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Integrative Medicine Research

journal homepage: www.imr-journal.com

Hypothesis

Taeeum-type people in Sasang constitutional medicine have a reduced mitochondrial metabolism

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ARTICLE INFO

Article history:
Received 19 September 2012
Received in revised form
28 September 2012
Accepted 3 October 2012
Available online 17 October 2012

Keywords:
obesity
Sasang constitutional medicine
thermogenesis hypothesis

ABSTRACT

Sasang constitutional medicine (SCM) is a traditional form of medicine that is widely used in Korea to clinically diagnose and treat disease. The main characteristic of SCM is its classification of people according to physical constitution. The theory asserts that four different types of physical constitution exist: Taeyang, Soyang, Taeeum, and Soeum. One noticeable clinical observation in SCM is that Taeeum-type people are prone to obesity. Although extensive clinical investigations have shown this tendency in SCM, no scientific hypothesis has been proposed to delineate its mechanism. According to SCM theory, Taeeum-type people have a hypoactive lung system and a hyperactive liver system. In this paper, we propose a new hypothesis explaining this finding from a physiological viewpoint. A functional weakness in the lung system indicates intrinsic hypoactivity in the consumption of metabolic energy, therefore we deduced that the tendency can easily induce body weight gain via an increase in anabolism.

1. Introduction

Oriental medicine in Korea applies several theories, and Sasang constitutional medicine (SCM), devised by Jema Lee in 1894,[1] is one of the most popular forms of traditional medicines. SCM has been successful in many patients, and its clinical relevance is well recognized in Korea. As stated in our review paper,[2] Lee constructed the framework of SCM by evaluating the Chinese and Korean medical literature and classified the physical constitution of a human being into four types: Taeyang, Soyang, Taeeum, and Soeum. According to a report on oriental medicine in 2004,[3] 23.8% of the total patients in the Korean oriental medical market were treated by SCM therapy.

Recent clinical studies have indicated that among the four physical constitutions, Taeeum-type subjects are prone to obesity. Chae et al[4] found relatively higher body-fat mass in Taeeum-type subjects by testing their psychological and physical characteristics, while Um et al[5] determined that the relative risk of being obese increases in these subjects. Also, interleukin-1α polymorphism was found to be related to obesity in Korean Taeeum women.[6,7] From these observations, Taeeum subjects were conjectured as being prone to obesity,

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http://dx.doi.org/10.1016/j.imr.2012.10.002

but no research has delineated the physiological mechanism for this hypothesis.

In this paper, a physiological hypothesis is proposed to explain why a specific group of people, according to SCM, are prone to obesity. The metabolic power of the Taeeum type is less than that of others due to particular metabolic characteristics. Based on the thermogenesis hypothesis, we hypothesized that the compensatory mechanism to maintain temperature homeostasis can easily increase the body weight of Taeeum subjects.

2. Introduction to SCM

SCM seeks to delineate human physiological and pathological phenomena by employing the characteristics of four organ systems: the lungs, pancreas, liver, and kidneys. In the SCM view, each of these organs represents the respiratory, digestive, preserving, and excretive systems, respectively. As explained in our review paper,[2] the lungs and the liver pair to control some physiological processes, and the pancreas and kidneys compose another pair. The pancreas and kidneys are related to the digestion of food and excretion of metabolites and perform in a counteractive (seesaw) manner. Hence, in this view, if one organ system is relatively robust, the other becomes weak. A similar metaphor to the seesaw in the pancreas and the kidneys is applied to the lungs and liver. These organ systems relate to and regulate the usage and storage of energy in the human body. According to SCM theory, every person is born with one unbalanced seesaw, and four different types of physical constitution exist. Jema Lee[1] termed these types as Taeyang, Soyang, Taeeum, and Soeum. The seesaw metaphor between organ systems was not scientifically explained. The systems biological approach, however, will be useful for delineating the balancing mechanism between organ systems.

3. Metabolic interpretation of SCM

From the perspective of internal medicine, the four organs in SCM make up a metabolic system. If we conjecture the concept of the pancreatic system based on the original SCM text written by Jema Lee,[1] it represents the digestive function of absorbing foods by the spleen, stomach, and pancreas. In contrast, the kidney system performs the excretory function by discharging stool and urine through the large intestine and kidneys. These two systems form the seesaw relationship. If one system becomes strong, the other becomes relatively weak. The lung system in SCM plays a key role in the consumption of metabolic energy. In a physiological sense, the respiratory system supplies oxygen to generate metabolic power in peripheral tissues. In SCM, the liver system is also hypothesized to preserve nutrition and energy, and thus the lungs and liver exhibit a seesaw relationship.

Among the four types of physical constitution in SCM, Taeeum subjects display an unbalanced seesaw of the lung and liver pair, with weak function of the lung system. According to SCM theory, this characteristic of Taeeum-type people represents an inherited weakness in consumption (or production) of metabolic energy. The function of the respiratory system is to supply oxygen to peripheral tissues for energy production via oxidative phosphorylation in mitochondria. It is also known that respiratory function is related to metabolic power in tissue. Mathieu et al[8] and Jansky[9] showed that the mitochondrial density of skeletal muscle was proportional to maximal aerobic rate. Therefore, weak lung function indicates weak maximal aerobic capacity and reduced mitochondrial density in tissue, eventually resulting in reduced energy production in the body.

4. Hypothesis on the relationship between the Taeeum type of physical constitution and obesity

Taeeum-type people are hypothesized to have a weakly functioning lung system, indicating a weak function in the production of metabolic energy. Some clinical evidence also suggests that Taeeum-type people are prone to obesity. If we assume that these two facts are valid, what is the scientific rationale? To explain this, we introduce the thermogenesis hypothesis.

Humans are homeothermic mammals, therefore their core temperature is maintained at a constant level regardless of the environmental temperature.[10] The short-term response to a cold environment involves activation of the autonomic nervous system in the hypothalamus to minimize heat loss and maximize heat production by increasing sympathetic activity, stimulating non-shivering thermogenesis, and increasing the thickness of the insulating shell or initiating piloerection. In the long term, adaptation to cold stress results in decreased heat dissipation by decreasing the body surface area relative to body volume, which is known as a Bergman's rule.[11] Moreover, increased body weight decreases the ratio of body surface to volume, thereby reducing the heat dissipation via the body surface relative to body heat production.

Rising et al[12,13] showed that low core body temperature (CBT) may indicate an obesity-prone syndrome in humans, and Jequier et al[14] reported that an increase in thermal body insulation is generally found in obese people, implying that the decreased energy production in obese people is compensated for by decreased energy dissipation to the environment. This decreased heat generation leads to a compensatory response by the body (with more heat generation and decreased heat dissipation) with eventual weight gain.[15]

The thermogenesis hypothesis can be introduced from the scaling law of metabolic rate, which is the only "law" accepted in biology; the basal metabolic rate of an organism is proportional to its body mass raised to the 3/4 power.[16,17] A corollary of the scaling relationship shows that unit cellular metabolic power *in vivo* is negatively correlated with body mass, or that an organism with a larger body mass will have a lower unit cellular metabolic power. According to this relationship, people with a weak unit cellular metabolic power would more easily gain body weight to compensate for decreased unit heat production and to prevent a decrease in core temperature (see Fig. 1). A similar tendency can be hypothesized for Taeeum-type people. Relatively lower aerobic ability induces a decrease of mitochondrial density in cells,[8] resulting in a

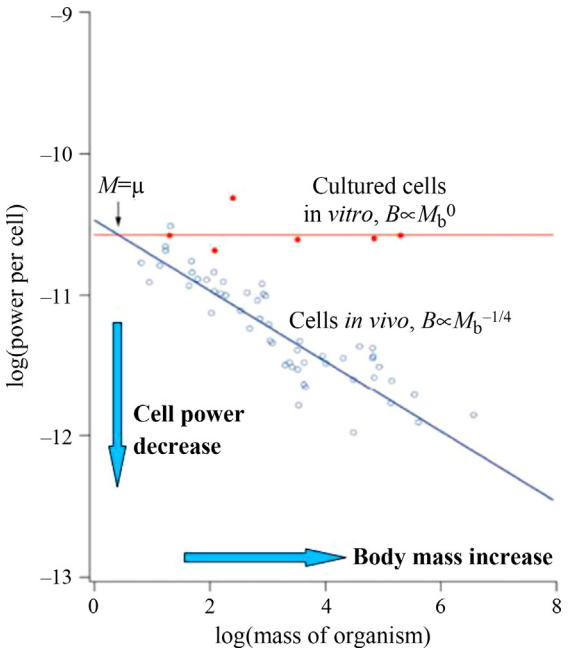

Fig. 1 – Scaling law showing that a weak metabolic power function can induce weight gain.

decrease in unit cellular power and eventual increase in body mass according to Fig. 1.

In summary, the hypothesis is explained as follows:

1) If we assume that Taeeum-type people have relatively weak function in the lung system, their maximal aerobic capability is considered to be weak.
2) Considering that maximal aerobic rate is directly related to the mitochondrial density in the cell and therefore cellular heat production, Taeeum-type people have a relatively poor ability to produce heat.
3) Taeeum-type people are therefore chronically exposed to cold stress. The human core temperature is maintained at nearly a constant level, therefore the compensatory mechanism is activated and the chronic cold stress activates the long-term adaptation mechanism leading to weight gain.

5. Analysis of the hypothesis using a mathematical formulation

To explain the physiological mechanism of the present hypothesis, we performed a theoretical analysis. For this purpose, we introduced two physical principles: the first law of thermodynamics and temperature homeostasis in the human body.

First, we consider mass conservation in the human body. Combustible energy in the body is modulated by energy balance, which is determined by energy intake (or food intake) and energy expenditure (or physical activity).[18] Hence, the following differential equation for change in body mass is derived:

$$\frac{dC}{dt} = EI - TEE \tag{1}$$

where C is total content of combustible energy in the body (in MJ), t is time scale (in days), EI is the energy intake (in MJ/day), and TEE is the total energy expenditure (in MJ/day). This equation can be converted into the equation below when we introduce body weight (M, in kg), basal metabolic rate (BMR, in MJ/day), and physical activity level (PAL).[18]

$$\frac{dM}{dt} = \frac{1}{c}(EI - PAL \times BMR) \tag{2}$$

Here, c is energy stored per kilogram of body weight (in MJ/kg). In general, EI and PAL are variable depending on the physiological or psychological states of the human body. To reflect this, we differentiate EI and PAL into 'basal' and 'adaptive' parts. Then, Eq. (2) is converted into:

$$\frac{dM}{dt} = \frac{1}{c}(EI_{basal} - PAL_{basal} \cdot BMR) + \frac{1}{c}\left(EI_{adaptive} - PAL_{adaptive} \cdot BMR\right) \tag{3}$$

In Eq. (3), the second term on the right-hand side is due to homeostatic function of the body and is thus rewritten as follows:

$$\frac{dM}{dt} = \frac{1}{c}(EI_{basal} - PAL_{basal} \cdot BMR) + (Homeostatic\ effect) \tag{4}$$

The homeostatic term in Eq. (4) includes the physiological, psychological, and habitual effects. To represent this term, an intuitive approximation is required. Here, we introduce the set-point theory[19] of body weight to model the homeostatic effect. According to the theory, there is a set-point of body weight that maintains a constant level. When the body weight is over the set-point value, the homeostatic regulatory function in the body will try to decrease body weight, and *vice versa*. We define this set-point as the thermal equilibrium weight (M_{TE}). Hence, the homeostatic effect is proportional to the difference between M_{TE} and body weight (M).

$$(Homeostatic\ effect) = \lambda \cdot (M_{TE} - M) \tag{5}$$

$$\frac{dM}{dt} = \frac{1}{c}(EI_{basal} - PAL_{basal} \cdot BMR) + \lambda \cdot (M_{TE} - M) \tag{6}$$

Here, is a proportional coefficient (λ) and also plays the role of Lagrange multiplier from a mathematical aspect. Let us consider the general equation, $y = f(x)$, with a constraint of $g(x) = 0$. Mathematical formulation of the Lagrange multiplier is represented as follows.

$$(y - f(x)) - \lambda \cdot g(x) = 0 \tag{7}$$

If we replace the functions of y, $f(x)$, and $g(x)$ in Eq. (7) with dM/dt, $\frac{1}{c}(EI - PAL \cdot BMR)$, and $(M_{TE} - M)$, respectively, then the equation completely coincides with Eq. (6). To define M_{TE}, we used the principle of temperature homeostasis.

Humans are homeothermic, and CBT is maintained at a constant level of 37 °C by the central temperature controller. The variation in CBT is governed by the balance between heat production and dissipation. When this balance is disturbed

(e.g., by mitochondrial dysfunction or hypothyroidism), the core temperature falls. The central temperature regulator will then activate an initial set of short-term control functions, such as increasing sympathetic activity, stimulating non-shivering thermogenesis, increasing the thickness of the insulating shell, and initiating piloerection. These short-term regulations are gradually replaced by changes in body mass and/or composition if the disturbances persist for a certain period of time. These long-term adaptations again help to restore the core temperature to normal levels, either by increasing heat production by means of increased body mass or decreasing heat dissipation with increased subcutaneous fat.

According to the first law of thermodynamics, temporal variation in body core temperature can be explained using the following equation[20]:

$$MC_P\frac{dT}{dt} = Q_{production} - Q_{dissipation} \tag{8}$$

where M is the body weight, Cp is the specific heat of the body, T is the CBT, and $Q_{production}$ and $Q_{dissipation}$ are heat production and dissipation, respectively. Heat is produced mainly by metabolic activity and dissipated to the environment by conduction, convection, evaporation, and radiation. Consequently, heat production and dissipation are represented by the following equations:

$$Q_{production} = k \cdot f(M) \tag{9}$$

$$Q_{dissipation} = \chi \cdot (T - T_A). \tag{10}$$

Eq. (9) represents heat production in the body as function of body weight. Here, k is the constant, representing a kind of personal characteristic such as mitochondrial function, level or sensitivity of thyroid hormone. $f(M)$ represents the function of the body weight. Regardless of the unclear characteristics of the function, it is a positively increasing function of body weight. Eq. (10), proposed by Chaui-Berlinck et al,[20] represents the general thermal conductance for heat exchange by conduction, convection, evaporation, and radiation. Here, χ is a function of the ambient temperature, T_A. Although χ can be changed according to heat balance, it is assumed in the present study that it does not affect the long-term heat balance.

Since humans are homeothermic, the CBT variation in Eq. (8) must be zero:

$$\Delta Q = Q_p - Q_d = 0 \tag{11}$$

Here, if we include the regulatory effect of body temperature, we get the following equation:

$$\Delta Q_{basal} + \Delta Q_{disturbed} - \Delta Q_{ST} - \Delta Q_{LT} = 0 \tag{12}$$

where ΔQ_{basal} is the difference between heat production and dissipation in basal state. $\Delta Q_{disturbed}$ represents the disturbance of heat production or dissipation due to thyroid hormone or mitochondrial dysfunction. ΔQ_{ST} and ΔQ_{LT} denote thermal variations due to short-term (ST) and long-term (LT) regulation of the CBT, respectively. In the normal state, heat production balances heat dissipation to maintain a constant body temperature. If this balance is disturbed, short-term regulatory mechanisms will be activated to restore the heat balance. If the disturbance persists, the short-term responses are gradually replaced by the long-term adaptation involving body weight changes. In this study, we consider only the long-term regulation, $\Delta Q_{ST} = 0$. Thus, Eq. (12) is changed into:

$$\Delta Q_{LT} = \Delta Q_{basal} + \Delta Q_{disturbed} \tag{13}$$

When the energy balance in Eq. (13) is satisfied, thermal equilibrium of the body is restored. We conjectured that the body weight at thermal equilibrium is M_{TE} in Eq. (6). If we insert Eq. (9) and (10) into Eq. (13), then Eq. (14) and (15) are derived.

$$[k \cdot f(M_{TE}) - \chi(T - T_A)] = (k \cdot f(M_{basal}) - \chi(T - T_A)) + \Delta Q_{disturbed} \tag{14}$$

$$f(M_{TE}) = f(M_{basal}) + \frac{\Delta Q_{disturbed}}{k} \tag{15}$$

One noticeable fact in Eq. (15) is that coefficient k depends on several physiological factors, such as mitochondrial function, level or sensitivity of thyroid hormone. If metabolic power is relatively large, then the relative value of k will be also high.

We explain the present hypothesis using the derived equations as follows:

1) Taeeum-type people have relatively weak function in the lung system and their maximal aerobic capability is considered to be weak. This indicates that Taeeum-type people may have relatively low value of k in Eq. (15), inducing higher value of $f(M_{TE})$.
2) Since $f(M_{TE})$ is a positively increasing function of M_{TE}, Taeeum-type people have relatively higher value of M_{TE}.
3) Taeeum-type people therefore have a relatively higher homeostasis effect in Eq. (6), indicating a large variation in body weight and thus they are prone to becoming obese.

6. Limitation of the present hypothesis

Although we have presented a hypothesis that can explain a specific constitutional characteristic of Taeeum people – that they are prone to be obese – it has several limitations. First, it is known that Taeeum-type people readily perspire. This means that Taeeum-type people might have higher chance of increasing their metabolism, which goes against our hypothesis. Although we conjectured that this phenomenon is due to temporary over-activation of regulatory function to restore homeostasis, there is no clear evidence about this. Second, to date there is no clinical or experimental evidence to support our hypothesis. Therefore, supporting data are needed from clinical studies to test our hypothesis. These limitations are not, however, expected to greatly alter the main findings of this study. In the future, we would like to design clinical studies to verify our hypothesis.

Conflict of interest

There is no conflict of the interest.

Acknowledgments

This study was supported by the Korean Ministry of Education, Science and Technology (Grant No. M1064302000-07N4302-00000 and Grant No. 20120009829).

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