Cutaneous thermal hyperemia: more than skin deep

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HUMAN SKIN is an amazingly complex circulation that lends itself to pharmacological studies due to the ease of access with limited invasiveness. Because of this, a growing body of literature has been directed toward a better understanding of the mechanisms behind regulation of cutaneous vascular tone. New information that helps to unravel mysteries of the skin brings much excitement to those of us who work to understand the physiological underpinnings of this fascinating circulation. But are studies in cutaneous microvascular function just skin deep? There is now much evidence that many of the pathways involved in regulation of cutaneous vascular tone are similar to those in other vascular beds. More importantly, a number of key studies have demonstrated that derangements in the thermal hyperemic response are reflective of more global changes in microvascular and endothelial function (9). This is exciting, as it may allow for the broader use of thermal hyperemia as a tool to understand disease progression or response to treatment in groups of patients, and possibly within an individual. But we must not get ahead of ourselves, and must remember that many questions remain regarding the basic physiology that underlies the thermal hyperemic response. The study by Medow et al. (6) in this issue of the Journal of Applied Physiology adds to our knowledge of skin physiology and is the first to investigate the possible role of reactive oxygen species (ROS) to the NO component of the thermal hyperemic response.

Local heating of the skin is known to produce a biphasic rise in skin blood flow (SkBF). A rapid initial increase in SkBF is seen within the first 90–120 s following the onset of heating, resulting in an “initial peak” in blood flow. This peak is followed by a prolonged rise in blood flow which reaches a plateau after 20–30 min of heating. A brief nadir is seen between the two phases.

The initial peak appears to be predominantly the result of a local sensory nerve axon reflex (7). These sensory nerves are thought to release calcitonin-gene related peptide and/or substance P in response to heat stimuli, although this is yet to be shown in human skin and there is the possibility of other factors. Recently, inhibition of TRPV-1 channels has been shown to attenuate the initial peak (12), and a portion is nitric oxide-dependent (4, 7). Thus a diminished skin blood flow response in the initial peak may be due to changes in a number of different pathways but seems to be reflective of sensory nerve function.

The plateau phase appears to be predominantly mediated by endothelial factors, and may be reflective of endothelial function. Kellogg et al. (4) first showed the plateau to be dependent on nitric oxide. Many studies have now demonstrated that nitric oxide is responsible for approximately 60–70% of the plateau response. However, the source of NO production and what factors may affect NO availability remain controversial.

Over the past ten years, several factors have been shown to affect plateau SkBF, including adenosine receptors (2) and TRPV-1 channels (12). These substances appear to predominantly act through increasing NO bioavailability, although slight NO-independent effects on SkBF have also been observed. The source of NO-independent vasodilation (which accounts for the remaining ~30–40% of plateau vasodilation) remains unknown. Interestingly, prostanooids, which are major players in hyperemia in response to other stimuli, do not appear to play a role in local heating (5), and so the NO-independent vasodilation must come from other relaxing factors. Future research will likely seek to determine the identity of these other factors.

The study by Medow et al. (6) shows that ROS are also involved in the local heating response. In addition, they have broken down the actions of ANG II type-1 (AT1) receptors, which are of particular interest from a clinical perspective. The authors have previously shown AT1 receptors to play a role in the diminished thermal hyperemic response in patients with postural tachycardia syndrome (10). It is possible AT1 receptors may also contribute to the attenuated thermal hyperemia seen in aging and hypertension.

In the current study, Medow et al. (6) explored the effects of inhibition of four substances on cutaneous thermal hyperemia through microdialysis infusion alone and in combination with administration of ANG II. These included two enzymes through which the actions of AT1 receptors are mediated, NADPH oxidase and xanthine oxidase (XO), and two media tors of oxidative stress, hydrogen peroxide (H2O2) and super oxide (SO). Of the four drugs they infused, only allopurinol, which inhibits XO, augmented the plateau phase during local heating. Assuming that XO mediates a downstream production of ROS, these results show ROS to be involved in thermal hyperemia, presumably limiting the availability of NO. Since the ROS inhibitors that were tested in the current study were not shown to also augment the plateau (and in fact, H2O2 inhibition with ebselen attenuated the plateau), further work will be needed to determine which ROS are acting here. In addition, these results indicate that AT1 receptors normally modulate vasodilation in healthy subjects. AT1 receptors have generally been found to be involved in disease states, but not as a normal modulator of vasodilation, making this finding not only novel, but also quite intriguing.

Reduction of H2O2 production with ebselen actually attenuated plateau blood flow by ~15%. The authors offer that this observation is consistent with studies showing H2O2 to have NO-independent vasodilatory effects. This finding may offer a solution to determining the portion of the plateau vasodilation which is NO-independent. Figure 1 gives a summary of the factors that have been shown to affect the plateau SkBF, including the factors put forth by Medow et al. (6).

The results from the second part of the study (drug infusions in combination with ANG II) are also interesting, and perhaps more clinically relevant. All four drugs infused were able to partially correct the attenuation in plateau skin blood flow...
caused by ANG II. Figure 2 shows the percentage of the attenuation caused by ANG II that each drug was able to correct. Inhibition of the enzymes NADPH oxidase and XO seem to account for all of the actions of ANG II, accounting for ~60% and ~40%, respectively. However, the two drugs would need to be given together in order to determine if any overlap of the drugs exists. 

H2O2 and SO seem to account for ~75% of the effects of ANG II. These results suggest that, while H2O2 and SO seem to be the predominant ROS produced through AT1 receptor activation, there must either be others produced which are yet to be tested, or AT1 receptors are also able to attenuate thermal hyperemia through a non-ROS mechanism. However, the latter is unlikely, since the authors and colleagues have previously shown all attenuation in plateau SkBF due to ANG II to be reversible with the antioxidant ascorbate (11).

The findings of Medow et al. (6) may offer some insight into the mechanisms at play in hypertension and aging, and possibly other disease states. For example, AT1 receptor activation is known to be upregulated in hypertension. Patients with hypertension exhibit an attenuated plateau SkBF (1), as has been seen in primary aging (8). Holowatz and colleagues (3) have performed a series of studies demonstrating the diminished plateau SkBF response is due to a reduction in NO availability, secondary to arginase upregulation, NOS uncoupling, and, germane to the Medow et al paper, increased oxidative stress. The findings put forth by Medow et al. suggest a role of ROS and AT1 receptors in both conditions and opens an avenue into further exploration of these disease states. The body of literature on the mechanisms behind thermal hyperemia provides an ever-strengthening argument that local heating of the skin reflects globalized changes in microvascular function. With an understanding of these mechanisms, the door opens for the development of clinical tests in the skin that can differentiate between derangements in the various pathways that are more than skin deep.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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