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The role of experimental models in developing new treatments for irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is characterized by chronic, recurrent abdominal pain and altered bowel habits and is currently defined by symptom criteria and the absence of detectable organic disease. The underlying pathophysiology remains incompletely understood. Despite considerable efforts by the scientific community and the pharmaceutical industry to develop novel pharmacological treatments aimed at chronic visceral pain, the traditional approach to identifying and evaluating novel drugs for this target have largely failed to translate into effective IBS treatments. However, several novel drugs aimed at normalizing bowel movements have produced clinical effects, not only on the primary target, but also on pain and discomfort. While some of the commonly used experimental animal models for the pain dimension of IBS have some face and construct validity, the predictive validity of most of the models is either unknown, or has been disappointing. A reverse translational approach is proposed, which is based on identification and characterization of brain endophenotypes in patients, followed by translation of these endophenotypes for pharmacological studies in rodent models.

Keywords

functional gastrointestinal disorders; intestinal transit; neuroimaging; visceral pain

Functional gastrointestinal disorders (FGID), including irritable bowel syndrome (IBS), are complex, polygenic, symptom-based disorders that frequently overlap with other complex conditions, including persistent generalized pain disorders such as interstitial cystitis/painful bladder syndrome, fibromyalgia and psychiatric disorders, all sharing a poorly defined pathophysiology. Even though the pathophysiology of IBS in humans remains incompletely understood, various animal models have been proposed that claim to model either the entire disease process or cardinal features of the disorder (e.g., chronic visceral hyperalgesia, stress hyperresponsiveness, intestinal transit, altered fecal pellet output). For example, various interventions have been used to produce either acute or chronic visceral hyperalgesia in

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animals, as assessed by the response to an acute pain stimulus. The most commonly used interventions include acute and chronic visceral inflammation, mucosal irritation and various types of stressors, including perinatal stress and acute and chronic stress in the adult animal [1]. More recently, transgenic mouse models have been proposed (such as the serotonin transporter knockout mouse) that are thought to mimic some aspects of the human syndrome [2]. There are multiple ways to measure the outcome in a model, including physiologic and reflex responses (e.g., gastrointestinal [GI] transit time, frequency and consistency of stool, visceromotor reflex), spontaneous behaviors (licking, posturing and so on), operant behaviors (learned escape, place aversion, and so on), pain-directed complex behaviors (anxiety, attention, social avoidance, and so on), or brain responses (functional brain imaging). These various animal models have helped to identify an increasing number of possible molecular targets on visceral afferent neurons, epithelial cells, immune cells, enterochromaffin cells, enteric neurons and central stress circuits [3], which have been used to develop highly selective candidate compounds. If shown to be effective and safe in the animal models, these compounds are then tested in Phase I studies for their pharmacokinetics and safety, and in Phase IIa clinical trials for their ability to normalize visceral hypersensitivity or altered colonic function. Eventually, the assessment of symptoms and their improvement with therapeutic interventions in Phase III in patients depends on subjective patient reports, requiring a large number of patients in different participating centers. Even though this approach to drug development for FGIDs appears to be rational at first glance, it is expensive and has generally produced disappointing results. Similar frustrations have been experienced in drug development for other symptom-based disorders, such as chronic pain and many psychiatric conditions [4–6].

In this article, we will first critically review evidence related to the correlation between readouts for intestinal transit and visceral pain obtained in preclinical and clinical models, and the limited predictive validity of existing models for IBS drug effectiveness. We will then focus on experimental models for visceral pain, propose a reverse translational strategy and address the potential benefit of new rodent models using functional brain imaging.

Transit time as a readout in experimental human & animal models

The measurement of gut transit is a clinically relevant readout to assess GI function primarily related to motility and secretion [7,8]. Although the identification of IBS subgroups (IBS diarrhea predominant or constipation predominant) is not based on gut transit measurements, there is some correlation between transit times and predominant bowel habit [9,10]. However, similar to visceral sensitivity testing assessed by barostat, transit time does not appear to be a strong predictor of overall IBS symptom severity [11]. Similarly, symptoms associated with stool frequency or ease of stool passage have been shown to be poor predictors of IBS symptoms or health-related quality of life (HRQoL) measures [11]. Thus, gut transit is a good surrogate marker for stool form and, therefore, may be a useful tool to evaluate drugs that affect primarily bowel habit in IBS (in particular in the subset of patients with demonstrated abnormalities in GI transit), but is not a satisfactory surrogate marker for overall IBS severity, abdominal pain and HRQoL.

Changes in GI transit or fecal pellet output in rodent models are often observed in response to stressors, and many drug effects (e.g., corticotropin-releasing factor 1 [CRF1] receptor antagonist, neurokinin 1 [NK1] receptor antagonist) have been evaluated on stress-induced acceleration of transit or increased fecal pellet output [12]. By contrast, in the majority of human transit studies, compounds have been evaluated in healthy control subjects, or in IBS patients in the absence of any acute stressor. This is important, as drugs aimed at stress-induced changes of GI function have consistently failed to show effects on baseline measures in the rodent models [12].

In summary, while there is a poor correlation between transit and symptoms, preclinical models have been relatively successful at translating objective GI transit measurements between animals and humans [8]. It is important to emphasize that despite the limited correlation between symptoms and GI transit in humans, several recently developed drugs aimed at accelerating intestinal transit and/or at normalizing bowel movements (including tegaserod, lubiprostone and linaclotide) have shown beneficial effects on abdominal pain/discomfort in Phase III clinical trials. Based on these findings, one may speculate that at least part of the pain/discomfort reported by IBS patients is not related to a primary visceral hypersensitivity, but may be secondary to discomfort and symptom-related anxiety associated with unsatisfactory bowel movements.

Visceral sensitivity in experimental human models

Perceptual responses to mechanical (and to a much lesser degree electrical or chemical) stimulation are common measures of visceral sensitivity in clinical studies, and mechanical rectosigmoid hypersensitivity has been referred to as a 'biological' marker of IBS [13], showing relative specificity to the IBS patient population. Results from a large number of studies comparing groups of IBS patients with healthy controls indicate that graded barostat-mediated distension is a reliable and valid approach for testing perception of visceral sensation and changes in perception to an acute aversive stimulus. However, to be useful as a biomarker or surrogate marker for IBS, abnormal visceral testing results ('visceral hypersensitivity') should be observed in all patients, should be syndrome specific and should be helpful in discriminating medications that do or do not have a positive impact on either specific or global IBS symptoms. Regrettably, there is no evidence for a strong correlation between this acutely evoked response and the presence and severity of spontaneous abdominal pain or global IBS symptoms. In fact, some drugs that produce a positive change on visceral sensitivity testing in human barostat studies fail to show beneficial effects on spontaneous IBS symptoms and vice versa (Table 1) [14–38]. For example, while the κ-opioid antagonist fedotozine or the synthetic somatostatin analogue octreotide have shown significant beneficial effects in human barostat studies, the positive impact of this class of compounds on IBS symptoms could not be verified in Phase II clinical trials. On the other hand, other compounds targeting the serotonergic system showed no clear effect on the perception of visceral stimuli in clinical experimental studies, but were found to have positive effects on global IBS symptoms.

In summary, these findings illustrate that while acute visceral perception testing procedures have been used in a wide range of preclinical and clinical studies to evaluate the potential benefits of candidate drugs as visceral analgesics/antihyperalgesics, and as potential medication for treating IBS symptoms, the weak predictability in discriminating compounds that may have a positive impact on either specific or global IBS symptoms suggests that these human tests may not be suitable as cost-effective drug development strategies for IBS.

Visceral sensitivity in animal models

Reflexive or behavioral nociceptive responses to acute colo-rectal distension (CRD) have become the standard readout for the assessment of visceral sensitivity in rodents, and the visceromotor response to distension is the most commonly used index of visceral pain response in rats [39]. The popularity of this measure is related to the fact that it has been assumed to be homologous to the subjective response to colorectal distension in humans, to the relative ease to perform and automate it, and the reproducibility across laboratories. However, based on the lack of a consistent clinical viscero-analgesic effect of a series of compounds that initially showed robust analgesic and anti-hyperalgesic effects in experimental animal models, predictive validity of these animal models has proven to be

disappointing (Table 2) [14–16,18,19,33,36,40–80,201]. For example, fedotozine, which showed robust visceroanalgesic and antihyperalgesic effects in several animal models, failed to show positive effect on visceral sensitivity testing in humans. Similarly, alosetron (a $5HT_3$ receptor antagonist) and tegaserod (a $5HT_4$ receptor agonist and $5HT_{2b}$ antagonist) exhibited visceral antihyperalgesic effects in preclinical testing using the model of CRD in sensitized animals, but produced no change in visceral sensitivity in human visceral pain testings. Pregabalin, an anticonvulsant and an α(2)δ ligand used in the treatment of seizures and pain syndromes, showed equivocal results on visceral sensitivity in rodent models [81,82], but was shown to normalize the increased perception threshold to rectal distension in IBS patients with rectal hypersensitivity [32].

However, it is important to emphasize that some of the compounds that showed positive effects on visceral hypersensitivity in rodents but failed to show visceral analgesic effects in human testing did produce positive results on IBS symptoms, presumably via mechanisms other than visceral analgesia. This demonstrates the limitations of the conventional approach of trying to translate between rodent and human pain studies.

The role of endophenotypes in bench-to-bedside translation

While the face validity (i.e., how well does a model mimic clinical features of IBS patients) of some rodent models of visceral pain has been good, the predictive validity (i.e., how well do drug studies performed in the model predict effectiveness in humans) has been disappointing. For example, adult rats having been exposed to the maternal-separation paradigm as pups show evidence for stress-induced fecal pellet output, stress-induced visceral hyperalgesia and anxiety-like behavior, all findings homologous to those reported in IBS patients [83]. However, several drugs that showed effectiveness in this model (e.g., antagonists for the CRF1 or NK1 receptors) have failed to show effectiveness in human models or in clinical trials. The problem of bench-to-bedside translation, however, does not simply originate in a failure of the animal models. Improved definition and classification of clinical states based on biological abnormalities are needed. Such improvement is dependent on the identification of robust endophenotypes in humans with adequate effect sizes for cardinal symptoms or global end points, which can be modeled in a transverse translational approach in rodents.

We propose a novel reverse translational approach, which begins with the identification and in-depth characterization of neurobiological endophenotypes in IBS patients or subsets of such patients. This approach does not aim to identify a rodent model of a complex, unique human disorder, but aims to use the rodent model to pharmacologically characterize the homologue of an endophenotype that has previously been characterized in patients. In contrast to biomarkers, which are thought to be specific for a particular disorder, endophenotypes are dimensional constructs that play a role across categorical disease definitions [84,85]. For example, in the case of IBS, the endophenotype of enhanced responsiveness of a stress and emotional arousal circuit is likely to be found in anxiety disorders, and in other stress-sensitive disorders. Similarly, the endophenotype of ineffective cerebral cortico-limbic inhibition is likely to be found in many, often overlapping disorders characterized by physical or emotional discomfort. It has been suggested that clusters of endophenotypes may be more similar among subsets of patients with different disorders, rather than being seen in all patients of a given disorder [86]. Rodent models of such endophenotypes are important to identify potential molecular targets, dose ranging and possible side-effect profiles of candidate compounds. As implied by the endophenotype concept, successful drug development based on this approach would be expected to be useful for subsets of patients with different syndromes, but not necessarily for all patients of a given syndrome.

Given the high incidence of mood and anxiety symptoms in IBS patients, as well as the growing acceptance of the importance of central pain amplification in the pathophysiology of IBS [87,88], the development of rodent homologues of such brain endophenotypes should be important. However, the question remains, what level of inquiry of the involved brain endophenotypes in humans is most promising for the preclinical assessment of candidate IBS drugs? A behavioral change, while capturing a broad spectrum of dysfunction, may lack specificity, while a neuromolecular change may not generalize across a disease that is likely multifactorial in origin and that is characterized by subtypes with overlapping symptoms. Pseudoaffective responses (e.g., electromyography, pain behavior) themselves do not allow for the elucidation of the underlying systems-level processes by which molecular, cellular and genetic profiles bias behavior and nociception. Neuroimaging can complement such association studies by identifying the biological effects of a compound at the brain endophenotype level, such as the level of integrated neural systems and circuits.

The utility of neuroimaging in CNS drug development

Our understanding of the functional and structural reorganization of the brain in response to chronic pain, and how the brain responds to pharmacological treatment, has been significantly changed as a result of developments in neuroimaging of the CNS. The key findings of these studies can be summarized as follows:

- In several chronic pain conditions, regional changes in gray matter density have been demonstrated with anatomical imaging. Even though the underlying neuroanatomical changes remain to be determined, these findings have great potential to function as endophenotypes for persistent pain conditions, or even as biomarkers for individual syndromes;
- Alterations in brain state and response of the brain circuits to drugs have been demonstrated with PET and functional MRI (fMRI);
- Changes in neurotransmitter levels (glutamate, aspartate, glycine and γ-amino butyric acid [GABA]) have been shown with magnetic resonance spectroscopy (MRS) [89].

Borsook *et al.* [89] have insightfully described how the use of fMRI, in particular, may help speed drug development for CNS indications at a number of levels that include:

- Evaluation of differential efficacy of drugs within and across pharmacological subtypes;
- Identification of potential for CNS side effects;
- Opportunities to define drug dosing and benefits of drug combinations;
- Potential for surrogate models using healthy subjects for drug evaluation;
- Setting up a potential method for re-evaluating failed drug candidates;
- An objective method to select and stratify patient populations to enable pro of-of-concept clinical investigations [90].

The potential applications of neuroimaging provide many opportunities for bidirectional translation between humans and rodents, which may help speed drug development for chronic visceral pain states, including IBS. An underlying assumption in this proposition is that pharmacologic subtypes and/or side effect profiles show specific brain mapping ‘signatures’ that are similar in humans and animals.

One of the potential strengths of integrating neuroimaging during the drug development process is its potential to translate findings of alterations in neural circuits across species,

enabling a more focused use of animal models in research. Neuroimaging may also serve as a useful proxy measure of pain responses that, in the animal, cannot be elicited verbally. While pain imaging of the CNS has been extensively explored in human subjects, neuroimaging technologies applied to rodents to study endophenotypes of persistent pain in animals is still in its infancy. A significant gap remains in 'bedside-to-bench' translation of well-studied brain-mapping abnormalities in IBS patients (reviewed in [91]).

The choice of imaging modalities in animal models

While structural imaging has the potential to greatly increase our understanding of the functional neuroanatomy of chronic pain conditions, the current lack of understanding of the mechanisms underlying such structural changes, and the temporal characteristics of these changes, makes it currently impractical to use such end points for drug development in rodents. In this regard, functional brain mapping and chemical imaging may represent more suitable approaches. Ideally, such imaging in animals would be performed under conditions that approximate those used in human subjects – that is, nonsedated animals with minimal interference with the subject's natural behavior. At the same time, the ideal imaging modality would optimize spatial and temporal resolution, allow for serial measurements across time, while providing 3D views of brain function. No method simultaneously meets all these criteria.

Past research on brain responses to noxious visceral stimulation in animals has relied predominantly on the measurement of early response genes, in particular c-Fos expression [92–95], with a broad variability reported between laboratories [92,96,97]. Unlike human imaging studies evaluating brain responses during acute CRD, c-Fos studies typically use prolonged exposure (>30 min) to high-intensity visceral stimuli, which may lead to the integration of a variety of nonspecific behaviors over the duration of pain exposure, including acute sensitization of the visceral afferent system. Furthermore, analysis is often limited to a few selected brain regions, lacking the whole-brain level analysis achieved in human studies. Thus, it is not surprising that translation of findings between human and animal brain mapping has been diffcult. It is noteworthy that studies examining increases in c-Fos expression in response to CRD in the lumbosacral region of the spinal cord have reported more consistent results within animals [92,98–100], but parallels to human imaging have not been explored extensively. Other region-specific analyses of neuronal responses to CRD have been carried out using *in vivo* electrophysiological recording [101,102], and such brain electrical recordings may prove useful once specific brain regions of vulnerability have been determined. Spatial resolution, with microPET and advanced image reconstruction software, remains at best approximately 1.2 mm at the center of the field of view. This represents approximately 7% and 13% of the width of the rat and mouse brain, respectively, and is poorly suited for the detection for all but the broadest changes in regional cerebral blood flow (rCBF) or metabolism in rodent models. In specific instances, however, such broad changes may suffice for the testing of specific compounds, as has been demonstrated for opiates [103]. Functional MRI and single photon emission computed tomography (SPECT, nanoSPECT), though they provide whole brain analysis and adequate temporal and/or spatial resolution, require sedation of the animal, limiting the types of brain responses that can be examined [97]. We have advocated in the past the use of autoradiographic methods of perfusion mapping, as this method can be applied in awake, nonrestrained animals and yield information at the circuit level across the entire brain, with a spatial resolution (~100 μm) appropriate for the rat or mouse models, and a temporal resolution (seconds–minutes) sufficient for capturing acute brain changes. Nevertheless, autoradiographic methods, although they provide 3D spatial information, contain no information about dynamic cerebral changes. Therefore, studies of disease progression or response to treatment using intra-animal comparisons cannot be performed. In addition,

because of the need for extensive cryosectioning of the brain, the method lends itself less well to high-throughput screening than perhaps MRI, nanoSPECT or microPET.

Homology between the rodent & human brain

Despite their differences, remarkable similarities exist between normal rats and humans at the level of brain anatomy, neurotrans-mitters and their respective receptors, and nociceptive processing. Our own work examining functional activation during acute noxious visceral stimuli in rats and humans has shown that many of the sensory, limbic and paralimbic brain regions that show significant changes in the rodent are analogous to those reported in normal human subjects [104,105]. Nevertheless, differences in neuroanatomy have been reported. Rats and mice appear to lack the lamina I spinothalamocortical pathway to the dorsal posterior insula by way of the posterior part of the ventromedial nucleus, as well as a pathway from lamina I to medial dorsal thalamus to the anterior cingulate cortex [106]. In addition, pain is a multifaceted problem, with pain perception engaging not only sensory and motor processes, but also emotional and cognitive ones. To what extent the emotional and cognitive components of human pain perception can be modeled in the animal remains open to debate. That emotional and cognitive input can modulate pain perception in the rat has been suggested by the accentuation of pain responses by acute and chronic stress [107,108]. Furthermore, work in the rat has shown that the opioid system of the anterior cingulate, a region thought to be involved in the affective–motivational dimension of pain, may selectively process the aversive quality of noxious mechanical stimulation, with little effect on the physical paw withdrawal [109]. Though indeed ‘rats are not monkeys are not humans’ [106], the use of select functional neuroimaging end points in animals may provide an improved means for the bidirectional translation of endophenotypes relevant to persistent pain between animal models and human disease conditions. Reverse translation of some of these endophenotypes into rodents may provide an important tool for evaluating pharmacological effects of candidate compounds, which cannot be performed in humans.

Brain imaging of noxious visceral stimulation in normal human subjects & animals

In human subjects, increases in rCBF to noxious somatosensory stimuli are consistently observed in the insula, in secondary somatosensory cortex (S2), in the anterior cingulate cortex (ACC), and with slightly less consistency in the contralateral thalamus and in primary somatic areas (S1) [110]. Studies of noxious visceral stimulation in normal human subjects (typically acute CRD) have also identified the insular cortex as the single most consistently activated brain region, with the posterior insula being a primary projection area for visceral afferent information, while mid- and anterior insula subregions are considered higher association areas for these bodily signals, where they are integrated with affective and cognitive inputs. A majority of studies have also reported activation in response to CRD of the dorsal ACC, S1/S2, prefrontal cortical regions and, to a lesser extent, posterior parietal cortex and thalamus (reviewed in [91]).

Functional brain mapping in normal rats during acute CRD has also clearly identified the insula as a region that is activated [105]. Using perfusion mapping of the brain, we found greater activation in the anterior insula in male than in female rats, similar to what had previously been reported in healthy human subjects [111], as well as in IBS patients [112,113]. Significant differences in response to CRD were also noted in the cingulate and somatosensory cortex and thalamus, although sex differences remain. Of note, in the insula and dorsal ACC of the animals, changes in rCBF showed a positive correlation with both electromyographic (EMG) and behavioral pain scores [114]. The clusters showing significant correlations with either EMG or pain score were noticeably smaller than those showing group differences in rCBF within a given region. Furthermore, not all brain regions that showed group differences correlated with EMG or pain score. This suggests that EMG

and behavioral measures are likely to reflect only part of the animal's response to the noxious visceral stimulus.

Activation of the insula was also noted during re-exposure to an environmental context previously paired with acute, noxious visceral stimulation [115]. In this study, the insula was activated in rats during avoidance of stepping down from a platform, a behavior that previously had been conditioned over 2 days (18 trials/day) to acute CRD. This suggests the importance of fear-conditioned responses in cerebral nociceptive circuits that persist independently of actual visceral stimulation. Similar insular activation relative to controls has also been reported in IBS subjects during anticipatory fear of CRD [116].

Relevant known alterations of brain circuits in IBS subjects that need to be examined in animal models of FGIDs include:

- A hyperresponsiveness of the homeostatic afferent network to distension;
- A hyperresponsiveness of the emotional arousal network during expectation;
- Compromised engagement of cortico–limbic–pontine systems during delivery of aversive visceral stimuli [91].

With regards to the emotional arousal network (locus coeruleus complex, amygdala, infralimbic ['infragenual'] and ventral cingulate cortex ['supragenual']), we have found a hyperresponsiveness of this network during acute CRD in female compared with male rats [105]. Also noted was a diminished response in females compared with males of cortical circuits that modulate activity in limbic and paralimbic areas. These results highlight the importance of sex as a factor in defining an animal model, and that female rats may model aspects of the functional brain response observed in IBS subjects (a majority of whom are women) more closely than male rats. Recent findings also point to the importance of strain differences in both the visceromotor response, as well as in the extent of prefrontal cortical activation [117,118].

Animal models typically do not take into account the biopsychosocial and environmental interactions that represent major components of the patient's pain complaints and responses to treatment. Based on the understanding that environmental infuences affect pain behavior in FGIDs, a strong clinical argument can be made for inclusion of measures of visceral hyperalgesia, in particular stress-induced visceral hyperalgesia. Visceral hyperalgesia is accentuated during periods of acute and chronic stress in IBS subjects, as well as in rodent models [108]; there is an increased incidence of life stressors in IBS subjects compared with controls [119–122]; and IBS subjects show an exaggerated stress hormone response and visceral perceptual alterations compared with controls [123–125]. It has been proposed that such increased history of early life stress, and alterations in the stress response, may trigger not only long-term changes in cognitive processing and mood, but also in visceral functions and visceral sensitivity to noxious stimuli [124,126,127]. Results from our laboratory in the rat model suggest that stress-induced visceral hyperalgesia is accompanied by exaggerated insula activation during CRD [128]. These three observations in the insula – activation during acute CRD, during recall of fear-conditioned CRD and in association with a stress-related model of visceral hyperalgesia – suggest that this brain region, and associated networks, is a promising candidate for an improved animal-to-human translation during drug development, despite well-known neuroanatomical differences between the human and the rodent insula. Possibilities exist in the future for applying connectivity analysis to animal brain mapping to understand cerebral responses at the network level [129], as has been begun to be undertaken in IBS human subjects [130].

Expert commentary

While animal model-based drug development efforts for diseases, such as cancer or inflammatory bowel disease, have shown significant promise, similar efforts in complex, symptom-based disorders, such as IBS, using rodent models have generally been disappointing. Traditional drug development for FGIDs has been partially successful in the development of novel treatments aimed at modulating biological targets such as slow transit or alterations in intestinal secretion. A substantial number of compounds aimed at these biological end points have been developed and have shown promise to be clinically effective in IBS, chronic diarrhea and chronic constipation [8]. By contrast, this approach has largely failed for the subjective, multidimensional aspect of FGIDs that is characterized by persistent pain or discomfort. Similar frustration using this approach has been experienced in psychiatry [5] and in pain research [6], putting into question the validity of animal models for such disorders in general.

The drug development for well-defined ‘organic’ disorders with agreed upon pathophysiology (including certain motility disorders, such as slow-transit constipation) has been successful since it is based on modeling objective, disease-specific, biological end points (‘biomarkers’) such as tumor regression, inflammation or colonic transit, which are highly correlated with the human disease. However, even though intestinal transit measures and the effect of candidate compounds on such readouts show good correlation between preclinical and clinical models, the correlation between such measures in humans and clinical symptoms is not very strong, since a large number of IBS patients have normal transit. For example, it is unclear why constipation-predominant IBS patients with normal colonic transit should benefit from a drug that is aimed at accelerating colonic transit.

As previously proposed for other human pain conditions [89,90,131,132], we propose that brain endophenotypes that influence central pain modulation (rather than the entire disease process) can be modeled in rodents in a reverse translational approach. Current research strongly suggests that brain imaging approaches in awake or minimally sedated rodents may provide improved quantifiable readouts, which can be translated directly to human brain imaging findings. In the future, transgenic and knockout mouse models hold promise for improving our understanding of specific molecular mechanisms that contribute to the respective phenotype.

Brain mapping has started to be invoked in drug development for pain conditions in human and animal studies over the past decade (reviewed in [90]), although at this early stage, standards for the value of neuroimaging in drug development remain to be defined. In addition, questions remain regarding whether a drug’s response ‘signature’ at the level of brain mapping may differ by disease state and chronicity, and whether neuroimaging should focus on resting state function or brain responses to acute experimental challenges. Functional brain mapping in rodents will likely complement behavioral measurements in animal models of visceral pain. While the optimal imaging strategy may differ between pain disorders and their chronicity, functional neuroimaging in rodents is beginning to validate the relevance of animal models to human conditions at the brain level [133–136].

Five-year view

Currently there is a need to clearly define, characterize and validate human endophenotypes that allow better prediction of relevant outcome measures in clinical trials, and to develop preclinical homologues of these human endophenotypes. Current measures of pain in animals are mainly focused on evoked acute pain responses and do not correspond to the spontaneous, on going or recurrent pain found in IBS. New functional and behavioral assays are needed that model such chronic pain conditions. This includes the replacement of

reflexive outcome measures with homologous measures, such as brain imaging approaches, and the replacement of measurements of evoked pain responses with measurements of spontaneous pain behavior. Spontaneous behaviors might include such measures as spontaneous locomotor activity, gait, posture, guarding, flinching, social behavior, anxiety, body weight and food intake (Figure 1) . In a recent study, a $5HT_{1A}$ receptor antagonist was found to inhibit the visceromotor response to CRD, while demonstrating no effect on the cardiovascular pseudo affective response. These results in animals contrast with a lack of clinical efficacy to reduce abdominal pain in IBS patients and illustrate the need to use multiple readouts for the measurement of pain to increase the predictive value of animal studies [67].

Key issues

- Perceptual responses to mechanical (and to a lesser degree electrical or chemical) stimulation are common measures of visceral sensitivity in clinical studies. The weak predictability of such acute visceral perception testing in discriminating compounds that may have a positive impact on either specific or global irritable bowel syndrome (IBS) symptoms suggests that these human tests may not be suitable as cost-effective drug development strategies for IBS.
- In rodent models of functional gastrointestinal disorders (FGID), reflexive or behavioral nociceptive responses to acute colorectal distension have become the standard readout for the assessment of visceral sensitivity; however, the predictive validity of these animal models has proven to be disappointing.
- While there is a poor correlation between transit and symptoms, preclinical models have been relatively successful at translating objective gastrointestinal transit measurements between animals and humans.
- The problem of bench-to-bedside translation, however, does not simply originate in the limitations of the animal models. Improved definition and classification of clinical states based on biological abnormalities are needed. Such improvement is dependent on the identification of robust endophenotypes in humans with adequate effect sizes for cardinal symptoms or global end points, which can be modeled in a transverse translational approach in rodents.
- Rather than trying to develop rodent models with good face validity for the human FGIDs, it may be more productive to translate robust human endophenotypes into homologous rodent readouts.
- Functional imaging may provide one means of identifying endophenotypes that can translate from the human to the animal. Imaging-based endophenotypes promise to provide improved end points to define treatment and drug development for FGIDs. Proof-of-concept studies with effective (and ineffective) candidate drugs are required to test this hypothesis.

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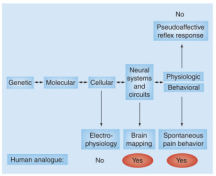

Figure 1. Spectrum of endophenotypes for translating nociceptive responses from humans to rodents

While spontaneous pain behavior and pseudoaffective reflex responses are individually lacking in this regard, it has been suggested that the use of combined multiple physiologic and behavioral readouts may improve the process of translating findings from humans to rodents.

Table 1

Drug effects on visceral sensitivity in irritable bowel syndrome.

Drug	Dose	IBS study subjects	Study design	Barostat methodology	Effect on Sensitivity in IBS	Effect on motor function	Effective on IBS symptoms	Conclusions from Phase II & III trials
Opiates								
Fentanyl [14]	Two doses (HD, LD), bolus + infusion	10 IBS (6 F)	DB, PC, crossover	Phasic pressure	HD and LD: ↑ DiscTh, ↑ SensTh HD: ↑ PainTh	None	NR	NR
Fedotozine −κ agonist [15]	100 mg single dose	14 IBS (8 F)	PC, crossover	Phasic pressure	↑ PainTh, ↑ SensTh	None	NR	Small but significant change in pain in small trial [16]
Asimodoline −κ agonist [17]	0.5 mg single dose	20 IBS (20 F), all hypersensitive	DB, PC, crossover	Phasic pressure	No change in PainTh, ↓ sensory ratings	None	NR	NR
5-HT								
Alosetron [18]	Either 0.25 mg b.i.d. or 4 mg b.i.d. × 7 days	22 IBS (9 F)	PC, parallel group study	Phasic pressure	No effect on PainTh (pressure)	↑ compliance	NA	Effective for global symptom relief [19]
Alosetron [20]	Either 1 mg alosetron or 4 mg alosetron b.i.d. × 4 weeks	25 IBS (19 F)	PC, parallel group study	Phasic pressure	No effect on rectal sensory scores	↑ rectal compliance	NA	NR
Ondansetron [21]	One dose at 0.15 mg/kg	12 IBS (6 F)	DB, PC, parallel group study	Phasic pressure	No effect on sensitivity	↑ rectal compliance	NA	No effect in pilot study [22]
Ondansetron [23]	16 mg 3 times/day	6 IBS	PC, crossover	Ramp volume and electrical stimulation	↑ SensTh	None	↓ number of episodes of abdominal pain	NR
Ondansetron [24]	Single dose of 0.15 mg/kg	5 IBS (3 F)	PC, parallel group study	Phasic pressure	No change in sensitivity	None	NR	NA
Granisetron [25]	Either 40 ug/kg or 160 μg/kg	12 IBS (8 F)	DP, PC, crossover	Ramp volume	↑ DiscTh, ↑ UrgeTh	None	Participants noted constipation	NR
Tegaserod [26]	6 mg b.i.d.	49 IBS (49 F	DB, PC, parallel group study	Phasic sigmoid pressure	No effect	↑ sigmoid accommodation	No symptom change	Effective for global symptoms and constipation [27]
Anitridepressants								
Amitriptyline [28]	10 mg hours × 2 weeks and then 25 mg hours for the following	12 IBS (7 F)	Parallel group study?	Phasic pressure	↑ PainTh	None	Symptom reduction	Some effectiveness in meta-analysis and in high-quality clinical

Drug	Dose	IBS study subjects	Study design	Barostat methodology	Effect on Sensitivity in IBS	Effect on motor function	Effective on IBS symptoms	Conclusions from Phase II & III trials
	4 weeks							trial [29]
Fluoxetine [30]	20 mg/day × 6 weeks	40 IBS	DB, PC, parallel group study	Phasic pressure and volume ramp	No change in sensitivity. ↓ abdominal pain in hypersensitivity patients	None	↓ number of patients reporting significant abdominal of pain	May be effective. Positive effect on pain in small trial [30]
Other CNS								
Gabapentin [31]	600 mg/day × 5 days	43 IBS-D (no sex data)	DB, PC, parallel group study	Phasic pressure	↑ PainTh, DiscTh	↑ compliance	NR	NR
Pregabalin [32]	50–200 mg t.i.d. titration over 21 days	26 IBS (19 F)	DB, PC, parallel group study	Ramp volume	↑ PainTh	↑ rectal compliance	Nonsignificant ↓ in abdominal pain	NR
Octreotide [33]	1.25 μg/kg(s.c.)	10 IBS	DB, PC, crossover	Phasic pressure	↑ PainTh, DiscTh	None	NR	Preliminary evidence suggests some effectiveness on IBS symptoms [34]
Octreotide [35]	100 μg (s.c.)	8 IBS-D	DB, PC, crossover	Ramp volume	↑ tolerance	↑ compliance	NR	NR
Octreotide [36]	0.175–0.820 μg/kg bolus followed by 0.41–1.5 μg/min (i.v.) infusion OR 1.5 μg/kg (s.c.)	7 IBS (4 F) 9 IBS (9 F)	DB, PC, crossover (2 studies)	Phasic pressure alone and after sigmoid stimulation	↑ DiscTh, ↓ sensitization from sigmoid stimulation	None	NR	NR
Talnetant [37]	25 and 100 mg	102 healthy controls (60 F)	DB, PC, parallel group study	Phasic rectal pressure	No effect	No effect	NA	Not different from placebo [38]

The table highlights the inconsistent correlation between results of visceral sensitivity testing in experimental barostat studies and spontaneous IBS symptoms.

↑: Increased: ↓. Decreased: 5-HT: Serotonin: b.i.d.: Twice a day: DB: Double-blind: DiscTh: Discomfort threshold: F: Female: HD: High dose: IBS: Irritable bowel syndrome: IBS-D: Diarrhea-predominant irritable bowel syndrome: iv.: Intravenous: LD: Low dose: M: Male: NA: Not applicable: NR: Not reported: PainTh: Pain threshold: PC: Placebo-controlled: s.c: Subcutaneous: SensTh: Sensory threshold: t..i.d.: Three-times a day: UrgeTh: Urgency threshold.

Table 2

Effect of irritable bowel syndrome candidate compounds on preclinical (rodents) and clinical readouts of altered visceral sensitivity and gastrointestinal transit.

Receptor targeted	Compound	Preclinical				Clinical		
		Motility	***Visceral analgesial anti-hyperalgesia***	***Anxiety***	***Transit***	***Perception***	***Brain imaging for visceral pain***	***IBS symptoms (Phase II or III)***
κ_1-opioid	Fedotozine (agonist)	↑ transit after ileus induced by laparotomy or irritation [42,43]	Reduced visceral hypersensitivity in a model of colonic irritation [44,45] Antinociceptive effect on duodenal pain reflexes in rats [46]	NR	NR	↓ gastric sensitivity to to distension in healthy humans [47] Relieved hypersensitivity CRD in IBS patients [15]	NR	Relief of abdominal pain and bloating in IBS patients compared with control. Effect on transit not reported [16]
μ-opioid	Fentanyl (agonist)	↓ GI transit [48–50]	Prevented the sensitizing response associated to repetitive CRD in mice [51,52]	Fentanyl attenuated fear-potentiated startle in rats [53] Anxiolytic effect of central μ-opioid agonist on pain-induced anxiety [54]	Slowed GI transit [55]	Attenuated the perception of phasic rectal distension in IBS patients [14]	NR	NR
5-HT_3	Alosetron (antagonist)	Reduction of colonic motility [56]	Centrally mediated visceral anti-hyperalgesic effect [57,58]	NR	Reduction of GI transit [59]	↑ colonic compliance Lack of true visceroanalgesic effect [18]	Changes in central modulation of gut function and pain [60]	Global improvement of symptoms in male and female patients with IBS-D [19]
5-HT_4, 5-HT_{2b}	Tegaserod (5-HT_4agonist, 5-HT_{2b} antagonist)	Enhanced GI motor function [61]	Reduction in visceral sensitivity [62,63]	NR	Acceleration of GI transit [64]	Generally no evidence for visceroanalgesic effect [65,66]	Modulation of central processing of visceral afferent information [67]	Effective in the treatment of constipation-predominant IBS symptoms [68]
$5HT_{1A}$	Robalzotan tartrate monohydrate	Inhibition of micturition [69]	Reduction of the visceromotor response to CRD but no change in the pseudoaffective cardiovascular autonomic response [69]	NR	No evidence for changes in bowel movements [70]	No evidence for changes in abdominal discomfort or pain [70]	NR	Not more effective than placebo in providing adequate relief from IBS symptoms [70]
Somatostatin	Octreotide (agonist)	Reduction of GI transit time [71]	Visceroanalgesic effect [72]	NR	Reduction of GI transit time [73]	Visceroanalgesic & antihyperalgesic effect during rectal distension [33,36,74–76]	NR	Overall symptom improvement [77]

Receptor targeted	Compound	Preclinical			Clinical			
		Motility	***Visceral analgesial anti-hyperalgesia***	***Anxiety***	***Transit***	***Perception***	***Brain imaging for visceral pain***	***IBS symptoms (Phase II or III)***
CCK_1	Dexloxiglumide (antagonists)	Accelerates transit time [78]	↓ sensitivity to CRD in rats with inflamed colon [79]	NR	Accelerates transit time [80	NR	NR	NR: therapeutic effect not confirmed [201]
NK_3	Talnetant (antagonist)	Inhibits motility, reduces excitatory reflex induced by stretch in the colon [81]	Anti-hyperalgesic effect [81]	Anxiolytic effect [82]	NR	Under evaluation (unpublished)	NR	NR

↑: Increased; ↓: Decreased; 5-HT: Serotonin; CRD: Colorectal distension; GI: Gastrointestinal; IBS: Irritable bowel syndrome; IBS-D: Diarrhea-predominant irritable bowel syndrome; NR: Not reported