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Rodent Model of Irritable Bowel Syndrome

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Abstract

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder with high prevalence. The main clinical symptoms of IBS include abdominal pain and defecatory irregularities which has profound negative impact on patients' life quality. Till now, the etiology and pathogenesis of this functional disorder have not been totally elucidated. However, it is widely accepted that the visceral hypersensitivity, the alteration in brain-gut axis and gut microbiota are involved in the process of IBS. And a series of animal models have been applied to imitate these pathological changes. Nowadays, there is no specific drug to cure IBS. Therefore, it is important to understand the pros and cons of the existing IBS animal models, to use these models and to establish better models for drug research and development.

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain, defecatory irregularities and bloating. The prevalence rates of IBS vary between 1.1% and 45% and it is highly disruptive to a patient's daily life [1]. Currently, the underlying pathogenic mechanisms of IBS remain ambiguous, although increased epithelial permeability, inflammation, visceral hypersensitivity, and altered brain-gut interaction are thought to play essential role in IBS [2]. It has been reported that multiple stimuli play essential role in the initiation and development of IBS. Available animal models mimicking the pathogenesis and the symptoms of IBS are essential for IBS research, which may contribute to the development of new therapy. Most of the IBS animal models are established withvarious stress stimulations. According to the action sites of stimulators, IBS animal models can be divided into three types: central stimulus induced animal model, peripheral stimulus induced animal model and combined central and peripheral stimulus induced complex animal model. Central stimulation induces the alteration of brain activity and further affects the function of gut through brain-gut axis. Peripheral stimulus induces IBS-like symptom via enteric nervous system.

Central stimulation induced animal model

Psychological stress induced animal model

Psychological pressure is an important cause of IBS. It is possible that chronic or severe stress results in long-lasting changes in the central nervous system (CNS) which provokes the symptoms of IBS [3].Psychological stress induced IBS model can be divided into two types based on the length and frequence of the treatments: acute stress model and chronic stress model. The former was established by giving animal transient stimulation whereas the latter was made by treating the animal with a longer continuous stimulation. Transient stressors can induce an immediate response, and continuous stressors can accumulate and potentiate the effects of stress on the host to produce a persistent reaction [4].

Water avoidance stress (WAS) induced model

Chronic water avoidance stress (CWAS) induced model

The most common method to construct this model is to put animal in a plexiglas tank with a block affixed to the center of the floor. The tank is filled with fresh room temperature water. And the block is 1 cm higher than the water level. The animal is placed on the block for continuous 1 h daily with consecutive 10 days. Several researches have reported that 10-day WAS can increase animal's visceral sensitivity, which is a significant feature of IBS [5-7]. This model was first proposed by Bradesi et al. [8], and it demonstrated a transient somatic antinociceptive response associated with sustained visceral hyperalgesia. In addition, the changes of mucosal immune status of the colon, the increased colonic motor function and increased anxiety-like behavior were also observed. Zhuo et al. [5] found the altered pattern of functional brain activation of CWAS rat is similar to that observed in IBS patients by brain imaging studies, providing further validation of the WAS model for IBS. Shi et al. [6] found calcitonin-gene-related peptide (CGRP) levels in serum and colonic tissue were both increased in CWAS rats. Tumor necrosis factor (TNF-α) level in colonic tissue was also significantly upregulated. However, the levels of 5-hydroxytryptamide (5-HT), serotonin transporter (SERT) and chromogranin A (CgA) in colonic tissue were decreased. Xu et al.[7] found that CWAS can lead to changes of intestinal flora characterized by the reduction of less-abundant families, and can induce low-level inflammation and increase intestinal sensitivity. Da Silva et al.[9] modified the method to establish the WAS model by placing the animal on the block for continuous 4 h daily with consecutive 4 days. They found CWAS could induce the visceral hypersensitivity and the alteration of intestinal flora with the decrease of Lactobacillus farciminis population, as observed in IBS patients. Myers gave the rats 1h stress per day for consecutive 7 days and found the chronic stress could also lead to sustained visceral sensitivity, which can be eliminated by glucocorticoid receptor blockers and mineralocorticoid receptor antagonists [10]. As a reproducible and non-invasive model, CWAS model could exhibit a series of characteristics of human IBS, such as visceral hypersensitivity and the alteration of intestinal flora although the mechanisms underlying these changes still need to be explored furtherly. The operations of CWAS are easy and stable. But some animals adapt themselves to this environment rapidly, which decreased their responses to the stress.

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Acute water avoidance stress (AWAS) induced model

AWAS only let animals suffer from stress for 1 h. AWAS model was used earlier than CWAS model in IBS related study. Myers et al. found such acute stress could lead to transient visceral hypersensitivity in rats, and it will disappear after 24 hours [10]. In other two studies, the rats' visceral hypersensitivity to colon distension has not been observed after 24h from AWAS. Suda et al. [11] found one hour WAS induced acceleration of distal colonic transit and defecation which was mediated by the parasympathetic pelvic efferent. In view of AWAS induced changes of gut mobility and visceral sensitivity cannot be kept for a long time, it is frequently used with other operations, such as maternal separation [12-13], to better mimic IBS. But if we look at the issue from another angle, this model can be used for studying the triggering effect of stressors on the animals that have genetic susceptibility to IBS.

Restraint stress induced animal model

The first restraint stress model was proposed by Williams [14], who constrained upper body of rat for 24 h. This model showed an inhibition of intestinal transport and an increased number of defecation without formation of ulcers. It has been considered as a classic IBS model. Nowadays, improved restraint stress models are widely used. Lv et al. [15] wrapped the shoulder, upper limbs and chest of rats with paper tape after anesthetized with ether to prevent scratching head and face for 1 hour, but other activities of rats were not limited. This model showed increased rectal motility and increased defecation with loose stools as well as visceral hypersensitivity, which indicated that it can be used for motility and visceral sensitivity associated studies. Agostini et al. [16] gave rats a partial restraint stress (PRS) by wrapping the upper forelimbs and the thoracic trunk for 2 h. This PRS significantly increased the number of abdominal contractions and intestinal permeability as well as visceral hypersensitivity. Asano et al. [17] found that the rats subjected to restraint stress displayed an increased number and wet weight of fecal pellets as well as the serum corticosterone level, and that aminophylline can reduce the number of defecation and fecal wet weight, but had no effects on serum cortisol levels. The study conducted by Liu et al. [18] reported that short time restraint stress can lead to a transient increase in sensitivity to nociceptive stress, but had no effect on the contraction of single muscle cells. Restraint stress can induce some changes of gastrointestinal function which is similar to IBS, but it is not suitable for long treatment which may induce somatic damages. In addition, the actual impact on different individuals of restraintis difficult to keep equal.

Neonatal maternal separation (NMS) induced animal model

It has been widely accepted that early life negative events, such as loss of family member, could have detrimental impacts on individuals. This personal injury can last for a long time up to adulthood and may be a significant predictor of psychiatric disorders in adulthood. It has been reported that early life stressors like maternal deprivation can increase the risk to develop IBS in adulthood [19]. Based on this, the NMS model is constructed to mimick the early deprivation of maternal care in human beings. The commonly used method is to separate neonatal rats from their mothers for 3 h daily between postnatal days 2-14. NMS could induce visceral hypersensitivity and changes of HPA-axis [20-23]. Barouei et al. [21] have found that suffering from NMS significantly increased Adrenocorticotropic Hormone (ACTH) levels in plasma and fecal counts of aerobes, anaerobes, enterococci, clostridia and Escherichia (E. coli), but reduced plasma IgA levels compared with non-NMS animals. Miquelet al. [22] separated wild-type C57Bl/AJ pups from their mother three hours per day, from postnatal day 2 to14 and resulted in a negative impact on fecal *Faecalibacterium prausnitzii* population. The report of Zhou indicated that the abundance of Fusobacterium, which is able to reduce the degree of visceral hypersensitivity was significantly decreased in the C57Bl/AJ mice that underwent NMS [23]. The research of McKernan et al. [24] showed that the mRNA expression of TLR3, TLR4 and TLR5 in distal and proximal colonic mucosa of NMS model was significant increased, suggesting that NMS modulated innate immune responses. Tjong and his colleagues showed NMS increased the Nitric oxide (NO) synthesis by NO synthase (nNOS)upregulation that interact with reactive oxygen species contributing to the visceral hypersensitivity [25]. All the evidence above suggested that the alteration of gut sensitivity, microbiota and immune function in NMS model is similar to that in IBS patient. However, the mothers' feed deprivation is liable to cause malnutrition [20].

Statistic analysis

All the descriptive data was expressed by mean±standard deviation. Statistical analyses were performed using SPSS 11.0. Student's t-test was used to compare the difference between the two groups and Dunnet-test (ANOVE) was used to compare the difference among three groups respectively. P value of less than 0.05 was considered statistically significant.

Intracerebral injection of corticotropin-releasing factor (CRF) induced animal model

Corticotropin-releasing factor (CRF), also known as corticotropin-releasing hormone or corticoliberin, is an important peptide hormone involved in stress response in the brain-gut axis. CRF is released in the paraventricular nucleus (PVN) and stimulates ACTH secretion from the pituitary gland. CRF is considered as an important mediator of visceral hypersensitivity. The effect of CRF is mediated by CRF receptors expressed on the cell membrane of effect organ [26]. Many reports proved that intracerebral injection of CRF (CRF microinjected intocerebral ventricle or the central nucleus of the amygdala with the dose of 0.1to 10μg•kg^{-1})increased colonic motility, visceral perception, and induced anxiety-like behavior [27,28] which can be blocked by administration of CRF receptor type 1 antagonist CP-15426 [28] or JTC017 [29]. It seems that intracerebral injection of CRF is an easy way to induce visceral hyperalgesia and colonic motility alteration which are important in pathophysiology of IBS. But the operators need to be skilled enough to perform it. More importantly, it is an invasive method and there exists the risk of organic cerebral injury. The injection dosage should be strictly controlled. Furthermore, the single-chemical injection approach is not likely to fully mimic the complex changes of neuroendocrine immune system in IBS patients.

These models are based on the sensitization of colonic primary afferent fibers which can be induced by inflammation, mechanical or chemical stimulation. The nociceptive signal is then transferred to the central system and cause visceral hypersensitivity. Locally, several mediators including 5-hydroxytryptamine, tachykinin, bradykinin, calcitonin gene-related peptide, and neurotrophin are of great importance for sensitizing nerve endings.

Chemical stimulation induced animal model

Chemical substance enema is the common method to establish these models. And the most widely used chemical mediators include acetic acid, butyric acid salt, mustard oil (MO), glycerin, yeast polysaccharide, turpentine, formaldehyde, and so on. It was reported that adult rats that underwent MO enema treatment neonatally exhibited chronic visceral hypersensitivity [30]. Kimball et al. [31] showed that 50μl of MO (1% in 70% ethanol) clyster under isoflurane anesthesia could induce hyper motility and cause diarrhea in rats and was used as a model of IBS-D. Liu et al. [32] inserted a plastic catheter into the rats' descending colon 8 cm from anus; then acetic acid (4%, 1 ml/rat) aqueous solution was instilled slowly for 30 s. The treatment led to the sparsity of microvilli on the surface of the intestine and the decreased expression of tight junction protein zonula occludens-1 and occludin. Liuet al. [33] gave rats' intracolonic injection with 0.1 ml zymosan suspension to induce obvious visceral pain. Low dose but not high dose of dextran sodium sulfate (DSS) didn't induce obvious damage on the histological structure of intestinal tissue [34,35]. Scanzi et al. [34] added 0.5% DSS to drinking water and fed mice for 12 days. The mice developed visceral hypersensitivity companied with the increased expression of Cav3.2 mRNA in the colon without colonic inflammation, which were also observed in IBS patients. This model revealed the involvement of iron channel Cav3.2 in hypersensitivity of IBS. Traubet al. [35] used deoxycholic acid (DCA) to induce the post infective IBS (PI-IBS): DCA was instilled into the rat colon one time daily for 3 days. DCA could induce a mild, transient colonic inflammation which would gradually vanish in 3 weeks. But the exaggerated visceromotor response, increased spinal c-fos expression, and the over activity of colonic afferent and dorsal horn neuron which appeared in the first week persisted for at least 4 weeks. The chemical stimulation induced model could mimic some functional defects of gut in IBS but not the full spectrum of the natural cause of IBS in human. And that the dosage of the chemical agents must be low enough to avoid the obvious damage on the histological structure of intestine unless the damage can heal itself soon to mimic PI-IBS.

Mechanical stimulation induced animal model

Colorectal distension (CRD) as a mechanical stimulation is a popular method to establish visceral pain model to study IBS. Abdominal withdrawal reflex (AWR) scores were used to assess the degree of visceral pain. In a research performed by Yang et al. [36], the researchers inserted a flexible latex balloon covered with lubricant into the descending colon and rectum of rat under ether anesthesia. Then the balloon was inflated with air at a speed of 0.133 kPa/s (0.998 mmHg/s) after rat was fully recovered from anesthesia and the upper limit of balloon pressure was set at 13.33 kPa (99.8 mmHg) to avoid the rectum damage. Lee's [37] study demonstrated that the expression of pain-related substances such as substance P (SP), c-fos, and phosphorylated extracellular signal-regulated kinase (p-ERK) in the dorsal root ganglion (DRG) and spinal cord were increased in response to CRD. And DA-9701, a prokinetic agent significantly decreased the CRD-induced visceral pain probably by down regulating pain-related factors. Saito et al. [29] found that CRD induced the increases of hippocampal noradrenaline release, ACTH release, colonic motility, somatic motor responses and anxiety in rats. CRD provides a reliable model for studying the mechanism of visceral pain and for developing drugs on visceral pain. But it easily causes mechanical injury of intestine with misoperation and it is at variance with the natural cause of IBS in human.

Bacterial infection induced animal model

It was reported that a chronic and persistent IBS symptoms could be developed after the remission of acute intestinal infection with harmful bacteria and it was defined as post infectious irritable bowel symdrome (PI-IBS). Infectious gastroenteritis is regarded as the major risk factor to develop PI-IBS. It has been reported that the alteration of gut microbiota with the decrease in beneficial bacteria such as bifidobacteria and the increase in harmful bacteria such as *E. coli*, *Campylobacter jejuni* (*C. jejuni*) may directly trigger pro-inflammatory signaling in intestinal epithelia [38]. PI-IBS models are always established through harmful bacteria infection and the commonly used species include *Citrobacter rodentium* (*C. Rodentium*) and *C. jejuni*, etc. In the study of Jee et al.[39], the rats were gavaged with *C. jejuni* 81-176.After the clearance of *C. jejuni*, small bowel bacterial overgrowth appeared and it seemed to be associated with the reduction of interstitial cells of Cajal which modified gut motility. In a recent study carried out by Mondelaers et al. [40], *C. Rodentium* infection induced transient visceral hypersensitivity in C57BL/6 and Balb/c mice, which persisted for about 2 weeks and 3 weeks, respectively. Bacterial infection can destroy the balance of intestinal flora and can effectively induce the pathological changes of intestine with some IBS-like symptoms. But the results to develop PI-IBS vary with different infectious agents.

Parasite infection induced animal model

Like bacterial infection, parasite infection can disturb the balance of intestinal microecology. *Cryptosporidium parvum* (*C. parvum*) are obligate intracellular protozoans which can cause gastrointestinal tract infection in animals and humans [41, 42]. Symptoms following *C. parvum* infection including diarrhea and abdominal pain are similar to those of IBS. In the study of Khaldiet al. [43], the five-day old rats were orally fed with 105 oocysts of Nouzilly (NoI) or Iowa (IoI) *C. parvum* isolate which induced villus atrophy, crypt hyperplasia, and inflammatory cell infiltration in jejunum or ileum and jejunal hypersensitivity to distension. The severity of infection and the onset of jejunal hypersensition are different which indicated that they are isolate dependent. Besides, Bai et al. [44] also confirmed this model's reliability and found that the agonist of somatostatin could prevent the development of jejunal hypersensitivity in cryptosporidiosis. *Trichinella spiralis* (*T. spiralis*) is also a commonly used parasite to establish the PI-IBS model. The decreased bile acid absorption contributing to IBS-associated diarrhea has been verified in *T. spiralis* infection model [45]. And the increased energy metablism, fat mobilization and disrupted amino acid metabolism have also been reported in this model [46]. A recent research showed that the mice with acute *T. spiralis* infection or post infection had the similar sensitivities with significantly decreased pain threshold compared to non-infection mice, and found a candidate biomarker for visceral hypersensitivity - Piezo2 [47]. In Yang's research [48], the mice exhibited a long-term colonic hypersensitivity after *T. spiralis* infection and the levels of IFN-γ and IL-17 were increased in the duodenum and ileum. Parasite infection induced a relevant animal model for studying PI-IBS with a long-lasting hypersensitivity but its impact on gut motility needs further study.

Parasite infection induced animal model

Cao et al. [49] established a visceral hypersensitivity animal model by injecting intraperitoneally 10 μg egg albumin (antigen) and 10 mg aluminum hydroxide (adjuvant) in 1 ml saline to induce

colonic anaphylaxis. They found that the visceral hypersensitivity rats exhibited an impaired decision-making behavior which is associated with the disruption of phase-locking in the anterior cingulate cortex. In the experiment of Mackey et al. [50] IgE-mediated passive systemic anaphylaxis was imposed on C57BL/6 male and female mice. Briefly, 12-week old mice were injected intraperitoneally with 10ug mouse monoclonal anti-DNP IgE and were challenged with 500 μg 2, 4-dinitrophenyl-human serum albumin 24 h after IgE injection. In this model, the mast cell responses to immunological stress are different between female and male mice implicating female predominance for IBS. Not only visceral hypersensitivity, but also increased mast cell (MC) degranulation, high intestinal barrier permeability and anxiety behavior can be observed in immunological stress induced animal model.

Combined animal model

To eliminate the possibility of rats habituating to single repetitive stimulus and to mimic the multiple pathogenetic factors of IBS, several combined animal models have been developed by exposing animals to variable stimuli. Zhuang et al. [51] combined acetic acid with restraint stress to establish an IBS model. They found this model presented gut visceral hypersensitivity, increased levels of IL-4 and IL-9 in serum and intestinal mucosa, promoted mast cell degranulation. In another study, Gong et al. [52] confirmed that there was no remarkable inflammation in the colon of this combined model. The combination of colorectal distension and restraint stress can induce immunologic alteration in rats. The increased dendritic cells (DCs) in colon stimulate $CD4^+$ T cells to secrete abundant IL-4, which led to MC degranulation and subsequently resulted in visceral hypersensitivity [53]. Some other models were established by combining parasitization with stress. Spreadbury et al. [54] found that chronic WAS stress combined with *C. Rodentium* infection significantly enhanced the excitability of DRG. Because of the complex etiology and multiple mechanisms of IBS which are still unclear, it is urgent and more realistic to developmore new IBS animal models using combined technical means and use these novel IBS models for pathophysiologic research and drug development.

Discussion

As a multifactorial disease, the pathogenesis of IBS is complex and has not been fully understood yet. Intervention studies are not feasible with human subjects. Animal models provide good approaches to investigate the pathogenesis of IBS without the potential risks of human study. Because of the variation of clinical manifestation of different IBS subtypes in different stages, many animal models can only mimic limited aspects of the pathophysiology of IBS. And at present, the explicit biomarkers for diagnosing IBS are still missing. It is necessary to establish accurate and effective standards to evaluate the objectivity and validity of IBS animal models although IBS-like alterations of motility and sensitivity are achieved in most models. Abdominal withdraw reflex score is widely used to evaluate the sensibility to CRD, but it is not a fully objective indicator.

There are advantages and disadvantages in existing IBS animal models which need to be improved continuously. With the development of neuroimaging technology, it will become more and more popular in IBS diagnosis and in the evaluation of IBS rodent models. This application provides many opportunities for bidirectional translation between IBS patients and IBS animal models [55] and will be helpful to provide a more objective and standardized evaluation for animal models. Furthermore, changes in the intestinal microbiota should be considered when establishing animal models of different subtypes [56]. We believe that the composited application of molecular biology, physiology, pathology, immunology, microbiology and other disciplines will facilitate the development of novel IBS models that are more representative and closer to the pathophysiology of human IBS.

Competing Interests

The authors have declared that no competing interest exists.

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