Shimane J. Med. Sci., Vol.20 pp.45-51, 2002

A YOUNG FEMALE PATIENT SUFFERING FROM HYPOTHERMIA IN A COOL ENVIRONMENT

Osamu SHIDO[a], Naotoshi SUGIMOTO[b], Sotaro SAKURADA[c], Shoetsu SHIMURA[d], Akira ASAI[d], Rhyo SUMITA[d] and Shoichi KOIZUMI[d]

[a]Department of Physiology, Shimane Medical University, Izumo 693-8501, Japan; [b]Department of Molecular Vascular Physiology, Kanazawa University, Graduate School of Medical Science, Kanazawa 920-8640, Japan; [c]International Research Center for Traditional Medicine, Toyama Prefecture International Health Complex, Toyama 939-8224, Japan; and [d]Department of Angiogenesis and Vascular Development, Kanazawa University Graduate School of Medical Science, Kanazawa 920-8640, Japan

(Accepted March 14, 2003)

A 17-year-old female patient suffering from severe hypothermia was admitted to the Kanazawa University Hospital in winter, 1998. Her body temperature at admission was 31.8℃. There were no overt abnormalities responsible for hypothermia in routine physical, neurological and hematological examinations. Magnetic resonance images showed no specific changes in the brain, especially in the hypothalamus. When the patient was exposed to mildly cool environments (20℃ and 24℃), her rectal temperature gradually and continuously fell without associated autonomic and behavioral thermoregulatory responses. The patient felt cool, but did not notice the drop in her core temperature. In additional observations, the patient appeared to produce heat during fever, and could perspire during exercise. Taken together, it appears that the threshold core temperatures for cold-defense responses of the patient shifted to extremely low levels, which then resulted in pronounced hypothermia in a cool environment.

Key words: hypothermia, poikilothermia, thermoeffector threshold, thermoregulation

INTRODUCTION

Overt hypothermia in humans is commonly a result of accidents, such as exposure to extreme cold and intoxication. In neonates or the elderly, hypothermia can be induced even in a mildly cool environment, since their thermoregulatory system is immature or somehow deteriorated with advancing age. In clinical cases, there are a number of reports of patients who showed chronic or periodic hypothermia. The disorder of body temperature control in these patients was typically associated with accountable hematological and neurological abnormalities or medical treatments, e.g., severe hypothyroidism, panhypopituitarism (1), agenesis of the corpus callosum (2), psychological derangement (3), multiple sclerosis (4,5), brain tumor extending into the hypothalamic region (6), hypothalamic surgery (7), localized degenerative lesion in the anterior hypothalamus (8), or anesthesia (9).

In 1998, we experienced a hypothermic patient, i.e., a young female who suffered from severe hypothermia in a cool environment. Although various medical and physiological tests were performed, we failed to find obvious physical, psychological, neurological or hematological abnormalities responsible for her hypothermia. Indeed, the patient enjoyed a normal school life, except for hypothermia in winter. This case seems to be quite rare especially in terms of its etiology and hence is reported here.

CASE REPORT

The patient of this report was a 17-year-old Japanese female. At birth, there were no particular abnormalities, and no delays of psychological, intellectual, or motor developments were pointed out. Her family history is unremarkable. In February 1998, she felt very poorly (her expression was nausea) during a regular exam in her high school and was brought to Kanazawa University Hospital. Her movements and conversation speed were slow, but

Correspondence: O. Shido, M.D., Ph.D. Department of Physiology, Shimane Medical University, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan
Tel: +81-853-20-2111
Fax: +81-853-20-2110
e-mail: o-shido@shimane-med.ac.jp

consciousness was clear and intelligence was not disturbed. Physical examination on admission was as follows: body temperature (oral temperature), 31.2℃; pulse rate, 30～40 beats/min and regular; arterial blood pressures, 84/42 mmHg; heart and respiratory sounds, clear and normal; abdominal region, no particular findings; skin, dry but not edematous; height, 151.9 cm; body mass, 52.3 kg. There were neither goiter, swollen lymph nodes in the cervical region, large tongue nor other physical deformities. In addition, there were no abnormal findings in routine neurological tests such as the patellar tendon reflex and pathological reflexes. A chest X-ray and ECG were also judged within normal.

Laboratory data of the patient are summarized in Table 1. There were various abnormal findings in the peripheral blood and blood chemistries, e.g., thrombocytopenia and increases in plasma levels of electrolytes, some enzymes (GOT, GPT and LDH) and energy substrates (triglyceride and blood sugar), although the magnitudes of these abnormalities were not significantly large. Plasma TSH (normal range, 0.27～5.00 μU/ml) level was slightly increased despite the normal plasma concentrations of free thyroxin and free triiodothyronin. Prolactin level (normal range, 3.0～32.2 ng/ml) was also elevated. On a different day from the hematological examination, urinary adrenaline, noradrenaline and DOPA levels were measured and those levels were judged within normal ranges.

Table 1 Laboratory findings of the patient on admission

<Peripheral Blood >		<Hormones>	
WBC	3,500 /μl	FT4	0.98 ng/dl
RBC	495×10^4 /μl	FT3	3.28 pg/ml
Hb	14.6 g /dl	TSH	5.63 μU/ml *
Ht	48.0 %	PRL	44.8 ng/ml *
Plts	10.4×10^4 /μl #	LH	<0.5 mIU/ml
		FSH	<0.5 mIU/ml
<Blood Chemistries>		ACTH	24.8 pg/ml
BUN	27 mg/dl *		
Cr	1.0 mg/dl		
Na	154 mEq/l *		
K	4.8 mEq/l		
Cl	114 mEq/l *		
Ca	5.3 mg/dl *		
P	3.7 mg/dl		
ALP	308 IU/l		
GOT	50 IU/l *		
GPT	63 IU/l *		
LDH	467 IU/l *		
ChE	9.87 IU/l		
T.Bil	0.2 mg/l		
TP	7.6 g/dl		
T-Cho	241 mg/dl *		
TG	349 mg/dl *		
FBS	127 mg/dl *		

FT4, free thyroxin; FT3, free triiodothyronin. # and * indicate that the values are lower and higher than normal ranges, respectively.

When the patient was 15 years old, estrogen and progesterone replacement therapy was commenced for a delay of puberty and menstruation was attained. In addition, possibilities of small pituitary body and hypopituitarism were suggested at 16 years old. Thus, a TRH-insulin stimulation test and magnetic resonance imaging (MRI) studies of the head, especially in the hypothalamo-pituitary region, were performed. However, plasma TSH, prolactin, cortisol and ACTH responded normally to the hormonal stimuli, and there were no abnormal findings in the MRI.

During admission, the patient was treated with l-thyroxin (levothyroxin sodium), suspecting hypothyroidism, although physical examinations and laboratory data were atypical for the disease. The hormone replacement therapy, however, minimally improved hypothermia, i.e., body temperature (oral temperature) of the patient stayed 34-35℃ indoors at room temperature. After a brief evaluation of her thermoregulatory function, the patient was discharged. The hypothermic episode in winter season still persists, although there are no difficulties or disturbances in her daily life and social activities except for eventual hypothermia.

THERMOREGULATORY FUNCTION TEST

Thermoregulatory function of the patient was examined simply by exposing the patient to 3 different ambient temperatures (T_a). Each test was conducted on different days, after the patient and her parents gave their informed consent. The patient was instructed to arrive at the laboratory by 13:30 h by walking after having lunch. She wore a T-shirt and shorts and entered a climatic chamber (TBR-2HAG2A, Tabai Espec, Osaka) initially set at a T_a of 28.0 ± 0.3℃. The relative humidity was

maintained at 60 ± 3% throughout the study. After all devices for measurements were fitted on the patient, the patient sat on a chair in an upright position and rested for 30 min. Then, the T_a of the chamber was changed to 20°C, 24°C or 40°C in ca. 20 min and the new T_a was maintained for 90, 90 or 40 min, respectively. The first two T_as were chosen for cold exposure tests and the last T_a was for a mild heat exposure test.

The patient's rectal temperature (T_{re}) was measured with a thermistor probe introduced 15 cm into the rectum. Skin temperatures were recorded at 7 body sites (forehead, trunk, forearm, hand, thigh, calf and foot) by skin thermistors held in place with surgical tape. The accuracy of the thermistors (Techno Seven., Yokohama) was estimated to be within ± 0.05°C. Heart rate was estimated by the count of R-wave in one min on an ECG. All data were sampled every 30 sec via a computer-based logging system (PC9801VX, NEC, Tokyo). In addition, oxygen consumption and carbon dioxide production were measured every 20 min using a respiratory gas analysis system (Vmax 08B, SensorMedics, Yorba Linda, CA, USA) before and during the exposure to the T_a of 24°C.

Cold Exposure Test: Figures 1 and 2 show changes in T_{re} and skin temperatures at the 7 sites of the patient before and during the exposure to the T_a of 20°C and 24°C, respectively. The initial T_{re} levels of the patient were not hypothermic (>37.0°C), maybe due to walking to come to the laboratory and movements required for preparation of the test. However, when the patient rested, her T_{re} started to drop even at the T_a of 28°C. During the 90-min temperature exposure tests, the patient's T_{re} gradually and continuously decreased. The T_{re} levels at the end of the temperature exposure tests to the T_a of 20°C and 24°C were 35.37°C and 35.55°C and the magnitudes of the fall in T_{re} during the two tests were 1.81°C and 1.34°C, respectively. Since the heart rate of the patient fell to near 40 bpm during the tests, the cold exposure was terminated to avoid cardiovascular complications. If the exposure would have been continued, the T_{re} of the patient may have dropped further.

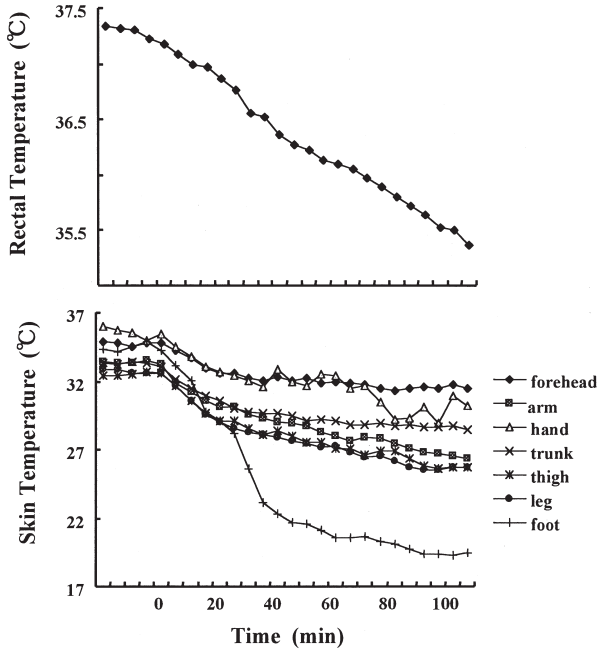

Fig. 1. Changes in rectal temperature and skin temperatures at 7 sites in the patient before and during exposure to an ambient temperature (T_a) of 20°C. The T_a was lowered from 28°C to 20°C at time 0.

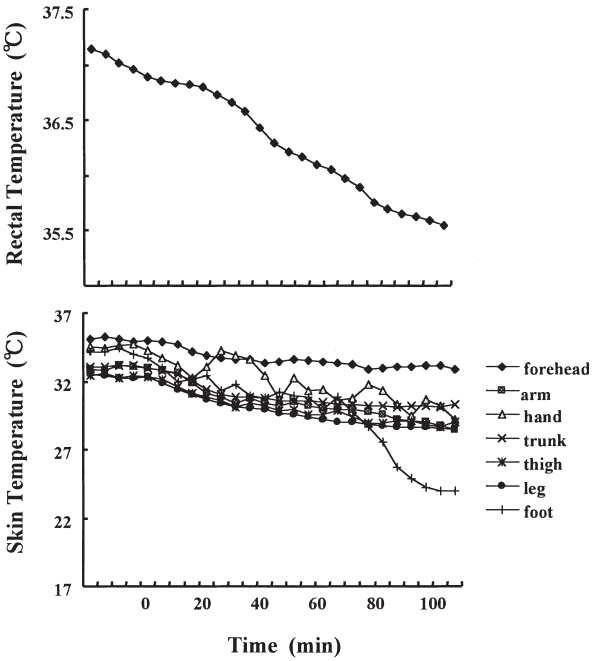

Fig. 2. Changes in rectal temperature and skin temperatures at 7 sites in the patient before and during exposure to an ambient temperature (T_a) of 24°C. The T_a was lowered from 28 °C to 24°C at time 0.

Skin temperatures of all sites dropped in association with the fall in T_a in both tests. Different from the other skin temperatures, the foot skin temperature sharply decreased and became close to the T_a, indicative of an occurrence of full vasoconstriction only in the foot skin. Skin vasoconstriction is the predominant autonomic thermoregulatory response to cold stimuli to reduce heat dissipation from the

body. It therefore appeared that the patient could respond to the mild cold and hypothermia with an activation of the heat conservation mechanism, but the responses were not induced in the whole body skin areas.

In addition to the regulation of heat loss, autonomic thermoregulation is accomplished by controlling heat production in endothermic animals. In subjects exposed to cold, shivering and nonshivering thermogenesis are induced to compensate for the increased heat loss to maintain core temperature (T_{cor}). In this patient, there were neither shivering, increased muscle tone nor other signs of thermogenesis during the cold exposure. Indeed, the oxygen consumption, an index of metabolic heat production, did not increase, but markedly decreased during the subjection to the T_a of 24°C (Fig. 3). The findings obviously suggest that autonomic thermogenic responses did not take place in the patient in the mildly cool environment. The absence of the thermogenic response, however, did not simply indicate a degradation of the thermogenic effector system. During admission, the patient accidentally caught a common cold, and her body temperature increased from 35 °C to 37°C without vigorous movements at room temperature. The event suggests that the patient could produce heat in response to febrile stimuli and her autonomic thermogenic function itself may not have been impaired.

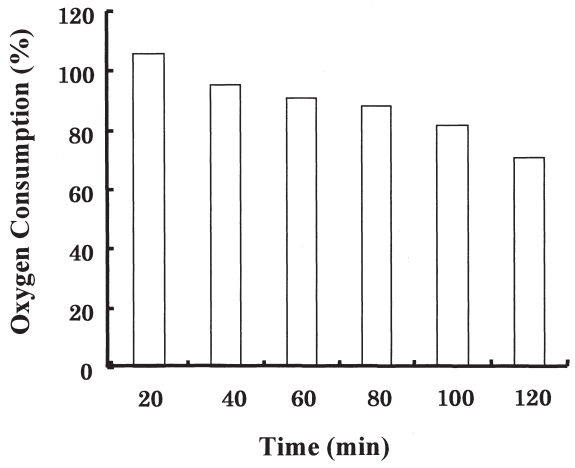

Fig. 3. Relative changes in oxygen consumption in the patient during exposure to an ambient temperature (T_a) of 24°C. The T_a was lowered from 28°C to 24°C at time 0. Values are expressed as percentages of the value before the start of the mildly cool exposure.

In addition to autonomic thermoregulation, animals use behavioral modes of effector responses to achieve a stable T_{cor}. In cold conditions, various heat conservation and thermogenic behaviors are induced to counteract changes in thermal balance and hence T_{cor}. For example, humans curl up to reduce the effective body surface area for heat loss, put on clothes, if available, to increase thermal insulation, produce heat by various types of movements, or try to escape from cold. In general, those behaviors are initiated by thermal discomfort caused by peripheral cold sensation and/or hypothermia (central cold sensation). During the cold exposure tests, the patient could feel coldness in her extremities, but did not complain of strong thermal discomfort. Indeed, the patient did not show any spontaneous activities or movements related to the cold defense responses, suggesting that thermoregulatory behaviors were not brought about.

Taken together, it is likely that in the present patient, both autonomic and behavioral thermoregulatory mechanisms were not practically activated in the cool environments even if profound hypothermia was induced by thermal imbalance.

Heat Exposure Test: Figure 4 shows changes in T_{re} and skin temperatures before and during the heat exposure test. Similarly to the cold exposure tests, T_{re} of the patient slightly fell at the T_a of 28°C. Then, T_{re} was gradually raised by the external body warming. Skin temperatures were also raised during the test. Since initial skin temperature levels were already high, sharp rises in those temperatures (indicators of cutaneous vasodilation) were not seen at any sites. During the heat exposure test, the patient complained of discomfort and headache and refused to continue the test. This behavior of the patient might be accounted as a representative heat-escaping behavior generally observed in animals and humans under thermal stimuli. At the termination of the test, in addition, there was slight sweating on the forehead of the patient. These findings reasonably suggest that there were no marked abnormalities in the autonomic and behavioral heat defense mechanisms in the patient. This assumption is supported by an interview with the patient, i.e., she could perspire during exercise and in summer time, and had never experienced a hyperthermic episode in her history.

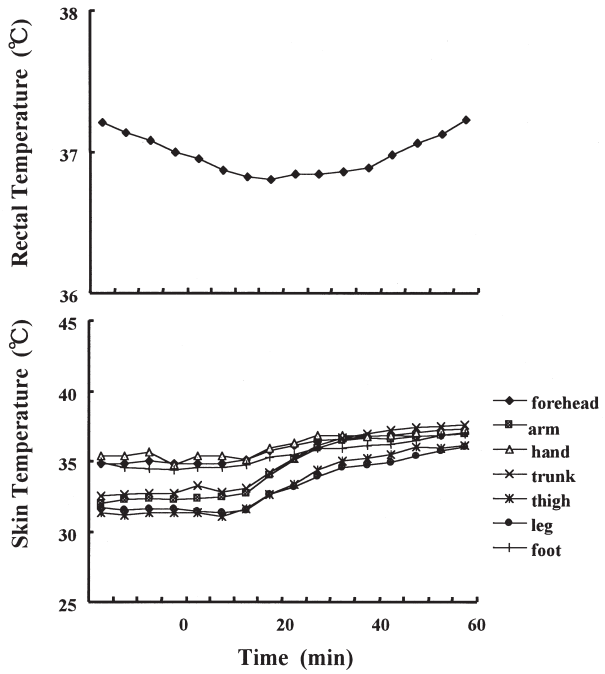

Fig. 4. Changes in rectal temperature and skin temperatures at 7 sites in the patient before and during exposure to an ambient temperature (T_a) of 40°C. The T_a was raised from 28°C to 40°C at time 0.

DISCUSSION

In the present patient, profound hypothermia was consistently induced in a mildly cool environment. There are various possibilities for the mechanism of the cold-induced drop in T_{cor}, e.g., unresponsiveness of the thermoregulatory center to cold or hypothermia, interruption of signal transduction from the thermoregulatory center to peripheral thermoregulatory effectors, and dysfunction of the effectors themselves. In this patient, heat loss and heat conservation response appeared to be preserved, since she could respond to heat or hyperthermia with perspiration and to cold or hypothermia with foot skin vasoconstriction. According to the febrile episode, the patient may be able to produce heat in the body. In addition, since there were no particular abnormalities in neurological and endocrinological studies, the system conveying thermoregulatory drives from the central nervous system to the periphery appeared to have been well maintained. Thus, it is likely that the thermoregulatory effector system, including the information transduction system, was not impaired in the patient.

In general, T_{cor} of endotherms is preferably controlled within a temperature zone between thresholds forheat dissipation and heat production (interthreshold zone) by the thermoregulatory system. When T_{cor} is shifted for some reasons and reaches either of these thresholds, the corresponding effector mechanism is activated and T_{cor} is returned to a temperature between the two thresholds. In other words, as long as T_{cor} stays within the interthreshold zone, neither autonomic nor behavioral thermoregulatory responses are brought about. In the present patient, hypothermia was reproducibly induced without an overt perception of thermal discomfort and an associated activation of autonomic and behavioral thermoregulatory responses. The observations strongly suggest that the patient's T_{cor} was maintained within her interthreshold zone, even though T_{cor} levels were extremely low. Considering minimum abnormalities in the heat loss system, therefore, the most plausible mechanism for the thermoregulatory disorder of the patient is that threshold T_{cor} for cold defense responses was reset at an abnormally low level. In this case, when the patient remains quiet in a cool environment, the amount of heat dissipation may physically overcome the resting metabolic heat production. Then, the heat balance could easily become negative and T_{cor} drops near the lowered heat production threshold. When the patient stayed in a warm condition, hypothermia could be prevented due to a positive heat balance. Although we could not determine the patient's thermoregulatory thresholds, our hypothesis appeared reasonable to explain the T_{cor} change and thermoregulation of the patient during the thermoregulatory tests (Figs. 1, 2 and 4) and her daily life.

In normal humans, the interthreshold zone is shown to be quite narrow, e.g., almost no zone between heat loss and heat production thresholds (10), or 0.6°C between the onset of sweating and full skin vasoconstriction (5). However, it has also been shown that in animals and humans, the interthreshold zone can be widened physiologically or pathologically due to downward shifts of thermogenic thresholds in some conditions. In rats, for example, endotoxin shock (11) and food deprivation (12) lowered threshold T_{cor} for nonshivering thermogenesis, while they had little influence on tail skin vasodilation threshold. Similar threshold shifts were

seen in propofol anesthetized humans (9). Recently, Kurz *et al*. (5) reported that in a patient with long-standing multiple sclerosis, the threshold for shivering markedly decreased by ca. 4℃ without an associated drop in sweating threshold. The patient's T_{cor} was near 35℃ in normal conditions (without heat exposure), and was decreased to as low as 32.8 ℃ in cool environments. That case is comparable with the present case in terms of body temperature control. In that patient, however, the characteristic white matter lesions of multiple sclerosis were diffusely distributed throughout the brain and spinal cord, and he was wheelchair-bound. As noted above, there were neither obvious neurological disorders nor significant findings by various medical checks in the present patient. Indeed, she can enjoy a normal life except for occasional hypothermia. Thus, the present hypothermic patient seems to be rather a rare case, and the etiology of this type of poikilothermia, i.e., the profound downward shifts of thermogenic thresholds, should be investigated. Further studies may help contribute to the treatment of the patient and to comprehensive understanding of the thermoregulatory system in humans.

There were several abnormal values in the laboratory findings of the present case, especially in plasma electrolytes and energy substrates. Cold and hypothermic stimuli inhibit antidiuretic hormone release from the pituitary gland directly or, if cutaneous vasoconstriction takes place, through unloading of the cardiopulmonary baroreceptors by the central shift of blood. A decline of the hormone facilitates water loss into urine and may develop hypovolemia with hemoconcentration. In addition, the metabolism of the patient should be depressed by hypothermia simply due to a Q_{10} effect. All these events associated with hypothermia might have caused the rise in blood levels of electrolytes and energy substrates in the present patient.

ACKNOWLEDGMENT

This study was supported by Grant-in-Aid for Scientific Research (№14370023) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

REFERENCES

1) MacKenzie MA, Hermus RMM, Wollersheim HCH, Pieters GFFM, Smals AGH, Binkhorst RA, Thien T, Kloppenborg PWC (1991) Poikilothermia in man: Pathophysiology and clinical implications. *Medicine* 70: 257-268.

2) Shapiro WR, Williams GH, Plum F (1969) Spontaneous recurrent hypothermia accompanying agenesis of the corpus callosum. *Brain* 92: 423-436.

3) Gray HH, Smith LDR, Moore RH (1986) Idiopathic periodic hypothermia and bizarre behaviour in the presence of occult syringomyelia. *Postgrad Med J* 62: 289-290.

4) Hutchinson FM, Bahandeka S, Moore RE (1987) Chronic hypothermia in multiple sclerosis. *J Neurol Neurosurg Psych* 50: 813-815.

5) Kurz A, Sessler DI, Tayefeh F, Goldberger R (1998) Poikilothermia syndrome. *J Int Med* 244: 431-436.

6) Nakasu Y, Takeichi T, Takayama S, Isozumi T, Handa J (1993) Poilkilotherima in a female patient with germinoma in the basal ganglia. *Acta Neurochir* 120: 190-192.

7) Regis J, Bartolomei F, de Toffol B, Genton P, Koyayashi T, Mori Y, Takakura K, Hori T, Inoue H, Schrottner O, Pendl G, Wolf A, Arita K, Chauvel O (2000) Gamma knife surgery related to hypothalamic hamartomas. *Neurosurgery* 47: 1343-1351.

8) Fox RH, Davis TW, Marsh FP, Urich H (1970) Hypothermia in a young man with an anterior hypothalamic lesion. *Lancet* 7665: 185-188.

9) Leslie K, Sessler DI, Bjorksten AR, Ozaki M, Matsukawa T, Schroeder M, Lin S (1994) Propofol causes a dose-dependent decrease in the thermoregulatory threshold for vasoconstriction but has little effect on sweating. *Anesthesiology* 81: 353-360.

10) Cabanac M, Massonnet B (1977) Thermoregulatory responses as a function of core temperature in humans. *J Physiol* 265: 587-596.

11) Romanovsky AA, Shido O, Sakurada S, Sugimoto N, Nagasaka T (1996) Endotoxin shock: thermoregulatory mechanisms. *Am J Physiol* 270: R693-R703.

12) Sakurada S, Shido O, Sugimoto N, Hiratsuka Y, Yoda T, Kanosue K (2000) Autonomic and behavioural thermoregulation in starved rats. *J Physiol* 526: 417-424.