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Comparison of the Effect of Kampo Medicines, Dai-Kenchu-To, Ninjin-To, Keishi-Ninjin-To, and Bishi-Richu-To of Levels of Gut-Regulated Peptides in Human Plasma

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Abstract

The traditional herbal (Kampo) medicines are empirically used to treat chronic hypofunction of the gastrointestinal tract. But the action mechanism is not well understood. So, we examined the effects of four Kampo medicines on plasma levels of five neuro peptides. We hypothesized that Ninjin-to and Bushi-richu-to might promote peristaltic reflex, Dai-kenchu-to, Ninjin-to, Keishi-ninjin-to, and Bushi-richu-to might have gastro protective effect by increase of mucosal blood flow

Keywords: Kampo medicine; Gut-regulatory peptide; Mucosal protection; Gastrointestinal motility

Introduction

The traditional herbal (Kampo) medicines are empirically used to treat chronic hypofunction of the gastrointestinal system, but they still require scientific clarification of action mechanism and objective clinical evaluations. Among these medicines, Dai-kenchu-to, Ninjin-to, Keishi-ninjin-to, and Bushi-richu-to contain the same constituents, but the clinical indications are quite different. At present, the action mechanism is not well understood.

In recent years, there are some reports that Kampo medicines to treat gastrointestinal diseases have been elucidated pharmacologically from the viewpoints of gastrointestinal peptide [motilin, somatostatin, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide (CGRP), and substance P] levels [1,2].

One of the gastrointestinal motility regulatory factors on those empirical effects has been assumed to be the induction of changes in the levels of peptides (motilin somatostatin, and VIP) in plasma. On the gastroprotective function as a neural emergency system, sensory afferent neurons in the gastrointestinal mucosa regulated neuropeptides (CGRP and tachykinins (substance P etc.)) levels and play various physiological roles. Motilin is a powerful inducer of gastrointestinal motor activity in the fundus and the antral pouch of the stomach. It plays an important physiological role in intestinal contractility, and is one of the most important factors controlling the regular occurrence of phase-3 contractions of migrating motor complex (MMC) [3]. Somatostatin is broadly distributed in the pancreatic islet, the gastrointestinal tract and the central nervous system. Somatostatin participates in regulating gastrointestinal motility. In the intestine, somatostatin stimulates peristalsis [4]. This peptide is associated with a mechanism of gastrointestinal motility involving the cholonergic nervous system. VIP is widely distributes in the central and peripheral nervous system. This peptide has vasodilating effect and increased blood flow, but there is a report that VIP may inhibit gastrointestinal motility. CGRP is a powerful vasoactive substance, which is released from the sensory afferent nerve endings against gastric mucosal injury in the stomach, and increases gastric mucosal flow as a gastro protective factor. Substance P, tachykinins, coexists with CGRP in the sensory afferent neurons of the gastrointestinal mucosa, and is released with acetylcholine in response to depolarizing stimuli in the enteric nerve system [5]. The purpose of this study is to examine the effects of four Kampo medicines (Dai-kenchu-to, Ninjin-to, Keishi-ninjin-to, Bushi-richu-to) on plasma levels of gastrointestinal peptides (motilin-, somatostatin-, VIP-, CGRP- and substance P-immunoreactive substance (IS)).

Results and Discussion

Dai-kenchu-to (7.5 g), Ninjin-to (6.0 g), Keishi-ninjin-to (6.0 g), Bushi-richu-to (4.5 g) or

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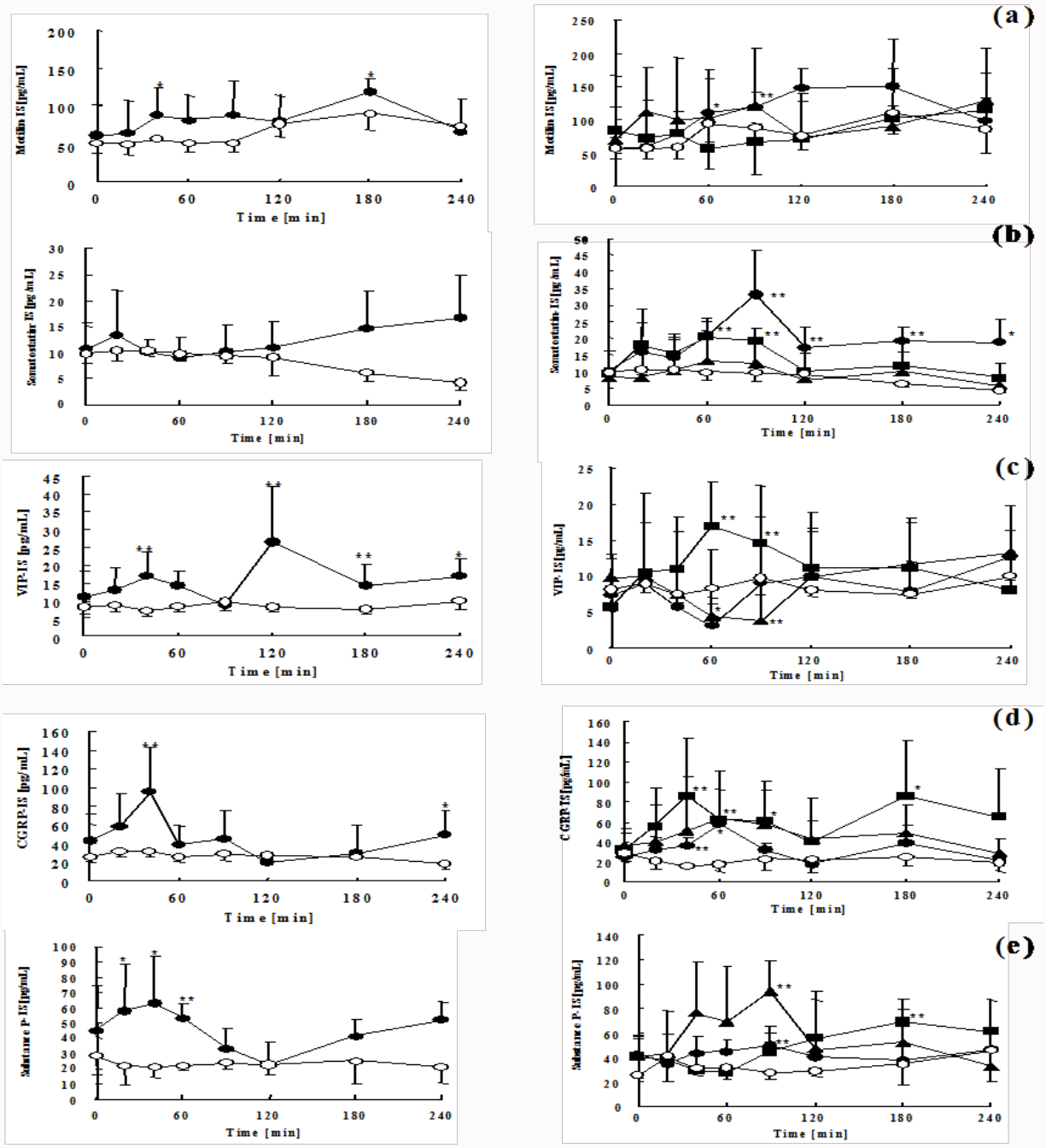

Figure 1: Effect of Dai-kenchu-to (left ●), Ninjin-to (right ●), Keishi-ninjin-to (▲), Bushi-richu-to (■) or placebo (○) on plasma motilin- (a), somatostatin- (b), VIP- (c), CGRP- (d), and substance P-IS (e). Each value represents the mean±S.D.

placebo was orally administered in five healthy male volunteers aged 25-29 years. Venous blood samples were taken before and till 240 min after administration. Plasma peptide levels were measured using a sensitive enzyme immunoassay.

Figure 1 shows the effect of Dai-kenchu-to, Ninjin-to, Keishi-ninjin-to, and Bushi-richu-to on gastrointestinal peptides after administration of the drugs. Dai-kenchu-to caused significant ($P < 0.05$ or $P < 0.01$) increase in motilin-, and VIP-IS at 40 and 180 min, and 40 and 120-240 min compared with the response of the placebo group, respectively. Dai-kenchu-to had no effect on plasma somatostatin-IS levels compared with the placebo group. Compared with the response of the placebo group, Ninjin-to caused significant increase in motilin- and somatostatin-IS at 60-90 min and 90-240 min, respectively. Keishi-ninjin-to trasiently decreased VIP-IS levels at 60-90 min. Bushi-richu-to caused increases in somatostatin- and VIP-IS levels at 60-90 min, and 60-90 min, respectively.

Figure 1 shows the effect of Dai-kenchu-to, Ninjin-to, Keishi-ninjin-to, and Bushi-richu-to on gastrointestinal mucosal regulated neuropeptides after administration of the drugs. All drugs caused significant increase in CGRP- and substance P compared with the placebo group.

Dai-kenchu-to and Ninjin-to caused significant increase of

motilin-IS. Molitin participates in regulating gastrointestinal motility, and stimulates gastric emptying and postprandial gastric contraction. We thought that both drugs have prokinetic effect.

Ninjin-to and Bushi-richu-to caused significant increase of somatostatin-IS. Somatostatin participates in the control of gastrointestinal motility by exerting both inhibitory and stimulating influences. Increased somatostatin might correspond with gastrointestinal motor regulation including the accelation of gastric emptying and peristaltic reflex, by these drug. Dai-kenchu-to and Bushi-richu-to caused significant increase of VIP-IS. VIP has a vasodilating effect and increases peripheral blood flow. VIP is also known as a major regulator of mammalian intestinal motility and induces relaxation of precontracted ileal longitudinal muscle, and mediates its peristaltic. It is known that both drugs enhance gastrointestinal motility and improve a peripheral and uncomfortable feeling of cold. The effects of both drugs might be due to changes of VIP-IS. On the other hand, Keishi-ninjin-to transiently decreased VIP-IS levels. This drug has the pharmacologic effects for waterly and infectious diarrhea. VIP plays an important role for the nervous control of the intestinal fluid secretion. The intestinal fluid secretion by VIP increases during diarrhea. Thus Keishi-ninjin-to might act in the gastrointestinal system, and part of its antidiarrheal action might be closely related to changes in VIP-IS levels in plasma.

All drugs caused increases in CGRP- and substance P-IS. Both CGRP and substance P are the major components of the afferent peptidergic innervation of the gastrointestinal tract, and are widely distributed around blood vessels. Recently, there are also many reports that capsaicin-sensitive afferent nerve All drugs caused increases in CGRP- and substance P-IS. Both CGRP and substance P are the major components of the afferent peptidergic innervation of the gastrointestinal trac, and are widely distributed around blood vessels. Recently, there are also many reports that capsaicin-sensitive afferent nerve is related to improve mucosal blood flow closely. Stimulation of the nerve causes the release of CGRP and substance P from the nerve endings. The result of this study was supported that the protective effects of these drugs might be caused by stimulating capsaicin-sensitive afferent nerves. All of these drugs also contains Zingiberis rhizome as one of its gradients. This herb contains 6-gingerol and 6-shogaol as bioactive components. It was reported that intraduodenal administration of 6-shogaol increases intestinal blood flow in a dose-dependent manner that is mainly mediated by CGRP [6]. Accordingly, Dai-kenchu-to, Ninjin-to, Keishi-ninjin-to, and Bush-richu-to may directly stimulate CGRP- and substance P-containing nerves or indirectly secrete these peptides accompanied by the stimulation of other secretory cells and mechanisms. And Zingiberis rhizome might be closely related, at least in part, to the release of CGRP and substance P in the autonomic system.

In conlusion, we hypothesized that Dai-kenchu-to, Ninjin-to and Bushi-richu-to might promote peristaltic reflex, and Dai-kenchu-to and Ninjin-to might accelerate gastric emptying, but Keishi-ninjin-to might regulate fluid secretion. Furthermore, on gastro protective effect, Dai-kenchu-to, Ninjin-to, Keishi-ninjin-to, and Bushi-richu-to might increase mucosal blood flow *via* capsaicin-sensitive afferent nerve.

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