AUTHOR(S): WAINWRIGHT, C.

TITLE: New insights into the yin and yang of the endocannabinoid system in health and disease.

YEAR: 2016

Publisher citation: WAINWRIGHT, C. 2016. New insights into the yin and yang of the endocannabinoid system in health and disease. British journal of pharmacology [online], 173(7), pages 1113-1115. Available from: https://dx.doi.org/10.1111/bph.13451.

OpenAIR citation: WAINWRIGHT, C. 2016. New insights into the yin and yang of the endocannabinoid system in health and disease. British journal of pharmacology, 173(7), pages 1113-1115. Held on OpenAIR [online]. Available from: https://openair.rgu.ac.uk

EDITORIAL

New insights into the yin and yang of the endocannabinoid system in health and disease.

Cherry L Wainwright

Centre for Cardiometabolic Health Research, Robert Gordon University, Aberdeen, Scotland

Address for Correspondence:

Centre for Cardiometabolic Health Research

Faculty of Health & Social Care

Sir Ian Wood Building

Garthdee Road

Aberdeen AB10 7GJ

Scotland

Tel: +44 1224 262450

Email: c.wainwright@rgu.ac.uk

Research carried out in the 1940's gave some of our first inklings of the pharmacological potential of chemicals extracted from *Cannabis sativa* (Loewe & Adams, 1947), but it was not until the early 1960's that Δ^9-tetrahyrocannabinol (Δ^9-THC) was shown to be one of the major constituents of cannabis that induces behavioural and psychoactive changes (Boyd et al., 1963). The next 30 years led to intensive research around the pharmacology of Δ^9-THC and other related plant-derived cannabinoids that, over time, led to the discovery and subsequent identification in the early 1990's of (i) G-protein-coupled CB_1 (Matsuda et al., 1990) and CB_2 (Munro et al., 1993) cannabinoid receptors, (ii) endogenous CB receptor ligands, of which *N*-arachidonoyl-ethanolamine (anandamide; AEA; Devane et al., 1992) and 2-arachidonyl glycerol (2-AG; Mechoulam et al., 1995) represent the most intensively studied, and (iii) the associated enzymatic apparatus which controls their synthesis and degradation (recently reviewed by Cascio & Marini, 2015). Taken together these three components were subsequently described as the endocannabinoid system (ECS), which has since been shown to comprise an endogenous signalling system that plays a pivotal role in a variety of centrally and peripherally regulated physiological processes, including pain sensation, appetite, memory, mood and inflammation, and in the pathophysiology of numerous disease states including cancer, diabetes, obesity and cardiovascular disease. To date in excess of 7,000 original articles and reviews have been published (>300 in the British Journal of Pharmacology) that have helped advance our knowledge about this complex and intriguing system. In this virtual themed issue of the BJP a further review and three original papers add additional insight and understanding of the role of the ECS in diabetes (and its complications; Gruden et al., 2015), obesity-related nephropathy (Jenkin et al., 2015) and drug withdrawal (Wang et al., 2014). Additionally Petrosino's paper (Petrosino et al., 2015) describes the intricate interaction between various elements of the ECS and their cellular targets.

Type 2 diabetes has been described as a pandemic, and the global incidence is persistently on the rise due to growing levels of obesity. The catastrophic consequences that follow the development of this condition, in the form of complications such as diabetic retinopathy, nephropathy, neuropathy and cardiovascular disease, only serves to heighten the need for effective treatments to both prevent and manage the disease. The ECS has been known for some time to play an important regulatory central role in food intake, however it is only in the last 10-15 years that we have come to appreciate an equally important role in peripheral tissues that contribute to energy metabolism and homeostasis, such as adipose tissue and pancreatic islets (reviewed by Silvestri and DiMarzo, 2013). In this themed issue of the BJP,

an excellent review from Pal Pacher's group provides an update on the role of the ECS in obesity and insulin resistance, alongside a detailed description of how the peripheral ECS is important in the pathogenesis of diabetic nephropathy, neuropathy and cardiomyopathy (Gruden et al., 2015). In this review they highlight the opposing effects of the two cannabinoid (CB_1 and CB_2) receptors in various cellular events implicated in the development of diabetic complications, including inflammation and oxidative stress, where activation of CB_2 or blockade of CB_1 both present potential opportunities for drug development in the treatment of diabetic complications. However the review also emphasises the challenges faced in terms of the selectivity of agents for each of the CB receptors and their centrally-mediated adverse effects, the latter requiring the development of peripherally restricted cannabinoid-based therapies. Of particular interest is the apparent association between a common polymorphism in the CB_1 receptor and the occurrence of nephropathy and retinopathy in Type 2 diabetics; although the functional importance of these remains to be demonstrated, this may provide a promising approach to the management of complications of this disorder.

Aligning well with the above review, also within this issue is an original contribution from Jenkin et al (2015) that focuses on the role of CB_2 in obesity-induced renal dysfunction. Using a high fat diet-induced rat model of obesity, they studied the effects of both activation (with AM1241) and blockade (with AM630) of the CB_2 receptor. While neither compound influenced weight gain, AM1241 markedly improved a number of renal function markers, while AM630 led to a worsening of the renal dysfunction, adding to the existing body of evidence that CB_2 receptor activation may be of benefit in obesity-related nephropathy. However, as noted in Gruden's review, the potential adverse effects on insulin resistance that have been reported following CB_2 receptor activation, albeit with a different CB_2 agonist (JH-133; Deveaux et al., 2009) underlines the need for the development of ligands that are highly selective for the CB receptor target.

Inflammation is one of the key events that contribute to the development of diabetic complications. To date the focus on the role of the ECS in the inflammatory process has been on the two most studied EC's anandamide (AEA) and 2-arachidonyl glycerol (2-AG). In the paper by Petrosino et al., (2015) we are reminded that other products of the same synthetic pathways that give rise to AEA play an important role in EC signalling. Palmitoylethanolamide (PAE) is an AEA congener that is synthesised alongside AEA, and various reports from the literature show that it can modulate the action of AEA at both CB

receptors. Moreover, this article similarly reminds us that AEA has actions not only at the G-protein coupled receptors, but also at other cellular targets, including TRPV1, while on the other hand 2-AG is relatively inactive at the CB receptors yet a "physiologically relevant" activator of TRPV1. Here Petrosino et al describe studies to demonstrate that, while PEA itself has very low affinity for both CB receptors and TRPV1, it appears to play an important role in modulating the activity of 2-AG at this receptor (so called pleiotropic effects). Using a combined *in vivo* and *in vitro* approach, PEA was found to elevate 2-AG levels in cultured keratinocytes and to raise plasma levels of 2-AG following oral administration in both humans and dogs. However at the cellular level, PEA only slightly augmented the activation of TRPV1 by 2-AG while increasing the 2-AG-induced desensitisation of TRPV1 to capsaicin. Through these experiments the authors have extended the previously described "entourage effect" of PEA on AEA signalling (De Petrocellis et al., 2001) to that for 2-AG, providing a plausible explanation for why antagonists of both CB receptors and TRPV1 attenuate responses to PEA.

Moving away from the topic of diabetes and obesity, the final paper in this themed issue tackles the subject of the involvement of the ECS in pathways that regulate drug addition. CB_1 receptors are highly expressed in regions of the brain linked with reward and drug addiction, and CB_1 activation has been shown to re-instate drug-seeking behaviour, while CB_1 blockade has the opposite effect. Previous evidence has suggested that synaptic plasticity occurs as both a short and long-term event in various areas of the brain associated with drug reward and addiction. Wang et al., (2014) have studied the role of the ECS in synaptic plasticity within the nucleus accumbens, where they have provided important evidence to show that the modulation of inhibitory synaptic transmission by endocannabinoids is magnified following short-term morphine withdrawal in rats. In the case of 2-AG, but not AEA, this was associated with an increased expression, of diacylglycerol lipase α (DAGLα), which is the enzyme responsible for 2-AG synthesis; although the precise mechanism underlying this remains to be identified, the findings of this study emphasise once more not only the complexity of the roles that the ECS plays in physiology (and pathophysiology), but also that the ECS is under exquisite control by both itself and other systems.

Despite the growing understanding of the ECS, one theme that emerges from all of the papers in this issue is that we need to know more about how the ECS works in order to be able to develop novel drugs targeting the this system. In particular we need to understand

how the ECS "self regulates", so that, when one pathway or receptor is blocked, we avoid activating a different pathway that would either negate what we are trying to achieve, or trigger adverse effects. Although advances are being made in the development of novel agents targeting only peripheral CB_1 receptors (to avoid the adverse psychiatric effects seen with centrally acting CB_1 antagonists) we still need to be cautious about how blockade of these receptors may impact upon the fine balance within the ECS that is helping to maintain physiological control, particularly in body systems that are unrelated to the target system. Drug selectivity is also key, since very few cannabinoid ligands (acting as either agonists or antagonists) appear to be completely selective for one receptor, reflecting in a way the promiscuity of the endogenous cannabinoid ligands themselves. Finally the behaviour of cannabinoid ligands at different receptors may vary depending upon whether or not they are being studied in cell systems, tissue preparations or *in vivo*; indeed, at least in terms of haemodynamic responses, recent data shows that the receptor activity profile of "selective" cannabinoid ligands can vary between *in vitro* and *in vivo* model systems (Walsh et al., 2015) which may reflect an involvement of the ECS and receptor cross-talk in intact animals that is not observed in isolated cells. There is therefore a strong possibility that such discrepancies may also be seen in other physiological systems.

References:

Boyd ES, Hutchinson ED, Gardner LC, Merritt DA (1963). Effects of tetrahydrocannabinols and other drugs on operant behaviour in rats. Arch Int Pharmacodyn Ther 144: 533-554.

Cascio MG, Marini P (2015). Biosynthesis and Fate of Endocannabinoids. Handb Exp Pharmacol 231: 39-58.

De Petrocellis L, Davis JB, Di Marzo V (2001). Palmitoylethanolamide enhances anandamide stimulation of human vanilloid VR1 receptors. FEBS Lett. 506: 253-6.

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258: 1946-1949.

Deveaux V, Cadoudal T, Ichigotani Y, Teixeira-Clerc F, Louvet A, Manin S, et al (2009). Cannabinoid CB2 receptor potentiates obesity-associated inflammation, insulin resistance and hepatic steatosis. PLoS One. 4: e5844.

Gruden G, Barutta F, Kunos G, Pacher P (2015). Role of the endocannabinoid system in diabetes and diabetic complications.Br J Pharmacol doi: 10.1111/bph.13226.

Jenkin KA, O'Keefe L, Simcocks AC, Briffa JF, Mathai ML, McAinch AJ, Hryciw DH (2015). Renal effects of chronic pharmacological manipulation of CB2 receptors in rats with diet-induced obesity. Br J Pharmacol doi: 10.1111/bph.13056.

Loewe S, Adams R (1947). Structure-activity relationship (SAR) and pharmacological peculiarities of new synthetic congeners of tetrahydrocannabinol. Fed Proc 6: 352.

Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346: 561-564.

Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. BiochemPharmacol 50: 83-90.

Munro S, Thomas KL, Abu-Shaar M (1993). Molecular characterization of a peripheral receptor for cannabinoids. Nature 365: 61-65.

Petrosino S, Moriello AS, Cerrato S, Fusco M, Puigdemont A, De Petrocellis L, Di Marzo V (2015). The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonyl-glucerol and potentiates its actions at TRPV1 cation channels. Br J Pharmacol doi:10.1111/bph.13084.

Silvestri C, Di Marzo V (2013). The endocannabinoid system in energy homeostasis and the etiopathology of metabolic disorders. Cell Metab. 17: 475-490.

Walsh SK, Hepburn CY, Keown O, Åstrand A, Lindblom A, Ryberg E, et al (2015). Pharmacological profiling of the hemodynamic effects of cannabinoid ligands: a combined in vitro and in vivo approach. Pharmacol Res Perspect 3: e00143.

Wang X-Q, Ma J, Cui W, Yuan W-X, Zhu G, Yang Q et al (2014). The endocannabinoid system regulates synaptic transmission in nucleus accumbens by increasing DAGL-α expression following short-term morphine withdrawal. Br J Pharmacol doi:10.1111/bph.12969.