Neurokinin B and VMS

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Introduction

This internal training is for the VEOZA™ TEAM. The objective of this training is for learners to describe the normal process of thermoregulation and explain how thermoregulation is altered during the menopausal transition. This training is for background information only and not for external distribution or promotional use.

Overview

This eTutorial will consist of narrated animations that introduce the function of the neuropeptide neurokinin B (NKB) and the neurokinin-3 receptor (NK_3R) in thermoregulation in the body and describe their role in vasomotor symptoms (VMS) experienced by women during menopause.

VMS and Thermoregulation

Learning Objective

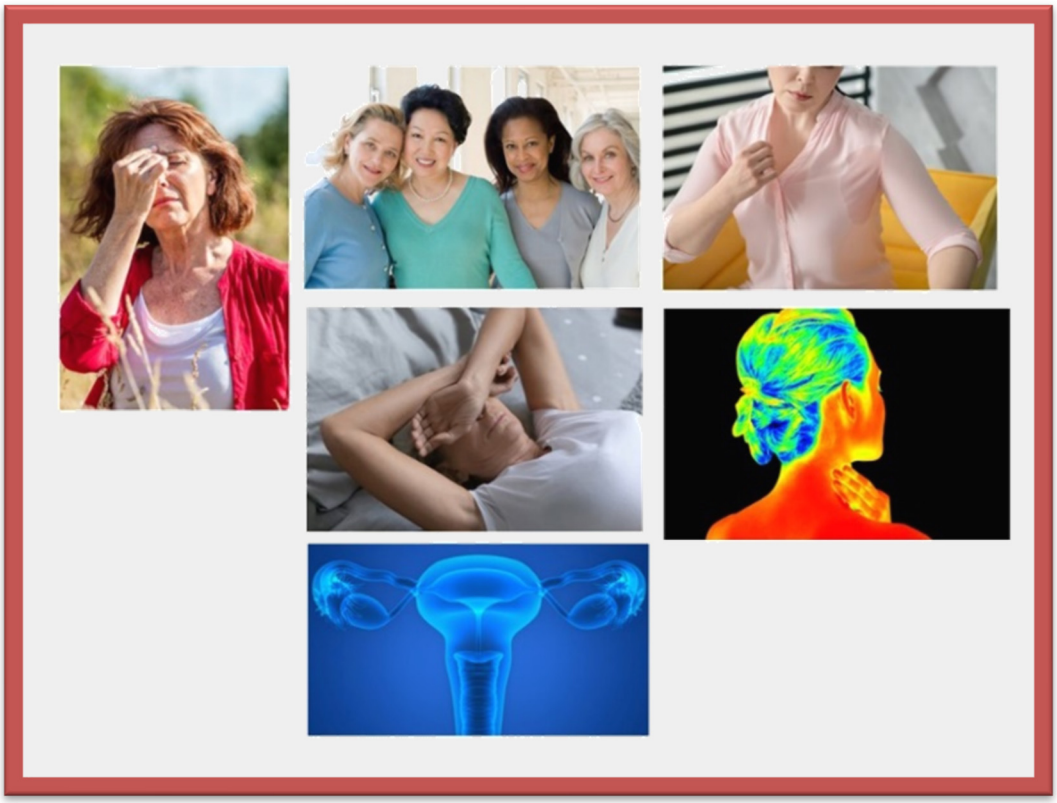
Let's get started with a discussion of how the body maintains its core temperature, a process called thermoregulation, using a structure in the brain called the hypothalamus.

Upon completion of this lesson, you should be able to describe the normal process of thermoregulation and explain how thermoregulation is altered during the menopausal transition.

VMS

VMS are characterized by hot flashes and night sweats (hot flashes that occur at night). VMS are the most commonly reported symptoms during the menopause transition. Approximately 20% to 40% of premenopausal women report these symptoms, increasing to 60% to 80% of women in perimenopause and postmenopause. There is also variation across racial and ethnic groups.

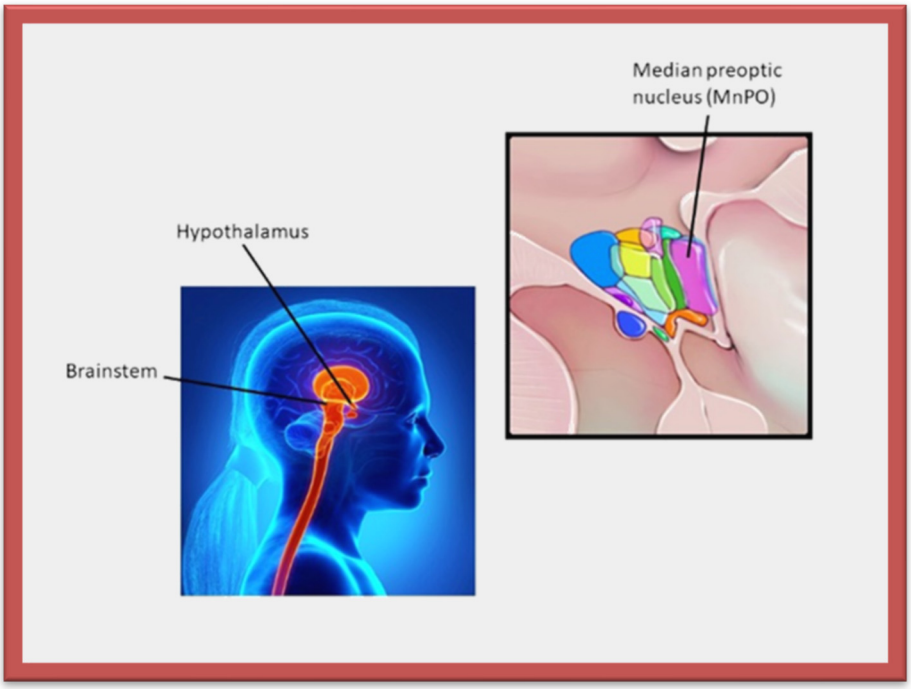
The underlying physiology of VMS is complex and most likely involves multiple interactive physiologic processes, including hormonal changes and altered thermoregulation. Thermoregulation is the process by which the body controls heat production and heat loss to maintain a core body temperature within a specific set of limits.



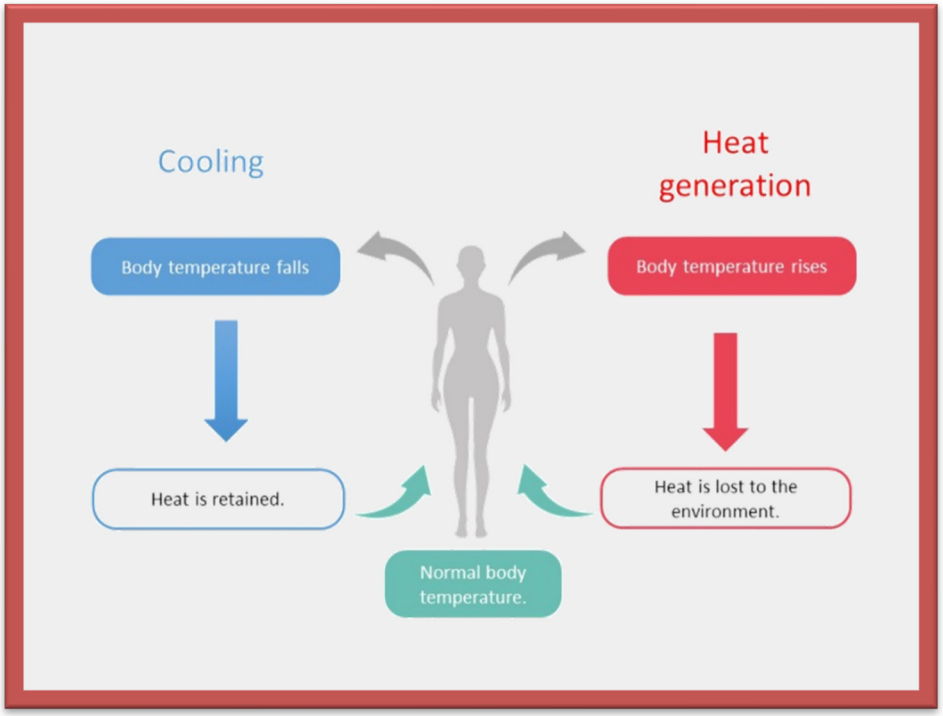
Thermoregulation

Thermoregulation occurs in the hypothalamus, a structure about the size of an almond that is found in the brain just above the brainstem.

The hypothalamus consists of multiple nuclei, or groups of nerve cells that all have a variety of functions. Some nuclei regulate food intake, while others regulate water balance and thirst. The median preoptic nucleus (MnPO) is located in the thermoregulatory center of the hypothalamus and plays a key role in thermoregulation. Hypothalamic neurons receive input from thermoreceptors. Subsequently, the body reacts accordingly to the change in temperature.

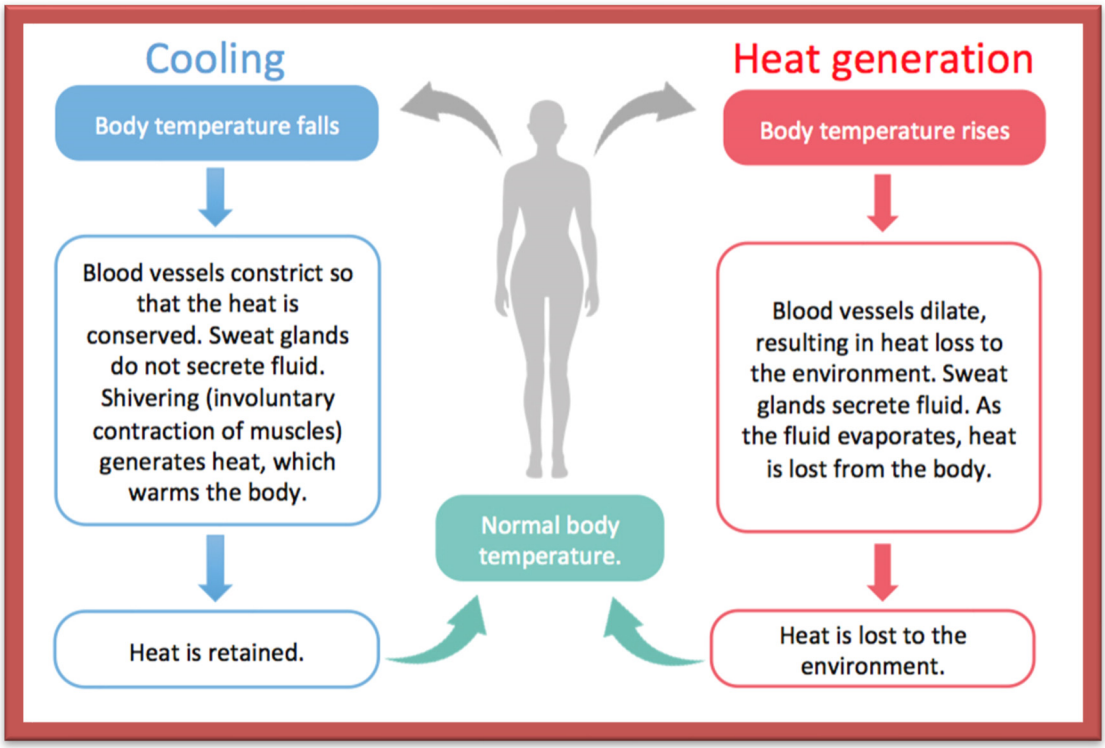


Depending on the signals sent to the hypothalamus, neurons within the MnPO initiate cooling or heat-generating actions to maintain a relatively constant body temperature through the release of neurotransmitters that initiate the release of hormones to carry out thermoregulatory processes within the body.



If body temperature is increased, thermoregulatory neurons in the MnPO trigger heat-dissipation mechanisms, such as vasodilation (widening of the blood vessels) and sweating, to cool the body back down. Vasodilation causes an increased flow of blood to the skin, from which heat can radiate and be lost from the body.

If body temperature is decreased, thermoregulatory neurons in the MnPO trigger heat-promotion mechanisms, such as vasoconstriction (constriction of the blood vessels) and shivering, to increase body temperature. Vasoconstriction restricts the flow of blood to the skin, diverting blood to vital organs.

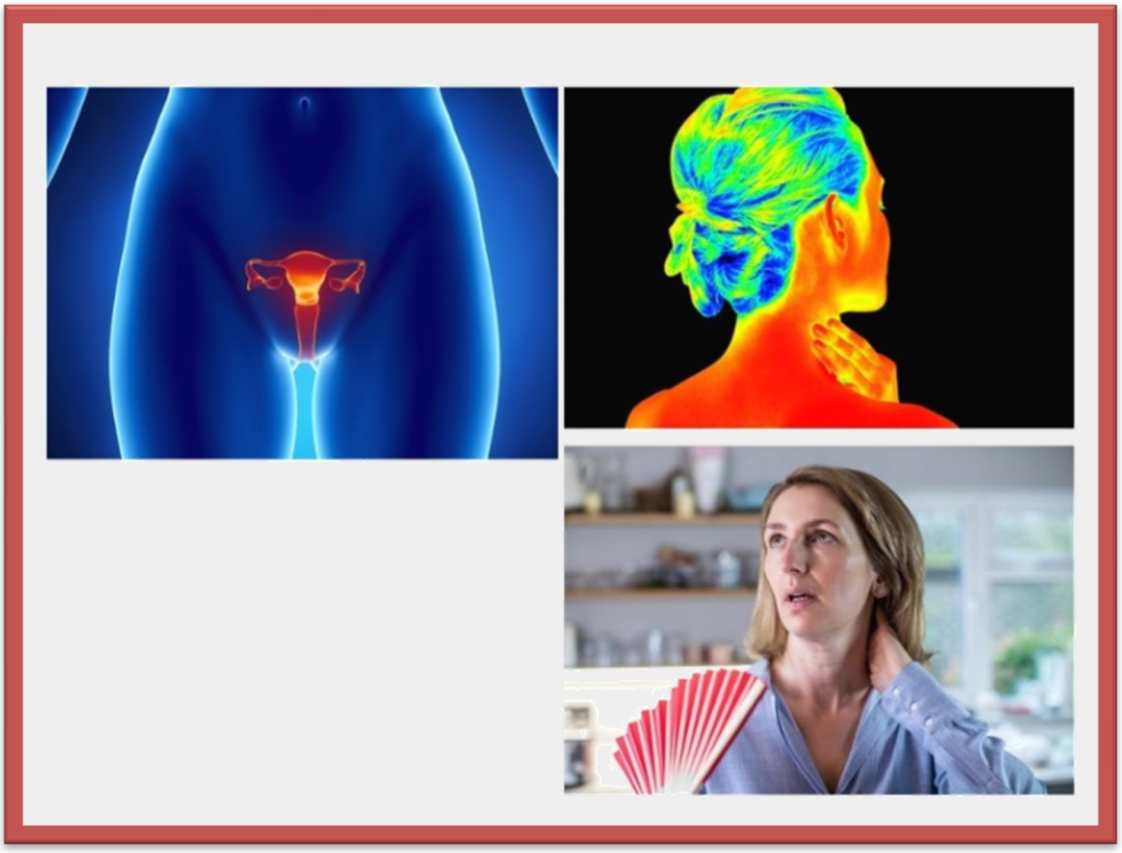


Physiology of VMS

Estrogen plays a role in thermoregulation. Declining estrogen levels during the menopausal transition result in increased activation of heat dissipation mechanisms, such as vasodilation and sweating. This can result in sudden, intense heat and flushing, characteristic of VMS.

Hormone therapy, which includes estrogen, estrogen and progestin, or estrogen and a selective estrogen receptor modulator, is the gold standard for treatment of VMS.

In the next section, we will discuss in more detail the signaling within the hypothalamus and MnPO that can lead to VMS.



Knowledge Check

1.1 Declining estrogen levels during the menopausal transition result in which one of the following activities?

A: Decreased activation of heat dissipation mechanisms, such as vasodilation and sweating

B: Increased activation of heat dissipation mechanisms, such as vasodilation and sweating

C: Decreased activation of heat-promotion mechanisms, such as vasoconstriction and shivering

D: Increased activation of heat-promotion mechanisms, such as vasoconstriction and shivering

1.2 If body temperature is increased, thermoregulatory neurons in the MnPO trigger which of the following heat-dissipation mechanisms to cool the body back down? Select all that apply.

[ ] Vasodilation

[ ] Vasoconstriction

[ ] Shivering

[ ] Sweating

Answers

1.1 B

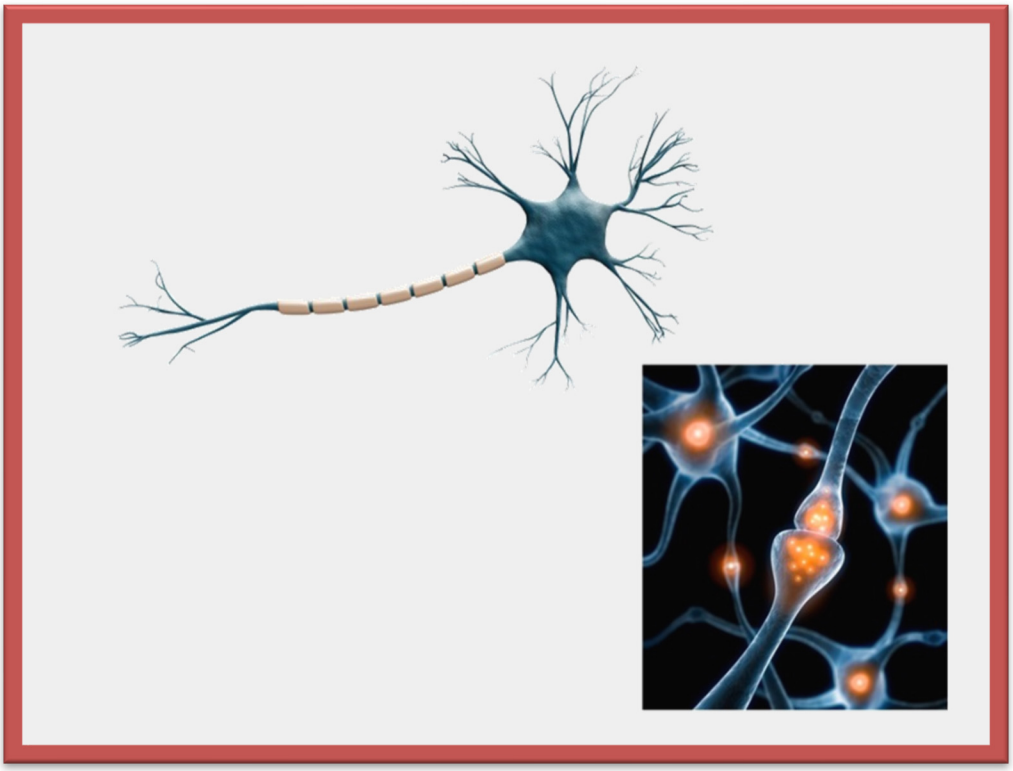
1.2 Vasodilation and Sweating

NKB and VMS

Learning Objective

This section will introduce the role of the neuropeptide neurokinin B (NKB) and kisspeptin-neurokinin B-dynorphin (KNDy) neurons in VMS. Note that this is not the only mechanism for regulatory control of VMS, but is one of several physiologic processes that may play a role in VMS.

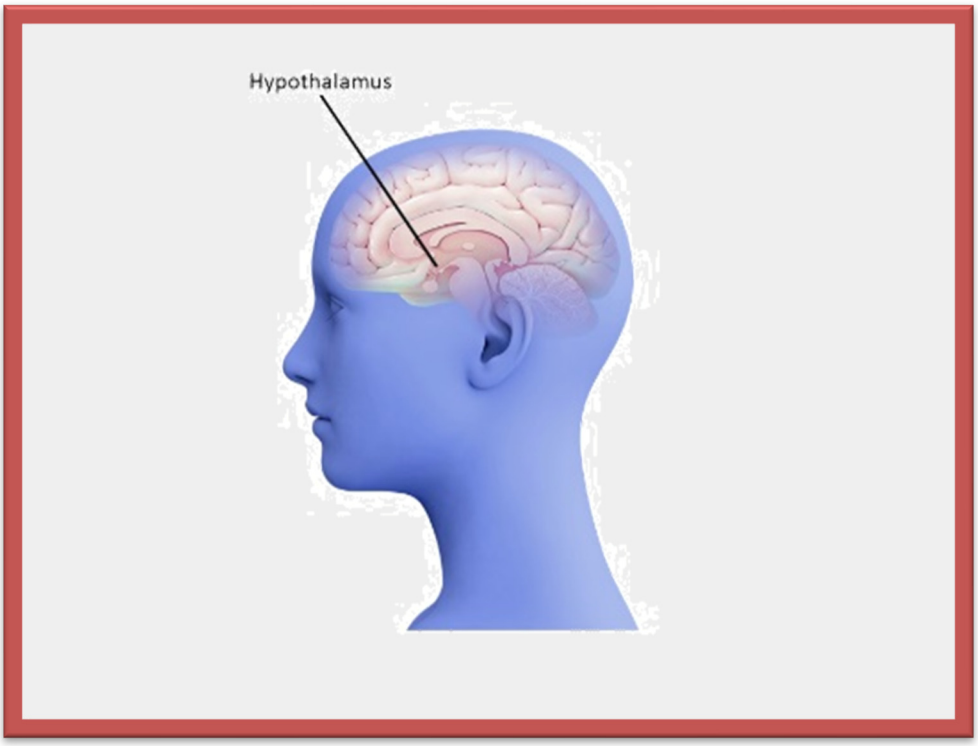
Upon completion of this lesson, you should be able to describe the role of the neuropeptide neurokinin B (NKB) and kisspeptin-neurokinin B-dynorphin (KNDy) neurons in VMS.



KNDy Neurons and Normal Thermoregulation

As you learned in the previous section, VMS may originate from alterations in signaling in the hypothalamus. Inside the thermoregulatory center in the hypothalamus, specific neurons, known as kisspeptin-neurokinin B-dynorphin (KNDy) neurons, contribute to the regulation of the body's temperature. Since KNDy neurons project to the site within the hypothalamus that is involved in thermoregulation (the MnPO), evidence suggests that KNDy neurons are involved in thermoregulation and VMS.

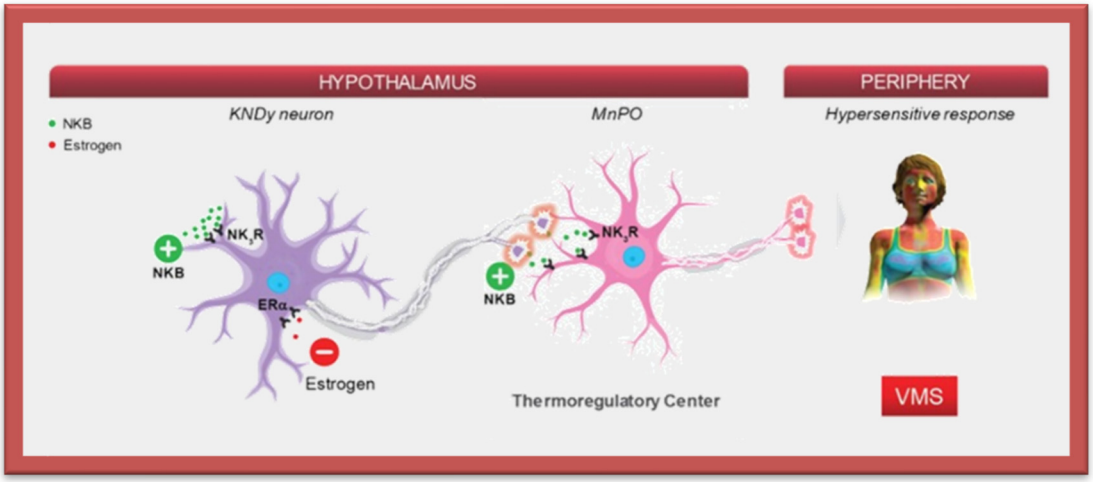
KNDy neurons are inhibited by estrogen acting on estrogen receptor α (ERα) and stimulated by the neuropeptide neurokinin B (NKB), acting on the neurokinin-3 receptor (NK_3R) in a delicate balance. KNDy neurons relay signals to the MnPO though the release of NKB, which binds to NK_3R expressed on neurons within the MnPO.



Loss of Thermoregulatory Control and VMS

Through the menopause transition, declining estrogen disrupts the balance with NKB. Unopposed, NKB signaling increases KNDy neuronal activity, leading to hypertrophy of the KNDy neuron and altered activity on the thermoregulatory center, resulting in VMS associated with menopause.

As a result, the thermoregulatory center triggers heat-dissipation effectors that are experienced as hot flashes and night sweats, or VMS.



Knowledge Check

2.1 Choose the correct answers from the drop-down choices below.
KNDy neurons are <stimulated, inhibited> by the binding of NKB to NK_3R and <stimulated, inhibited> by the binding of estrogen to ERα in a delicate balance.

2.2 Choose the correct answers from the drop-down choices below.
KNDy neurons relay signals to the MnPO through the release of <estrogen, ERα, NKB>, which binds to NK_3R expressed on neurons within the MnPO, stimulating neurons in the MnPO to initiate downstream <heat-dissipation, heat-conservation> responses.

Answer

1.1 stimulated, inhibited

1.2 NKB, heat-dissipation

Glossary

brainstem	the portion of the brain (comprising the medulla oblongata, the pons, and the mesencephalon) that performs motor, sensory, and reflex functions; the 12 pairs of cranial nerves from the brain arise mostly from the brainstem
hormone	a complex chemical substance produced in one part or organ of the body that initiates or regulates the activity of an organ or a group of cells in another part of the body
hypertrophy	an increase in the size of a cell
hypothalamus	a part of the brain that activates, controls, and integrates the peripheral autonomic nervous system, endocrine processes, and many somatic functions, such as body temperature, sleep, and appetite
neurotransmitter	a chemical that modifies or results in the transmission of nerve impulses between synapses
nucleus/nuclei	a group of nerve cells of the central nervous system having a common function
thermoreceptors	nerve endings that are sensitive to heat or a rise in body temperature
thermoregulation	the control of heat production and heat loss, specifically the maintenance of body temperature through physiological mechanisms activated by the hypothalamus
vasoconstriction	a decrease in the diameter of a blood vessel
vasodilation	an increase in the diameter of the blood vessel

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