Adenosine triphosphate (ATP) may potentially be involved in the control of cutaneous active vasodilation and sweating during heat stress, both of which are crucial in maintaining stable body temperature in humans. Previous studies have demonstrated mechanisms of cutaneous active vasodilation and sweating during passive heating at rest and during exercise in the heat, however the exact pathways remain equivocal. Whether ATP can modulate thermoeffector organs such as skin vessels and eccrine sweat glands is unknown. Cutaneous vasodilation in humans in vivo can be induced via intradermal administration of ATP. Previous studies with ACh have shown a combined role of nitric oxide synthase (NOS) and cyclooxygenase (COX) in modulating cutaneous active vasodilation. Moreover, purinergic receptors are present in human sweat glands and human skin. ATP has been shown to increase sweating in vivo; however, sweating responses differ in vivo. Further, ATP catalyzes adenosine in humans and adenosine when bound to P1 purinergic receptors can influence cutaneous vascular regulation. Both pathway type (NOS and/or COX) and receptor type (P1 or P2) in which ATP modulates cutaneous vasodilation in vivo is unknown.

**Methodology**

**Protocol A**
- 12 young adults (7 males, 5 females)
- 4 microdialysis (MD) fibres; left forearm = 4 cm apart, 25 gauge needles
- 1 Lactated Ringer (control)
- 2.10 mM L-NNA
- 3.10 mM Keto
- 4.10 mM L-NNA + Keto

**Protocol B**
- 8 young adults (4 males, 4 females)
- Insert a MD fibres in left forearm; attach sweat capillaries and heat dropsers as in Protocol A
- 1 Lactated Ringer (control)
- 2.10 mM Thapsagline
- Perfuse ATP; administer 5 doses; measurements and procedure is identical to Protocol A

**Results**

We assessed individual and combined roles of NOS and COX in cutaneous vascular and sweating responses to increased levels of intradermal administration of ATP in humans in vivo. It was found that 30 and 300 μM ATP caused the greatest increase in CVC. Initially, we predicted that cutaneous vasodilation at 30 μM ATP would be influenced by inhibition of COX; this was not the case. In accordance with our predictions, CVC was slightly reduced by an inhibition of NOS. Furthermore, increases in CVC were partially mediated by NOS-dependent mechanisms since perfusion of L-NNA and L-NNA + Ketorolac reduced CVC by ~20% at 30 μM ATP compared to Control (Figure 3a). This response was not observed at the ketorolac site. Thus, ATP does not influence the adenosine receptor antagonist and it does not increase sweat rate. Additionally, ATP can cause activation of P2 receptors and this creates a calcium ion influx. Increased calcium levels induce NOS-dependent cutaneous vasodilation. P2 receptors are found on sensory nerves and it is possible that ATP-mediated cutaneous vasodilation elicited from these sensory nerves.

Adenosine alone can cause pronounced cutaneous vasodilation in humans. Our results demonstrate that CVC did not differ between Control and Theophylline (adenosine receptor inhibitor) at all doses of ATP (Figure 4) indicating that observed cutaneous vasodilation was independent of adenosine-dependent pathways. Although P2 receptors are found in the human sweat gland, activation of these receptors by ATP in humans in vivo does not influence human sweating.

**Applicability and Significance**

Patient populations with endothelial damage, reduced bioavailability of ATP and/or hyperhidrosis benefit from assessing the principal pathways involved in ATP-mediated vasodilation and sweating. This is significant for understanding how oxygen delivery and blood flow are impaired within these populations. Future studies are warranted to assess the importance of ATP in modulating cutaneous blood flow and sweating during exercise.

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