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REVIEW

Endocannabinoids and the haematological system

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Endocannabinoids are blood borne and may also be secreted by the endothelium. Accordingly, there has been interest in the interactions between (endo)cannabinoids and blood cells. There is certainly evidence that (endo)cannabinoids may promote platelet activation, indicating that they may be thrombogenic. Platelets are involved both in the metabolism and release of endocannabinoids, and so it is possible that their circulating levels may be regulated by platelets. This process is altered in disease states such that platelet-derived endocannabinoids contribute towards hypotension in cardiovascular shock. Not only may endocannabinoids regulate platelet function and possibly lead to thrombogenesis, but they may also influence haematopoiesis. Given these emerging roles, the aim of this review is to examine the interactions between cannabinoids and blood.
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Keywords: cannabinoids; endocannabinoids; anandamide; 2-arachidonoyl glycerol; platelets; thrombosis; haematopoesis; endothelium; fatty acid amide hydrolase

Abbreviations: 2-AG, 2-arachidonoylglycerol; 12(S)-HAEA, 12(S)-hydroxyeicosatetraenoylethanolamide; CSFs, colony-stimulating factors; FAAH, fatty acid amide hydrolase; LDL, low-density lipoprotein; MAG lipase, monoacylglycerol lipase; PEA, palmitoylethanolamide; THC, Δ-9-tetrahydrocannabinol

Introduction

The cardiovascular actions of cannabinoids and endocannabinoids have been extensively reviewed (Randall *et al*., 2004; Pacher *et al*., 2006), but far less is known about their actions on blood. There is evidence that endocannabinoids may be produced in the endothelium (Mechoulam *et al*., 1998; Maccarrone *et al*., 2002; Gauthier *et al*., 2005) and blood cells may themselves act as a source; but what is the relationship between endocannabinoids and the haematological system?

Cannabinoids and the risk of thromboembolism

Not only might endocannabinoids affect the functioning of blood, but also cannabinoids used either medicinally or as drugs of abuse should also be considered. Smoking cannabis was identified in the Determinants of Myocardial Infarction Study as a risk factor for initiating a myocardial infarction, such that the risk was increased 4.8-fold in the 60 min after its use (Mittleman *et al*., 2001). Acutely cannabis smoking is associated with cardiovascular effects including tachycardia and hypertension with orthostatic hypotension. The tachycardia clearly acts as a stressor, and smoking cannabis (when compared to placebo controls) has been shown provoke symptoms in stable angina (Aronow and Cassidy, 1974). Accordingly in patients with atherosclerotic plaques, the risk of myocardial infarction triggered by cannabis smoking might be related to cannabis-induced thromboembolism.

Despite the acute administration of cannabis being associated with an increased risk of myocardial infarction, the Coronary Artery Risk Developing in Young Adults trial (Rodondi *et al*., 2006) indicated that long-term cannabis smoking was not associated with increased cardiovascular risk. This large-scale trial took account of diet, alcohol consumption and tobacco smoking, and concluded that cannabis was not an independent risk factor for cardiovascular disease but was associated with an unhealthy lifestyle.

Consistent with an increased acute risk of thromboembolism, Deusch *et al*. (2004) recently reported that Δ-9-tetrahydrocannabinol (THC) increased the expression of glycoprotein IIb–IIIa and P-selectin on platelets. Specifically, Deusch *et al*. reported that exposure of human platelets to THC (100 nM–10 μM) resulted in platelet activation, which would favour thromboembolism. In their study, they also detected platelet expression of cannabinoid CB_1 and CB_2 receptors, which they speculated might be involved in the THC-induced response, but this was not confirmed pharmacologically. In view of the risk of thrombosis posed by THC, this raises questions over the safety of THC as a medicine. Accordingly, it would be prudent to take account of the patient's cardiovascular risk factors when using it as a medicine.

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Much of the early work on endocannabinoids and platelet function was carried out by Maccarrone and colleagues. In 1999, Maccarrone *et al*. reported that anandamide caused the activation of platelets. In this study on human platelets, it was found that high concentrations of anandamide (1.3 mM) caused platelet activation with the release of intracellular calcium. These effects of anandamide were unaffected by inhibition of cyclo-oxygenase and fatty acid amide hydrolase (FAAH) activities, but was sensitive to hydro(pero)oxide derivatives of anandamide. Work carried out by Braud *et al*. (2000) also confirmed that anandamide causes activation of rabbit platelets, although at lower concentrations (optimum range: 3–10 μM). However, in that study, the effects of anandamide were sensitive to both cyclo-oxygenase and FAAH inhibition, but was insensitive to the cannabinoid CB_1 receptor antagonist rimonabant and occurred at concentrations similar to those of arachidonic acid which cause platelet activation. Furthermore, the synthetic cannabinoid receptor agonist, HU210, did not mimic the effects of anandamide. Accordingly, they concluded that anandamide caused platelet activation via FAAH-dependent liberation of arachidonic acid. This could indicate that there are species differences with respect to the ways in which endocannabinoids affect platelets.

In subsequent studies, Maccarrone *et al*. (2001a) also reported that 2-arachidonoylglycerol (2-AG) caused activation of human platelets at lower concentrations (50–400 μM) than reported for anandamide, and that these effects were inhibited by high concentrations of the cannabinoid CB_1 and CB_2 receptor antagonists, rimonabant and SR144528. In addition, the effects of 2-AG were also reduced by anandamide. It was also found that platelets exhibited specific binding of the synthetic cannabinoid radioligand, ^{3}H-CP55940, which is consistent with the expression of a CB-type receptor, but the binding characteristics did not fit in to the classical CB_1 and CB_2 classification. Also of interest was the finding that 2-AG's actions were opposed by ADP and collagen, but enhanced by serotonin. More recent work in this area has confirmed that serotonin enhances the binding of 2-AG to platelets such that platelet activation (including increases in inositol trisphosphate and decreases in cAMP) occurs at lower concentrations (Maccarrone *et al*., 2003). It was also found that 2-AG enhances the binding of serotonin to platelets. Perhaps, these findings suggest that 2-AG exerts a modulatory role in platelet activation as opposed to a direct action.

Morphological confirmation of platelet activation was provided by Malorni *et al*. (2004). In their study, they reported that 200 μM 2-AG caused rapid (within 6 min) morphological changes in human platelets with protrusions and rearrangement of the cytoskeleton. These changes are consistent with platelet activation and confirm that 2-AG is an endogenous platelet activator.

Although some of the work discussed above has examined the actions of endocannabinoids at high concentrations and so their physiological relevance may not be clear, in their 2001(a) paper, Maccarrone and colleagues provided some interesting evidence. They mentioned unpublished findings which indicated that 2-AG is the most abundant endocannabinoid in platelets, and that its platelet concentration may be as high as 1.4 mM and this clearly sheds light on the possible significance of their findings.

Maccarrone *et al*. (2002) have also shown that anandamide derived from cultured endothelial cells stimulated with oestrogens may in fact reduce the release of serotonin from ADP-stimulated human platelets. On this basis, they suggest that endothelium-platelet interactions may be involved in the vascular effects of oestrogens.

In conclusion, based on these findings, it is clear that high concentrations of endocannabinoids may cause platelet activation and this may be relevant as there is an indication that the endothelium may be a source of endocannabinoids (Mechoulam *et al*., 1998; Gauthier *et al*., 2005) and this may also be relevant to thrombosis. However, there is also evidence that the endothelium may be a site of endocannabinoid metabolism (Ho and Randall, 2007), and this may enable the endothelium to represent an antithrombogenic surface. Accordingly, the balance between the release of thrombogenic endocannabinoids and their endothelium-dependent metabolism will determine the role of endocannabinoids in thrombosis but this may be altered in disease states, including atherosclerosis.

Endocannabinoids and atherosclerosis

The link between white blood cells, platelets and atherosclerosis is well established, but do endocannabinoids play a role? There has been little work in this area, but the first clue came from Steffens *et al*. (2005), who reported that low doses of THC acting via CB_2 receptors caused a reduction in the development of atherosclerotic plaques in a murine knockout model of atherogenesis. These effects appeared via suppression of macrophage chemotaxis. Whether endocannabinoids play a role in atherosclerosis remains to be determined, but a recent study has shown that low levels of palmitoylethanolamide (PEA) may protect low-density lipoprotein (LDL) against oxidation, which is a feature of atherogenesis (Zolese *et al*., 2005). By contrast, higher concentrations of PEA appear to promote the oxidation.

The role of platelets in endocannabinoid reuptake and metabolism

Not only may platelets be activated by endocannabinoids, although at very high concentrations, but they may also be involved in metabolic conversion. Edgemond *et al*. (1998) reported that human platelets convert anandamide via 12-lipoxygenase to 12(S)-hydroxyeicosatetraenoylethanolamide (12(S)-HAEA). This metabolite is pharmacologically active at both CB_1 and CB_2 receptors with similar affinities to anandamide. Furthermore, 12(S)-HAEA was shown to be relatively resistant to metabolism by FAAH, and the authors proposed that the platelet-dependent conversion was a means by which the activity of endogenous cannabinoid ligands might be prolonged in the circulation.

Maccarrone *et al*. (1999, 2001a) also provided evidence of platelet-dependent metabolism of endocannabinoids. In their initial paper (Maccarrone *et al*., 1999), it was reported

that platelets exhibited uptake of anandamide by a system which was stimulated by nitric oxide donors (and one could speculate that endothelium-derived nitric oxide may have similar effects). From these observations of cellular uptake, it was also suggested that platelets might be a site of FAAH activity. These findings were then extended to 2-AG, when they reported that platelets show uptake for 2-AG and FAAH-dependent hydrolysis with a $K_m = 8\,\mu M$. To date, the precise mechanisms of uptake of endocannabinoids into cells are unclear and the existence of a specific transporter is controversial; indeed the uptake may be a passive process driven by a FAAH-dependent gradient. In the case of platelets, Fasia *et al*. (2003) have examined the uptake of tritiated anandamide into rabbit platelets. From these studies, it was found that rabbit platelets exhibit temperature-independent and non-saturable uptake of anandamide, which indicates that this process is carrier-independent. On entry into the platelets, there was evidence of rapid FAAH-dependent metabolism of anandamide and the production of methanol/water soluble metabolites. On this basis, the authors suggested that the products of FAAH metabolism might have undergone further metabolism, possibly via cyclo-oxygenases. A question to emerge is, the metabolism designed to regulate levels of endocannabinoids or generate pharmacologically active metabolites?

Although the precise role platelets play in the regulation of circulating levels of endocannabinoids is unclear, an interesting observation has been reported by Cupini *et al*. (2005). In their paper, they argue that anandamide might be involved in modulating pain associated in migraine. In their investigation, they examined the metabolism of anandamide in a number of patients with migraine. Intriguingly, they reported that the uptake of anandamide and FAAH activity were both upregulated in platelets from female, but unaffected in male patients with migraine. From these findings, they suggested that sex-related differences might mean that in female patients with migraine, the circulating levels of anandamide were reduced by platelets and that this might reduce the pain threshold and contribute towards the pathophysiology of migraine. Although it should be noted that Akerman *et al*. (2004) have proposed that anandamide may, in fact, be involved in or modulate the neurovascular mechanisms in migraine, depending whether it acts via transient release potential family vanilloid type-1 receptors or cannabinoid CB_1 receptors. These findings would suggest that in the central nervous system, endocannabinoids contribute towards the symptoms of migraine.

Interest in cannabinoids, platelets and migraine actually goes back to the 1980s when Volfe *et al*. (1985) reported that THC inhibited the release of serotonin in platelets incubated in plasma obtained from patients during a migraine attack. This clearly provides a link between cannabinoids and the modulation of migraine.

The uptake of endocannabinoids in other blood-borne cells

Platelets do not necessarily represent the sole sink for endocannabinoids in blood. A mechanistic study by Bojesen and Hansen (2005) has demonstrated in ghost human red cells that there is a transport system which does not require ATP-derived energy but is saturable. However, whether this is of relevance to the metabolism of endocannabinoid is dependent on the absence or presence of FAAH in the red blood cells.

The role of endocannabinoids in haematopoiesis

The production of blood cells is a tightly regulated process and is designed to maintain physiological levels of cells but also to respond to pathophysiology. Valk *et al*. (1997), reported that *in vitro* anandamide (at low micromolar concentrations) acted via cannabinoid CB_2 receptors to synergize with colony-stimulating factors (CSFs), interleukin-3 and erythropoietin to stimulate haematopoesis. This finding at low concentrations may suggest a role in the modulation of blood cell production, while the effects on white cells may contribute towards their established role in immune responses. More recently, the same group has also reported that 2-AG acts via cannabinoid CB_2 receptors to cause haematopoietic cell migration and this effect was synergistic with interleukin-3 and granulocyte-CSF (Jorda *et al*., 2002). This may indicate that 2-AG is important in immune cell mobilization.

There has also been interest in the involvement of endocannabinoids in abnormal blood cell development. Specifically, Jorda *et al*. (2004) have reported that the CB_2 receptor is expressed in acute myeloid leukaemia blast cells from patients, but is absent in normal myeloid cells. The expression of CB_2 receptor was also associated with oncogenic effects such as altered cell differentiation and migration.

The production of endocannabinoids by platelets and other blood cells

The ability of various blood cells to produce endocannabinoids is well established (Bisogno *et al*., 1997). Interest in the role endocannabinoids play in cardiovascular pathophysiology was initiated when Wagner *et al*. (1997) demonstrated, in a rat model of haemorrhagic shock, that activated macrophages release anandamide which may contribute towards the hypotension. Subsequently it was also found in endotoxic shock that the synthesis of 2-AG in platelets and anandamide in macrophages are increased and that these may contribute towards the associated hypotension (Varga *et al*., 1998). Further studies have confirmed that circulating cells produce endocannabinoids, for example, macrophages produce and release 2-AG (Di Marzo *et al*., 1999). Platelet-activating factor has also been shown to stimulate both platelets and a mouse macrophage cell line to produce 2-AG (Berdyshev *et al*., 2001). So, clearly blood cells represent an important circulating source of endocannabinoids which may participate in pathophysiological responses. Additionally, Maccarrone *et al*. (2001b) reported that lipopolysaccharide, a key component in endotoxic shock, causes a downregulation of FAAH expression in

human lymphocytes, and the reduction in the metabolism of anandamide leads to increased levels. This mechanism could lead to further increases in circulating levels of anandamide in endotoxic shock.

Endotoxic shock is associated with disseminated intravascular coagulation (which involves widespread platelet aggregation). If the endocannabinoids released in circulatory shock are associated with causing uncontrolled platelet aggregation, then this might be the means of causing microemboli formation and contribute towards tissue-perfusion mismatches contributing to multi-organ failure.

On a methodological note, blood cell production and release of anandamide may complicate measurement of endocannabinoids in blood. This complication arises from the observation that *ex vivo* blood samples have high rates of anandamide release and this may clearly confound analytical measurements (Vogeser *et al*., 2006).

White blood cells, inflammation and cannabinoids

This review has focused on the emerging roles of endocannabinoids on the haematological system. However, it is well established that cannabinoids have significant effects on white blood cells and inflammation, such that endocannabinoids are viewed as important immunomodulators. Indeed, the therapeutic potential of cannabinoid-based drugs in managing inflammation and neuroinflammation is under investigation. This area of cannabinoid pharmacology is now well established and the reader is referred to reviews elsewhere (for example, Maccarrone *et al*., 2002; Walter and Stella, 2004; Croxford and Yamamura, 2005).

Conclusions

The effects of cannabinoids and the physiological/pathophysiological actions of endocannabinoids on blood cells is clearly an important and fertile area for research. To date, much work in this area has emanated from Professor Maccarrone's group and includes important findings such as endocannabinoids being thrombogenic. However, platelets may also act as an important site of endocannabinoid metabolism, perhaps regulating their circulating levels. It is tempting to speculate that role of endocannabinoids in both vascular control and thrombosis may be governed by the relationship between the endothelium and platelets (Figure 1).

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Conflict of interest

The author states no conflict of interest.

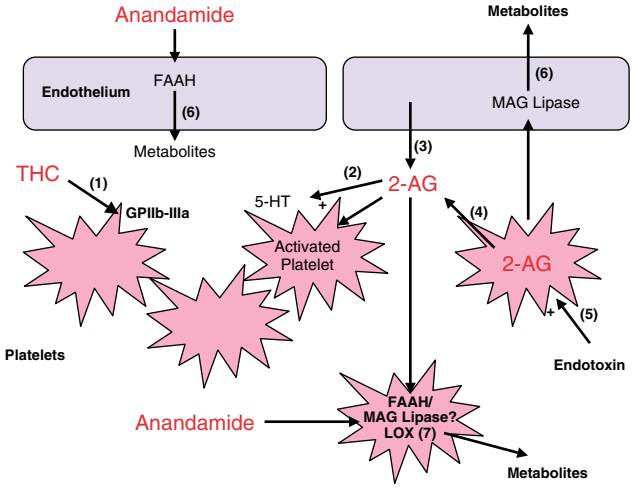

Figure 1 A schematic diagram of established and putative interactions between cannabinoids, platelets and the endothelium. (1) The ability of THC to increase expression of glycoprotein (GP) IIb–IIIa (Deusch *et al*., 2004); (2) the positive interactions between 2-AG and 5-hydroxytryptamine (5-HT) (Maccarrone *et al*., 2001a, 2003); (3) endothelial release of 2-AG (Mechoulam *et al*., 1998; Maccarrone *et al*., 2002); (4) the production and release of 2-AG from platelets (Maccarrone *et al*., 2001a; (5) the increased production of 2-AG in endotoxic shock (Varga *et al*., 1998); (6) endothelium-dependent metabolism of endocannabinoids (Ho and Randall, 2007); (7) metabolism of endocannabinoids by platelets (Edgemond *et al*., 1998; Maccarrone *et al*., 1999, 2001a). 2-AG, 2-arachidonoylglycerol; THC, Δ-9-tetrahydrocannabinol.

References

Akerman S, Kaube H, Goadsby PJ (2004). Anandamide acts as a vasodilator of dural blood vessels *in vivo* by activating TRPV1 receptors. *Br J Pharmacol* **142**: 1354–1360.

Aronow WS, Cassidy J (1974). Effects of marijuana and placebo-marijuana smoking on angina pectoris. *New Engl J Med* **291**: 65–67.

Berdyshev EV, Schimd PC, Krebsbach RJ, Schmid HHO (2001). Activation of PAF receptors results in enhanced synthesis of 2-arachidonoylglycerol (2-AG) in immune cells. *FASEB J* **15**: 2171–2178.

Bisogno T, Maurelli S, Melck D, De Petrocellis L, Di Marzo V (1997). Biosynthesis, uptake, and degradation of anandamide and palmitoylethanolamide in leukocytes. *J Biol Chem* **272**: 3315–3323.

Bojesen IN, Hansen HS (2005). Membrane transport of anandamide through resealed human red cell membranes. *J Lipid Res* **46**: 1652–1659.

Braud S, Bon C, Touqui L, Mounier C (2000). Activation of rabbit platelets by anandamide through its cleavage into arachidonic acid. *FEBS Lett* **471**: 12–16.

Croxford JL, Yamamura T (2005). Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? *J Neuroimmun* **166**: 3–18.

Cupini LM, Bari M, Battista N, Argiro G, Finazzi-Argo A, Calabresi P *et al*. (2005). Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs. *Cephalalgia* **26**: 277–281.

Deusch E, Kress HG, Kfraft B, Kozek-Langenecker SA (2004). The procoagulatory effects of delta-9-tetrahydrocannabinol in human platelets. *Anesth Analg* **99**: 1127–1130.

Di Marzo V, Bisogno T, De Petrocellis L, Melck D, Orlando P, Wagner JA *et al*. (1999). Biosynthesis and inactivation of the endocannabinoid 2-arachidonoylglyerol in circulating and tumoral macrophages. *Eur J Biochem* **264**: 258–267.

Edgemond WS, Hillard CJ, Falck JR, Kearn CS, Campbell WB (1998). Human platelets and polymorphonuclear leukocytes synthesize oxygenated derivatives of arachidonylethanolamide (anandamide):

their affinities for cannabinoid receptors and pathways of inactivation. *Mol Pharmacol* **54**: 180–188.

Fasia L, Karava V, Siafaka-Kapadai A (2003). Uptake and metabolism of [^{3}H]anandamide by rabbit platelets. Lack of transporter? *Eur J Biochem* **270**: 3498–3506.

Gauthier KM, Baewar DV, Hittner S, Hillard CJ, Nithipatikom K, Reddy DS *et al.* (2005). Endothelium-derived 2-arachidonylglycerol: an intermediate in vasodilatory eicosanoid release in bovine coronary arteries. *Am J Physiol* **288**: H1344–H1351.

Ho W-SV, Randall MD (2007). Endothelium-dependent metabolism by endocannabinoid hydrolases and cyclooxygenases limits vasorelaxation to anandamide and 2-arachidonoylglycerol. *Br J Pharmacol* **150**: 641–651.

Jorda MA, Rayman N, Tas M, Verbakel SE, Battista N, Van Lom K *et al.* (2004). The peripheral cannabinoid receptor Cb2, frequently expressed on AML blasts, either produces a neutrophilic differentiation block or confers abnormal migration properties in a ligand-dependent manner. *Blood* **104**: 526–534.

Jorda MA, Verbakel SE, Valk PJM, Vankan-Berkhoudt YV, Maccarrone M, Finazzi-Agro A *et al.* (2002). Haematopoietic cells expressing the peripheral cannabinoid receptor migrate in response to the endocannabinoid 2-arachidonoylglycerol. *Blood* **99**: 2786–2793.

Maccarrone M, Bari M, Battista N, Finazzi-Argo A (2002). Estrogen stimulates arachidonoylethanolamide release from human endothelial cells and platelet activation. *Blood* **100**: 4040–4048.

Maccarrone M, Bari M, Del Principe D, Finazzi-Agro A (2003). Activation of human platelets by 2-arachidonoylglycerol is enhanced by serotonin. *Thromb Haemost* **89**: 340–347.

Maccarrone M, Bari M, Menichelli A, Del Principe D, Finazzi-Agro A (1999). Anandamide activates human platelets through a pathway independent of the arachidonate cascade. *FEBS Lett* **447**: 7–282.

Maccarrone M, Bari M, Menichelli A, Giuliani E, Del Principe D, Finazzi-Agro A (2001a). Human platelets bind and degrade 2-arachidonoylglycerol, which activates these cells through a cannabinoid receptor. *Eur J Biochem* **268**: 819–825.

Maccarrone M, De Petrocellis L, Bari M, Fezza F, Salvati S, Di Marzo V *et al.* (2001b). Lipopolysaccharide downregulates fatty acid amide hydrolase expression and increases anandamide levels in human peripheral lymphocytes. *Arch Biochem Biophys* **393**: 321–328.

Malorni W, Bari M, Straface E, Battista N, Matarrese P, Finazzi-Argo A *et al.* (2004). Morphological evidence that 2-arachidonoylglycerol is a true agonist of human platelets. *Thromb Haemost* **92**: 1159–1161.

Mechoulam R, Fride E, Ben-Shabat S, Meiri U, Horowitz M (1998). Carbachol, an acetylcholine receptor agonist, enhances production in the rat aorta of 2-arachidonoyl glycerol, a hypotensive endocannabinoid. *Eur J Pharmacol* **362**: R1–R3.

Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE (2001). Triggering myocardial infarction by marijuana. *Circulation* **103**: 2805–2809.

Pacher P, Batkai S, Kunos G (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* **58**: 389–462.

Randall MD, Kendall DA, O'Sullivan SE (2004). The complexities of the cardiovascular actions of cannabinoids. *Br J Pharmacol* **142**: 20–26.

Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S (2006). Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *Am J Cardiol* **98**: 478–484.

Steffens S, Veillard NR, Arnaud C, Pelli G, Burger F, Staub C *et al.* (2005). Low doses of oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature* **434**: 782–786.

Valk P, Verbakel S, Vankan Y, Hol S, Mancham S, Ploemacher R *et al.* (1997). Anandamide, a natural ligand for the peripheral cannabinoid receptor is a novel synergistic growth factor for haematopoietic cells. *Blood* **90**: 1448–1457.

Varga K, Wagner JA, Bridgen DT, Kunos G (1998). Platelet- and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension. *FASEB J* **12**: 1035–1044.

Vogeser M, Hauer D, Azad SC, Huber E, Storr M, Schelling G (2006). The release of anandamide from blood cells. *Clin Chem Lab Med* **44**: 488–491.

Volfe Z, Dvilansky A, Nathan I (1985). Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. *Int J Clin Pharmacol Res* **5**: 243–246.

Wagner JA, Varga K, Ellis EF, Rzigalinski BA, Martin BR, Kunos G (1997). Activation of peripheral CB_1 cannabinoid receptors in haemorrhagic shock. *Nature* **390**: 518–521.

Walter L, Stella N (2004). Cannabinoids and neuroinflammation. *Br J Pharmacol* **141**: 775–785.

Zolese G, Bacchetti T, Ambrosini A, Wozniak M, Bertoli E, Ferrett G (2005). Increased plasma concentrations of palmitoylethanolamide, endogenous fatty acid amide, affect oxidative damage of human low-density lipoproteins: an *in vitro* study. *Atherosclerosis* **182**: 47–55.