Pharmacological Properties of Traditional Medicines (XXVII).¹⁾ Interaction between Ephedra Herb and Gypsum under Hyperthermal Conditions in Rats

Dan YUAN,^a Hiroshi SUNOUCHI,^b Tetsuro SAKURAI,^b Ken-ichi SAITO,^b and Yoshihiro KANO^{*,b}

^a Department of Traditional Chinese Medicinal Sciences, Shenyang Pharmaceutical University; 103 Wenhua Road, Shenyang, China; and ^b Department of Traditional Chinese Medicinal Sciences, Hokkaido College of Pharmacy; 7-1 Katsuraoka-cho, Otaru 047-0264, Japan. Received December 25, 2001; accepted April 9, 2002

There are many important considerations in the interactions among the herbal constituents in a prescription of traditional Chinese medicine (TCM). Ephedra Herb (麻黄) (Eph) is described a warm and acrid agent in TCM. The combination of Eph and Gypsum (石膏) (Eph-Gyp) shows specific actions in patients with different body temperatures. Previous reports suggested that Gypsum prevents the thermogenesis effect induced by ephedrine at an ambient temperature of 22 °C. In this investigation, the properties of Eph-Gyp in hyperthermal rats were studied in detail. It was shown that Gypsum Extract (GyE) enhanced the thermogenesis of Eph in hyperthermal rats, although not in normal rats. The results support not only the opposite actions of Eph-GyE but also the clinical differences in the symptomatic patterns of body temperature for Makyo-Kanseki-To (麻杏甘石湯) and Dai-Seiryu-To (大青竜湯).

Key words ephedrine; gypsum; Ephedra; interaction; body temperature; traditional Chinese medicine

Advances in modern science have resulted in rapid developments in medicine. However, many drugs only relieve symptoms without curing patients, because the life sciences are not sufficiently developed. The cure of lifestyle-related conditions depends on patients' self-control and inherent healing systems. Therefore various forms of traditional medicine, such as complementary medicine, alternative medicine, and traditional Chinese medicine (TCM), are popular, with differing clinical results. However, these medical systems lack the scientific evidence necessary for the modern medicine. One of the important aspects in understanding TCM is to clarify the interactions between the herbs or herbal constituents in a preparation.

Ephedra Herb (Eph), traditionally used as "a warm and acrid herb that releases the exterior (辛温解表藥)," mainly elevates body temperature.²⁾ The classical medical tomes mention that the elevation of body temperature may be prevented or enhanced when it is used in combination with Gypsum Extract (GyE). Opposite effects occur in different prescriptions.³⁾

Our studies focus on the investigation of the effects of some ephedrine-containing traditional prescriptions on heat and water loss from both the respiratory organs and body surface, as well as body temperature.^{4–6)} The effect of Makyo-Kanseki-To (MKT) on the maintenance of body temperature was also clarified and found to be different from the pharmacological thermogenesis of Eph or Ephedra Herb.^{5,6)}

The present study was undertaken to elucidate the differences in the effects of on the body temperature between ephedrine-containing traditional prescriptions to provide additional scientific evidence.

MATERIALS AND METHODS

Animals Male Wistar rats (6 weeks old) weighing 150–180 g were purchased from Nihon SLC Co. Ltd. (Japan). They were housed in groups of 5–6 in an air-conditioned room with controlled temperature of 23 ± 1 °C, relative hu-

midity of 50 ± 5%, and lighting from 06:00 to 18:00. Food and tap water were available ad libitum. The rats underwent preliminary measurement of rectal temperature every day during a 1-week period before the experiments to adapt to long-term testing. After 1 week, at 7 weeks of age, the mean rat body weight was 220 g.

Drugs Eph was commercially obtained from Dainippon Seiyaku Co. Ltd. (Japan). Gypsum was purchased from Tochimoto Tenkaido Co. Ltd. (Japan). Gypsum powder (passed through a 0.5-mm mesh sieve) was boiled with 20 portions (w/v) of distilled water until the volume was reduced by one-half. The extracts were filtered, while warm through a filter paper (No. 2, Toyo Roshi Kaisha Ltd., Japan), and the filtrate was then condensed and adjusted to the required concentration. The contents (mg) of Ca, Sr, Si, Fe, Na, Al, K, Mg, Br, B, and Ba in GyE prepared from 10 g of Gypsum were 19.29, 2.71, 1.21, 0.36, 0.14, 0.05, 0.07, 0.08, 0.06, 0.06, and 0.01, respectively.

Materials were dissolved or suspended in distilled water. All the solutions were stored at 25 °C prior to administration.

Experimental Methods The experiments were performed in a climatic chamber (EYELA, KCL-1000, Tokyo Rikakikai Co. Ltd., Japan) in which the temperature and relative humidity were maintained at 22 °C or 32 °C and 45%, respectively.

The rectal temperature was determined with a modified digital thermometer (OMRON MC-148, Omron Co. Ltd., Japan). The rats were placed in the conditioned climatic chamber for 1 h, then given saline orally, and rectal temperature was determined 60, 90, and 120 min after saline administration. The rectal temperature of the control group was expressed as the mean of three measured values. Subsequently, the test drugs were administered orally, and the rectal temperature was taken at 30-min intervals for 2 h there after.

Statistical Analysis The data were subjected to analysis of variance (ANOVA) followed by the Scheff's test. Differences of $p < 0.05$ were considered statistically significant.

* To whom correspondence should be addressed. e-mail: kano@hokuyakudai.ac.jp

RESULTS

Effects of Eph on Body Temperature in Different Thermal Environments The rectal temperature of saline-treated rats remained at 37.6 °C or 37.9 °C when the environment was 22 °C or 32 °C. When Eph 4 mg/kg was orally administered to the rats, significant increase in rectal temperature occurred when the surrounding environment was either 22 °C or 32 °C. The rat body temperature returned to nearly normal 2 h after the administration of Eph. When the environment was 22 °C, the rectal temperature of the rats that were given Eph 4 or 8 mg/kg dose dependently rose to 37.9 °C or 38.5 °C 60 min after administration. When the environment was 32 °C, the mean rat body temperature increased to 38.5 °C at the dose of Eph 4 mg/kg and to a fatal 39.1 °C at the dose of 8 mg/kg (Fig. 1).

The effects of Eph on body temperature were thus confirmed, and Eph dose was 4 mg/kg in subsequent experiments.

Effect of Combined Eph-GyE on the Body Temperature in a 22 °C Environment When the ambient temperature was 22 °C, the effects of Eph and Eph-GyE were compared (Fig. 2).

The rectal temperature reached a peak 30–60 min after Eph administration. When combined Eph-GyE in which the Eph dose was 4 mg/kg and the GyE dose was 5.54 mg/kg⁶⁾ was administered to the rats, Eph-GyE did not produce a significant increase in rectal temperature in spite of the significant elevation after the administration of Eph alone at the same dose. The thermogenesis of ephedrine was completely inhibited by GyE. The results suggest that there may be some constituents in GyE which prevent Eph thermogenesis.

Effects of Combined Eph-GyE on Body Temperature in a 32 °C Environment When the ambient temperature was 32 °C, GyE did not inhibit the effect of Eph on body temperature when combination of Eph-GyE was administered at same dose as used in the ambient temperature of 22 °C. On the contrary, rat body temperature was further elevated (Fig. 3).

DISCUSSION

Eph alone elevated mean rat body temperature when the ambient temperature was 22 °C, and 32 °C, while GyE had no effect.⁶⁾ Combination of Eph-GyE at the same dose ratio as in MKT and Dai-Saiko-To (大青竜湯, DST) did not result in Eph-induced thermogenesis when the ambient temperature was 22 °C.^{5,6)} On the other hand, in hyperthermal rats at an ambient temperature was 32 °C, Eph-GyE enhanced the elevation of body temperature significantly more than with Eph administration alone. The rats entered a nearly fatal condition with hemorrhages in the nose and eyes, and the experiments often had to be halted. Thus GyE enhanced the thermogenesis of Eph in hyperthermal rats, although not in normothermal (22 °C) rat.

The above results suggest the possibility of opposite effects of Eph-GyE described in the classical Materia Medica Sinica.³⁾ The opposite effect of the combination on thermogenesis may be explained by the examples of MKT and DST. DST was composed of Ephedra Herb, Apricot Kernel (杏仁) Jujube (大棗), Licorice (甘草), Gypsum, Cinnamon Bark

Fig. 1. Effects of Eph on Rectal Temperature of Rats at Ambient Temperature of 22 °C and 32 °C

○, Saline; ●, Eph 4 mg/kg; □, Eph 8 mg/kg. Each point represents the mean $\pm$ S.D. of 9–10 animals. * p < 0.05 versus controls.

Fig. 2. Effects of Eph and Eph-GyE on Rectal Temperature in Rats in Ambient Temperature of 22 °C

●, Eph 4 mg/kg; □, combined of Eph 4 mg/kg and GyE 5.54 mg/kg. The Each bar represents the mean $\pm$ S.D. of 6–7 animals. The symbols are same in Fig. 1.

Fig. 3. Effects of Eph and Eph-GyE on Rectal Temperature in Rats at Ambient Temperature of 32 °C

●, Eph 4 mg/kg; □, combined of Eph 4 mg/kg and GyE 5.54 mg/kg. The others are same as Fig. 1.

(桂皮), Ginger (生姜). Ephedra Herb, Apricot Kernel, Licorice, and Gypsum are also components of MKT. However, the two traditional prescriptions are indicated for different pathogenic conditions in TCM.⁷⁾ The differences in the symptomatic pattern and therapeutic indications are illustrated in Fig. 4.

Fig. 4. Schematic Diagrams of Comparison of Symptomatic Pattern and Therapeutic Points between MKT (I) and DST (II)

Solid thick line (—), normal body temperature; solid thin line (—), actual body temperature; dotted line (---), set-point of body temperature. A, B, C, and arrows denote the period of contraction, return to normal temperature set-point, recovery, and administration of prescription, respectively.

Despite external fever and irritability, the basal body temperature was elevated in the patients with the symptoms for which DST is prescribed, *i.e.*, severe chill. Body temperature does not increase in the presence of chill, and thus those patients are not treated with sweating despite the high body temperature. The effects of DST are to first promote an elevation in body temperature to the normal range and then to relieve other fever symptoms through encouraged sweating. On the other hand, the temperature set-point remains normal in patients for whom MKT is indicated, and the body temperature rises due to increased metabolism. This pathogenic condition often occurs in childhood asthma of the thermogenetic-type, and MKT is often used clinically to achieve bronchodilation with the ephedrine component, but without its side effect of thermogenesis. The difference in such therapeutic points is described in the terms of the opposing effect of Eph-GyE in the classical materia medica.⁷⁻⁹⁾ If the classical theories of TCM are reasonable, the opposite effects may be experimentally confirmed in different animal models.

In the present study, rats in a 22 °C environment were regarded as an animal model exhibiting the symptoms for which MKT is indicated, and those in a 32 °C environment exhibiting the symptoms for which DST is indicated. Eph and GyE were used as substitutes for Ephedra Herb and Gyp-

sum. The results clearly showed that GyE prevented ephedrine thermogenesis in normal rats, but enhanced it in hyperthermal rats. The present study thus experimentally confirmed not only the opposite effects of TCM in different situations, but also are consistent with the differences in the therapeutic indications for DST and MKT. However, it is necessary to conduct further study to determine whether the animal models in a 22 °C or 32 °C exhibit symptoms for which MKT or DST is indicated. Further study should also clarify whether the inorganic ions of GyE affect the thermogenesis of ephedrine.

CONCLUSIONS

Gypsum extracts prevented the thermogenesis of ephedrine in normal rats, but enhanced it in hyperthermal rats. These experimental results may suggest the reasons why MKT and DST are prescribed for patients with different symptomatic patterns.

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