Models of visceral inflammation and pain

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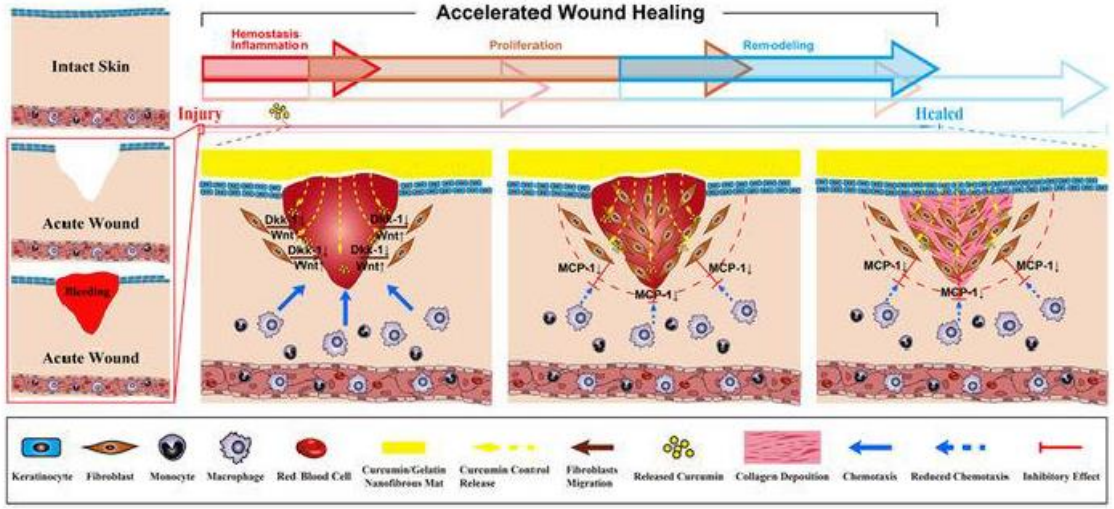
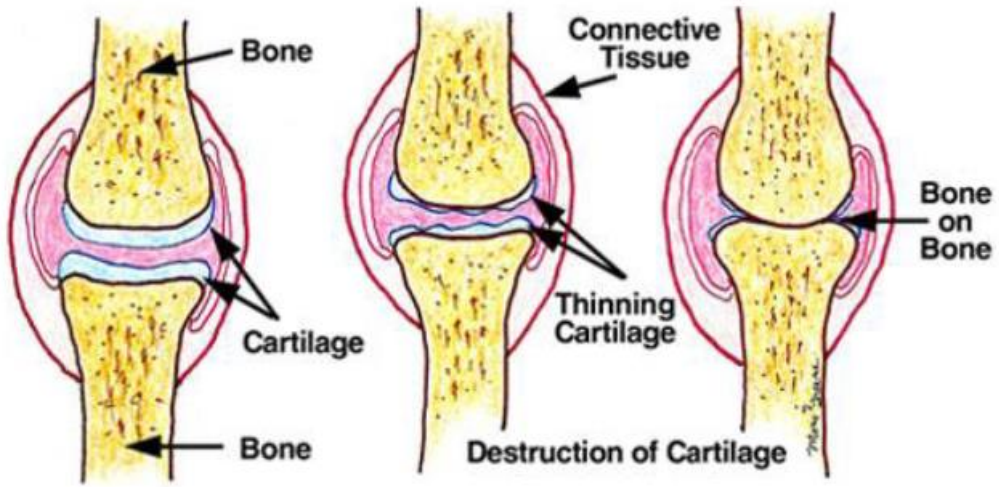
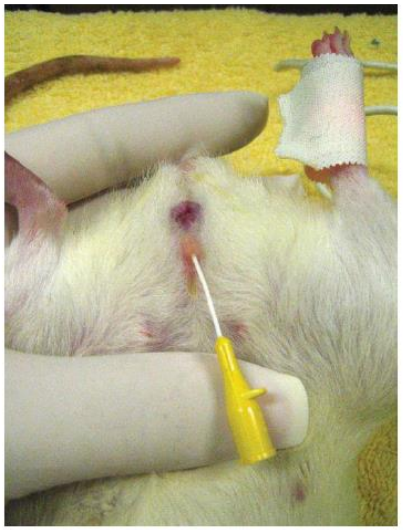
Inflammation is a response characterized by pain, swelling, redness and stiffness:

Like many, while it may have a role in healing, it becomes a question of balance



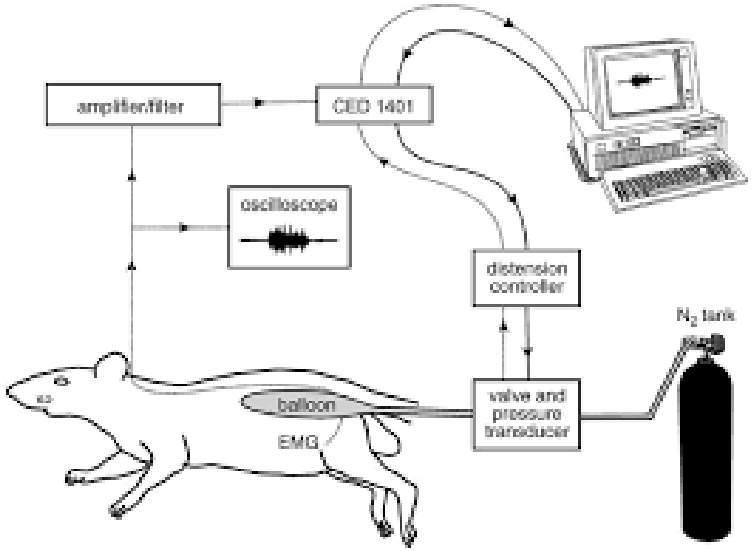


Methods to induce visceral inflammation and pain

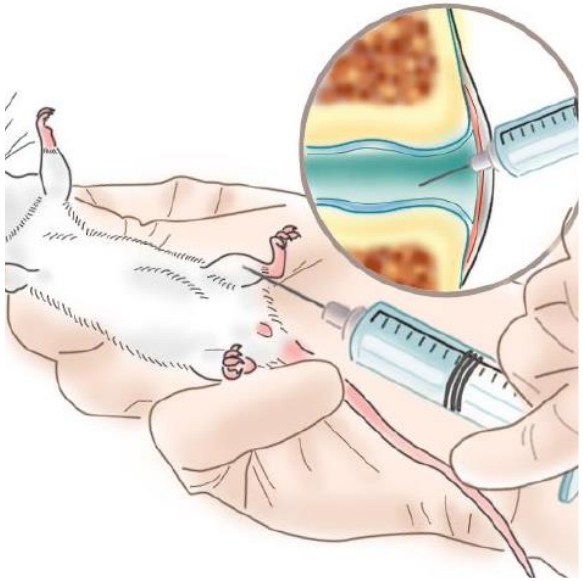


Lab Animal **40**, 111–112 (2011)

Chemical/biological



Mechanical



Systemic/local

Anim Models Exp Med. 2020;3:215–228.

Methods to induce visceral inflammation and pain

TABLE 2 Inflammatory models for the study of visceral pain

Animal	Inflammatory agents	Injection site	Purpose of the study	Findings	References
Rat	TNBS in 50% ethanol	Colon	To develop a simple and reproducible model of chronic colonic inflammation by the intraluminal instillation of a solution containing a barrier breaker and a hapten	The combined administration of TNBS and ethanol resulted in the development of severe, transmural, granulomatous inflammation of the distal colon which may be useful for the study of the etiopathogenesis of chronic intestinal inflammation as well as providing an inexpensive model suitable for assessing potential treatments	Morris et al[87]
Rat	Dibutyltin dichloride, 10% ethanol	Tail vein injection, orally	Nociception in persistent pancreatitis and responsivity of Morphine	Animals with the dibutyltin dichloride-induced experimental pancreatitis expressed serum, histologic, and behavioral characteristics similar in duration to those present during acute attacks experienced by patients with chronic pancreatitis and pain-related measures were found to be abrogated by morphine	Vera-Portocarrero et al[13]
Mice	Zymosan	Colon	Examination of contributions of 2 proteins, TRPV1 and ASIC3, on development of behavioral hypersensitivity and assessment of the function of colon mechanoreceptors of hypersensitive mice	Zymosan sensitized the colonic mechanoreceptors acutely in vitro and chronic behavioral hypersensitivity (≥7 wk) in the quiescent inflammation. TRPV1 and ASIC3 proteins may be important peripheral mediators for development of functional visceral hypersensitivity	Jones et al[8]
Guinea pig	TNBS	Ileal lumen	Morphological and functional changes in neurons projecting to the ileal mucosa at the early stage after inflammatory damage	Inflammation may be an important contributing factor to the neuronal hyperexcitability at the acute stage of inflammation	Nurgali et al[76]

(Continues)

TABLE 2 (Continued)

Animals	Inflammatory agents	Injection site/stimuli	Purpose of the study	Findings	References
Wild mice	Intraluminal distension (100-120 mmHg)	Colorectal	To identify the extrinsic nerve pathway(s) underlies nociception from the colorectum to the spinal cord of rodents	The visceral pain pathway activated by acute noxious distension of the terminal 15 mm of mouse colorectum is transmitted predominantly, if not solely, through rectal/pelvic afferent nerve fibers to the spinal cord. The sensory neurons of this spinal afferent pathway lie primarily in the lumbosacral region of the spinal cord, between L_6 and S_1	Kyloh et al[88]
Male rat	Balloon	Colon	Balloon distension of colon to investigate nonsteroidal anti-inflammatory drug's effectiveness in CRD-induced visceral pain model	Metamizole, dexketoprofen and meloxicam show antinociceptive effect with different duration of action on CRD-induced visceral pain model	Baskın et al[89]
Rat	Intra-colonic infusion of 0.5% acetic acid	Intra-colonic	To investigate whether NO- mediated colonic motility was altered in rat IBS model, using different forms of NO-synthase (NOS) inhibitors	The mean pressure values of spontaneous contractions and KCL (80 mmol/L) responses of distal colonic segments were similar in normal and IBS rats. L-NAME and ARL-17477 significantly increased the mean pressure of spontaneous colonic contractions in normal rats versus own base values ($P < .05$), but this increase did not significantly different when compared to IBS rats	Temiz et al[90]
Rat	TNBS	Ileum	Investigation of the visceral hypersensitivity provoked by TNBS-induced ileitis rats	Transmural ileitis including granuloma and VH	Shah et al[10]
Rat	0.5% acetic acid	Intra-colonic	To investigate in vitro effects of varenicline on spontaneous contractile responses of proximal and distal colon smooth muscle in control and IBS rats	Varenicline significantly decreased the mean pressure of spontaneous colonic contractions in both control and IBS rats compared to their baseline values in only distal colon ($P < .05$). The relaxation responses of distal colons were not significantly different between IBS and control groups ($P > .05$)	Kaya Temiz et al[91]
Goat	TNBS	Ileum	To testify the effect of electroacupuncture (EA) on ileitis-provoked VH, and to confirm whether EA attenuates VH through JAK2/STAT3) signaling pathway in the PAG-RVM-SDH axis	EA attenuates VH probably through inhibiting JAK2/STAT3 signaling pathway in the PAG-RVM-SDH axis	Wan et al[7]

Abbreviations: ASIC3, Acid sensing ion channel-3; CRD, Colorectal Distension; EMG, electromyography; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; JAK, Janus Kinase; NO, Nitric Oxide; PAG, periaqueductal gray; RVM, rostral ventromedial medulla; SDH, spinal dorsal horn; STAT, signal transducers and activators of transcription; TNBS, 2,4,6-trinitrobenzene sulfonic acid; TNFα, Tumor Necrosis Factor-alpha; TRPV1, Transient Receptor Potential Vanilloid Type 1; UBD, urinary bladder distention; VH, visceral hypersensitivity.

Methods to evaluate visceral inflammation and pain

TABLE 1 Different methods used to quantify visceral pain in laboratory animals

Animal	Animal model	Method	Purpose of the study	Findings	References
Mice	Experimental study	Telemetry	To study post laparotomy pain in laboratory mice by telemetric recording of heart rate and heart rate variability	Real-time telemetric recordings of heart rate and heart rate variability found to be indicative of mild to moderate post laparotomy pain which cannot easily be detected by direct observation	Arras et al[57]
Rat	Inflammatory	Intracolonic manometry	To test the efficacy of pregabalin on visceral pain responses and colonic compliance	Pregabalin reduced the viscerosomatic and autonomic responses associated with CRD induced visceral pain and increased colonic compliance	Ravnefjord et al[62]
Mice	Inflammatory	Automated behavior analysis	To automate analysis of abdominal licking behavior associated with intracolonic capsaicin induced visceral pain	The neurokinin-1 receptor antagonist GR205171A dose dependently inhibited capsaicin induced licking which was automatically detected by applying commercially available image analysis software	Hayashi et al[54]
Mice	Inflammatory	Burrowing	To investigate whether a change in burrowing behavior is a sensitive measure of animal welfare in murine models of colitis	Changes of spontaneous burrowing behavior correlate with the onset of inflammation in acute DDS induced colitis	Jirkof et al[53]
Rat	Inflammatory	Electrophysiology & behavioral studies	To study the reactive oxygen species mediated visceral pain related amygdala plasticity and behaviors	ROS contribute to visceral pain related hyperactivity of amygdala neurons and amygdala dependent behaviors through a mechanism that involves increased excitatory transmission and excitability of CeA neurons	Ji et al[73]
Rat	Stress	EMG	To study MS induced visceral hypersensitivity	Visceral hypersensitivity of MS rats is more pronounced in the post-weaning period and slightly restored in adults. Thus, visceral hypersensitivity in the post-weaning period might play a more meaningful pathophysiologic role in the formation of adult irritable bowel syndrome	Li et al[63]
Rat	Inflammatory	RGS, burrowing, CBS	To assess whether the RGS, CBS and burrowing could identify pain in an acute and chronic colitis model	RGS increased as DAI scores increased during both acute and chronic phases. Burrowing only decreased during the acute phase but CBS scores did not increase significantly during either colitis phase	Leung et al[49]

Abbreviations: CBS, Composite Behavior Score; CeA, Central Amygdala; CRD, Colorectal Distension; DAI, Disease Activity Index (assessing fecal blood, stool consistency and weight loss); DDS, dextran sulfate sodium; EMG, electromyography; MS, maternal separation; RGS, rat grimace scale.

Models of Inflammatory diseases:

+ + + + +	- - - - - - - -
Isolation of factors	Multifactorial
Mechanistic insights (GMOs)	Interspecific diferences (anatomical, biochemical)
Therapy assays	Self-healing

Advantages and Disadvantages of Techniques for Measuring Visceral Pain in Animal Models.

Method to Induce Visceral Pain for Measurement	Description	Advantages	Disadvantages
Colorectal Distension (CRD)	A balloon is inserted via the anus to the distal colon of the rodent under sedation and then pressure is applied in an ascending stepwise fashion via a customized barostat. Repeatable air inflation and pressures can be applied to the distal colon region.	• Closely replicates human experience of visceral pain (Christianson and Gebhart 2007) • Used for high throughput studies • Relatively simple • Widely accepted	
Response to Colonic Instillation of Algesic Substances	Algesic compounds such as acetic acid, capsaicin, mustard oil, or zymosan are applied intracolonically	• Simple to administer • Used for high throughput studies	• Poor reproducibility • Questionable relationship to human pathology • Long-lasting and inescapable pain
Technique for Measuring Visceral Pain			
Electromyography	Quantifies magnitude of abdominal contractions in response to CRD or colonic instillation of algesic substances	• Quantifies the visceromotor response • Non-invasive	
Manometry	Measures pressure and pattern of muscle contractions in visceral organs in response to CRD or to evaluate analgesic substances. In CRD, monitors pressure changes within the descending balloon (Arvidsson et al., 2006).	• Reliable noninvasive, non-surgical method in mice (Arvidsson et al., 2006).	
Brain Imaging in Response to CRD (microPET, fMRI	Examination of pain processing in the brain in response to CRD	• Non-invasive (Lazovic et al., 2005; Johnson et al., 2010; Wouters et al., 2012) • Allows examination of the brain in live animals	• Expensive • Requires specialized equipment/expertise
Abdominal Withdrawal Reflex and other visually assessed rodent pain behaviours	AWR is an involuntary motor reflex in response to CRD. The animal is graded on a scale ranging from immobility, to mild contraction of the abdomen to severe contraction including body arching and lifting of the pelvis (Al-Chaer et al., 2000)	• Does not require surgery like some measures of the visceromotor reflex (O'Mahony et al., 2012)	• Labour intensive • Time consuming • Lacks objectivity and reproducibility (Regmi and Shah 2020)

Mice are not men

H. Shaw Warren, Ronald G. Tompkins, Lyle L. Moldawer, Junhee Seok, Weihong Xu, Michael N. Mindrinos, Ronald V. Maier, Wenzhong Xiao, and Ronald W. Davis

PNAS January 27, 2015 112 (4) E345; published ahead of print December 24, 2014 https://doi.org/10.1073/pnas.1414857111

This article has Replies. Please see:

Reply to Warren et al. and Shay et al.: Commonalities across species do exist and are potentially important

Genomic responses in mouse models greatly mimic human inflammatory diseases

Genomic responses in mouse models poorly mimic human inflammatory diseases

See related content:

Genomic responses to inflammation in mouse models mimic humans: We concur, apples to oranges comparisons won't do - Jan 27, 2015

A vibrant discussion of the merits and limitations of animal models is long overdue. The limitation of space precludes addressing many of the questionable approaches and statements by Takao and Miyakawa (**1**).

Despite the different approaches used by Takao and Miyakawa (**1**), their results actually support the conclusion that "Genomic responses in mouse models poorly mimic human