Inflammation and Impaired Gut Physiology in Postoperative ileus

Hyojin Park,M.D, Ph.D
Dept. of Int Med
Yonsei University
Seoul, Korea

Inflammation and Impaired Gut Physiology in Postoperative ileus

- Introduction
- Mechanisms
- Targets for treatment
- Summary & Conclusions

Definition

- Transient **cessation of coordinated bowel motility** after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of intake.

	Definition	Duration	Frequency
POI	Time until first flatus or stool + adequate oral intake during 24 hrs	2-4 days	Almost every abdominal surgical procedure
Prolonged or paralytic ileus	Precipitated by complication of surgery	>6 days	10-25%

Time to recovery

- Small intestinal function generally normalizes first, often within several hours of surgery.
- Gastric motility usually returns to normal within 24-48 hours after surgery.
- The colon is usually the final portion of the GI tract to regain normal motility, which usually occurs within 48-72 hours after surgery.

→ POI, main cause of delayed hospital discharge after abdominal surgery

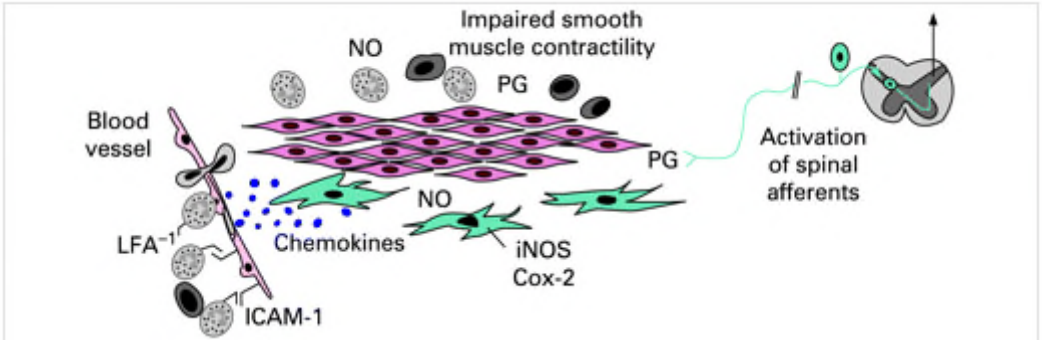
Mechanisms leading to generalized hypomotility in POI

- Local inflammatory response activates

- Increased production of NO and COX-2 metabolites

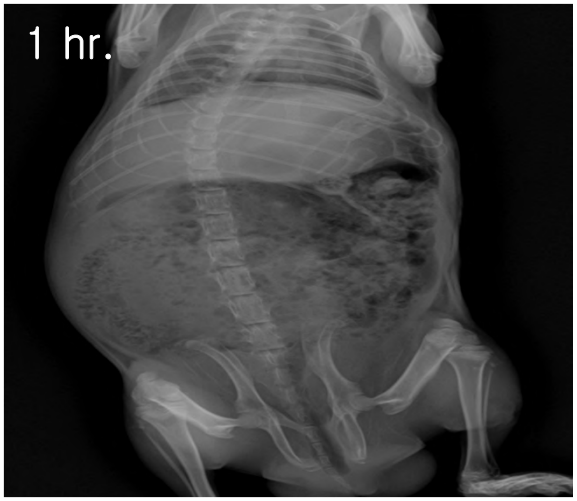
- An adrenergic inhibitory pathway

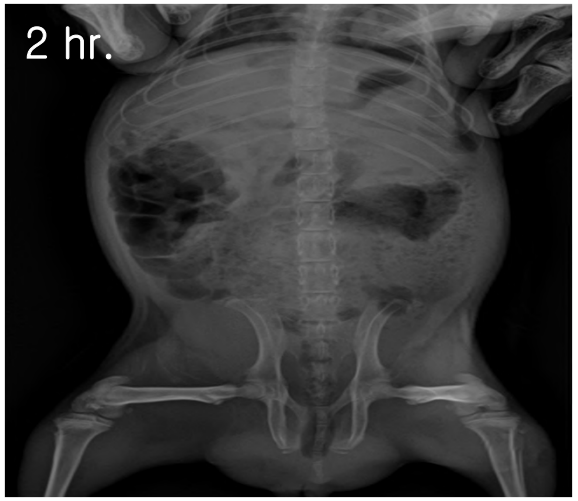
impairing motility of distant area.

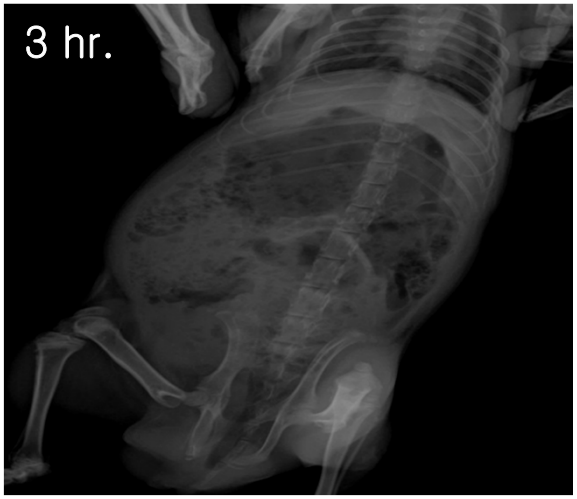


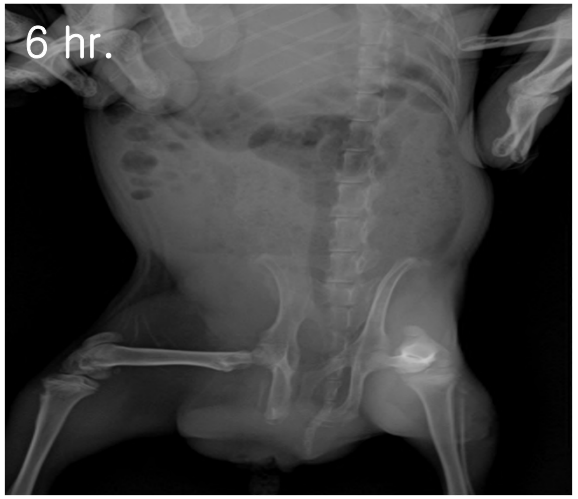
(Boeckxstaens GE et al., 2009)

Experimental Model of Postoperative Ileus in Guinea Pig



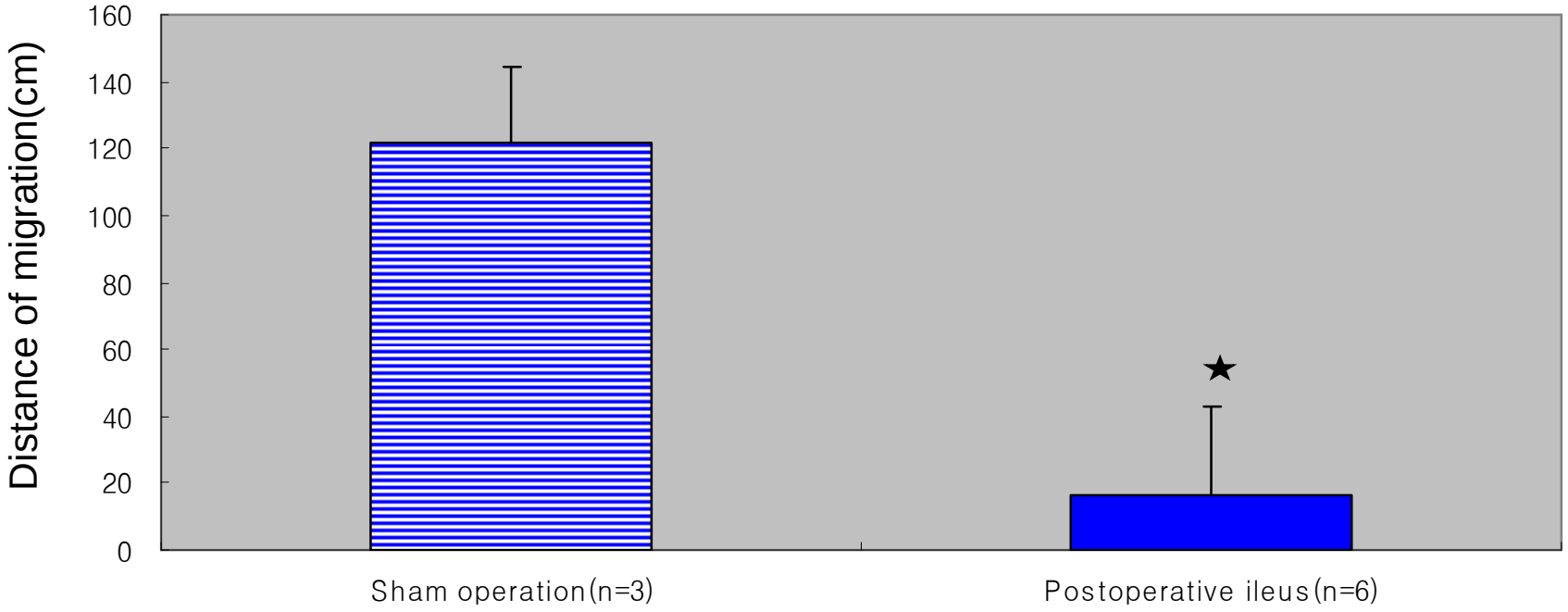






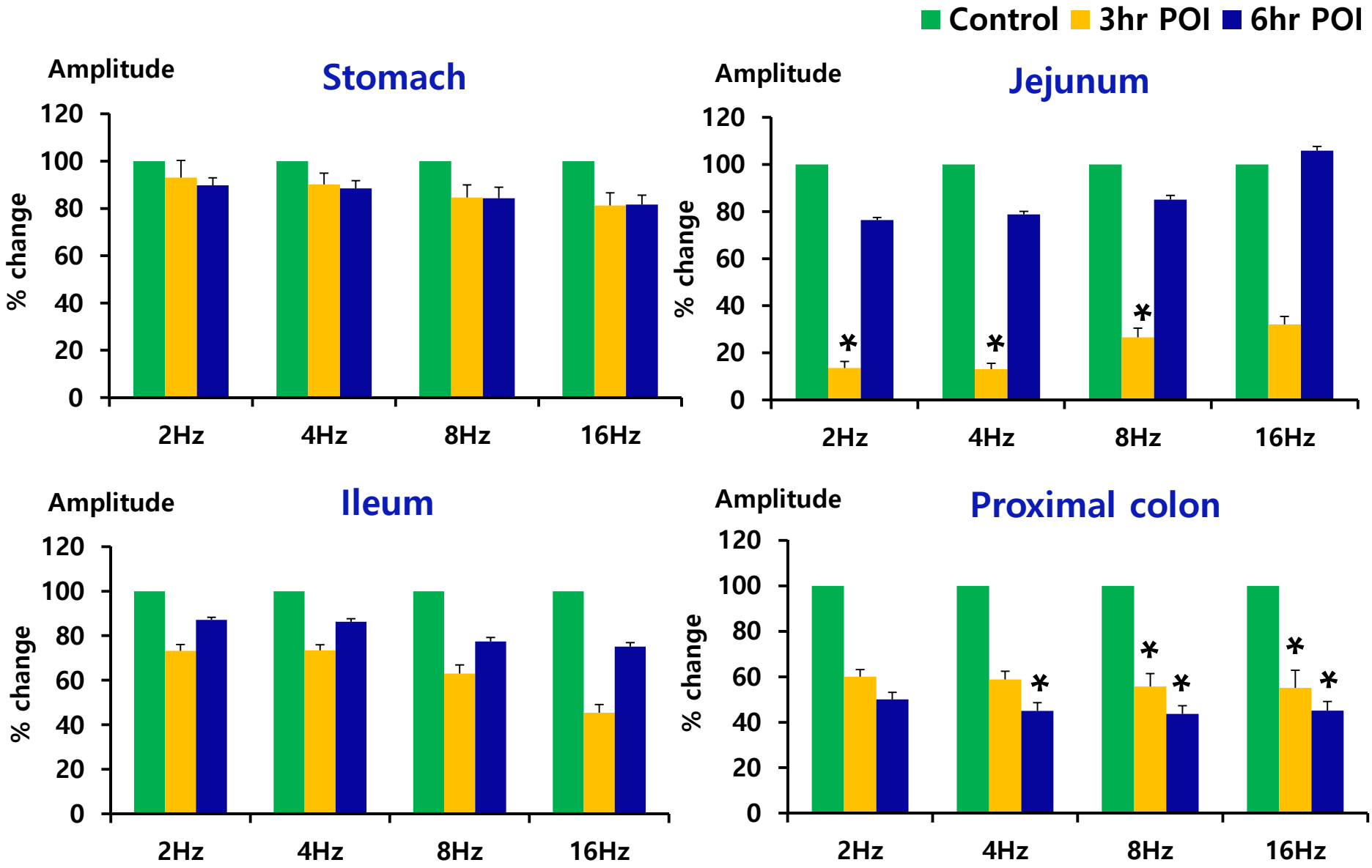
UGI transit in sham operation group and postoperative ileus group

(★: $p<0.05$)



(Lim HC & Park H, 2008)

Contractile Amplitude

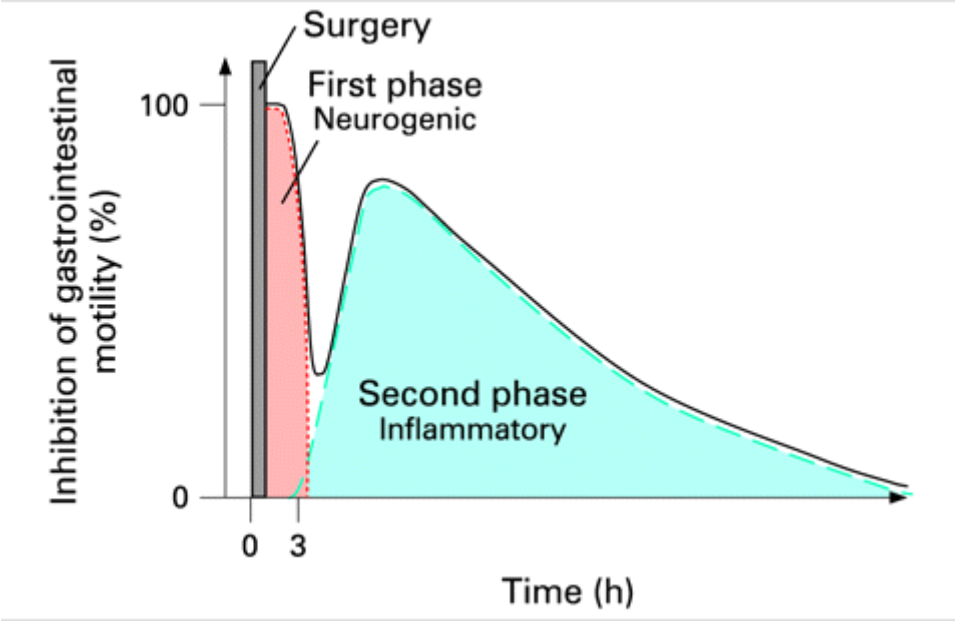


*p<0.05 in one way ANOVA

Mechanism

- Neurogenic mechanisms with overactivation of sympathetic pathways
- Intestinal inflammatory response to bowel manipulation and surgical trauma.
- Inhibition of GI motility by opioid analgesics

Two phases involved in POI.



•The first phase starts during abdominal surgery and ends soon after it.
•Initial mechanical factors-> activate neural reflexes suppressing bowel motility via the sympathetic adrenergic pathway.

• The second inflammatory phase lasts much longer and is therefore **clinically relevant**.

(Boeckxstaens GE et al., 2009)

The inflammatory phase of POI

- **Macrophages** and **Mast cells**

- **Intestinal manipulation** activates resident **MP** in intestinal muscularis externa

-> cytokine and chemokine release

-> influx of leucocyte starting 3-4 h after surgery.

-> Accumulation of inflammatory cells in the muscularis

Original Article

http://dx.doi.org/10.3349/ymj.2013.54.6.1336
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 54(6):1336-1341, 2013

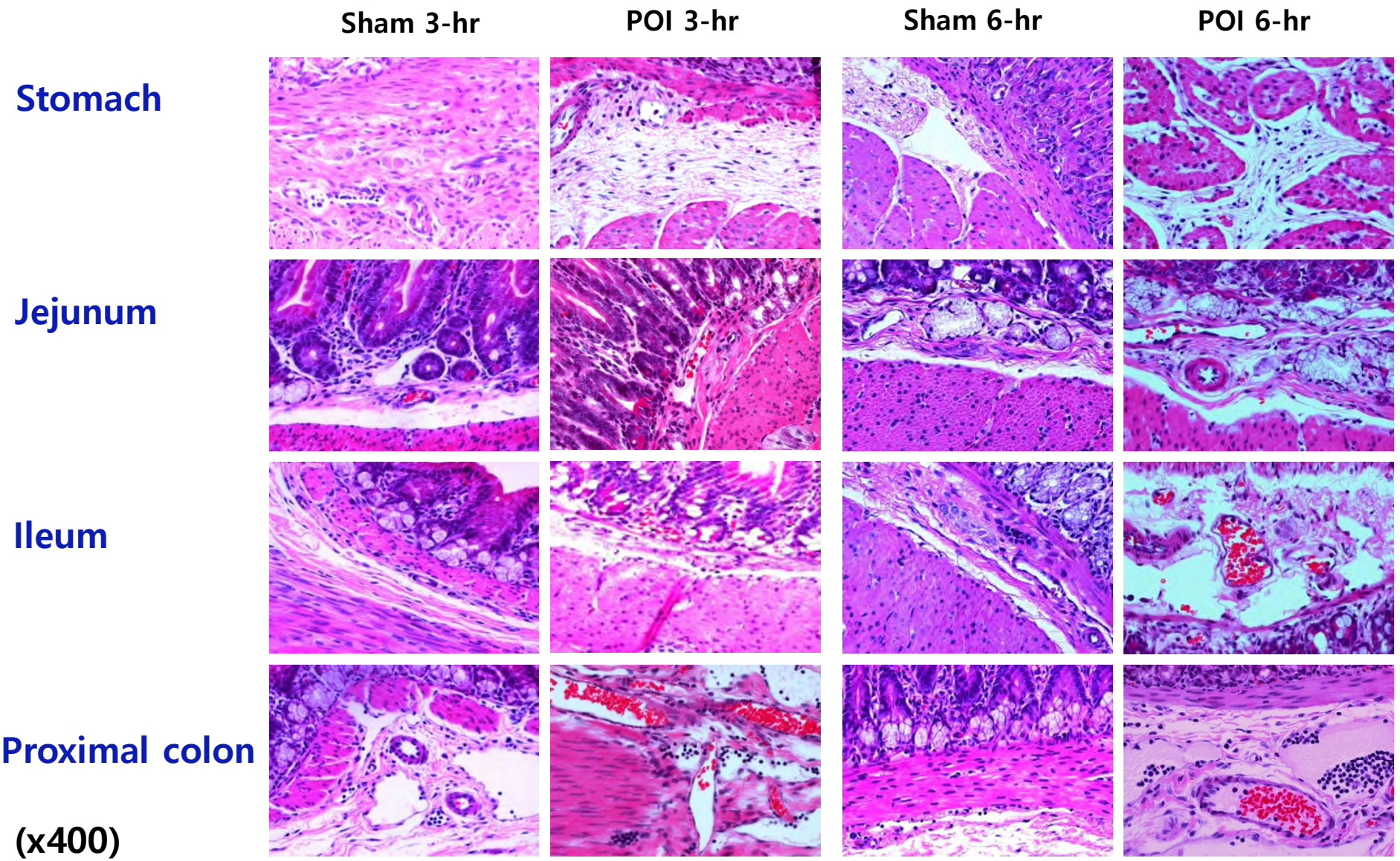
YMJ

Inflammatory Responses in the Muscle Coat of Stomach and Small Bowel in the Postoperative Ileus Model of Guinea Pig

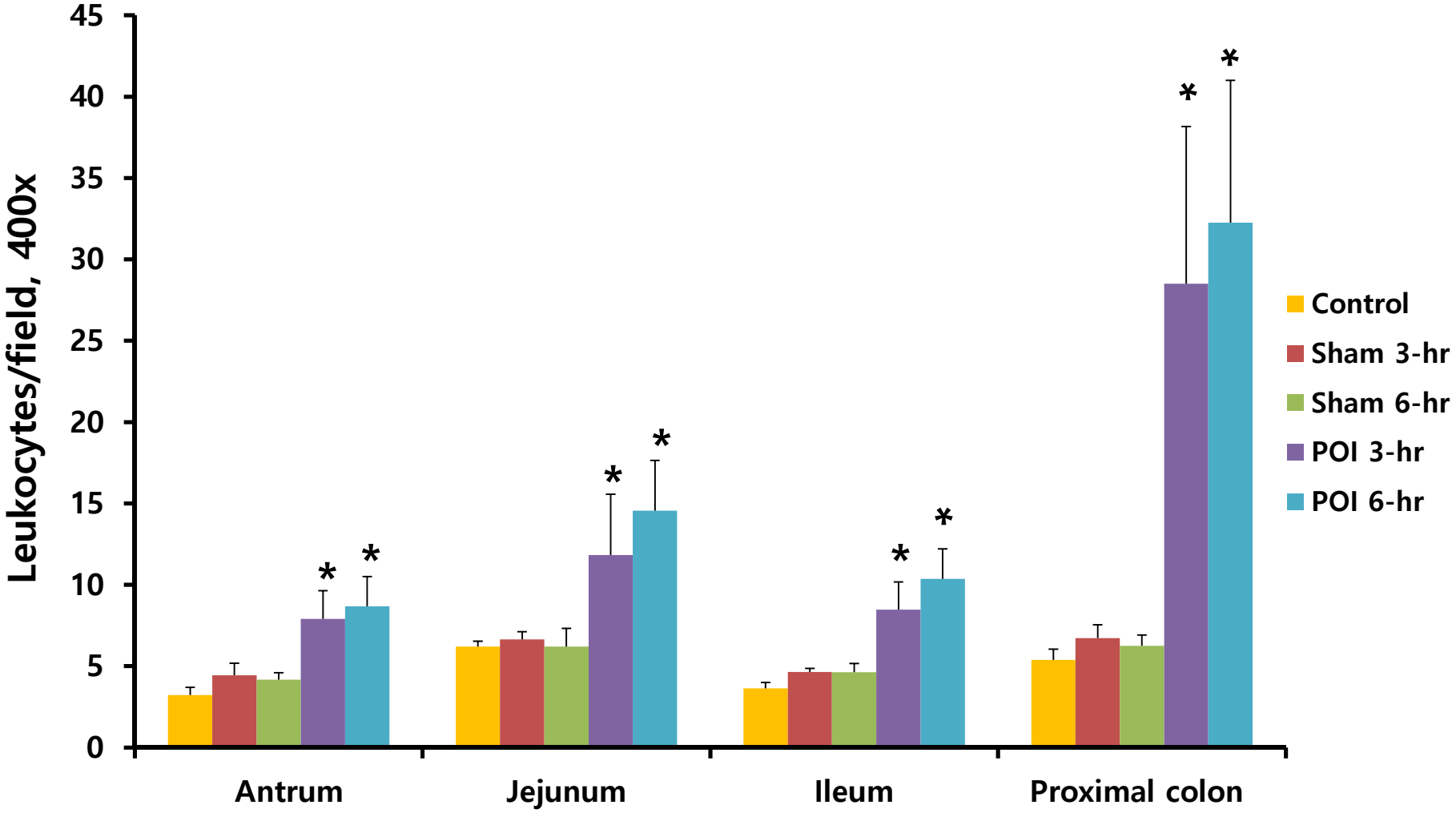
Hong Kyu Choi,[1] Young Ho Lee,[2] Jong Pil Park,[3] Kevin Min,[4] and Hyojin Park[1]

Departments of [1]Internal Medicine, [2]Physiology, and [3]Pathology, Yonsei University College of Medicine, Seoul, Korea;
[4]Department of Medical Science, Medical School, McMaster University, Ontario, Canada.

Degree of inflammation

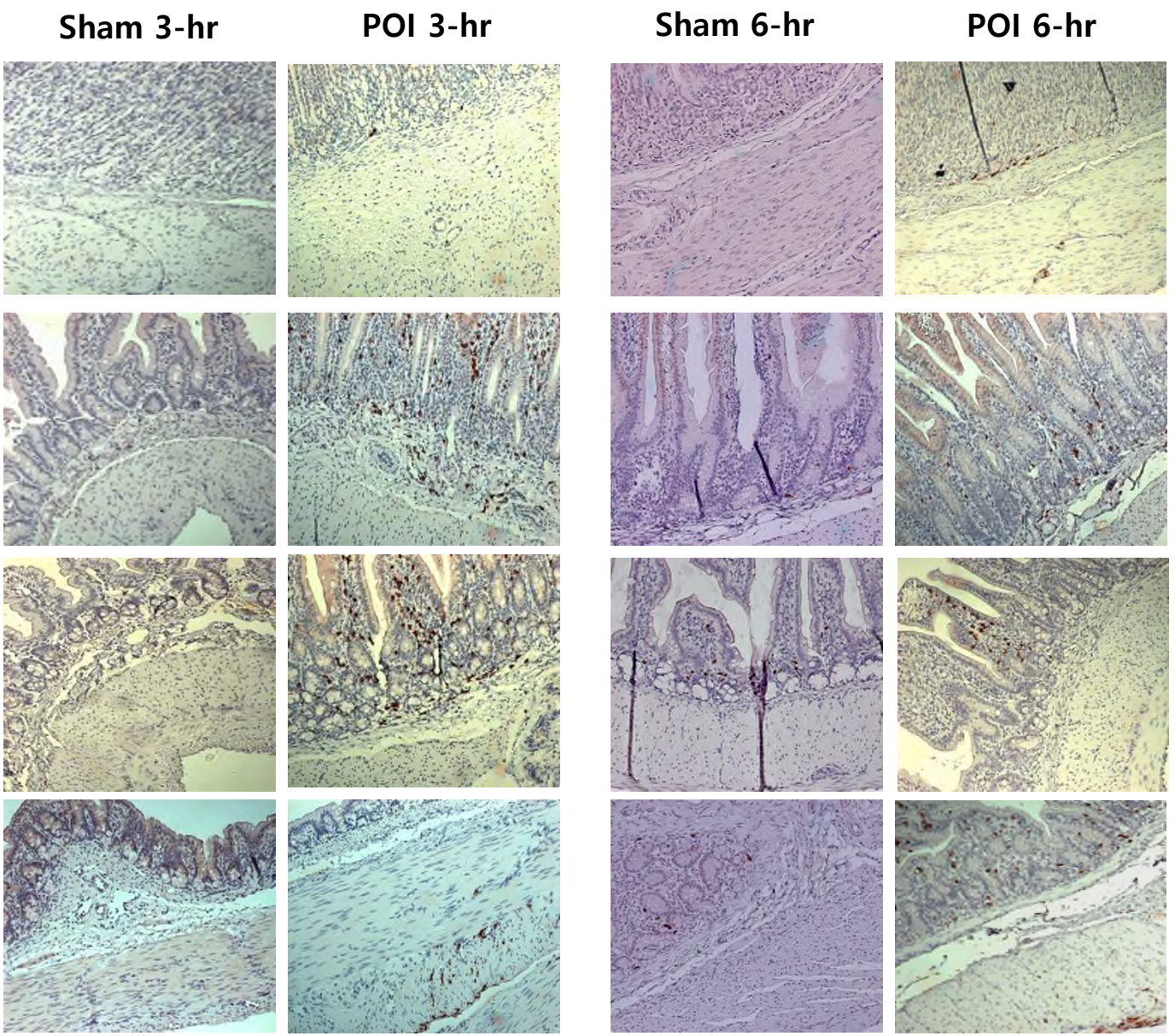


Degree of inflammation

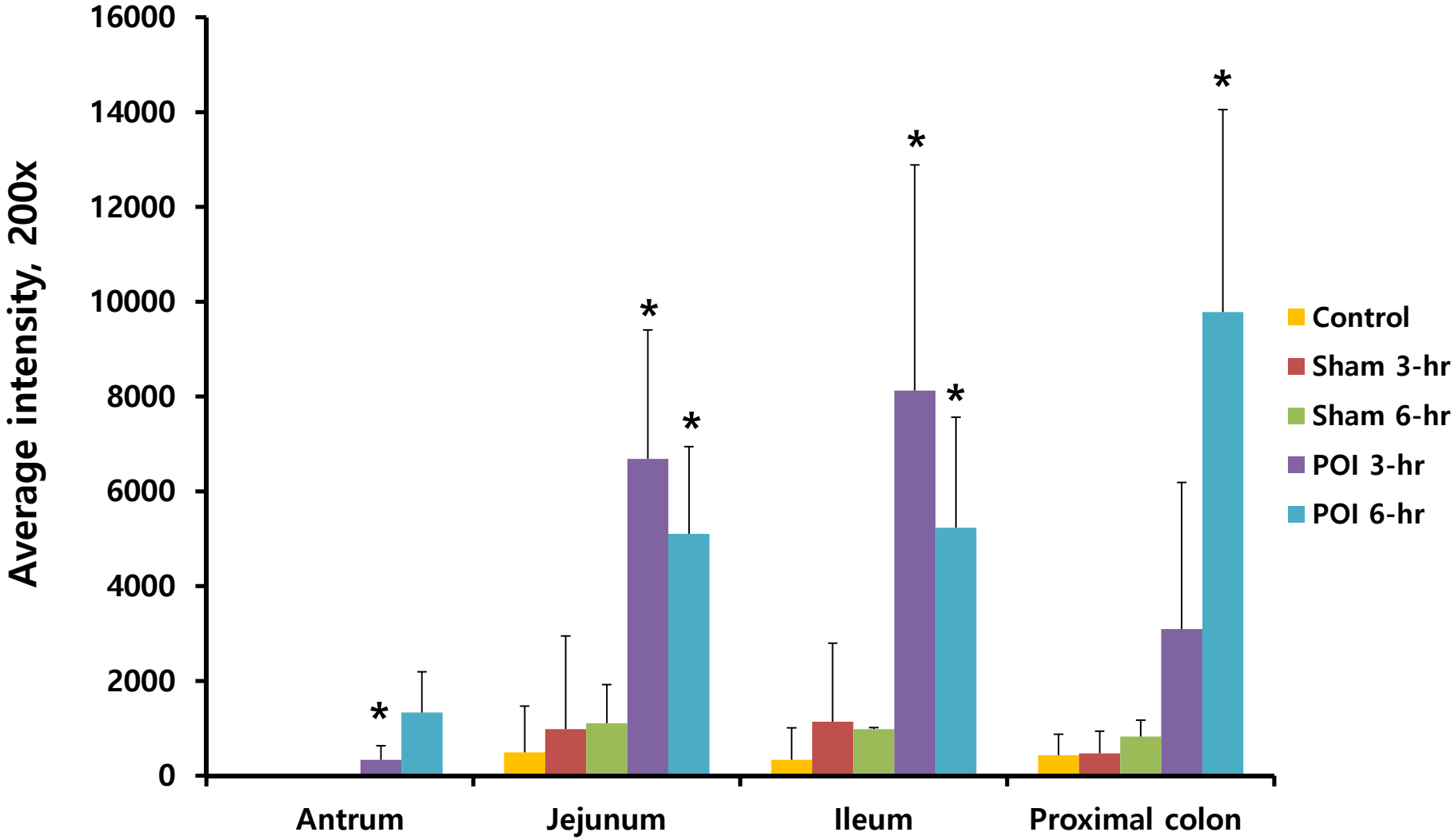


*p<0.05 vs. sham

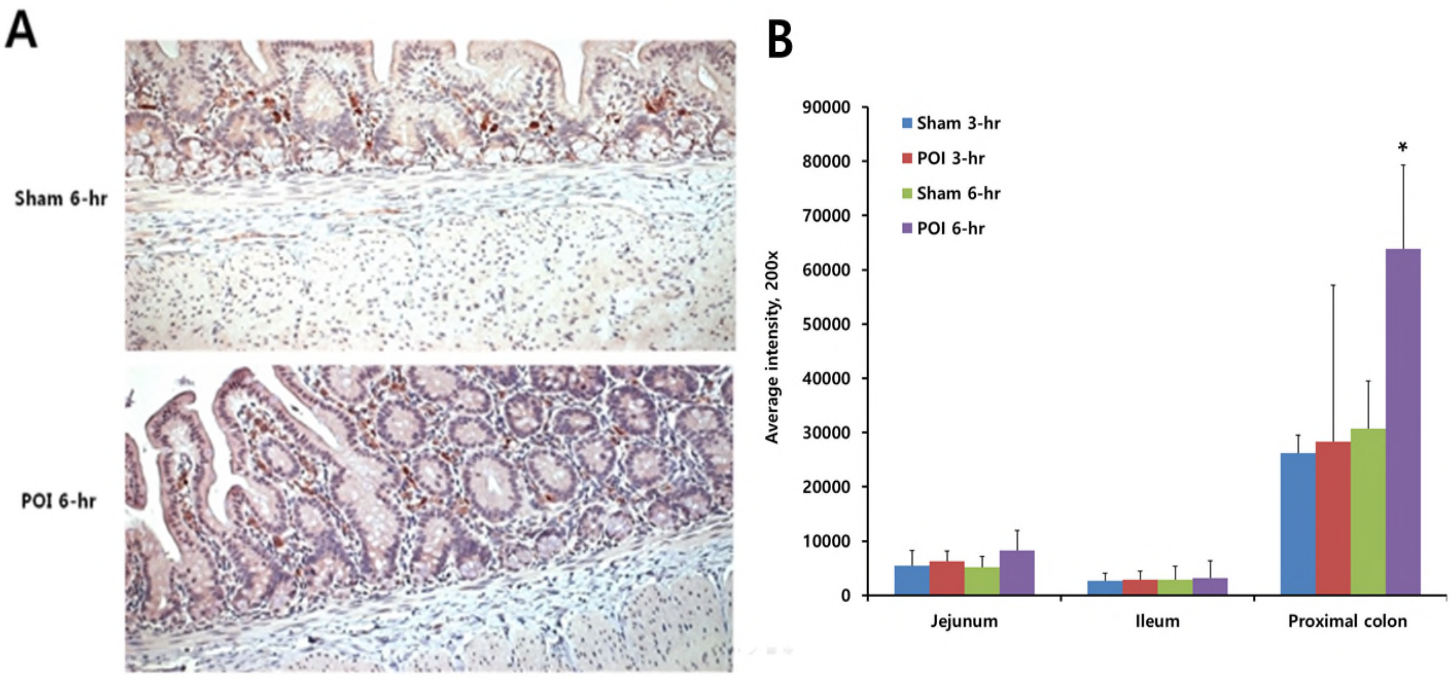
Expressions of calprotectin



Expressions of calprotectin



*p<0.05 vs. sham



(A) Representative picture of the IHC of mast cell tryptase in proximal colon.
(B) (B) Mast cell tryptase expressions in jejunum, ileum and proximal colon of POI and sham groups.

*Significant *p* value compared with the same time-point in the POI group compared with sham.

Neurogastroenterology & Motility

Neurogastroenterol Motil (2012) **24**, 172–e91 doi: 10.1111/j.1365-2982.2011.01820.x

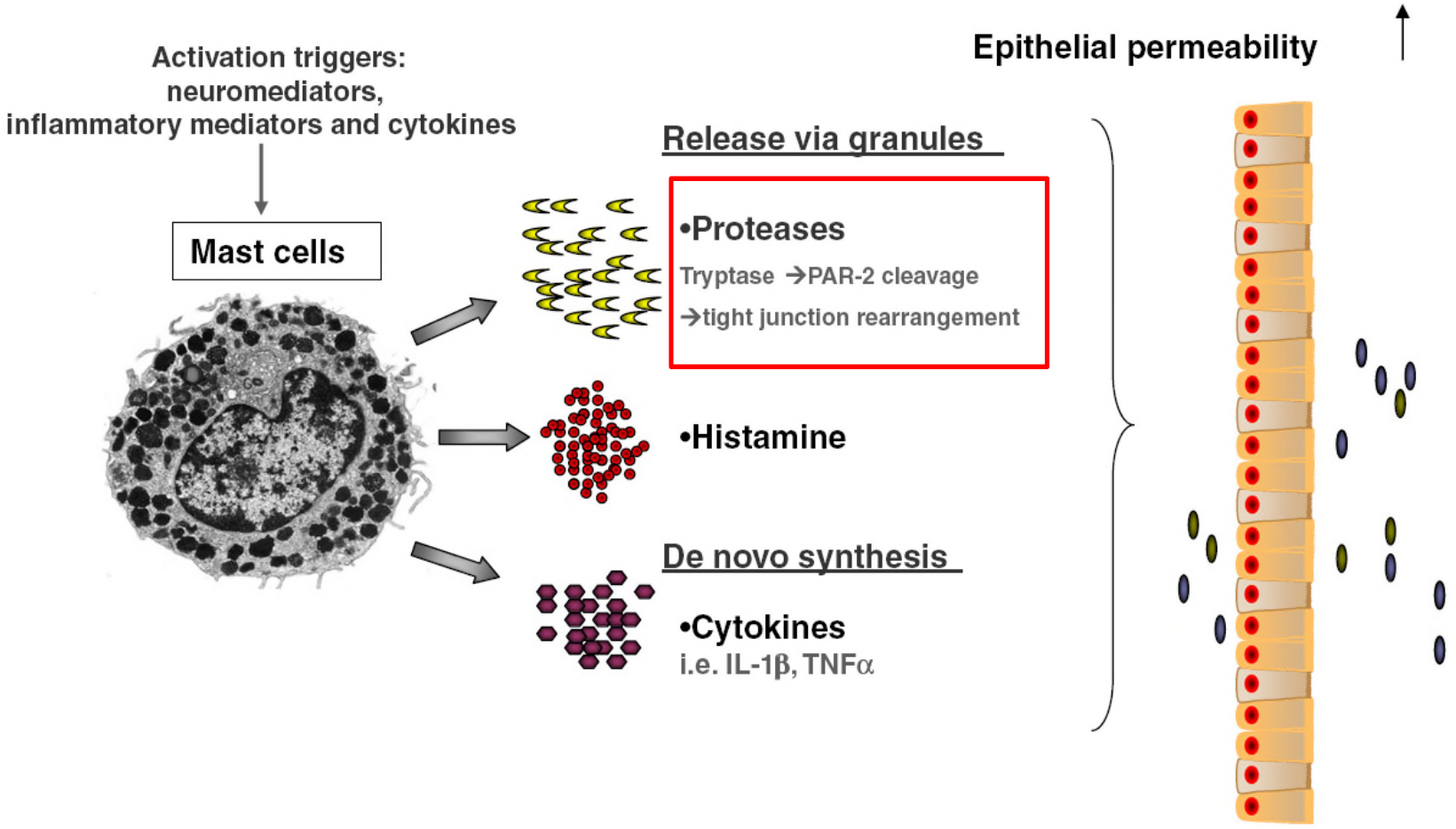
Mast cells trigger epithelial barrier dysfunction, bacterial translocation and postoperative ileus in a mouse model

S. A. SNOEK,* S. DHAWAN,* S. H. VAN BREE,* C. CAILOTTO,* S. A. VAN DIEST,* J. M. DUARTE,* O. I. STANISOR,* F. W. HILBERS,* L. NIJHUIS,* A. KOEMAN,† R. M. VAN DEN WIJNGAARD,* C. J. ZUURBIER,† G. E. BOECKXSTAENS*,‡ & W. J. DE JONGE*

*Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands
†Laboratory of Intensive Care and Anesthesiology, Department of Anesthesiology, Academic Medical Centre, Amsterdam, The Netherlands
‡Department of Gastroenterology, Catholic University of Leuven, University Hospitals Leuven, Leuven, Belgium

- **Mast cell activation** during abdominal surgery causes epithelial **barrier dysfunction and inflammation** of the muscularis externa of the bowel.

- The impairment of the epithelial barrier likely contributes to the pathogenesis of POI.



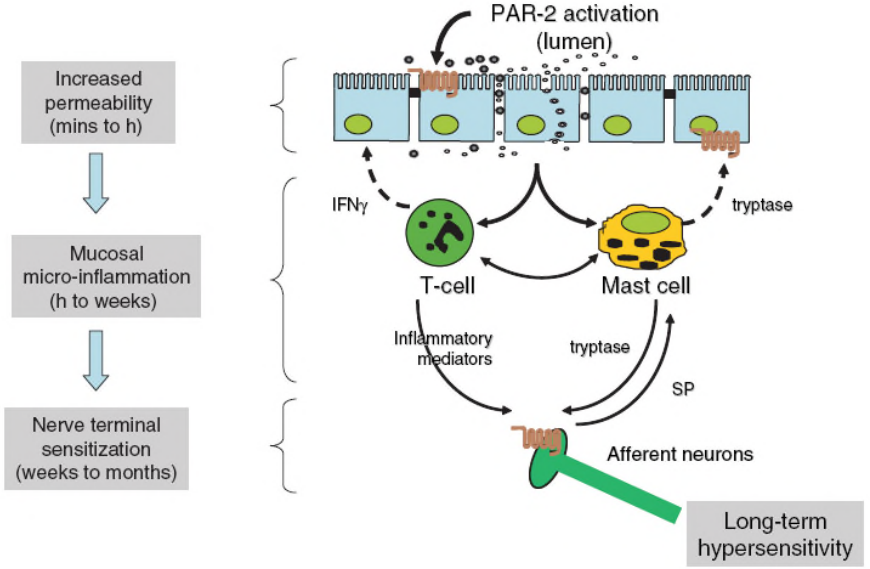
(B.Y.De Winter et al, 2012)

PAR in the Field

PAR-2 in the Gut

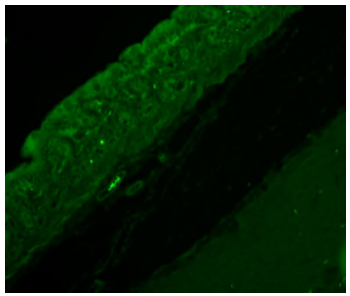
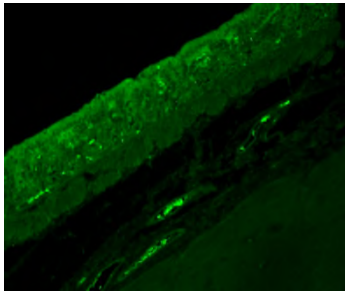
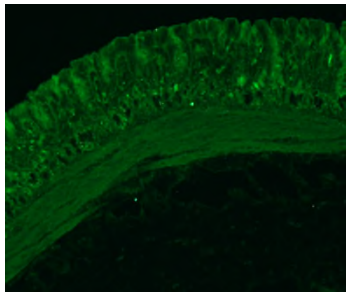
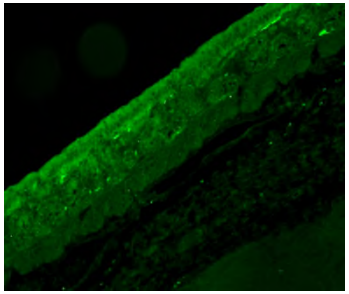
- **PARs** belong to a family of 7 transmembrane domain **G-protein receptors** that are activated by cleavage of their N-terminal domain by selective proteolytic enzymes.

- Enterocytes, mast cells, smooth muscle cells, myenteric neurons, and on colonic epithelial cells



(Bueno L & Fioramonti J, 2008)

Expressions of PAR-2

	Sham 3-hr	POI 3-hr	Sham 6-hr	POI 6-hr
Proximal colon (x200)				

Epithelial permeability

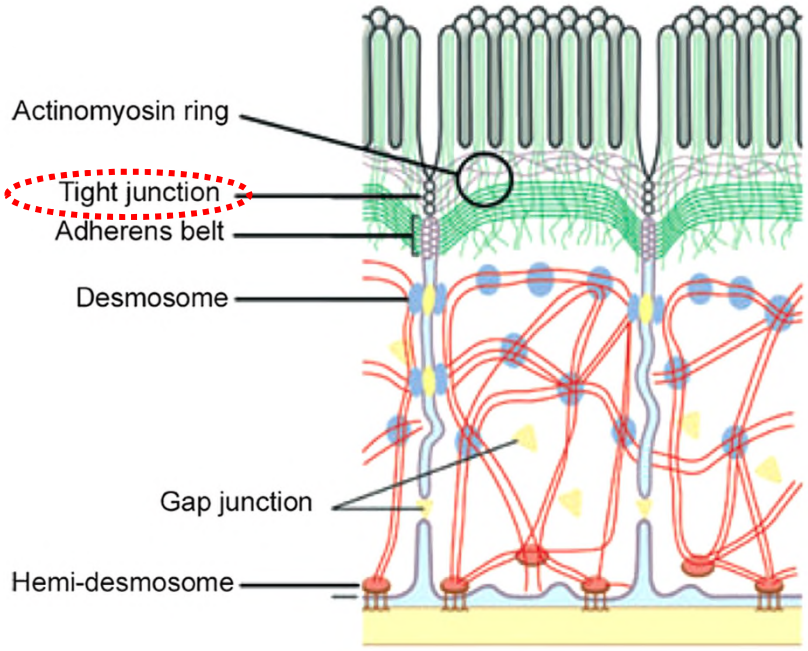
•Alterations of both tissue and luminal level of protease

-> PAR2 activation

-> Cytoskeleton contraction (triggering phosphorylation of myosin light chain)

-> Changes in tight junction permeability

•Gut paracellular permeability mainly depends on the configuration of TJ protein.



(Bueno L & Fioramonti J, 2008)

Conditions associated with Gut permeability

Evidence level	GI	Extra-GI
Established	IBD GVHD Celiac disease	Type I DM HIV/ AIDS MOF
Possible	IBS Food allergy Postoperative ileus ?	Autism Eczema
Limited	NAFLD Cirrhosis Acute pancreatitis	Psoriasis Parkinson's disease Fibromyalgia Depression Chronic fatigue Asthma

(Odenwald & Turner, 2013)

Mechanisms of altered intestinal permeability

- Alteration in **tight junction** protein expression or localization
- Abnormal regulation of tight junction function

- **Dysbiosis** in microbial flora resulting in the lack of signals to maintain barrier function
- Dysbiosis resulting in an increase in signals that break the barrier

- Presence of active inflammation and increased presence of pro-inflammatory cytokines and oxidative species

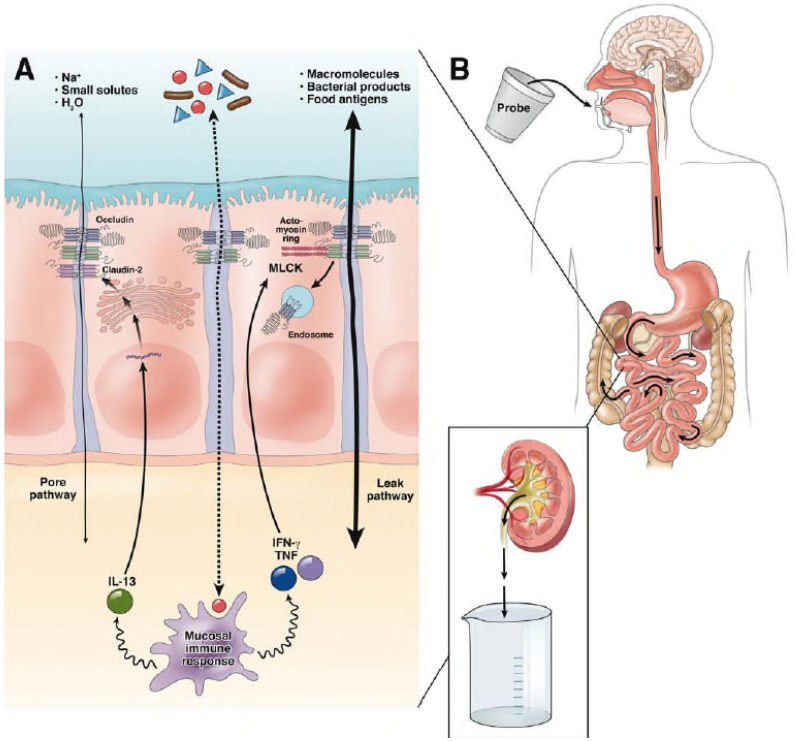
- Increased density of epithelial gaps caused by increased cell shedding

Assessment of Intestinal Permeability

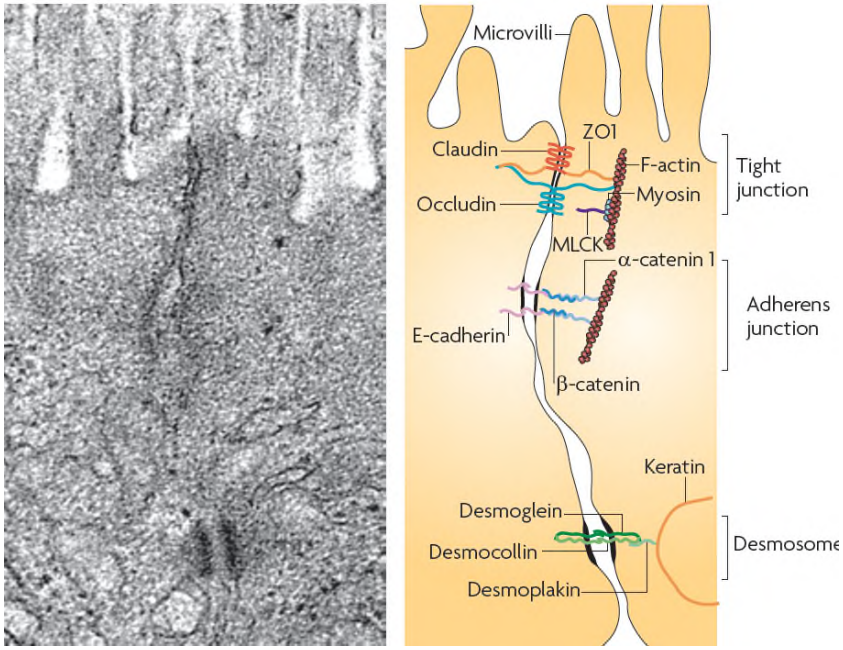
In vitro methods

- Morphology (IHC, EM)
- Function (Ussing chamber)
- TJ molecular biology

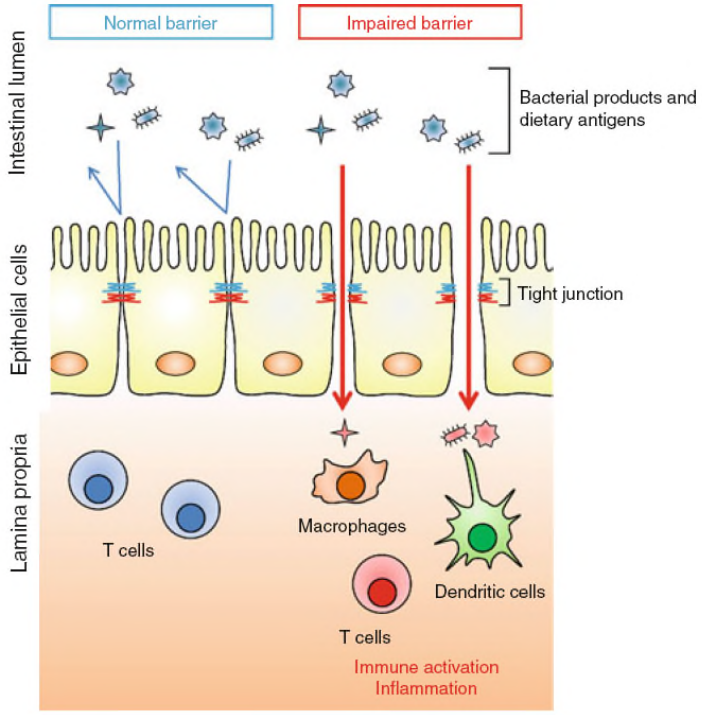
In vivo methods



Tight Junction Protein



(Turner JR et al., 2009)



(Suzuki T, 2013)

J Neurogastroenterol Motil, Vol. 24 No. 1 January, 2018
pISSN: 2093-0879 eISSN: 2093-0887
https://doi.org/10.5056/jnm17012
Journal of Neurogastroenterology and Motility

Original Article

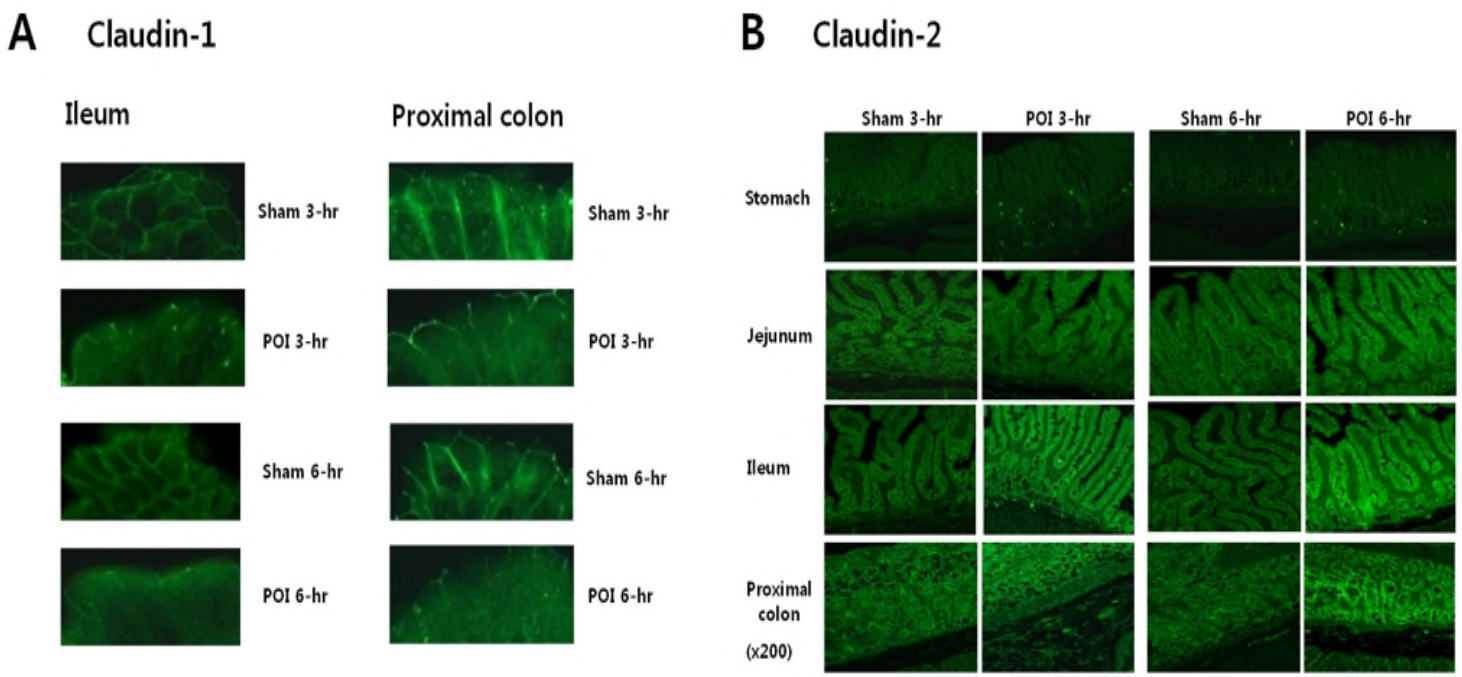
Inflammation, Impaired Motility, and Permeability in a Guinea Pig Model of Postoperative Ileus

Yoo Jin Lee,[1] Zahid Hussain,[2] Cheal Wung Huh,[2] Young Ju Lee,[2] and Hyojin Park[2]*

Claudin

- **Claudin-1** : Barrier-forming
  Decreasing paracellular permeability

- **Claudin-2** : Pore-forming
  Increasing paracellular permeability

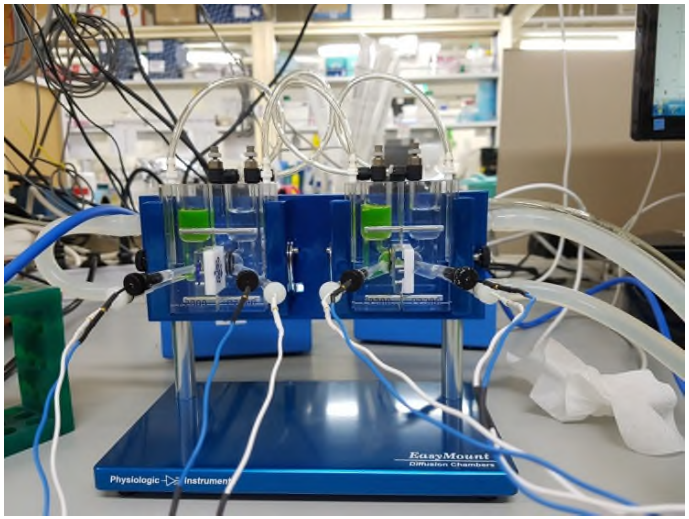


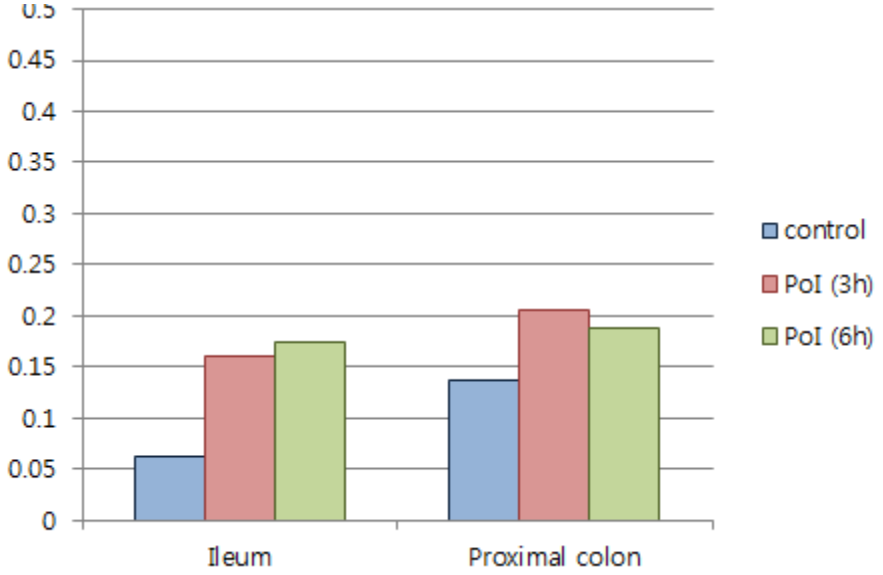
Expression of junctional proteins by Immunofluorescence (IF) stain in POI and sham groups.

(A) Claudin-1 expression in ileum and proximal colon. The decreased expression of claudin-1 was observed in POI groups compared with sham groups.

(B) (B) Claudin-2 expression. The expression of claudin-2 was increased in POI groups compared with sham groups

Increased Permeability in POI





- Our findings are valuable in encouraging future studies on the **role of inflammation and permeability** in the pathophysiology of POI.

- **Macrophages and mast cells** initiate and orchestrate the cascade of inflammatory events. Thus, these immune cells seem to be the most interesting **targets for the purgative therapy for POI.**

Perioperative inflammatory marker as a predictive factor for prolonged postoperative ileus after gastrectomy for gastric cancer

Kim YS, Park HJ

2018 Gastrointestinal Cancers Symposium
MULTIDISCIPLINARY CARE: LOCAL PRACTICE, GLOBAL OUTCOMES
January 18-20, 2018 | Moscone West Building | San Francisco, CA | #GI18

◆PPOI group was significantly associated with elevated perioperative inflammatory marker (pre- and post-operative CRP, NLR, and PLR).

Variables	Control (N=258) (n,%)	PPOI (N=132) (n,%)	P value
Preoperative marker			
CRP (mg/L)	2.55 (± 0.39)	5.25 (±13.76)	**0.034**
NLR	2.02 (±1.19)	2.28 (±1.27)	**0.041**
PLR	134.34 (±56.14)	146.89 (±73.49)	0.087
POD1 marker			
CRP (mg/L)	46.19 (±27.50)	51.31 (±28.09)	0.085
NLR	6.74 (±4.01)	7.79 (±4.79)	**0.023**
PLR	172.59 (96.68)	194.37 (±128.82)	0.063
POD3 marker			
CRP (mg/L)	103.31 (±58.77)	137.32 (±69.84)	**<.001**
NLR	5.33 (±3.02)	6.76 (±3.81)	**0.04**
PLR	172.42 (±81.81)	191.97 (±100.97)	**<.001**

NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, CRP = c-reactive protein

- **The perioperative inflammatory markers may be used as clinically relevant predictive markers for PPOI following gastric cancer surgery.**

Outlines

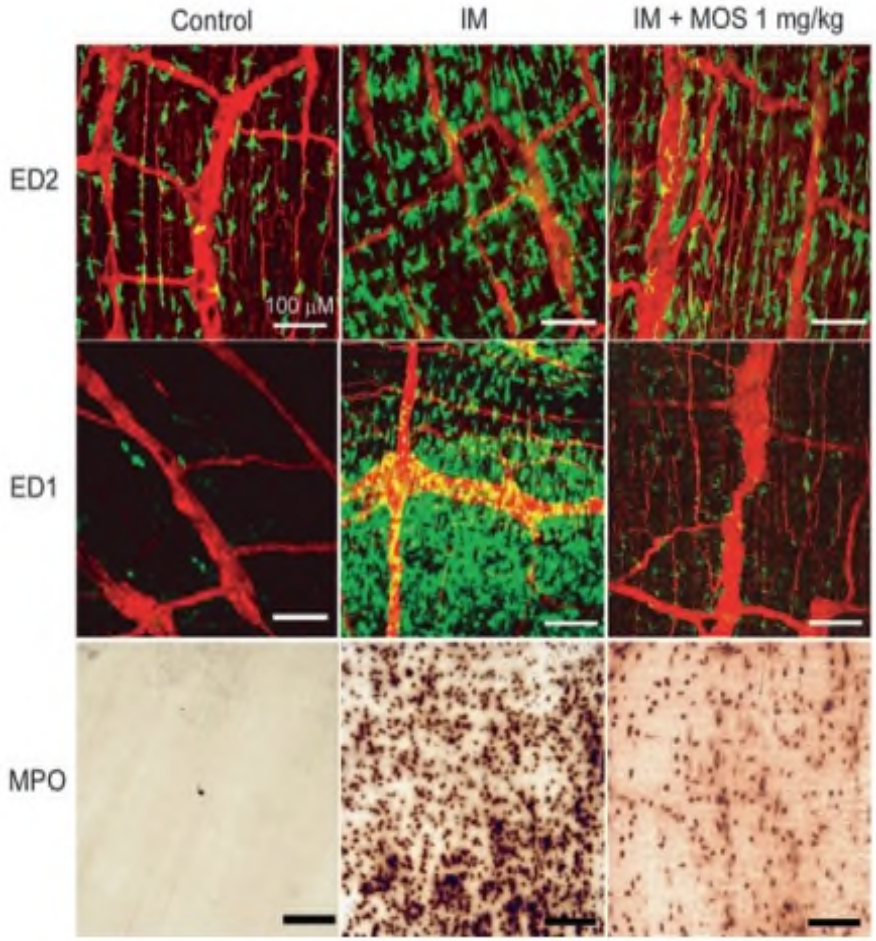
- Introduction
- Mechanisms
- Targets for treatment
- Summary & Conclusions

Targets for treatment

- Therapy should aim to **prevent** or **reduce** the **inflammatory** response to intestinal handling.

- **Macrophages and Mast cells**

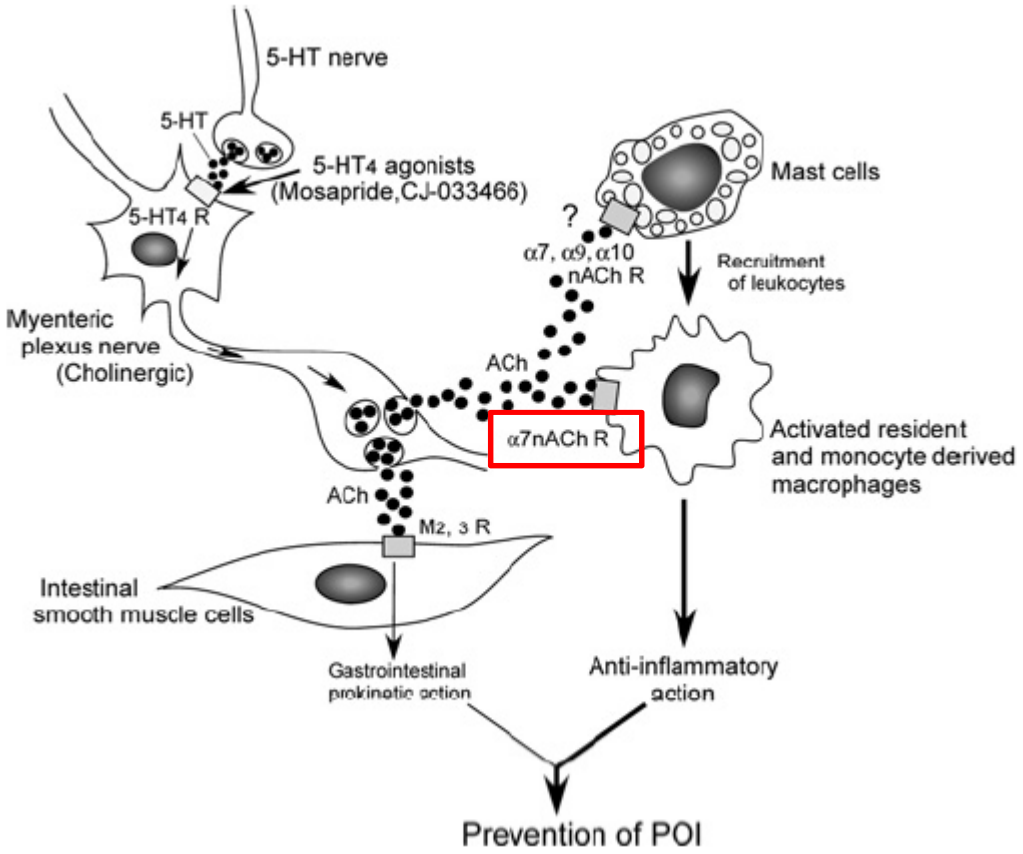
5-HT4R stimulation inhibited inflammation induced by intestinal manipulation



ED2 positive resident macrophage,
ED-1 positive monocyte-derived macrophage
MPO positive neutrophil

(Tsuchida Y et al, 2011)

Anti-inflammatory mechanisms of 5-HT4 receptor stimulation in POI



(Tsuchida Y et al, 2011)

Original Article

http://dx.doi.org/10.3349/ymj.2013.54.4.845
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 54(4):845-853, 2013

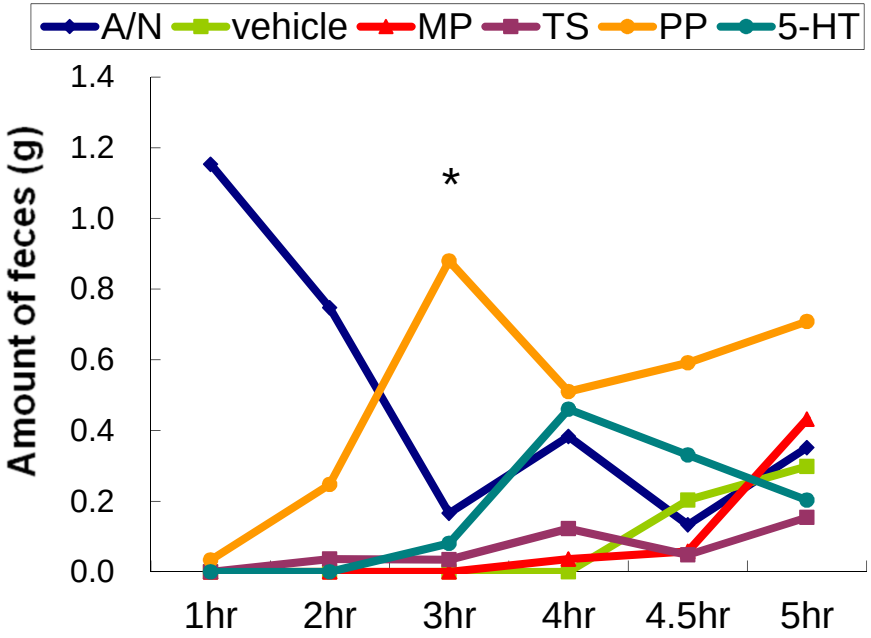
YMJ

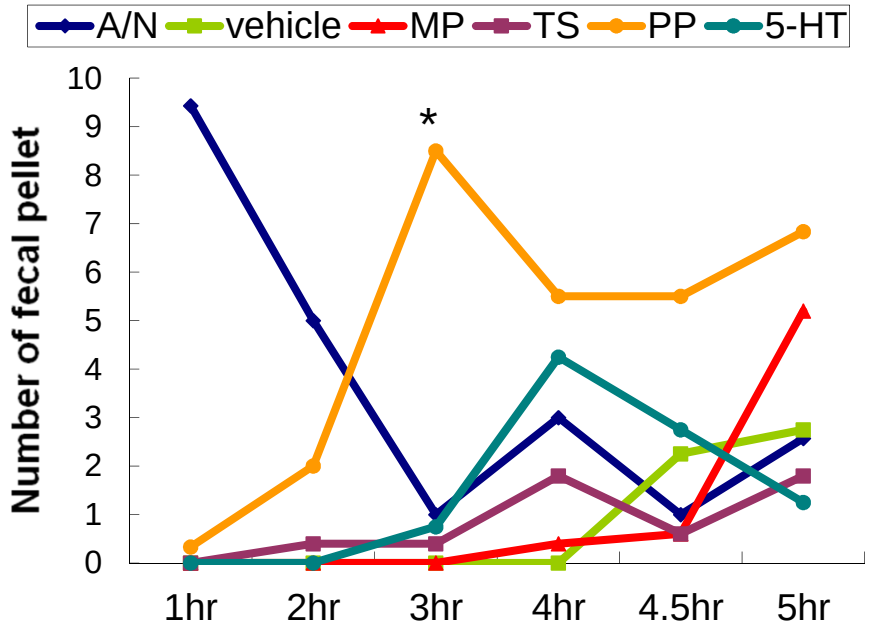
The Effects of Prucalopride on Postoperative Ileus in Guinea Pigs

Soo Jung Park, Eun Ju Choi, Young Hoon Yoon, and Hyojin Park

Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

5-HT$_4$ receptor Agonists in POI
: Fecal pellet expulsion



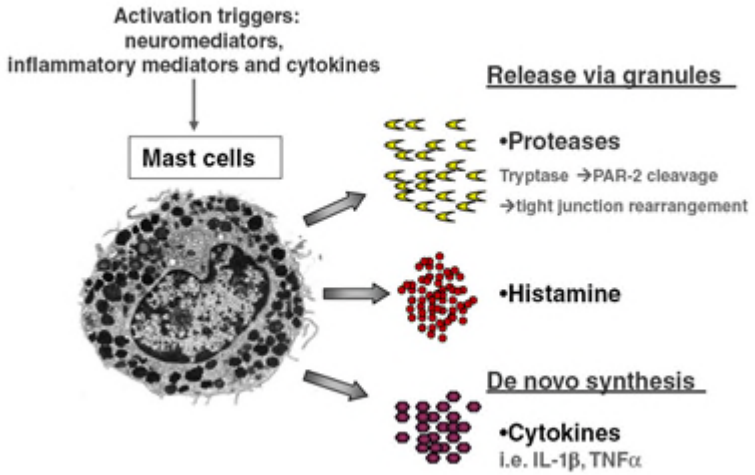


A/N, Anesthesia only; vehicle, POI with vehicle; MP, POI with mosapride;

TS, POI with tegaserod; PP, POI with prucalopride; 5-HT, POI with 5-HT

Mast cell-inflammation cascade may represent a new therapeutic approach for POI

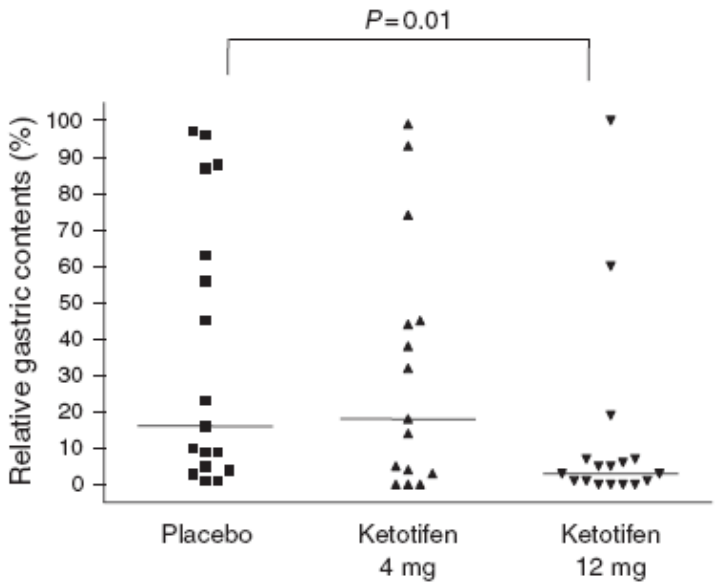
- One of the initial steps attracting inflammatory cells to the site of manipulation is **mast cell degranulation**
- Pretreatment of mice with the **mast cell stabilizing** agents prevents the occurrence of inflammation and normalizes postoperative gastric emptying.



The Role of Mast Cell Stabilization in Treatment of Postoperative Ileus: A Pilot Study

Frans O. The, MD, PhD[1], Marrije R. Buist, MD, PhD[2], Aaltje Lei, BN[1], Roelof J. Bennink, MD, PhD[3], Jan Hofland, MD, PhD[4], René M. van den Wijngaard, PhD[1], Wouter J. de Jonge, PhD[1] and Guy E. Boeckxstaens, MD, PhD[1,5]

(Am J Gastroenterol 2009)

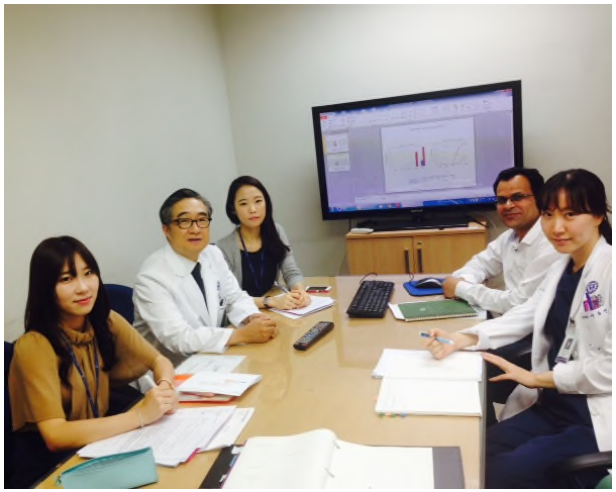


- **Ketotifen** significantly improves gastric emptying after abdominal surgery and warrants further exploration of **mast cell stabilizers** as putative therapy for POI.

Summary & Conclusions

- **Intestinal manipulation** induces **barrier dysfunction** that is to **perpetuate** the **inflammatory** reponse.
- The **increased inflammation** and mucosal **permeability** might play an important role for the **different recovery time** of GI organs in POI.
- **Macrophages and mast cells** initiate and orchestrate the cascade of inflammatory events, these immune cells seem to be the most interesting **targets for treatment** in POI.

감사합니다.
Thank you



GI Motility Research Program