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Endocannabinoid-mediated modulation of stress responses: physiological and pathophysiological significance

Short title: Endocannabinoid system and stress

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List of abbreviations:

2-AG, 2-arachidonoylglycerol

5-HIAA, 5-hydroxyindoleacetic acid

AA-5-HT, N-arachidonoyl-serotonin

ACTH, adrenocorticotrophic hormone

BDNF, brain-derived neurotrophic factor

BLA, basolateral amygdala

CB, cannabinoid

CCK, cholecystokinin

CRF, corticotrophin releasing factor

DOPAC, 3,4-dihydroxyphenylacetic acid

ERK, extracellular signal-regulated kinase

FAAH, fatty acid amide hydrolase

FCA, Fear-conditioned analgesia

GABA, gamma-aminobutyric acid

HPA, hypothalamo-pituitary-adrenal

MGL, monoacylglycerol lipase

mRNA, messenger ribonucleic acid

PAG, periaqueductal grey

PTSD, post-traumatic stress disorder

PVN, paraventricular nucleus

RVM, rostral ventromedial medulla

SIA, stress-induced analgesia

SSRI, selective serotonin reuptake inhibitor

TRPV1, transient receptor potential vanilloid receptor 1

Abstract

The stress response is associated with a broad spectrum of physiological and behavioural effects including hypothalamo-pituitary-adrenal (HPA) axis activation, altered central nervous system activity, neuroimmune alterations, anxiety- and depressive-like behaviour and analgesia. While the acute stress response has essential survival value, chronic stress and dysfunction of the stress response can be maladaptive, contributing to the development and severity of psychiatric and pain disorders. The endogenous cannabinoid (endocannabinoid) system has emerged as an important lipid signalling system playing a key role in mediating and/or modulating behavioural, neurochemical, neuroendocrine, neuroimmune and molecular responses to stress. The weight of evidence, reviewed here, points largely to a system which serves to constrain HPA axis activity, facilitate adaptation or habituation of HPA axis and behavioural responses to stress, reduce anxiety- and depressive-like behaviour and mediate analgesic responses to unconditioned or conditioned stress. Possible involvement of the immune system and associated signalling molecules (e.g. cytokines) in endocannabinoid-mediated modulation of neuroendocrine and behavioural responses to stress is considered. The goal now should be to exploit our understanding of the role of the endocannabinoid system in fundamental stress physiology and pathophysiological processes to better understand and treat a range of stress-related disorders including anxiety, depression and pain.

Introduction

Stress may be defined as a complex dynamic condition in which the normal homeostasis, or the steady-state internal milieu of an organism, is disturbed or threatened (Wilder, 1995). All animals are exposed to a plethora of acute and chronic stressors throughout their lives which can be physical, psychological or immunological in nature. Stress may derive from the influence of external (e.g. bereavement, exposure to a virus) or internal (e.g. autoimmune disease) forces. The process of evolution has equipped animals with the biological machinery necessary to deal with many different types of stress. This complex physiological coping mechanism has been termed the stress response. The ability to mount an adequate response to stress is crucial for survival. It follows that disturbances in the biochemical processes necessary for the stress response may result in the development of a number of pathological states including psychiatric conditions such as anxiety and depression and chronic pain disorders such as rheumatoid arthritis. For example, exposure to stress may predispose individuals to depression (Anisman and Zacharko, 1991; Connor and Leonard, 1998) and exacerbate the inflammatory symptoms of rheumatoid arthritis (Affleck et al., 1987). Furthermore, malfunctions in the biochemistry of the stress system are evident in these diseases (Arborelius et al., 1999; Chikanza et al., 1992; Hatzinger, 2000; Masi and Chrousos, 1996; Mokrani et al., 1997; Sternberg et al., 1992) and are often resolved or reversed following successful treatment (Barden et al., 1995; Gudbjornsson et al., 1996; Hall et al., 1994; Nemeroff et al., 1991). Thus, in addition to its fundamental physiological significance, a greater understanding of the stress response and the factors that modulate it may prove useful in understanding the aetiology of stress-related disorders and in developing new approaches for their treatment.

The endogenous cannabinoid (endocannabinoid) system is a neuroactive lipid signalling system comprised of two $G_{i/o}$ -protein coupled receptors, CB_1 and CB_2 (Devane et al., 1988; Matsuda et al., 1990; Munro et al., 1993), endogenous ligands (endocannabinoids) that bind to and activate these receptors, and enzymes which either synthesise or degrade the endocannabinoids. The two best characterized endocannabinoids are *N*-arachidonylethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG) (Devane et al., 1992; Sugiura et al., 1995). Synthesis and degradation of these and other arachidonic acid-derived endocannabinoids likely occur via multiple biochemical pathways (for recent review see Ahn et al., 2008). Anandamide can be synthesised through the action of *N*-acylphosphatidylethanolamine specific phospholipase D (Di Marzo et al., 1996) while 2-AG synthesis is catalysed by the enzyme diacylglycerol lipase (Stella et al., 1997). In turn, fatty acid amide hydrolase (FAAH) and monacylglycerol lipase (MGL) are the enzymes primarily responsible for catalyzing the degradation of anandamide and 2-AG, respectively (Cravatt et al., 1996; Dinh et al., 2002; Ueda et al., 1995). The CB_1 receptor is expressed widely and in high density throughout the rodent and human brain (Herkenham et al., 1991; Mackie, 2005; Mato and Pazos, 2004; Tsou et al., 1998). Its localization is predominantly presynaptic and it responds to endocannabinoids that are synthesised 'on demand' in the postsynaptic neuron and signal in a retrograde manner (Lovinger, 2008; Wilson and Nicoll, 2002). The CB_2 receptor is expressed in tissues and cells of the immune system (Munro et al., 1993; Parolaro, 1999). Its localization on glial cells (Cabral and Marciano-Cabral, 2005; Massi et al., 2008; Walter et al., 2003) means that it too may be capable of modulating central nervous system functioning and some recent evidence also suggests that CB_2 receptors may be expressed in neurones (Gong et al., 2006; Onaivi et al., 2008; Van Sickle et al., 2005). The above is a

cursory introduction to a signalling system whose intriguing complexity has become more and more evident with the proliferation of research papers on this topic in recent years. Pharmacological tools and the development of transgenic mice have facilitated elucidation of the role of the endocannabinoid system in health and disease. It is also clear that novel, non-CB₁/non-CB₂ receptor targets for exogenous cannabinoids and endocannabinoids exist. A detailed discussion of the complexities of the endocannabinoid system is beyond the scope of the present review but readers can find excellent overviews of this system elsewhere in this special issue (**insert refs to other articles in the issue once known**) and in the recent scientific literature (Ahn et al., 2008; Alexander and Kendall, 2007; Di Marzo, 2008a; Di Marzo, 2008b; Fowler, 2008; Pacher et al., 2006; Pertwee, 2006).

The present review will focus on the dual aspects of how stress impacts on the endocannabinoid system and how, in turn, the endocannabinoid system acts to regulate physiological and behavioural responses to stress. The concept of the endocannabinoid system as a key regulator of the stress response, facilitating adaptation or habituation to stress, protecting against the development of stress-related disease and dysfunction and, ultimately, promoting survival, will be discussed. The effects of exogenously administered agonists which act directly at cannabinoid receptors will not be considered in detail as a number of recent reviews have dealt comprehensively with this literature (see Chhatwal and Ressler, 2007; Steiner and Wotjak, 2008; Valverde, 2005; Viveros et al., 2005 and others referenced throughout manuscript). Instead, the review will first focus on the role of endocannabinoids and their receptors in regulation of stress-induced alterations in hypothalamo-pituitary-adrenal (HPA) axis. Endocannabinoid-mediated modulation of behavioural stress coping (anxiety- and depression-related behaviour and stress-

induced analgesia) will then be considered. The review will finish by speculating on the potential role of the immune system in mediating or facilitating the effects of endocannabinoids on neuroendocrine and behavioural responses to stress and highlighting some areas which deserve further research.

Regulation of the HPA axis by the endocannabinoid system

The HPA axis is the principal neuroendocrine component of the response to stress. Exposure to acute stress results in release of corticotrophin-releasing factor (CRF) from neurones of the hypothalamic paraventricular nucleus (PVN) which terminate in the median eminence. CRF then stimulates release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which travels in the systemic circulation to induce the increased synthesis and release of glucocorticoids from the adrenal cortex: cortisol in humans or corticosterone in rodents. Glucocorticoids help maintain homeostasis during times of stress, however, it is critical that the HPA axis response is adequate to meet the challenge but not excessive or prolonged. Dysfunction of the HPA axis has been linked with stress-related disorders including anxiety disorders, depression and rheumatoid arthritis. A body of evidence has emerged indicating a key role for the endocannabinoid system both in regulating basal HPA axis activity and in ‘fine-tuning’ the HPA axis response to stress.

A number of studies have examined basal HPA axis activity in transgenic mice lacking the CB₁ receptor (Barna et al., 2004; Cota et al., 2007; Frideri et al., 2005; Haller et al., 2004a; Uriguen et al., 2004; Wade et al., 2006). Although there are some discrepancies between studies which are likely due to differences in background genetic strain or other methodological differences related

to sampling or animal handling, the weight of evidence points towards increased CRF mRNA in the PVN, decreased glucocorticoid receptor mRNA in the CA1 hippocampus and significantly higher ACTH secretion from pituitary corticotrophs in response to CRF and forskolin challenges as compared with pituitary cells derived from wild type mice. These alterations in the central components of the HPA axis are accompanied by increased circulating levels of corticosterone and ACTH in plasma at the onset of the dark cycle and an impaired inhibitory response to low dose dexamethasone (Cota et al., 2007). These findings are supported by pharmacological studies which have shown that acute systemic administration of the CB₁ receptor antagonist/inverse agonist rimonabant (SR141716) to rodents results in increased circulating corticosterone levels (Patel et al., 2004; Steiner et al., 2008a; for an excellent recent summary of relevant studies using genetic and pharmacological approaches see Table 3 in Steiner and Wotjak, 2008; Wade et al., 2006). Together, these studies suggest that basal HPA axis activity is under tonic inhibitory control by CB₁ receptors and the actions of endocannabinoids thereon.

Mice lacking the CB₁ receptor also exhibit enhanced stress-induced secretion of ACTH and corticosterone compared with wild type controls (Aso et al., 2008; Barna et al., 2004; Haller et al., 2004a; Steiner et al., 2008a; Uriguen et al., 2004). Acute stressors studied include novelty stress, restraint, forced swimming and tail suspension. Once again, these findings are paralleled by pharmacological studies demonstrating that systemic administration of the CB₁ receptor antagonist/inverse agonist rimonabant potentiates stress-induced increases in circulating levels of corticosterone (Finn et al., 2004b; Gonzalez et al., 2004; Patel et al., 2004; Steiner et al., 2008a; Steiner and Wotjak, 2008), suggesting that alterations in HPA axis activity in CB₁ knockout mice are not a result of developmental compensation. The studies above demonstrate that

pharmacological blockade of the CB₁ receptor potentiates the HPA axis response to either psychological (e.g. open-field exposure, social defeat, restraint) or combined physical-psychological (22 kHz ultrasound exposure, forced swimming) stressors. Interestingly, our recent work has shown that these effects of rimonabant also generalize to the immune stress of systemic lipopolysaccharide administration in rats (Roche et al., 2006) (Figure 1). Further evidence that endocannabinoids act at CB₁ receptors to constrain stress-induced activation of the HPA axis comes from the work of Patel *et al.* (2004) who demonstrated that pretreatment of mice with either the endocannabinoid transport inhibitor AM404, or the FAAH inhibitor URB597 decreased or eliminated restraint-induced release of corticosterone in a manner similar to the CB₁ receptor agonist, CP55940. The inhibitory effects of URB597 on HPA axis activity may be stressor specific since it did not affect corticosterone responses to injection stress or forced swimming (Steiner and Wotjak, 2008).

Clearly then, the endocannabinoid system is an important negative modulator of basal and acute stress-induced HPA axis activity. But what are the sites and cellular mechanisms underpinning this activity? While the possibility of actions at the level of the pituitary or adrenal glands remains to be clarified, it seems unlikely that these represent critical sites of action given the sparse expression of CB₁ receptors in rodent corticotrophs (Wenger et al., 1999) and adrenal glands (Buckley et al., 1998; Galiegue et al., 1995; Niederhoffer et al., 2001). We know from the work of Manzanares and colleagues that direct intracerebroventricular administration of rimonabant increases plasma levels of both ACTH and corticosterone in rats (Manzanares et al., 1999), suggesting that CB₁ receptors located supraspinally play in a key role. Moreover, Patel *et al.* (2004) demonstrated that the potentiation of restraint stress-induced corticosterone secretion

by rimonabant was accompanied by a potentiation of restraint-induced c-Fos expression in the hypothalamic PVN. Additional convincing evidence of a key role for endocannabinoid-CB₁ signalling at the level of the PVN comes from *in vitro* studies demonstrating that the negative fast-feedback actions of glucocorticoids on CRF-containing neurons in the PVN are dependent on the endocannabinoid system. Thus, glucocorticoids are capable of inducing the synthesis and release of the endocannabinoids anandamide and 2-AG in the PVN, which in turn act on CB₁ receptors located on presynaptic glutamatergic terminals to inhibit excitatory neurotransmission onto post-synaptic CRF neurons and negatively regulate the HPA axis (Di et al., 2003; Di et al., 2005; Malcher-Lopes et al., 2006). These data from *in vitro* studies, however, are somewhat at odds with a study *in vivo* which has shown that acute exposure of mice to 30 minutes of restraint stress results in a significant reduction in levels of 2-AG in the hypothalamus and no change in anandamide levels (Patel et al., 2004). It is possible, however, that the reduction in 2-AG levels observed 30 min post-restraint reflects depletion of a hypothalamic storage pool due to earlier release/mobilization of 2-AG as suggested by Gorzalka *et al.* (2008), and further profiling of the temporal and spatial kinetics of stress-induced alterations in subregions/nuclei of the hypothalamus is warranted. Interestingly, although acute restraint was associated with reduced hypothalamic 2-AG, repeated exposure to restraint for 5 days resulted in increased tissue levels of 2-AG in the hypothalamus and an accompanying attenuation of the corticosterone response to restraint (Patel et al., 2004). These findings have been interpreted as a sensitization of the hypothalamic 2-AG response to repeated homotypic stress, the purpose of which may be to facilitate habituation of the HPA axis response to this type of repeated challenge to homeostasis (Gorzalka et al., 2008; Patel and Hillard, 2008).

The PVN receives regulatory input from a number of extrahypothalamic CB₁-containing brain regions, including the amygdala and hippocampus. It has been shown that systemic administration of the FAAH inhibitor, URB597, or genetic deletion of FAAH, prevents restraint-induced increases in c-Fos expression in the central nucleus of the amygdala in mice (Patel et al., 2005a). Furthermore, acute restraint stress results in significant reductions in tissue levels of anandamide in the mouse amygdala and hippocampus (Gorzalka et al., 2008; Patel et al., 2004; Patel et al., 2005b). The stress-induced reduction in hippocampal anandamide may be mediated by increased levels of glucocorticoids since recent work has shown that a single acute administration of corticosterone to rats results in reduced tissue levels of anandamide in the hippocampus 18 hours later. Finally, an interesting study by Steiner et al (2008c) demonstrated that conditional mutant mice lacking CB₁ receptor expression in principal forebrain neurons (CaMK-CB1(-/-)) exhibit increased forced swim stress-induced corticosterone secretion compared with wildtype controls. Overall then, it is likely that the endocannabinoid-mediated regulation of the HPA axis occurs at the level of local PVN circuitry and possibly also via modulation of neuronal activity in extrahypothalamic regions which regulate the activity of the PVN.

Endocannabinoid-mediated modulation of behavioural responses to stress

Aberrant regulation of neurochemical and neuroendocrine responses to stress is believed to play a key role in the precipitation, maintenance and/or exacerbation of a number of psychiatric and neurological disorders including anxiety, depression and chronic pain. Preclinical work utilising animal models of behavioural stress coping have illuminated our understanding of the

neurobiological mechanisms underpinning behavioural responses to stress. Studies that have focused on the role of the endocannabinoid system in modulating behavioural responses of relevance to anxiety, depression and pain will now be reviewed. Again the focus will be on the endogenous cannabinoids and their receptors. Excellent reviews of the plethora of studies assessing the behavioural effects of exogenously administered synthetic cannabinoid receptor agonists or phytocannabinoids can be found elsewhere (Bambico and Gobbi, 2008; Chhatwal and Ressler, 2007; Lafenetre et al., 2007; Moreira and Lutz, 2008; Valverde, 2005; Viveros et al., 2005)

Anxiety-related behaviour

Broadly speaking, studies can be divided into those that have assessed unconditioned, innate anxiety-related behaviour and those that have investigated conditioned fear/aversion. A number of studies have assessed unconditioned anxiety-related behaviour in transgenic mice lacking expression of the CB₁ receptor. These mice exhibit an anxiogenic profile in the elevated plus-maze (Haller et al., 2002; Haller et al., 2004b; Uriguen et al., 2004) (but see also Houchi et al., 2005; Ledent et al., 1999; Marsicano et al., 2002), the light-dark box (Maccarrone et al., 2002; Martin et al., 2002; Uriguen et al., 2004), open-field arena (Maccarrone et al., 2002; Uriguen et al., 2004) and social interaction test (Uriguen et al., 2004). Contrasting results have been obtained with transgenic mice deficient for FAAH, the enzyme which degrades anandamide. Following an initial study demonstrating no differences in the behaviour of these mice versus wild type mice in the elevated plus-maze (Naidu et al., 2007), a more recent study reported reduced anxiety-like behaviour of FAAH knockout mice in the elevated plus maze and light-dark

box compared with wild type mice and these effects were prevented by systemic administration of the CB₁ receptor antagonist/inverse agonist rimonabant (Moreira et al., 2008). This latter study, together with data from CB₁ knockout mice, support the hypothesis that endocannabinoids act at CB₁ receptors to reduce anxiety.

Findings in transgenic mice are supported by pharmacological studies which have administered CB₁ receptor antagonists/inverse agonists, endocannabinoid degradation inhibitors or endocannabinoids themselves, to probe the role of the endocannabinoid system in unconditioned anxiety in rodents. A review of the literature, however, suggests that the effects of rimonabant may be different in rats versus mice. For example, in the rat elevated plus-maze (Arevalo et al., 2001; Navarro et al., 1997), defensive withdrawal test (Navarro et al., 1997) and ultrasonic vocalisation test (McGregor et al., 1996) systemic administration of rimonabant had an anxiogenic profile. Syrian hamsters too exhibited an anxiogenic response to rimonabant in the elevated plus-maze (Moise et al., 2008). In mice, however, rimonabant reduced anxiety-related behaviour in the elevated plus-maze (Haller et al., 2002; Rodgers et al., 2003) and in the light-dark test (Akinshola et al., 1999). Interestingly, the study by Haller *et al.* (2002) found that the anxiolytic effects of rimonabant were still evident in mice lacking the CB₁ receptor, suggesting that a novel target for rimonabant may be involved in mediating its anxiolytic effects in mice. However, in a follow-up study, these workers found that another CB₁ receptor antagonist, AM251, had an anxiogenic effect in wild type mice tested on the elevated plus-maze, an effect which was abolished in CB₁ receptor knockout mice (Haller et al., 2004b). It is of importance to note, however, that clinical data on rimonabant tie in more closely with the rat literature and suggest that this drug may be associated with increased anxiety and depressed mood (Curioni and

Andre, 2006; Doggrell, 2008; Rosenstock et al., 2008; Scheen, 2008; Van Gaal et al., 2008). These adverse psychiatric effects of rimonabant have led to the rejection of marketing approval for rimonabant by the US Food and Drug Administration (<http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4306b1-00-index.htm>; <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf>) and recent suspension of its use and marketing as an anti-obesity drug across the European Union following a recommendation issued by the European Medicines Agency (www.emea.europa.eu; Doc. Ref. EMEA/CHMP/537777/2008).

If pharmacological blockade of CB₁ receptors is associated with anxiety, then one might hypothesise that pharmacological enhancement of endocannabinoid levels and signaling would result in anxiolysis. Preclinical data largely support this idea. Thus, systemic administration of the FAAH inhibitors URB597 and URB532 reduced anxiety-related behaviour in the rat elevated zero-maze and isolation-induced ultrasonic vocalisation tests (Kathuria et al., 2003). These effects were dose-dependent and blocked by rimonabant. URB597 has also been shown to be anxiolytic in the rat elevated plus-maze and open field tests (Hill et al., 2007) and has recently been shown to reduce anxiety-related behaviour in the elevated plus-maze in Syrian hamsters (Moise et al., 2008). The FAAH inhibitor and endocannabinoid re-uptake inhibitor AM404 also exhibits a dose-dependent anxiolytic profile in the elevated plus-maze, defensive withdrawal test and ultrasonic vocalisation test (Bortolato et al., 2006). These anxiolytic effects of AM404 were blocked by rimonabant and accompanied by an increase in tissue levels of anandamide, but not 2-AG, in the medial prefrontal cortex. However, the effect of anandamide itself on unconditioned anxiety is complex and appears to depend on dose with low doses tending to be anxiolytic and

higher doses anxiogenic (Akinshola et al., 1999; Chakrabarti et al., 1998; Rubino et al., 2008; Scherma et al., 2008). Caution should be exercised when attributing the effects of anandamide, or drugs which increase its availability, to CB₁ receptors, since anandamide (and indeed AM404) has direct agonistic activity at the vanilloid receptor TRPV1 (De Petrocellis et al., 2000; De Petrocellis et al., 2001; Di Marzo et al., 2001; Ross et al., 2001; Smart et al., 2000; Zygmunt et al., 1999; Zygmunt et al., 2000) and recent evidence suggests that this ion channel also plays a role in regulation of anxiety-related behaviour (Marsch et al., 2007; Rubino et al., 2008; Santos et al., 2008; Terzian et al., 2008). Moreover, since simultaneous blockade of TRPV1 and FAAH inhibition with the dual FAAH/TRPV1 blocker, N-arachidonoyl-serotonin (AA-5-HT) results in more potent anxiolysis than selective blockers of FAAH or TRPV1 alone, it has been suggested that simultaneous indirect activation of CB₁ receptors and antagonism of TRPV1 might represent an effective therapeutic strategy for the treatment of anxiety (Micale et al., 2008).

Conditioned fear/anxiety is also subject to regulation by the endocannabinoid system. Understanding the role of the endocannabinoid system in conditioned fear and aversive memories is important because a number of anxiety disorders including post traumatic stress disorder (PTSD) and phobias are thought to result from dysregulated fear neurocircuitry (Rauch et al., 2006). Aspects of conditioned fear which have been studied include acquisition, expression and extinction of fear-related behaviour and all appear to be dependent on endocannabinoid signalling although there appear to be differences between contextual fear conditioning and cued fear conditioning (for review see Chhatwal and Ressler, 2007). Contextually-induced fear responding was abolished in mice lacking the CB₁ receptor, an effect mimicked by systemic administration of the CB₁ receptor antagonist AM251 30 minutes before behavioural testing (Mikics et al.,

2006). These workers found, however, that cannabinoids did not affect expression of cue-induced conditioned fear but did promote its extinction (but see also Arenos et al., 2006). Similarly, Marsicano *et al.* (2002) demonstrated that CB₁ knockout mice acquired and expressed cue-induced conditioned fear in a manner comparable with that observed in wild type mice, but exhibited impaired short- and long-term extinction of cue-induced conditioned fear responding. Again these results were mimicked by pharmacological blockade of CB₁ with rimonabant (Marsicano et al., 2002) and have been replicated by other groups both for extinction of cue- or context-induced fear responding (Chhatwal et al., 2005; Lafenetre et al., 2007; Lutz, 2007; Niyuhire et al., 2007; Suzuki et al., 2004). Moreover, the study by Chhatwal *et al.* (2005) demonstrated that pharmacological activation of endocannabinoid signaling with systemic administration of AM404 promoted extinction of fear memories, a finding recently replicated following either systemic (Pamplona et al., 2008) or intracerebroventricular (Bitencourt et al., 2008) administration of this endocannabinoid transport inhibitor. Additional work has suggested that the CB₁ receptor mediates fear extinction primarily via habituation-like processes rather than through associative safety learning (Kamprath et al., 2006). CRF or corticosterone appear not to be involved in CB₁-mediated acute fear adaptation (Kamprath et al., 2008) but a recent study demonstrated that interactions between the endocannabinoid and cholecystokinergic system at the level of the basolateral amygdala (BLA) may play a key role in endocannabinoid-mediated enhancement of fear extinction (Chhatwal et al., 2009). Our work has shown that administration of rimonabant systemically (Finn et al., 2004a) or directly into the right BLA (Roche et al., 2007b), attenuated the short-term extinction of contextually-induced fear in rats. In the latter study, the rimonabant-induced prolongation of contextually-induced aversive behaviour was accompanied by reduced dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC), levels in the

hippocampus, and increased levels of dopamine and 5-hydroxyindoleacetic acid (5-HIAA) in the periaqueductal grey (PAG) (Roche et al., 2007b). Again focusing on the PAG, a recent study demonstrated that intra-dorsolateral PAG administration of AM404 or anandamide reduces expression of contextually-induced fear in rats (Resstel et al., 2008). These effects were blocked by pretreatment with the CB₁ receptor antagonist AM251, which, when administered alone, was without effect (Resstel et al., 2008). In a shock-probe burying test of active and passive avoidance, CB₁ knockout mice had lower burying scores and fewer contacts with the probe compared with wild-type mice, indicative of an anxiolytic profile in this test (Degroot and Nomikos, 2004). In another study, CB₁ knockout mice showed a significant increase in the conditioned responses produced in the active avoidance model (Martin et al., 2002).

Overall then, genetic models and pharmacological studies with endocannabinoid system modulators (as opposed to more potent exogenous agonists) suggest that endocannabinoid signaling through CB₁ receptors in key brain regions acts largely to reduce or extinguish anxiety-related behaviour. As was the case for the HPA axis response to stress, it appears that behavioural responses to stress are also modulated by the HPA axis via adaptive, habituation-like processes which may involve interaction with or recruitment of a number of other signalling/neurotransmitter systems.

Behavioural despair and behavioural adaptation to stress

Many animal models of depression or tests for antidepressant-like activity assess behavioural despair or behavioural adaptation to stress. Modulation of endocannabinoid signalling influences

both of these responses. A brief overview of the literature supporting a role for the endocannabinoid system in the pathophysiology of depression and as a target for development of novel antidepressants will be provided but for more detailed considerations, please refer to recent reviews covering this topic (Bambico and Gobbi, 2008; Gorzalka et al., 2008; Hill and Gorzalka, 2005b; Mangieri and Piomelli, 2007; Patel and Hillard, 2008; Serra and Fratta, 2007; Vinod and Hungund, 2006; Wotjak, 2005).

Genetic deletion or pharmacological blockade of CB₁ receptors has been shown generally to reduce immobility in the forced swim and tail suspension tests of behavioural despair (Griebel et al., 2005; Shearman et al., 2003; Steiner et al., 2008a; Tzavara et al., 2003) although some studies report no effects of either genetic deletion (Jardinaud et al., 2005; Shearman et al., 2003; Steiner et al., 2008a) or pharmacological blockade (Gobbi et al., 2005; Gobshtis et al., 2007; Hill and Gorzalka, 2005a; Hill et al., 2007) of CB₁ receptors, or even increases in immobility (Aso et al., 2008; Steiner et al., 2008b). The depressive-like behaviour observed in the CB₁ receptor knockout mice in the latter studies was associated with reduced levels of brain-derived neurotrophic factor (BDNF) in the hippocampus (Aso et al., 2008; Steiner et al., 2008b), a finding which supports the idea that CB₁-mediated stimulation of neurotrophin release and neurogenesis in this brain region may be important in maintaining healthy mood states. Indeed, there is a body of evidence in support of a role for the endocannabinoid system in regulating neurogenesis and neural progenitor cell proliferation (for review see Galve-Roperh et al., 2006, 2007). A recent study demonstrated efficacy of subthreshold doses of rimonabant or AM251 in the forced swim or tail suspension tests when co-administered with selective serotonin re-uptake inhibitors (SSRIs) (Takahashi et al., 2008), perhaps suggesting involvement of brain

monoaminergic systems in endocannabinoid-mediated modulation of behavioural despair. Further evidence for endocannabinoid-monoaminergic interactions during behavioural stress coping come from the work of Gobbi *et al.* (2005) who demonstrated that systemic administration of the FAAH inhibitor URB597 exerted potent antidepressant-like effects in the mouse forced swim and tail suspension tests and increased the firing of serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the locus coeruleus. Gorzalka, Hill and colleagues also showed that both URB597 and AM404 reduce immobility time in the rat forced swim test (Hill and Gorzalka, 2005a; Hill *et al.*, 2007). Together with the studies described above, these reports suggest that either genetic deletion/pharmacological blockade of CB₁ receptors, or pharmacological enhancement of endocannabinoid signalling at CB₁ receptors can reduce behavioural despair in the forced swim test. A full explanation for these seemingly paradoxical findings is needed. However, for studies of this nature, it should be noted that differences in methodological aspects and testing conditions between studies can have a significant impact. A recent study found, for example, that genetic deletion or pharmacological inhibition of FAAH had no effect on immobility in the forced swim or tail suspension tests unless ambient light was altered and sample sizes increased (Naidu *et al.*, 2007). It is likely that the manner in which the test is set up and run, impacts on the extent to which it is stressful or aversive to the rodent, which, in turn, may affect endocannabinoid levels in key brain regions, providing a basis for differential effects of endocannabinoid modulating drugs or gene deletion dependent on the nature of the experimental paradigm.

When one analyses studies that have looked at the role of the endocannabinoid system in behavioural responses to repeated or chronic stress then the picture is somewhat clearer but

dependent on whether the stressor is a repeated homotypic challenge (i.e. same stressor) or chronic heterotypic stress (e.g. chronic mild stress or chronic unpredictable stress paradigms). Systemic administration of rimonabant to mice, for example, reinstates the behavioural escape response to restraint stress, following habituation of this response after 5 days of repeated restraint exposure (Patel et al., 2005b). Moreover, tissue levels of 2-AG in the forebrain and amygdala (Patel et al., 2005b) or hypothalamus (Patel et al., 2004) were increased following 5 days of repeated restraint stress. Taken together, these data suggest that 2-AG may act at CB₁ receptors in these key limbic brain regions to facilitate behavioural adaptation or habituation to repeated restraint stress. Another behavioural consequence of repeated restraint stress in mice and a symptom of depression in humans is anhedonia. It has been shown that the restraint-induced reduction in sucrose preference in mice could be reversed by pre-treatment with the FAAH inhibitor URB597 and enhanced by the CB₁ receptor antagonist rimonabant (Rademacher and Hillard, 2007). After 10 days of repeated restraint, when the behavioural effect of rimonabant was most potent, 2-AG tissue levels were increased in the prefrontal cortex, amygdala and ventral striatum and anandamide tissue levels were reduced in the prefrontal cortex and amygdala were observed (Rademacher et al., 2008). These data strongly suggest that the endocannabinoid system is progressively recruited to counteract the effects of repeated homotypic stress on reward-motivated behaviour.

In line with the above findings, Martin *et al.* (2002) showed that CB₁ receptor knockout mice exhibited a depressive-like phenotype in a chronic mild stress paradigm. However, this contrasts with the work of Griebel and colleagues who showed that 5 weeks of treatment with rimonabant improved the deleterious effects of chronic mild stress in mice (Griebel et al., 2005). These

discrepancies may relate to methodological differences in stress paradigms and end-points used to assess depressive-like phenotype. Alternatively they may be due to differences in the adaptive changes that result from genetic deletion of CB₁ versus pharmacological blockade of CB₁ with a drug which has a complex pharmacology. Supporting the idea that increased endocannabinoid signalling results in an antidepressant-like phenotype, chronic administration of the FAAH inhibitor URB597 to mice for 5 weeks attenuated chronic mild stress-induced reductions in body weight gain and sucrose intake, effects accompanied by increased tissue levels of anandamide in the midbrain, striatum and thalamus (Bortolato et al., 2007). Chronic unpredictable stress is also associated with reduced CB₁ receptor expression, reduced tissue levels of 2-AG and increased expression of FAAH in the rat hippocampus (Hill et al., 2005; Hill et al., 2008a; Reich et al., 2009), although differential effects of chronic unpredictable mild stress on CB₁ receptor expression in male versus female rats have also been demonstrated (Reich et al., 2009). C Reduced CB₁ receptor expression in the hypothalamus and ventral striatum and decreased tissue levels of anandamide in the prefrontal cortex, hippocampus, hypothalamus, amygdala, midbrain and ventral striatum have also been reported (Hill et al., 2008a). The reductions in CB₁ receptor density in the hypothalamus and ventral striatum, but not those reductions in CB₁ receptor density in the hippocampus or tissue levels of anandamide, were reversed by chronic treatment with the tricyclic antidepressant imipramine (Hill et al., 2008a). Other studies have demonstrated effects of other antidepressants from different classes on CB₁ receptor density and tissue levels of anandamide in a number of brain regions implicated in depression (Hill et al., 2006; Hill et al., 2008b). Using [³⁵S] GTPγS autoradiography, we recently showed that chronic treatment of rats for 14 days with the SSRI citalopram, reduced cannabinoid receptor agonist stimulated G-protein coupling in the hypothalamic PVN, the hippocampus and the medial geniculate nucleus (Hesketh

et al., 2008). Though the effects are dependent on the individual antidepressant administered, it is nevertheless very clear that, in general, antidepressants are capable of altering CB₁ receptor density and function under basal conditions. Moreover, it is possible that the therapeutic efficacy of antidepressants used routinely in clinical practice lies partly in their ability to normalise dysfunctional endocannabinoid signalling. One recent study demonstrated that increases in CB₁ receptor density and functionality in the prefrontal cortex in the rat olfactory bulbectomy model of depression were reversed by chronic treatment with fluoxetine, effects which were also accompanied by an attenuation of the open-field hyperactivity observed in this model (Rodríguez-Gaztelumendi et al., 2009). It follows then, based on the preclinical data reviewed above and recent clinical data demonstrating that women with minor or major depression have altered plasma levels of endocannabinoids (Hill et al., 2008c; Hill et al., 2009), that direct modulation of the endocannabinoid system, probably by increasing endocannabinoid signalling through CB₁, may represent a viable therapeutic option for the treatment of depressive disorders.

Stress-induced analgesia

We have seen how the endocannabinoid system plays a key role in facilitating adaptive neuroendocrine and neuropsychiatric responses to stress. Another evolutionarily conserved behavioural response to stress is that of adaptive pain suppression or stress-induced analgesia (SIA) (Amit and Galina, 1986; Ford and Finn, 2008) and a number of lines of evidence suggest that the endocannabinoid system plays a critical role in mediating this important survival response (for review see Ford and Finn, 2008; Hohmann and Suplita, 2006; Vaughan, 2006)

(Table 1). Early work had indicated that SIA was mediated via both opioid and non-opioid mechanisms and then in 2000, it was shown that transgenic mice lacking the CB₁ receptor did not exhibit opioid-mediated antinociception following a forced swim in water at 34°C (Valverde et al., 2000). In 2004, Finn and colleagues demonstrated that systemic administration of the CB₁ receptor antagonist/inverse agonist rimonabant to rats completely prevented the suppression of formalin-evoked nociceptive behaviour expressed upon re-exposure to an aversively conditioned context previously paired with footshock (i.e. fear-conditioned analgesia; FCA) (Finn et al., 2004a). A series of studies from Hohmann and colleagues then demonstrated a key role for the endocannabinoid system in an opioid-independent form of unconditioned SIA in rats (footshock followed immediately by tail-flick testing) and identified some of the brain regions involved. SIA was attenuated in rats tolerant to the cannabinoid receptor agonists WIN55,212-2 or Δ^9 -tetrahydrocannabinol (Hohmann et al., 2005; Suplita et al., 2008). Furthermore, rats exposed acutely to footshock were hypersensitive to the antinociceptive effects of WIN55,212-2 and Δ^9 -tetrahydrocannabinol and, in turn, acute Δ^9 -tetrahydrocannabinol and WIN55,212-2 administration potentiated SIA, suggesting a bidirectional sensitization between endocannabinoid-mediated SIA and exogenous cannabinoid-induced antinociception. Systemic administration of CB₁ receptor antagonists (Hohmann et al., 2005), or direct administration into the dorsolateral PAG (Hohmann et al., 2005; Suplita et al., 2005), brainstem rostral ventromedial medulla (Suplita et al., 2005), BLA (Connell et al., 2006), but not spinal cord (Suplita et al., 2006), suppressed SIA. Footshock stress was shown to increase the formation of anandamide and 2-AG in the PAG (Hohmann et al., 2005) and systemic or intra-PAG administration of drugs which inhibit the enzymatic degradation or transport of endocannabinoids was shown to potentiate SIA (Hohmann et al., 2005; Suplita et al., 2005). Similar potentiation of SIA was

observed following direct injection of a FAAH inhibitor into the rostral ventromedial medulla (Suplita et al., 2005) or intrathecal injection of FAAH and MGL inhibitors (Suplita et al., 2006). Thus, although endocannabinoids at the spinal level were capable of regulating this form of unconditioned SIA, mediation of this behavioural response was critically dependant on endocannabinoid-CB₁ signalling in key supra-spinal sites including the PAG and rostral ventromedial medulla. Although intra-BLA administration of rimonabant suppressed unconditioned SIA (Connell et al., 2006), inhibitors of endocannabinoid hydrolysis had no effect on SIA when injected into this brain region (Connell et al., 2006). Moreover, we have recently shown that that injection of rimonabant into the right (Roche et al., 2007b) or bilateral (Roche et al., 2007a) BLA has no effect on FCA in rats. Differences in the effects of rimonabant injected into this brain region may relate to differences in the models of unconditioned vs conditioned SIA studied. For example, unlike the model used by Hohmann and colleagues, our model of conditioned SIA/FCA has an opioid-mediated component. Indeed, we have recently shown that the enhancement of FCA in this model, by systemic administration of the FAAH inhibitor URB597, is prevented by co-administration of the opioid receptor antagonist naloxone, as well as by rimonabant and the selective CB₂ receptor antagonist SR144528 (Butler et al., 2008). The URB597-induced enhancement of FCA was also accompanied by reduced expression of phosphorylated extracellular signal-regulated kinases (ERK) 1 and 2 in the amygdala, although the extent to which these signalling molecules may be causally involved in endocannabinoid-mediated FCA remains unclear (Butler et al., 2008). Recent work in mice has suggested that interactions between the endocannabinoid system and the cholecystokinergic system (particularly CCK 2 receptors) are important for expression of an opioid-dependent form of unconditioned SIA (Kurrikoff et al., 2008). In summary, it is clear that the endocannabinoid

system plays a key role in mediating non-opioid and opioid-dependent forms of endogenous pain suppression in response to either unconditioned or conditioned stressors.

Could the immune system play a role in endocannabinoid-mediated regulation of stress responses?

A number of the review articles in this special issue of *Immunobiology* (see ... **include references to relevant articles in special issue once known**) and others in the recent literature (Correa et al., 2005; Klein and Cabral, 2006; Massi et al., 2006; Wolf et al., 2008; Wolf and Ullrich, 2008) have provided detailed coverage of the interactions between the endocannabinoid and immune systems. This final section will consider the possible involvement of the immune system in mediating or modulating the effects of the endocannabinoid system on neuroendocrine and behavioural responses to stress. The section is necessarily speculative because, although the field of psychoneuroimmunology has grown considerably in recent years, there is currently a paucity of studies investigating whether endocannabinoid-mediated modulation of immune function may underpin some of the effects of this lipid signalling system on HPA axis and behavioural responses to stress. Clearly, the endocannabinoid system is capable of modulating the function of all of the major types of immune cells and tissues, including glial cells of the central nervous system. These cells release a range of chemokines and cytokines which allow for bidirectional communication between the brain and immune system. There is now very good evidence to suggest that cytokines directly modulate HPA axis activity (Dunn, 2000; Jara et al., 2006; Mastorakos and Ilias, 2006; Mulla and Buckingham, 1999; Rivest, 2001; Savastano et al., 1994; Torpy and Chrousos, 1996; Turnbull and Rivier, 1999), anxiety- and depression-related

behaviour (Anisman and Merali, 1999; Breese et al., 2008; Connor and Leonard, 1998; Craddock and Thomas, 2006; Leonard, 2001; Leonard, 2006; Nautiyal et al., 2008; O'Brien et al., 2004; Schiepers et al., 2005; Silverman et al., 2007; Wichers and Maes, 2002) and pain (McMahon et al., 2005; Moalem and Tracey, 2006; Sommer and Kress, 2004; Thacker et al., 2007; Watkins et al., 2003; Wieseler-Frank et al., 2005a; Wieseler-Frank et al., 2005b). Our recent work (Roche et al., 2006; Roche et al., 2008), and that of others (Crocì et al., 2003; Panikashvili et al., 2001; Smith et al., 2000; Smith et al., 2001a; Smith et al., 2001b), has demonstrated a role for the endocannabinoid system in regulating peripheral and brain cytokine responses to immune challenge/stress *in vivo*. It is not inconceivable that, in addition to modulation of classical neurotransmitters such as GABA, glutamate and the monoamines, or neuropeptides such as cholecystokinin or CRF, modulation of cytokine signalling may also mediate the effects of endocannabinoids on HPA axis and behavioural (e.g. anxiety, despair, analgesia) responses to stress. Such a neuroimmunological mechanism of action has already been proposed for other psychotropic drugs, including antidepressants (Craddock and Thomas, 2006; Leonard, 2001; O'Brien et al., 2004). In this context, it is also interesting to note that a number of recent studies have demonstrated a role for the CB₂ receptor, classically associated with the immune system, in anxiety- and depression-related behaviour. Thus, intracerebroventricular administration of antisense oligonucleotide sequence directed against CB₂ mRNA reduced anxiety-like behaviour in the mouse elevated plus-maze (Onaivi et al., 2008). Moreover, a high incidence of the Q63R polymorphism in the CB₂ receptor gene was found in Japanese subjects diagnosed with depression (Onaivi et al., 2008). The CB₂ receptor appears now to be expressed on both glia (Cabral and Marciano-Cabral, 2005; Massi et al., 2008; Walter et al., 2003) and neurons (Gong et al., 2006; Onaivi et al., 2006a; Van Sickle et al., 2005) of the brain, albeit at much lower levels

than the CB₁ receptor. CB₂ receptor protein and mRNA was found to be increased in the mouse brain following a 4-week chronic mild stress paradigm (Onaivi et al., 2006b). The extent to which CB₁ or CB₂ receptor-mediated modulation of anxiety-, depression, or pain-related behaviour may involve alterations in cytokines and neuroimmune signalling remains to be determined.

Concluding remarks

The endocannabinoid system has emerged as one of the most important facilitators of stress adaptation in the body. We have seen how it responds to stress in a way which enables HPA axis responses to be restrained. At the behavioural level, despite complexities associated with some of the tools and animal models used to study the system and its effects, the picture is largely one of a system that serves to facilitate habituation to stress, reduce innate anxiety responses, promote extinction of conditioned fear responding, reduce behavioural despair or anhedonia and mediate analgesic responses to unconditioned and conditioned stress. In other words, the endocannabinoid system promotes activities and responses which are beneficial for our survival in the face of challenges to homeostasis. Resilience to stress-related disease and dysfunction may depend, at least in part, on the physiological integrity and proper functioning of the endocannabinoid system. The bulk of our understanding has come from laboratory animal studies and there is a relative paucity of clinical studies. Studies which investigate the role of the endocannabinoid system in regulation of basal and stress-induced HPA axis activity in humans are required. So too, are clinical trials which investigate the potential therapeutic efficacy of drugs that enhance endocannabinoid levels in anxiety disorders including phobias and PTSD.

Furthermore, lipidomic profiling of alterations in levels of endocannabinoids and related compounds in anxiety, depression and pain should be pursued to explore the potential usefulness of endocannabinoids as biomarkers of these disorders. The hope then is that we may be able to exploit our understanding of the role of this intriguing lipid signalling system in fundamental physiological and pathophysiological processes to better understand and treat a range of stress-related disorders.

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Pharmacological or genetic intervention	Route of admin.	Species	Model	Effect	Reference
CB ₁ KO	NA	Mice	Forced swim (34 °C) + hot plate test	SIA abolished	Valverde et al., 2000
Rimonabant	i.p.	Rats	FCA: conditioned fear + formalin test	FCA abolished	Finn et al., 2004a
Rimonabant	Intra-BLA	Rats	FCA: conditioned fear + formalin test	No effect on FCA	Roche et al., 2007a and Roche et al., 2007b
URB597	i.p.	Rats	FCA: conditioned fear + formalin test	Enhancement of FCA; blocked by rimonabant, SR144528 or naloxone	Butler et al., 2008
WIN55,212-2 tolerance induction	i.p.	Rats	Footshock + tail-flick test	SIA attenuated	Hohmann et al., 2005
WIN55,212-2 and Δ^9 -tetrahydrocannabinol administered acutely	i.p.	Rats	Footshock + tail-flick test	Enhancement of SIA	Suplita et al., 2008
Rimonabant	i.p. intra-dIPAG intra-RVM intra-BLA	Rats	Footshock + tail-flick test	SIA attenuated	Hohmann et al., 2005; Suplita et al., 2005; Connell et al., 2006
URB597	i.p. intra-dIPAG intrathecal intra-BLA	Rats	Footshock + tail-flick test	Enhancement of SIA; blocked by rimonabant No effect on SIA	Hohmann et al., 2005; Suplita et al., 2006 Connell et al., 2006
AA-5-HT	i.p. intra-dIPAG intra-RVM intrathecal	Rats	Footshock + tail-flick test	Enhancement of SIA; blocked by rimonabant	Suplita et al., 2005; Suplita et al., 2006

Palmitoyltrifluoromethylketone	i.p.	Rats	Footshock + tail-flick test	Enhancement of SIA; blocked by rimonabant	Suplita et al., 2005
URB602	Intra-dIPAG Intrathecal	Rats	Footshock + tail-flick test	SIA potentiated; blocked by rimonabant	Hohmann et al., 2005; Suplita et al., 2006
	Intra-BLA			No effect on SIA	Connell et al., 2006
Rimonabant	i.p.	Mice	Footshock + tail-flick test	SIA attenuated in wild-type mice but not in CCK2 receptor KO mice	Kurrikoff et al., 2008

Table 1. Summary of studies investigating the role of the endocannabinoid system in stress-induced analgesia (SIA).

NA: not applicable; KO: knockout; i.p. intraperitoneal; FCA: fear-conditioned analgesia; dIPAG: dorsolateral periaqueductal grey;

RVM: rostral ventromedial medulla; BLA: basolateral amygdala

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