Physiology and Pharmacology

Physiol Pharmacol 24 (2020) 89-100 **www.phypha.ir/ppj**

Review Article

Relative contribution of central and peripheral factors in superficial blood flow regulation following cold exposure

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Abstract

The aim of the present study was to evaluate the extent of contribution of thermal regulators in cold stress. Hypothermia is described as a diminution in core body temperature below 35°C. Thermoregulation is the equilibrium between heat generation (thermogenesis) and heat loss (thermolysis). Thermoregulatory control of skin blood flow (SBF) is critical to preserve body temperature homeostasis during thermal changes. The obtained results from different studies revealed that following cold exposure, some areas of the brain like preoptic/anterior hypothalamus, known as body thermostat, involve in thermoregulation by affecting on SBF. Furthermore, some peripheral factors participate in the thermal control through alteration of skin blood flow. Sympathetic neural control of SBF includes the noradrenergic vasoconstrictor system and a sympathetic active vasodilator system. Overall, further future studies are required to elucidate the imbalance of these regulators in some disorders.

http://dx.doi.org/10.32598/ppj.24.2.50

Keywords:
Hypothermia;
Skin blood flow;
Thermoregulation

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Received 4 December 2019; Received in revised form 7 February 2020; Accepted 2 March 2020

Introduction

Body temperature, usually reflects the central core and peripheral shell temperatures. The core temperature refers to the temperature within the “deep” body tissues with a high level of basal metabolism (including the heart, brain and liver). The shell temperature refers to skin blood flow (SBF), which is elevated with a high core temperature and environmental temperature. The surface area-to-mass ratio of end organs is high (Taylor et al., 2014), that is important for the thermal energy transmission. During cold stress, skin blood flow is diminished, resulting in a decrease in shel l temperature and conservation of heat to the core. Temperature gradients between the core and skin can be a beneficial nonspecific monitor of thermal status. The hypothalamus is the coordinating or central integration center for thermoregulation. Evidence suggests that preoptic anterior hypothalamus is the most important region for autonomic temperature control (Romanovsky, 2007).

Human physiological thermoregulation refers to four mechanisms: sweating, shivering, vasodilation and vasoconstriction. This active equilibrium, which maintains body temperature near 37°C, permits the

enzyme systems to operate within a narrow optimum activity. Major studies have focused on assessing SBF in response to hypothermia. In state of mild hypothermia, the thermoregulatory mechanisms function at a maximum in an attempt to combat heat loss, with trembling (shivering), cutaneous vasoconstriction, reduced peripheral perfusion, increase cerebral blood flow and blood pressure. Cutaneous vasodilation and sweating in exercise and heat exposure are important for heat loss. During cold exposure, skin blood vessels constricted to reduce heat loss and protect from hypothermia. Therefore, alteration of skin blood flow has important clinical implications and can suppress the mechanism of heat balance (Charkoudian, 2003). The temperature of body core is maintained within a very small range by the balance between heat loss and gain. The main function of posterior hypothalamus and its functional relations with the anterior hypothalamus in thermoregulation is to integrate temperature signals reaching from cold and warm-sensitive nerve endings located on the skin, through the sympathetic nerve system. Since skin has more cold sensors than warm that are closer to the surface, so it has the rapid detection of cold than of warmth (Arens and Zhang, 2006).

During menopause, changes in reproductive hormone levels make alterations in thermoregulation control of skin blood flow that might contribute to the occurrence of hot flashes (Brooks and Kenney, 1997). In type 2 diabetes mellitus, the ability of skin blood vessels to dilate is impaired that contributes to the increased occurrence of heat illness during exposure to increased ambient temperatures (Semenza et al., 1999; Kenney et al., 2014). We will consider three questions: What induces thermoregulation center? What determines its direction and magnitude? What are some possible functions of skin in physiological thermoregulation? In this review, we will discuss the normal processes of the human physiological thermoregulation, as well as central regulatory control of SBF including sympathetic vasoconstrictor control and nitric oxide (NO) involvement. In the following, we will introduce important peripheral factors in SBF regulation including hormonal responses like renin-angiotensin-aldosterone system that results in control of blood pressure in hypothermia. Also, we will focus on the blood-derived thermoregulatory factors. Finally, we will describe the clinical perspectives of cold exposure.

Overview of the role of the skin in human physiological thermoregulation

The skin plays a functional role in the thermoregulatory process. In response to increased or decreased internal temperature, SBF is altered by sympathetic vasodilation and vasoconstriction mechanisms, respectively (Tansey and Johnson, 2015). When vasoconstriction happens in response to cold, then blood is shunted away from the skin surface through the deeper veins. Heat is thus saved, and a spreading of the gradient between core and peripheral temperature occurs. In response to cold, sympathetic vasoconstrictor nerves act mainly on α-noradrenergic receptors to make blood vessel smooth muscle contraction and vasoconstriction. Other sympathetically released co-transmitters also contribute to this vasoconstriction, such as ATP and neuropeptide Y (Stephens et al., 2004; Romanovsky, 2007).

Human physiological thermoregulation contains alteration in heat loss via cutaneous vasodilation and sweating and heat production via shivering in response to various internal and external thermal stimuli. The preoptic/anterior hypothalamus in the brain is the thermoregulatory center that receives direct or indirect thermal information from internal (core) and superficial (skin) receptors. This area then processes the temperature information and relays via efferent neural pathways (Boulant, 2010; Boulant, 2000). This region of hypothalamus acts as a thermostat which initiates heat loss and heat gain responses when the temperature is remarkably low or high. The route of thermoregulation by the preoptic/anterior hypothalamus is shown in Figure 1 (Charkoudian, 2003).

Skin blood flow at rest in normothermic environments is about 250 ml/min, which makes 80 to 90 kcal/h of heat loss, about the level of resting metabolic heat production (Johnson et al., 1986a; Johnson and Proppe, 1996). Main physiological responses to lose heat during exercise are cutaneous vasodilation and sweating (Johnson, 1992; Johnson and Proppe, 1996). Cutaneous vasodilation and sweating during exercise increases blood flow to the skin via augmented cardiac output and displaces blood flow through splanchnic vasoconstriction without

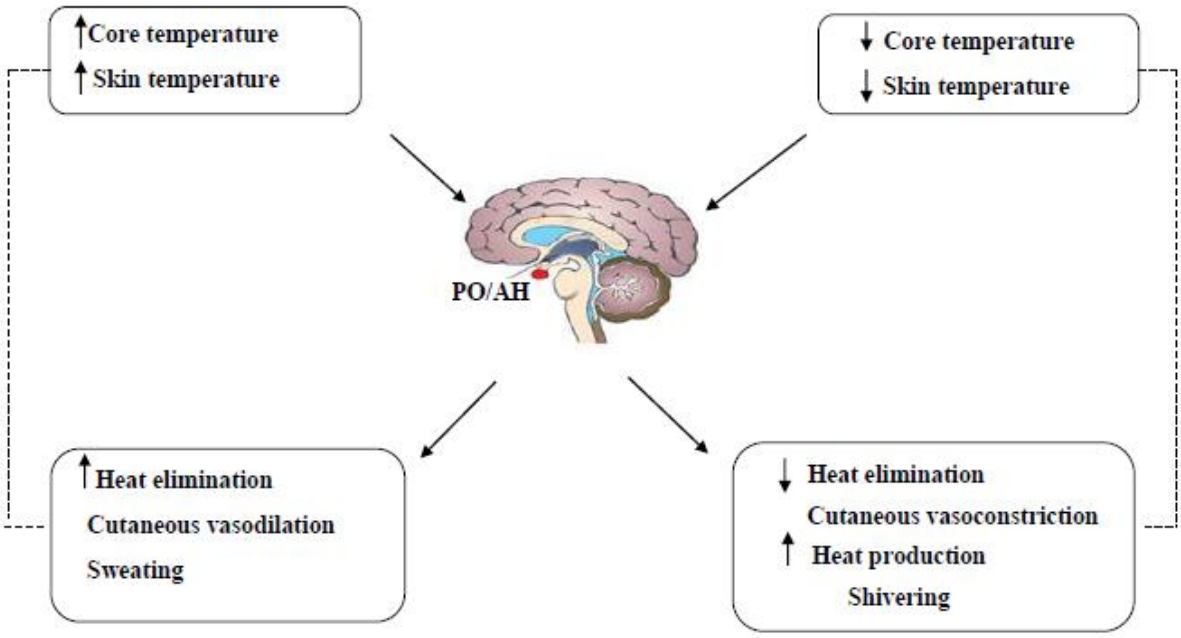

Fig.1. Thermoregulatory loop by involvement of hypothalamus. Dotted line shows the modification of error signal (change in skin and/or internal temperature) by the suitable effector response. Preoptic/anterior hypothalamus (PO/AH) gather information about rising of internal and/or skin temperatures and then makes augmented heat loss via cutaneous vasodilation and sweating, to adjusts the initiated changes. Diminished skin or internal temperature via reflex decreases heat loss (cutaneous vasoconstriction) and augmented heat production (shivering), adjusts the first changes (Charkoudian, 2003).

consistent alterations in oxygen supply to the organs such as heart but sufficient to match the demand of amplified skin blood flow (Johnson and Proppe, 1996).

Furthermore, the evaporation of sweat reduces skin temperature as well as cutaneous vasodilation. Hence, skin blood flow and sweating continue to increase until a heat balance is reached at which the rate of heat generation is equal to the heat loss. Internal temperature drops and then returns to normal level, when cutaneous vasodilation and sweating cause cooling of the blood. This mechanism defined as classic negative feedback (Fig. 1; Charkoudian, 2003). In negative control increment of core temperature leads to cutaneous vasodilation to reduce the core temperature.

In other study, it is revealed that the lateral parabrachial nucleus (LPB) receives spinal input from cold-sensitive neurons. Third-order LPB neurons ascend from these areas, which then project to the median preoptic nucleus and then median preoptic nucleus (MPO). Activation of these pathways will recruit heat gain process (Fig. 2; Tansey and Johnson, 2015). One of the neuropeptides that involves in thermoregulation is orexin. Orexin neuropeptides that are produced in the lateral part of the hypothalamus area activate postsynaptic neurons via two G-protein coupled receptors (Babasafari et al., 2019; Rezaei et al., 2020). Administration of orexin A activates thermogenesis, without limiting feeding or increasing physical activity (Messina, Dalia et al. 2014).

Cutaneous vasodilation and sweating begin at internal temperature thresholds (Johnson, 1992; Johnson and Proppe, 1996). Furthermore, the slope of skin blood flow-internal temperature relationship is considered as the gain or sensitivity of the sweating or vasodilator response. For example, lower skin blood flow at a given level of internal temperature during heat stress could be due to active vasodilator activity that is initiated in higher internal temperatures (an increased threshold for vasodilation), in a decrement of the response sensitivity or combination of both (Charkoudian, 2003). Factors influencing on the threshold and/or sensitivity of cutaneous vasodilation are heat adaptation, exercise training (Roberts et al., 1977), circadian rhythm (Stephenson and Kolka, 1985; Aoki et al., 2001) and reproductive hormone level (Brooks and Kenney, 1997; Charkoudian and Johnson, 1997; Charkoudian and

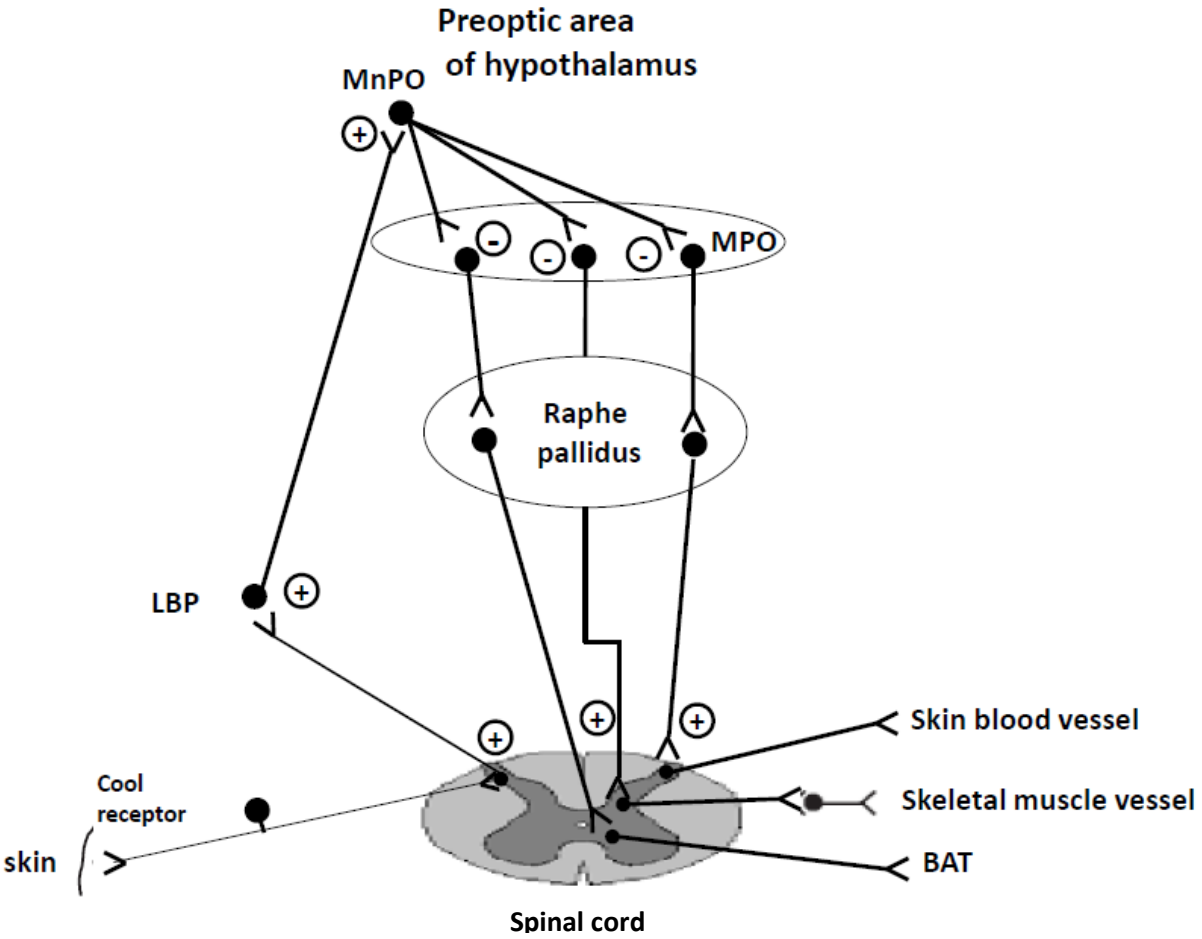

Fig.2. Central thermoregulation circuitry in response to cold. The lateral parabrachial nucleus (LPB) receives spinal input from cold-sensitive neurons. Third-order LPB neurons ascend from these areas, which then project to the median preoptic nucleus (MnPO) and then median preoptic nucleus (MPO). Activation of these pathways will recruit heat gain process (Tansey and Johnson, 2015).

Johnson, 1999b).

Skin blood flow reduces through cutaneous vasoconstriction when the person is exposed to cold temperatures. As the temperature cools down, the shivering starts. Muscle contraction accompanied by vascular contraction with augmentation of heat generation and diminishing heat loss declines heat transfer from the core to the surface and thus conservation of core temperature in the face of cold (Charkoudian, 2003).

Laser doppler flowmetry or venous occlusion plethysmography are two techniques for measurement of skin blood flow (Johnson et al., 1984; Oberg, 1990; Johnson and Proppe, 1996). Laser doppler measurement of SBF is based on the fact that a laser light beam incident on tissue is dispersed in static structures as well as in moving red cells and then shift based on the doppler effect (Oberg, 1990). This method has several advantages. It is specific to the cutaneous microcirculation and the signal is constant and has an outstanding frequency response (Saumet et al., 1988; Oberg, 1990). Potential unresolved problems contain weakness of ability to measure absolute flow values (ie, flow is measured in arbitrary laser doppler units or volts rather than in milliliters per minute) and the limitation to a relatively small area of measurement (Charkoudian and Johnson, 1997; Kellogg et al., 1998; Charkoudian and Johnson, 1999a).

Venous blocking plethysmography can be exerted to evaluate blood flow in the limbs including forearm, lower leg or finger. In the forearm or the lower leg, it is usually used to assess deviations in skin blood flow in circumstances in which blood flow to underlying muscle does not alter (ie, passive heat stress). In the finger, both glabrous and nonglabrous skin blood flow is measured which can limit interpretation, depending on the issues being addressed. The advantage of this method is the measurement of the total alterations in SBF but the disadvantage is that measurements

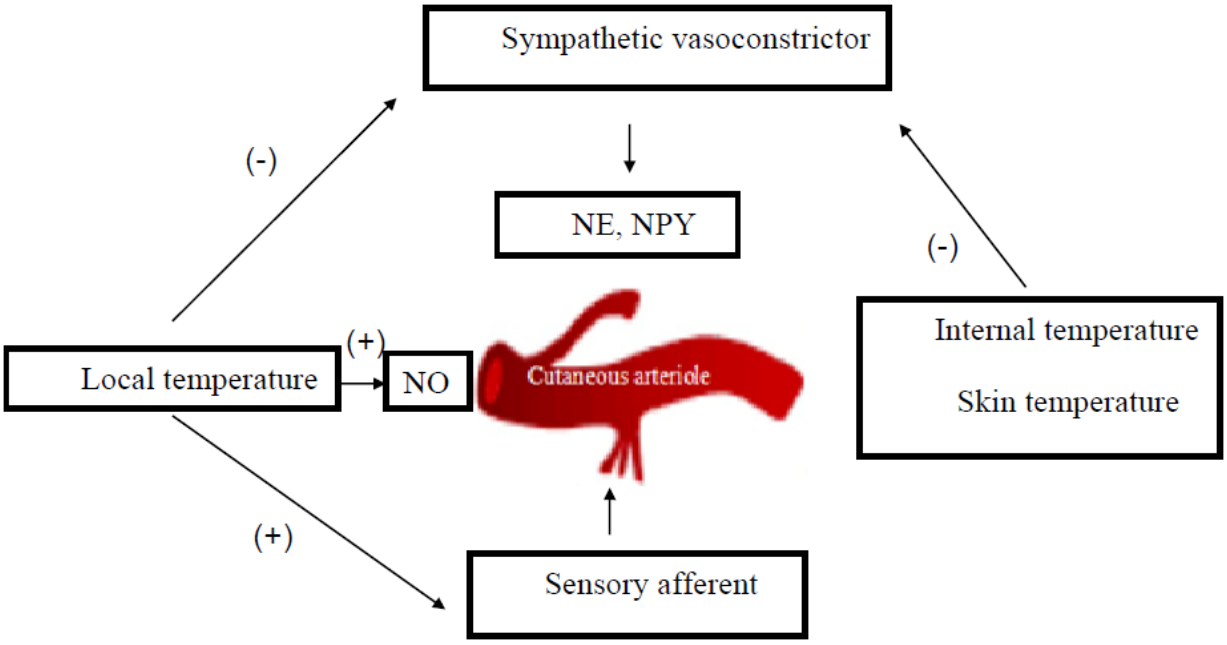

Fig.3. Local reductions in temperature make vasoconstriction by the release of norepinephrine (NE) and neuropeptide Y (NPY). Local warming stimulates sensory nerves to make vasodilation and then resultant NO causes vasodilation in the slower phase. Plus and minus signs are positive and negative effects, repectively. Any rises in temperature reduces activity and vice versa (Kourosh et al., 2005; Charkoudian, 2003).

cannot be taken uninterruptedly and not being specific to the skin (Charkoudian, 2003).

Contribution of central factors in skin blood flow regulation

Thermoregulatory center and skin blood flow

The greatest amount of thermoresponsive neurons were initiated in the nucleus raphe magnus (NRM) (Dickenson, 1977). Previous studies have shown that the medullar raphe is important in the rat tail blood flow (TBF) regulation which is the chief organ of heat loss in this species (Rathner and McAllen, 1999; Asahina et al., 2003). Sudomotor and vasomotor responses to alteration of environmental temperature are important in thermoregulation by the NRM through regulation of the SBF (Berner et al., 1999; Korsak and Gilbey, 2004). Previous studies have reported that electrical stimulation of mid to caudal raphe magnus produced an increase of sweat secretion and SBF in forepaw pads of decerebrate cats (Asahina et al., 2003; Malakouti et al., 2008).

Excitation of the raphe neurons mediates fluctuations in the cutaneous bed without affecting arterial pressure and altering blood pressure in the mesenteric bed (Blessing and Nalivaiko, 2000; Nalivaiko and Blessing, 2002). In another study in anesthetized hyperthermic rats, chemical stimulation of rostral ventrolateral medulla could diminish tail temperature (Key and Wigfield, 1992). Evidence shows the contribution of medullar raphe in the control of rat tail blood flow. Labeled sympathetic premotor neurons are recognized in the medullary raphe nuclei following tracer injection into tail artery (Smith and Gilbey, 1998). Excitatory neurons in the medullary raphe nuclei were found to be a novel group of sympathetic premotor neurons for thermoregulatory function (Nakamura et al., 2004). A rising of Fos expression immunoreactivity was shown in the raphe following cold exposure (Tanaka et al., 2002). In our previous study, injection of lidocaine (the fast activity anesthetic agent, block sodium channels) interrupt local neuronal activity in the NRM (Kourosh Arami et al., 2006). In hypothermia, lidocaine injections into the medullary raphe result in suppressing the tail vasoconstriction and thus, lidocaine inhibits the thermoregulatory effect of NRM and decreases TBF (Kourosh Arami et al., 2006).

During cold exposure, cutaneous vasoconstriction reduces heat loss and protect from hypothermia. Therefore, alteration of skin blood flow has important clinical implications and can weaken the mechanism of heat balance. In our previous study, microinjection of lidocaine into nucleus raphe magnus significantly decreased TBF. Therefore, we concluded that the

NRM has thermoregulatory effect in response to hypothermia (Malakouti et al., 2008). In next step, to find the underlying mechanism of NRM in TBF regulation we examined the effect of nitric oxide donor and inhibitor. In that research we indicated that injection of sodium nitroprusside (exogenous NO donor) into NRM results in the elevation of blood flow. According to our previous study, when TBF reduced in response to hypothermia the injection of glutamate in the raphe magnus resulted in increases in blood flow of tail cutaneous bed. It is proposed that glutamate by a reduction in sympathetic outflow may be responsible for its hypothermic action in the NRM. So, our work highlights the importance of interaction between glutamate and thermoregulatory pathway in the nervous system (Kourosh Arami et al., 2006). However, further investigations are thought to be necessary in order to evaluate the thermoregulatory action. In the next step, we found that this effect of L-glutamate was reduced by prior intra NRM administration of nitric oxide synthase inhibitor (L-NAME) (Arami et al., 2015). Therefore, NO in the nucleus raphe magnus may interact with excitatory amino acids and modulate cutaneous blood flow in rats. Evidence shows that hypertension may decrease the skin blood flow. Moreover, in other set of our studies, we found that the renin, angiotensin and aldosterone levels were increased in response to hypothermia. Activation of renin and so angiotensin may increase blood pressure and hence may decrease the skin blood flow. In addition, aldosterone elevation in hypothermia may increase the blood pressure by the maintenance of sodium and water that will lead to skin blood flow decrement (Kourosh et al., 2005).

Vasoconstrictor control of skin blood flow by sympathetic nervous system

The vasoconstriction is a manner to control the skin circulation (Edholm et al., 1957). The sympathetic vasoconstrictor nerves innervate glabrous skin including palms, soles and lips (Johnson and Proppe, 1996). In glabrous skin, arteriovenous anastomoses (AVA) which are low resistance pathways can alter flow rates directly from arterioles to venules through opening or closing of these AVA (Lossius et al., 1993). AVA is the elaborate system in rats tail that regulates heat dissipation by sympathetic regulation during hypothermia (Blessing and Nalivaiko, 2001).

The skin vasoconstrictor activity is regulated by the sympathetic nervous system and depends on both core and skin temperatures. Cooling the skin initiates an increased vasoconstrictor nerve activity, the release of norepinephrine and NPY which interacts with postsynaptic α1 and α2 receptors on cutaneous arterioles and AVA and a reduction in skin blood flow (Fig. 3; Stephens et al., 2001; Stephens et al., 2002; Smith and Johnson, 2016). In response to cold temperature, thermoregulatory vasoconstriction can limit the skin blood flow by variation of the vasoconstrictor outflow to cutaneous arterioles and particularly arteriovenous anastomoses, a counter-current exchange of heat to further reduction of heat loss (MacKenzie et al., 1996). The vasoconstrictor system in human skin is characteristically active at normal brain and skin temperatures (Pergola et al., 1994). This system is responsible for the protection of normal body temperature. Delicate changes in skin or body temperature are equal to minor changes in skin blood flow and heat elimination and hence, body temperature remains in a very narrow range (Smith and Johnson, 2016).

Vasodilator control of skin blood flow by nitric oxide

NO, as a prominent second messenger, plays an important role in thermoregulation in the central and peripheral nervous systems (Leger et al., 1998). NO as a central activator of heat defense mechanism is synthesized in all mesencephalic raphe nuclei cells (Leger et al., 1998). In our previous study, we found that injection of sodium nitroprusside into NRM prevents thermal vasoconstriction of rat tail vessels in response to cold exposure but the injection of L-NAME, known as an inhibitor of nitric oxide synthase, disrupts the excitatory effect of glutamate on the NRM and then on TBF (Arami et al., 2015). It has been reported that the creation of NO and resultant cGMP levels increase by stimulation of NMDA receptors. Furthermore, NO rises the release of excitatory amino acids by cGMP-dependent processes in the dorsomedial medulla (Dias et al., 2007). In a study demonstrated that L- NAME reduced NO facilitation of excitatory amino acid-evoked excitation of NTS neurons (Dias et al., 2005). Based on the reports of various studies, administration of NOS blockade (Eriksson et al., 1997; Mathai et al., 2004), or administration of NO

donor (Mathai et al., 2004), exert a tonic restraint in central sympathetic outflow. Sympathetic fibers play an important role in stimulating vasoconstriction of the superficial vascular beds, so it is probable to propose that a reduction in the sympathetic outflow by NO in the raphe may be responsible for its thermoregulatory action in the CNS (Arami et al., 2015). Moreover, there are two phases of vasodilation during local warming: a rapid phase and a slower phase. In the first phase, local nervous activity is involved but in the slower phase, NO has an important role in starting and maintaining of this phase so that when local L-NAME is administered prior to local heating, vasodilation is inhibited (Johnson et al., 1986b; Kellogg et al., 1999). During postnatal development, some glutamatergic synapses first contain NMDA receptors (Kourosh Arami, Semnanian et al., 2011, Arami, Hajizadeh et al., 2016), which mainly yield hyperpolarization and inhibitory effects (D'yakonova, 2000). Synchronized application of glutamate and nitroprusside, which is a NO donor, however, established an opposite effect, as cells responded to glutamate with depolarization and excitation.

Contribution of peripheral factors in skin blood flow regulation

Hormonal thermoregulation of skin blood flow

The evidence demonstrated that cold air exposure for 3 weeks, increases plasma renin activity and then returns to a normal level. It is also known that plasma renin activity increment in response to hypothermia can result from the effect of sympathetic activation. It is observed that the plasma concentration of norepinephrine increases 30 minutes to an hour after hypothermia and remains elevated during cold exposure (Kourosh et al., 2005). In one study, a significant drop in heart rate, cardiac output, arterial pressure and left ventricular contractility were observed during cold exposure (Talwar and Fahim, 1998). This reduction in arterial pressure stimulates renin secretion by juxtaglomerular cells and thereby activates angiotensin production. Furthermore, a remarkable increment in serum aldosterone level is observed (Kourosh et al., 2005).

In a study, decreased Na-K ATPase pump activity in the corticorenal region in response to cold exposure resulted in rising of aldosterone synthesis and secretion (Johnson et al., 1996; Lee et al., 1996). In an experiment renin-angiotensin stimulation in response to hypothermia induced catecholamine activation and hence increment of NaCl intake in mice (Dejima et al., 1996). It has been reported that renin-angiotensin is activated in a hypothermic intervention during cardiopulmonary bypass. It was shown that aldosterone level increases in pulsatile and nonpulsatile cardiopulmonary bypass (Sun et al., 1997).

Hypothermia and blood pressure regulation

Exposure to stress, activates many neurochemical systems. The main physiological response to a stressor is the activation of the hypothalamic-pituitary-adrenal axis. A previous study showed that a moderate exposure to the cold, results in systemic activation of the renin-angiotensin-aldosterone system in rats that causes increase of blood pressure associated with lowering the blood flow to the skin, and this problem is gradually getting worse if the hypertension is not treated (Cowburn et al., 2017). A substantial decrease in skin blood flow reserve in chronic hypertension has been shown. This reduction at sites with significant arteriovenous perfusion is greater than at nutritive sites (Rendell et al., 1996). This is another reason for cold-induced reduction of skin blood flow. In one study, exposure to sever cold elevated blood pressure, cortisol, aldosterone and noradrenaline. Administration of dexamethasone significantly reduced increment of aldosterone and cortisol in response to cold but had not any effect on blood pressure and noradrenaline. Therefore, it was concluded that among the various hormones, noradrenaline is the only hormone responsible for an elevation of blood pressure in response to cold (Hiramatsu et al., 1984). The finding of a study demonstrated that whole-body cold stress results in greater increases in sympathetic outflow directed to the cutaneous vasculature and subsequently, greater reductions in skin blood flow in hypertensive adults. Therefore, control of cutaneous vasculature by the sympathetic nervous system is not only preserved, but also exaggerated in hypertension (Greaney et al., 2017).

Blood-derived thermoregulatory factors

The viscosity of the blood increases with declining temperature. Low temperature affects shear-induced platelet aggregation (Van Poucke et al., 2014). The

reduction in platelet count observed in vivo returned to a normal level during hypothermia (Van Poucke et al., 2014). A study suggested that platelet-poor plasma is an essential potential activator of angiogenesis (Shahidi et al., 2018). Angiogenesis is a complex process that organizes the formation of blood vessels from the pre-existing vasculature. Skin blood flow can reduce in response to hypothermia. Furthermore, reduction of skin blood flow in hypothermic rats leads to decrease of angiogenesis (Ramasamy et al., 2016). In addition, in angiogenesis, total blood volume of the tissue increased but the rate of flow decreased. This is another reason for the reduction of blood flow in skin vessels. In addition, reduction of skin blood flow may be produced in response to the enhancement of blood viscosity by hypothermia (Van Poucke et al., 2014). Mild hypothermia has been shown to enhance angiogenesis in focal cerebral ischemia (Xie et al., 2007), spinal cord injury (Kao et al., 2011) and traumatic brain injury models (Kuo et al., 2010). Effect of hypothermia on angiogenesis might be diverse in different tissues. Mild hypothermia enhances angiogenesis in the ischemic brain, which might be enhanced in part via brain-derived neurotrophic factor.

Brown adipose tissue

Brown adipose tissue is involved in non-shivering thermogenesis, where oxidative metabolism is uncoupled from ATP creation and energy is expended. This tissue is thermogenic by augmentation of the metabolic rate. Brown adipose tissue until recently was thought to be only important in small mammals and neonates. Although, evidence shows the stimulation of brown adipose tissue in adult humans in cold exposure (Nedergaard et al., 2007; Saito et al., 2009; van der Lans et al., 2013). Sympathetic nervous system can activate brown adipose tissue thermogenesis. Catecholamines through β_3-adrenergic receptors can stimulate an uncoupling protein on the inner mitochondrial membrane. The uncoupling protein permits H^+ to transfer across the mitochondrial membrane without ATP making (Klingenspor, 2003).

Shivering

In hypothermia, animals will save heat by mechanisms including vasoconstriction and piloerection, which are energetically inexpensive and by changes in behavior. If these alterations are inadequate to preserve temperature, shivering occurs. The beginning of shivering shows that maximal vasoconstriction has previously been accomplished (DeGroot and Kenney, 2007). It is started by the hypothalamic preoptic area but mediated by the somatic motor cortex in response to signals from skin cold receptors; hence, the normal stimulus for shivering is temperature of the skin rather than the core temperature (DeGroot and Kenney, 2007).

Shivering is involuntary, fast, oscillating contractions of skeletal muscle. ATP is hydrolyzed, but no work is done by contraction and hence the energy formed is released as heat. In adults, shivering, at its maximum rate, produces heat creation comparable to five times the basal metabolic rate (Eyolfson et al., 2001); though, in neonates, because of immaturity of their skeletal muscles, non-shivering thermogenesis happens (Stern, 1980).

Clinical perspectives

With menopause, variations in reproductive hormone levels make alternations in thermoregulatory control of skin blood flow. The occurrence of hot flashes may also be caused by this altered control (Brooks and Kenney, 1997). In patients with type 2 diabetes mellitus, impairments in cutaneous vasodilation may contribute to the increased occurrence of heat illness (heat shock, heat exhaustion) during increased ambient temperatures (Semenza et al., 1999; Kenney et al., 2014). There was a markedly decreased cutaneous vasodilation to local iontophoresis of acetylcholine and sodium nitroprusside in diabetes mellitus patients with or without neuropathy (Arora et al., 1998). Impairments of local and/or reflex thermoregulatory control of the skin circulation appears to cause microvascular disorders including Raynaud phenomenon and erythromelalgia. The pathophysiology of these conditions remain unclear, but alterations in local neural mechanisms and neuropeptides and endothelial vasoactive factors contribute to these diseases (Bunker et al., 1996; Alba et al., 2019).

Conclusion

Specific fundamental mechanisms for hypothermia-induced reduction of skin blood flow discussed in this

review. Current understanding of skin blood flow control includes important roles for nucleus raphe magnus that have thermoregulatory effect in response to hypothermia. Cutaneous sympathetic vasoconstrictor and renin-angiotensin activation and then aldosterone elevation in hypothermia participate in increasing the blood pressure and skin blood flow attenuation. Furthermore, NO as an important factor in the raphe magnus can modulate central cutaneous blood flow in rats during hypothermia.

Acknowledgments

The authors wish to thank the Iran University of Medical Sciences for assisting us in conducting this study.

Conflict of interest

The authors declare that they have no conflict of interests.

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