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Responses to hyperthermia. Optimizing heat dissipation by convection and evaporation: Neural control of skin blood flow and sweating in humans

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ABSTRACT

Under normothermic, resting conditions, humans dissipate heat from the body at a rate approximately equal to heat production. Small discrepancies between heat production and heat elimination would, over time, lead to significant changes in heat storage and body temperature. When heat production or environmental temperature is high the challenge of maintaining heat balance is much greater. This matching of heat elimination with heat production is a function of the skin circulation facilitating heat transport to the body surface and sweating, enabling evaporative heat loss.

These processes are manifestations of the autonomic control of cutaneous vasomotor and sudomotor functions and form the basis of this review. We focus on these systems in the responses to hyperthermia. In particular, the cutaneous vascular responses to heat stress and the current understanding of the neurovascular mechanisms involved. The available research regarding cutaneous active vasodilation and vasoconstriction is highlighted, with emphasis on active vasodilation as a major responder to heat stress. Involvement of the vasoconstrictor and active vasodilator controls of the skin circulation in the context of heat stress and nonthermoregulatory reflexes (blood pressure, exercise) are also considered. Autonomic involvement in the cutaneous vascular responses to direct heating and cooling of the skin are also discussed. We examine the autonomic control of sweating, including cholinergic and noncholinergic mechanisms, the local control of sweating, thermoregulatory and nonthermoregulatory reflex control and the possible relationship between sudomotor and cutaneous vasodilator function. Finally, we comment on the clinical relevance of these control schemes in conditions of autonomic dysfunction.

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1. Introduction

Under normothermic conditions, subtle changes in body temperature are met by equally subtle vasomotor adjustments in the skin (Savage and Brengelmann, 1996; Charkoudian and Johnson, 2000), constituting the major means of homeothermy. During hyperthermia, elevated core (Tcore) and skin temperature (Tsk) elicit cutaneous vasodilation and sweating responses via the autonomic nervous system, and may be modulated by non-thermal factors. Conversely, under hypothermic conditions, cutaneous vasoconstriction is the first line of defense against heat loss, with metabolic heat production via shivering and non-shivering thermogenesis occurring in more severe conditions. The regulation of body temperature is largely accomplished by the autonomic nervous system and the skin as a target organ, with both the vasculature and eccrine sweat glands being of primary importance. In this review we provide an overview of the autonomic control of these responses to hyperthermia, focusing on skin sympathetic nerve activity, local signaling mechanisms at the skin, the influence of non-thermal factors, and a brief introduction of the clinical relevance of autonomic dysfunction in thermoregulation.

1.1. Central regulatory control

The thermoregulatory control center in humans is located in the preoptic anterior hypothalamus (POAH) (Moorhouse, 1911; Ott, 1887), which receives afferent input from both central and peripheral (skin) thermoreceptors (Benzinger, 1959). The importance of this area for thermoregulation has been demonstrated in animal models whereby local warming of the preoptic area elicits cutaneous vasodilation, panting, sweating, and behavioral modifications to increase heat loss (Gisolfi et al., 1988; Kanosue et al., 1994). The POAH receives, integrates and weights central and peripheral afferent signals. In warm environments a 9:1 ratio of core:shell (skin) afferent signals are integrated at the POAH, versus a ratio of approximately 4:1 in thermoneutral to cold conditions. Efferent sympathetic sudomotor signals originating from the POAH, travel via the ipsilateral brainstem via the tegmentum of the Pons and the medullary raphe nuclei before activating preganglionic neurons in the intermediolateral cell column of the spinal cord. After exiting from the ventral horn and passing via the white ramus communicans, these neurons synapse in close proximity to the spinal cord in the sympathetic ganglia. In the particular instance of heat stress, sudomotor and vasomotor control originate from these central centers. In this review we focus on the peripheral manifestations of those controls.

1.2. Skin sympathetic nerve activity (SSNA)

Sympathetic innervation of the skin is complex due to the presence of cutaneous vasodilator, vasoconstrictor, sudomotor, pilomotor and sensory fibers contained within cutaneous nerves. SSNA is measured via microneurography, in which 'bursts' of activity are recorded and the frequency and characteristics analyzed. The temporal variation of SSNA differs from that of muscle, allowing identification of the different nerve branches. However, the complexity of SSNA poses significant challenges to identifying individual efferent signals, and therefore direct links with specific physiological responses. Attempts have been made to identify individual fiber activity, with evidence of sudomotor bursts being shorter in duration (Bini et al., 1980) and displaying a greater conduction velocity than vasoconstrictor bursts (Fagius and Wallin, 1980). Due to considerable variation and subsequent overlap between bursts, this is not a reliable means of differentiation among signals (Fagius and Wallin, 1980). Compared to normothermia, SSNA increases during hyperthermic conditions, reflecting increases in sudomotor and/or vasodilator activity. Notably, approximately 80% of SSNA bursts are synchronous with galvanic skin responses and pulsatile sweat expulsion during heat stress, indicating a potential dominance of the sudomotor signal under such conditions (Sugenoya et al., 1998). SSNA is typically measured in the leg, whilst skin blood flow (SkBF) and sweating response are frequently measured in the ventral forearm. The potential heterogeneity of SSNA to sudomotor and vasomotor function is currently unclear, both in a young, healthy population and with disease conditions involving autonomic dysfunction. Such heterogeneity may help explain the non-uniform age-related decrements in sweating and SkBF in different body regions despite similar cholinergic responsiveness (Smith et al., 2013a). SSNA declines with age in response to thermal stimuli (Grassi et al., 2003), contributing to thermoregulatory dysfunction and increased risk of heat-related illness and injury.

2. Autonomic control of the skin circulation during hyperthermia

Blood flow to the skin displays an incredible potential range, from nearly zero in extreme cold to 6–7 l/min during extreme heat stress (Johnson and Kellogg, 2010; Johnson et al., 2014; Rowell, 1974; Koroxeni. et al., 1961). Under normothermic conditions, total SkBF is approximately 250 – 300 ml/minute. This entire range can be accomplished by autonomic adjustments involving two distinct nerve types, adrenergic vasoconstrictor and non-adrenergic vasodilator nerves.

2.1. Vasoconstrictor control

The vasoconstrictor control of the skin circulation is adrenergic and similar to that in other regional circulations. Norepinephrine and cotransmitters are released by the activity of adrenergic nerves, acting postsynaptically on appropriate receptors (for a detailed review of vasoconstriction refer to Johnson and Kellogg, 2010 and Johnson et al., 2014). The role the vasoconstrictor system plays in heat stress is one of withdrawal — "passive vasodilation" as opposed to the active vasodilation addressed below. This role is dependent on initial conditions. If there is extant vasoconstrictor nerve activity, heat stress will cause that activity to cease and a vasodilaton will ensue (Edholm et al., 1957). On the contrary, if there is no vasoconstrictor nerve activity to skin, no withdrawal is possible and there will be no contribution to the cutaneous vasodilation with heating (Roddie et al., 1957; Hodges et al., 2009). The circulation to glabrous skin as represented by palmar

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