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ABOUT COVER

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MINIREVIEWS

Animal models of cathartic colon

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Abstract

The incidence of cathartic colon has been increasing, but satisfactory treatments are still lacking. In order to study the pathological mechanisms of the disorder and identify effective treatment methods, researchers have established different animal models of cathartic colon. This minireview briefly summarizes several common cathartic colon animal models, induced with anthraquinone laxatives such as rhubarb, total anthraquinone, rhein, and emodin, or induced with diphenylmethane laxatives such as phenolphthalein. The advantages and limitations of these models are evaluated and analyzed. We hope that this review will facilitate the selection of suitable models and improve relevant modeling methods. We anticipate the development of more convenient and stable models that can reflect the characteristics of cathartic colon in humans, and serve as useful tools for further studies.

Key Words: Cathartic colon; Animal model; Laxative; Anthraquinones; Diphenylmethane; Constipation

Core Tip: To our knowledge, this is the first review on various cathartic colon animal models. In this minireview, the experimental animals, agents, and methods frequently used to establish cathartic colon animal models are summarized for reference.

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INTRODUCTION

Cathartic colon is a common form of refractory functional constipation. It is characteristic of slow transit constipation (STC), typically characterized by long-term consumption of large doses of stimulating laxative drugs as the main pathogenic factor, and decreased colonic motility as the main pathological feature[1]. STC is also characterized by delayed colonic transit, difficulty in defecation caused by decreased colonic motility, and/or reduced frequency of defecation, and dry stool[2]. The condition is often accompanied by abdominal distension, abdominal pain, stomach pain, nausea, vomiting, and perianal diseases, as well as cardiovascular disease and colon cancer, and may seriously affect the quality of life[3,4]. In order to relieve symptoms, patients often rely on laxative defecation. Thus, the effects of the condition worsen, as the administered dose of laxatives is usually increased. Such a vicious cycle may lead to cathartic colon, with or without melanosis coli.

Although the pathological mechanisms of cathartic colon have not been discovered entirely, its main cause is the long-term overuse of laxatives. The main types of laxatives commonly used in clinical practice are: (1) Bulking or hydrophilic agents; (2) Osmotic agents; (3) Lubricants; and (4) Stimulants. The stimulants include anthraquinones (AQs), diphenylmethane, and their derivatives, which can stimulate the intestinal wall to increase intestinal motility, and are thought to be likely causes of cathartic colon[5].

Treatment of cathartic colon is particularly difficult owing to the lack of more effective laxative drugs that do not aggravate cathartic colon, and the fact that patients with a severe condition may even require a colectomy to alleviate the symptoms. Understanding the pathological mechanisms of cathartic colon forms the basis of its prevention and treatment. Animal models are often required in related studies. This review attempts to summarize and evaluate existing cathartic colon animal models.

RECOGNITION OF CATHARTIC COLON

In 1943, Heilbrun[6] first identified the main features of cathartic colon based on radiographic findings in a patient with STC, who had been using stimulant laxatives for a long period of time. The imaging findings included loss of haustration, pseudostrictures (that is, variable sandglass formed spasms), dilated lumen, dilated terminal ileum, and gaping of the ileocecal valve. Smith[7] has since identified 12 cases of pathological and anatomical changes in the colons of laxative addicts, including three main features: (1) Loss of intrinsic innervation; (2) Atrophy of smooth muscle coats; and (3) Melanosis coli. Clain *et al*[8] also found discrete linear ulcers and eosinophilic granulocyte infiltration in the cecum of one patient. Studies of the pathophysiology of the cathartic colon have been focused on the enteric nervous system, gastrointestinal hormones, and interstitial cells of Cajal. Although studies on cathartic colon have reported some useful results, the pathological mechanisms of the disease have still not been completely clarified, and treatment methods are unsatisfactory.

MODELING METHOD

Animal models used in studies of cathartic colon have been based mainly on methods first established in 1998 by Zhang *et al*[9]. Adult Wistar rats were selected, and half of the study animals were male. The rats were fed either rhubarb powder or phenolphthalein. The initial dose of rhubarb powder in the feed was 200 mg/kg/d, which was subsequently increased by 200 mg/kg/d. About half of the animals had loose stool when the dose was increased to 1000 mg/kg/d. This dosage was maintained until the loose stool was no longer evident. The dose was then again increased by 200 mg/kg/d. Thus, more than half of the animals had diarrhea for 3 mo. The final dose of rhubarb powder is 2600 mg/kg/d[9]. In the other experimental group, the initial dose of phenolphthalein was 200 mg/kg/d. The first median diarrheal dose (the dose that was able to induce diarrhea in half of the animals in the group) was 1600 mg/kg/d. The final adjusted dose was 3600 mg/kg/d[9].

Based on the two aforementioned methods, various animal species and strains, drug types and doses, drug dosage increase over time, and administration methods were modified in the following studies (Table 1).

Table 1 Summary of cathartic colon animal models

Chemical	Initial/final dose (mg/kg/d)	Method of administration	Animals	Molding cycle (d)	Melanosis coli	Ref.
Rhubarb	100/3200	Drug-containing fodder	Wistar rat, male and female	30	No	[9]
	200/2400			90		[39,40]
	200/3600					[41]
	200/2600					[9]
	200/2400		SD rat, male and female			[42]
	200/3200	Gavage				[32]
	200/3800		SD rat, male	84		[43]
	300/5400		Wistar rat, male	136		[21]
	1000/9000		SD rat, male and female	-		[44]
	6000/6000		Guinea pig, male	60	Yes	[31]
	3000/3000					
	12000/12000					
	24000/24000					
	1160/1160		Guinea pig, male and female	56		[45]
	1160/1160			28		
	2000/2000		Guinea pig	30		[46]
	4000/4000					
	2000/2000			60		
	4000/4000					
Emodin	100/6400	Drug-containing fodder	KM mouse, male	82	No	[47]
Rhein	240/320	Gavage	Wistar rat, male	115		[48,49]
	240/320		SD rat, male and female	110		[27,28,33]
	240/320		Wistar rat, male	114		[21]
Total anthraquinone in rhubarb	500/4500	Gavage	SD rat, male	92		[18]
Senna	460/460		Guinea pig, male and female	28	Yes	[45]
	460/460			56		
Phenolphthalein	100/4000	Drug-containing fodder	Wistar rat, male and female	30	No	[9]
	200/3400			-		[29]
	200/3200			90		[39]
	200/3600					[9]
	200/3600					[50]
	200/4200	Gavage	SD rat, male and female			[32]
	15430/15430		Guinea pig, male and female	28	Yes	[45]
	15430/15430			56		

SD: Sprague-Dawley.

COMPARISION OF LAXATIVE AND ANIMAL SELECTION

Comparison of chemicals

AQs, including rhein, emodin, chrysophanol, aloe emodin, emodin methyl ether, aurantio-obtusin, obtusin, obtusifolin, and physcion, among others[10,11], are components of many herbal medicines. These medicines include *Cassiae semen* (Juemingzi in Chinese medicine)[11]; *Rhizoma et Radix Polygoni Cuspidatum* (Huzhang in Chinese medicine)[12]; *Radix et Rhizoma Rhei* (Dahuang in Chinese medicine)[13,14]; *Radix Polygoni Multiflori* (Heshouwu in Chinese medicine)[15]; A*loe* (Luhui in Chinese medicine)[16]; and *Senna leaf* (Fanxieye in Chinese medicine)[16]. For thousands of years, they have all been used as traditional medicines to treat constipation in many East Asian countries, including China, Japan, and Korea.

In plants, AQs are predominantly glycosylated, and after oral administration, cannot be broken down by α-glucosidase in gastric acid or in the small intestine, because of the β-glycosidic bond between the sugar and the AQ ring. Thus, AQs go directly into the large intestine, where they are broken down by bacterial beta-glucosidases and reductases. AQ derivatives stimulate intestinal nerves, inhibit Na^+-K^+-ATP enzymes, increase retention of bowel fluid, induce peristalsis in the large intestine, reduce absorption of colonic fluid and Na^+, and promote defecation[17].

AQ-related drugs, which are often used to establish cathartic colon models, include rhubarb, total AQ in rhubarb, rhein, and emodin, among others. *Radix et Rhizoma Rhei* (rhubarb) is the most common drug used to establish cathartic colon animal models because of its low cost and availability. Total AQ in rhubarb is an AQ extract from rhubarb[18]. Rhein is a lipophilic AQ, which has no cathartic effect. However, its metabolite, anthrone rhein, which is formed by the action of intestinal micro-organisms, has cathartic activity[19]. Emodin is an AQ derivative that has been isolated mainly from the rhizome of rhubarb in Polygonaceae. Many experiments have proved that emodin can significantly increase movement of intestinal smooth muscle and promote secretions from the intestinal epithelium. Therefore, emodin has been used as a laxative for many years[20].

Although rhubarb has been widely used to induce cathartic colon animal models in many studies, its composition is complex, its laxative effects are unstable, and it can be easily affected by its source, variety, processing, and storage methods. In addition, the long-term use of rhubarb may affect other physiological systems, and thereby affect the development of cathartic colon[21]. Pharmacological studies have shown that rhubarb has both laxative and antidiarrheal components. When rhubarb was soaked or decocted for a short time, the dissolution rates of AQ glycosides and other diarrheal components can be high. Nevertheless, the dissolution rate of tannin and other antidiarrheal components may be high[22]. Therefore, when rhubarb is used to induce cathartic colon animal models, the effects of decoction time on the bioactivity of rhubarb should be considered.

Rhein is a monomer with stable pharmacodynamics. Its quality remains stable and its concentration is easy to control[21].

The establishment of cathartic colon animal models by emodin and total AQ in rhubarb is rare, and needs further verification. Interestingly, the intestinal wall reportedly becomes thinner, telescopic function is poorer, and the time required for free stretching is prolonged in the cathartic colon model induced by total AQ in rhubarb[18]. This is consistent with the findings of Smith[7] in patients with cathartic colon.

In addition, diphenylmethane drugs and their derivatives, including phenolphthalein, bisacodyl, and sodium picosulfate, among others, are also commonly used to establish models of cathartic colon[5]. Among these agents, phenolphthalein is the most common, even though it is almost insoluble in water. After oral administration, the soluble sodium salt is produced in the alkaline environment of the intestinal tract, which stimulates the intestinal plexus and directly affects the intestinal smooth muscle to increase intestinal peristalsis. Phenolphthalein can also inhibit intestinal absorption of water and electrolytes to cause defecation[23]. The phenolphthalein-induced model has good reproducibility, and the dosage is easy to control. However, long-term use can easily lead to water and electrolyte disorders, hypoimmunity, and death in animals.

Feeding animals drug-containing diets ensures that they can freely obtain sufficient feed under conditions with limited human interference; however, it is difficult to strictly control the drug dosage administered to each animal. In contrast, intragastric administration can facilitate stricter control of the dosage and standardize the model, but also increase the influence of external factors. In addition, the method of administration may be affected by the solubility of the drug. For example,

phenolphthalein is insoluble in water, but some researchers have used a phenolphthalein solution to induce a model of cathartic colon. This may have affected the effectiveness of the model. Furthermore, in many studies, the final doses of drugs are much higher than the typical clinical doses, which needs to be acknowledged.

Animals selection

The animals used to establish the cathartic colon model in most studies include rats, mice, and guinea pigs, among others. Rats are the first choice to establish this model. The anatomical and physiological characteristics of the rat are similar to those of humans, and it shows good adaptability to its environment, with low feeding costs. Wistar and Sprague-Dawley rats, 6-8 wk old, or 180-320 g in weight, male or female, are often used because they typically do not die easily, and yield high success rates. Mice, like rats, can be easily obtained and fed. However, compared with rats, only a few studies on cathartic colon models have used mice. Most pathological changes in cathartic colon (except melanosis coli) can be reproduced in the rat or mouse.

Guinea pigs are a little more expensive and have greater feeding requirements than rats and mice. However, melanosis coli can be easily induced in guinea pigs. This may be related to the fact that neither humans nor guinea pigs could synthesize vitamin C on their own[24]. Most studies theorize that melanosis coli is caused by damage to the intestinal mucosa after the long-term administration of laxatives, which may lead to apoptosis of colonic epithelial cells and the formation of apoptotic bodies. Apoptotic bodies can be phagocytized by mononuclear macrophages. Under the action of lysosomes, apoptotic bodies become decomposed and produce lipofuscin, which accumulates in the lamina propria to produce melanosis coli[25]. Interestingly, studies have shown that vitamin C protects intestinal epithelial cells from oxidant-induced apoptosis[26]. The mechanism by which vitamin C works in response to laxative-induced melanosis coli is unclear, and warrants further investigation.

MODEL VERIFICATION

The validity of the cathartic colon animal model has often been verified by examining the general physiological status, fecal water content, and intestinal transport functions in animals.

Evaluation of general physiological condition

Based on the changes in food intake, water intake, defecation frequency, stool characteristics, body weight, and hair color, disorders in animals may be evaluated[21].

Measurement of fecal moisture content

Low water content in feces is an indicator of constipation, and can be assessed to determine the severity of constipation in animals. The specific methods entail the collection of two to four fresh fecal pellets, and drying of those pellets in an oven at 150 °C for 15 min. To determine the moisture content of feces, the dry-to-wet ratio is calculated using the following formula: Dry fecal particle mass/fresh fecal particle mass × 100%[27].

Determination of intestinal motility

Slowing down of intestinal motility is one of the important clinical signs of cathartic colon. This can be determined by observing the first black stool of animals or calculating the propulsion rate of carbon powder.

Observing expulsion time of the first black fecal pellet: After being fasted for 24 h with free access to water, rats were given 2-3 mL 100 mL/L active carbon suspension by oral administration. The duration from the completion of gastric administration to the expulsion of the first black stool was recorded, to determine whether intestinal motility had slowed down[28].

Calculation of the propulsion rate of carbon powder in the intestines: Rats were sacrificed 30 to 40 min after gavage of active carbon, and the abdominal cavity was opened. The whole small intestine from the pylorus to the end of the rectum was removed. The entire length of the small intestine and the propulsion distance of the active carbon were measured under no strain. The propulsion rate of active carbon was calculated as distance travelled by the carbon from the pylorus/total length of intestine × 100%[9,18,21].

APPLICATION OF MODELS

Animal models are often used to investigate the pathogenic mechanisms of cathartic colon by observing histopathological changes in the intestines, and measuring the expression of related mRNAs and proteins by PCR and Western blot analysis.

Histopathological examination of the colon

A segment of colonic tissue was fixed in 40 g/L polyformaldehyde, dehydrated with gradient alcohol, embedded with paraffin, and stained with hematoxylin and eosin or undergoes intermuscular plexus argyrophil staining or melanin staining. Inflammatory cell infiltration[18], changes in intermuscular neurons[29], epithelial cell exfoliation, weakening or disappearance of argyrophilia of the myenteric plexus[9], and brown pigment granules have all been observed in the colon of cathartic colon animal models[30].

Expression of related factors in intestinal tissue

The mRNA and protein expression of opioid receptors and opioid receptor signal-regulating proteins (RGS4 and β-arrestin2) was increased in animals with cathartic colon[29]. However, the expression of the mRNA and protein of the tyrosine kinase receptor (c-Kit) and its ligand stem cell factor (SCF) was significantly decreased[27,28]. The increased expression of TNF-α have also been reported[31]. Moreover, abnormal P75 (a nerve growth factor receptor) levels in the colon have been detected through immunohistochemical methods[32].

EXPECTATIONS

Overall, there are presently an insufficient number of animal models of cathartic colon available. Particularly, there are few models with melanosis coli except cathartic colon guinea pigs. We cannot yet determine whether or not melanosis coli occurs in rat and mouse models, owing to the short duration in establishing the model. The dynamic changes in rats or mice with cathartic colon should be observed over a longer period.

Second, standard operating procedures for cathartic colon modeling should be established. The process of cathartic colon modeling is closely related to the patient's constitution, age, and the type, dose, and time of laxative administration. However, the age, strain, and the type, dose, and time of laxative administration may vary in the models established in different studies. Furthermore, it is difficult to set a time point at which to modify the dose of the laxative, based on the presence or absence of dilute feces, as described in existing studies[1]. Further studies are required to improve the reproducibility of cathartic colon animal models.

Third, the pathological processes of the presented animal models are not completely consistent with those of clinical patients. For example, most patients abuse laxatives because of constipation, while almost all animals are healthy before administration of the laxative[33]. Novel methods are needed to guide the establishment of animal models or modification of existing models.

Moreover, some obese patients abused laxatives to lose weight, which induced cathartic colon. Some studies have shown that low body mass index, lower fiber intake, and less physical activity all increase the likelihood of chronic constipation[34]. While some studies have found that fiber is not beneficial to constipation[35-37]. In addition, the prevalence of chronic constipation increases with age, and is higher in women than in men[2]. Anxiety, depression, and other psychological factors are also risk factors for constipation[38]. These indicated that age, gender, body mass index, physical activity, mood, and abnormal fiber intake also influence the outcomes of cathartic colon animal modeling.

CONCLUSION

Although the existing animal models can be used as powerful tools to study cathartic colon to some extent, there are still challenges that must be acknowledged. Therefore, we still need to explore and establish more standardized modeling programs, which could more effectively reproduce animal models that are similar to the physiological conditions of patients with cathartic colon.

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