Pharmacological Properties of Galenical Preparation. XIV.¹⁾ Body Temperature Retaining Effect of the Chinese Traditional Medicine, "Goshuyu-to (呉茱萸湯)" and Component Crude Drugs

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We orally administered Goshuyu-to (呉茱萸湯) or Evodia fruit (呉茱萸) extract and Ginger (生姜) extract to untreated rats, and found a slight but not significant rise in their body temperature. In rats treated with chlorpromazine, the administration of Goshuyu-to prevented decrease in the body temperature. After administration of each extract of component crude drugs (Evodia fruit, Ginger, Ginseng: 人參, Jujube: 大棗), such an effect was recognized only by Evodia fruit, and other component crude drugs exhibited no body temperature retaining effect in this experiment system. We further studied the effect of Evodia fruit alkaloid hydroxyevodiamine, evodiamine, rutaecarpine and evocarpine used individually and confirmed that the body temperature retaining effect occurred mainly with evodiamine.

Keywords Goshuyu-to; Evodia fruit; *Evodia officinalis*; Rutaceae; evodiamine; body temperature; crude drug; alkaloid

The concept of a body temperature retaining action in a crude drug signifies a recovery action from the low body temperature state of the entrails. Specifically, a decrease in the metabolism rate will be followed by cause an insufficiency of thermogenesis, with the result that the temperature of internal organs will drop and their functions will be reduced; as a result, a characteristic syndrome (sho: 証) characteristic of cold hands and feet, a pale face, migraine, vomiting, etc. are observed.²⁾

Goshuyu-to, known as a drug which maintains the body temperature, is a Chinese traditional medicine designed for the treatment of such symptoms. It is given to treat migraines and vomiting accompanying a cold.³⁾

Hon-zo-kou-moku (本草綱目) mentions that Evodia fruit, the main drug of this prescription, warms the interior of the body and cures chills and fever.⁴⁾ According to Sho-kan-ron (傷寒論), it can be used to treat lesser yin disease (sho-yin-biyo: 少陰病),⁵⁾ cold hands and feet, and perennial chills. Thus, it seems that Evodia fruit affects body temperature. We studied the body temperature retaining effect of Goshuyu-to and component crude drugs.

Experimental

Animals We bred male Wistar rats (6 weeks old, weighing 150—200 g, purchased from Japan SLC) in a breeding room 24±1°C temperature, and 50±5% humidity, with lighting from 6:00 to 18:00. During this time, they ate and drank freely.

Administered Drugs We purchased chlorpromazine hydrochloride, Tween 80 (polyoxyethylene (20) sorbitan monooleate) from Wako Co., Ltd. As component crude drugs for Goshuyu-to (Evodia fruit 3 g, Ginger 2 g, Ginseng 2 g, Jujube 4 g), were used those conforming to the Japanese pharmacopoeia XI. Evodia fruit alkaloids (I, hydroxyevodiamine; II, evodiamine; III, rutaecarpine and IV, evocarpine: Chart 1) to be used, were extracted from Evodia fruit. They were then refined and identified

Chart 1

as standard samples.

Equipment We used a thermistor (Omron Digital Thermometer MC-14B, Tateishi Co., Ltd.).

Preparation of Sample Drugs We added water (about 20 times the weight of the crude drug) to Goshuyu-to or each crude drug, boiled it until its quantity was halved, and filtered it through 5-layer gauze. The boiled liquid was then freeze-dried and stored at 4°C. Extract yield of Goshuyu-to, Evodia fruit, Ginger, Ginseng and Jujube per 1 g was 0.25, 0.09, 0.28, 0.27 and 0.68 g, respectively. Goshuyu-to (1.0 or 3.0 g) and each drug (0.2 or 1.0 g) in the crude drug equivalent was dissolved or suspended in 1.0 ml of 2% Tween 80, and orally administered to rats at a dose of 5 ml/kg body weight.

We prepared Evodia fruit alkaloid components so that each component concentration was 5 ml/kg as a dose (suspension with 2% Tween 80), and orally administered it to the rats.

Selecting the Preparation Conditions for Low Body Temperature Animal Models Rats were intraperitoneally administered with chlorpromazine at 4-stage dose of 2.0, 4.0, 8.0, 20.0 mg/kg, and their rectum temperature measured. The dose was 1.0 ml/kg, and the drug liquid to be administered was heated to the rats temperature prior to administration.

Measuring the Body Temperature We measured the rectum temperature of 10 rats in one group using a thermistor 0, 0.5, 1.0, 2.0, 3.0 and 4.0 h after oral administration (Chart 2).

In measuring the temperature of low body temperature animals, since chlorpromazine was administered 1.0 h after oral administration of the sample drug or 2% Tween 80, we also measured the rectum temperature 1.5 h after oral administration (Chart 2). A transitory rise in temperature observed with oral administration. Chlorpromazine was administered 1 h later when the influence of oral administration had disappeared.

Data Analysis Statistical analysis was performed by Student's *t*-test.

Results

Preparing the Low Body Temperature Models After the intraperitoneal injection of 2.0, 4.0, 8.0 and 20.0 mg/kg of chlorpromazine, the rats gradually became calm, and their body temperature dropped below normal level. Figure 1 shows the time course of this temperature drop induced by

Chart 2

Fig. 1. Effect of Chlorpromazine on Rat Body Temperature ($n=10$)

○, control; △, 2.0 mg/kg; □, 4.0 mg/kg; ●, 8.0 mg/kg; ▲, 20.0 mg/kg.
Mean $\pm$ S.D. at 2.0 h: ○, 37.50 ± 0.37 ; △, 37.39 ± 0.39 ; □, 37.17 ± 0.43 ; ●, 36.18 ± 0.35 ; ▲, 35.49 ± 0.43 .
a) $p < 0.05$, b) $p < 0.01$.

Fig. 2. Effect of Goshuyu-to, Evodia Fruit, Ginger, Ginseng and Jujube on Rectal Temperature of Normal Rats ($n=10$)

○, control; ■, Goshuyu-to (15 g/kg); ●, Evodia fruit (5.0 g/kg); ▲, Ginger (5.0 g/kg); □, Ginseng (5.0 g/kg); △, Jujube (5.0 g/kg).
Mean $\pm$ S.D. at 0.5 h: ○, 37.44 ± 0.52 ; ■, 37.92 ± 0.59 ; ●, 37.89 ± 0.61 ; ▲, 37.73 ± 0.72 ; □, 37.66 ± 0.58 ; △, 37.48 ± 0.61 .

each chlorpromazine dose and the time. With a 2.0 mg/kg chlorpromazine administration, the body temperature returned to normal within 1.0 h after injection, but with a 20.0 mg/kg injection, the body temperature was 35°C or lower even, 3.0 h after administration. Thereafter, it became impossible to take measurements.

As a condition for producing a particular body temperature for subsequent experiments, we selected a chlorpromazine dose of 8.0 mg/kg. This value is preferable both for its reproducibility and for its effectiveness in lowering temperature.

Effects of Goshuyu-to and Its Component Crude Drugs on Body Temperature **A) Changes in Normal Body Temperature** After oral administration of 3.0 and 15.0 g/kg Goshuyu-to in the crude drug equivalent to untreated rats, there was a tendency for the animal's normal body temperature to rise, as shown in Fig. 2. The rise, however, did not depend on the dose and there was no significant difference. Meanwhile, after orally administering the sample drugs of Goshuyu-to component crude drugs Evodia fruit, Ginger, Ginseng and Jujube prepared at 1.0 and 5.0 g/kg in terms of crude drug weight, we measured normal body temperature. Evodia fruit and Ginger slightly raised temperature, but in this case, too, the reaction amount did not correlate to the dose, nor was there any significant

Fig. 3. Effect of Goshuyu-to, Evodia Fruit, Ginger, Ginseng and Jujube on Low Temperature Mode of Rats Induced by Chlorpromazine ($n=10$)

○, control; △, chlorpromazine (8.0 mg/kg); ●, Goshuyu-to (15 g/kg); ▲, Evodia fruit (5.0 g/kg); ■, Ginger (5.0 g/kg); ▼, Ginseng (5.0 g/kg); □, Jujube (5.0 g/kg).
Mean $\pm$ S.D. at 3.0 h: ○, 37.43 ± 0.33 ; △, 36.19 ± 0.41 ; ●, 37.21 ± 0.39 ; ▲, 37.38 ± 0.37 ; ■, 36.04 ± 0.44 ; ▼, 36.18 ± 0.33 ; □, 36.49 ± 0.35 .
a) $p < 0.05$, b) $p < 0.01$.

Fig. 4. Effect of Hydroxyevodiamine, Rutaecarpine, Evocarpine and Evodiamine on Low Temperature Mode of Rats Induced by Chlorpromazine ($n=10$)

○, chlorpromazine (8.0 mg/kg); ▲, evodiamine (5 mg/kg); ●, evodiamine (10.0 mg/kg); ■, dl-evodiamine (20.0 mg/kg); ▼, hydroxyevodiamine (10.0 mg/kg); □, rutaecarpine (10.0 mg/kg); △, evocarpine (10.0 mg/kg).
Mean $\pm$ S.D. at 3.0 h: ○, 36.09 ± 0.42 ; ▲, 37.23 ± 0.29 ; ●, 37.46 ± 0.41 ; ■, 37.08 ± 0.34 ; ▼, 36.37 ± 0.37 ; □, 36.50 ± 0.52 ; △, 36.16 ± 0.38 .
a) $p < 0.05$, b) $p < 0.01$.

difference.

B) Changes in the Low Body Temperature State Intra-peritoneally administering 8.0 mg/kg of chlorpromazine to rats 1.0 h after orally administering sample drugs, we measured body temperature in a time series (Fig. 3). As in the chlorpromazine administered control group, the 3.0 g/kg Goshuyu-to administered group showed a drop in body temperature, but no improvement in the low body temperature state. Meanwhile, in the 15.0 g/kg Goshuyu-to administered group, there was no drop in body temperature due to chlorpromazine, and instead the drug prevented such reduction, with the result that the group maintained a body temperature equal to that of the untreated normal rats.

Five g/kg of Evodia fruit proved to significantly prevent a drop in body temperature; the dose-dependence of what drop there was recognized. However, Ginger, Ginseng and Jujube showed no direct effect on the retention of temperature.

Effects of Alkaloid on Body Temperature **A) Changes in Normal Body Temperature** Since the body temperature retaining effect of Evodia fruit was recognized, we studied the main alkaloids in this component. First, we orally ad-

ministered to rats 10.0 mg/kg each of hydroxyevodiamine, evodiamine, rutaecarpine and evocarpine, and measured their normal body temperature. No alkaloid showed a significant effect on this temperature.

B) Changes in Low Body Temperature State Orally administering rats with hydroxyevodiamine (10.0 mg/kg), rutaecarpine (10.0 mg/kg) and evocarpine (10.0 mg/kg), evodiamine (2.0, 5.0 and 10.0 mg/kg) and intraperitoneally administering them with chlorpromazine (8.0 mg/kg) 1.0 h later, we sequentially measured their body temperature (Fig. 4). A body temperature retaining effect was recognized in the evodiamine (5.0 mg/kg) administered group, and a definite effect in preventing a drop in temperature was recognized in the 10.0 mg/kg administered group. However, no effect was observed with the other alkaloids.

Discussion

Goshuyu-to is a Chinese traditional medicine used for a syndrome characterized by cold hands and feet as a systemic symptom and migraines and vomiting as characteristic symptoms.

Evodia fruit and Ginger mixed with Toki-sigyaku-to can be used to treat chilblains and cold hands and feet. There is a strong possibility that the effect of Evodia fruit is related to thermogenesis and body temperature retention. Regarding this effect, Hon-zo-kou-moku mentions that it serves to warm the interior of the body and treats chills and fever.⁴⁾ Also, Sho-kan-ron mentions that it can be used for lesser yin disease, cold hand and feet, and for treating those who have felt cold for a long time.⁴⁾ Thus, there are expressions suggesting that it is concerned with retaining the temperature in the body's interior.

There have been reports⁶⁾ of a cardiogenic effect of Evodia fruit or alkaloids. It has further been reported that the methanol extract of Evodia fruit causes a slight rise in the body temperature of rabbits and that Toki-sigyaku-kagoshuyu-shokyo-to causes a significant rise in the body temperature⁷⁾ of humans, but there have been no experiments clarifying improvements in the low body temperature state. The body temperature retaining action can be regarded as an intrinsic effect of Evodia fruit, and the authors confirmed this physiological action by low body temperature rat models, and searched for the substances responsible for this action.

We orally administered Goshuyu-to or Evodia fruit extract (the equivalent of 100 times the dose for an adult in terms of body weight), and Ginger extract (the equivalent of 150 times) to normally bred and untreated rats. A slight rise in body temperature was observed but it was not significant. On this point, we were unable to obtain experimental results which proved the conventional body temperature rise effect.

However, a significant body temperature retaining action (prevention of temperature reduction) was recognized when Goshuyu-to was administered to experimental low body temperature rats which had been given chlorpromazine. The action of Evodia fruit did not further raise the temperature when it was normal, but did affect it when it was low; only then was it effective. It is very interesting to have proven

this fact and to have experimentally been able to understand the Chinese traditional medicine's effect. In addition, a similar effect was recognized in Evodia fruit alone, a component herbal medicine. No body temperature retaining effect was recognized in the other three component crude drugs, Ginger, Ginseng and Jujube. At least in these experiments, we were not able to prove the body temperature retaining action of these crude drugs.

Goshuyu-to prevents reduction in the body temperature of rats treated with chlorpromazine. The main cause of this effect is thought to be Evodia fruit, and the effect of the other compound crude drugs is believed to be indirect. Furthermore, each action of Evodia fruit alkaloid hydroxyevodiamine, evodiamine, rutaecarpine and evocarpine was studied during these experiments, and the body temperature retaining action recognized in Goshuyu-to and Evodia fruit was confirmed only in evodiamine. In a quantitative relation, while the 15.0 g/kg Goshuyu-to administration contained 4.1 g of Evodia fruit, a body temperature retaining effect was confirmed with the administration of 5.0 g/kg (almost the same weight as in the Evodia fruit extract administration). Since approximately 3 mg of evodiamine was contained in 5 g of the Evodia fruit aqueous extract in the crude drug equivalent, the body temperature retaining effect was confirmed in the 5.0 mg/kg of evodiamine used alone. This suggests that the main part of the retention effect of Goshuyu-to is due to evodiamine.

On the other hand, no marked effect was recognized in low temperature rats treated with chlorpromazine. The Ginger extract did, however, show a slightly higher body temperature than the normal rat body temperature. This suggests the involvement of a different action mechanism of the Ginger extract, which demonstrated the effect of slightly raising the normal rats body temperature. From the viewpoint of crude drug, Evodia fruit and Ginger which are believed to have body temperature production action, are involved with the improvement of the body temperature syndrome through independent and different action mechanisms. In this case, there is a possibility of developing a complex action, and this is now being studied.

We believe that the scientific endorsement of the efficacy of some crude drugs which these experiments have provided will contribute to the further scientific analysis of these drug.

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