Table 5: Reasons for discontinuation of therapy.

	Group A, Pts (%)	Group B, Pts (%)	Group C, Pts (%)	Group D, Pts (%)	Total, Pts (%)
Progressive disease	2 (18.2)	1 (7.1)	1 (4.8)	9 (20.5)	13 (14.4)
Others					
Neuropathy	0	6 (42.9)	4 (19.0)	10 (22.7)	20 (22.2)
Myelosuppression	2 (18.2)	1 (7.1)	0	3 (6.8)	6 (6.7)
Allergy	0	0	2 (9.5)	3 (6.8)	5 (5.6)
Other toxicities	1 (9.1)	2 (14.3)	7 (33.3)	9 (20.5)	19 (21.1)
Resection	1 (9.1)	2 (14.3)	3 (14.3)	1 (2.3)	7 (7.8)
Patient refusal	0	1 (7.1)	0	0	1 (1.1)
Change of therapy	0	0	0	5 (11.4)	5 (5.6)
Continuing	5 (45.5)	1 (7.1)	4 (19.0)	4 (9.1)	14 (15.6)

Group A, GJG; Group B, Ca/Mg; Group C, GJG + Ca/Mg; Group D, no therapy.
GJG, goshajinkigan; Ca, calcium gluconate; Mg, magnesium sulfate.

Table 6: Tumor response to treatment (RECIST).

	Group A	Group B	Group C	Group D
CR	0	0	0	0
PR	6	5	9	20
SD	4	5	10	19
PD	1	3	1	3
NE	0	1	1	2
Response Rate	6 (54.5%)	5 (35.7%)	9 (42.9%)	20 (45.5%)
(CR+PR)	(P = .589)	(P = .522)	(P = .844)	
Disease Control Rate	10 (90.9%)	10 (71.4%)	19 (90.5%)	39 (88.6%)
(CR+PR+PD)	(P = .829)	(P = .121)	(P = .823)	

Group A: GJG, Group B: Ca/Mg, Group C: GJG+Ca/Mg, Group D: no therapy.
CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: no evaluate.
P-values are for Groups A, B, and C versus. Group D by the χ^2-test.
GJG: goshajinkigan, Ca: calcium gluconate, Mg: magnesium sulfate.

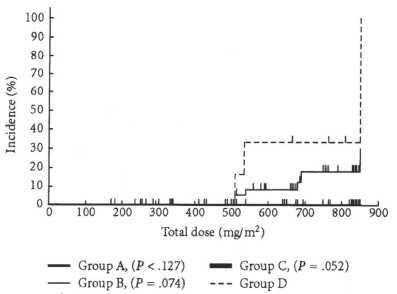

Figure 3: Kaplan-Meier analysis of Grade 3 peripheral neuropathy in relation to the total dose of oxaliplatin. Group A, GJG; Group B, calcium gluconate (Ca) and magnesium sulfate (Mg); Group C, GJG + Ca/Mg; Group D, no therapy. P-values are for comparison to Group D with the log-rank test.

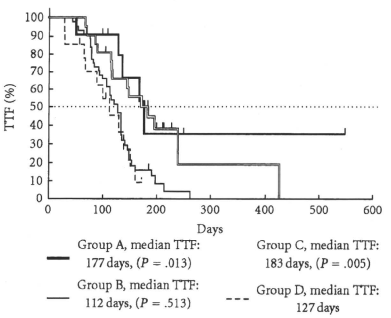

Figure 4: Kaplan-Meier analysis of TTF. Group A, GJG; Group B, calcium gluconate (Ca) and magnesium sulfate (Mg); Group C, GJG + Ca/Mg; Group D, no therapy. P-values are for comparison to Group D with the log-rank test.

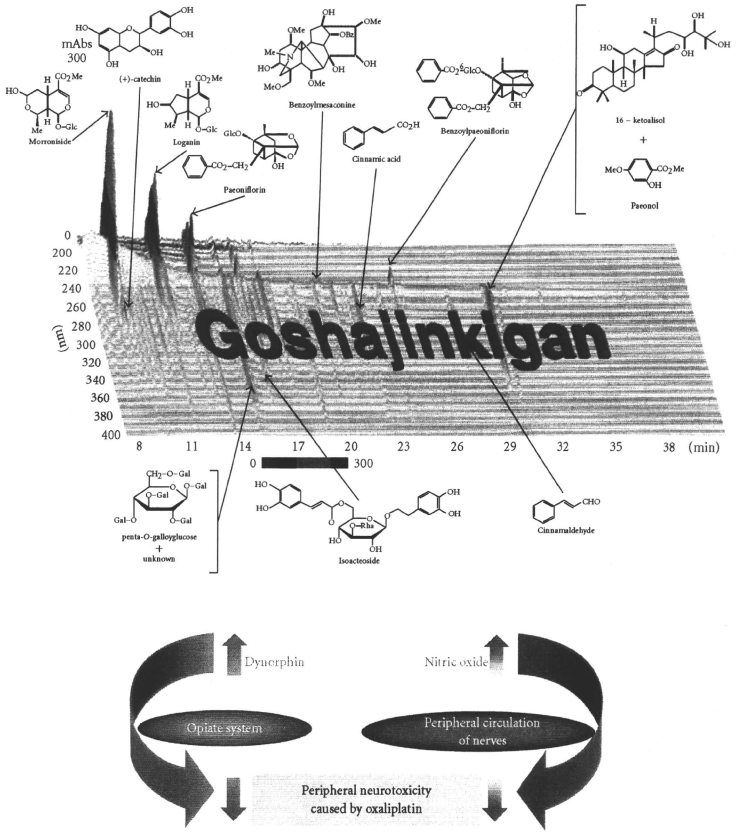

FIGURE 5: Two mechanisms of pharmacological actions of GJG for peripheral neurotoxicity. This shows a representative 3D high performance liquid chromatography of the GJG formulation. Two mechanisms are suggested by which GJG may alleviate peripheral neurotoxicity caused by oxaliplatin.

4. Discussion

Peripheral neurotoxicity is a characteristic adverse effect of oxaliplatin [20]. It is a major obstacle to continuing treatment with regimens that contain this agent; for example, FOLFOX. The main symptoms of peripheral neurotoxicity are typically paresthesia and dysesthesia of the extremities induced by exposure to cold. These symptoms occur in 85%–95% of patients, and the symptom duration becomes longer with increasing repetitions of chemotherapy courses. It has been shown that an increase in the total dose of oxaliplatin leads to the occurrence of pain and sensory dysfunction. De Gramont et al. [5] reported that functional impairment occurred in 10% of patients at a total oxaliplatin dose of 850 mg m^{-2}, and this increased to 20% at a total dose of 1020 mg m^{-2}. Thus, it is important to control peripheral neurotoxicity in order to allow continued administration of oxaliplatin. However, control of this side effect is difficult, because the mechanisms underlying the development of neuropathy have not been clarified.

Gamelin et al. [6] suggested that a possible mechanism may be the effect of oxalate, a metabolite of oxaliplatin, on neuronal sodium channels. However, based on this hypothesis, treatment with a sodium channel blocker did not achieve satisfactory results [20]. This suggested that sodium channels may only be involved in acute peripheral neurotoxicity. Neuronal damage has also been attributed to the accumulation of platinum in the dorsal root ganglion based on the results from animal experiments [20]. Thus multiple mechanisms may be involved.

GJG is comprised of 10 herbs and each contains numerous active ingredients (Figure 5). Thus, in Western medical terms, GJG is a complex drug, and its overall pharmacological action is difficult to explain. Until recently, many Japanese people harbored prejudice toward Kampo medicine, doubted their efficacy and showed little interest in their mechanisms [21]. This ignorance of the potential benefits of some herbal medicines is hardly a rare phenomenon, because skeptics of herbal medicine abound wherever herbal medications are used, although herbal medicine has been used throughout the world since time immemorial [22]. Two mechanisms have been suggested by which GJG may alleviate peripheral neurotoxicity (Figure 5) [23–25]. The first is that GJG promotes the release of dynorphin, and thus improves numbness/pallesthesia via the opiate system. The second is that GJG promotes nitric oxide production, and thus improves the circulation and the blood supply to the nerves.

The present study was a retrospective analysis of peripheral neuropathy inhibition in patients that received FOLFOX therapy combined with GJG, Ca/Mg, GJG + Ca/MG or no concomitant drug. Although the number of patients was small, we found that the incidence of peripheral neuropathy was markedly lower in the groups that received GJG when compared with those that did not receive GJG; moreover, there was no Grade 3 peripheral neuropathy in the patients given GJG. In addition, more courses of chemotherapy could be given to patients that received GJG than to those not given GJG; thus, the former also received a higher total dose of oxaliplatin. Furthermore, the TTF was longer in patients that received GJG and there were fewer discontinuations due to peripheral neuropathy than for the other groups. In the group of patients given GJG alone (Group A), almost half the patients had continued oxaliplatin therapy throughout the study, and none discontinued treatment due to peripheral neurotoxicity. Group A showed a higher discontinuation due to hematological toxicity than the other groups. As far as we know, it has never been reported that hematological toxicity was observed in the patients who used GJG in Japan. GJG has been safely used for 25 years in Japan for the improvement of symptoms of numbness, cold sensation and pain of the extremities associated with diabetic neuropathy [12–15]. Therefore, hematological toxicity is not likely to have theadverse effect of GJG. The reason why Group A showed a higher discontinuation due to hematological toxicity is probably because Group A patients received higher dose of total oxaliplatin and 5-FU than other groups. In addition, that group had higher tumor response rates and disease control rates than the other groups, indicating that GJG treatment did not impair anti-tumor activity. Based on these results, we concluded that concomitant administration of GJG contributed to the inhibition of peripheral neurotoxicity and prolonged treatment with oxaliplatin.

Several authors have previously reported suppression of peripheral neurotoxicity by Ca/Mg; however, we could not confirm this effect in this study. In fact, the patients that received GJG + Ca/Mg developed worse neuropathy than those that received GJG alone. Accordingly, we suggest that GJG alone (rather than combined with Ca/Mg) may be more effective for suppression of peripheral neurotoxicity. In addition, the tumor response rate was lower in the group that received GJG + Ca/Mg than in the other groups; this suggested that some interaction may have occurred when GJG and Ca/Mg were combined.

A limitation of the present study was that it was a retrospective review. Also, the number of patients was small, and some of the baseline characteristics differed between the groups. Nevertheless, our findings suggested that the peripheral neurotoxicity of oxaliplatin could be suppressed by administration of GJG. It will be necessary to confirm the usefulness of GJG by performing larger prospective studies in the future [26].

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8. Endogenous calcitonin gene-related peptide and adrenomedullin are target peptides for Daikenchuto (Da-Jian-Zhong-Tang), an extracted traditional Japanese medicine -New possibility for Crohn's disease management-

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Abstract. Daikenchuto (DKT) is a Japanese herbal medicine (Kampo) and is a mixture of extract powders from dried *Japanese pepper, processed ginger, ginseng radix* and *maltose powder*, and has been commonly used for treatment of bowel disorders, including postoperative ileus, adhesive bowel obstructions and Crohn's disease (CD) in Japan. Experimental evidence reveals the mechanisms that DKT increases gastrointestinal motility by an up-regulation of the calcitonin gene-related peptide (CGRP) as well as acetylcholine release and plasma motilin. CGRP, a member of calcitonin family peptides, is the most powerful vasoactive substance that is expressed in a large population of sensory neurons supplying the gut, and is considered to serve as an important

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protective mechanism for maintaining mucosal integrity. Moreover, CGRP cross reacts another calcitonin family peptide, adrenomedullin (ADM)(ADM/CGRP system). ADM is ubiquitous in gastrointestinal tract, and plays important role for the regulation of microcirculation, angiogenesis, antifibrosis, antibiosis, and down-regulation of proinflammatory cytokines. DKT attenuated dysfunction of microcirculation, mucosal damage and intestinal adhesion, and inhibited mucosal proinflammatory cytokines, including TNFα, in a CD animal model via up-regulation of ADM/CGRP system. DKT may be a unique therapeutic agent for bowel disorders as an ADM/CGRP system-enhancer.

Introduction

Herbal medicine has been used not only in eastern world but also western world since time immemorial. According to the data from 2007 National Health Interview Survey of 24,000 persons conducted by the Center for Disease Control and Prevention's National Center for Health Statistics, approximately 20% of U.S. adults reported use of herbal supplements [1]. Results from the latest American hospital association annual survey revealed that 60% of the hospitals did not provide complementary alternative medicine (CAM) therapies which include herbal medicine. Probable reasons for the low use of CAM in hospitals included lack of convincing, evidence-based information on herbal medicine for physicians. Over the last few years, the Food and Drug Administration (FDA) began shifting its focus on traditional Japanese medicines (called "Kampo") whose exceptionally high quality and standardized ingredients were noteworthy of their attention.

Traditional Japanese medicines are primarily extract granules and their pharmacological actions have been studied and elucidated at the molecular level contrary to herbal medicinal products from many other less well-regulated countries. Until recently, many Japanese people harbored prejudice toward Kampo medicine, doubted their efficacy and showed little interest in their mechanisms. This ignorance of the potential benefits of some herbal medicines is hardly a rare phenomenon, because skeptics of herbal medicine abound wherever herbal medications are used.

Daikenchuto

Daikenchuto (DKT)(Da-Jian-Zhong-Tang), a distinctively unique traditional Japanese medicine, is the most frequently prescribed traditional medicine in Japan, especially in Japanese gastroenterological surgeons. Those Chinese characters translate as, "to reconstruct strongly the diseased gastrointestinal tract to the health" Fig. 1.

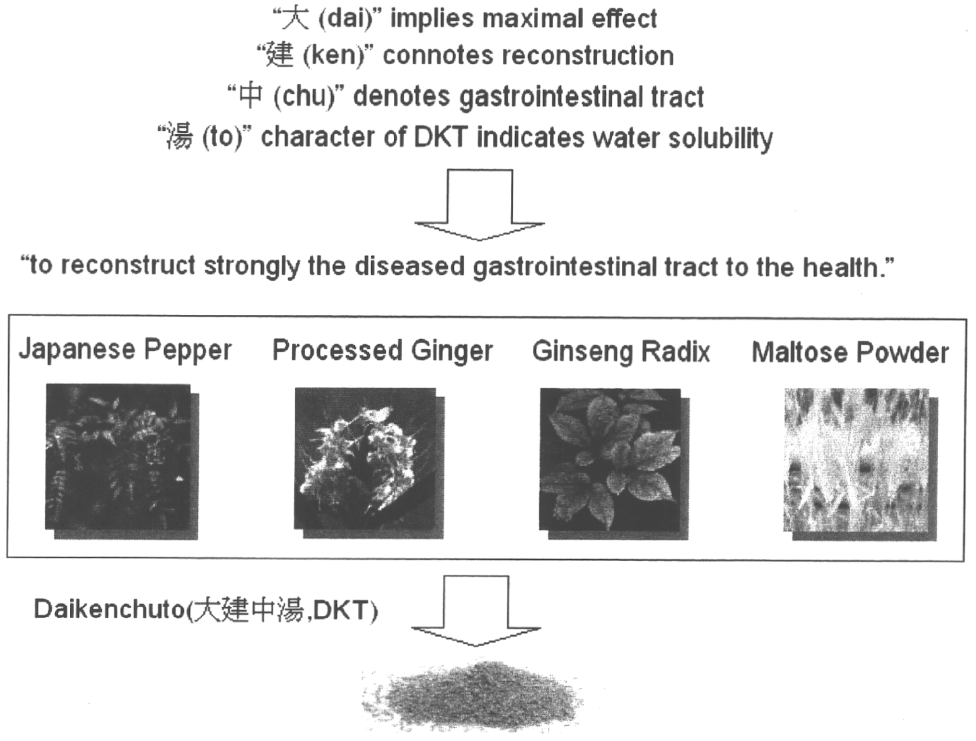

Figure 1. Daikenchuto (Da-Jian-Zhong-Tang).

DKT has been prescribed for abdominal discomfort including pain, distention, and coolness of the abdomen and Japanese government insurance started to cover the medical fee of DKT since 1986. Approximately 500 million DKT sachets (2.5 g) are prescribed annually in Japan, and major adverse events have not been reported to date. DKT has been in the Japanese market for several decades with proven effectiveness for bowel disorders and very few side effects [2]. Although the actual incidences of DKT-related adverse events have not been investigated, 36 cases of minor side effects have been reported by the medical institutions from 1992 to 2007. Our recent study revealed the mechanism of DKT effects at the molecular level [3]. Therefore, a multicenter, double-blind, placebo-controlled study of DKT involving 80% of nationwide university hospitals was launched to explicate the benefits and mechanism of actions of DKT at the clinical level. Results from these large-scale studies are highly anticipated. The objective of this chapter is to introduce the experimental evidence-based information of DKT and to address the concept of appropriate use of DKT.

The formulation of DKT is composed of extract granules of *Japanese pepper*, *processed ginger*, *ginseng radix*, and *maltose powder from rice* (Fig. 1).

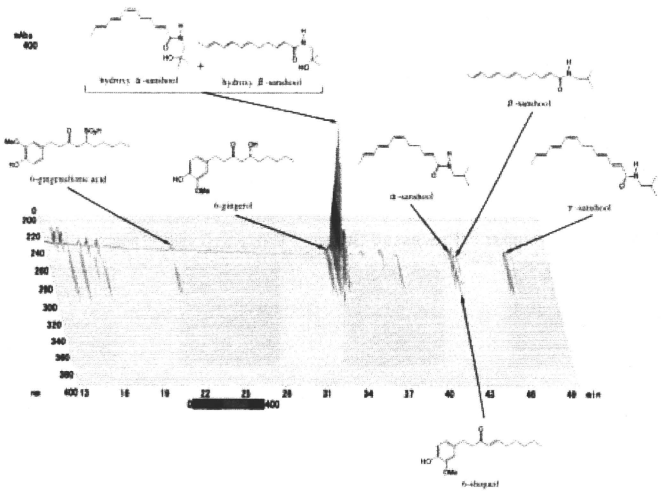

Figure 2. Three-dimensional high-performance liquid chromatography of Daikenchuto.

DKT extract powder (Tsumura Co., Tokyo, Japan) is manufactured as an aqueous extract containing 2.2% *Japanese pepper*, 5.6% *processed ginger*, 3.3% *ginseng*, and 88.9% *maltose syrup powder*. As a chief ingredient compromising nearly 90% of the formulation, maltose confers a sweet taste and improves the palatability of formulation. Other benefits of high maltose (a disaccharide) content include low calorie and controlled sweetness to approximately 1/3 of comparable, sweetened products. The standard dosage of DKT is 15 g/day, and the water-soluble nature of DKT, due to its high maltose content, makes this dosage possible.

As shown in Fig. 2, the ingredients of DKT include hydroxy-α-sanshool (*Japanese pepper*), 6-shogaol (*processed ginger*), ginsenoside Rb1 (*ginseng radix*), and maltose, have been identified by three-dimensional high-performance liquid chromatography. Contamination studies have certified DKT to be free of unexpected pharmaceutical ingredients, toxins, pesticides, microbes, and heavy metals.

In the digestive surgery area, DKT has been employed for speeding the recovery from postoperative ileus after abdominal surgery and its clinical efficacy has been well established [4-7].

DKT and calcitonin gene-related peptide (CGRP)

Several important neural mechanisms have been suggested as mediating the increased effective intestinal motility of DKT [8,9]. One of these mechanisms involves in the release of calcitonin gene-related peptide (CGRP), a neuropeptide produced by the sensory neurons of gut. CGRP is one of the most potent mediators of microvascular vasodilatation in human body and its vasodilating effects following stimulated-release from the extrinsic sensory innervation is considered to serve as an important protective mechanism for maintaining mucosal integrity [10-13]. Because blood flow has to not only meet the relatively high metabolic needs of the gastrointestinal tract, but also provide both valuable buffering and a pathway for removal of toxins that may have entered into tissue [14]. Therefore,

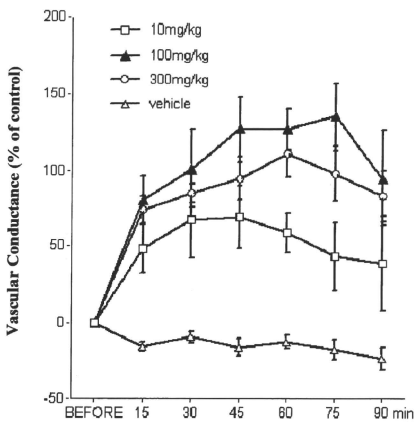

Figure 3. Effects of Daikenchuto (DKT) on colonic vascular conductance (VC) in rats. The rats received an intracolonal injection of vehicle or various doses of DKT (10 and 100 mg/kg). Colonic blood flow was measured by non-contact laser tissue blood flowmetry (LaserMed, ALF21N, Advance Co., Tokyo, Japan) which is a well-characterized technique for the measurement of blood flow in the intestine. Mean colonic vascular conductance (VC) was calculated as the quotient of mean blood flow divided by mean AP and was expressed as ml/mmHg. VC was used as a reliable index of colonic blood flow. VC was calculated every 15 min after the administration of either DKT or vehicle. Data are mean ± S.E.M (n = 8). —△— $P<0.01$ vs. all DKT, —□— $P<0.01$ vs. 100 mg/kg and 300 mg/kg, respectively.

maintaining or increasing blood flow is thought to be a central element in protecting the gastrointestinal tract and even in the prevention of intestinal adhesions resulting from inflammation [15,16].

We have reported that intraduodenal [17] or intracolonic [3] administration of DKT to normal rats increases small or large intestinal blood flow in a dose-dependent manner (Fig. 3). Nervous mechanisms are important for the regulation of gastrointestinal blood flow (Fig. 4). A number of neuropeptides such as CGRP, VIP and SP has been localized immunohistochemically in sensory nerves innervating various viscera, including the gastrointestinal tract [18-23]. Exogenous application of these peptides has been shown to dilate arterioles [13,24,25]. Our study showed that CGRP receptor antagonist, CGRP (8–37), completely abolished DKT-induced hyperemia, whereas the VIP receptor antagonist, [4-Cl-DPhe6, Leu17]-VIP, and SP receptor antagonist did not attenuate the hyperemic response [3](Fig. 5). The pharmacological study suggests that DKT-induced hyperemia of rat intestine is mediated by CGRP, but neither by VIP nor SP release.

Therefore, these observations strongly suggested that direct intra-intestinal administration of DKT directed endogenous CGRP release from the sensory nerve terminals of the mucosa, thereby caused an immediate increase in colonic blood flow [3]. Moreover, the results from the study by RT-PCR

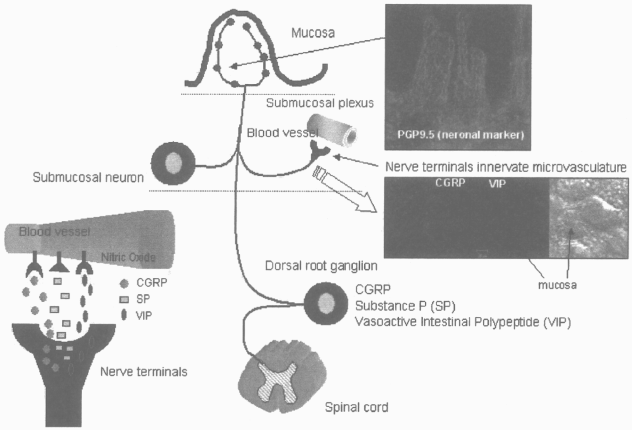

Figure 4. Schematic representation of the neuropeptides-containing sensory neurons in the intestine.

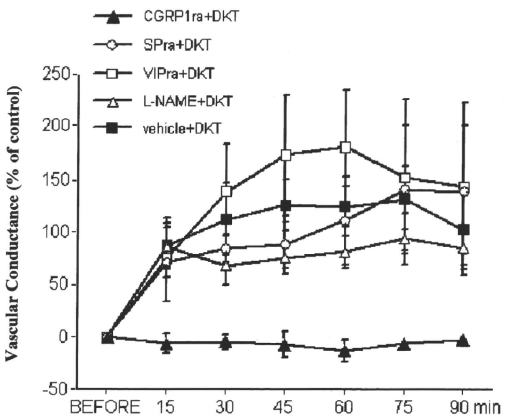

Figure 5. Effects of antagonists on DKT-induced hyperemia. Daikenchuto (DKT, 100 mg/kg) significantly increased colonic vascular conductance (VC) (closed circle). Calcitonin gene-related peptide (CGRP) 1 receptor antagonist completely suppressed the DKT hyperemia (closed triangle). Nitric oxide (NO) blocker, N^G-*nitro*-L-arginine methyl ester (L-NAME), also, but only partially, suppressed VC between at 45 min and at 60 min (open circles). DKT (100 mg/kg) significantly increased colonic VC (closed circles). Vasoactive intestinal polypeptide (VIP) receptor antagonist, *[4-Cl-DPhe6, Leu17]-VIP* and substance P (SP) receptor antagonist, *spantide* did not affect the hyperemic response (open squares and open triangles, respectively). VC is expressed as the quotient of mean blood flow divided by mean AP and was expressed as ml/mmHg. Data are mean ± S.E.M (n = 8). ▲ P<0.01 vs. vehicle + DKT, ▲ P<0.05 vs. Vehicle + DKT ; CGRP1ra: CGRP1 receptor antagonist *CGRP(8–37)*(45 μg/kg), Spra: SP receptor antagonist *spantide* (100 μg/kg), VIPra: VIP receptor antagonist, *[4-Cl-Dphe6, Leu17]-VIP* (15 μg/kg/h), N^G-*nitro*-L-arginine methyl ester: L-NAME (200 μg/kg).

revealed that DKT had an up-regulatory effect on CGRP [3](Fig. 6). However, the increase in intestinal blood flow by DKT was not observed with intra-gastric administration of DKT, suggesting that the actions of DKT to produce this effect were involved locally rather than systemically (unpublished data).

Another important factor for understanding the mechanism of actions of DKT is through study of the receptors involved. CGRP binds to the receptor termed calcitonin receptor-like receptor (CRLR), a receptor with seven

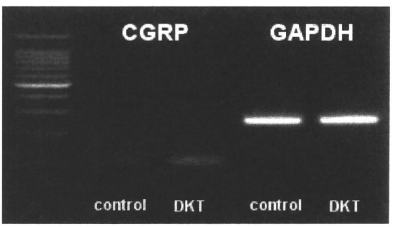

Figure 6. Evaluation of CGRP mRNA from the rat colon after DKT administration. The panel shows representative photos of gel electrophoresis of RT-PCR products and a molecular marker (M), 100 bp DNA ladder. The panel exhibits colonic CGRP mRNA (102 bp) products from the rat colon of vehicle control or Daikenchuto (DKT).

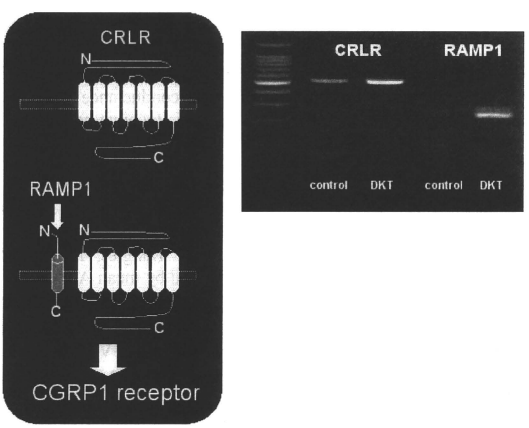

Figure 7. a: Diagrammatic representation of CRLR (show in yellow) and RAMP1(shown in red). Model illustrating the CGRP receptor and showing the interactions between the 7-transmembrane domain G-protein-coupled receptor known as the calcitonin receptor-like receptor (CRLR) and the single-domain receptor-associated membrane protein 1 (RAMP1). **b:** Evaluation of CRLR and RAMP1 mRNA from the rat colon after DKT administration. The right panel shows representative photos of gel electrophoresis of RT-PCR products and a molecular marker (M), 100 bp DNA ladder. The panel exhibits colonic CRLR mRNA (504 bp) and RAMP1 mRNA (230 bp) products from the rat colon of vehicle control or Daikenchuto (DKT).

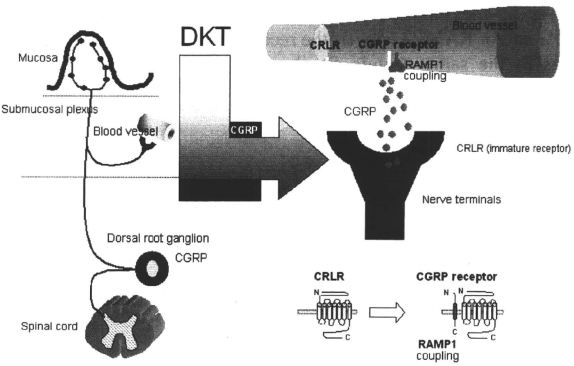

Figure 8. Schematic illustration of the mechanisms of action of DKT locally on sensory neurons of the gut and DKT activates the endogenous calcitonin gene-related peptide (CGRP) system.

transmembrane domains [26, 27]. This receptor can be considered an "immature" receptor with various patterns of expression. This receptor "matures" to the CRLR through the binding of receptor activity modifying protein 1 (RAMP1), a specific type of modulating membrane protein from the family of RAM proteins [28](Fig. 7). Therefore, to confirm the existence of a CGRP1 receptor, it is necessary to determine the existence of not only CRLR but also RAMP1. Our RT-PCR study revealed that DKT had an up-regulatory effect on CRLR and RAMP1 [3](Fig. 7). These lines indicate that when DKT firstly stimulates CGRP release from sensory nerve endings at mucosa, secondarily up-regulates CRLR and RAMP1, and develops up-regulation of CGRP receptor as well as endogenous CGRP up-regulation. Thus, DKT may be used as an endogenous CGRP up-regulator for intestine (Fig. 8).

Ablation of sensory neurons containing CGRP resulted in a marked increase in the severity of inflammation in experimental colitis [29]; inhibition of endogenous CGRP in the colon also increased mucosal damage in experimental models of Crohn's disease [29, 30]. Therefore, we hypothesize that DKT has therapeutic effect on Crohn's disease via up-regulation of endogenous CGRP and its receptor component.

DKT and adrenomedullin (ADM)

It is very interesting that the CRLR family can function as a CGRP receptor or as an adrenomedullin (ADM) receptor depending on which

members of the modifying membrane proteins are expressed, binding of RAMP2 and/or RAMP3 convert the receptor to ADM receptors (Fig. 9). ADM belongs to the same peptide family as CGRP and has potent vasodilating effects in the microvascular system [31]. ADM is ubiquitous in GI tract and plays

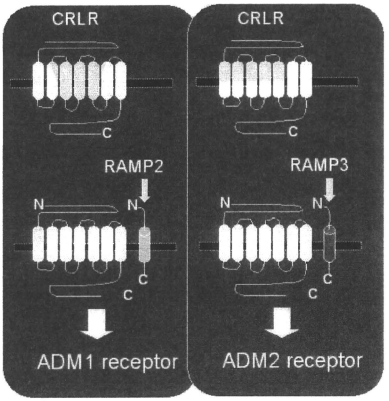

Figure 9. Model illustrating the adrenomedullin (ADM) receptor and showing the interactions between the 7-transmembrane domain G-protein-coupled receptor known as the calcitonin receptor-like receptor (CRLR) and the single-domain receptor-associated membrane proteins (RAMP2 and RAMP3). The subtype of ADM receptor formed by the association of CRLR with RAMP2 is termed ADM1, whereas that formed by association with RAMP3 is termed ADM2.

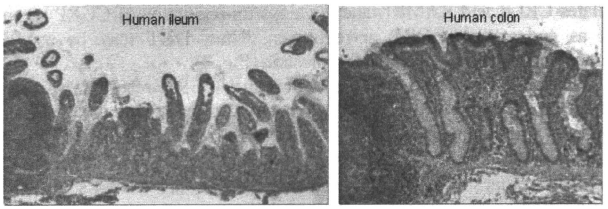

Figure 10. Expression of adrenomedullin (ADM) in mucosal epithelium of intestinal tract. Ileum and colon were obtained from the operated patients, and immuno-histochemical analysis was performed using anti-ADM antibody. ADM was present immuno-histochemically on the apical side of intestinal mucosa surface columnar epithelia.

important roles in the regulation of microcirculation [32,33], angiogenesis [34,35], antifibrosis [36], antibiosis [37,38], and down-regulation of proinflammatory cytokines [39-41].

The main difference between the microvascular activities of ADM and CGRP is their comparative potencies. The potency of ADM is less than that of CGRP, 1/3- to 1/10-fold less in rat skin [42], 1/20-fold less in hamster cheek pouch [43], and approximately 1/300-fold less in mouse mesentery [44]. CGRP is the primary vasodilator in physiologic conditions and acts peripherally. The major difference between the production cells of ADM and CGRP is that the former is not produced by neuronal cells, but rather by epithelial and smooth muscle cells and other non-neuronal tissues [45].

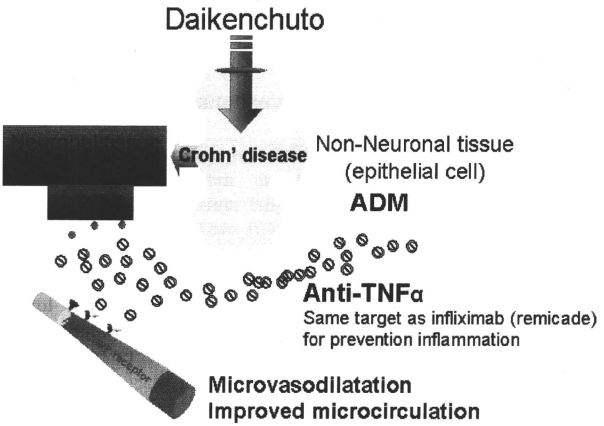

Figure 11. New possibility for Crohn's disease management. Schematic illustration of the mechanisms of action of DKT locally on sensory neurons of the gut as well as on non-neuronal tissues and DKT activates the endogenous adrenomedullin (ADM)/calcitonin gene-related peptide (CGRP) system. ADM and CGRP are peptides of the calcitonin family and are known, potent endogenous vasodilators. ADM plays important roles in the regulation of microcirculation and down-regulation of pro-inflammatory cytokines (TNF-α etc.). CGRP is expressed in sensory neurons supplying the GI tract, and plays important roles in the regulation of microcirculation. A heterodimer complex of the calcitonin receptor-like receptor (CRLR) and receptor activity-modifying protein (RAMP) 1 forms the CGRP receptor, while a complex of CRLR and RAMP2 or RAMP3 forms the ADM receptor. ADM and CGRP cross-react with each other's receptors. So these peptides share many common points of biologic action. DRG: dorsal root ganglion.

One of the characteristics of the small intestines is the production of ADM by the intestinal epithelial cells in human, rat and mouse (Fig. 10). Like CGRP, ADM has anti-inflammatory and powerful anti-cytokine effects, and is especially noted for its ability to inhibit TNFα [41].

Furthermore, results from preliminary studies in a rat-derived intestinal epithelial cell line (IEC-6 cells) indicate the ability of DKT to stimulate release of ADM from the intestinal mucosal epithelium, and to increase expressions of RAMP2 and RAMP3 to promote the maturation of ADM receptors (unpublished data). These studies provide strong evidence that DKT can activate CGRP secretion from mucosal sensory nerve endings and ADM release from mucosal epithelial cells. The vasodilating effect of DKT was abolished in normal rats by pretreatment with an antagonist or antibody of ADM (unpublished data). Therefore, both ADM and CGRP are key peptides for understanding the mechanism of actions of DKT.

New possibility for Crohn's disease management

ADM, which is a potent vasodilator in microvascular system and has having some immune-regulatory effects, may be a potential treatment approach in Crohn's disease. Indeed, the anti-colitis effect of ADM was demonstrated in mouse [40] and rat [46] models of Crohn's disease and acetic acid-induced colonic ulceration in rats [47]. In addition, several investigators have suggested that the effect of ADM might play an important role in mucosal defense as an antimicrobial peptide [37,38]. Invasion of microbes through the mucosal barrier stimulates the host immune system and intimately correlates with development of morbidity in experimental and human inflammatory bowel disease (IBD).

Interestingly, in our study, immune-reactive ADM was shown to distribute at the apical surface of the epithelial cells of intestinal mucosa. This observation may indicate that epithelial ADM contributes to the control of intestinal microflora. Invasion of microbes through the mucosal barrier stimulates the host immune system and intimately correlates with the development of morbidity in experimental and human inflammatory bowel disease [48]. Combined results of these studies support the potential treatment of Crohn's disease with ADM, as exogenous ADM administration has proven efficacy in animal models.

Other clinical and experimental studies in the field of gastrointestinal pathology support stronger associations between CGRP, ADM and Crohn's disease than previously speculated [40,46,49]. Decreases in colonic flow and augmentation of the inflammation of Crohn's disease appear to correlate with

decreased CGRP secretion from damaged neuronal cells as a result of recurrent transmural inflammation; indeed experimental support for this concept derives from studies showing the successful treatment of Crohn's disease with exogenous CGRP and ADM in experimental animal models of intestinal inflammation. Although the combined results of these studies suggest a novel approach to the treatment of Crohn's disease with CGRP and ADM, exogenous administration of these peptides is clearly not practical because of the potential systemic effects of these agents as well as the metabolic clearance which makes chronic delivery of a small peptide impractical [16,50-52]. Nevertheless, endogenous administration of CGRP and ADM in the experimental setting provides a protective effect in maintaining colonic mucosal flow and decreasing inflammation; therefore, a potential role for DKT in enhancing the local, endogenous secretion of CGRP and possibly ADM has led to the formulation of the following hypothesis: DKT may be effective in improving blood flow and reducing inflammatory changes via augmenting secretion of ADM from the intestinal mucosal epithelium, which in turn may supplement the decreased production of CGRP from damaged neuronal tissues in Crohn's disease (Fig. 11).

The inhibitory effect of ADM on TNFα production has also received considerable attention in the field of Crohn's disease similar in many respects to therapeutic use of infliximab (which targets TNFα) has advanced our treatment of Crohn's disease [53]. Iinfliximab, a murine chimeric monoclonal antibody against TNFα, has the disadvantage of all foreign proteins of stimulating autoantibody production, restricting its long term use as well as its exorbitant medical cost. Despite the introduction of the anti-TNF agents, 20-40% of patients fail to respond to initial induction therapy, and only 60-70% of the initial responders will maintain a sustained response at 1 year. Based on these facts, use of DKT in conjunction with infliximab-treatment (which is currently administered once every 8 weeks) may in theory lead to a decrease in the frequency and dosage of the antibody treatment.

The rapidly increasing number of patients with Crohn's disease in Japan has prompted an upsurge of clinical trials with DKT to collect high quality evidence. While the level of each ingredient are underway, the experimental studies addressing colonic vascular conductance, CGRP and ADM production in models of intestinal epithelial cell culture, and inhibition of various cytokines have identified specific mechanisms of actions of the active ingredients of *Japanese pepper* (hydroxy-α-sanshool) and *processed ginger* (6-shogaol) on endogenous release of CGRP and ADM.

Parting ways with complementary and alternative medicine

This overview of herbal medicine use in Japan was designed to provide a review of the accumulating scientific evidence of the mechanism and action of DKT. Use of traditional Japanese medicines (Kampo), including DKT, has a relatively 'short' history of 500 years of clinical use. In contrast, herbal therapies have been used for over 3,000 years in China, as well as in Greece and India for centuries. Only in the last 30 years, the Japanese government has officially recognized herbal medicine as a valid form of treatment alongside the typical western medicines. The official approval from the government signifies the quality of Kampo as being equivalent in principle to western drugs and with an aspect that distinguishes Kampo medicines from herbal medicines of other countries. Licensed Japanese physicians are the only medical practitioners able to prescribing conventional drugs and Kampo medicines; thus, they shoulder the responsibility of establishing basic and clinical evidence-based studies to support the use of Kampo worldwide. Physicians and researchers who recognize the value of Kampo are increasingly making an effort to conduct high-level studies of Kampo formulations in addition to studies of DKT [54].

Based on recent experimental studies for the mechanisms, several forms of traditional Japanese medicine may emerge as the leading candidates for the next series of clinical and further experimental researches.

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