Cutaneous blood flow: uncomfortable in our own skin?

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WHAT KIND OF WORLD is it where some postganglionic sympathetic nerves secrete acetylcholine and where norepinephrine in conjunction with neuropeptide Y facilitates a key vasodilator response? It is the upside-down world of the human skin that possesses perhaps the most complex regional circulation in nature. Skin responds to environmental stimuli in ways that might be described as beautiful and mysterious by some investigators and confusing and frustrating by others. The capacity of human skin to vasodilate is especially remarkable, and the mechanisms that cause the dilation are especially mysterious.

In response to whole body heat stress and a rise in core temperature, skin blood flow can increase from a few hundred milliliters per minute to values as high as 6–8 l/min (8). The acetylcholine mentioned above stimulates the sweat glands and may play a modest, but not obligatory, role in the cutaneous dilation seen during whole body heat stress, but it is clearly not the transmitter (7, 9). Thus this response is largely dependent on sympathetic vasodilator nerves that release an unknown transmitter or transmitters operating on a number of potential receptor systems (5). This rise in flow can also be modulated by baroreceptors and in some circumstances opposed by sympathetic nerves that do release norepinephrine (2).

For example, nitric oxide (NO) appears to contribute to the cutaneous vasodilator responses to whole body heating. However, it is unclear whether the NO is released by the nerves or substances secreted by the nerves that stimulate the endothelium or both (9). Over the past 10–20 years, studies using a local drug administration have tested a number of hypotheses and have raised as many questions as they have answered.

Like whole body heating, local heating can also evoke a powerful vasodilator response. This response is confined to the heated area, but after that simple observation, the fun begins. First, the pattern of the skin blood flow response is dependent on the rate and magnitude of local heating. With fast local heating, there is a bimodal response with an early peak that is due to an axon reflex and a later plateau that is caused by the local release of NO (6). The early response is dependent on the release of vasodilating substances from granules associated with the sensory nerves via (probable) stimulation of capsaicin-sensitive channels (11). Additionally, the magnitude of the response and the perceptual responses to the heating appear linked (10). However, this early peak is much less evident when the rate of heating is slow. In this context, the rate, magnitude and perhaps the pattern of the hyperemia seem matched to the thermal “threat” to the skin and offer protection from thermal injury.

In the current study, Hodges and colleagues (3) from the Johnson laboratory at the University of Texas Health Sciences Center in San Antonio, TX, explore ideas from Houghton et al. (4) about how sympathetic nerves interact with the axon reflex that causes an initial response to local heating. A key observation from these studies is that bretylium, a substance that prevents sympathetic nerves from releasing their neurotransmitters, blunts or eliminates the early peak blood flow response to either fast or slow local heating. In other words, acutely eliminating a vasoconstrictor mechanism has the paradoxical effect of lowering a vasodilator response. Importantly, this occurs when the subjects are thermoneutral and when it is unlikely that the sympathetic vasoconstrictor nerves to the skin are active. This modulation appears to depend on more than norepinephrine and include neuropeptide Y, but how apparently silent sympathetic nerves are engaged to facilitate a vasodilator response is mysterious and certainly counterintuitive. In other words, it appears that local skin heating causes silent sympathetic nerves and their vasoconstricting transmitters to enhance vasodilation caused by a local axon reflex. Where else but the skin?

Next, Hodges and colleagues focused on what the sympathetic nerves do during the plateau phase of the skin blood flow response to local heating. They found that the tendency of the plateau phase to “die off” and fade after about an hour of local heating required intact sympathetic function (1). This observation is consistent with the “normal” vasoconstrictor role of the sympathetic nerves. It also explains a phenomenon that was first noticed many years ago and might be explained by the effects of temperature on norepinephrine release from sympathetic nerves. However, in the context of the current experiment, the “die off” still happened in the absence of efferent sympathetic vasoconstrictor activity to the skin.

What does all of this mean? It means that the number of “paradoxical” sympathetic responses in human skin is increasing. First, there are sympathetic nerves that secrete the “wrong” transmitter (acetylcholine) to cause sweating. Second, there are sympathetic vasodilator nerves that secrete an unknown dilating substance. Third, vasoconstricting substances presumably released from silent vasoconstrictor nerves facilitate the early dilator response to local heating. Fourth, vasoconstricting substances presumably released from silent vasoconstrictor nerves seem to act “normally” and limit the dilator response later during local heating. A final caveat about human skin is that there is no good animal model for it, so solving the puzzles outlined above will take creative studies in humans.

Thus we have another example (like the coronary and skeletal muscle circulations) of a highly redundant physiological system that is critical to whole body homeostasis. The control of skin blood flow defies simple reductionist explanations and was recognized as a complex physiological system long before the noninformative term systems biology was coined and came into vogue. Thus the beautiful and mysterious features of human skin will continue to be a fertile ground for exploration by those who ask insightful questions and use clever techniques like Hodges and colleagues did in their study.

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