A Rat Model of Ischemic Enteritis

- Pathogenic Importance of Enterobacteria, iNOS/NO, and COX-2/PGE_2 -

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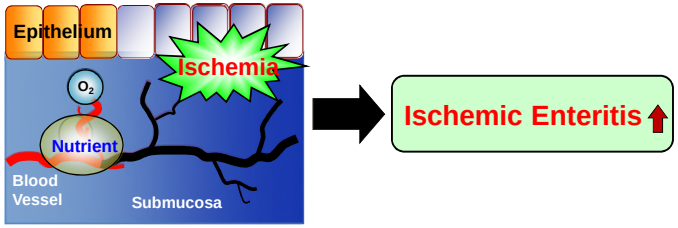
Disclosure of COI

**In relation to this presentation,
I have no conflict of interest that needs
to be disclosed.**

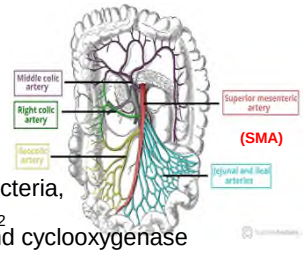
Backgrounds (1)

Ischemic enteritis, one of the most dramatic abdominal emergencies, is caused by a significant decrease of arterial inflow to the small intestine. Patients of various ages are at risk of generating intestinal ischemia since a disorder in the mesenteric circulation may develop as a result of various diseases such as arteriosclerosis and diabetes. The incidence of ischemic enteritis is increasing, and its mortality rate remains very high. However, an animal model of ischemic enteritis that has high clinical predictability has not been available.



Backgrounds (2)

We recently invented a new rat model of ischemic enteritis caused by partial ligation of the superior mesenteric artery (SMA).

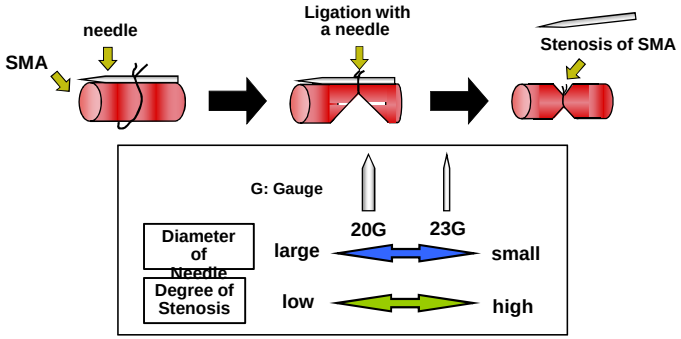


Aim

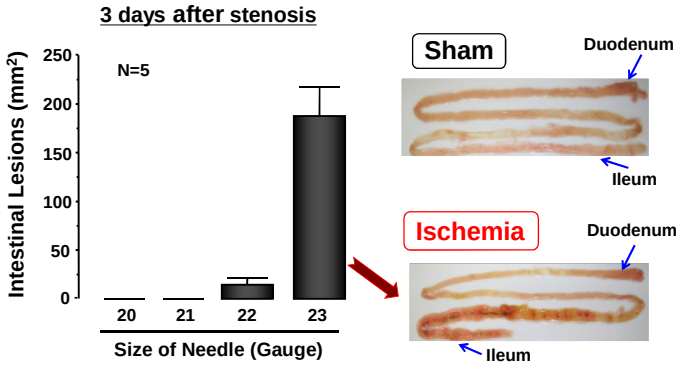
- We introduce a model of ischemic enteritis in rats induced by stenosis of the SMA made by partial ligation.
- We demonstrate the roles of enterobacteria, nitric oxide (NO), and prostaglandin E_2 (PGE_2), together with NO synthase and cyclooxygenase in the pathogenesis of this lesion model.
- We show which EP receptor subtype is responsible for the protective effects of PGE_2 against this model of ischemic enteritis.

Materials and Methods (1)

Induction of Intestinal Ischemia: Male SD rats (200-230 g) were used after 18 h fasting. Under ether anesthesia, the superior mesenteric artery (SMA) was exposed, and a calibrated stenosis was produced by placing a 20-23 guage needle on a blood vessel, ligating both the vessel and needle together, and then removing the needle from the ligature. After operation, the animals were fed normally and killed 1-3 days later, and the small intestines were examined for lesions.



Development of Ischemic Enteritis in Rats after Stenosis of SMA



Materials and Methods (2)

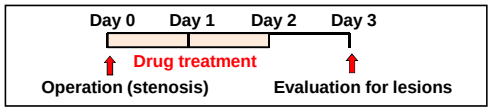
Induction of Ischemia

We used a 23-gauge needle to induce stenosis of the SMA, and investigated the pathogenic roles of various factors in this model of ischemic enteritis.

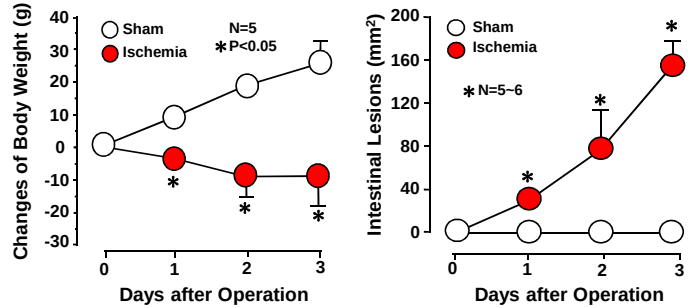
Drugs

- Ampicillin (a broad spectrum antibiotic: 800 mg/kg, p.o.)
- Aztreonam (a gran-negative bacterium-specific antibiotic: 250 mg/kg, p.o.)
- Vancomycin (a gram-positive bacterium-specific antibiotic: 50 mg/kg x 2, p.o.)
- L-NAME (a nonselective NOS inhibitor: 10 mg/kg, s.c.)
- Aminoguanidine (a selective iNOS inhibitor: 20 mg/kg, s.c.)
- Indomethacin (IM: a nonselective COX inhibitor: 0.6 mg/kg, s.c.)
- SC-560 (a selective COX-1 inhibitor: 5 mg/kg, s.c.)
- Rofecoxib (a selective COX-2 inhibitor: 5 mg/kg, s.c.)
- PGE_2 (0.01-0.1 mg/kg, i.p.)
- AE-829 (a selective EP1 antagonist: 3 mg/kg, i.p.)
- AE5-599 (a selective EP3 antagonist: 10 mg/kg, i.p.)
- AE3-208 (a selective EP4 antagonist: 3 mg/kg, i.p.)
- 17-phenyl PGE_2 (a selective EP1 agonist: 0.03 mg/kg, i.p.)
- NT-012 (a selective EP3 agonist: 1 mg/kg, i.p.)
- AE1-329 (a selective EP4 agonist: 1 mg/kg, i.p.)

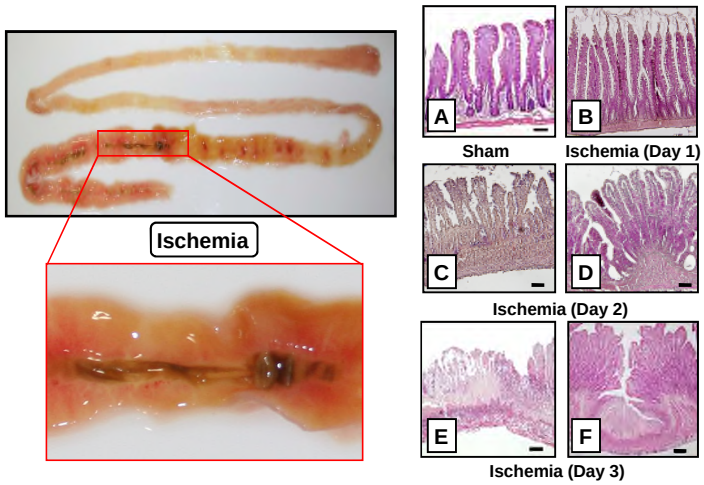
Experimental Schedule



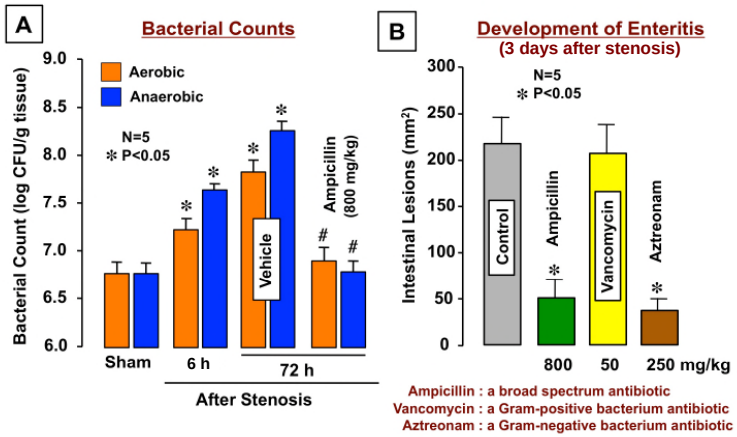
Time-Course Changes in Body Weight (A) and Intestinal Lesions (B) in Rats with or without Stenosis of SMA



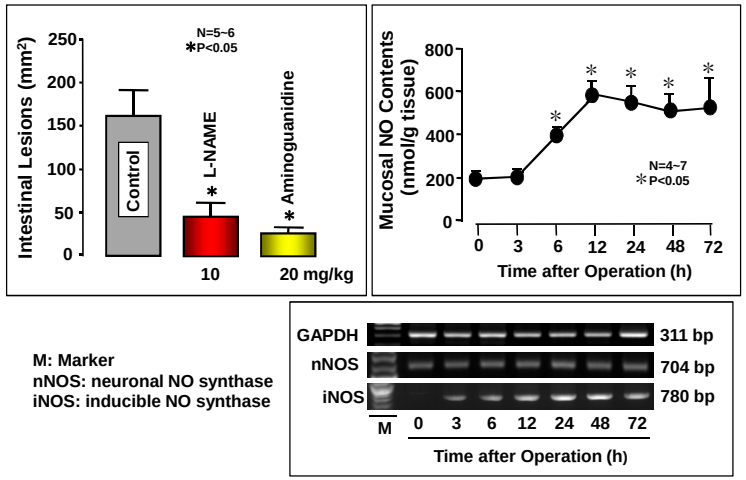
Gross Appearance and Histological Observation of Small Intestine Following Stenosis of SMA



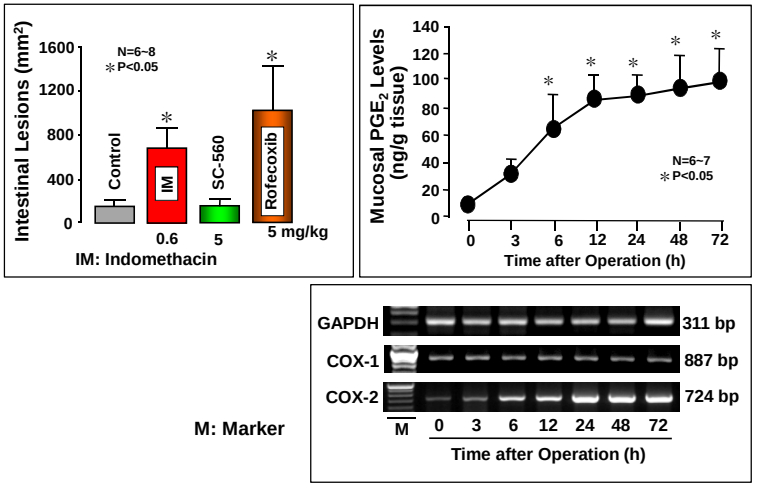
Enterobacterial Invasion in the Small Intestine after Stenosis of SMA (A) and Effects of Various Antibiotics on Ischemic Enteritis caused by the Stenosis (B) in Rats



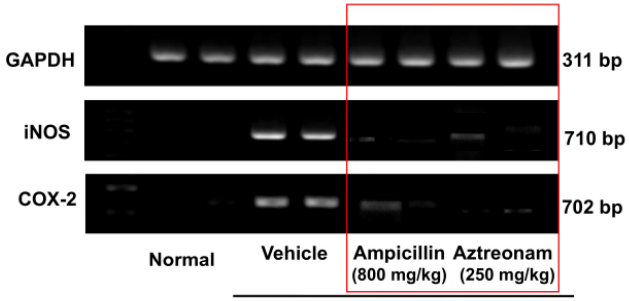
Effects of L-NAME and Aminoguanidine on Ischemia-Induced Enteritis in Rats



Effects of Various COX Inhibitors on Ischemia-Induced Enteritis in Rats

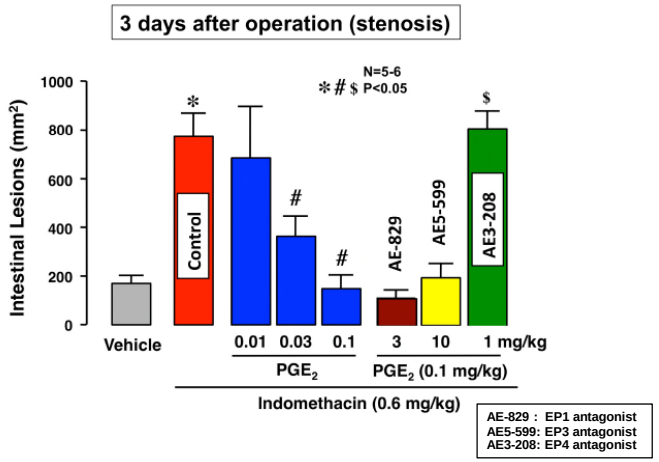


Effects of Ampicillin and Aztreonam on the Expression of iNOS and COX-2 mRNA in the Rat Small Intestine after Stenosis of SMA

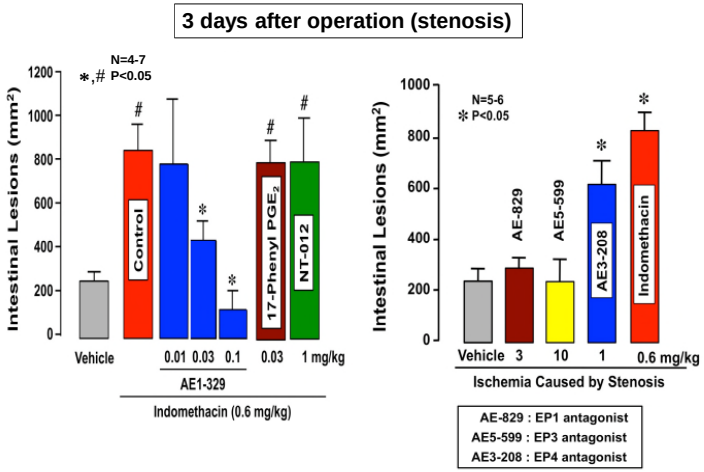


*48 h after operation (stenosis)

Effects of PGE_2 on Aggravation by Indomethacin of Ischemia-Induced Intestinal Lesions in Rats

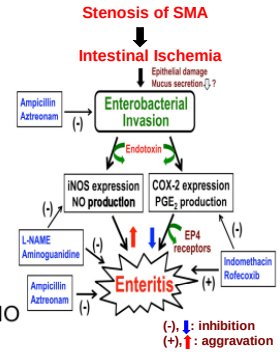


Effects of Various EP Agonists and Antagonists on Ischemia-Induced Intestinal Lesions in Rats



Conclusion

- Intestinal ischemia caused by stenosis of SMA generated intestinal lesions, accompanied by enterobacterial invasion, the up-regulated expression of iNOS and COX-2 in the small intestine, together with increases in the mucosal production of NO and PGE_2.
- The development of these lesions was prevented by repeated treatment with antibiotics as well as iNOS inhibitors, suggesting the involvement of enterobacteria, especially gram-negative bacteria, and iNOS/NO in the pathogenesis of these lesions.



- PGE_2, either administered exogenously or generated endogenously by COX-2, contributes to intestinal mucosal defense during ischemia via the activation of EP4 receptors, while indomethacin or rofecoxib aggravated the ischemic enteritis caused by the stenosis of SMA.
- This model may be useful for screening drugs against ischemic enteritis.

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