Endocannabinoids are lipid mediators, isolated from brain and peripheral tissues, which include amides, esters and ethers of long chain polyunsaturated fatty acids (1, 2). These compounds exhibit “cannabimimetic activity”, i.e. they mimic Δ-9-tetrahydrocannabinol, the active principle of Cannabis sativa preparations like hashish and marijuana, by activating central (CB1) and peripheral (CB2) cannabinoid receptors (3). The discovery of anandamide (N-arachidonylethanolamine; AEA, from “ananda”, the Sanskrit word for “bliss”) in pig brain, and the finding that this compound was cannabimimetic, confirmed the hypothesis of the existence of endogenous ligands for the cannabinoid receptors. Thus, together with its congeners it was termed “endocannabinoid” in analogy with the “endorphins”, i.e. the endogenous ligands of opiate receptors. In just one decade, the endocannabinoids have been shown to play manifold roles, both in the central nervous system and in the periphery (4). In particular, AEA has cardiovascular (5), immune (6) and anti-inflammatory activity (7), and is critical in the peripheral control of pain initiation (8). In addition, AEA and the other bioactive endocannabinoid 2-arachidonoylgllycerol act as (co-)agonists of human platelets (9). AEA is also a powerful vasodilator, through activation of vanilloid receptors (VR1) on perivascular sensory nerves and the subsequent release of calcitonin-gene-related peptide (10). It also causes mesenteric vasodilatation and hypotension by binding to an “endothelial-type” cannabinoid receptor different from CB1 or CB2 receptors (11). Human umbilical vein endothelial cells (HUVEC) have functional CB1 receptors (12), and terminate the biological activity of AEA at these receptors by means of an AEA membrane transporter (AMT) and of an AEA-hydrolyase (fatty acid amide hydrolase, EC 3.5.1.4; FAAH) (13).

Recently, attention has been focused on the possible role of AEA and other endocannabinoids in regulating cell growth and differentiation, which might account for some pathophysiological effects of these lipids. As a matter of fact, growing evidence is being collected suggesting that AEA has pro-apoptotic activity, both in vitro and in vivo, which implicates sustained ceramide accumulation and extracellular signal-regulated kinase (ERK) activation (14), or inhibition of the ras cascade-dependent tumor growth (15). Also other signal transduction pathways can be triggered by AEA in order to induce programmed cell death, including activation of Raf1/ERK, of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK), and of phosphatidylinositol 3-kinase/protein kinase B (16, 17).

In this issue of Thrombosis and Haemostasis a study dealing with the pro-apoptotic potential of AEA in HUVEC is published (18). It shows that AEA induces apoptosis by triggering phosphorylation of JNK and p38 MAPK, paralleled by increased activity of caspase-3. It also shows that a critical step in AEA-induced apoptosis is the dissipation of mitochondrial membrane potential, followed by release of cytochrome c. It is remarkable that some of these events are typical of different pro-apoptotic stimuli unrelated to (endo)cannabinoids (19), suggesting that AEA shares with other inducers common signalling pathways. On the other hand, the pro-apoptotic effects of AEA were all mediated by activation of VR1, whereas CB1 receptors protected HUVEC against the toxic effects of the endocannabinoid (18). Also these findings are interesting, because they extend to endothelial cells previous observations in human neuroblastoma and lymphoma cells (20), where AEA induces apoptosis through a series of events ultimately leading to disruption of mitochondrial integrity, release of cytochrome c, and activation of caspases 3 and 9 (20). Taken together, the two studies (18, 20) demonstrate that, among the different apoptotic pathways potentially triggered by AEA, human neuronal, immune and endothelial cells choose one which depends on mitochondrial signals. In addition, they show that AEA exerts

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opposite effects, i.e. a pro-apoptotic activity at vanilloid receptors and an anti-apoptotic action at cannabinoid receptors, but it remains to be clarified if the different localization of the binding sites of these receptors (intracellular for VR1 and extracellular for CBR) plays a role in discriminating this dual effect. It is tempting to speculate that modulation of intracellular and extracellular levels of AEA through fine tuning of FAAH (and possibly of AMT) activity is a “checkpoint”, as suggested by several observations on the pivotal role of this enzyme in controlling AEA metabolism (21).

A further point of interest raised by the study (18) concerns the clinical implications of the pro-apoptotic potential of AEA. Indeed, it has been demonstrated that AEA increases during shock conditions (5). The fundamental pathological lesion in idiopathic thrombotic thrombocytopenic purpura and adult/sporadic haemolytic uremic syndrome (HUS) is thrombotic microangiopathy, which is characterized by localized endothelial injury (18 and references therein). Since preliminary work suggests that serum levels of endogenous AEA are extremely elevated in HUS patients vs healthy subjects (18), it can be proposed that AEA may mediate endothelial injury associated with HUS by inducing apoptosis. These findings, though not yet generalizable, seem to be relevant also from the perspective of acting on the endocannabinoid system in the treatment of vascular pathologies. In this context, recent evidence suggests that AEA released from HUVEC previously challenged by 17β-estradiol complement some of the actions of this hormone on human platelets (22). Therefore, the integration between hormone and endocannabinoid networks might be critical for the beneficial effects of estrogen replacement therapy in post-menopausal women and, more in general, for vascular biology and (patho)physiology. Overall, it can be anticipated that the therapeutic potential of modulating the endocannabinoid system, which has already found grounds for the therapy of cancer (23, 24) and malignant lymphoblastic disease (25), will be extended to the cardiovascular system.

References