Journal of Kerman University of Medical Sciences
2022; 29(4):401-410

10.22062/JKMU.2022.92016

Review Article

http://jkmu. kmu. ac. ir/

Central and Peripheral Thermoregulatory Responses to Cold Exposure: Involvement of Sympathetic System, Nitric Oxide, and Orexin

Zahra Rezaei [1], Sohrab Hajizadeh [2*]

1. Department of Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran
2. Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

ABSTRACT

In hypothermia, the core temperature of the body decreases below 35°C. In this situation, the body initiates some thermal regulatory process. Thermal regulation is the balance between heat production (thermogenesis) and heat loss (thermolysis) during thermal changes. Thermoregulation in skin blood flow can maintain body temperature and so homeostasis. A large body of literature has shown that in cold exposure, the hypothalamus contributes to thermoregulation by affecting skin blood flow. Moreover, some peripheral factors contribute to thermoregulation through modification of skin blood flow. Furthermore, the sympathetic nervous system can regulate the body temperature through a noradrenergic vasoconstrictor and a vasodilator system. As orexin receptors are also found in several peripheral mammal tissues, the activation of the orexin may stimulate the autonomic nervous system to increase blood pressure leading to control of heat balance. The present study aimed to evaluate the activity level and involvement of thermal regulators in cold stress. Generally, more experiments should be accomplished to find the regulatory pathways in these situations. Furthermore, this study was focused on the effect of orexin on thermoregulatory functions. This brief review intended to report the studies revealing the prime effects of orexin on the body temperature through influences exerted on the sympathetic nervous system.

Keywords: Cold exposure, Blood flow, Thermal regulation, Central and peripheral thermoregulation, Orexin

Citation: Rezaei Z, Hajizadeh S. Central and peripheral thermoregulatory responses to cold exposure: involvement of sympathetic system, nitric oxide, and orexin. Journal of Kerman University of Medical Sciences 2022; 29(4): 401-410. doi: 10.22062/JKMU.2022.92016

Received: 20. 01. 2022
Accepted: 12. 04. 2022
***Correspondence:** Sohrab Hajizadeh; Email: hajizads@modares.ac.ir

Published by Kerman University of Medical Sciences

Introduction

Physiological thermoregulation includes changes in heat production and heat loss by shivering and cutaneous vasodilation, respectively, in response to various internal and external thermal stimuli (1).

The main thermoregulatory center is the preoptic-anterior hypothalamus which collects information on temperature from internal (core) and surface (skin) receptors directly or indirectly. This region of the hypothalamus processes thermal information and relays it through efferent neural pathways (2, 3); then, like a thermostat, it recruits heat loss and heat gain responses when the temperature is low or high. The route of thermoregulation is shown in figure 1.

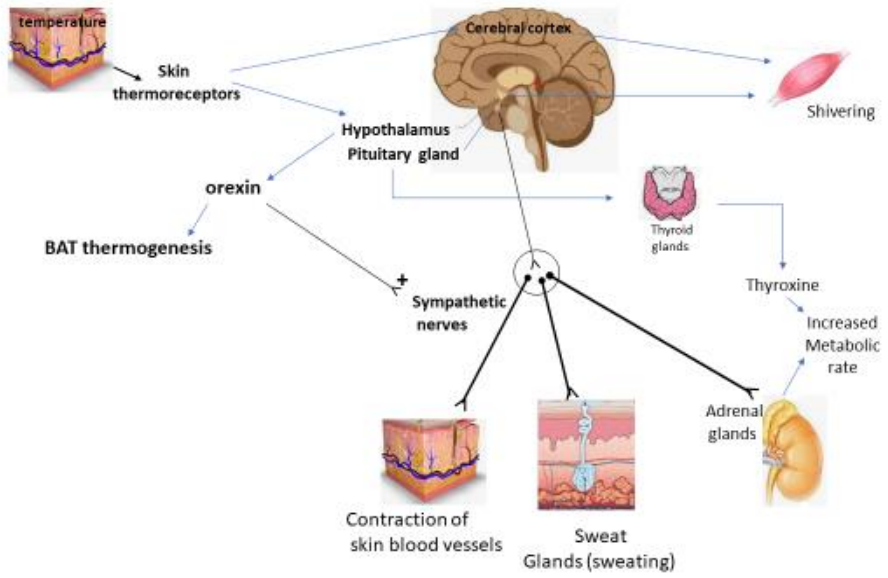

Figure 1. Thermoregulatory loop by the involvement of hypothalamus. Hypothalamus gather the information about rising of internal and/or skin temperatures and then makes augmented heat loss via cutaneous vasodilation and sweating, to adjust the initiated changes. Diminished skin or internal temperature causes reactions that decrease heat loss (cutaneous vasoconstriction) and increase heat production (shivering), which adjusts the first change.

The skin plays an important role in thermoregulation. Enhancement or reduction of core temperature results in activation of the sympathetic nervous system and thus vasodilation and vasoconstriction effects, respectively (4). In hypothermia, to save the heat, vasoconstriction occurs, then blood is shifted from the skin surface to the deeper veins and organs; therefore, the spreading of the temperature between core and peripheral organs occurs according to the temperature gradient. In response to hypothermia, the sympathetic vasoconstrictor system through activation of α-noradrenergic receptors causes the contraction of the smooth muscles of the blood vessels, which is called vasoconstriction. Neuropeptide Y and ATP are other transmitters that contribute to this vasoconstriction (5, 6).

Hypothermia was classified as "mild," "moderate," or "severe" based purely on the CBT (mild hypothermia: 32.2–35 °C, moderate hypothermia: 28–32.2 °C, profound hypothermia: <28 °C). In mild hypothermia, the thermoregulatory mechanisms including shivering and heat-seeking behavior are not seen yet, but ataxia may be detected. Moderate hypothermia brings about the progressive loss of the thermoregulatory system with a reduction of consciousness and initial cardiovascular instability. In severe hypothermia, whole loss of the thermoregulatory system, an inability to shiver, comatose states, and susceptibility to ventricular fibrillation were detected (7).

Neural control of thermoregulation

Regulation of body temperature is a role of a central mechanism. The key thermoregulatory center is the hypothalamus, principally the preoptic area (POA) that is the integration center of the sensory inputs of body temperature (2). Other areas of the central nervous system, including the brainstem and spinal cord, also

contribute to thermoregulation. The hypothalamic POA possesses three groups of neurons:

1. Warm-sensitive neurons, which represent ~ 20% of POA neurons, enhance the firing rate at higher temperatures and reduce it when the brain temperature drops. In inflammation, the warm receptors are stimulated. Previous studies have shown the anti-inflammatory effect of calcium channel blockers (8); therefore, we have shown that calcium channel blockers can inhibit the increased blood flow and so the temperature in chronic inflammation.

2. Cold-sensitive neurons that characterize ~ 10% of POA neurons are normally inhibited by the warm-sensitive neurons but are activated by the firing rate reduction of warm-sensitive neurons during cooling.

3. The remaining 70% of neurons of the preoptic area are temperature-insensitive (2).

Rabbits adapted to lower temperatures display lower temperature set points than the control ones. Therefore, the temperature has setpoints that are not permanent and change by the neural system and can alter during the individual development.

Lower optimal temperatures cause hypothalamic thermosensitivity and enhance the number of warm-sensitive neurons. Higher optimal temperatures show the opposite effect (9).

There is no evidence showing any genes regulate set points for the temperature in warm-blooded animals. Thermoregulation has three stages: afferent sensing, central control, and efferent responses. There are receptors for both heat and cold throughout the human body. Afferent sensing activates these receptors to inform the body's core temperature. The hypothalamus is the central regulator of thermoregulation (10). There is also an efferent behavioral component that replies to variations in body temperature. For example, if a person feels too warm, he/she removes an outer article of clothing. If a person feels too cold, he/she wears more layers of clothing. Efferent responses also contain automatic responses by the body to defend itself from exciting variations in temperature, like sweating, vasodilation, vasoconstriction, and shivering (11).

The balance between them which preserves body temperature near 37°C, permits the enzyme systems to operate in a narrow optimum activity. Many studies have evaluated skin blood flow (SBF) in response to hypothermia. In mild hypothermia, the thermoregulatory mechanisms function is at a maximum level in an effort to contest heat loss by shivering, cutaneous vasoconstriction, diminished peripheral perfusion, and enhance cerebral blood flow, and blood pressure (12). Cutaneous vasodilation and sweating during exercise and heat exposure are substantial for heat loss. During hypothermia, skin blood vessels constrict to diminish heat loss and protect from hypothermia. Thus, changes in skin blood flow have important clinical consequences and can put down the mechanism of heat balance (13). The core temperature is preserved in a very small range close to 37°C during rest by the equilibrium between heat loss and heat gain. The core function of the posterior hypothalamus is the integration of temperature signals reaching from cold- and warm-sensitive nerve endings located on the skin through the sympathetic nervous system. There is also a functional relation between the posterior hypothalamus and the anterior hypothalamus in thermoregulation. The skin has more cold receptors than warm ones, which are closer to the surface; therefore, it has a more rapid recognition of cold compared to warmth (14).

The thermoresponsive neurons are situated mostly in the nucleus raphe magnus (NRM) (14). The medullar raphe regulates the rat tail blood flow (TBF) which is the main organ of heat loss in this species (15, 16).

The nucleus raphe magnus (NRM) regulates vasomotor responses to modification of environmental temperature through regulation of the SBF (17, 18). Considerable evidence has reported that electrical stimulation of mid to caudal raphe magnus augments sweat secretion and SBF in forepaw pads of decerebrate cats (15, 19, 20).

Excitation of the raphe neurons changes the cutaneous blood flow without disturbing arterial pressure and changing blood pressure in the mesenteric bed (21, 22). In another study, chemical stimulation of the rostral ventrolateral medulla in anesthetized hyperthermic rats could reduce tail temperature (23). The evidence displays that medullar raphe is involved in the regulation of rat tail blood flow. An increment of Fos immunoreactivity resulted from the raphe stimulated by cold exposure (24). In our earlier study, injection of lidocaine interrupted local neuronal activity in the NRM (25). In hypothermia, lidocaine injections into the medullary raphe decrease the tail

vasoconstriction and so lidocaine decreases the thermoregulatory effect of NRM and diminishes TBF (25).

During cold exposure, cutaneous vasoconstriction decreases heat loss and protects the body from hypothermia (26). Thus, changes in SBF have important clinical consequences and can suppress the mechanism of heat balance. In our previous study, microinjection of lidocaine into the NRM significantly reduced the TBF; therefore, it was concluded that the NRM has a thermoregulatory effect in response to hypothermia (27).

In postnatal development, some glutamatergic synapses possess NMDA receptors (28-30) which mostly cause hyperpolarization and have inhibitory roles (31). Synchronized application of glutamate and nitroprusside, which is a NO donor, exhibited an opposite effect. Therefore, cells showed depolarization and excitation (32). It can be assumed that NO contribute to inhibitory responses to glutamate (31). According to our previous study, when TBF decreased in hypothermia, the injection of glutamate in the raphe magnus enhanced the blood flow of the tail cutaneous bed. Then, we found that this effect of L-glutamate was diminished by prior intra NRM administration of neuronal nitric oxide synthase (nNOS) inhibitor (L-NAME) (33). Thus, nitric oxide (NO) in the nucleus raphe magnus may interact with excitatory amino acids and control cutaneous blood flow in rats. In the central nervous system (CNS), nNOS-produced nitric oxide involves in the regulation of body temperature (34). Our previous study suggested that alteration of nitric oxide causes the same skin blood flow changes in both morphine-dependent and intact rats (35). Also, central administration of dopamine as a neurotransmitter involved in modulatory system (36) shows an important effect in thermoregulation (37).

Overview of the role of skin in human physiological thermoregulation

Body temperature regularly imitates the central core and peripheral shell temperatures. The core temperature reflects the temperature within the “deep” body tissues and organs with a high level of basal metabolism (including the heart, brain, and liver). The shell temperature reflects skin blood flow, which is raised with a high core temperature and environmental temperature. The surface area-to-mass ratio of end organs is high (38), which is important for thermal energy transmission. During cold stress, skin blood flow is reduced, causing a reduction in shell temperature and preservation of heat in the core. The temperature gradient between core and skin can be a valuable nonspecific monitor of thermal status. The hypothalamus is the directing or central integration center for thermoregulation. The evidence suggests that the preoptic anterior hypothalamus is the most important region for autonomic temperature control (5).

Resting SBF in environments with normothermic temperature is about 250 mL/min, which makes 80 to 90 kcal/h of heat loss, which is about the same level of resting metabolic heat production (39, 40). Key physiological responses to losing heat during exercise are cutaneous vasodilation and sweating (39, 41). Cutaneous vasodilation and sweating during exercise augment blood flow to the skin through amplified cardiac output and displaces blood flow through splanchnic vasoconstriction without steady changes in oxygen supply to the organs such as the heart, but adequate to fulfil the demand of amplified skin blood flow (39).

Additionally, the evaporation of sweat, like cutaneous vasodilation, decreases skin temperature. Therefore, skin blood flow and sweating remain increasing until a heat equilibrium is reached, at which the rate of heat production is equal to the heat loss. Internal temperature or core body temperature, which is the temperature of the internal organs located deep within the body, decreases and then returns to a normal level when cutaneous vasodilation and sweating cause cooling of the blood. Internal temperature thresholds induce cutaneous vasodilation and sweating (39, 41). Furthermore, the slope of skin blood flow-internal temperature relationship is measured as the heat gain or sensitivity of the sweating or vasodilator response (42). Lower skin blood flow at a given internal temperature in heat stress is caused by active vasodilator activity originating from higher internal temperatures (an increased threshold for vasodilation), a reduced response sensitivity, or a combination of both (13). Factors affecting the sensitivity of skin vasodilation are heat adaptation, circadian rhythm (43, 44), exercise training (45), and female reproductive hormone level (46).

Skin blood flow decreases due to cutaneous vasoconstriction in cold exposure. As the temperature decreases to a lower level, the

shivering begins. Muscle contraction associated with vascular contraction, enhancement of heat production, and reduction of heat loss decay heat transfer from the core to the surface, and so maintain the core temperature in cold exposure (13).

The laser-Doppler flowmetry and venous blocking plethysmography are two techniques for the measurement of skin blood flow (39, 47, 48). Venous blocking plethysmography can be exerted to assess blood flow in the limbs including the forearm, lower leg, or finger (13).

Contribution of central factors in skin blood flow regulation

Vasoconstriction control of skin blood flow by the sympathetic nervous system

Vessel constriction is performed to regulate skin circulation, especially by the sympathetic nervous system (49). The glabrous skin (including palms, soles, and lips) is innervated by the sympathetic vasoconstrictor nerves (39). In glabrous skin, the blood flow rates from arterioles to venules are altered through the opening or closing of arteriovenous anastomoses (AVA) (50). Arteriovenous anastomoses, like the elaborate system in rats' tails, control heat dissipation by sympathetic activation in cold exposure (51).

Cold exposure recruits an augmented vasoconstrictor nerve activity and the release of norepinephrine. NPY which activates postsynaptic α1 and α2 receptors on cutaneous arterioles and AVA causes skin blood flow decrement (52-54). This thermoregulatory vasoconstriction can limit the skin blood flow by changes of the vasoconstrictor outflow to cutaneous arterioles and mainly arteriovenous anastomoses, which is a countercurrent exchange of heat to make an additional decrease of heat loss (55). The vasoconstrictor system of human skin is active at normal brain and skin temperatures (56) that is responsible for the regulation of normal body temperature. Slight deviations of body temperature lead to minor alterations in skin blood flow and heat removal; therefore, the body temperature is maintained in a very fine range (54).

Vasodilation control of skin blood flow by nitric oxide

Nitric oxide, as a gaseous second messenger, plays the main role in thermoregulation in the central and peripheral nervous systems (57). Nitric oxide is synthesized in all mesencephalic raphe nuclei cells and is a dominant activator of the heat defense mechanism (57). In a previous study, it was demonstrated that intra-NRM microinjection of SNP stops thermal vasoconstriction of rat tail vessels in cold exposure, but injection of an NO synthase (L-NAME) inhibitor, restrains the excitatory effect of glutamate on the NRM and TBF (58). Nitric oxide and subsequent cGMP levels augment through stimulation of NMDA receptors. Moreover, NO increases the release of excitatory amino acids in the dorsomedial medulla through cGMP (59). It is established that L- NAME diminished NO facilitation of excitatory amino acid-evoked excitation of NTS neurons (60). Also, NOS inhibitor (61, 62), or NO donor (61), causes a tonic limitation in central sympathetic outflow. Sympathetic nerves cause vasoconstriction of the skin vascular beds. Therefore, a decrease in the sympathetic outflow by NO in the raphe may be responsible for thermoregulatory processes in the CNS (58). In addition, during local warming, vasodilation happens in two phases including a rapid phase and a slower phase; the local nervous activity and NO contribute to these two phases, respectively (63, 64).

Orexin and hypothermia

Orexin neuropeptides are produced in the lateral part of the hypothalamus area and activate postsynaptic neurons through two G-protein coupled receptors (65, 66). Orexins are involved in memory (67), development of morphine dependence (68-70), and formalin-induced nociceptive behaviors (71, 72). They are distributed across many brain regions including locus coeruleus and hippocampus (73). Hypothalamic orexin neurons are involved in thermoregulation. Orexin receptor antagonist causes alteration of core body temperature after exercise (74). Orexin plays a role in the central adjustment of sleep, energy metabolism, and the cardiovascular system (75). Heat loss is a critical feature of sleep. There is an elevated body temperature during sleep in orexin knockout mice (76).

Orexin neurons may not be implicated in the alteration of basal body temperature in an awake state and at rest, but are involved in the alteration of body temperature in spontaneous movements and during sleep even without stimulation of the animals (77).

Orexin neurons in the lateral hypothalamus innervate the rostral raphe pallidus, and this is a central path for brown adipose tissue (BAT) thermogenesis in cold temperatures (78). Orexin neurons attach to upstream factors of the thermoregulatory circuit, like the preoptic area. An orexinergic projection from the perifornical hypothalamus to raphe pallidus enhances BAT thermogenesis in rats (79).

In stressful conditions, the orexinergic system may modify the thermogenic response at the central level with an augmentation of orexin levels in the cerebrospinal fluid. The antagonist of the orexin receptor reduces the rise in core body temperature in resting and exercise states. Orexin is important in the thermoregulation response to stressful events (74).

Orexin-A can enhance sympathetic discharge and body temperature. For instance, the caudal raphe nuclei in the medulla known as the sympathetic preganglionic motor neurons, which are contributed to thermal and cardiovascular regulation, are innervated by orexin-A fibers. It was reported that orexin-A might also show an important role in thermoregulation. Moreover, the thermosensitivity of orexin neurons may play an important role in maintaining energy homeostasis during fever (80).

Conclusion

The nucleus raphe magnus possesses the thermoregulatory role in response to hypothermia. Cutaneous sympathetic vasoconstriction reactions in hypothermia include enhancing the blood pressure and reducing the skin blood flow. Moreover, NO as an important factor in the raphe magnus can regulate central cutaneous blood flow in rats during cold exposure. Orexin is involved in the modification of body temperature in spontaneous movement and during sleep even without stimulation of the animals. In the future, underlying mechanisms of the thermoregulatory effect of orexin should be elucidated.

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

The authors agree with publication.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Tansey, E.A. and C.D. Johnson, Recent advances in thermoregulation. Advances in physiology education, 2015.
2. Boulant, J.A., Role of the preoptic-anterior hypothalamus in thermoregulation and fever. Clinical infectious diseases, 2000. 31(Supplement_5): p. S157-S161.
3. Boulant, J.A., Hypothalamic neurons regulating body temperature. Handbook of Physiology. Environmental Physiology, 1996: p. 105-126.
4. Tansey, E.A. and C.D. Johnson, Recent advances in thermoregulation. Adv Physiol Educ, 2015. 39(3): p. 139-48.
5. Romanovsky, A.A., Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. American journal of Physiology-Regulatory, integrative and comparative Physiology, 2007. 292(1): p. R37-R46.
6. Stephens, D.P., et al., Neuropeptide Y antagonism reduces reflex cutaneous vasoconstriction in humans. American Journal of Physiology-Heart and Circulatory Physiology, 2004. 287(3): p. H1404-H1409.
7. Turk, E.E., Hypothermia. Forensic science, medicine, and pathology, 2010. 6(2): p. 106-115.
8. Khaksarihadad, M., et al., Decrease in blood flow and temperature of rat knee joint by calcium. Hormozgan Medical Journal, 2007. 10(4): p. 311-320.
9. Tzschentke, B. and I. Halle, Influence of temperature stimulation during the last 4 days of incubation on secondary sex ratio and later performance in male and female broiler chicks. British Poultry Science, 2009. 50(5): p. 634-640.
10. Arami, M.K., A. Komaki, and S. Gharibzadeh, Contribution of nucleus raphe magnus to

thermoregulation. Physiology & Pharmacology, 2020. 24(3).

11. Zhao, Z.-D., et al., A hypothalamic circuit that controls body temperature. Proceedings of the National Academy of Sciences, 2017. 114(8): p. 2042-2047.
12. Arami, M.K., et al., The effect of hyperglycemia on nitric oxidergic neurons in nucleus tractus solitarius and blood pressure regulation in rats with induced diabetes. Iranian Journal of Diabetes and Lipid Disorders, 2005. 4(3): p. E2.
13. Charkoudian, N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. in Mayo Clinic Proceedings. 2003. Elsevier.
14. Dickenson, A.H., Specific responses of rat raphe neurones to skin temperature. J Physiol, 1977. 273(1): p. 277-293.
15. Asahina, M., et al., Cutaneous sympathetic function in patients with multiple system atrophy. Clinical Autonomic Research, 2003. 13(2): p. 91-95.
16. Rathner, J.A. and R.M. McAllen, Differential control of sympathetic drive to the rat tail artery and kidney by medullary premotor cell groups. Brain Res, 1999. 834(1): p. 196-199.
17. Berner, N.J., D.A. Grahn, and H.C. Heller, 8-OH-DPAT-sensitive neurons in the nucleus raphe magnus modulate thermoregulatory output in rats. Brain Res, 1999. 831(1): p. 155-164.
18. Korsak, A. and M.P. Gilbey, Rostral ventromedial medulla and the control of cutaneous vasoconstrictor activity following icv prostaglandin E 1. Neurosci, 2004. 124(3): p. 709-717.
19. Malakouti, S.M., et al., Reversible inactivation and excitation of nucleus raphe magnus can modulate tail blood flow of male wistar rats in response to hypothermia. Iranian Biomedical Journal, 2008. 12(4): p. 237-240.
20. Masoomeh, A., H. Sohrab, and S. Abdorahman, the effect of nitric oxide level of nucleus raphe magnus in hypothermia in male wistar rats. Korean Journal of Physiology & Pharmacology, 2006. 10: p. 164-0.
21. Blessing, W.W. and E. Nalivaiko, Regional blood flow and nociceptive stimuli in rabbits: patterning by medullary raphe, not ventrolateral medulla. j Physiol, 2000. 524(1): p. 279-292.
22. Nalivaiko, E. and W.W. Blessing, Potential role of medullary raphe-spinal neurons in cutaneous vasoconstriction: an in vivo electrophysiological study. J Neurophysiol, 2002. 87(2): p. 901-911.
23. Key, B. and C. Wigfield, Changes in the tail surface temperature of the rat following injection of 5-hydroxytryptamine into the ventrolateral medulla. Neuropharmacology, 1992. 31(8): p. 717-723.
24. Tanaka, M., et al., Role of the medullary raphe in thermoregulatory vasomotor control in rats. J Physiol, 2002. 540(2): p. 657-664.
25. Kourosh Arami, M., et al., The Effect of Nucleus Tractus Solitarius Nitric Oxidergic Neurons on Blood Pressure in Diabetic Rats. Iranian Biomedical Journal, 2006. 10(1): p. 15-19.
26. Nazari, S., et al., Relative contribution of central and peripheral factors in superficial blood flow regulation following cold exposure. Physiology and Pharmacology (Iran), 2020. 24(2): p. 89-100.
27. Malakouti, S.M., et al., Reversible inactivation and excitation of nucleus raphe magnus can modulate tail blood flow of male Wistar rats in response to hypothermia. Iran Biomed J, 2008. 12(4): p. 203-208.
28. Arami, M.K., S. Hajizadeh, and S. Semnanian, Postnatal development changes in excitatory synaptic activity in the rat locus coeruleus neurons. Brain research, 2016. 1648: p. 365-371.
29. Arami, M.K., et al., Postnatal developmental alterations in the locus coeruleus neuronal fast excitatory postsynaptic currents mediated by ionotropic glutamate receptors of rat. Physiology and Pharmacology, 2011. 14(4): p. 337-348.
30. Kourosh-Arami, M. and S. Hajizadeh, Maturation of NMDA receptor-mediated spontaneous postsynaptic currents in the rat locus coeruleus neurons. Physiology International, 2020.
31. D'yakonova, T., NO-producing compounds transform neuron responses to glutamate. Neuroscience and behavioral physiology, 2000. 30(2): p. 153-159.
32. Kourosharami, M., M. Mohsenzadegan, and A. Komaki, A Review of Excitation-Inhibition Balance in the Nucleus Tractus Solitarius as a Gateway to Neural Cardiovascular Regulation.

Journal of Advances in Medical and Biomedical Research, 2020. 28(126): p. 47-53.

33. Arami, M.K., et al., Nitric oxide in the nucleus raphe magnus modulates cutaneous blood flow in rats during hypothermia. Iran J Basic Med Sci, 2015. 18(10): p. 989-92.
34. Kourosh-Arami, M., et al., Neurophysiologic implications of neuronal nitric oxide synthase. Reviews in the Neurosciences, 2020. 1(ahead-of-print).
35. Safari, F., et al., Effect of nitric oxide on skin blood flow of intact and morphine-dependent rats. Physiology and Pharmacology, 2007. 10(4): p. 267-274.
36. Kourosh-Arami, M., A. Komaki, and M.-R. Zarrindast, Dopamine as a potential target for learning and memory: contribution to related neurological disorders. CNS & Neurological Disorders Drug Targets, 2022.
37. Zheng, X. and H. Hasegawa, Central dopaminergic neurotransmission plays an important role in thermoregulation and performance during endurance exercise. European Journal of Sport Science, 2016. 16(7): p. 818-828.
38. Taylor, N.A., et al., Hands and feet: physiological insulators, radiators and evaporators. European journal of applied physiology, 2014. 114(10): p. 2037-2060.
39. Johnson, J.M. and D.W. Proppe, Cardiovascular adjustments to heat stress. Handbook of Physiology. Environmental Physiology, 1996. 1: p. 215.
40. Johnson, J.M., et al. Regulation of the cutaneous circulation. in Federation proceedings. 1986.
41. Johnson, J.M., Exercise and the cutaneous circulation. Exercise and sport sciences reviews, 1992. 20: p. 59-97.
42. Charkoudian, N., Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. Journal of applied physiology, 2010. 109(4): p. 1221-1228.
43. Stephenson, L.A. and M.A. Kolka, Menstrual cycle phase and time of day alter reference signal controlling arm blood flow and sweating. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 1985. 249(2): p. R186-R191.
44. Aoki, K., D.P. Stephens, and J.M. Johnson, Diurnal variation in cutaneous vasodilator and vasoconstrictor systems during heat stress. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 2001. 281(2): p. R591-R595.
45. 45. Roberts, M.F., et al., Skin blood flow and sweating changes following exercise training and heat acclimation. Journal of Applied Physiology, 1977. 43(1): p. 133-137.
46. 46. Charkoudian, N. and J.M. Johnson, Reflex control of cutaneous vasoconstrictor system is reset by exogenous female reproductive hormones. Journal of Applied Physiology, 1999. 87(1): p. 381-385.
47. Johnson, J.M., et al., Laser-Doppler measurement of skin blood flow: comparison with plethysmography. J Appl Physiol Respir Environ Exerc Physiol, 1984. 56(3): p. 798-803.
48. Oberg, P.A., Laser-Doppler flowmetry. Crit Rev Biomed Eng, 1990. 18(2): p. 125-63.
49. Edholm, O.G., R.H. Fox, and R.K. Macpherson, Vasomotor control of the cutaneous blood vessels in the human forearm. J Physiol, 1957. 139(3): p. 455-65.
50. Lossius, K., M. Eriksen, and L. Walloe, Fluctuations in blood flow to acral skin in humans: connection with heart rate and blood pressure variability. J Physiol, 1993. 460: p. 641-55.
51. Blessing, W. and E. Nalivaiko, Raphe magnus/pallidus neurons regulate tail but not mesenteric arterial blood flow in rats. Neuroscience, 2001. 105(4): p. 923-929.
52. Stephens, D.P., et al., Sympathetic nonnoradrenergic cutaneous vasoconstriction in women is associated with reproductive hormone status. American Journal of Physiology-Heart and Circulatory Physiology, 2002. 282(1): p. H264-H272.
53. Stephens, D.P., et al., Nonnoradrenergic mechanism of reflex cutaneous vasoconstriction in men. American Journal of Physiology-Heart and Circulatory Physiology, 2001. 280(4): p. H1496-H1504.
54. Smith, C.J. and J.M. Johnson, Responses to hyperthermia. Optimizing heat dissipation by convection and evaporation: Neural control of skin blood flow and sweating in humans. Autonomic Neuroscience, 2016. 196: p. 25-36.
55. MacKenzie, M., et al., Skin blood flow and autonomic reactivity in human poikilothermia. Clinical Autonomic Research, 1996. 6(2): p. 91-97.

56. Pergola, P.E., et al., Reflex control of active cutaneous vasodilation by skin temperature in humans. American Journal of Physiology-Heart and Circulatory Physiology, 1994. 266(5): p. H1979-H1984.

57. Leger, L., et al., Comparative distribution of nitric oxide synthase-and serotonin-containing neurons in the raphe nuclei of four mammalian species. Histochem Cell Biol, 1998. 110(5): p. 517-525.

58. Arami, M.K., Nitric oxide in the nucleus raphe magnus modulates cutaneous blood flow in rats during hypothermia. Iranian journal of basic medical sciences, 2015. 18(10): p. 989.

59. Dias, M.B., et al., Raphe magnus nucleus is involved in ventilatory but not hypothermic response to CO2. J Appl Physiol, 2007. 103(5): p. 1780-1788.

60. Dias, A.C.R., et al., Nitric oxide modulation of glutamatergic, baroreflex, and cardiopulmonary transmission in the nucleus of the solitary tract. American Journal of Physiology-Heart and Circulatory Physiology, 2005. 288(1): p. H256-H262.

61. Mathai, M.L., et al., Central blockade of nitric oxide synthesis induces hyperthermia that is prevented by indomethacin in rats. J Therm Biol, 2004. 29(7): p. 401-405.

62. Eriksson, S., et al., Central application of a nitric oxide donor activates heat defense in the rabbit. Brain Res, 1997. 774(1): p. 269-273.

63. Kellogg, D.L., Jr., et al., Role of nitric oxide in the vascular effects of local warming of the skin in humans. J Appl Physiol (1985), 1999. 86(4): p. 1185-90.

64. Johnson, J.M., et al., Effect of local warming on forearm reactive hyperaemia. Clin Physiol, 1986. 6(4): p. 337-46.

65. Babasafari, M., et al., Alteration of Phospholipase C Expression in Rat Visual Cortical Neurons by Chronic Blockade of Orexin Receptor 1. International Journal of Peptide Research and Therapeutics, 2019: p. 1-7.

66. Rezaei, Z., et al., Orexin type-1 receptor inhibition in the rat lateral paragigantocellularis nucleus attenuates development of morphine dependence. Neuroscience Letters, 2020: p. 134875.

67. 67.Kourosh-Arami, M., et al., Phospholipase Cβ3 in the hippocampus may mediate impairment of memory by long-term blockade of orexin 1 receptors assessed by the Morris water maze. Life Sciences, 2020. 257: p. 118046.

68. Babaie, F., M. Kourosh-Arami, and M. Farhadi, Administration of Orexin-A into the Rat Thalamic Paraventricular Nucleus Enhances the Naloxone Induced Morphine Withdrawal. Drug Research, 2022. 72(04): p. 209-214.

69. Kourosh-Arami, M., et al., Neural correlates and potential targets for the contribution of orexin to addiction in cortical and subcortical areas. Neuropeptides, 2022: p. 102259.

70. Kourosh-Arami, M., M. Javan, and S. Semnanian, Inhibition of orexin receptor 1 contributes to the development of morphine dependence via attenuation of cAMP response element-binding protein and phospholipase Cβ3. Journal of Chemical Neuroanatomy, 2020. 108: p. 101801.

71. Kourosh-Arami, M., et al., Persistent effects of the orexin-1 receptor antagonist SB-334867 on naloxone precipitated morphine withdrawal symptoms and nociceptive behaviors in morphine dependent rats. International Journal of Neuroscience, 2021. 132(1): p. 67-76.

72. Samani, F. and M.K. Arami, Repeated Administration of Orexin into the Thalamic Paraventricular Nucleus Inhibits the Development of Morphine-Induced Analgesia. Protein and Peptide Letters, 2022. 29(1): p. 57-63.

73. Mousavi, Z., et al., An immunohistochemical study of the effects of orexin receptor blockade on phospholipase C-β3 level in rat hippocampal dentate gyrus neurons. Biotechnic & Histochemistry, 2020: p. 1-6.

74. Martin, T., et al., Dual orexin receptor antagonist induces changes in core body temperature in rats after exercise. Scientific reports, 2019. 9(1): p. 1-9.

75. Piri, Z., et al., Alteration of Hematologic Parameters in Morphine-Dependent Rats by Long-Term Administration of Orexin Type 1 Receptor Antagonist. International Journal of High Risk Behaviors and Addiction, 2020. 9(3).

76. Mochizuki, T., et al., Elevated body temperature during sleep in orexin knockout mice. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 2006. 291(3): p. R533-R540.

77. Kuwaki, T., Thermoregulation under pressure: a role for orexin neurons. Temperature, 2015. 2(3): p. 379-391.

78. Takahashi, Y., et al., Orexin neurons are indispensable for prostaglandin E2-induced fever and defence against environmental cooling in mice. The Journal of physiology, 2013. 591(22): p. 5623-5643.

79. Tan, C.L. and Z.A. Knight, Regulation of body temperature by the nervous system. Neuron, 2018. 98(1): p. 31-48.

80. Messina, G., S. Chieffi, and M. Monda, Orexin A exerts more thermogenic than orexinergic functions. PeerJ PrePrints, 2014. 2: p. e392v1.