Transient receptor potential channel is a target for extracted Japanese herbal medicine, Daikenchuto

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INTRODUCTION

Kampo
Kampo has a history of 500 years of clinical use in Japan, however, only in the last 30 years has the Japanese government officially recognized Kampo as a valid form of treatment alongside Western medicine. Japanese physicians are the only licensed medical practitioners who are capable of prescribing conventional Western drugs and Kampo; thus, they shoulder the responsibility of establishing basic and clinical EBM to disseminate Kampo worldwide.

Daikenchuto
Daikenchuto (TU-100), a most popular Kampo, is orally used to improve paralytic postoperative ileus, being submitted for FDA approval as a new medicine. Recently, a placebo-controlled double-blind clinical trial in Mayo Clinic showed that TU-100 significantly increased intestinal motility. Contrary to herbal medicinal products of many countries, traditional Japanese medicines are primarily extract granules and their pharmacological actions have been elucidated at the molecular level. The objective of this presentation is to introduce TU-100 and provide evidence based information on Kampo.

Transient receptor potential channel
Transient receptor potential channels (TRP channels) are a group of ion channels located mostly on the plasma membrane of numerous human and animal cell types. Many of these channels mediate a variety of sensations like the sensations of pain, hotness, warmth or coldness, different kinds of tastes, pressure, and vision. Some TRP channels activated by molecules found in spices like garlic (allicin), chilli pepper (capsaicin), wasabi (allyl isothiocyanate); others are activated by menthol, camphor, peppermint, and cooling agents. (by Wikipedia)

Daikenchuto and TRP channel
Biological roles of transient receptor potential A1 (TRPA1) in the nociceptive sensory neurons are well studied, but those of TRPA1 in intestinal epithelial cell are not understood. Some pungent plant ingredients such as allyl isothiocyanate (AITC) and cinnamaldehyde (CNA) are known to be specific activator of TRPA1 channel. We previously reported that TU-100 increased the intestinal blood flow via release of adrenomedullin (ADM), a vasodilatory peptide, from intestinal epithelial cells, and that one of the active ingredients was hydroxy-α-sanshool. This compound is known as an activator of TRPV1 and TRPA1. Therefore, we examined expression of TRP channels in intestinal epithelial cells, and investigated which TRP channel is critical to response to TU-100.

Crohns’ disease
Anastomotic recurrence after bowel resection is a major problem in Crohn's disease (CD) surgery. Anastomotic recurrence after resection in CD may be related to ischemia
caused by microvascular dysfunction in bowel of CD at the anastomosis. Therefore, we also investigated whether hydroxy-α-sanshool improve intestinal microvascular dysfunction in CD via TRP channel.

METHODS
TRPV1 activators (capsaicin, 6-gingerol and anandamide), TRPA1 activators (AITC and CNA), or TU-100 were added to culture of IEC-6 cell line, rat intestinal epithelial cell. ADM content in 24 h culture fluid was measured by EIA method. Gene knockdown of TRP channel was performed following siRNA protocol provided by Dharmacon Inc. Expression of ADM and TRP channels in intestinal epithelial cell was determined by immunostain method. Intestinal blood flow of rat large intestine was measured using laser Doppler blood flowmetry. Colitis was induced by rectal instillation of trinitrobenzene sulfonic acid (TNBS) into rats.

RESULTS
ADM production was prominently enhanced by addition of the respective TRPA1 activators, while TRPV1 activators did not affect to ADM production. TU-100 increased ADM as previously reported. The ADM enhancement of TRPA1 activator or TU-100 was significantly reduced by treatment with TRPA1-specific, but not TRPV1-specific siRNA. Immunostain analysis revealed that ADM and TRPA1 channel were expressed in IEC-6 cell and intestinal epithelial cells isolated from rat small and large intestines. Luminal administration of CNA or TU-100 into large intestine showed remarkable increase of blood flow in TNBS-treated animals. This vasodilatory effect of CNA and TU-100 was completely abolished by co-administration with selective TRPA1 antagonist HC-030031, but not by selective TRPV1 antagonist BCTC or other TRP channel antagonists.

CONCLUSIONS
Our study indicates that TRPA1 channel acts as a sensor molecule for intestinal epithelial cells, and regulates bowel blood flow. TU-100 increased bowel blood flow via up-regulation of ADM from intestinal epithelial cell as a result of activating TRPA1 channel, providing an agent to improve ischemia-related gastrointestinal disorders including ischemic colitis and CD.

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