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Action Mechanism of Kampo Medicine and the Intestinal Microbiota

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Running title: Kampo medicine and intestinal microbiota

Abstract

Administration of Kampo medicine is mainly oral except for several other extraordinary ways such as topical, through the nasal cavity or smoking. What does this mean? Of course in those days, intravenous administration was not available. However, this oral intake may have some significant meaning. Sometimes, the main purpose of Kampo treatment is focused to improve the condition of the digestive system. For instance, Kenchuto like Daikenchuto, Shokenchuto or Tokikenchuto contains the word "Ken" and"Chu". "Ken" means "construct" or "reconstruct" and "Chu" means digestive system. Taken together, "Kenchu" means "reconstruct the function of digestive system". This concept is essential in Kampo medicine thought. Also the digestive system is very important for the immune boosting of the host. This effect is owed at least partially to the polysaccharide or the glycoside in Kampo formula. Glycoside in Kampo formula is not absorbed until the sugar is separated and used by the intestinal bacteria. Sugar of the glycoside of the Kampo formula is useful for the gut bacteria and this action is essential for the glycoside to be absorbed. This symbiotic relationship between the host and the microbiota is called commensal. Serum concentration of aglycon, the form without sugar of glycoside, depends on the host gut microbiota. In this meaning, microbiota is one of the factors which decide the individual constitution (Sho). Also, in some gene expression, Kampo formula is active only when the gut microbiota exists. Taken together, intestinal microbiota is essential to elucidate the mechanism of action of Kampo formula.

Key words: Kampo medicine

Reconstruction of the digestive system is the first priority in Kampo treatment

Currently in Japan, more than 70% of the physicians use Kampo medicine in daily practice [1]. In daily practice, a patient with multiple complaints visits the Kampo practitioner. Among several problems, to recover the function of the digestive system is the first priority in the treatment strategy of Kampo medicine. There are names of Kampo formula which express the digestive system. Ifuto and Heiisan include "I" which is stomach in written form and means stomach function. Shokenchuto, Tokikenchuto or Daikenchuto contain "Ken" and "Chu". "Ken" means reconstruct and "Chu" is abdomen in written form and means digestive function. "Hochuekkito" contains "Hochu" and "Ho" means compensation. So "Hochu" means compensate the digestive function.

These Kampo formulas not only improve the digestive function and absorptive function, but also activate the whole body function.

For the treatment of atopic dermatitis, "Ogikenchuto" is often used especially for children [2]. This Kampo formula is indicated for the patient with a weak digestive system and who sometimes has diarrhea when exposed to the cold environment. This Kampo formula also belongs to "Kenchuto" family and with this, patients recover the skin barrier and atopic dermatitis is improved. Skin, large intestine and lungs belong to Gold in the five elements theory and are related each other. All these tissues are exposed to the external environment. Needless to say that skin is exposed to external environment, digestive system is also exposed to the foreign substances from the mouth and lung to the external air. Recently, the common molecules in the skin and the intestine have started to be understood. It is expected that the five element theory will be understood scientifically in the near future. Anyway, it is not usual to treat the intestine for a skin disease from the aspect of western medicine, because western medicine is tissue or organ directed and does not mind the relationship between organs.

Sometimes the patient with cancer manifests appetite loss. With Kampo treatment, appetite is recovered and the patient feels more energetic. I thought this was because eating is the basic behavior of maintaining life and the patient is pleased that he/she recovered this behavior. The truth is that food taken orally reaches the gut and stimulates the mucosal immune system of the intestines. For instance, nutrition support team is featured because medical professionals have become aware of the importance of oral food intake. As a matter of fact, nutrition state is much improved with oral intake of the food compared to the intravenous nutrition supplement.

Immune boosting by Kampo formula

In addition to the oral food intake, it is well known that Kampo formula boosts the immune system. For the diseases in which immune abnormality is involved, Kampo medicine is useful. For example, allergic reactions like atopic dermatitis, bronchial asthma, allergic rhinitis or collagen diseases like systemic lupus erythematosis, rheumatoid arthritis, or other autoimmune disorders are good indications of Kampo treatment. The mechanism of action is well investigated [3-5]. Kampo medicine is administered orally and the ingredients reach the gut. There exists more than 60% of whole lymphocytes in the gut. It is not difficult to imagine that Kampo ingredients stimulate these lymphocytes in the gut followed by immune boosting in the whole body. It has been shown that components in Kampo formula stimulated the lymphocytes in the pyer patch [6]. We have also shown with gene-chip analysis that many genes related to immunology were up-regulated by Kampo formula. This intestinal immune boosting affects the whole body protection against the infection or other foreign attack.

Components of Kampo formula

This immune boosting is partially due to the direct action of the ingredients of Kampo formula or metabolites of high molecule. Basically components of Kampo formula are divided into three categories (Fig. 1). One is small molecule components which are absorbed directly in a short time and peak serum level of these components is reached in 1 hour. These components disappear in 8 hours. Although it is quite often misunderstood that Kampo formula is effective only when it is taken for long, this is not true. Shoseiryuto is effective for nasal allergy in a fairly short time because ephedrine in Shoseiryuto is absorbed as it is in short time. The second category is glycoside which is absorbed as aglycon after the sugar is used by the intestinal bacteria. This is thought to be a natural prodrug and resistant to gastric acid. The representative component is glycyrrhizin. This is metabolized by the intestinal bacteria with glucronidase to glycyrrhetic acid, which is an aglycon form of glycyrrhiz and then absorbed. The peak of the serum level is reached between 6-12 hours. When an antibiotic is administered, the intestinal microbiota is changed and the serum level does not reach to the level without an antibiotic [7]. In order to reach the certain serum level, probiotics are helpful to be administered together with herbal medicine [8]. The third category is polysaccharide or other high molecule components. The molecular weight of this category ranges between 10,000 and 1,000,000. Representative molecule is beta glucan in the Reishi or Agaricus and other mushrooms. The mechanism of action is not clear how these high molecules act on the body. They may be broken to the small molecules

by the intestinal bacteria and absorbed, or caught by M cells or dendritic cells and absorbed as it is. Another option is to act directly on the gut surface mucosal cell.

【Low molecular component】 ①

Absorbed as it is.

【Glycoside】 ②

Resistant to the gastric juice. Sugar is used by bacteria and then aglycon is absorbed.

【Polysaccharide】 ③

Large molecule (sometimes over 100,000)

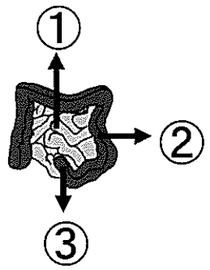


Fig. 1 Components of Kampo formula

Intestinal microbiota is changed by Kampo formula

Sugar of the Kampo formula is used by the intestinal bacteria. It is necessary to grow for the bacteria. This means that the intestinal microbiota is changed as a result of Kampo administration. Although this change of the intestinal microbiota has been speculated about for long period, it has not been proven. The main reason is that the culturable bacteria are only 10-15% and it is very difficult to elucidate the change of the gut microbiota. In these days, comprehensive molecular biological analyses of the microbiota are available. For example, terminal restriction fragment polymorphism (T-RFLP), a culture-independent molecular biological technique, is used to show the change of the intestinal flora. With this technique, each Kampo formula is shown to change the microbiota to a proper direction [9].

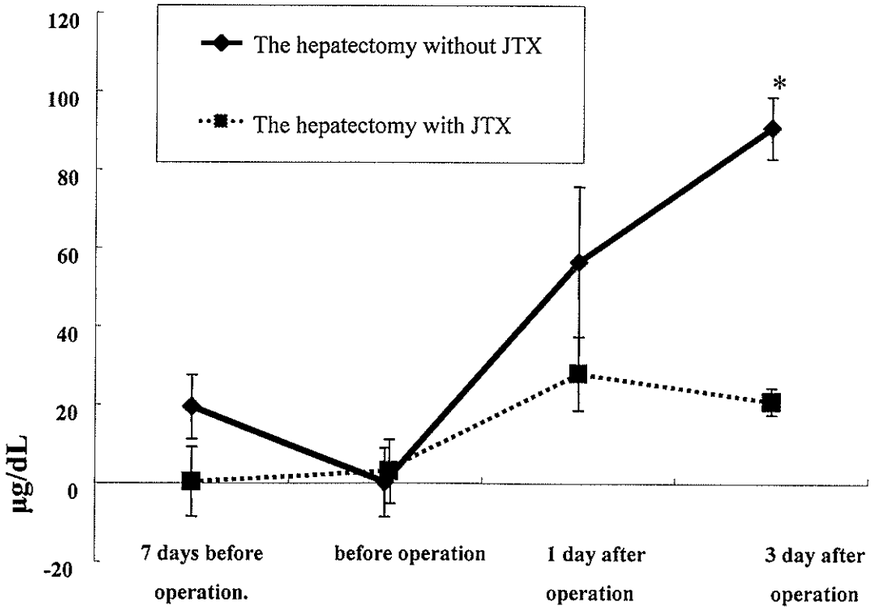
This change of the microbiota also influences the host gene expression. We have shown that Kampo formula can change the host gene expression only under the condition with intestinal microbiota [10]. This means that the change of the intestinal microbiota itself may affect the host gene expression.

Serum ammonium level is decreased with Kampo medicine

Serum ammonium level is elevated after partial hepatectomy. We examined the preventive effect of the Kampo medicine Juzentaihoto (JTX) on post-partial hepatectomy-induced hyperammonemia. With pre-surgical JTX administration, this post-surgical hyperammonemia is suppressed significantly. To explain this phenomenon,

we first hypothesized that JTX prevents further damage of the liver, a site of ammonia metabolism. However, post-surgical liver dysfunction is not improved with JTX. Thus we focused on the other source of ammonia, the intestinal flora, as the source of the hyperammonemia. To examine the possible effect of JTX on intestinal flora, T-RFLP was used and we documented that partial hepatectomy changed the intestinal flora. Then we demonstrated that with oral JTX administration, this post-surgical change of the intestinal flora was not observed even after partial hepatectomy. We also showed that the representative ammonia-producing bacteria genus, *Bacteroides*, increased with partial hepatectomy and decreased with JTX administration. Cluster analysis of fecal microbiota suggests that JTX administration stabilized the intestinal flora and maintained the pre-surgical floral environment of the gut. This study suggests that JTX is useful to prevent the clinically significant increases in serum ammonia levels after partial hepatectomy.

Fig. 2 The change of serum ammonia levels after partial hepatectomy and effect of JTX



*p<0.05

Atopic dermatitis and microbiota

Atopic dermatitis is also related to the intestinal environment. In atopic dermatitis patients, the intestinal mucosal barrier function is weakened, permitting frequent invasion by antigens. Polyamines and short-chain fatty acids (SCFA) produced by intestinal bacteria are involved in the promotion of intestinal mucosal barrier functions. Many pro-biotic effects on the alleviation of allergic and atopic diseases have been reported. Some researchers show that these effects depend on the improvement of helper T cell balance (Th1/Th2). It is generally believed that the Th1/Th2 balance is improved on stimulation of the intestinal microbiota. In this context, Kampo formula may play a role to change the gut microbiota and improve atopic dermatitis as a result. We have not shown this clinically, but we have administered yogurt to a long-course atopic dermatitis patient with Kampo treatment and this intervention was effective against intractable adult-type atopic dermatitis and this effect depends on the recovery of the intestinal mucosal barrier function and the induction of the Th-1 type cytokine by polyamines and SCFA, particularly, butyrate, produced by the altered intestinal microbiota [12].

「Sho」 in Kampo medicine and microbiota

Taken together, it is obvious that Kampo formula and intestinal environment are closely related. Especially, the microbiota in the gut influence Kampo components and Kampo medicine changes the intestinal microbiota. From the evidence that glycoside is absorbed after sugar is separated by bacteria, the serum level of the aglycon depends on the microbiota. This may explain the individual body constitution, which is relevant to "Sho". Indeed, the microbiota is very different in the different individual. This diversity may be caused by body constitution from the birth or by food. For example, a Jissho (excess) patient like a Sumo wrestler has a strong stomach function and eats a lot. On the contrary, a Kyosho (deficiency) patient with weak digestive function eats a little. As a result, intestinal microbiota is different. Different microbiota causes different pharmacodynamics of the Kampo component. From this point of view, Sho might be explained by the pattern of intestinal microbiota. In order to elucidate this hypothesis, a large clinical trial is necessary. This is not the case in only Kampo treatment, but also for individualization of the treatment, the research of intestinal microbiota would be very important.

Table 1 Glycoside in Herbs

Herbs	Glycoside	Aglycon	Enzyme	Bacteria
大黄 Rhei Rhizoma	Sennoside	Reinanthron	β-glucosidase	Bifidobacterium
甘草 Glycyrrhizae	Glycyrrhizin	glycyrrhetic acid	β-glucronidase	Eubacterium
黄芩 Scutellariae	Baicalin	Baicalein	β-glucronidase	Broad spectrum
山梔子 Gardeniae	Geniposide	Genipine	β-glucosidase	Klebsiella Pneumonia et.al
人参 Ginseng	Ginsenoside Rb1	Compound K	β-glucosidase	Eubacterium
柴胡 Bupleuri	Saicosaponine	Saicosapogenine	Fucocidase	Eubacterium
地黄 Rehmanniae	Aucubine	Aucubigenine	β-glucosidase	Bifidobacterium

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