Estrogenic modulation of female thermoregulatory behavior in a cold environment

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Abstract Thermoregulation is categorized as either autonomic (i.e., sweating, shivering) or behavioral (i.e., wearing clothes, usage of air conditioner) thermoregulation. Compared to autonomic thermoregulation, the neural pathway of behavioral thermoregulation in cold environments remains unclear. A decrease in ambient temperature is perceived through thermoreceptors for detecting cold, including transient receptor potential (TRP) channels, such as TRPM8 and TRPA1, which are expressed in the sensory nerve endings of the skin. From these receptors, nerves connect to the dorsal root ganglion and dorsal horn in the spinal cord, and arrive at the lateral parabrachial nucleus in the pons, which is the same neural pathway that is used for autonomic thermoregulation. Following this, an unknown neural pathway induces thermoregulatory behavior, such as cold-escape behavior. Both young and climacteric women complain of an unpleasant thermal comfort, which is attributed to “hie-sho” (chill or poor blood circulation). The altered thermal sensation and comfort by an absence or a fluctuation of estrogen (E2) may modulate behavioral thermoregulation in females. This effect is unknown in women. However, in ovariectomized rats, E2 facilitated thermoregulatory behavior in the cold, as evaluated by an operant system and tail-hiding behavior, a possible new behavioral indicator that we reported. E2 decreased neural activity in the insular cortex, as assessed by cFos immunohistochemistry, while tail-hiding behavior increased in colder temperatures. We speculate that the suppression of neural activity in the insular cortex by E2 may be related to behavioral thermoregulation in a cold environment. Therefore, it is necessary to clarify the effects of E2 on TRPM8 and TRPA1 channels, and the neural pathway of behavioral thermoregulation.

Keywords: estrogen, behavioral thermoregulation, insular cortex

Introduction

Whereas shell temperature can change under various ambient temperatures (T_a), the core temperature (T_b) of the body is maintained. The T_b is determined by a balance between heat production (e.g., metabolism in the liver and adipose tissues, muscle shivering) and heat dissipation (e.g., sweating, vasodilation, heat-escape behavior, wearing less clothes). T_b values increase or decrease when the heat production is greater or less than heat dissipation. Thermoregulation is categorized as autonomic (e.g., sweating, shivering) or behavioral (e.g., putting on clothes) thermoregulation. Humans lose body fluid and sodium ions during sweating, as well as energy due to muscle movement during shivering. Rather than losing one’s own energy, humans use warm clothes and electrical products to maintain T_b. Therefore, behavioral thermoregulation conserves more energy than autonomic thermoregulation.

Mechanisms of behavioral thermoregulation in the cold

Thermal sensation is a recognition of the temperature in the external environment. It is expressed as “This is cold.” and “This is hot.” Thermal comfort and discomfort are subjectively sensitive to temperature, and can be expressed as “I feel cold.” and “I feel hot.” Thermal sensation depends on the change velocity of the stimulus temperature, initial skin temperature, and stimulus area. On the other hand, thermal comfort can affect T_b. When a certain stimulus temperature disrupts the normal T_b, or augments hyper- or hypothermia, we feel thermal discom-
fort. Thermal discomfort for cold environments triggers thermoregulatory behavior under cold conditions.

A neural pathway for behavioral thermoregulation in the cold is unclear, although the neural mechanism underlying autonomic thermoregulation is well known. Recently, peripheral thermal acceptability in the cold was explained by cold thermoreceptor transient receptor potential (TRP) channels, such as TRPM8 and TRPA1, expressed in the sensory nerve endings supplying the skin\(^1\). From these receptors, nerves connect to the dorsal root ganglion and dorsal horn in the spinal cord, and arrive at the lateral parabrachial nucleus (LPB) in the pons, which is the same neural pathway that is used for autonomic thermoregulation. Then, an unknown neural pathway induces thermoregulatory behavior, such as cold-escape behavior\(^2\).

A few nuclei have been reported to be related to behavioral thermoregulation. In humans, blood flow in the amygdala increased in association with thermal discomfort against cold stimulus, as assessed by functional MRI\(^3\). In a PET experiment, the insular cortex in humans was activated during cold stimulus\(^4\). Secondary somatosensory areas in rats were activated by cold stimulation, when measured by microPET\(^5\). In the rat LPB, the expression of cFos, a neural marker, was increased by cold stimulus\(^6\). cFos expression in the parastrial nucleus (PS) was increased in association with increased heat-escape behavior\(^7\). Thus, it is possible that these nuclei are in the neural pathway of behavioral thermoregulation in cold environments.

**Estrogen and disorders of thermoregulation**

In females, the follicles and corpus luteum secrete E\(_2\) and progesterone, respectively. After ovulation, the estrus cycle is divided into the follicular phase with greater E\(_2\), and the luteal phase with an abundance of progesterone. Females are exposed to a fluctuation and a lack of plasma estrogen during their young and climacteric periods. A deficiency or a disturbance of E\(_2\) is a cause of climacteric disorder, osteoporosis, and Alzheimer’s disease. Therefore, E\(_2\) is important for mental and physical health during a female’s lifetime.

In Japan, approximately 30% of climacteric women complain of “hie-sho” (poor blood circulation and feel cold), which is regarded as a disorder of thermoregulation\(^7\). Hie-sho is not defined in Western medicine; however, it was recently described in international journals using various rate scales defined by Nagashima\(^8,9\) and Sakakita\(^10\). Young women in the hie-sho group complained of cold discomfort despite being in a thermoneutral environment\(^8\). Thus, it is possible that both young and climacteric women can exhibit a cold discomfort. We speculate that the altered cold sensation and discomfort due to E\(_2\) deficiency and fluctuation may change thermoregulatory behavior in the cold.

**Effect of estrogen on thermoregulatory behavior in the cold**

In young Japanese women (age: 22 ± 1 year), there were no differences in their cold sensation and comfort, skin temperature, and oxygen consumption between the follicular and luteal phases during cold exposure (T\(_a\) = 23.5°C)\(^11\). On the other hand, cold discomfort and oxygen consumption in the luteal phase of Japanese women (age: 27 ± 1 year) were greater than in the follicular phase in the cold (T\(_a\) = 15°C). In addition, the subjects in the luteal phase wore warmer clothes sooner than in the follicular phase\(^11\). These results indicate that the estrus cycle in young women influences cold sensation, comfort, and thermoregulatory behavior at 15°C. However, the effect of E\(_2\) on these measures is unclear because plasma E\(_2\) concentration was not measured, and E\(_2\) replacement was not performed in these experiments. A drop in skin temperature and the perception of cold sensation in climacteric women were at a later time point than in young women, when the subjects moved to a cold environment\(^11\). Therefore, thermoregulatory behavior in climacteric women may be delayed in a cold environment.

In an operant system, lever-presses were used to quantify the motivation for warm air in the cold\(^14\) as well as a temperature gradient system, in which rats selected their preferred temperature\(^15\), providing a way to measure thermoregulatory behavior. Administration of E\(_2\) to ovariectomized rats augmented their thermoregulatory behavior at -7°C, as assessed by an operant system\(^16\); however, E\(_2\) administration did not affect behavior at 15°C\(^17\). These results show that E\(_2\) may increase behavioral thermoregulation during extreme cold.

We reported “tail-hiding behavior” that rats place their tails underneath their body trunks in cold environments as a possible behavioral indicator\(^18,19\). The T\(_b\) was lower in rats that fasted for 42-h and were prevented from performing tail-hiding behaviors, compared to the T\(_b\) in rats that were allowed to perform the behavior\(^19\). Thus, tail-hiding behavior could be a simple behavioral indicator of an animal’s thermal status in the cold\(^19\). We studied whether E\(_2\)’s influence on behavioral thermoregulatory responses in the cold could be assessed by behavioral observations of tail-hiding behavior. E\(_2\) administration of ovariectomized rats increased the duration of tail-hiding behaviors during mild cold exposure (T\(_a\) = 16°C). In addition, the T\(_b\) of rats prevented from performing tail-hiding behavior was lower than in the rats allowed to perform the behavior\(^20\). These results demonstrate that E\(_2\) may affect a behavioral thermoregulatory response in mildly cold environments in female rats.

The operant system and tail-hiding behavior were sensitive to the effects of E\(_2\) on the thermoregulatory behavior in extremely and mildly cold environments, respectively. It is speculated that the tail-hiding behavior could be an indicator of this response, even though the cold stimulus
was weak, because this behavior is a natural thermoregulatory behavior. In conclusion, E2 may facilitate behavioral thermoregulation in cold environments in female rats, although it is unclear if this effect also occurs in women.

**Mechanism of estrogenic modulation to thermoregulatory behavior in the cold**

*In vitro*, deficient E2 levels reduced TRPM8 responsivity in sensory nerve endings in the skin of rodents\(^{21}\). We hypothesized that E2 may modulate cold thermoreceptors, such as TRPM8 and TRPA1, and may increase thermoregulatory behavior during cold exposure in rats. Our experiments regarding this hypothesis are currently ongoing.

The effect of E2 on cFos expression in the nuclei, which may be related to thermoregulatory behavior\(^{2-6}\), and in the medial preoptic area was investigated, when increased tail-hiding behavior was observed in E2-treated rats in the cold. The cFos expression in the amygdala, insular cortex, secondary somatosensory area, medial preoptic area, LPB, and PS increased during cold exposure (T<sub>a</sub> = 16ºC) in rats with and without E2. In addition, in rats with E2, cFos expression in the insula was less than in rats without E2\(^{20}\). The E2 receptors α and β mRNA\(^{22}\) and E2 receptor β\(^{23}\) were distributed in the insula in female rats. Therefore, we speculated that E2 may inhibit the neural activity in the insula through E2 receptors, and facilitate tail-hiding behavior. The detailed mechanisms are not yet known. Further research is necessary to identify this neural network.

In conclusion, E2’s influence on the central insula (insular cortex) might be related to the facilitation of thermoregulatory behavior in the cold, though the effect of E2’s influence on peripheral thermoreceptors is still unknown.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

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