial colonization. Gastrointestinal motility, intestinal permeability, and immune activation was tested 3 weeks later to determine whether colonization was successful [27].

3.3 IBS-D Infection and Low-grade Inflammation

The drug preparation model mainly used a single slow infusion of 0.8 mL Trinitromethyl benzene solution for 1 week. After the resolution of the acute inflammation caused by drug stimulation, the gastrointestinal sensitivity increases and the colonic movement speed increases, and the typical symptoms of diarrhea IBS appear. This IBS resulting from a history of acute gastrointestinal infection is called post-infection IBS [28][29].

3.4 IBS-D Mold Development in Mice with Abnormal Bile Acid Metabolism

studies has shown that moderate bile acids can promote intestinal peristalsis and accelerate the digestion of lipids in the gut, but they can cause diarrhea when the bile acids are too high. Bile acid can also play a bactericidal effect, bile acid excess is one of the intestinal sensitivity, one of the main reasons for pain [30]. According to statistics, more than 60% of IBS-D patients are accompanied by abnormal bile acids. Unregulated bile acids can promote the release of 5-h and further bind to 5-h 3r receptors on neurons in the intestinal mucosa, and enhance the visceral sensitivity under the action of peripheral sensitization mechanism [32][33]. There are no such study on stable molding methods of IBS-D pathological types.

4. Discussion

The pathogenesis of IBS-D is complex, and it is mostly studied from the perspectives of brain-gut interaction and visceral hypersensitivity. In the process of model building, minimizing the multivariable intervention can effectively increase the modeling rate of the model. The general use of large mice in the study of disease and its pathogenesis, so other types of animals are less involved, which not only complies with the principles of quality control of animal experimental design, but also reduces the cost to some extent. When evaluating whether the model is successful, we should combine various methods, such as the animal general condition, behavioral evaluation, molecular biology detection, to avoid the differences in the model due to subjective influence. Therefore, although the preparation of animal models based on pathogenesis is widely used and a large number of animal experiments have been carried out, the currently recognized and highly compatible disease syndrome combined animal models are still lacking. In view of a certain pathogenesis, the research model is relatively single, the quality is uneven, and it is difficult to reproduce the complex clinical symptoms. A unified and objective evaluation standard should be formulated, which will lay a foundation for the future research of experimental reproducibility, pathophysiology of the disease and the development of new treatment strategies.

In conclusion, IBS requires in-depth research of the relationship between pathogenesis and animal models, and then highly simulate the pathogenesis of IBS patients to provide high-quality basis for basic research on IBS. To drive scientific advances and clinical applications in the field of IBS-D.

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