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The endocannabinoid system and emotional processing: pathophysiology and therapeutic potential

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Although the pharmacological and medicinal properties of the plant *Cannabis sativa* have long been known and appreciated, the discovery of the endocannabinoid system began with the isolation of Δ^9 -tetrahydrocannabinol (THC), the major psychoactive component of the plant, in the mid-1960s (Gaoni and Mechoulam, 1964). Extensive pharmacological studies followed, and, by the end of the last century, the endogenous cannabinoid (endocannabinoid) system was known to comprise at least two metabotropic receptors, cannabinoid receptor types 1 and 2 (CB₁ and CB₂); two endogenous ligands, the ethanolamine of arachidonic acid, also known as anandamide (AEA), and 2-arachidonoyl-glycerol (2-AG); and the enzymes responsible for their synthesis and catabolism. However, in the last decade (2000–2010), our understanding of the endocannabinoid system has experienced a true revolution. Novel lipid molecules with endocannabinoid activity have been identified; endocannabinoids have been reported to activate additional targets, including the Transient Receptor Potential Vanilloid 1 (TRPV1) channel, nuclear peroxisome proliferator activated receptors (PPARs) and the G protein-coupled receptor GPR55. Moreover, novel pathways for endocannabinoid synthesis and degradation have been discovered. In this special issue, Pamplona and Takahashi (2012) review the discovery of the endocannabinoid system and present the most recent advances in our understanding of the physiology of this system. This issue will focus on the role of the endocannabinoid system in emotional processing, particularly in coping with stress and/or fearful situations, and will consider endocannabinoid system involvement in neuropsychiatric pathologies as well as the promising benefits of its therapeutic exploitation.

One way to think of the endocannabinoid system is as a regulatory buffer system for emotional responses, as proposed by Ruehle et al. (2012) in their review article in this issue. Thus, one of the key functions of the endocannabinoid system may be to ensure that an appropriate response to stress is mounted. Such a function is vital because inappropriate responses to stress can predispose to the development of neuropsychiatric disorders. In particular, anxiety- and fear-related behaviour is subject to modulation by the endocannabinoid system. Cannabinoid receptor agonists demonstrate bidirectional effects on anxiety-related behaviour in a manner that is probably dose- and context-dependent (Finn, 2010; Marco et al., 2009; Moreira and Lutz, 2008; Viveros et al., 2005b). In general, elevation of endocannabinoids tends to have an anxiolytic effect and there is a body of evidence showing that increased endocannabinoid tone serves to enhance the extinction of

conditioned fear responding in rats (Bitencourt et al., 2008; Chhatwal et al., 2005; Pamplona et al., 2008). Putative neuroanatomical substrates involved in cannabinoid-mediated modulation of anxiety and defence behaviour are discussed by Moreira et al. (2012). Key brain regions include the medial prefrontal cortex, amygdaloid complex, bed nucleus of stria terminalis, hippocampus and dorsal periaqueductal grey (PAG), with likely involvement of additional brain areas including the ventromedial hypothalamus and nucleus accumbens. TRPV1 is presented as a possible candidate for the mediation of endocannabinoid modulation of defence responses. However, most of the findings emphasize the dynamic and plastic nature of the endocannabinoid system, coupled with the dual functionality that arises from CB₁ expression on GABAergic and glutamatergic neurons. Indeed, differential effects of stress on elements of the endocannabinoid system expressed in GABAergic and glutamatergic neurons are suggested to explain, at least in part, the opposing effects of cannabinoids in different brain regions. As an example, Wang et al. (2012) present new evidence for endocannabinoid-mediated modulation of gamma-aminobutyric acid (GABA) release in the hippocampus during acute restraint stress in rats. Their results suggest that acute restraint stress enhances endocannabinoid-dependent modulation of GABA release in hippocampal CA1 cells as measured by whole-cell voltage clamp of inhibitory post-synaptic currents. Acute restraint stress also enhances depolarization-induced suppression of inhibition in the CA1 hippocampus, an effect probably mediated by stress-induced increases in 2-AG levels and dependent on the activation of glucocorticoid receptors.

Stress responses also include an important peripheral component, including the cardiovascular response, largely mediated by activation of the sympathetic nervous system. In this issue, O'Sullivan et al. (2012) explore the contribution of the endocannabinoid system to the cardiovascular response to stress. Cardiovascular function is modulated by the endocannabinoid

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system (Hiley, 2009; Pacher et al., 2008), and a protective role has been proposed for this system in response to stressors, possibly through cardioprotection, vasodilatation and/or anti-inflammatory effects (O'Sullivan et al., 2009; Randall et al., 2004). In contrast, increased endocannabinoid signalling may also involve negative consequences for the cardiovascular system and metabolism, possibly through the activation of glucocorticoid pathways. Evidence for a central role of the endocannabinoid system in cardiovascular activity is presented, with a particular emphasis on its contribution to stress-induced cardiovascular responses. Moreover, the potential therapeutic exploitation of the endocannabinoid system is extensively discussed.

Although research on cannabinoid-induced modulation of emotionality has tended to focus primarily on the CB₁ receptor, more recently there has been increasing interest in alternative strategies that modulate endogenous cannabinoid tone, or that target additional and/or novel endocannabinoid-sensitive receptors. Compounds that enhance endocannabinoid tone may have advantages over direct cannabinoid receptor agonists, including a more favourable side-effect profile. This pharmacological approach holds promise as an anti-anxiety and antidepressant therapy, and also in the management of pain (Petrosino and Di Marzo, 2010). In the present issue, Finn and colleagues (Butler et al., 2012) have investigated the effects of URB597, an inhibitor of the enzyme fatty acid amide hydrolase (FAAH) that hydrolyses AEA, on the modulation of pain and fear responding as well as on the reciprocal relationship shared by these two phenomena, fear-conditioned analgesia. Moreover, biochemical and molecular substrates underlying such responses were also assessed in the PAG. The data presented provide evidence for a role of the endocannabinoid system in the suppression of pain responding by conditioned fear, in pain-related modulation of fear responding, and in fear-related increases in aversive behaviour. More recently, following the demonstration of CB₂ receptor expression and function in different brain regions (Onaivi et al., 2006; Suarez et al., 2008; Van Sickle et al., 2005; Xi et al., 2011), investigation of the potential involvement of this receptor in neuropsychiatric disorders has significantly increased (Onaivi, 2009; Roche and Finn, 2010). The CB₂ receptor is thought to play an important role in the regulation of immune and inflammatory responses, and neuroinflammation has been implicated in a number of autoimmune and neurological disorders. Onaivi et al. (2012) summarize our current understanding of CB₂ receptors, from genes to receptor expression in rodents and human subjects, in relation to vulnerability to neuropsychiatric disorders beyond neuro-immuno-cannabinoid activity. Interestingly, the authors also review emerging evidence for opposing physiological actions of CB₁ and CB₂ receptors. Cannabidiol, a non-psychoactive phytocannabinoid present in the plant *Cannabis sativa* and which appears to have activity at non-CB₁/non-CB₂ targets, has been receiving considerable interest for some time now, notably because of its anxiolytic and anti-inflammatory properties. In this issue, Gomes et al. (2012) demonstrate for the first time that direct injection of cannabidiol into the bed nucleus of the stria terminalis reduced expression of contextual fear-related freezing and associated cardiovascular responses in rats via a 5-HT_{1A}-dependent mechanism. It is worth noting that cannabidiol is one of the active constituents of the cannabinoid-based therapeutic, Sativex®, which is currently licensed in Canada and some

European countries for the treatment of spasticity or neuropathic pain in multiple sclerosis patients.

The endocannabinoid system is also known to be involved in energy homeostasis (Cota et al., 2009; Viveros et al., 2012). Cota and colleagues (Bermudez-Silva et al., 2012) in this issue review the central and peripheral mechanisms underlying the regulation of food intake and energy balance by the endocannabinoid system. Obesity, a condition reaching epidemic proportions in many developed countries, is characterized by an up-regulated endocannabinoid system; thus, pharmacological blockade of CB₁ receptors has emerged as a potential therapy for the treatment of diet-induced obesity. Indeed, chronic administration of rimonabant, a CB₁ receptor antagonist/inverse agonist, successfully decreased food intake and body weight and improved lipid and glucose metabolism in rodents and humans (Cota, 2008; Di Marzo and Despres, 2009). Unfortunately, adverse psychiatric side effects led to the withdrawal of rimonabant from the European market soon after its approval as an anti-obesity drug. However, research in this field continues, with the focus shifting to drugs that do not cross the blood-brain barrier or that reduce endocannabinoid tone by decreasing the availability of cannabinoid precursors (Clapper et al., 2010; Minkkila et al., 2010; Petrosino and Di Marzo, 2010). Potential synergies with other systems involved in the regulation of food intake and body weight are also being investigated, so an effective therapy against obesity may rely on an adjunctive strategy. Still on the topic of rimonabant, Horder et al. (2012) in this issue present data demonstrating that seven days of rimonabant treatment in healthy volunteers results in negative bias in a memory recognition task in the absence of changes in subjective mood. These effects of rimonabant on emotional memory biases may in part underlie the depressogenic and anxiogenic effects of rimonabant. Understanding the mechanisms that underlie the psychiatric secondary effects of chronic rimonabant administration may enable the development of agents with a more favourable pharmacological profile, similarly efficacious but devoid of adverse psychological effects.

Cannabis is the most commonly used illicit drug in Western societies. Genetic studies have demonstrated that different polymorphisms of the CB₁ receptor (CNR1) and FAAH genes are associated with addiction to drugs of abuse, including not only cannabis but also alcohol, nicotine and cocaine (Agrawal and Lynskey, 2009; Benyamina et al., 2011). One of the most compelling associations is with the C385A single nucleotide polymorphism (SNP), which is found in the FAAH gene (Agrawal and Lynskey, 2009; Haughey et al., 2008; Schacht et al., 2009). However, it is difficult to draw definitive conclusions given the heterogeneity that exists in the studies performed to date. Lopez-Moreno et al. (2012) in this issue review the most relevant genetic studies on this topic. The authors highlight the importance of defining and limiting drug addiction phenotypes in future research, and point to the development of pharmacogenetics as a promising strategy for the treatment of drug addiction in the future. Stokes et al. (2012), in this special issue, make an original contribution to the literature on cannabis abuse in a manuscript that presents the results of a [¹¹C]-raclopride binding PET study investigating dopamine D₂/D₃ receptor availability in the striatum of volunteers with a self-reported history of heavy cannabis use. There were no differences in overall striatal binding potential values in any functional striatal subdivision between the ten heavy cannabis users and controls, nor was there any correlation between lifetime

frequency of cannabis use and binding potential values. Although, as the authors acknowledge, there are some caveats/limitations of the study, these findings suggest that a history of cannabis use is not associated with alterations in striatal dopamine D2/D3 receptors. Thus, if cannabis use is associated with an increased vulnerability to drug abuse, the results of this study provide no evidence that this is mediated by changes in D2/D3 receptor availability.

The critical contribution of the endocannabinoid system to emotional homeostasis has been extensively investigated in adult animals (Finn, 2010; Marco et al., 2009; Moreira and Lutz, 2008; Viveros et al., 2005b), and such a role seems to be relevant also in developing animals (Viveros et al., 2005a). In this issue Marco and Laviola (2012) review the role of the endocannabinoid system in emotionality and anxiety-related disorders throughout the lifespan and discuss potential therapeutic strategies based on the pharmacological modulation of this system in developing rodents. Pharmacological or environmental insults during critical neurodevelopmental periods, namely neonatal age and adolescence, may increase vulnerability to neuropsychiatric disorders in later life. Viveros et al. (2012), writing in this issue, review the literature on the role of the endocannabinoid system during neurodevelopment, and the impact on this of stress and/or drugs of abuse. As an example, a single episode of maternal deprivation in rat pups is reported to be associated with a distinctive behavioural phenotype which may model some symptoms of neuropsychiatric disorders, and also with significant enduring alterations in the endocannabinoid system that are still evident in adulthood. Endocannabinoid system alterations in this model appear to occur in a sex-dependent manner. Indeed, gender differences are also apparent with respect to interactions of cannabinoids and other drugs of abuse, particularly during the critical neurodevelopmental period of adolescence. The extent to which cannabinoid exposure during adolescence might contribute to vulnerability to neuropsychiatric disorders, including anxiety, depression and schizophrenia, is also discussed in detail. Public concern is growing in relation to the adverse effects of cannabis consumption on mental health, mainly due to the high prevalence of cannabis use among adolescent people reported in many countries (for review see Hall and Degenhardt, 2007). Indeed, the scientific community is still debating the existence of a clear relationship between cannabis use and risk of developing psychiatric disorders, particularly when cannabis use becomes heavy and occurs during adolescence (Casadio et al., 2011; Hall and Degenhardt, 2009; Jager and Ramsey, 2008). In this special issue, Rubino et al. (2012) summarize the most recent literature on the relationship between adolescent exposure to cannabinoids and increased risk for certain neuropsychiatric diseases, taking into account both human and animal studies. Their review is focused on the consequences of adolescent cannabis exposure on cognition, emotional reactivity, psychotic-like behaviour and vulnerability to drug abuse. Machielsen and colleagues have contributed an original research paper to this special issue (Machielsen et al., 2012) with an investigation into the effects of three different antipsychotics (risperidone, clozapine and olanzapine) on craving for cannabis in cannabis-dependent schizophrenic patients. Treatment with risperidone was associated with significantly more craving compared with clozapine or olanzapine. The authors speculate that differences in dopamine D2 receptor occupancy and dissociation rates and the D1/D2 ratio may explain these divergent effects of antipsychotic medication on cannabis craving. Clearly these results could have important

implications for the treatment of schizophrenic patients who may also be dependent on cannabis.

Together, the papers published in this special issue demonstrate the central importance of the endocannabinoid system in the regulation of mood, homeostasis, stress responses, neurodevelopment, and drug abuse liability. At a purely physiological level, the endocannabinoid system has emerged over the past decade as one of the most important mammalian neuromodulatory systems. From a therapeutic perspective, its status as such presents both opportunities and challenges. There is now very good evidence that perturbations in the functioning of the endocannabinoid system (e.g. arising from cannabis abuse or stress) may, at least in part, underlie a number of neuropsychiatric disorders, including anxiety disorders, depression, schizophrenia and addiction, as well as stress-related metabolic disorders. Pharmacological normalization of endocannabinoid system activity represents one exciting and novel approach for the treatment of these conditions. However, the challenge posed relates to the ubiquitous distribution of the endocannabinoid system throughout the tissues and organs of the body and its key role in numerous physiological processes. It remains to be seen whether it will be possible to develop novel and efficacious therapeutics that can target endocannabinoid system dysregulation during disease in a selective and specific manner, avoiding unwanted adverse effects in the process. However, the current vibrancy of the endocannabinoid research field means that new targets and opportunities continue to emerge, and, in that context, there are many reasons to be optimistic.

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