PERSPECTIVES

In search of a vasodilator: is ATP the answer?

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Control of the blood flow to various tissues and organs of the body has received major attention for more than a century. Some progress has been made towards the identification of mechanisms and possible compounds that contribute to the precise control of muscle hyperaemia to match O_2 delivery with tissue demands. Just making a list of all the compounds that have been proposed through the years would fill a page.

There are three key control sites for the regulation of the microcirculatory blood flow: (a) inhibition of sympathetic vasoconstrictor activity, mediated by noradrenaline (NA) and its binding to alpha receptors on smooth muscle cells, (b) dilatation of small feeding arterioles by conducted (ascending), vasodilatation and (c) smooth muscle local relaxation. When nitric oxide (NO) was first shown to be the regulator of resting smooth muscle tonus, it was soon believed to play a similar role in regulating the vasodilatory response. NO is a vasodilator, but in contracting skeletal muscle its role is limited. Prostaglandins (PGs) closely interact with NO and thereby also contribute to the exercise hyperaemia, but the total effect is far from a maximum blood flow response. In the recent article in *The Journal of Physiology* by Crecelius *et al.* (2012) they confirm that these two vasodilators are insufficient to explain observed peak perfusion, but of greater importance is that they not only demonstrate that luminal ATP is a powerful dilator but also that the likely mechanism by which ATP works – and in accordance with data from *in vitro* studies of various animal models – is to hyperpolarize the endothelium, an effect that is subsequently transferred to the smooth muscle cells, thereby affecting both ascending and local vasodilatation ((b) and (c), above). The experiments were performed on the forearm of humans by infusing various combinations of NO and PG inhibitors with ATP, and using ouabain and $BaCl_2$ to block Na^+/K^+–ATPase and

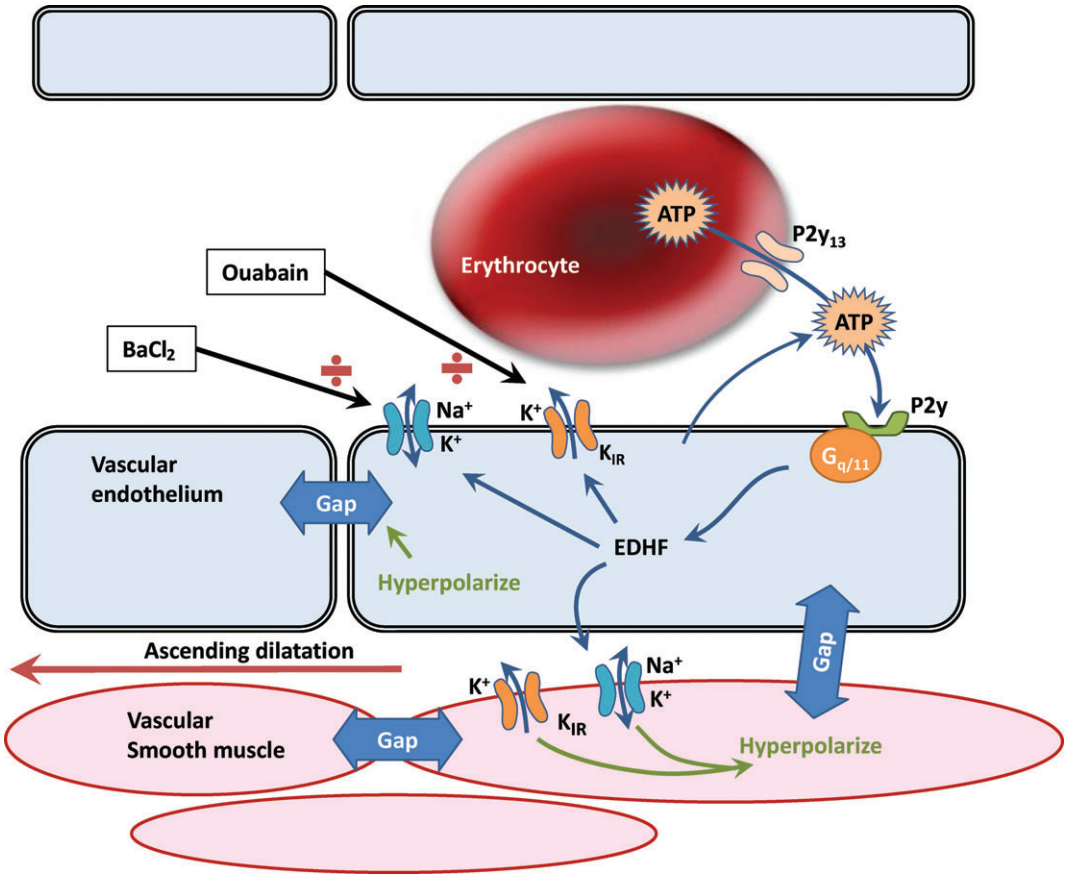

Figure 1. Schematic illustration of how luminal ATP release, primarily from red blood cells via P2y receptors on the endothelial cells, induces hyperpolarization, which is subsequently transferred to the smooth muscle cells, thereby eliciting both ascending and local vasodilatation
It is an augmented outward flux of potassium that causes the hyperpolarization. In the present study of the human forearm Crecelius *et al*. 2012 use ouabain to block Na^+/K^+-ATPase and $BaCl_2$ to block K_{IR}. EDHF, endothelial hyperpolarizing factor; Gap, gap junction; Gq/11, G-protein-coupled pyrinergic receptor.

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the inwardly rectifying potassium channels (K_{IR}), respectively.

The blood flow of the forearm was measured with venous occlusion plethysmography (VOP), which has been the common method in these types of studies in the past, but in spite of its common use, VOP is not ideal for the determination of blood flow. However, the observed blood flow changes are convincing and provide support that the likely mechanism, also in humans, is an ATP-mediated vasodilatation, which occurs with the binding of ATP to P2y receptors on the endothelial cells. This binding to the receptor induces hyperpolarization by the activation of Na^+/K^+–ATPase and K_{ir} (Fig. 1). A question may be raised about how well the forearm represents other microvascular regions of the human body (Newcomer *et al.* 2004). In regard to the effect of luminal ATP and the K^+ kinetics it may be the same in the leg. In a study by Juel *et al.* (2007) potassium was infused in the femoral artery with and without $BaCl_2$. The effect of the K_{IR} blocker was similar to the one reported by Crecelius *et al.* (2012).

The present findings of a major vasodilatory role of luminal ATP open up a redirection of the research focus, from NO and PG to ATP, via P2y receptors induced intracellular signalling within the endothelial cells and further to the smooth muscle cells, but also to the availability of ATP. Endothelial cells produce and release ATP, but the ATP in the luminal space, binding to endothelial P2y receptors, is commonly believed to be released from the red blood cells (Ellsworth *et al.* 2009). The situation is complex, however, as this release of ATP from red blood cells appears not always to be mandatory for an appropriate vasodilatation to occur. In the interstitial space of contracting skeletal muscles, ATP is elevated to levels above what is observed in the vascular space, but an exchange between the interstitial and luminal space is unlikely. Recently, a role for interstitial ATP has been proposed, which could be to act as the blocking compound of NA vasoconstrictor activity (functional sympatholysis (a) above), and P2y receptors are also present on cells in the interstitial space (Hellsten *et al.* 2012). Thus, combining these possibilities with the demonstration by Crecelius and colleagues of a marked ATP-induced vasodilatory effect through hyperpolarization of the vascular cells provide a basis for and inspiration to further document that ATP really is a key player in skeletal muscle vasodilatation.

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