

Abnormalities in neuroendocrine stress response in psychosis: the role of endocannabinoids

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The aim of this article is to summarize current evidence regarding alterations in the neuroendocrine stress response system and endocannabinoid system and their relationship in psychotic disorders such as schizophrenia. Exposure to stress is linked to the development of a number of psychiatric disorders including psychosis. However, the precise role of stress in the development of psychosis and the possible mechanisms that might underlie this are not well understood. Recently the cannabinoid hypothesis of schizophrenia has emerged as a potential line of enquiry. Endocannabinoid levels are increased in patients with psychosis compared with healthy volunteers; furthermore, they increase in response to stress, which suggests another potential mechanism for how stress might be a causal factor in the development of psychosis. However, research regarding the links between stress and the endocannabinoid system is in its infancy. Evidence summarized here points to an alteration in the baseline tone and reactivity of the hypothalamic–pituitary–adrenal (HPA) axis as well as in various components of the endocannabinoid system in patients with psychosis. Moreover, the precise nature of the inter-relationship between these two systems is unclear in man, especially their biological relevance in the context of psychosis. Future studies need to simultaneously investigate HPA axis and endocannabinoid alterations both at baseline and following experimental perturbation in healthy individuals and those with psychosis to understand how they interact with each other in health and disease and obtain mechanistic insight as to their relevance to the pathophysiology of schizophrenia.

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Introduction

There is a relative paucity of studies investigating the role of the endocannabinoid system in human response to stress, with even fewer examining the effect of experimental modulation of the endocannabinoid system. This is particularly true in terms of studies that have considered the interaction between the endocannabinoid and stress response systems in the pathophysiology of psychosis. Most studies that have investigated the role of endocannabinoids in regulating the stress response have done so in relation to affective and anxiety disorders. However, there is increasing recognition of the role of environmental factors in schizophrenia, such as exposure to cannabis, that have an effect on the endocannabinoid system as well as exposure to stressful life events (van Os &

Kapur, 2009). Therefore, there is a pressing need to understand how these systems interact with each other and the role such interplay may have in pathogenesis of schizophrenia. The purpose of this selective review is to summarize current available evidence in this area, mainly drawing upon human studies, to help identify gaps in knowledge and propose future directions for research. To this end, first we briefly summarize evidence relating to the role of the hypothalamic–pituitary–adrenal (HPA) axis alterations in psychosis, then introduce the endocannabinoid system and summarize current evidence of endocannabinoid abnormalities in psychosis before finally focusing on the relationship between the HPA axis and the endocannabinoid system and its potential relevance to psychosis.

Stress, cortisol and psychosis

Stress plays a major role in many different mental disorders, including anxiety, depression and psychotic disorders such as schizophrenia (Bebbington *et al.* 1993; Bramon & Murray, 2001; Cantor-Graae &

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Selten, 2005; Gracie *et al.* 2007; Aiello *et al.* 2012; Belvederi Murri *et al.* 2012; for a review, see Myin-Germeys & van Os, 2007). With particular regard to schizophrenia, a chronic disorder that typically affects young adults, early-life (Bramon & Murray, 2001; Beards *et al.* 2013) and adult (van Winkel *et al.* 2008) exposure to stress has been linked to an increased risk of development of the disorder. Stress in adulthood has also been associated with increased risk of relapse of pre-existing psychosis (Ventura *et al.* 1989). Consistent with this, the stress–vulnerability model implies that the interaction between vulnerability and stress increases the likelihood of psychosis, more than would be expected if the two factors were to occur independently (Zubin & Spring, 1977). A dose–response relationship has also been suggested, with psychotic symptoms developing when total load of stressors exceed the vulnerability threshold in a given individual (Myin-Germeys & van Os, 2007).

Stress has also been shown to be associated with an increase in negative affect and reduction in positive affect in psychosis patients, their relatives and healthy controls (Myin-Germeys *et al.* 2001), though the cross-sectional nature of the evidence precludes inference about a causal relationship. However, evidence that risk factors for developing psychosis and suffering relapse, including growing up in an urban area (Sundquist *et al.* 2004) and/or in a highly expressed emotional household (Brent & Giuliano, 2007), positively correlate with stress levels (van Winkel *et al.* 2008) further reinforces the strength of the association. Furthermore, longitudinal studies show that stressful life events often precede relapse of illness in schizophrenia (Ventura *et al.* 1989; Hirsch *et al.* 1996; Pallanti *et al.* 1997), and may alone contribute to about a quarter of the risk of relapse (Hirsch *et al.* 1996).

This raises the question that if stress is causally related to the onset of psychosis, exacerbation of symptoms or relapse of the illness in those with a pre-existing disorder, how may it be doing so? The HPA axis mediates the biological response to stress. When humans are faced with a stressor, corticotrophin-releasing hormone is released from the periventricular nucleus of the hypothalamus. This results in the secretion of adrenocorticotrophic hormone from the pituitary gland, which then leads to the release of glucocorticoids (cortisol in humans) from the adrenals. While the main role of cortisol is to increase blood sugar, suppress the immune response and aid metabolism, the association between the exogenous administration of glucocorticoids and the development of psychosis has been known for a long time, especially in descriptions of ‘steroid psychosis’ (Clark *et al.* 1952; Munck *et al.* 1984).

Consistent with this and evidence referred to in the previous paragraph, a number of studies have

reported abnormalities in cortisol levels in response to stress in patients with psychosis (Aiello *et al.* 2012). These may be broadly grouped into two categories: (i) those that have investigated cortisol reactivity following awakening, exposure to stress or pharmacological challenge (Table 1); and (ii) those that have investigated baseline or diurnal abnormalities in cortisol (Table 2). Most studies have employed one or more of these strategies to investigate differences between healthy controls and patients with psychosis or those who are at high risk of developing psychosis either because they have a high genetic (e.g. first-degree relatives of patients with psychosis) or clinical (e.g. those having an ‘at-risk mental state’ for psychosis) risk. Stress and awakening cortisol reactivity studies generally show a blunted cortisol response in patients, but pharmacological challenge studies show higher cortisol levels in patients. Diurnal levels of cortisol are generally higher in patients and their relatives.

While the evidence summarized above generally tends to suggest an abnormality of the HPA axis both at baseline and following perturbation, in those with psychosis as well as in those at risk of developing psychosis, the precise mechanism through which abnormal cortisol levels may increase the risk of psychosis is unclear. A few putative mechanisms have been suggested, such as abnormal cortisol levels following recurrent stress exposure causing an activation of the dopaminergic system (Walker & Diforio, 1997; Walker *et al.* 2008) or affecting neuroplasticity through an interaction with the immune system, neurotrophins and *N*-methyl-D-aspartate receptors (McEwen, 2000). Similarly, stress-induced cortisol changes affecting declarative memory (Kirschbaum *et al.* 1996) suggest a potential pathway to the neurocognitive changes observed in psychosis (Ivleva *et al.* 2012). Emerging neuroimaging evidence in healthy volunteers also suggests that the effects of exposure to stress may converge on neural substrates implicated in psychosis (Akdeniz *et al.* 2014). However, the precise mechanism through which exposure to stress heightens the risk of developing psychosis, the exacerbation of symptoms and an increased risk of relapse is far from clear. Therefore, the consistent nature of the evidence emerging from studies carried out by different groups suggests that there is a need to move beyond the investigation of association of stress exposure and/or HPA axis abnormalities and psychosis to studies that may suggest complementary mechanistic insight.

The endocannabinoid system

The endocannabinoid system is a lipid-signalling system involved in regulating brain development, motor control, cognition, emotional responses and homeostasis

Table 1. Summary of studies investigating cortisol reactivity in patients as compared with controls

Author	Participants (n); diagnosis	Measurement details	Medication	Findings
Response to stress Jansen <i>et al.</i> (1998)	10 schizophrenia patients 10 healthy controls	Saliva cortisol samples taken at 0, 20, 25, 50, 70 and 90 min	Patients were all receiving stable doses of antipsychotics for at least 3 weeks	An increase in cortisol levels seen in response to public speaking task in controls but not patients ($p = 0.033$)
Jansen <i>et al.</i> (2000)	18 schizophrenia patients 21 healthy controls	Saliva cortisol samples taken at 0, 20, 25, 50, 70 and 90 min	Patients were all receiving stable doses of antipsychotics for at least 3 months	Schizophrenia patients showed a blunted response to psychosocial but not physical stressor ($p < 0.05$)
Marcelis <i>et al.</i> (2004)	51 first-degree relatives 50 patients with a lifetime history of psychosis 50 controls	Plasma cortisol taken at 0, 10, 60, 90, 120, 150 min	Of the 50 patients, 47 were on antipsychotic medication, 17 used benzodiazepines, 9 antidepressants and 3 lithium In the group of relatives, one person used an antipsychotic, 2 used antidepressants and 4 benzodiazepines No information	Increases in cortisol levels seen in reaction to metabolic stress is more pronounced in patients compared with controls ($p < 0.013$); no difference in metabolic stress-induced increase in cortisol between relatives of patients with psychosis compared with healthy controls
Collip <i>et al.</i> (2011)	60 siblings of psychosis patients 63 controls	Salivary cortisol at 10 time points between 07.30 and 22.30 hours for 6 consecutive days	No information	Higher stress response levels in siblings compared with controls ($p = 0.027$)
van Venrooij <i>et al.</i> (2012)	11 first-episode psychosis patients 11 healthy controls	Plasma cortisol at -20, 0, 15, 25, 30, 35, 50, 70 and 90 min between 10.00 and 13.00 hours	No medication for at least 2 weeks prior to the study	Flattened cortisol levels in response to public speaking task in first-episode patients ($p = 0.042$)
Pruessner <i>et al.</i> (2013a)	21 patients with an ARMS for psychosis 21 healthy controls	Salivary cortisol at -45, -30, -15, -1, 1, 10, 20, 40 and 60 min between 13.00 and 16.00 hours	6 on antidepressants, none on antipsychotics	Attenuated cortisol in response to public speaking task in ARMS compared with controls ($p = 0.042$)
Response to awakening Mondelli <i>et al.</i> (2010)	50 first-episode psychosis patients 36 healthy controls	Salivary cortisol immediately after awakening (0 min) and 15, 30 and 60 min after awakening, and again at 12.00 and at 20.00 hours	7 drug-naïve patients, 10 less than 2 weeks, 33 treated with antipsychotics for more than 2 weeks Healthy controls medication naïve	Patients had a blunted cortisol awakening response ($p = 0.049$)
Pruessner <i>et al.</i> (2013b)	58 first-episode psychosis patients 33 healthy controls	Salivary cortisol immediately, 30 and 60 min after awakening	Only 5 patients were not on any medication All controls not on medication	Patients had a blunted cortisol awakening response ($p = 0.023$)

Table 1 (*cont.*)

Author	Participants (<i>n</i>); diagnosis	Measurement details	Medication	Findings
Cullen <i>et al.</i> (2014)	33 children with multiple antecedents of schizophrenia 22 children with a family history of schizophrenia or schizo-affective disorder 40 typically developing peers	Salivary cortisol at awakening, and at 15, 30, and 60 min after awakening, and at 12.00 and 20.00 hours	Antipsychotic naive	Blunted cortisol awakening response in those with a family history of schizophrenia ($p = 0.01$) but not in those with antecedents of schizophrenia compared with typically developing peers
Day <i>et al.</i> (2014)	73 ARMS 55 healthy controls	Salivary cortisol upon awakening (0 min), +30, and +60 min post-awakening, and at 12.00 and 20.00 hours	6 ARMS on antidepressants, 3 antipsychotics, 1 anxiolytic, 1 mood stabilizer Healthy controls were medication naive	ARMS had a blunted cortisol awakening response ($p = 0.024$)
Monteleone <i>et al.</i> (2014)	16 onset of schizophrenia after cannabis exposure (can+) 12 onset of schizophrenia with no cannabis (can-) exposure 15 healthy controls	Salivary cortisol at awakening and after 15, 30 and 60 min	Patients stable on antipsychotics for at least 3 months	Can+ patients showed enhanced baseline cortisol ($p = 0.007$) and flattened awakening response compared with healthy controls ($p < 0.7$). No difference between can- patients and healthy controls
Response to pharmacological challenge				
Walsh <i>et al.</i> (2005)	10 first-episode psychosis patients 10 healthy controls	Plasma cortisol at 13.00 hours	Drug naive	Higher cortisol in patients ($p < 0.02$) in response to 10 mg of metoprololamide
Spelman <i>et al.</i> (2007)	38 first-episode psychosis patients 38 healthy controls	Plasma cortisol at 08.30 hours	Drug naive	Higher cortisol levels in patients ($p < 0.001$) in response to a glucose tolerance test
Phassoulidis <i>et al.</i> (2013)	21 first-episode psychosis patients 20 healthy controls	Plasma cortisol at 09.00 hours and 09.00 hours the day after dexamethasone tablet	All less than 10 days of treatment	Patients had increased rate of hyper-suppression following dexamethasone administration compared with controls ($p = 0.04$)

ARMS, At-risk mental state; can+, cannabis exposure; can-, no cannabis.

Table 2. Cortisol levels in patients as compared with controls

Author	Participants (n); diagnosis	Measurement details	Antipsychotic treatment	Findings
Abel <i>et al.</i> (1996)	13 schizophrenia patients 13 healthy controls	Plasma cortisol between 08.00 and 09.00 hours	12 antipsychotic naive, 1 previous history (1 year ago for 2 weeks) of antipsychotic medication	Higher cortisol levels in patients ($p=0.0059$)
Jansen <i>et al.</i> (2000)	18 schizophrenia patients 21 healthy controls	Salivary cortisol every 2 h between 08.00 and 22.00 hours	Stable dosing of antipsychotics for at least 3 months	Basal levels no different between groups
Ryan <i>et al.</i> (2003)	26 FEP patients 26 healthy volunteers	Plasma cortisol at 08.00 hours	All antipsychotic naive	Higher cortisol levels in patients ($p=0.0001$)
Ryan <i>et al.</i> (2004a)	19 FEP patients 19 healthy controls	Plasma cortisol at 08.30 hours	All antipsychotic naive	Higher cortisol levels in patients ($p<0.003$)
Ryan <i>et al.</i> (2004b)	12 FEP patients 12 healthy controls	Plasma cortisol (multiple time points between 13.00 and 16.00 hours)	All antipsychotic naive	Higher cortisol levels in patients (AUC, $p<0.01$)
Strous <i>et al.</i> (2004)	37 FEP patients 27 healthy controls	Plasma cortisol at 08.00–10.00 hours	All antipsychotic free	No difference between groups
Gunduz-Bruce <i>et al.</i> (2007)	16 FEP patients 29 healthy controls	Salivary cortisol at four time points throughout the day	10 patients antipsychotic naive, 6 on antipsychotics (range of duration of treatment –21 days)	Higher cortisol levels in patients (AUC, $p<0.04$)
Mittal <i>et al.</i> (2007)	39 schizotypal personality disorder 47 controls 28 other personality disorders	Four saliva cortisol samples between 09.00 and 13.00 hours	Participants were medicated as follows: stimulants (27%); antidepressants (25%); antipsychotics (14%)	Higher levels in schizotypal personality disorder group ($p\leq 0.05$)
Hempel <i>et al.</i> (2010)	27 FEP patients 38 healthy controls	Salivary cortisol (multiple time points)	5 drug free, 22 on antipsychotic medication	Cortisol decrease more in patients than controls ($p<0.001$)
Kale <i>et al.</i> (2010)	31 FEP patients 48 healthy controls	Plasma cortisol (time not stated)	All drug naive	Higher cortisol in patients ($p=0.0005$)
Mondelli <i>et al.</i> (2010)	50 FEP patients 36 healthy controls	Salivary cortisol (multiple time points during the day)	7 drug naive, 43 on antipsychotic medication	Patients had a trend for higher diurnal cortisol levels. Those with less than 2 weeks of treatment ($p=0.002$) had significantly higher cortisol levels than patients with more than 2 weeks of treatment and controls
Collip <i>et al.</i> (2011)	60 siblings of psychosis patients 63 controls	Salivary cortisol at 10 time points between 07.30 and 22.30 hours for 6 consecutive days	No information	Higher diurnal levels in siblings compared with controls ($p<0.001$). Increase in psychotic experience and negative affect associated with increase in cortisol levels in siblings ($p<0.001$)
Garner <i>et al.</i> (2011)	39 FEP patients (23 followed up) 25 controls	Serum cortisol at 09.00–10.00 hours (baseline and 12 weeks follow-up)	Patients 14 drug naive, 25 on antipsychotic treatment Controls all drug free	No significant difference at baseline. Decrease in cortisol associated over time associated with symptom improvement

Table 2 (cont.)

Author	Participants (<i>n</i>): diagnosis	Measurement details	Antipsychotic treatment	Findings
Garcia-Rizo <i>et al.</i> (2012)	33 FEP patients 33 healthy controls	Serum cortisol at 08.00–09.00 hours	All drug naïve	No difference
Phassoulidis <i>et al.</i> (2013)	21 FEP patients 20 healthy controls	Plasma cortisol at 09.00 hours	All less than 10 days of treatment	Patients had lower basal cortisol levels compared with controls
Cullen <i>et al.</i> (2014)	33 children with multiple antecedents of schizophrenia 22 children with a family history of schizophrenia or schizo-affective disorder 40 typically developing peers	Salivary cortisol at awakening, and at 15, 30, and 60 min after awakening, and at 12.00, and 20.00 hours	Antipsychotic naïve	No difference in diurnal cortisol levels between groups
Manzanares <i>et al.</i> (2014)	65 psychotic disorder patients 16 ARMS 25 healthy controls	One saliva sample between 08.30 and 09.30 hours	9 psychotic disorder patients were treated with anti-psychotics and 13 ARMS patients Healthy controls drug naïve	No difference between diagnostic groups

FEP, First-episode psychosis; AUC, area under the curve.

(Monory & Lutz, 2009). The messengers of the endocannabinoid system are known as endogenous cannabinoids or endocannabinoids. So far, five different endocannabinoids have been identified. Two of the most researched of these are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are primarily broken down by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, respectively (Kozak *et al.* 2000; Kim & Alger, 2004; Marrs *et al.* 2010). Two G-protein-coupled receptors involved in the endocannabinoid system have also been discovered: cannabinoid receptors 1 and 2 (CB1R and CB2R). Unlike CB2R, which is more common peripherally, CB1R is mostly localized in the central nervous system, particularly the cerebral cortex, basal ganglia, anterior cingulate cortex and cerebellum (for a review, see Breivogel & Sim-Selley, 2009). It is present at high densities at pre-synaptic axon terminals (Kim & Alger, 2010). It is thought to play a central role in homeostasis by directly or indirectly modulating the release of neurotransmitters such as glutamate, serotonin, dopamine and noradrenaline (Melis & Pistis, 2007; López-Moreno *et al.* 2008; Mátyás *et al.* 2008; Wang & Lupica, 2014). These neurotransmitters, particularly dopamine, have been implicated in the pathophysiology of psychosis (Dean *et al.* 2001; Zavitsanou *et al.* 2004; Stone *et al.* 2007; Reynolds *et al.* 2014). Therefore, the endocannabinoid system seems an obvious target to study, both in terms of understanding what causes the alterations in these neurotransmitters (such as hyperactive dopamine transmission) that are observed in schizophrenia, as well as in identifying potential translational entry points for correcting these abnormalities. Alterations in the endocannabinoid system have been reported in psychosis (Giufrida *et al.* 2004). Indeed, there has been a cannabinoid hypothesis of schizophrenia posited much like the dopamine hypothesis (Müller-Vahl & Emrich, 2008).

The genesis of the cannabinoid hypothesis of schizophrenia

While it has been known for a very long time that cannabis use may induce paranoia and acute psychosis (for a review, see Murray *et al.* 2007), more systematic investigation of this relationship dates back several decades (Chopra & Smith, 1974; Rottanburg *et al.* 1982; Andréasson *et al.* 1987). Several epidemiological studies since the study by Andréasson *et al.* (1987) have consistently shown an association between cannabis use and psychotic symptoms/schizophrenia (Tien & Anthony, 1990; Arseneault *et al.* 2002; Van Os *et al.* 2002; Zammit *et al.* 2002; Ferdinand *et al.* 2005; Fergusson *et al.* 2005; Rössler *et al.* 2012), some of which have been summarized in a number of competent and insightful reviews (Arseneault *et al.* 2004;

Moore *et al.* 2007). Hence, we will not focus on the evidence here, but summarize the main issues. Although the association between cannabis use and psychosis is generally accepted, whether this association is causal in nature is strongly debated (Gage *et al.* 2013). Reverse causality has been suggested as a potential explanation for the association between cannabis use and psychosis, as a result of which individuals with pre-existing psychosis are more likely to start using cannabis. However, evidence of a temporal relationship, where this is available and credible, suggests that cannabis use often predates the onset of psychosis (for a review, see Moore *et al.* 2007). Furthermore, other strategies such as the use of statistical modelling (Fergusson *et al.* 2005) suggest that the direction of causality is from cannabis use to psychotic symptoms, although data using a sibling-pair design (McGrath *et al.* 2010) also suggest that individuals vulnerable to psychosis were at greater risk of commencing cannabis use which in turn increased their risk of subsequently developing a non-affective psychotic disorder. Similarly, another potential explanation is that cannabis use is a marker for another causative agent, such as amphetamine. Longitudinal studies that have taken such a possibility into consideration still find evidence in support of the association, albeit at a reduced strength (Zammit *et al.* 2002). This does not necessarily rule out the possibility of an unknown 'true' causative agent driving the association between cannabis use and psychosis, though it is unclear what this agent might be (Gage *et al.* 2013). Approaches (either statistical modelling or sibling-pair design) taken to control for unmeasured confounding (Fergusson *et al.* 2005; McGrath *et al.* 2010) suggest that the association between cannabis use and psychosis is unlikely to be due to unmeasured residual confounding factors. Evidence summarized in a meta-analysis (Moore *et al.* 2007) as well as further new evidence (Di Forti *et al.* 2014) also suggest a dose-response relationship such that heavier or more frequent use of cannabis as well as use of high-potency cannabis is associated with a greater risk. Evidence has also emerged that genetic vulnerability may influence the risk of psychotic disorder in cannabis users. While the initial studies suggested a moderating effect of functional polymorphism in the gene for catechol-O-methyltransferase (Caspi *et al.* 2005; Henquet *et al.* 2006; Henquet *et al.* 2009), these results were not replicated in subsequent studies (Zammit *et al.* 2007, 2011; van Winkel, 2011). Data from two independent cohorts instead suggest a greater risk of development of psychosis in cannabis users carrying risk variants of a polymorphism at the rs249732 locus in the gene coding for protein kinase B (AKT1). This is also consistent with independent experimental evidence (Bhattacharyya *et al.* 2012a, 2014) that

functional polymorphism at a related locus (rs1130233) in the *AKT1* gene, that is in strong linkage disequilibrium (Di Forti *et al.* 2012) with the rs249732 locus mentioned earlier, moderates the sensitivity of healthy individuals to the acute psychotomimetic, cognitive and neurophysiological effects of Δ -9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis. Complementary experimental evidence that THC produces its behavioural effects by binding to an integral component of the endocannabinoid system, the CB1R (Huestis *et al.* 2001), and can induce transient psychotic symptoms similar to those seen in schizophrenia (Bhattacharyya *et al.* 2010, 2012a, b) also points toward a potential role of endocannabinoid dysfunction in schizophrenia.

The endocannabinoid system and psychosis

Independent of the evidence linking cannabis use with the development of psychotic disorders, evidence has been accumulating regarding alterations of components of the endocannabinoid system in patients with psychosis or schizophrenia, which is summarized subsequently.

Pre-clinical evidence

Complementary preclinical evidence has emerged suggesting that endocannabinoid alteration may have a role in psychosis. Rodents deficient in the dopamine transporter (DAT), involved in clearing dopamine from the synapses particularly in subcortical brain regions such as the striatum (Ciliax *et al.* 1995) and consequently exhibiting hyperdopaminergia, are considered a valid animal model that recapitulates aspects of schizophrenia (Giros *et al.* 1996; Hill & Tasker, 2012). Marked reductions in AEA have been observed in the striatum, but not in the cortex, cerebellum or hippocampus of DAT-deficient mice (Tzavara *et al.* 2006). Furthermore, repeated administration of THC, which has been linked to an increased risk of psychosis, has also been shown to result in the down-regulation of AEA in the central nervous system of rats; the limbic forebrain exhibited an almost fourfold increase in AEA whereas the striatum exhibited a decrease in AEA content after 8 days of THC treatment (Di Marzo *et al.* 2000). Similarly and in line with evidence that the earlier the onset of cannabis use, the greater the risk for the development of psychosis (Arseneault *et al.* 2002), Rubino *et al.* (2014) have found that THC interrupts the maturational processes that the endocannabinoid system undergoes during adolescence. Adolescent exposure to THC led to alterations in cognition and the endocannabinoid system in adult rats.

Human studies

As summarized earlier, regular, frequent use of cannabis, which affects the endocannabinoid system, has been shown to be a robustly replicated environmental risk factor for the development of schizophrenia as well as for exacerbations of pre-existing disease (Hides *et al.* 2006). Similarly, those at risk for psychosis experience higher transition rates if they use cannabis (Kristensen & Cadenhead, 2007). Acute intoxication with THC may lead to transient psychotic symptoms including paranoia and hallucinations (Bhattacharyya *et al.* 2012b) that resolve without treatment and an exacerbation of existing positive and negative symptoms in patients with schizophrenia (D'Souza *et al.* 2005). Research using imaging techniques has found that these effects may be due to THC's effect on activation in striatal areas (Fusar-Poli *et al.* 2009; Bhattacharyya *et al.* 2012a, b). The striatum is rich in dopaminergic terminals and striatal function (Beckmann & Lauer, 1997; Lauer & Beckmann, 1997; Simpson *et al.* 2010) and the dopaminergic system (Guillin *et al.* 2007) are altered in schizophrenia. While some studies (see Sami *et al.* 2015) have shown that acute administration of THC may increase dopamine levels (Bossong *et al.* 2008), suggesting that the psychotomimetic effects of cannabis are mediated by dopamine, the evidence is equivocal, as others did not find this in healthy users (Stokes *et al.* 2009; Barkus *et al.* 2011; Kuepper *et al.* 2013). However, Kuepper *et al.* (2013) reported THC-induced dopamine release in those with increased risk of psychosis. Conversely, others have found that cannabis users have reduced dopamine synthesis capacity compared with non-users, which was not associated with cannabis-induced psychotic symptoms (Bloomfield *et al.* 2014), suggesting perhaps that psychosis induced by cannabis use may be characterized by a reduced dopamine synthesis capacity and an increased sensitivity of the D2/D3 receptor (Murray *et al.* 2014).

Consistent with this, evidence has emerged of alterations in different components of the endocannabinoid system, from the target receptors to endogenous cannabinoids such as AEA, in patients with psychosis. Table 3 summarizes current evidence regarding these alterations in the different components of the endocannabinoid system in psychosis. The earliest studies investigated CB1Rs (which are the primary target for THC in the brain) in post-mortem brains of patients. Inconsistencies in the results from earlier studies reporting an increase in the density of CB1R (Dean *et al.* 2001; Zavitsanou *et al.* 2004; Newell *et al.* 2006) and more recent studies reporting reduced CB1R mRNA expression levels in schizophrenia (Eggen *et al.* 2008, 2010) may be due to methodological reasons

such as examining different brain areas. However, an important reason for difference may be that studies reporting increased CB1R density employed receptor autoradiography to estimate this, while studies that reported lower levels investigated mRNA expression or protein levels. A more recent study employing both techniques in the same post-mortem brain specimens reported reduced CB1 mRNA and higher CB1R binding levels in the prefrontal cortex (PFC) of schizophrenia and suggested that this discrepancy may be a result of higher affinity of the CB1R or its altered trafficking into the membrane (Volk *et al.* 2014).

There have also been a number of studies (Table 3) investigating endocannabinoid levels in body fluids including in peripheral blood samples, because of easy accessibility (De Marchi *et al.* 2003). Use of peripheral blood samples raises the issue of whether alterations in peripheral blood are related to any changes in the brain and vice versa. However, studies investigating levels in cerebrospinal fluid (CSF) have also found similar changes. Elevated levels of AEA have been reported in early psychosis, with higher AEA levels being linked to delayed transition to psychosis in those at risk, suggestive of a protective role for AEA in psychosis (Koethe *et al.* 2009). This work would need to be replicated but if true it suggests that pharmacological treatment that increases AEA may be useful in schizophrenia. However, AEA normalized in patients prescribed typical antipsychotics but remained elevated following atypical antipsychotics (Giuffrida *et al.* 2004). In psychosis patients, regular use of cannabis led to the down-regulation of AEA compared with low-frequency users (Leweke *et al.* 2007). However, the cross-sectional nature of a majority of these studies makes it difficult to infer whether these alterations in different parameters of the endocannabinoid system are causally linked to psychosis or a consequence of the disease process. Nevertheless, they raise the possibility that altered peripheral endocannabinoid measures might be a marker of illness and or treatment response in psychosis. There is also a need to reconcile the nature of endocannabinoid alterations in blood/CSF with CB1R changes in the brain, perhaps using *in vivo* techniques such as positron emission tomography (PET) imaging in patients with psychosis to understand the extent to which peripheral measures reflect central changes.

Links between the stress response and endocannabinoid systems

Although there is considerable professional and public health concern regarding the effect of cannabis on mental health, most individuals who use it

Table 3. Summary of human studies investigating endocannabinoid system alterations in psychosis

Author	Participants (n); diagnosis	Antipsychotic treatment	Cannabis use	Findings
Studies with post-mortem brain				
Dean <i>et al.</i> (2001)	14 schizophrenia patients 14 no history of psychosis	All on antipsychotic medication at time of death	2 met criteria for cannabis abuse at death and 2 during their lifetime but not at death	Increase in density of [³ H]CP-55940 (a synthetic cannabinoid which mimics the effects of THC) binding to CB1R in DLPFC in schizophrenia patients compared with controls ($p < 0.05$). Increase in density of CB1R in the caudate-putamen in subjects who had recently consumed cannabis which was independent of diagnosis ($p < 0.05$)
Zavitsanou <i>et al.</i> (2004)	10 schizophrenia patients 9 matched healthy controls	8 medicated at time of death	1 ingested cannabis before death and half had used cannabis in their lifetime Cases with significant history of drug abuse excluded	64% significant increase in [³ H]SR141716A (a selective antagonist for CB1R) specific binding seen in schizophrenia group compared with healthy controls in the anterior cingulate cortex
Newell <i>et al.</i> (2006)	8 male schizophrenia patients 8 male matched controls	Patients all medicated at time of death Controls no medication at time of death	Subjects excluded if used cannabis close to death	25% significant increase in [³ H]CP-55940 binding to CB1R in superficial layers (layer I and II) of posterior cingulate cortex in schizophrenia patients compared with controls. No difference between groups in the deeper layers (layer s III–VI)
Eggan <i>et al.</i> (2008)	23 schizophrenia patients 23 matched controls 18 macaque monkeys with long-term exposure to haloperidol, olanzapine or placebo	3 patients not on medication Other groups no information	Patients 7 cannabis use Controls no information	CB1R mRNA lower by 14.8% in schizophrenia patients in the DLPFC compared with controls. No change across groups in monkeys
Eggan <i>et al.</i> (2010)	12 schizophrenia patients 12 matched controls	9 patients on antipsychotics Controls no medication	3 history of cannabis abuse	CB1R immunoreactivity levels 19% lower in schizophrenia patients
Eggan <i>et al.</i> (2010)	14 schizophrenia patients 14 matched healthy controls 14 MDD patients 4 macaque monkeys exposed to haloperidol 4 matched control monkeys	3 schizophrenia patients not on medication Controls no medication MDD patients no antipsychotics	3 schizophrenia patients history of cannabis abuse Controls no information MDD patients 3 history of cannabis abuse	CB1R immunoreactivity levels 20% lower in schizophrenia compared with healthy participants and 23% lower compared with MDD patients. CB1R not altered in monkeys

Table 3 (cont.)

Author	Participants (n); diagnosis	Antipsychotic treatment	Cannabis use	Findings
Studies with blood				
De Marchi et al. (2003)	12 patients with schizophrenia 20 healthy volunteers	No medication 30 days prior to the study	No abuse of cannabis in the year preceding the study	Anandamide significantly higher in patients. Clinical remission was associated with lower levels of anandamide and of the mRNA transcripts for CB2 receptors and FAAH
Studies with cerebrospinal fluid				
Leweke et al. (1999)	10 psychosis patients 11 healthy controls	5 patients medication naive, 2 no medication for 7 days, 3 on antipsychotics	4 patients had a history of intermittent consumption of cannabis resin	Elevated levels of anandamide and the lipid N-palmitoylethanolamine in patients ($p < 0.05$)
Giuffrida et al. (2004)	47 schizophrenia patients 84 healthy controls 13 dementia patients 22 affective disorder patients	Schizophrenia patients antipsychotic naive Controls medication free Dementia patients pharmacological treatment Affective disorder patients pharmacological treatment	Patients – no specific information, but cannabis use in patients reported to be similar to that of the healthy controls Healthy controls – 57 lifetime frequency of cannabis use of up to five times, but not within the last 12 months before inclusion into the study; 27 lifetime cannabis use of 20 to 50 times but not within the last 6 months prior to the study Antipsychotic naive	Anandamide higher in anti-psychotic-naive schizophrenia patients compared with other patients and controls ($p = 0.000$) and correlated with psychotic symptoms ($p = 0.001$). This elevation was not seen in those treated with typical antipsychotics but was in those treated with atypical antipsychotics
Leweke et al. (2007)	47 first-episode psychosis patients 81 healthy controls	Patients 25 LFU (defined as less than 5 times in a lifetime), 19 HFU (defined as more than 20 times) Controls 55 LFU, 26 HFU	Patients no cannabis use 6 weeks prior to study 55 controls (68%) had taken cannabis <20 times/lifetime and 26 (32%) had used cannabis >20 but <50 times/lifetime	First-episode psychosis LFU had higher anandamide levels than HFU ($p = 0.008$) and healthy controls (LFU: $p < 0.001$; HFU: $p < 0.001$)
Koethe et al. (2009)	27 prodromal patients 81 healthy controls	Patients no cannabis use 6 weeks prior to study 55 controls (68%) had taken cannabis <20 times/lifetime and 26 (32%) had used cannabis >20 but <50 times/lifetime	8 received medication	Patients had higher anandamide levels. Patients who had lower levels transitioned earlier ($p = 0.095$)

THC, Δ -9-Tetrahydrocannabinol; CB1R, cannabinoid receptor 1; DLPFC, dorsolateral prefrontal cortex; MDD, major depressive disorder; FAAH, fatty acid amide hydrolase; LFU, low frequency users; HFU, high frequency users.

recreationally do so for its relaxing effect and a perceived beneficial effect on stress, which is consistent with the distribution of CB1Rs in brain regions associated with regulating the stress response (for example, the hypothalamus, hippocampus and amygdala: Herkenham *et al.* 1991; Tsou *et al.* 1998). This is also consistent with human experimental evidence that cannabinoids modulate the function of limbic structures, such as the amygdala, anterior and posterior cingulate cortex (Phan *et al.* 2008; Fusar-Poli *et al.* 2009; Bhattacharyya *et al.* 2010) and that these neural effects may be related to an anxiogenic or anxiolytic effect (Fusar-Poli *et al.* 2009; Bhattacharyya *et al.* 2010). Animal (Di *et al.* 2005; Malcher-Lopes *et al.* 2006) as well as human studies have shown that glucocorticoids cause elevation in endocannabinoid levels (Dlugos *et al.* 2012). In this section, we will focus on current evidence that points towards an inter-relationship between the stress response and endocannabinoid systems, drawing particularly upon the relevant pre-clinical literature.

Pre-clinical evidence

A significant body of evidence has amassed which indicates that the endocannabinoid system is intimately involved in the regulation of the stress response (for a review, see Hill & Tasker, 2012). The first studies, which were *in vitro* studies in rat tissue, showed that the endocannabinoid system was capable of reducing HPA axis response (Di *et al.* 2003) and that glucocorticoids can in turn induce endocannabinoid signalling (Di *et al.* 2005). However, *in vivo* studies involving mice have shown that while exposure to acute stress reduced 2-AG in the hypothalamus, it had no effect on AEA (Patel *et al.* 2004). In contrast within the amygdala, restraint stress reduced AEA but had no effect on 2-AG. Furthermore, there was no effect of restraint stress in the forebrain and cerebellum (Patel *et al.* 2005) or in the medial PFC or ventral striatum (Rademacher *et al.* 2008). *In vivo* studies using rats (like in the *in vitro* studies) showed an elevation of AEA and 2-AG in the periaqueductal grey (Hohmann *et al.* 2005), suggesting a species difference in the effects of stress on the endocannabinoid system, making it difficult to predict what might occur in man. Furthermore, the types of stress that may potentially be employed in animal studies are not necessarily directly translatable to the human experience or experimental context and research has shown that the effects on the endocannabinoid system depend on the specific type of experimental stress employed. For example, restraint stress has been shown to lead to an increase in 2-AG and a reduction in AEA in the medial PFC (Hill *et al.* 2010) while chronic unpredictable stress has been shown to lead to a reduction in AEA in the absence of

a concomitant change in 2-AG in the PFC (Hill *et al.* 2008). Therefore, while preclinical studies may provide the broad framework and suggest pointers, an accurate understanding of the interactions between the endocannabinoid and the stress response system warrants studies in man. For such understanding to have relevance to psychosis, which is believed to be a uniquely human disease, human studies are critical.

Human studies

In healthy participants, acute stress leads to an increase in circulating endocannabinoids and structurally similar lipids (Hill *et al.* 2009b; Dlugos *et al.* 2012). The 'Trier Social Stress Test' (TSST), which involves subjecting participants to social evaluative stress, induces moderate psychological stress in a laboratory setting (Kirschbaum *et al.* 1993). It is an experimental paradigm that has often found favour with researchers investigating the effects of experimental stress induction in man and has proven to be a useful tool for measuring cortisol response to psychological stress (Kudielka & Kirschbaum, 2005). Dlugos *et al.* (2012) compared the TSST with a no-stress condition in healthy volunteers and found that compared with the no-stress condition, stress increased the concentration of AEA immediately after the stress exposure. Further, increases in cortisol were correlated with *N*-palmitoylethanolamine (Dlugos *et al.* 2012). A trend for individuals with lower levels of AEA to have higher cortisol release after stress compared with those with higher levels of AEA was also found. While pre-clinical studies have shown that peripheral concentrations of endocannabinoids correlate with levels in stress-related brain areas (Patel *et al.* 2004), Dlugos *et al.* (2012) acknowledge that the source of the circulating endocannabinoids is essentially unknown. Lack of information on previous history of stressful life events in their study participants also makes it difficult to infer the extent to which the acute effects of the TSST are moderated by previous exposure to stress, especially in light of independent evidence that previous exposure to stress can permanently alter the stress response (Heim *et al.* 2000). Nevertheless, this study clearly suggests a link between the stress response and endocannabinoid systems in man. In a similar study comparing the effect of the TSST in depressed relative with non-depressed women, Hill *et al.* (2009b) reported no change in AEA levels following acute stress but a change in 2-AG immediately after stress induction compared with baseline (Hill *et al.* 2009b). Although, the magnitude of these changes was not different between depressed and control subjects, baseline levels of AEA and 2-AG were significantly lower in the depressed subjects compared with the controls. While apparently inconsistent, the results of the two studies may be reconciled by the fact that the Hill

et al. (2009a, b) study included only female participants (Hill *et al.* 2009b) and subgroup analyses from the Dlugos *et al.* (2012) study found that the results they found were only significant in males (Dlugos *et al.* 2012). Another study which investigated the effect of parabolic flight on stress responses showed that stress-tolerant individuals demonstrate an increase in 2-AG. In contrast, highly stressed individuals do not show such an increase but have a significantly enhanced HPA axis response (Strewe *et al.* 2012). Together with other evidence summarized in previous sections, this may suggest a protective role of increased endocannabinoid system signalling in maintaining homeostasis under acutely stressful conditions.

Chronic stress

In contrast to the studies investigating the acute effects of exposure to stress, a study of individuals who were exposed to chronic stress and developed post-traumatic stress disorder (PTSD) found that they have higher levels of 2-AG relative to healthy individuals who had also been exposed to trauma (Hauer *et al.* 2013) but did not develop PTSD. It was also found that 2-AG levels in both trauma-exposed groups (PTSD and no PTSD) were higher than in controls with no history of exposure to trauma. This led the authors to conclude that exposure to stress may cause an increase in 2-AG, which may have a protective role in the short term to maintain homeostasis of the HPA axis (Hill *et al.* 2010), but that chronic allostatic load might in turn have harmful consequences, such as the development of PTSD.

Relevance for psychosis

From the above, it is clearly evident that the endocannabinoid system both regulates and responds to the HPA axis stress response system and habituation to stress involves alterations in the endocannabinoid system (Gorzalka *et al.* 2008). However, how exposure to daily-life stress alters the HPA axis and the endocannabinoid system and whether such alterations are causally related to psychosis are unknown. Not every individual who is exposed to stress develops a psychiatric disorder, least of all psychosis. Therefore, it has been hypothesized that those who do so may have a pre-existing dysfunction in the endocannabinoid system due to its integral role in habituation to stress that makes them particularly vulnerable to adverse mental health consequences (Gorzalka *et al.* 2008). Furthermore, why similar types of stress may lead to different types of psychological outcomes (e.g. affective disorder such as depression as opposed to a non-affective disorder such as schizophrenia) is unclear. Endocannabinoids have

been found to generally constrain corticosterone (the primary glucocorticoid involved in the stress response in non-human species) release (Hill & Tasker, 2012). It has been found that administration of a CB1 antagonist leads to an increase in corticosterone secretion in animals (Wade *et al.* 2006). This demonstrates the endocannabinoid system's role in modulating the HPA axis and may be useful in understanding how increased stress reactivity arises and how it may ultimately lead to psychosis. Chronic restraint stress in mice leads to an increase in FAAH activity and a reduction of AEA (Hill *et al.* 2013). As mentioned earlier, AEA may have a protective role in stress as animal studies show that chronic restraint stress can cause a reduction of AEA (Hill *et al.* 2013), while increased AEA signalling due to blockade of its metabolic enzyme (FAAH) decreases anxiety-like behaviours (Moreira *et al.* 2008). Similarly, a cannabinoid receptor agonist prevented endocrine alterations in a rat model of stress (Ganon-Elazar & Akirav, 2011). However, this needs to be confirmed in man. Stress-induced alterations in AEA have also been linked to alterations of the HPA axis (Rademacher *et al.* 2008; Hill *et al.* 2009a) putatively via an increase in FAAH (Hill *et al.* 2009a), the enzyme that degrades AEA. These studies suggest that enhancing the availability of certain endocannabinoids may help augment tolerance to stress. However, despite the growing body of evidence suggesting that stress-induced alterations in the HPA axis and the endocannabinoid system may have a role in psychosis, the precise nature of these relationships have not been investigated in a systematic manner in humans. Due to the abundance of evidence demonstrating the role of stress in psychosis, and the relationship between the endocannabinoid system and psychosis, a thorough understanding of the links between these two systems in man is essential.

Conclusions and future directions

Evidence summarized here generally suggests that both the baseline tone and reactivity of the HPA axis to stress, and awakening and pharmacological challenge are abnormal in those with psychosis and at risk of developing the disorder. Similarly, evidence has also emerged of alterations in components of the endocannabinoid system, from receptors (in post-mortem brain samples) to endocannabinoid levels in CSF and peripheral blood, in patients with psychosis. Evidence from basic research as well as human studies also suggests that the endocannabinoid system regulates as well as responds to the HPA axis stress response system and habituation to stress is associated with alterations in the endocannabinoid system. However, the precise nature of the inter-relationship between these two systems is unclear in man, especially in the

context of psychosis. It is worth noting that the direction of alteration observed in either the HPA axis/stress response system or in components of the endocannabinoid system is not always consistent across studies, perhaps related to different methodological approaches employed. Evidence available to date, especially related to endocannabinoid alteration in man, is also limited by modest sample sizes studied. The biological relevance of endocannabinoid alteration observed peripherally in blood to effects in the brain remains unclear as well. In particular, there is a lack of evidence about how these systems interact in man and whether these are altered in those with psychosis or at risk of developing the disorder. Thus, there is a need to simultaneously investigate alteration in these two systems in the same group of subjects (healthy individuals *v.* patients with psychosis). Consistent evidence of alteration in these two systems emerging from studies carried out by different groups suggests that there is also a need to move beyond the investigation of statistical association of stress exposure and/or HPA axis abnormalities or endocannabinoid system abnormalities and psychosis to studies that may suggest complementary mechanistic insight, perhaps by employing a combination of experimental perturbation of either of these systems in healthy and diseased individuals. Relating peripheral endocannabinoid measures to central measures, such as CB1R density using PET, is particularly important to establish biological relevance.

As reviewed here, evidence regarding the link between abnormalities in the stress response system and the endocannabinoid system in man is limited, and this is particularly true in terms of their relationship to psychosis. It has been postulated that individuals who are susceptible to depression may possess a dysfunctional endocannabinoid system that prevents them from coping and adapting to stress adequately (Gorzalka *et al.* 2008). Similarly, it may be the case that those susceptible to psychosis may possess a dysfunctional endocannabinoid system that predisposes them to altered stress sensitivity and is a mechanism for the affective pathway to psychosis (Myin-Germeys & van Os, 2007). This dysfunctional endocannabinoid system may, in some cases, have its genesis in the abuse of cannabis.

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Declaration of Interest

None.

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