Endocannabinoids and striatal function: implications for addiction-related behaviours

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Since the identification and cloning of the major cannabinoid receptor expressed in the brain almost 25 years ago research has highlighted the potential of drugs that target the endocannabinoid system for treating addiction. The endocannabinoids, anandamide and 2-arachidonoyl glycerol, are lipid-derived metabolites found in abundance in the basal ganglia and other brain areas innervated by the mesocorticolimbic dopamine systems. Cannabinoid CB1 receptor antagonists/inverse agonists reduce reinstatement of responding for cocaine, alcohol and opiates in rodents. However, compounds acting on the endocannabinoid system may have broader application in treating drug addiction by ameliorating associated traits and symptoms such as impulsivity and anxiety that perpetuate drug use and interfere with rehabilitation. As a trait, impulsivity is known to predispose to addiction and facilitate the emergence of addiction to stimulant drugs. In contrast, anxiety and elevated stress responses accompany extended drug use and may underlie the persistence of drug intake in dependent individuals. In this article we integrate and discuss recent findings in rodents showing selective pharmacological modulation of impulsivity and anxiety by cannabinoid agents. We highlight the potential of selective inhibitors of endocannabinoid metabolism, directed at fatty acid amide hydrolase and monoacylglycerol lipase, to reduce anxiety and stress responses, and discuss novel mechanisms underlying the modulation of the endocannabinoid system, including the attenuation of impulsivity, anxiety, and drug reward by selective CB2 receptor agonists. *Behavioural Pharmacology* 26:59–72

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Introduction

Drug addiction is a chronic, relapsing brain disorder characterized by compulsive drug seeking and repeated bouts of binge intoxication and withdrawal. Research over a number of decades has defined the principal pharmacological mechanisms underlying the primary reinforcing effects of many substances abused by people, which directly or indirectly activate the mesolimbic dopamine (DA) system (Di Chiara and Imperato, 1988; Nestler, 2005). Yet fundamental questions remain, including especially how drugs come to dominate behaviour so powerfully and why addiction afflicts only a small subset of all users. A common framework to address these questions rests on the principle that addiction is a progressive disorder involving a series of transitions from (i) initial drug contact and experimentation, (ii) recreational and mostly occasional use, (iii) a preoccupation to use drugs more regularly and (iv) consumption levels that ultimately lead to harm and are life threatening (Everitt and Robbins, 2005; Belin *et al.*, 2009, 2013; Koob and Volkow, 2010). Diagnostic criteria of addiction or substance use disorder, based on the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5; American Psychiatric Association), include taking substances in larger amounts than originally intended, a persistent desire to cut down or moderate drug use, longer periods of time using the drug or recovering from its effects, and intense craving. Neurally, the development of addiction is hypothesized to align with the emergence of drug seeking habits controlled by dopaminergic mechanisms in the dorsal striatum and a shift away from prefrontal cortical control mechanisms (Jentsch and Taylor 1999; Everitt and Robbins, 2005; Kalivas and Volkow, 2005; Belin *et al.*, 2013).

Although a distinguishing feature of addiction is a persistent underlying change in the brain reward and stress systems, caused by protracted drug use (Kalivas and Volkow, 2005; Nestler, 2005; Koob and Volkow, 2010), the path to addiction for some may be predestined by underlying impairments in self-control (Wills *et al.*, 1994; Verdejo-García *et al.*, 2008; Van den Heuvel *et al.*, 2009). Indeed, increasing evidence suggests that certain personality traits, including the seeking out of intense forms of sensation, novelty, and impulsivity may predispose to addiction (Sher *et al.*, 2000; Adams *et al.*, 2003;

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Verdejo-García *et al.*, 2008). Moreover, prospective studies in adolescents unambiguously demonstrate that impulsivity precedes the onset of drug use and possibly the development of addiction (Nigg *et al.*, 2006; Wong *et al.*, 2006), consistent with analogous research in rodents (Belin *et al.*, 2008; Diergaarde *et al.*, 2008; Economidou *et al.*, 2009; Dalley *et al.*, 2007).

A complementary view, the opponent process theory, focuses on progressive drug-induced changes in the hedonic state of addicts (Koob and Le Moal, 1997). It is derived from the concept of homoeostasis, the capacity of an organism to maintain a constant internal environment despite change, and allostasis, where prolonged contact with salient stimuli results in adaptations at pathological set-points. According to this theory addicts take drugs because they are initially reinforcing. However, with more protracted drug use not only does this driving mechanism diminish, a concomitant increase in the activity of anxiety-related and stress-related circuits ensues. At this point drug use is driven by compulsive behaviour and attempts to avoid the aversive reactions associated with its withdrawal. This hypothesis, therefore, emphasizes changes in emotional states, in line with the view that anxiety and stress contribute to the maintenance of addiction (Cleck and Blendy, 2008; Kessler *et al.*, 2010). The growth of the opponent process governing negative reinforcement involves reductions in DA, gamma-amino-butyric acid (GABA) and endogenous opioid neurotransmission together with facilitated noradrenaline (NA) and corticotrophin-releasing factor activity. Key structures mediating this altered motivational state include the central amygdala and bed nucleus of the stria terminalis (Koob, 2013).

Despite considerable research investment a surprisingly small number of medications have been developed and approved for the treatment of addiction (Xi, 2011; Pierce *et al.*, 2012). This deficiency may reflect in part the dominance over many years of DA-based theories, which although intuitively attractive have led to no major breakthroughs in treatment. An alternative approach is to treat underlying traits that predispose and are often comorbid with addiction, notably as discussed above impulsivity and anxiety. Understanding the biological mechanisms of these addiction-linked behavioural traits may provide new targets for pharmacological intervention in addiction. In this article we review putative applications of drugs targeting the endocannabinoid system in ameliorating impulsivity and anxiety.

Endocannabinoids are lipid-derived substances found mainly in the DA-rich basal ganglia, which play a major role in regulating synaptic function and plasticity in the striatum (Lovinger and Mathur, 2012). Cannabinoid receptors in the brain mediate the effects of cannabis (or marijuana), a widely abused drug that carries significant adverse health effects, especially among young people (Volkow *et al.*, 2014). Nevertheless, considerable work, reviewed below, suggests that pharmacological modulation of the endocannabinoid system can moderate high levels of anxiety and impulsivity and attenuate the reinstatement of drug seeking. We first review the defining features and neural substrates of impulsivity and anxiety before considering how these addiction-relevant traits can be selectively modulated by compounds that facilitate or suppress the function of the endocannabinoid system. Finally, we discuss the implications of this research for the treatment of drug addiction.

Impulsivity and addiction

Impulsivity is a heterogeneous construct defining behaviours that are premature, poorly planned, inappropriate, risky and poorly inhibited (Monterosso and Ainslie, 1999; Evenden, 1999b). Although it can be advantageous to take risks in certain circumstances, when excessively and inappropriately expressed, impulsiveness can lead to suboptimal outcomes (Dickman, 1990). Moreover, impulsivity has been suggested to contribute to specific disorders such as addiction, attention deficit hyperactivity disorder, obsessive–compulsive disorder, bipolar disorder, aggression, self-harm and suicidality (Moeller *et al.*, 2001; Skegg, 2005; Hawton and van Heeringen, 2009; Coccaro *et al.*, 2011; Bari and Robbins, 2013). As a result, therefore, there has been a growing interest in investigating the biological mechanisms of impulsivity to facilitate the development of new therapies for a range of neuropsychiatric disorders (Jupp and Dalley, 2014).

Different classifications have been proposed to define impulsivity, which can be deconstructed in several ways (Evenden, 1999b). In its simplest forms, impulsivity can be divided into (i) impulsive action, involving impaired motor inhibition, and (ii) impulsive choice, defined by the abnormal preference for small immediate or likely rewards versus larger-magnitude but delayed or uncertain rewards (Pattij and Vanderschuren, 2008; Dalley and Roiser, 2012). On the basis of this dichotomy a variety of tests have been developed for studying impulsivity in humans and laboratory animals (Winstanley, 2011; Jupp *et al.*, 2013). Impulsive action can be assessed as responses that are premature, mistimed or difficult to suppress. Some of the main paradigms are the 5-choice serial reaction time task (5-CSRTT) and its analogues (Robbins, 2002; Voon *et al.*, 2014), the stop-signal reaction time task (Eagle *et al.*, 2008), the go/no go task (Harrison *et al.*, 1999) and differential reinforcement of low rates of responding (Evenden, 1999a). Impulsive choice can be assessed by tasks that measure aversion for delayed rewards and are often referred to as delay discounting procedures (Monterosso and Ainslie, 1999; Bari and Robbins, 2013).

Neurally, impulsivity depends on subregions of the prefrontal cortex (PFC), basal ganglia (particularly the ventral region of the striatum), hippocampus, and modulation

by serotonin (5-HT), DA and NA (Evenden, 1999a, 1999b; Cardinal *et al.*, 2004; Pattij and Vanderschuren, 2008; Dalley *et al.*, 2011; Dalley and Roiser, 2012). In humans, the delineation of substrates underlying impulsivity has relied on neuroimaging and psychological analysis in healthy individuals and patients with brain damage or psychiatric disorders such as attention deficit hyperactivity disorder (Castellanos *et al.*, 2006; Garavan and Hester, 2007). In experimental animals, considerable research has shown that distinct corticostriatal 'loops' underlie several distinct forms of impulsivity (Winstanley, 2011), including the proposed subdivision of waiting versus stopping impulsivity (Dalley *et al.*, 2011). Work over many years has established that impulsivity, in its many forms, is sensitive to modulation by drugs that affect monoaminergic transmission, including psychostimulant drugs (Pattij and Vanderschuren, 2008) and drugs that block the reuptake of catecholamines in the brain such as atomoxetine (Economidou *et al.*, 2012; Ansquer *et al.*, 2014; Feldman and Reiff, 2014). Increasingly, however, current research has shifted to new targets that offer putative explanatory mechanisms, including evident GABA-ergic dysfunction in the nucleus accumbens core of trait impulsive rats (Caprioli *et al.*, 2014) and pharmacological agents that reduce both impulsivity and addiction-like behaviours in animal models (Jupp and Dalley, 2014). This research has revealed several promising lead compounds targeting cholinergic, glutamatergic and opioid-ergic transmission, in addition to continued interest in the endocannabinoid system (Pattij and Vanderschuren, 2008).

Impulsivity is a widely recognized risk marker for addiction (Perry and Carroll, 2008; Verdejo-García *et al.*, 2008; de Wit, 2009) predicting the onset and escalation of drug use (Diergaarde *et al.*, 2008; Zernicke *et al.*, 2010; Dalley *et al.*, 2011), rates of relapse (Economidou *et al.*, 2009; Ersche *et al.*, 2010), and the development of compulsive drug-taking (Belin *et al.*, 2008). It is widely recognized that impulsive choice for immediate rewards is present in opiate addicts (Kirby and Petry, 2004), alcoholics (Vuchinich and Simpson, 1998) and stimulant abusers (Kirby and Petry, 2004; Monterosso *et al.*, 2007). Other forms of impulsivity, including impulsive action, as assessed with such tasks as the stop-signal reaction time task and go/no go, are evident in alcoholics (Noël *et al.*, 2007), and abusers of cocaine (Fillmore and Rush, 2002; Hester and Garavan, 2004) and methamphetamine (Monterosso *et al.*, 2005). On the basis of the research in experimental animals different subtypes of impulsivity appear to affect distinct stages of drug addiction. Thus, increased impulsive action on the 5-CSRTT was found to predict an increased motivation to initiate and maintain nicotine self-administration, whereas impulsive choice on a delay discounting procedure predicted impaired inhibition of drug seeking and an higher probability for relapse (Diergaarde *et al.*, 2008).

Impulsivity may also arise, in turn, as a consequence of chronic drug abuse through perturbation of prefrontal cortical control over basal ganglia function (Jentsch and Taylor 1999). As a result impulsivity has been hypothesized to facilitate the shift in behavioural control over drug-taking from the PFC to the striatum, as well as promoting a maladaptive ventral to dorsal striatal transition in the control over drug seeking (Everitt and Robbins, 2005). Elucidating the molecular mechanisms underlying the transitions from initial drug use to habitual and eventual compulsive drug taking remains an area of intensive research activity (Belin *et al.*, 2013; Everitt, 2014).

Anxiety and addiction

Anxiety is postulated to contribute to an evolutionary preserved repertory that prepares and optimizes behavioural and physiological defensive responses for approaching, confronting, avoiding or escaping innate or learnt threatening stimuli (Canteras *et al.*, 2010). However, excessive levels of anxiety may impair performance and lead to suboptimal behavioural responses and ultimately to psychiatric disorders including generalized anxiety disorder, panic disorder, post-traumatic stress disorder and obsessive–compulsive disorder. Such disorders are highly prevalent and have significant individual and social impacts (Kessler *et al.*, 2010).

Anxiety is often assessed as a subjective state in humans in conjunction with objective measures of autonomic function (Canteras *et al.*, 2010). In laboratory rodents, anxiety-like responses can be quantified by measuring avoidance or escape responses to innate or conditioned aversive stimuli. Typical tests include the elevated mazes and the light–dark shuttle box, which assess ethological aspects of fear, in addition to tests of conditioned aversive responses to cues and contexts previously paired with noxious stimuli (Cryan and Sweeney, 2011; Blanchard *et al.*, 2013). The neuroanatomical substrates of anxiety-related behaviours have been extensively investigated and include the amygdala-ventral striatal interactions underlying cue-conditioned fear, the hippocampal-dependent processing of contextual fear, the medial hypothalamic nuclei and the periaqueductal grey underlying escape behaviour, and the PFC in stress and extinction of conditioned aversive responses (Canteras *et al.*, 2010). A number of neurotransmitters modulate anxiety-related responses, including GABA and the monoamines 5-HT and NA, which are the major targets for currently available anxiolytic drugs, as well as glutamate, DA and the endocannabinoids (Griebel and Holmes, 2013).

Anxiety and exaggerated stress-related responses are known to predispose to drug use (Cleck and Blendy, 2008; Kessler *et al.*, 2010) whilst facilitating the acquisition of stimulant drug self-administration (Piazza and Le Moal, 1998). Furthermore, the interruption of chronic

drug consumption results in the emergence of negative emotional states that lie at the core of the motivational withdrawal/abstinence syndrome, one of the major catalysts for relapse and persistent drug-taking behaviour (Koob and Le Moal, 1997, 2008). This shift in motivational state is a putative consequence of neural adaptations resulting from chronic drug exposure and involves, in particular, the recruitment of locus coeruleus noradrenergic neurons and corticotrophin-releasing factor in the central nucleus of the amygdala and the bed nucleus of the stria terminalis (Koob, 2008). Thus, the anxiety and stress systems of the brain have a major impact on the escalation and persistence of drug abuse. In experimental animals, trait anxiety-like behaviour predicts the escalation of intravenous cocaine self-administration, but not an increased propensity to acquire cocaine self-administration (Dilleen *et al.*, 2012), indicating that high anxiety may be a predisposing endophenotype underlying the loss-of-control over cocaine intake. These data further suggest that the mechanisms underlying the initiation of drug use are not necessarily the same as those contributing to the development of addiction. Anxiety also correlates with vulnerability to alcohol intake. Thus, a high comorbidity between anxiety disorders and alcohol abuse has been reported; this has led to the tension-reduction hypothesis, which posits that anxious or stressed individuals tend to consume more alcohol to alleviate anxiety (Cappell and Herman, 1972; Pohorecky, 1981; Young *et al.*, 1990). Accordingly, experimental studies in rats show that higher levels of anxiety-like behaviour in the elevated plus maze predicts higher alcohol intake and escalation of intake in voluntary drinking procedures compared with low-anxious animals (Spanagel *et al.*, 1995; Hayton *et al.*, 2012). Such findings accord with the notion that many drugs may be used to self-medicate high levels of anxiety and other negative emotional states (Khantzian, 1985).

Cannabis sativa, cannabinoids and the endocannabinoid system

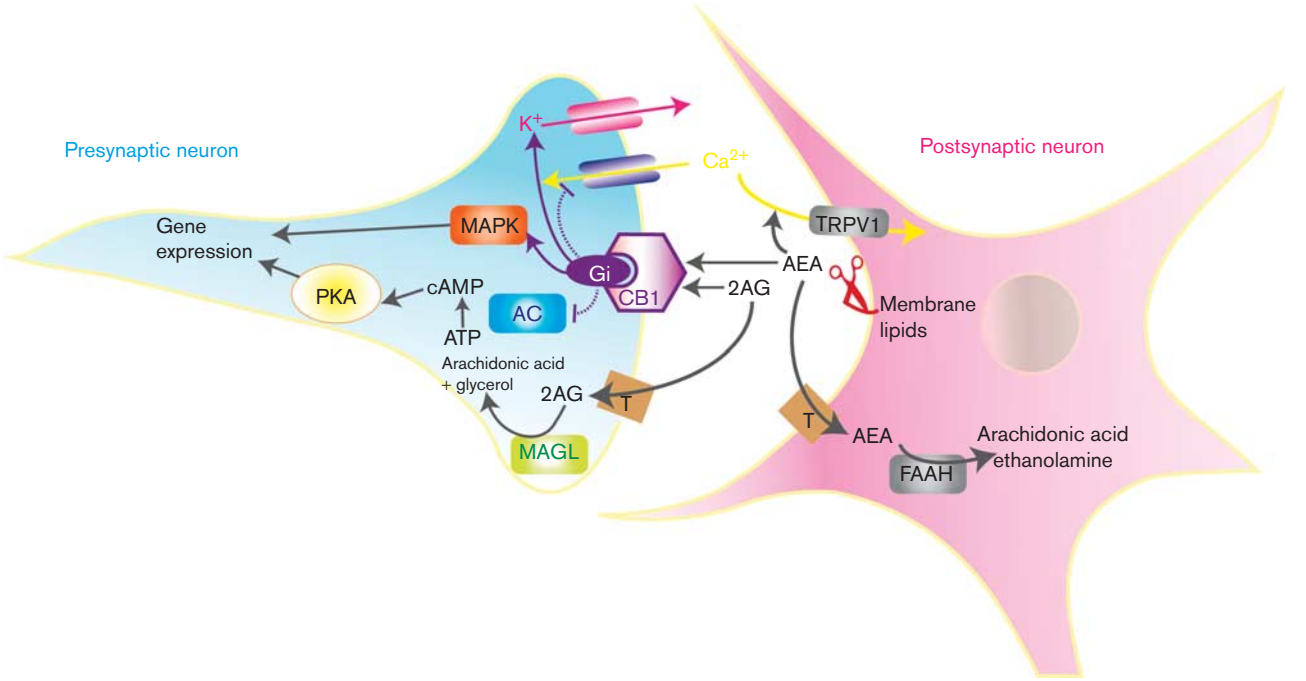
Biochemical and neurophysiological processes that inherent to the endocannabinoid system have been extensively reviewed elsewhere (Howlett *et al.*, 2002; Piomelli, 2003; Di Marzo, 2008; Pertwee *et al.*, 2010; Castillo *et al.*, 2012). Here we provide a brief synopsis of endocannabinoid pharmacology and its relevance to impulsivity, anxiety and addiction.

The endocannabinoid system is named after the herb *Cannabis sativa* ('hashish', 'marijuana'), which although widely abused can have beneficial effects in some settings (Zuardi, 2006; Russo, 2007). Its main active constituent Δ^9-tetrahydrocannabinol (Δ^9-THC) is one of more than 60 compounds, termed phytocannabinoids, found in *C. sativa* (Mechoulam, 1970). The chemical characterization of this plant and subsequent development of synthetic cannabinoids provided the impetus for the identification and cloning of the major brain expressed cannabinoid-1 (CB1) receptor (Devane *et al.*, 1988; Matsuda *et al.*, 1990), which is Gi-protein-coupled (Fig. 1) and densely expressed throughout the brain, particularly in mesocorticolimbic brain areas (Herkenham *et al.*, 1990, 1991b; Tsou *et al.*, 1998). Soon after the discovery of the CB1 receptor, the endogenously produced cannabinoid (endocannabinoid) and arachidonic acid derivative, arachidonoylethanolamide (AEA) was isolated and coined with the name anandamide after the Sanskrit word for 'bliss' (Devane *et al.*, 1992). Subsequently, a second metabotropic cannabinoid receptor was discovered, the cannabinoid-2 (CB2) receptor (Munro *et al.*, 1993) as well as a second endocannabinoid, 2-arachidonoyl glycerol (2-AG) (Mechoulam *et al.*, 1995). Interestingly, although CB2 receptors are postulated to be predominately expressed in the peripheral immune system, with low expression levels in the brain, CB2 selective compounds can modulate several centrally mediated processes, including cocaine reward (Onaivi *et al.*, 2006; Xi *et al.*, 2011).

The synaptic effects of anandamide are mainly terminated by cellular uptake and hydrolytic catabolism by fatty acid amide hydrolase (FAAH) (Di Marzo *et al.*, 1994; Cravatt *et al.*, 1996; Beltramo *et al.*, 1997). By contrast, the inactivation of 2-AG is mediated by monoacylglycerol lipase (MAGL) (Dinh *et al.*, 2002). Unlike conventional neurotransmitters and modulators, endocannabinoids act as retrograde neural messengers (Wilson and Nicoll, 2002), being synthesized from membrane lipids of postsynaptic neurons in response to increased neural activity. Newly synthesized endocannabinoids diffuse across the synaptic cleft where they activate CB1 receptors located on presynaptic terminals. The CB1 receptor is coupled to a myriad of signal transduction mechanisms, initiated by Gi-protein activation and culminating in the inhibition of adenylate cyclase, the activation of MAP kinase, inhibition of calcium influx, and facilitation of potassium efflux. Collectively, these interactions result in the inhibition of neuronal activity and neurotransmitter release (Egertova *et al.*, 1998; Pettit *et al.*, 1998; Kreitzer and Regehr, 2001; Ohno-Shosaku *et al.*, 2001; Wilson and Nicoll, 2001). It should be noted, however, that CB1 receptor expression and function is not necessarily exclusively mediated at presynaptic terminals and that other receptors and endocannabinoids have been proposed; these include the transient receptor potential vanilloid type-1 channel (TRPV1) for which anandamide may act as the main endogenous agonist (Starowicz *et al.*, 2007) (Fig. 1).

Cannabinoids are known to regulate the activity of a number of neuroactive substances through effects mediated presynaptically by CB1 receptors located on glutamatergic and GABA-ergic nerve terminals (Katona *et al.*, 1999; Marsicano and Lutz, 1999; Hermann *et al.*, 2002; Julian *et al.*, 2003; Katona *et al.*, 2006; Haring *et al.*, 2007). Activation of CB1 receptors inhibits the release of

Fig. 1



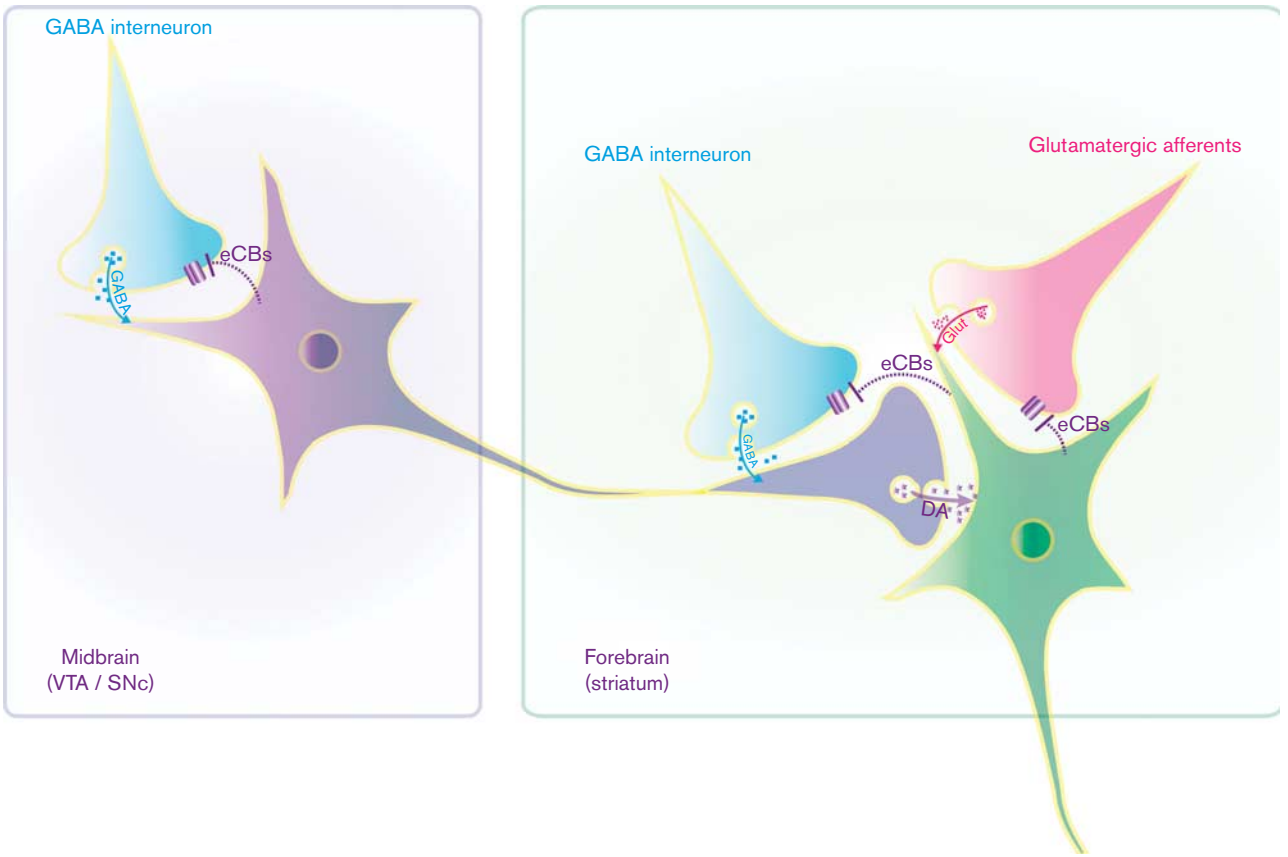
A schema of the currently proposed model for endocannabinoid neurotransmission. Anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) are synthesized and released from postsynaptic membranes to activate Gi-protein-coupled CB1 cannabinoid receptors. This interaction initiates a cascade of signal transduction mechanisms that include inhibition of adenylate cyclase (AC), activation of MAP kinase (MAPK), inhibition of calcium influx and facilitation of potassium efflux. AEA also activates transient receptor potential vanilloid type-1 (TRPV1) channels to facilitate calcium influx. The effects of AEA and 2-AG are terminated by internalization facilitated by a specific membrane transporter (T), followed by hydrolysis by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively.

glutamate, GABA and acetylcholine in the nucleus accumbens (Schoffelmeer *et al.*, 2006) where it also suppresses excitatory transmission at glutamatergic synapses (Robbe *et al.*, 2002; Fig. 2). In addition, stimulation of CB1 receptors increases the firing rate of dopaminergic neurons and facilitates DA release in the nucleus accumbens through a GABA-ergic disinhibitory mechanism (Chen *et al.*, 1990; French, 1997; Tanda *et al.*, 1997; Sperlagh *et al.*, 2009). Endocannabinoids can therefore strongly influence information processing in the striatum by modulating DA inputs not only from the ventral tegmental area (Szabo *et al.*, 2002; Riegel and Lupica, 2004; Melis *et al.*, 2004b) but also the substantia nigra zona compacta innervating the dorsal striatum (Melis *et al.*, 2000; Szabo *et al.*, 2000), as well as excitatatory glutamatergic afferents from the PFC (Fitzgerald *et al.*, 2012). CB1 receptors are densely located in the ventral and dorsal striatum (Herkenham *et al.*, 1990, 1991a; Herkenham, 1992; Tsou *et al.*, 1998) where they are present on medium spiny neurons (Rodriguez *et al.*, 2001; Pickel *et al.*, 2006) positive for D1 and D2 receptors (Hermann *et al.*, 2002; Robbe *et al.*, 2002; Monory *et al.*, 2007; Martin *et al.*, 2008) and glutamatergic terminals (Fitzgerald *et al.*, 2012). The endocannabinoid hydrolyzing enzymes, FAAH and MAGL, are also expressed in the striatum and related projection areas (Egertova *et al.*, 1998). Thus, endocannabinoids are ideally placed to fine-tune processing in mesocorticolimbic brain networks by regulating inhibitory and excitatory synaptic transmission (Sidhpura and Parsons, 2011; El Khoury *et al.*, 2012).

The endocannabinoid system and impulsivity

An involvement of the endocannabinoid system in impulsivity has come to light from current research in humans and experimental animals. In this regard marijuana users tend to have higher levels of impulsivity than nondrug abusing controls (Cousijn *et al.*, 2013; Dougherty *et al.*, 2013). Acute use of this drug induces altered time perception, psychomotor and cognitive impairment, reduced inhibitory control, and increased risk-taking behaviour (Hall and Solowij, 1998; Iversen, 2003; Murray *et al.*, 2007). Moreover, Δ^9-THC administration to healthy volunteers elicits impulsive responding on the stop-signal task but has no effect on delay discounting or go/no-go discriminative performance (McDonald *et al.*, 2003). The impairing effect of Δ^9-THC on stopping behaviour has been replicated (Ramaekers *et al.*, 2006b; Van Wel *et al.*, 2013) and is generally consistent with the disruptive effects of marijuana on tasks requiring motor inhibition and risk evaluation (Lane *et al.*, 2005; Ramaekers *et al.*, 2006a; Metrik *et al.*, 2012).

Fig. 2



Brain loci underlying the modulation of dopamine (DA)-mediated neurotransmission by the endocannabinoid system. Endocannabinoids (eCBs) inhibit local gamma-aminobutyric acid (GABA)-ergic interneurons that synapse on dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SNc). In the striatum, eCBs inhibit glutamate (Glut) release from afferents arising from different cortical regions (e.g. prefrontal cortex, amygdala, hippocampus) and indirectly stimulates dopamine release by inhibiting GABA-ergic interneurons.

Complementary research in rodents confirms a role of the endocannabinoid system in specific subtypes of impulsivity, as summarized in Table 1. Thus, although acute administration of Δ^9-THC was reported not to affect impulsivity assessed by the 5-CSRTT this substance decreased impulsivity on a delay discounting task, an effect that was blocked by the CB1 receptor antagonist/inverse CB1 receptor agonist, rimonabant (Wiskerke *et al.*, 2011). In other studies, the synthetic cannabinoid WIN55,212-2 had no effect on impulsivity assessed on a lateralized reaction time task (Arguello and Jentsch, 2004) or the 5-CSRTT (Pattij *et al.*, 2007). Interestingly, however, this compound normalized enhanced levels of delay discounting impulsivity in spontaneously hypertensive rats compared with Wistar–Kyoto rats (Adriani *et al.*, 2003). These rats also exhibit a reduced density of CB1 receptors in the PFC, suggesting a potential contribution of the endocannabinoid system in this region to the enhanced levels of impulsivity (Adriani *et al.*, 2003). Anandamide, a non-selective endogenous ligand exerts a plethora of effects through multiple mechanisms, including the TRPV1 channel. Systemic administration of this cannabinoid reduced anticipatory responding (i.e. impulsivity) on the 5-choice task; however this compound also significantly increased omission errors, possibly reflecting attentional interference (Panlilio *et al.*, 2009). Intriguingly, these effects were blocked by the TRPV1 antagonist capsazepine, but not rimonabant. However, the FAAH inhibitor, URB597, which increases endogenous levels of anandamide, failed to mimic the effects of anandamide (Panlilio *et al.*, 2009).

To date the majority of studies have focused on the blockade of the endocannabinoid system in the assessment of impulsivity. Rimonabant has been widely used for this purpose and has shown to be effective, for example, in reducing impulsivity on the 5-choice task but not the delay discounting task (Pattij *et al.*, 2007). This relatively selective effect on motor impulsivity was later confirmed and extended to other CB1 receptor antagonists (O-2050, SLV330), which unlike rimonabant do not act as an inverse agonist at the CB1 receptor (De Bruin

Table 1 A summary of the effects of acute pharmacological interventions on the endocannabinoid system on two major subtypes of impulsivity in experimental animals

Substance (dose)	Subjects	Impulsive action	Impulsive choice	References
Cannabinoids				
Δ^9-THC (0.5, 1, 2[a] mg/kg)	Wistar rats	=	↓	Wiskerke *et al.* (2011)
WIN55,212–2 (2[a] mg/kg)	Wistar–Kyoto rats	X	=	Adriani *et al.* (2003)
	Spontaneously hypertensive rats (highly impulsive)	X	↓	
WIN55,212–2 (1, 2.5 mg/kg)	Long-Evans rats	=	X	Arguello and Jentsch (2004)
WIN55,212–2 (0.3, 1, 3 mg/kg)	Wistar rats	=	=	Pattij *et al.* (2007)
CB1 receptor antagonists/inverse agonists				
Rimonabant (0.1, 0.5, 1 mg/kg)	Long-Evans rats	=	X	Arguello and Jentsch (2004)
Rimonabant (0.3[a], 1[a], 3[a] mg/kg)	Wistar rats	↓	=	Pattij *et al.* (2007)
Rimonabant (1[a], 3[a] mg/kg)	Wistar rats	↓	=	Wiskerke *et al.* (2011)
		↓[b]	↑[c]	
Rimonabant (1, 3[a] mg/kg)	Wistar rats	↓[d]	X	Wiskerke *et al.* (2012)
		=[e]	X	
Rimonabant (1[a], 3, 10[a] mg/kg)	Lean Zucker rats	X	↑	Boomhower *et al.* (2013)
	Obese Zucker rats(highly impulsive)	X	↓	
Rimonabant (1.5 mg/kg)	Long-Evans Rats	X	↓[f]	Hernandez *et al.* (2014)
O-2050 (0.3[a], 1[a], 3[a] mg/kg)	Wistar rats	↓	=	Wiskerke *et al.* (2011)
		↓[b]	↑[c]	
SLV330 (1, 3[a], 10[a] mg/kg)	Wistar rats	↓	X	De Bruin *et al.* (2011)

Modulation of stimulant-induced changes in impulsivity.
↑, increased impulsivity; ↓, decreased impulsivity; =, no effect; X, not investigated; CB1, cannabinoid-1; Δ^9-THC, Δ^9-tetrahydrocannabinol.
[a]Effective doses.
[b]Amphetamine-induced high impulsivity.
[c]Amphetamine-induced low impulsivity.
[d]Nicotine-induced high impulsivity.
[e]GBR12909-induced high impulsivity.
[f]Chronic cocaine-induced high impulsivity.

et al., 2011; Wiskerke *et al.*, 2011). Both compounds were also effective in attenuating the effects of amphetamine on delay discounting and motor impulsivity (Wiskerke *et al.*, 2011). Subsequently, rimonabant was shown to antagonize nicotine-induced motor impulsivity (Wiskerke *et al.*, 2012) and cocaine-induced impulsivity in a delay discounting task (Hernandez *et al.*, 2014). Rimonabant has also been investigated in obese Zucker rats, which show a preference for immediate, small-magnitude rewards compared with lean rats. Obese rats also exhibit increased levels of endocannabinoids and higher CB1 receptor expression in brain regions that regulate feeding (Boomhower *et al.*, 2013). Consistent with a role of CB1 receptors in mediating behavioural choice in the delay discounting paradigm rimonabant reduced impulsivity in obese Zucker rats but increased impulsivity in lean rats (Boomhower *et al.*, 2013). Given the paucity of studies in this field it is difficult to draw firm conclusions. Nevertheless, CB1 receptor antagonists appear to reduce impulsivity in a baseline-dependent manner, particularly when this behaviour is elevated in various trait models or evoked by psychostimulant drugs. Interestingly, the same profile of effects can be achieved using selective CB2 receptor agonists (e.g. JWH133) in DBA/2 mice, which express a number of behaviours, including some that appear to reflect increased impulsivity (Navarrete *et al.*, 2012). Notably, DBA/2 mice also show higher levels of CB2 receptor expression in the cingulate cortex, nucleus accumbens, and amygdala compared with a less impulsive mouse strain (Navarrete *et al.*, 2012).

The studies reviewed above have mainly investigated the acute effects of cannabinoids on impulsivity. Yet an important question is whether evident neurocognitive impairment in adolescent cannabis users (Hester *et al.*, 2009; Gonzalez *et al.*, 2012; Solowij *et al.*, 2012), including increased risky and impulsive decision-making (Solowij *et al.*, 2012), extends well into adulthood. Possibly relevant to this question are data showing that inhibition of anandamide hydrolysis during adolescence, a manipulation that persistently stimulates endocannabinoid receptors, blocked the expected increase in impulsivity of adult rats previously deprived of early maternal contact (Marco *et al.*, 2007). This interesting and potentially important study merits further research to understand how the endocannabinoid system influences the developmental trajectory of inhibitory control circuitry during adolescence, which also has an impact on social behaviours during this period (Trezza and Vanderschuren, 2008; Trezza *et al.*, 2014).

The endocannabinoid system and anxiety

The involvement of the endocannabinoid system in anxiety has been more extensively investigated than its role in impulsivity (Viveros *et al.*, 2005; Moreira and Lutz, 2008; Moreira and Wotjak, 2010; Marco *et al.*, 2011). *C. sativa* induces a well-described state of relaxation and reduced anxiety; unfortunately, however, this has not been easily demonstrated in experimental settings. Studies administering pure Δ^9-THC or synthetic CB1 receptor agonists to laboratory animals report complex findings, which depend on the dose, route of

administration, and animal species used (Viveros *et al.*, 2005). Also, the effects of CB1 receptor agonists depend on environmental stress, which may vary between different laboratories. As a general rule, however, low doses of cannabinoids tend to have anxiolytic effects, whereas higher doses induce anxiogenic effects (Moreira and Wotjak, 2010; Marco *et al.*, 2011). Finally, the anxiolytic-like properties of CB1 receptor agonists are often restricted by nonspecific motor impairment resulting in narrow dose–response effects. Despite this complexity, however, the anxiolytic-like effects of CB1 receptor agonists can be reliably detected under appropriate doses and experimental conditions (Moreira and Lutz, 2008).

As an alternative, drugs that increase endogenous levels of anandamide by inhibiting its neuronal internalization and/or hydrolysis diminish anxiety-like responses in animals with a more favourable pharmacological profile compared with CB1 receptor agonists (Moreira and Wotjak, 2010). Anandamide is normally produced and released at low physiological levels but its synthesis and release increases in response to increased neural activation (Piomelli, 2003). Interestingly, FAAH inhibitors, which increase anandamide levels, appear to have more consistent effects on anxiety responses under highly aversive conditions, presumably because anandamide appears to be recruited as a protective mechanism in response to stress (Kathuria *et al.*, 2003; Patel and Hillard, 2006; Naidu *et al.*, 2007; Moreira *et al.*, 2008). Recent research has revealed that blocking the degradation of 2-AG may also be a useful approach to reduce anxiety-like responses (Busquets-Garcia *et al.*, 2011). Endocannabinoid hydrolysis inhibitors may therefore be a promising strategy for developing new anxiolytic drugs (Batista *et al.*, 2014). Intriguingly, the effect of MAGL inhibitors appears to be mediated by CB2 rather than CB1 receptors (Busquets-Garcia *et al.*, 2011) and confirms recent interest in the CB2 receptor as a target to modulate aversive responses (Garcia-Gutierrez *et al.*, 2012). Alternative potential targets include: (i) the TRPV1 channel, whose function in modulating anxiety seems to be diametrically opposite to the CB1 receptor (Moreira and Wotjak, 2010; Moreira *et al.*, 2012b); (ii) dual FAAH and TRPV1 blockade (Micale *et al.*, 2009) and (iii) site-specific inhibition of cyclo-oxygenase (Hermanson *et al.*, 2013).

The effects of CB1 receptor antagonists/inverse agonists, particularly rimonabant and AM251, have been extensively investigated in experimental animals and, in the case of rimonabant, in humans as well (Bergamaschi *et al.*, 2014). Most studies demonstrate that these compounds tend to magnify responses to aversive stimuli in mice and rats. Thus, in tests used to assess anxiety, they exert anxiogenic-like effects (Moreira and Wotjak, 2010) and impair the extinction of conditioned aversive memories (Marsicano *et al.*, 2002). CB1 receptor blockade also interferes with stress coping responses and increases the activation of the neuroendocrine stress axis, with possible implications for mood regulation in humans (Hill *et al.*, 2009; Gunduz-Cinar *et al.*, 2013). These preclinical data have been confirmed in humans treated with rimonabant for obesity. The clinical efficacy of rimonabant was similar to other antiobesity drugs, with a modest reduction in body weight, but unfortunately its use was accompanied by anxiety, depression and suicidal thoughts (Moreira and Crippa, 2009). The CB1 receptor exhibits constitutive activity when expressed in artificial cell systems, in which rimonabant and other cannabinoid blockers act as inverse agonists. Thus, neutral antagonists have been investigated as a safer alternative to reduce CB1-mediated signalling (McLaughlin, 2012) These compounds reduce body weight similarly to rimonabant, without inducing anxiogenic-like effects or reducing motivation for reward in rats (Sink *et al.*, 2010; Meye *et al.*, 2013). This research opens the interesting possibility of dissociating the effects of CB1 receptors on motivation and aversion based on constitutive receptor activity, with potential therapeutic implications. A summary of the predominant effects on anxiety of pharmacological interventions that target the endocannabinoid system is shown in Table 2.

The neuroanatomical loci underlying the effects of cannabinoid-related compounds on anxiety have been extensively investigated using selective molecular approaches and intracranial pharmacology. As anticipated from their behavioural pharmacological profile, cannabinoids modulate brain regions involved in generating defensive responses against stressful and threatening stimuli, including the medial PFC, amygdala, hippocampus and the midbrain periaqueductal grey (Moreira *et al.*, 2012a). Neurochemically, these effects involve interactions with various neurotransmitters and neuromodulators, including GABA, glutamate, 5-HT and DA (Marco *et al.*, 2004; Bambico *et al.*, 2010; Terzian *et al.*, 2011; Rey *et al.*, 2012). Through such mechanisms, facilitation of the endocannabinoid system leads to a reduction in aversive responses to both innate and

Table 2 A summary of the effects of genetic and pharmacological interventions on the endocannabinoid system on anxiety-like responses

Target	Main effects of pharmacological activation on anxiety	Main effects of pharmacological or genetic inhibition on anxiety
CB1	↓[a]	↑[b,c]
CB2	?	?
TRPV1	↑	↓
AT	–	↓
FAAH	–	↓[d]
MAGL	–	↓

↓, anxiolytic; ↑, anxiogenic; ?, unclear; AT, membrane anandamide transporter; CB1, cannabinoid type-1 receptor; CB2, cannabinoid type-2 receptor; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; TRPV1, transient receptor potential vanilloid type-1 channel.

[a]Tends to be anxiolytic at low doses and anxiogenic at high doses.

[b]Increase anxiety particularly under highly aversive environments.

[c]Inverse agonists are more anxiogenic than neutral antagonists.

[d]Anxiolytic-like effects tent to be more consistent under highly aversive environment.

conditioned threatening stimuli whilst facilitating the extinction of already acquired aversive responses (Moreira and Wotjak, 2010; Marco *et al.*, 2011).

Implications for addiction

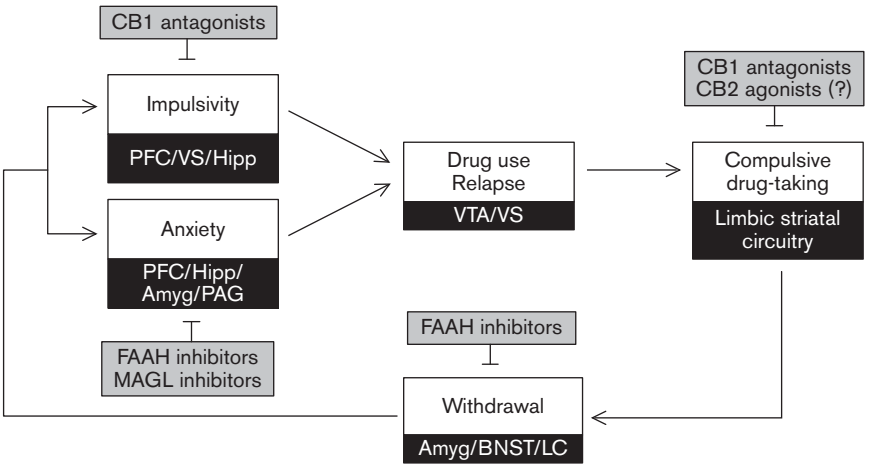
On the basis of the research findings reviewed above some general conclusions can be made about the putative efficacy of cannabinoid-based compounds to treat addiction. Impulsivity and anxiety have been extensively investigated as behavioural endophenotypes in addiction (Koob and Le Moal, 1997, 2008; Jentsch and Taylor 1999; Everitt *et al.*, 2008; Dalley *et al.*, 2011; Ersche *et al.*, 2012) where their causal impacts appear to manifest at quite distinct stages of the addiction process. Specifically, whereas impulsivity is widely regarded as an antecedent behavioural marker involved in the initiation of drug use and in facilitating the development of stimulant addiction (Kreek *et al.*, 2005; Belin *et al.*, 2008; Koob and Le Moal, 2008; Dalley *et al.*, 2007) anxiety is considered to have its greatest impact following protracted drug use where continued drug intake increasingly comes to depend on negative reinforcement mechanisms (Koob and Le Moal, 2008). Leaving aside the possibility that the separation between impulsivity and anxiety, in terms of temporally distinct risk markers for addiction, could be driven in part by the class of predominately abused drug (i.e. stimulants vs. opiates/alcohol) cannabinoid-based treatments may have utility during both the early and late stages of addiction. Thus, for example, whereas natural and synthetic cannabinoids reduce inhibitory control and increase risk-taking behaviour (Tanda *et al.*, 1997; Giuffrida *et al.*, 1999; Melis *et al.*, 2004a; Lafourcade *et al.*, 2007; Pillolla *et al.*, 2007; Sperlagh *et al.*, 2009; Chiu *et al.*, 2010), CB1 receptor antagonists generally strengthen impulse control (Pattij *et al.*, 2007) thereby putatively reducing the initiation of drug abuse and later emergence of compulsive drug intake in vulnerable individuals (Fig. 3).

Notably, CB1 receptor antagonists attenuate several drug-evoked/motivated behaviours, including sensitization, self-administration and reinstatement (De Vries *et al.*, 2001; Gerdeman *et al.*, 2008; Xi *et al.*, 2008). Likewise, CB1 receptor antagonists block the acquisition and expression of nicotine-induced conditioned place preference in rats and mice (Le Foll and Goldberg, 2004; Merritt *et al.*, 2008) and reduce self-administration of this drug (Cohen *et al.*, 2002; Shoaib, 2008). CB1 receptor antagonists also reduce opioid and alcohol intake. Indeed, there is evidence for functional interactions between the endogenous cannabinoid and opioid systems. Thus, CB1 receptor antagonists and genetic deletion of the CB1 receptor impair conditioned place preference and self-administration of morphine and heroin (Navarro *et al.*, 2001; De Vries *et al.*, 2003; Solinas *et al.*, 2003). Moreover, CB1 receptor antagonists reduce ethanol consumption and conditioned place preference (Arnone *et al.*, 1997; Wang *et al.*, 2003; Economidou *et al.*, 2006). In addition, CB1 receptor knock-out mice show reduced responses to alcohol (Houchi *et al.*, 2005; Thanos *et al.*, 2005).

There is thus substantial evidence that CB1 receptor antagonists reduce responses to drugs of various classes, including cocaine, nicotine, opioids and alcohol (for a detailed review, see Serrano and Parsons, 2011). It should be noted, however, that CB1 receptor antagonists can augment the consequences of aversive stimuli, as discussed above, and may therefore be more appropriate as therapeutic agents for individuals in which impulsivity, rather than anxiety, is the driving endophenotype in addiction. In this regard, neutral antagonists, lacking inverse agonistic actions, might represent a superior approach, as discussed above. In addition, interventions targeting the CB2 receptor may have utility since selective CB2 receptor agonists reduce impulsivity (Navarrete *et al.*, 2012), as well as the primary reinforcing actions of cocaine, effects that are presumed to depend on the mesocorticolimbic dopaminergic systems (Xi *et al.*, 2011). Furthermore, pharmacological blockade or genetic deletion of this receptor reduces nicotine-induced conditioned place preference and self-administration in mice (Navarrete *et al.*, 2013). CB2 receptor knock-out mice also exhibit increased responses to ethanol in both conditioned place preference and self-administration paradigms (Ortega-Álvaro *et al.*, 2013). However, the precise mechanism through which CB2 receptors modulate drug-motivated behaviours requires further elucidation.

Therapies targeting the endocannabinoid system may be useful adjuncts to treat anxiety and elevated stress associated with chronic addiction (Fig. 3). As reviewed above, much research suggests that the endocannabinoid system functions as a protective mechanism against diverse forms of aversive stimuli and is a key modulator of anxiety, stress and depression (Hill *et al.*, 2009; Moreira and Wotjak, 2010; Gunduz-Cinar *et al.*, 2013). Natural and synthetic CB1 receptor agonists can attenuate anxiety-like behaviour at specific doses but with ancillary effects on motor and mnemonic functions and with attendant psychotomimetic effects, these compounds do not represent an attractive approach to treat addiction. Indeed, CB1 receptor stimulation can facilitate drug-induced and cue-induced relapse, possibly by indirectly stimulating the dopaminergic mesocorticolimbic pathways (Fattore *et al.*, 2007). As an alternative, the CB2 receptor has emerged as a potential target for alleviating anxiety (Garcia-Gutierrez *et al.*, 2012) and reportedly reducing impulsivity in rodents (Navarrete *et al.*, 2012). In addition, FAAH inhibitors selectively enhance the 'on-demand' actions of anandamide and attenuate anxiety and stress responses (Moreira *et al.*, 2012b). Thus, FAAH, and possibly MAGL inhibitors as well, may be useful therapies to alleviate withdrawal symptoms that trigger relapse and perpetuate drug use (Panlilio *et al.*, 2013).

Fig. 3



Putative sites of action of compounds selective for the endocannabinoid system underlying the remediation of impulsivity, anxiety and perpetuation of drug abuse. Amyg, amygdala; BNST, bed nucleus of the stria terminalis; CB1, cannabinoid-1 receptor; CB2, cannabinoid-2 receptor; FAAH, fatty acid amide hydrolase; Hipp, hippocampus; LC, locus coeruleus; MAGL, monoacylglycerol lipase; PFC, prefrontal cortex; PAG, periaqueductal grey; VS, ventral striatum; VTA, ventral tegmental area.

Conclusion

The research findings reviewed in this article indicate that pharmacological interventions that selectively target the endocannabinoid system can moderate the expression of impulsivity and anxiety, two behavioural endophenotypes that predispose to the development of drug addiction. The effects of such agents are mediated within the basal ganglia, including especially the striatum and limbic afferents to this region from the PFC, hippocampus and amygdala. Although this field is still relatively nascent, findings to date suggest several promising leads for research, not least the delineation of specific functions and molecular targets of anandamide and 2-AG, and the clear value of additional studies to define the neuropsychopharmacology of selective CB2 receptor agonists, which show promise as novel therapies in addiction. Such research may reveal novel mechanisms underlying the aetiology of predisposing behavioural endophenotypes in addiction, thereby enabling the development of new therapies to facilitate abstinence and rehabilitation.

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Conflicts of interest

There are no conflicts of interest.

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