Angiotensin II in human skin: An age-dependent role for core temperature regulation?

Ryan McGinn, Robert D. Meade, and Glen P. Kenny

Human and Environmental Physiology Research Unit School of Human Kinetics, University of Ottawa, Ottawa, Ontario, Canada, K1N 6N5

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Address for correspondence:

Glen P. Kenny
125 University Private
Room 367, Montpetit Hall
Ottawa, Ontario, Canada, K1N 6N5
E-mail: gkenny@uottawa.ca
Phone: 613-562-5800 ext. 4282
Fax: 613-562-5497
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The production of angiotensin II in humans has long been known to stem from the renin-angiotensin system in the kidney. The production of angiotensin II causes an increase in blood pressure through vasoconstriction and water retention (i.e., increased blood volume) which makes it one of the most common targets for hypertensive therapy. However, a separate renin-angiotensin system has also been found in human skin along with angiotensin type 1 receptors in the cutaneous vasculature (10). As a result, recent work has aimed to delineate a possible thermoregulatory role for angiotensin II. Recently, Stewart and colleagues demonstrated that exogenous angiotensin II administration via intradermal microdialysis attenuated cutaneous vasodilatory response to local skin heating (12) and blunted nitric-oxide mediated cutaneous vasodilation in patients with low-flow postural tachycardia syndrome (11). However, given its systemic vasoconstrictor effects, it is plausible that angiotensin II in the skin also plays an important role governing cutaneous vasoconstrictor activity.

The study recently published in the *American Journal of Physiology – Heart and Circulatory Physiology* by Lang and Kolb (6) elegantly demonstrates for the first time that endogenous levels of angiotensin II in the skin can modulate reflex cutaneous vasoconstrictor activity. Specifically, the authors reported an impaired vasoconstrictor response to whole-body cooling (i.e., mean skin temperature was reduced to 30.5°C over a 30 min period and maintained for 10 min) in older adults during local administration of an angiotensin type 1 receptor inhibitor (losartan). Interestingly, the results were age-dependent such that no role for angiotensin II in modulating reflex cutaneous vasoconstriction was observed in younger individuals. Furthermore, the younger adults were shown to be less sensitive to exogenous angiotensin II administration relative to their older counterparts. The mechanisms underlying these age-related differences were astutely elucidated by Lang and Kolb (6) to be the result of the angiotensin II-induced
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recruitment of Rho-A/Rho-kinase vasoconstrictor pathways in older adults. Collectively, the results of this landmark study by Lang and Kolb (6) demonstrate that endogenous levels of angiotensin II in the skin enhance reflex cutaneous vasoconstriction and may play an important role in minimizing heat dissipation in older adults during cold exposure.

In recent years, there has been a particular focus on determining the precise mechanisms underlying the human heat loss responses of cutaneous blood flow and sweating. During cold exposure, the physiological response is to minimize heat loss through marked cutaneous vasoconstriction which is primarily mediated by norepinephrine along with neuropeptide Y, adenosine, Rho-A/Rho-kinase (4). In addition, Lang and Kolb (6) have recently elucidated a role for angiotensin II. On the other hand, heat exposure causes a robust cutaneous vasodilator response along with pronounced increases in sweat production. The reports by Stewart and colleagues implicate a role for angiotensin II in modulating cutaneous vasodilation in humans (11, 12). Furthermore, the presence of angiotensin type 1 receptors has also been confirmed in human eccrine sweat glands (13), suggesting that angiotensin II may play a role in modulating heat loss during whole-body heat stress. In line with this notion, Fujii et al. (1) recently demonstrated that exogenous angiotensin II administration via intradermal microdialysis attenuated the heat loss responses during resting ambient heat exposure (i.e., 35°C) as well as during recovery from exercise in the heat, albeit these impairments were not observed during an exercise-induced heat stress. Importantly, the angiotensin II-mediated reductions in cutaneous blood flow and sweating during ambient heat exposure and postexercise recovery recorded in young adults were shown to be associated with an oxidative stress-dependent (for sweating) and –independent (for cutaneous blood flow) mechanisms. Thus, taking the findings from Fujii et al.
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(1) together with those from Lang and Kolb (6), it appears that angiotensin II may be an important modulator of heat dissipation during exposure to both heat and cold.

While the study by Fujii and colleagues did not include a group of older adults (1), the study by Lang and Kolb (6) suggests that the angiotensin II-induced reduction in heat loss during heat exposure may be exacerbated in aged skin. In particular, older adults have clearly been shown to have marked impairments in local (8) and whole-body (9) heat dissipation during exercise relative to their younger counterparts. While some studies have implicated a role for reduced nitric oxide bioavailability with age (2, 7), the underlying mechanisms remain incompletely understood. Considering that older adults exhibit greater sensitivity to angiotensin II administration (6) and the reported interplay between angiotensin II and nitric oxide pathways (11), it is plausible that endogenous levels of angiotensin II in aged skin would play a critical role in modulating cutaneous blood flow and sweating, and thereby core temperature regulation during heat stress. In addition, future research in this area may have particular relevance for certain clinical populations such as hypertensive and diabetic patients who typically present with chronic elevations of angiotensin II.

There has been significant focus on the physiological changes associated with healthy aging including the consequences for core temperature regulation. Observational studies have shown that older individuals are the most affected by heat stress as a result of a compromised thermoregulatory system (5). Moreover, aging is also independently associated with a pronounced risk for chronic diseases including hypertension and diabetes mellitus, which affect ~50% and ~35% of older adults, respectively (3). In fact, a growing body of evidence indicates that older individuals diagnosed with hypertension and/or diabetes mellitus have more pronounced impairments in heat loss than their healthy counterparts, placing them at particular
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risk during passive- and/or exercise-induced heat stress (5). These health conditions are associated with pronounced perturbations in macro- and microvascular function, although the underlying mechanisms and ultimate clinical impact remain to be determined. However, as mentioned, hypertension and diabetes as well as other pathophysiological conditions are associated with chronically levels of angiotensin II. Therefore, given the age-related increase in angiotensin II sensitivity (6) together with the findings implicating angiotensin II as a modulator of cutaneous vasodilation and sweating (1), it is plausible to suggest that older individuals with chronic health conditions may exhibit an angiotensin II-induced impairment in the ability to regulate core temperature during heat exposure.

In summary, angiotensin II is a metabolite with many local and systemic effects throughout the human body. Following the confirmation of a separate renin-angiotensin system in the skin, recent evidence has indicated an important role for angiotensin II in governing heat dissipation during cold and heat exposure. In particular, it seems that older adults are more sensitive to the beneficial effects of angiotensin II for cutaneous vasoconstriction during cold exposure; however, they may be at greater risk for angiotensin II-mediated impairments in core temperature regulation during whole-body heat stress. Regarding heat stress, the age-related decrease in cutaneous vasodilation and sweating may be explained in part by upregulated angiotensin II signalling in the skin. Furthermore, these impairments may become exacerbated in individuals diagnosed with chronic diseases including hypertension and diabetes mellitus associated with augmented angiotensin II production and signalling. Clearly, more research is needed to elucidate the involvement of angiotensin II in mediating core temperature regulation and to identify the individuals who are most at risk.
REFERENCES


