

Division of Pathophysiology. Department of Pharmacological Sciences.

Faculty members

Professor; Kenji IIZUKA, M.D., Ph.D.

Associate Professor; Takuji MACHIDA, Ph.D.

Assistant Professor; Sachiko HIRAIDE, Ph.D.

Outline and research fields

Major research projects of pathophysiology division have been focused on following two fields.

1) Vascular smooth muscle pathophysiology & pharmacology

Elevated mechanical stress on blood vessels associated with hypertension has direct effect on the function of vascular endothelial cells and smooth muscle cells. Our laboratory has developed an original design pulsatile pressure-loading apparatus which simulates various hypertension model *in vitro*. By using this apparatus, we are trying to clarify the effect of pressure stress on vascular cell function to gain a deeper understanding of mechanisms of progression of cardiovascular diseases.

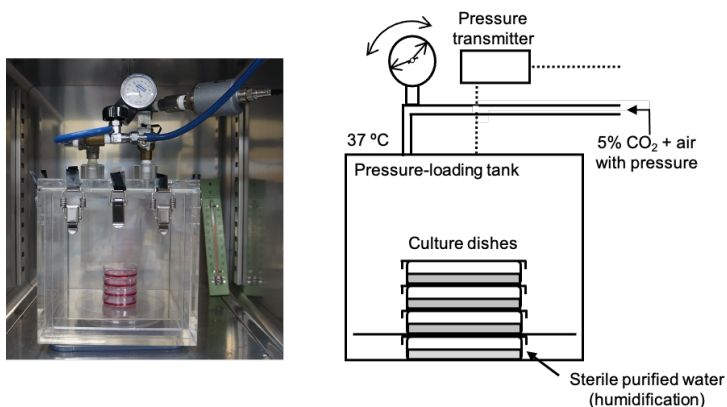


Fig. 1. An original design pulsatile pressure-loading apparatus.

This device allows for applying various pressure conditions to cultured cells.

2) Gastrointestinal pathophysiology & pharmacology

The important gastrointestinal signaling molecule, 5-hydroxytryptamine (5-HT), is critical in the maintenance of intestinal physiology. The changes of 5-HT dynamics in the intestine have important roles for chemotherapy-induced nausea and vomiting. Our laboratory is focused on elucidating the role of 5-HT in the mechanism of anticancer drug-induced delayed emesis. Our laboratory also studies the role of 5-HT in oral iron administration-induced gastrointestinal disorders and sepsis.

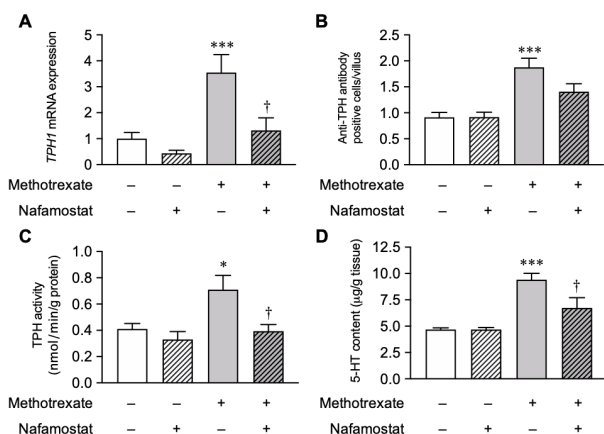


Fig. 2. Effect of nafamostat (1 mg/kg) on methotrexate-induced 5-HT dynamics in rat small intestine.

Current publications

Molecular mechanisms underlying the pathogenesis of septic multiple organ failure. Matsuda N, Machida T & Hattori Y. *Nihon Yakurigaku Zasshi* 159;101–106, 2024.

Impaired monoamine neural system in the mPFC of SHRSP/Ezo as an animal model of attention-deficit/hyperactivity disorder. Suzuki N, Hiraide S, Shikanai H, Isshiki T, Yamaguchi T, Izumi T & Iizuka K. *J Pharmacol Sci.* 154;61–71, 2024.

Pressure stress delays cyclooxygenase-2 expression induced by interleukin-1 β in cultured human pulmonary artery smooth muscle cells. Hiraide S, Machida T, Takihana S, Ohshita M & Iizuka K. *Heliyon* 9;e21008, 2023.

Consideration of the characteristics of oral iron preparations from the viewpoint of the mechanism of nausea and vomiting. Machida T & Iizuka K. *Yakugaku Zasshi* 143;599–606, 2023.

Low-dose nafamostat mesilate ameliorates tissue injury and inhibits 5-hydroxytryptamine synthesis in the rat intestine after methotrexate administration. Yamamoto T, Machida T, Tanno C, Hasebe S, Tamura M, Kobayashi N, Hiraide S, Hamaue N & Iizuka K. *J Pharmacol Sci.* 152;90–102, 2023.

Ferric citrate hydrate has little impact on hyperplasia of enterochromaffin cells in the rat small intestine compared to sodium ferrous citrate. Machida, T., Hiraide, S., Yamamoto, T., Shiga, S., Hasebe, S., Fujibayashi, A. & Iizuka K. *Pharmacology* 107;574–583, 2022.

Noradrenaline increases intracellular Ca²⁺ concentration in epithelial cells via α 2-adrenoceptors in isolated mouse ileal crypts. Kimyo, T., Machida, T., Iizuka K., Minami, M. & Hirafuji, M. *J Pharmacol Sci.* 148;337–341, 2022.

Methotrexate mediates the integrity of intestinal stem cells partly through nitric oxide-dependent Wnt/ β -catenin signaling in methotrexate-induced rat ileal mucositis. Machida, M., Machida, T., Kikuchi, M., Shimizu, A., Ida, S., Tawaraya, Y., Kato, R., Haramaki, K., Yama, K., Shiga, S., Hirafuji, M. & Iizuka, K. *J Pharmacol Sci.* 148;281–285, 2022.

Methotrexate induces hyperplasia of enterochromaffin cells in mouse jejunum. Machida, T., Tanaka, A., Kobayashi, M., Imai, K., Hirafuji, M. & Iizuka K. *BPB Reports.* 4:112–115, 2021.

Administration of cyclophosphamide to rats induces pica and potentiates 5-hydroxytryptamine synthesis in the intestine without causing severe intestinal injury. Kamiya, A., Machida, T., Hirano, M., Machida, M., Shiga, S., Hamaue, N., Hirafuji, M. & Iizuka K. *J Pharmacol Sci.* 147:251–259, 2021.

Abnormal pressure stress reduces interleukin-1 β -induced cyclooxygenase-2 expression in cultured rat vascular smooth muscle cells. Machida, T., Endo, H.E., Oyoshi, R., Yutani, M., Machida M., Shiga, S., Murakami, H., Hiraide, S., Hirafuji, M. & Iizuka K. *Biol Pharm Bull.* 44:853–860, 2021.

Effects of nafamostat mesilate on 5-hydroxytryptamine release from isolated ileal tissues induced by anti-cancer drugs in rats. Kikuchi, K., Hamaue, N., Machida, T., Iizuka K., Minami, M., & Hirafuji, M. *Biomed Res.* 41:253–257, 2020.

【 Education Field 】

Pharmacotherapeutics

Pharmacology

Pathophysiology

【 Research Field 】

Vascular pharmacology

Gastrointestinal pharmacology

Pathophysiology

Neuropsychopharmacology

Cardiology