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Pharmacologic, Pharmacokinetic, and Pharmacogenomic Aspects of Functional Gastrointestinal Disorders

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This article reviews medications commonly used for the treatment of patients with functional gastrointestinal disorders. Specifically, we review the animal models that have been validated for the study of drug effects on sensation and motility; the preclinical pharmacology, pharmacokinetics, and toxicology usually required for introduction of new drugs; the biomarkers that are validated for studies of sensation and motility end points with experimental medications in humans; the pharmacogenomics applied to these medications and their relevance to the FGIDs; and the pharmacology of agents that are applied or have potential for the treatment of FGIDs, including psychopharmacologic drugs.

Keywords: Pain; Diarrhea; Constipation; Animal Models; Dyspepsia; Transit; Sensation.

Medications are commonly used for the treatment of patients with functional gastrointestinal disorders (FGIDs). This article summarizes the pharmacokinetics and pharmacology of medications used to treat FGIDs. Methods included literature review, consensus evaluation of the evidence for each topic assigned originally to 1 or 2 authors, and broader review at a harmonization session as part of the Rome IV process. Clinicians and basic scientists involved in the treatment or investigation of FGIDs or disease models need to have a comprehensive understanding of a vast range of medications.

Preclinical Pharmacology: Animal Models Validated for Study of Sensation and Motility

The development of new drugs for the treatment of patients with FGIDs is facilitated by preclinical animal models that must reproduce the pathophysiology of FGIDs as closely as possible. This section reviews the most commonly used animal models of visceral pain and disturbed gastrointestinal motility (Figure 1).

Visceral Pain

Mechanical Stimuli. Experiments are performed in awake or anesthetized rats, and the most frequently used stimulus of pain in animals is distention of a gut segment with a balloon connected to a barostat to measure simultaneously compliance and the response to gastrointestinal distention. Balloons can be acutely or chronically implanted in the gut.[1] A number of factors influence reproducibility of balloon distention studies across laboratories: balloon construction and unfolding, distention protocols, and frequency of balloon distentions in the same animal (which can lead to sensitization), and species (eg, rats vs mice) or strain differences within species.

Chemical Stimuli. In rats, infusion of glycerol into the colon through an implanted catheter induces abdominal cramps that are typically demonstrated by observed behaviors (eg, back arching or writhing) or by psychoactive responses, including reflex electromyographic activity measured in the abdominal wall muscles (discussed in the section End Points Used to Evaluate Sensation).[2] Intracolonic injection of glycerol results in an increase in long spike burst activity, which was eliminated by previous administration of lidocaine, suggesting there is an induction of a viscerovisceral reflex.[3] Two separate studies provide contradictory results regarding the role of glycerol-induced activation of serotonin/5-hydroxytryptamine (5-HT) type 3 receptors on visceral afferent pathways. The 5-HT_3 antagonist granisetron did not modify this reflex in a human study, whereas alosetron significantly attenuated the glycerol-induced visceral pain in rats.[2,3] It is conceivable that glycerol's effects on contractile activity and tone might be inhibited by alosetron independently of any effects on visceral afferents or viscus compliance.[4] Other stimuli are used to sensitize the colon to balloon distention in order to investigate visceral pain modulation in animal models; they produce an initial inflammatory response[5] that resolves, but

†Deceased.

Abbreviations used in this paper: **CFTR, cystic fibrosis transmembrane regulator; cGMP, cyclic guanosine monophosphate; CYP, cytochrome P450; FD, functional dyspepsia; FDA, Food and Drug Administration; FGID, functional gastrointestinal disorder; GC-C, guanylate cyclase-C; GI, gastrointestinal; 5-HT, 5-hydroxytryptamine; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; OIC, opioid-induced constipation.**

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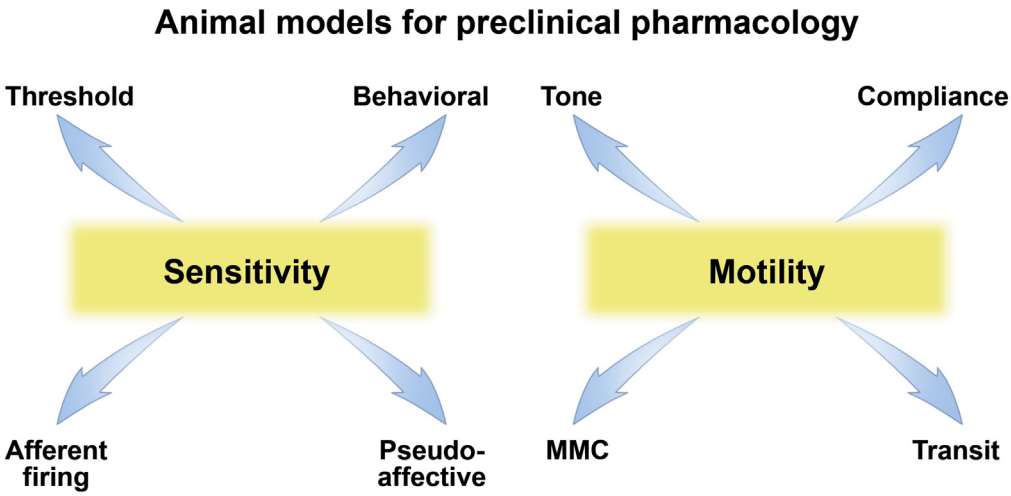

Figure 1. End points in experimental animal models of sensitivity and motility are applied in preclinical pharmacology of lead compounds.

later leads to sensitization of visceral afferents. Other chemical irritants include trinitrobenzene sulfonic acid, dioctyl sodium sulfosuccinate, and zymogen and parasite infestations (such as *Nippostrongylus brasiliensis* or *Trichinella spiralis*). Long-term colonic hyperalgesia may also be induced by colonic inflammation.[6] At present, there is no consensus on the best model to study visceral pain.

Nonchemical Models Used to Study Visceral Sensitivity

Other models used to study colonic and rectal hypersensitivity are stress (eg, maternal deprivation, water avoidance models) and lipopolysaccharide injection.[7,8] Long-term colonic hyperalgesia may be induced by neonatal maternal deprivation.[9]

End Points Used to Evaluate Sensation

Nociceptive responses to stimuli, called "pseudo-affective" responses, are brainstem or spinal reflexes that cease when the noxious stimulus is terminated. The most commonly used end point in the rat is the contraction of abdominal muscles induced by rectal or colorectal distention; the contractions are typically recorded by electromyography.[2,5,10] The numbers of spike bursts or integrated signals correspond to abdominal contractions during the period of distension, and they correlate with the intensity of the stimulus applied.[5]

In mice, colorectal distention triggers only one sustained contraction at the onset of the distention.[11] It is, however, also possible that the electromyographic recording may reflect contractions associated with a distention-induced defecation reflex, rather than being a measure of pain. This inference is supported by the observation that gastric distention in rats does not induce abdominal contractions. In contrast, stretching of the body or lifting of the head and electromyography of neck muscles appear to reflect nociceptive responses to gastric distention.[12]

Visceral distension also induces viscerovisceral reflexes, such as relaxation of anal sphincters during rectal distention or rectocolonic inhibition of gastric emptying.[13]

Change in blood pressure is a pseudo-affective response widely used to assess visceral pain. Cardiovascular and muscular responses are mediated via brainstem reflexes; both are vigorous in decerebrated, but not spinalized, rats.

Electrophysiologic recordings from sensory neurons or second order neurons in the spinal cord may provide the most direct evidence that a drug alters afferent function.[14,15]

Measurements of the effect of the medication on viscus compliance are essential to differentiate effects on volume thresholds to activate sensory fibers from drug-induced contraction or relaxation.[16]

Several behavioral end points have been used and involve brain centers higher than the brainstem. They do not cease when the noxious stimulus is terminated and, therefore, are not pseudo-affective responses. Referred somatic hyperalgesia is evaluated in mice by application of von Frey hairs on the abdomen; the subsequent behavioral response is a measure of sensation. Functional magnetic resonance imaging studies of rat brain activity in response to colorectal distention have also been reported.[17]

Allodynia and Hyperalgesia

Several models permit evaluation of allodynia (decrease in the sensitivity threshold to distention) and hyperalgesia (enhanced response to painful stimulus). Gastric hypersensitivity to distention has been induced by inflammation and intestinal hypersensitivity by helminth infection.[12,18]

Motility

The techniques used to record motility or measure transit in animals may differ from techniques used in humans, but the end points are identical.