Control of cutaneous blood flow by central nervous system

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Keywords: cutaneous vasoconstriction, medullary raphe, preoptic area, psychological hyperthermia, sympathetic nervous system

Abbreviations: AVAs, arteriovenous anastomoses; CLPO, caudolateral preoptic region; GABA, γ-aminobutyric acid; PGE2, prostaglandin E2; RMPO, rostromedial preoptic region; RVLM, rostral ventrolateral medulla oblongata; 5-HT, 5-hydroxytryptamine.

Hairless skin acts as a heat exchanger between body and environment, and thus greatly contributes to body temperature regulation by changing blood flow to the skin (cutaneous) vascular bed during physiological responses such as cold- or warm-defense and fever. Cutaneous blood flow is also affected by alerting state; we ‘go pale with fright’. The rabbit ear pinna and the rat tail have hairless skin, and thus provide animal models for investigating central pathways regulating blood flow to cutaneous vascular beds. Cutaneous blood flow is controlled by the centrally regulated sympathetic nervous system. Sympathetic premotor neurons in the medullary raphe in the lower brain stem are labeled at early stage after injection of trans-synaptic viral tracer into skin wall of the rat tail. Inactivation of these neurons abolishes cutaneous vasomotor changes evoked as part of thermoregulatory, febrile or psychological responses, indicating that the medullary raphe is a common final pathway to cutaneous sympathetic outflow, receiving neural inputs from upstream nuclei such as the preoptic area, hypothalamic nuclei and the midbrain. Summarizing evidences from rats and rabbits studies in the last 2 decades, we will review our current understanding of the central pathways mediating cutaneous vasomotor control.

Introduction

The skin acts as a protective barrier between the body and the external environment. The skin, especially hairless (glabrous) skin, also functions as a variable capacity heat exchanger. Regulating blood flow to the glabrous skin is an important mechanism determining heat exchanges between the body and the environment, and thus contributes to thermoregulation, while the primary function of the cutaneous vascular bed is to supply substances to the skin itself. Increasing blood flow to the skin by cutaneous vasodilatation enhances heat dissipation from the skin surface, a part of the heat-defense response. Decreasing skin blood flow by cutaneous vasoconstriction greatly contributes to accumulation of central core heat, as a part of the cold-defense response or of the fever response. Cutaneous vasoconstriction also occurs, when the individual is aroused, especially under aversive situation.

Thermo-receptors in the skin are part of the thermoregulatory system. Nakamura and Morrison recently discovered thermal afferent pathways that convey temperature signals from the periphery to the thermoregulatory center in the preoptic area1 (For a review see refs.2-4), focusing on thermogenesis as an index of thermoregulatory response.1 The same afferent pathways are involved in thermoregulatory cutaneous vasomotor responses.5

The cutaneous vascular bed is dilated and constricted by hormonal and neural control. In response to acute thermoregulatory or aversive events such as cold exposure or sudden exposure to alerting stimuli, neural influence is predominant. Arteriovenous anastomoses (AVAs) play an important role in cutaneous blood flow regulation. Dilating AVAs provides low-resistance bypasses, which increase cutaneous vascular volume and thus deliver more blood to the skin.6 The AVAs are abundant in the glabrous skin, and are densely innervated by sympathetic nerve fibers.7,8 The sympathetic nerve terminals release noradrenaline, and the noradrenaline binds α-adrenergic receptors on cutaneous vascular smooth muscle resulting in cutaneous vasoconstriction.9-11 Functional studies show that cutaneous blood flow is regulated by...
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that chemical activation of neurons in the medullary raphé at the rostrocaudal level of the caudal third of the facial nucleus increases tail sympathetic nerve activity in rats. Following this report, Blessing and colleagues showed that disinhibition of neurons in the medullary raphé with bicuculline (γ-aminobutyric acid (GABA)A receptor antagonist) causes strong cutaneous vasoconstriction in the rat tail and the rabbit ear, measured with Doppler flow probes. Inhibition of neurons in the medullary raphé causes cutaneous vasodilatation in the rat tail and the rabbit ear.

Cold exposure decreases tail blood flow (cutaneous vasoconstriction). Inhibiting neurons in the medullary raphé reverses cold-evoked cutaneous vasoconstriction in anaesthetized rats by reducing the activation of cutaneous sympathetic nerves (Fig. 2). Heat exposure or warming the preoptic area causes cutaneous vasodilatation and increases tail skin temperature. Blocking GABAergic inhibitory inputs to the medullary raphé neurons with bicuculline suppresses the tail cutaneous vasodilatory response (Fig. 3A).

Cutaneous vasoconstriction also occurs in fever, and contributes to an increase in body temperature by reducing heat dissipation from the skin surface. Injection of pyrogenic substances such as lipopolysaccharide and prostaglandin E2 (PGE₂), a final humoral mediator that elicits fever, increases cutaneous sympathetic nerve discharge and elicits cutaneous vasoconstriction. Inhibition of the medullary raphé neurons reverses the PGE-elicited cutaneous vasoconstriction.

Cold exposure and fever increases fos immunoreactivity in neurons of the medullary raphé/parapyramidal region. The medullary raphé contains a population of spinally projecting neurons that respond to cooling truncal skin. Anatomical studies with transneuronal viral tracing approaches show that the medullary raphé is among the earliest infected cell groups after injection of pseudorabies virus into the rat tail.

These functional and anatomical evidences strongly indicate that the medullary raphé contains sympathetic premotor neuron linking to the central neural pathway mediating thermoregulatory signals to sympathetic preganglionic neurons controlling cutaneous sympathetic vasoconstrictor nerves. Functional magnetic resonance imaging suggests involvement of neurons in the medullary raphé in cold-defense response in humans.

It should be added that disinhibition of neurons in the caudal portion of the medullary raphé nuclei at the level of the rostral part of the inferior olivary nucleus causes cutaneous vasodilatation rather than vasoconstriction. The caudal medullary raphé...
region also contains neurons labeled transneuronally after pseudorabies virus injection in the rat tail.\textsuperscript{36,39,40} The inhibitory transmitter GABA is present in spinally-projecting medullary raphé neurons,\textsuperscript{42,43} although their peripheral targets and physiological roles have not been identified. GABA modulates activity of sympathetic preganglionic neurons.\textsuperscript{44-46} Thus, sympathetic premotor neurons may exist in the caudal medullary raphé that inhibit cutaneous vasoconstrictor sympathetic outflow.

Rostral ventrolateral medulla oblongata (RVLM)

The rostral ventrolateral medulla oblongata (RVLM) contains sympathetic premotor neurons for the cardiovascular system, controlling vasoconstriction, heart rate and arterial pressure.\textsuperscript{47,48} Neurons in the RVLM, like the medullary raphé, are infected at the same early stage after injection of pseudorabies virus into the rat tail.\textsuperscript{39} In rats, electrical stimulation of the RVLM reduces tail temperature, indicating cutaneous vasoconstriction.\textsuperscript{49} In rabbits, inhibition of neurons in the RVLM increases ear pinna blood flow.\textsuperscript{50} Otsuka and McAllen demonstrated that chemical inactivation of neurons in the RVLM inhibits ongoing tail cutaneous sympathetic fiber discharges and abolishes its normal excitatory response elicited by cooling truncal skin\textsuperscript{51} (Fig. 4A). These studies suggest that neurons in the RVLM can also influence the thermoregulatory control of cutaneous vasomotor activity. However, further strong skin cooling still increases tail sympathetic discharges after inactivation of neurons in the RVLM (Fig. 4A), but not in the medullary raphé (Fig. 4B). Thus tonic background drive from the RVLM as well as the medullary raphé is necessary to maintain cutaneous sympathetic activity, while the medullary raphé neurons play a major role in thermoregulatory drive to the cutaneous vascular bed at least during cold- and heat-defense responses. The predominant role of the medullary raphé in cutaneous vasomotor control during thermoregulatory response is partly supported by a report that blockade of inhibitory signal inputs to the medullary raphé but not to the RVLM suppresses cutaneous vasodilatation during heat-defense response\textsuperscript{23} (Fig. 3).

**Hypothalamic and Midbrain Nuclei Associated with Cutaneous Vasomotor Control**

**Preoptic area**

The preoptic area plays a key role in controlling body temperature, integrating temperature information from shell and core of the body and then sending efferent signals to thermoregulatory effector organs.\textsuperscript{52} The preoptic area contains neurons, which respond to local brain, core and skin temperature.\textsuperscript{53-58} Warming the preoptic area elicits cutaneous vasodilation in the rat tail (Fig. 3), and inhibits cold-induced activation of cutaneous sympathetic fibers supplying the rat tail (Fig. 5).\textsuperscript{59} Tanaka and colleagues performed detailed mapping in the preoptic area with nano-injections of GABA. They found 2 distinct preoptic regions providing an inhibitory drive to the tail cutaneous sympathetic fibers; a rostromedial preoptic region (RMPO) surrounding the organum vasculosum of the lamina terminalis and the ventral part of the median preoptic nucleus, and a preoptic region centered 1mm caudolaterally (CLPO).\textsuperscript{51} Inhibition of neurons with GABA in both the RMPO and the

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**Figure 4.** Tail sympathetic fiber response to bilateral inhibition of RVLM neurons with muscimol (336 pmol in 160 nl per side, 2 arrows) or to inhibition of the medullary raphé neurons with muscimol (360 pmol in 120nl) in anesthetized rats. (A) After the inhibition of the RVLM neurons, either of L-glutamate (L-Glu, 6 nmol in 120 nl) injection into the medullary raphé or strong cooling was still able to activate tail sympathetic fibers. (B) After neuronal inhibition in the medullary raphé, either of L-Glu injection into the RVLM or strong cooling fails to reactivate the tail fibers. Horizontal bars on skin temperature traces show periods when cooling was performed. Modified from Otsuka and McAllen.\textsuperscript{51} © American Physiological Society. Permission to reuse must be obtained from the rightsholder.

**Figure 5.** Warming the preoptic area (POA) significantly reduces cold-elicited increase in tail sympathetic nerve activity in anesthetized rats. The left record shows a control cutaneous sympathetic excitatory response to cooling via the water jacket. The right record shows the cold-elicited response was reversed by preoptic warming to 45°C. The inset shows thermode tip locations in 4 experiments (black dots) on a coronal section of the preoptic area. An arrow marks the site warmed in the record. ac, anterior commissure nucleus; CPu, caudate-putamen; LV, lateral ventricle; OX, optic chiasm. Modified from Owens et al.\textsuperscript{59} © Wiley. Permission to reuse must be obtained from the rightsholder.
CLPO activate tail cutaneous sympathetic nerves under warm condition when their activity is low, suggesting that neurons in the 2 preoptic regions are active in the warm (warm-responsive), and that the warm-responsive preoptic neurons provide tonic inhibitory influence on the cutaneous sympathetic outflow.31

Several studies indicate that the preoptic area provides major descending outputs to the medullary raphé for controlling cutaneous vasomotor activity in the rat tail.23,30,34 As already mentioned, blockade of an inhibitory input to the medullary raphé by bicuculline reverses cutaneous vasodilatory response to warming the preoptic area (Fig. 3A). Furthermore, warm-responsive neurons projecting directly to the medullary raphé are found in the preoptic area, mainly in the CLPO (Fig. 6). These findings suggest the importance of an inhibitory input from the preoptic area (possibly from the warm-responsive neurons) to the medullary raphé for thermoregulatory cutaneous vasomotor control. Since few warm-responsive neurons which project directly to the medullary raphé are found in the RMPO,30 an inhibitory drive from the RMPO could be indirect.

Interestingly, some of the raphé-projecting preoptic neurons are activated by skin cooling (cold-responsive). Most of the cold-responsive raphé-projecting neurons are in the RMPO (Fig. 6).30 Under warm conditions, disinhibition of neurons in the RMPO, but not in the CLPO, with bicuculline increases tail cutaneous sympathetic nerve discharges followed by an increase in body temperature30 (Fig. 7). Moreover, blockade of excitatory inputs to the medullary raphé with glutamate receptor antagonist kynurenic acid abolishes the cutaneous sympatho-excitation in response to skin cooling or to bicuculline microinjected into the RMPO (Figs. 8 and 9).30 These findings suggest that an excitatory pathway from the cold-responsive RMPO neurons to the medullary raphé mediates cutaneous vasoconstriction response during cold-defense,30 and that
the cold-responsive RMPO neurons receive tonic inhibitory GABAergic inputs under warm condition, though the origin of the GABAergic input is unknown (Fig. 1). Thus, the medullary raphé may receive excitatory as well as inhibitory signaling from the preoptic area to regulate cutaneous vasomotor activity.

The preoptic area is also the key brain structure for febrile action of PGE2. Several studies have indicated that the RMPO is the most PGE2 sensitive region to cause febrile responses including cutaneous vasoconstriction.31,60,61 The prostaglandin E receptor 3 (EP3 receptor) is considered to be the critical receptor responding to PGE2 to mediate febrile response, and is strongly expressed in the RMPO.62-64,65 More than 85% of EP3-expressing neurons in the preoptic area are GABAergic,35 and PGE2 exerts inhibitory action on neurons via EP3 receptors.66-68 The data support the simplest hypothesis that PGE2 inhibits those preoptic neurons (probably warm-responsive) through EP3 receptors,35,69 and then withdraws tonic inhibitory drive to the medullary raphé, causing a febrile response.

Tanaka and colleagues have recently suggested that the excitatory pathway from the RMPO to the medullary raphé might be also involved in the fever response. Microinjection of PGE2 into the RMPO causes a rapid increase in tail cutaneous sympathetic discharges, and subsequent microinjection of glutamate receptor antagonists into the medullary raphé reverses the response (Fig. 10).34 Furthermore, inhibition of neurons in the RMPO with glycine or muscimol injection substantially reduces cutaneous sympatho-excitation elicited by PGE2 injected into the RMPO.34 These results reveal that the cutaneous vasoconstrictor response during experimental fever depends upon an excitatory synaptic relay in the medullary raphé, and that an excitatory drive from the RMPO contributes to the cutaneous vasoconstrictor responses during fever.

It is not clear how PGE2 activates preoptic neurons. One possibility is that PGE2 activates the cold-responsive RMPO neurons, indirectly by inhibiting interneurons in the RMPO35(Fig. 1), but it remains to be tested. It also remains to be determined whether the fever-driven excitation of cutaneous vasoconstrictor premotor neurons in the medullary raphé comes directly from the RMPO, as does the mechanism through which PGE2 might activate RMPO neurons.

Bilateral injections of bicuculline in the dorsal preoptic area that corresponds to the CLPO region inhibit fever responses elicited by systemic administration of lipopolysaccharide, and elicit cutaneous vasodilatation in the rat tail70(Fig. 11). GABAergic drive to warm-responsive neurons in the CLPO may be promoted during fever responses, and greatly contribute to cutaneous vasoconstrictor responses.

The RMPO and CLPO neurons probably act synergistically to control cutaneous vasomotor activity. This view is supported by a report that combined lesioning of both region, but not independent lesioning of either one, elicits an increase in body temperature.71

**Dorsomedial hypothalamus**

It has been proposed that the dorsomedial hypothalamus (DMH) integrates thermoregulatory responses to cold and fever.72 Electrical stimulation of the DMH elicits cutaneous vasoconstriction in the rabbit ear pinna.73,74 Pharmacological activation of neurons in the DMH increases cutaneous sympathetic vasoconstrictor activity in rats.28,75 However, the inhibition of the DMH neurons fails to suppress the cutaneous vasoconstriction elicited by PGE2 injected into the preoptic area or by skin cooling, suggesting that the DMH is not involved in cutaneous vasoconstriction during cold-defense and fever responses.28

The DMH has been implicated as mediating behavioral and autonomic physiological response to aversive or psychological
Cutaneous vasoconstriction is also elicited by aversive environmental events (see ‘Cutaneous vasoconstriction elicited by psychological stimuli’ section in below). The DMH may be important in this response.

**Ventral tegmental area and periaqueductal gray matter**

Apart from direct projections from the preoptic area to the medullary raphé, the midbrain area seems to participate in cutaneous vasomotor control. Zhang and colleagues found cutaneous vasconstrictor neurons in the ventral tegmental area (VTA), and cutaneous vasodilator neurons in the rostral ventrolateral periaqueductal gray matter (rvl PAG). Cutaneous vasodilatory response to warming the preoptic area is inhibited by electrical and pharmacological activation of neurons in the VTA (Fig. 12). Blocking downstream signaling from the VTA by transection of area caudal to the VTA elicits cutaneous vasodilatation. Blocking signal inputs from upstream to the VTA by transection of area rostral to the VTA suppresses the cutaneous vasodilatory response to warming the preoptic area.

Stimulation of neurons in the rvl PAG elicits cutaneous vasodilatation. Furthermore, blocking signal outputs from the rvl PAG to downstream by transection of regions in the caudal PAG suppresses the cutaneous vasodilatory response to warming the preoptic area. Environmental heat exposure increases fos immunoreactivity in the rvl PAG. Considering that there are direct projections from the preoptic area to the rvl PAG and the VTA, it is possible that these regions contribute to thermoregulatory cutaneous vasomotor control by receiving excitatory inputs in the rvl PAG from the warm-responsive neurons in the preoptic area, and by receiving inhibitory inputs in the VTA from the warm-responsive neurons. In addition, there are direct projections to the medullary raphé from the rvl PAG, but not from the VTA. The medullary raphé is likely to mediate the thermoregulatory signals via these areas by receiving excitatory drive from the VTA and inhibitory drive from the rvl PAG.

**Contribution of Serotonin in the Regulation of Cutaneous Vasomotor Activity**

Neurons in the medullary raphé region include bulbospinal neurons that synthesize 5-hydroxytryptamine (5-HT), known to affect body temperature. Activation of 5-HT1A receptors decreases body temperature, while activation of 5-HT2A receptors increases body temperature. Acute and chronic inhibition of 5-HT synthesizing neurons in the brain causes hypothermia. Transneuronal viral tracing studies in rats have shown that 5-HT neurons in the medullary raphé are infected at the earliest stage after injection of virus into the rat tail. In the study by Toth and colleagues, 90% of virus-infected neurons in the medullary raphé, the parapyramidal region bordering and lateral to the pyramid are found to be 5-HT positive, suggesting that 5-HT is one of the candidate neurotransmitter of bulbospinal neurons controlling tail cutaneous vascular bed. Serotonergic terminals...
are found in the intermediolateral cell column in the spinal cord. Serotonergic-immunoreactive terminals are juxtaposed to sympathetic preganglionic cells. Pharmacological studies show that 5-HT agonists activate functionally-unspecified sympathetic preganglionic neurons. 5-HT antagonists inhibit excitation of sympathetic preganglionic neurons elicited by stimulation of the medullary raphe. These studies suggest that some of the 5-HT neurons in the medullary raphe are likely to function as cutaneous sympathetic premotor neurons.

5-HT1A receptors

Ootsuka and Blessing conducted a series of studies to investigate contribution of 5-HT system to cutaneous vasomotor control. The 5-HT1A receptors are considered to be inhibitory somatodendritic autoreceptors, that are expressed principally on 5-HT cells, although the receptors are also present on non-5-HT neurons. Systemic administration of a 5-HT1A agonist, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) inhibits sympathetically-mediated cutaneous vasoconstriction during cold-defense and fever responses. The systemic administration of 8-OH-DPAT does not affect ear pinna cutaneous post-ganglionic sympathetic nerve discharge evoked by electrical stimulation of preganglionic sympathetic fibers. Thus the cutaneous sympatho-inhibitory action of the 8-OH-DPAT is not in the periphery, but in central nervous system, possibly in the medullary raphe. This view is confirmed by further studies in rabbits. Focal injection of 8-OH-DPAT into the medullary raphe inhibits cutaneous vasoconstriction and sympatho-excitation during cold exposure. Furthermore, focal injection of a 5-HT1A antagonists, WAY100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide) reverses sympathetically-mediated cutaneous vasomotor changes elicited by intravenous injection of 8-OH-DPAT (Fig. 13). Neurons in the medullary raphe inhibited by systemic administration of 8-OH-DPAT increase their activity in response to cold exposure. Thus it is likely that inhibitory 5-HT1A receptors are present in the medullary raphe that mediates cutaneous vasoconstriction in response to cold exposure.

5-HT1A antagonists themselves do not affect resting cutaneous blood flow, suggesting no tonic action through 5-HT1A receptors in the signaling process of cutaneous vasomotor control. The physiological role of intrinsic 5-HT1A receptor antagonists in cutaneous vasomotor control remains to be established. 5-HT1A receptors might be related to menstrual-related temperature increase. 5-HT1A receptor antagonists like buspirone are used as an anxiolytic agent. The combination of anxiolytic and cutaneous sympathoinhibitory properties might therefore be therapeutically useful.

5-HT2A receptors

Cutaneous vasomotor activity is also affected by 5-HT2A receptor agonists and antagonists. Activation of 5-HT2A receptors by systemic administration of 5-HT2A agonist, DOI (R(-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride) elicits sympathetically-mediated cutaneous vasoconstriction (Fig. 14A). This cutaneous sympathoexcitatory effect of 5-HT2A agonists occurs even after the blockade of signaling from the medullary raphe to the spinal cord (Fig. 14B), strongly suggesting the involvement of spinal 5-HT2A receptors in the excitation of sympathetic preganglionic cutaneous vasomotor neurons. Indeed, cutaneous sympathetic
vasomotor discharges elicited by the stimulation of the medullary raphé is reduced by the blockade of spinal 5-HT2A receptors after focal application of the 5-HT2A antagonist, SR46349B (trans-4-((3 Z)-3-[(2-dimethylaminoethyl)oxyimino]-3-(2-fluorophenyl)propen-1-yl)-phenol, hemifumarate) to the cerebrospinal fluid in the thoracic spinal cord where ear pinna sympathetic vasomotor preganglionic neurons are located (Fig. 15). These studies support a view that 5-HT neurons in the medullary raphé contribute to the regulation of sympathetic cutaneous vasomotor discharges.

It must be noted that the blockade of 5-HT2A receptors does not completely suppress cutaneous vasomotor sympathetic excitation elicited by electrical stimulation of the medullary raphé (Fig. 15B). Subsequent additional blockade of glutamate receptors abolishes the raphé-elicited cutaneous sympatho-excitation (Fig. 15C). A transneuronal tracing study demonstrates that the majority of virus-positive medullary raphé neurons express vesicular glutamate transporter 3 after injection of pseudorabies virus into the rat tail. Thus, this suggests that the glutamate is as important as 5-HT as a neurotransmitter in the medullary raphé-spinal neurons regulating cutaneous sympathetic outflow. It remains to be investigated whether glutamate co-localizes with 5-HT in the medullary raphé-spinal neurons that regulate cutaneous sympathetic outflow.

To identify neurochemical properties of raphé-spinal sympathetic cutaneous vasomotor neurons, single neural recordings from a neuron labeled transneuronally from cutaneous vascular bed and its immunohistochemical identification are required. So far there are no such studies. Nevertheless, studies with orthodromic activation of descending axons of the raphé-spinal neurons show that their conduction velocity is about 1 m/s in rabbits and in rats (unpublished data, Ootsuka and McAllen). This conduction velocity is within the range of unmyelinated fibers, to which serotonergic axons in the spinal cord belong.

**Cutaneous Vasoconstriction Elicited by Salient/Alerting Stimuli**

Majority of the studies on central neural mechanisms of cutaneous vasomotor control have been performed from the thermoregulatory point of view, since cutaneous blood flow are closely associated with changes in body temperature. Cutaneous blood flow is also affected by salient or aversive environmental event. Thus, changes in cutaneous blood flow are actually a reliable index to assess alerting state condition as well as thermoregulatory state in experimental animals.

Cutaneous vasoconstriction is also part of the patterned cardiovascular response to aversive stimuli or conditioned fear as well as thermoregulatory stimuli, a response known as ‘pale with fright’. The sympathetically-mediated cutaneous vasoconstrictor response to salient stimuli is associated with occurrence of hippocampal theta rhythm, a marker of alertness. The physiological role of the psychologically-elicited cutaneous vasoconstriction is not properly established yet, but it partly contributes to an increase in body temperature, a response referred to as emotional hyperthermia or ‘psychological fever’. The cutaneous vasoconstriction may also contribute to equalizing skin surface temperature to surrounding environmental temperature, so that individuals may have more chance to slip through thermal detection by predators such as rattlesnakes and vampire bats. The cutaneous vasoconstriction may provide some protection to the loss of blood in case of a cut or break in the skin during attacking from predators.
Blessing and colleagues have established an animal model of cutaneous vasoconstriction elicited by salient/alerting events, and have investigated brain mechanisms for the response. Cutaneous blood flow falls without changing intestinal, renal or skeletal muscle blood flow, when individuals confront salient or aversive situations (Fig. 16A).\textsuperscript{20,110} Similarly to thermoregulatory-elicited response, the psychologically-elicited cutaneous vasoconstriction is reversed by inhibition of neurons in the medullary raphé (Fig. 16B),\textsuperscript{20,125} and by 5-HT\textsubscript{1A} agonist and 5-HT\textsubscript{2A} antagonists.\textsuperscript{126,127} It should be noted that microinjection of glutamate receptor antagonists in the medullary raphé does not affect cutaneous vasoconstriction elicited by conditioned fear, suggesting that the vasoconstriction response during the fear response is not under local glutamatergic control unlike the febrile response.\textsuperscript{125} Dopamine D2 agonists, by its central action, suppress the cutaneous vasoconstriction elicited by alerting stimuli,\textsuperscript{115} suggesting the involvement of central dopamine system in cutaneous vasomotor control.

Alerting-related signals are processed in the forebrain nuclei. Stimulation of the amygdala complex, which has been suggested to have an important role in vigilance and arousal, elicits a robust selective fall in cutaneous blood flow.\textsuperscript{73} Inactivation of the amygdala complex inhibits the psychologically-elicited cutaneous vasoconstriction.\textsuperscript{111,128,129} Interestingly, removing noradrenergic axons from the locus coeruleus to the amygdala substantially inhibits the psychologically-elicited cutaneous vasoconstriction,\textsuperscript{130} suggesting that noradrenergic innervation into the amygdala facilitates the forebrain process driving cutaneous vasoconstriction during aversive psychological events. The psychologically-
elicit cutaneous vasoconstriction is also attenuated by ablation of orexin neurons in the lateral hypothalamus, which has an important role in regulating wakefulness, motivation and appetite. Recently, Ootsuka and Mohammed discovered that disinhibition of neurons in the habenula complex, a phylogenetically ancient nucleus in the dorsal diencephalon, elicits strong vasoconstriction selectively in the thermoregulatory cutaneous vascular bed followed by an increase in body temperature in anesthetized rats.

Signals from these higher brain centers driving the psychologically-elicited cutaneous vasomotor changes may be integrated in the lower brain stem thermoregulatory pathway including the medullary raphé. The amygdala-induced cutaneous vasoconstriction is reversed by inhibition of neurons in the medullary raphé.

**Conclusion**

Many investigations have suggested possible brain nuclei that contribute to cutaneous vasomotor control. So far only 2 nuclei have been thoroughly investigated; the medullary raphé and the preoptic area. Some other nuclei such as the VTA, PAG, hypothalamic and other forebrain nuclei are likely involved in the pathways controlling cutaneous vasomotor activity. Further studies are required to characterize these nuclei and their anatomical and functional connections, including connection from cutaneous vasodilative neurons in the rvl PAG, and cutaneous constrictor neurons in the VTA to the medullary raphé. The local circuitry in the preoptic area also remains to be delineated.

Central mechanisms controlling blood flow to cutaneous vascular bed is essentially integrated into the circulatory system that functions to distribute blood flow to tissues proportional to their activity. Under certain circumstances, central mechanisms of cutaneous blood flow control are overridden by signals from other system such as thermoregulatory and alerting systems. The medullary raphé seems to be a common nucleus controlling cutaneous vasomotor outflow for all purposes.

This review does not address thermogenesis, but it is important to note that the medullary raphé is also an important relay for thermogenesis. Significant research progress has enhanced our understanding of central mechanisms controlling thermogenesis focusing on brown adipose tissue (For a review see refs.2,4, 137). Although both cutaneous vasomotor and brown adipose tissue thermogenesis control depend on synaptic relays in the medullary raphé, these 2 thermo effectors targets are controlled by independent neural pathways. From the thermoregulatory point of view, changing cutaneous vasomotor activity is the most cost effective way to cope with thermoregulatory events, and thus the first-choice during a thermoregulatory challenge, because it requires less water resources compared to panting and sweating, and less bodily fuel compared to shivering and non-shivering thermogenesis in brown adipose tissue. This consideration may explain the necessity of the independent pathways.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest are disclosed.

**Funding**

Our series of studies was supported by Australian Research Council, Japan Grants-in-Aid for Scientific Research, High Blood Pressure Research Council of Australia, National Health and Medical Research Council, and Flinders Medical Center Foundation.
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