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COMMENTARY

Evolving the concept of regulation of vascular tone in humans

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Elucidation of mechanisms regulating microcirculatory vascular tone is a key issue in the knowledge of human pathophysiology. Anandamide is an endogenous lipidic cannabinoid (CB) characterized by potent vasodilator activity acting mainly through the activation of CB receptors, located on the vessel walls, and the vanilloid receptor 1, located on sensory peptidergic nerve endings within the external layers of vessel walls. In humans, cutaneous anandamide administration causes forearm skin vasodilation by activating vanilloid receptor 1 presumably on primary sensory nerves, while intrabrachial infusion of the same compound is devoid of effect on forearm muscle microcirculation. Taken together, these results indicate that, apart from a possible distrectual difference, the effect of anandamide is specific for the abluminal, but not for the endoluminal, part of the vessel wall. Thus, it is conceivable that, at least in the peripheral microcirculation, this compound could act as an autocrine/paracrine agent and not as a circulating hormone. In line with this possibility, it has been demonstrated that anandamide can be produced by macrophages and therefore its biological effect might increase in clinical conditions characterized by augmented activity of this cell line, including cardiogenic, hemorrhagic and endotoxic shock and even in atherosclerosis, inflammation and ischemia. Moreover, increased serum values of anandamide have been found in patients with endotoxic shock. However, decisive information concerning the role of anandamide in humans will be obtained when specific antagonists or inhibitors will be available. In that case, the anandamide system might represent a potential target for the treatment of important cardiovascular conditions, including severe shock.
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Abbreviations: CB, cannabinoid (CB); CGRP, calcitonin gene-related peptide; NO, nitric oxide; VR1, vanilloid receptor 1

Microcirculatory vascular tone is a crucial determinant of blood pressure values and regional blood flow, thereby regulating the perfusion of vital organs, including the brain, heart and kidney (Folkow, 1989). Although the mechanisms and pathways involved in the regulation of vascular tone have formed the subject of intensive investigation, the issue is so complex that the principles of vascular function seem far from totally elucidated. In addition, since alterations in microvascular function and structure represent both the cause and target of cardiovascular disease, it is important to focus on improving knowledge of this aspect in order to achieve a significant advancement in the comprehension of cardiovascular pathophysiology and hence discover new therapeutic strategies.

In this issue of *British Journal of Pharmacology*, Movahed *et al*. (2005) produce the first convincing evidence that anandamide plays a significant role in the modulation of microvasculature tone in humans. Anandamide is an endogenous lipidic cannabinoid (CB) derivative characterized by potent vasodilator activity in *in vitro* models and *in vivo* in animal studies (Högestätt & Zygmunt, 2002). Although the compound can evoke vascular relaxation through several mechanisms (including the release of different endothelium-derived relaxing factors or by directly acting on smooth muscle cells) (Högestätt & Zygmunt, 2002), a preferential activity is related to the stimulation of CB receptors (Hillard, 2000), which are potent vasodilators especially in certain critical conditions such as hemorrhagic, septic and cardiogenic shock (Högestätt & Zygmunt, 2002). Furthermore, anandamide is a full endogenous agonist at the vanilloid receptor 1 (VR1). These receptors are located on sensory peptidergic nerve endings within the external layers of vessel walls. Activation of these receptors can lead to relaxation through the release of the neuropeptide calcitonin gene-related peptide (CGRP), which is a potent vasodilator. It has also been described that anandamide can activate nitric oxide (NO) synthesis, inhibit L-type calcium channels, activate K^+ channels, inhibit intracellular calcium mobilization and increase cAMP formation (Högestätt & Zygmunt, 2002) (Figure 1).

The major finding of the present study is that cutaneous anandamide administration causes forearm skin vasodilation by activating VR1 receptors presumably on primary sensory nerves, while intrabrachial infusion of the same compound is devoid of effect on forearm muscle microcirculation.

Apart from a possible distrectual difference of effect, which is a common feature in human pathophysiology (Deanfield *et al*., 2005), the different route of anandamide administration (abluminal *versus* endoluminal) makes the results difficult to compare. If in the human peripheral microcirculation the stimulation of sensory nerves is the preferential target of anandamide, as supported by these results, intravascular administration does not allow the compound to reach the abluminal part of the vessel wall, where nerve endings are

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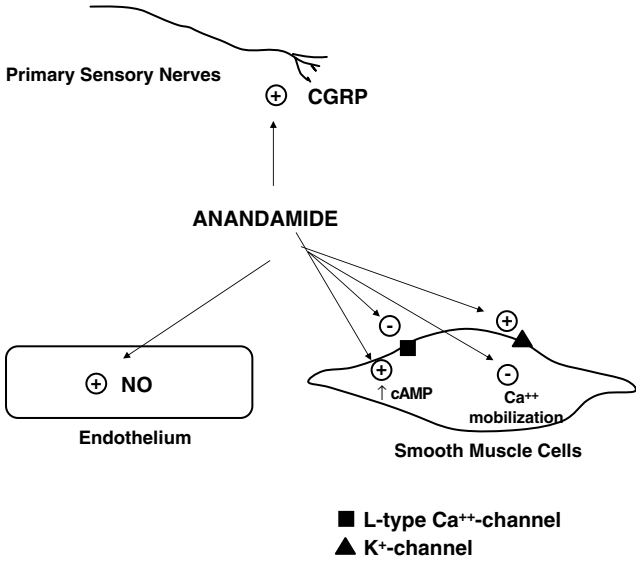

Figure 1 Proposed mechanisms for anandamide-induced vasodilation. Anandamide can act on primary sensory nerves to release CGRP, on endothelial cells to release NO and to smooth muscle cell to inhibit L-type calcium channels or intracellular calcium mobilization and stimulate K^+ channels or increase cAMP formation. Un to now, the only mechanism confirmed in humans is the stimulation of primary sensory nerves.

represented. Consequently, while the lack of effect of intrabrachial anandamide administration on forearm blood flow rules out the presence of anandamide-sensitive receptors (CB?) on the endoluminal vessel surface as well as the possibility that this compound could act as a circulating hormone, it does not exclude an effect of the CB on muscle microcirculation.

On the other hand, the suggestion that anandamide may act as an autocrine/paracrine hormone does not limit a possible relevant role in cardiovascular pathophysiology. Of course such an effect can be crucial in regional blood flow regulation without affecting blood pressure values. In line with this hypothesis, experimental evidence indicates that anandamide can increase coronary flow in different rat experimental models (Högestätt & Zygmunt, 2002). Moreover, the paracrine activity of the hormone could be sustained by the fact that anandamide can be produced by macrophages and therefore its biological effect might increase in clinical conditions characterized by increased activity of this cell line, including cardiogenic, hemorrhagic and endotoxic (Wagner *et al*., 2001) shock and even in atherosclerosis, inflammation and ischemia (Högestätt & Zygmunt, 2002). It should be taken into account that increased serum values of anandamide have been found in patients with endotoxic shock (Wang *et al*., 2001). Finally, further evidence for the local activity of this system derives from the link between anandamide and the NO pathway, since, at least in certain experimental conditions, the relaxing activity of the CB substance is increased in presence of reduction in NO availability (Mendizábal *et al*., 2001).

Considering the relevance of anandamide in regulation of the cardiovascular system in different experimental models, the present demonstration of the existence of anandamide-induced responses in a human vascular bed is potentially of importance. However, the best methodological approach to assess the biological activity of any pathway in humans *in vivo* is to test specific antagonists or inhibitors (Taddei *et al*., 1999). In the future, it will be necessary to have available for human research selective inhibitors of receptors (CB? RV1?) activated by anandamide or endogenous CB in order to genuinely understand the role of this system in the regulation of cardiovascular homeostasis. It is conceivable that potentiation of anandamide effects might be useful to increase regional flow during an ischemic condition, while blockade of these effects could be a fascinating therapeutic target for improving the prognosis of patients with severe shock, such as cardiogenic shock, as up to now such conditions are unresponsive to standard or experimental treatment regimens (Cotter *et al*., 2000).

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