Available online at www.sciencedirect.com
SCIENCE DIRECT
Neuroscience and Biobehavioral Reviews 30 (2006) 680–695
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
www.elsevier.com/locate/neubiorev

Review

Cannabinoids and prefrontal cortical function: Insights from preclinical studies

Alice Egerton [1], Claire Allison, Ros R. Brett *, Judith A. Pratt

Department of Physiology and Pharmacology, Strathclyde Institute for Biomedical Sciences, University of Strathclyde, Glasgow G4 0NR, UK

Received 14 July 2005; received in revised form 18 November 2005; accepted 19 December 2005

Abstract

Marijuana use has been associated with disordered cognition across several domains influenced by the prefrontal cortex (PFC). Here, we review the contribution of preclinical research to understanding the effects of cannabinoids on cognitive ability, and the mechanisms by which cannabinoids may affect the neurochemical processes in the PFC that are associated with these impairments. In rodents, acute administration of cannabinoid agonists produces deficits in working memory, attentional function and reversal learning. These effects appear to be largely dependent on CB_1 cannabinoid receptor activation. Preclinical studies also indicate that the endogenous cannabinoid system may tonically regulate some mnemonic processes. Effects of cannabinoids on cognition may be mediated via interaction with neurochemical processes in the PFC and hippocampus. In the PFC, cannabinoids may alter dopaminergic, cholinergic and serotonergic transmission. These mechanisms may underlie cognitive impairments observed following marijuana intake in humans, and may also be relevant to other disorders of cognition. Preclinical research will further enhance our understanding of the interactions between the cannabinoid system and cognitive functioning.

Keywords: Cannabinoids; Prefrontal cortex; Working memory; Attention; Behavioural flexibility; Dopamine; Acetylcholine; Serotonin; Animal models

Contents

Abbreviations: Anandamide, arachidonylethanolamide (AEA); 2-AG, 2-arachidonoyl–glycerol; CP55,940, [1α,2β,-(*R*)5α]-(−)-5-(1,1-dimethylheptyl)-2-[5-hydroxypropil)cyclohexyl]phenol; HU-210, (6aR,10aR)-3-(1,1′-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol; SR141716A (rimonabant/Acomplia), *N*-(piperidine-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride; Δ^9-THC, Δ^9-tetrahydrocannabinol; WIN55212-2, *R*-(+)-[2,3-dihydro-5-methyl-3[morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-napthalenyl) methanone mesylate.

* Corresponding author. Tel.: +44 141 548 4159; fax: +44 141 552 2562.
E-mail address: ros.brett@strath.ac.uk (R.R. Brett).
[1] Current address: Department of Psychological Medicine, Division of Neuroscience and Mental Health, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK

0149-7634/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2005.12.002

1. Introduction

In humans, marijuana use or intoxication has been associated with performance deficits across several cognitive domains; impairments in selective and sustained attention, working memory and mental flexibility have been reported amongst other effects (Block and Ghoneim, 1993; Bolla et al., 2002; Fletcher et al., 1996; Ilan et al., 2004; Miller and Branconnier, 1983; Pope et al., 2001; Pope and Yurgelun-Todd, 1996; Solowij, 1995; Solowij et al., 1995, 2002). These effects have been ascribed to the primary psychoactive compound found in marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC), which acts at CB_1 cannabinoid receptors to influence neural transmission in many brain areas (Devane et al., 1988). Several synthetic cannabinoid compounds that are available for research purposes, such as WIN55212-2, CP55,940 and HU-210, also possess agonist activity at CB_1 receptors, where they inhibit adenylyl cyclase activity (Howlett et al., 1988) with varying potencies (Griffin et al., 1998; Selley et al., 1996). Endogenously occurring compounds with action at CB_1 receptors have also been identified. These endocannabinoid compounds include anandamide (AEA) (Devane et al., 1992), and 2-AG (Mechoulam et al., 1995; Sugiura et al., 1995). In addition, Sanofi Synthelabo have developed a CB_1 antagonist, SR141716A (Acomplia/rimonabant) (Rinaldi-Carmona et al., 1994), which is currently under clinical trial for use in aiding cessation of smoking and alcohol consumption, and for helping weight loss in obesity. The application of these pharmacological tools in preclinical investigation has greatly aided neuroscientific understanding of the cannabinoid system, including the mechanisms by which marijuana may adversely affect cognitive function.

Optimal performance of tasks which assess working memory, attention and cognitive flexibility requires effective communication between several interacting brain regions; deficits may, therefore, arise as a consequence of transmissional interference at a variety of loci. To date, preclinical research into the underlying neural basis of the cognitive effects of marijuana has principally focused on the hippocampal system, where stimulation of CB_1 receptors may profoundly affect neural transmission (Gessa et al., 1998b; Katona et al., 1999; Misner and Sullivan, 1999; Shen et al., 1996). However, in recent years, scientific understanding of the pivotal contribution that prefrontal cortical areas make to cognitive processes in normal and disordered states has greatly increased. Due to the growing emphasis of neuroscientific research on the prefrontal cortex (PFC), we felt that it was timely to review the effects of cannabinoid administration on the functionality of this brain area, particularly with respect to preclinical findings.

At the outset, it should be noted that the rodent PFC, the focus of this discussion, is functionally and anatomically heterogeneous (see Dalley et al., 2004 for review). Of particular relevance are the anterior cingulate, prelimbic and infralimbic regions of the medial PFC, which are implicated in working memory (Delatour and Gisquet-Verrier, 1999), attentional function (Muir et al., 1996) and attentional set-shifting (Birrell and Brown, 2000); these areas constitute the common locus of neurochemical recording during experimental procedures. The orbitofrontal cortex is also of importance, and is involved in processes such as reversal learning (McAlonan and Brown, 2003) and some forms of impulsive behaviour (Chudasama et al., 2003; Winstanley et al., 2004), and response perseveration (Chudasama et al., 2003). Relatively few of the studies that have investigated the effects of cannabinoids on prefrontal function have accounted for this recently recognized topographical complexity, but where findings relate to specific prefrontal subdivisions these anatomical loci are discussed in the text.

Preclinical investigation into the interactions of cannabinoids with prefrontal systems is still in its infancy; at present there is no clear overall mechanistic explanation for the effects of cannabinoids in this area. However, as will be discussed in this review, several lines of research indicate that cannabinoids may modulate prefrontal cortical functionality and resultant cognitive ability. This has raised several interesting and exciting hypotheses for future preclinical research into the role of cannabinoids in prefrontal-dependent cognitive processes in normal and pathological states.

2. Localisation of cannabinoid effects to the PFC

2.1. Cannabinoid receptor distribution

A significant role of the cannabinoid system in modulating prefrontal cortical neurotransmission is first suggested by the abundance of CB_1 receptors in this brain area. Autoradiographic studies employing [3H]CP55,940 have demonstrated CB_1 receptor binding in the frontal cortex of rats (Hajos and Freund, 2002; Herkenham, 1992; Herkenham et al., 1990, 1991; Mailleux and Vanderhaeghen, 1992) and humans (Glass et al., 1997; Mato and Pazos, 2004). In the rat brain, binding of [3H]CP55,940 shows a fairly even distribution across forebrain cortical regions; generally, moderate densities of CB_1 receptors are indicated in cortical layers I and IV and lower binding is observed in the intermediate cortical layers (Herkenham et al., 1991). The presence of CB_1 receptors in cortical areas has been confirmed using immunohistochemistry (Tsou et al., 1998), where the higher levels of cellular resolution available revealed that CB_1 receptors are present on neuronal cell bodies, axons and dendrites (Tsou et al., 1998). Cell bodies which produce CB_1 receptors may also be present in cortical regions, as CB_1 receptor mRNA is also detected in cortical areas (Mailleux and

Vanderhaeghen, 1992; Matsuda et al., 1993). In addition, the endocannabinoids anandamide and 2-AG are also present in cortical regions (Bisogno et al., 1999; Di Marzo et al., 2000a–c) as is fatty acid amide hydrolase (FAAH, anandamide amidohydrolase) (Egertova et al., 2003; Thomas et al., 1997; Tsou et al., 1999), the enzyme responsible for anandamide and 2-AG hydrolysis (Beltramo and Piomelli, 2000; Cravatt et al., 1996; and for review see Ueda et al., 1998). These latter findings suggest that the endocannabinoid system may be involved in the tonic modulation of neural transmission in this area. Indeed, the endocannabinoid system has been implicated in the phenomena of depolarisation-induced suppression of excitation (DSE) and inhibition (DSI) in which endocannabinoids released from depolarised neurones act retrospectively on presynaptic terminals to suppress neurotransmitter release (see Diana and Marty, 2004 for review). The physiological significance of these phenomena to behavioural effects in vivo remains to be established. Nevertheless, there is some evidence that stimulation of the prefrontal cortex induces 2-AG mediated suppression of excitation in midbrain dopamine neurones (Melis et al., 2004), which raises the possibility of a role for the endocannabinoid system in regulating dopamine modulation of cortical processing.

Therefore, exogenous cannabinoid compounds are capable of acting in the PFC to affect local neural transmission via CB_1 receptors, and endogenous cannabinoid compounds are appropriately positioned to play a potential role in the normal physiological regulation of frontal neural activity.

2.2. Alterations in prefrontal neural activity

In addition to the localization of cannabinoid receptors to cortical areas, several studies have also demonstrated alterations in PFC metabolic activity occurring in response to cannabinoid administration. In humans, marijuana intake affects prefrontal activity, as evidenced by alterations in regional cerebral blood flow and metabolism (Amen and Waugh, 1998; Block et al., 1999, 2002; Kanayama et al., 2004; Lundqvist et al., 2001; Mathew and Wilson, 1992, 1993; Mathew et al., 1997, 2002; O'Leary et al., 2000, 2002; Volkow et al., 1996). Cannabinoid administration also alters activity in the rodent PFC; using the 2-deoxyglucose mapping technique to measure local rates of cerebral glucose utilization (LCGU), decreases in metabolic activity in the infralimbic and anterior cingulate regions of the PFC following Δ^9-THC administration have been reported (Freedland et al., 2002; Whitlow et al., 2002). In other studies performed in our laboratory (Brett et al., 2001) and by Margulies and Hammer (1991), Δ^9-THC appeared to produce differential effects on cortical 2-deoxyglucose uptake with respect to dose; increases in metabolic activity occurred at lower doses (1 mg/kg or less), with decreases occurring at doses above 2 mg/kg. In addition, alterations in frontal cortical activity following cannabinoid administration may also be observed using other imaging techniques; a recent blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) study showed that the potent synthetic cannabinoid agonist HU-210 produced CB_1 antagonist-sensitive increases in BOLD activity in a number of brain regions including the cingulate cortex (Shah et al., 2004).

In rodents, the effects of drugs on regional neural activity may also be indexed by the alternative approach of examining alterations in immediate early gene (IEG) protein and mRNA expression levels, as regional IEG transcription is rapidly altered in response to a variety of stimuli (for review see Morgan and Curran, 1989). This technique has also been used to map the effects of cannabinoid administration on neural activity in different brain regions of the rat brain (Mailleux et al., 1994; Miyamoto et al., 1996; Porcella, et.al., 1998). Amongst other localized effects, these studies have shown that administration of Δ^9-THC increases mRNA encoding the IEGs zif-268, c-fos and c-jun (Mailleux et al., 1994) and FosB protein (Porcella, et.al., 1998) in the cingulate area of the rat PFC, although effects in other prefrontal areas were not described. We have extended these studies to demonstrate marked Δ^9-THC-induced increases in mRNA encoding

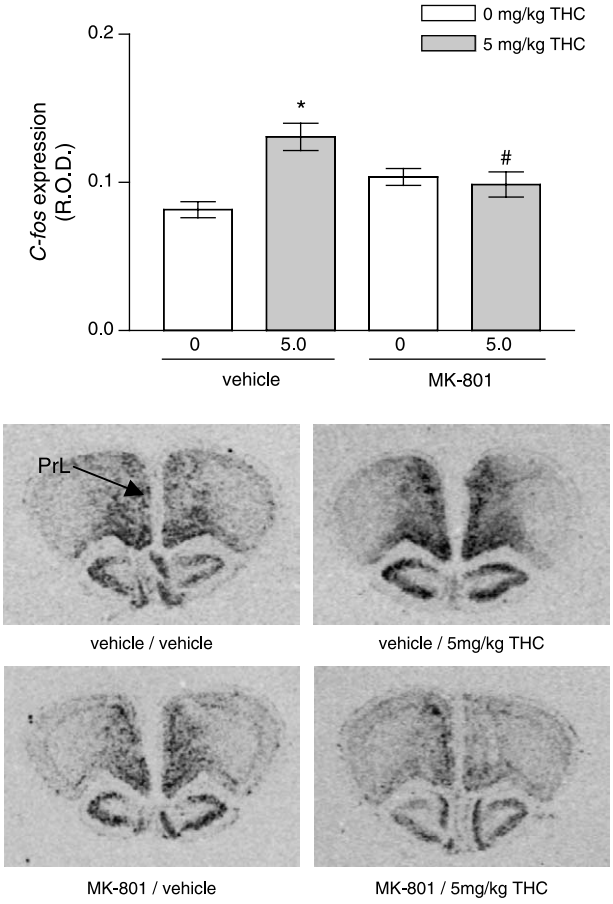

Fig. 1. Δ^9-THC significantly increases immediate early gene expression in the rat prelimbic cortex; blockade by MK-801. The graph and associated autoradiogram images illustrate the significant increase in *c-fos* expression in the prelimbic subdivision of the rat prefrontal cortex that occurs 75 min following i.p. administration of 5 mg/kg Δ^9-THC (THC) relative to saline (vehicle)-treated control rats (*$p < 0.05$). This effect was not apparent when rats received 0.1 mg/kg MK-801 (dizocilpine) i.p. 10 min prior to Δ^9-THC administration, and *c-fos* expression was significantly lower in Δ^9-THC-treated rats that had received MK-801 compared to vehicle (saline) pretreated rats (#$p < 0.05$).

a variety of IEGs, belonging to different families, in both the medial prefrontal cortical areas (prelimbic and anterior cingulate cortices) and also in the ventral and lateral orbital cortices of the rat brain (Egerton et al., 2001). In addition, pretreatment with MK-801 revealed that these effects were dependent on activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors (Egerton et al., previously unpublished data). The ability of Δ^9-THC administration to increase IEG mRNA expression in the PFC is illustrated in Fig. 1, using *c-fos* expression in the prelimbic subdivision as an example.

In summary, the alterations in both metabolic activity and IEG expression following cannabinoid administration indicate that cannabinoid compounds may alter neural activity in the PFC. As the PFC controls key aspects of cognitive performance, deregulation of neural activity in this area following cannabinoid administration may precipitate cognitive deficits that are associated with marijuana intake.

3. Preclinical investigations of the effects of cannabinoids on cognitive function

Preclinical investigation of the effects of cannabinoids on cognitive functions ascribed to the PFC is possible as anatomical homology exists between the PFC of the rodent and primate brain, although the degree of this homology varies according to the anatomical criteria used for regional definition (Groenewegen and Uylings, 2000; Uylings and van Eden, 1990; Brown and Bowman, 2002; Ongur and Price, 2000; Preuss, 1995; Rose and Woolsey, 1948). Importantly, several aspects of cognitive performance can be behaviourally assessed in rats using careful experimental designs and species-appropriate measurements (for review, see Brown and Bowman, 2002; Sarter, 2004). Through this approach, understanding of the extent and limitations of regional functional homology which exists across species has greatly increased in recent years (Birrell and Brown, 2000; Brown and Bowman, 2002; Dalley et al., 2004). As outlined below, preclinical research has greatly contributed to neuroscientific understanding of the effects that cannabinoids may exert over several aspects of cognition, and the mechanisms by which these impairments may be mediated.

3.1. Working memory

The disruptive effect of cannabinoids on mnemonic processes has been the topic of extensive preclinical research. Overall, studies have shown that, whilst cannabinoids may markedly impair aspects of short-term working memory, long-term or reference memory appears to be relatively unaffected (for review, see Lichtman et al., 2002). These findings are in accordance with the deficits in short-term memory that have been reported in marijuana users (Macavoy and Marks, 1975; Miller and Branconnier, 1983; Pope et al., 2001).

In rats, the effects of cannabinoids on working memory performance have been investigated using both maze-based and instrumental tasks. Performance of maze-based tasks requires effective use of spatial cues; these tasks utilize the navigational behaviours of rodents normally used for foraging or to escape from predators (Olton, 1987). Cannabinoids disrupt spatial working memory in maze-based tasks that are driven by motivation to locate a food reward, such as in the T-maze (Jentsch et al., 1997; Nava et al., 2000, 2001), or the 8-arm radial maze (Braida and Sala, 2000; Inui et al., 2004; Lichtman et al., 1995; Lichtman and Martin, 1996; Mishima et al., 2001, 2002; Molina-Holgado et al., 1995; Nakamura et al., 1991). Similarly, cannabinoid-induced spatial working memory deficits are also evidenced in water maze tasks (Fadda et al., 2004; Ferrari et al., 1999; Hill et al., 2004; Varvel et al., 2001), where animals must use spatial cues to navigate whilst swimming in order to find a hidden platform in a pool of water (Morris, 1984).

Instrumental working memory tasks include the delayed match to sample (DMTS) or delayed non-match to sample (DNMS) paradigms. During these tasks, the animal is initially presented with a sample stimulus (sample phase), then, following a delay period, both the original sample stimulus and a novel stimulus are presented. Usually by pressing a lever, the rat must indicate either the sample (match) stimulus or the novel (non-match) stimulus according to the task rule. Disruptive effects of cannabinoids on working memory performance have been observed using DMTS or DMNS tasks in rats (Deadwyler et al., 1990; Hampson and Deadwyler, 1999a,b, 2000; Heyser et al., 1993; Mallet and Beninger, 1998; Miyamoto et al., 1995) and monkeys (Schulze et al., 1988; Winsauer et al., 1999; Zimmerberg et al., 1971).

A large amount of evidence, therefore, suggests that stimulation of the cannabinoid system impairs working memory performance, and that this effect appears to be observed across a variety of behavioural paradigms. Importantly, cannabinoid-induced working memory impairments appear to be dependent on CB_1 receptor activation; several studies have demonstrated that cannabinoid induced working memory impairments are not observed in the presence of the CB_1 antagonist SR141716A (Braida and Sala, 2000; Lichtman and Martin, 1996; Mallet and Beninger, 1998; Varvel et al., 2001). Whilst cannabinoid-induced working memory deficits may recover on repeated drug administration (Hill et al., 2004), suggesting the occurrence of some degree of tolerance, this process may be dependent on the precise task demands, as tolerance has not been observed using alternative paradigms (Nava et al., 2001). Worsening of impairments on repeated cannabinoid administration has also been reported to occur under some conditions (Miyamoto et al., 1995). Therefore, although acute cannabinoid exposure impairs working memory capacity, further preclinical investigation is required to characterize the degree of persistence of this impairment both during repeated drug exposure and following periods of drug abstinence.

3.2. Locus of cannabinoid-induced disruption of working memory performance

Cannabinoid-induced disruption of working memory has typically been assigned to a principal disruption of

hippocampal rather than prefrontal cortical function (for review, see Lichtman et al., 2002). CB_1 receptors are highly expressed in the hippocampus (Herkenham et al., 1991, 1990) and modulate hippocampal neurotransmission (Gessa et al., 1998b; Katona et al., 1999; Misner and Sullivan, 1999; Shen et al., 1996). Cannabinoid-induced disruption of working memory performance does indeed appear to be intimately associated with hippocampal activity, as performance deficits following cannabinoid administration in DMTS tasks are associated with decreases in hippocampal cell firing during sample phases (Hampson and Deadwyler, 2000; Heyser et al., 1993) and alterations in hippocampal cell firing characteristics during the delay period (Heyser et al., 1993). In addition, deficits in spatial working memory task performance are observed following both systemic and intra-hippocampal administration of the cannabinoid agonist CP55,940 (Lichtman et al., 1995). Finally, cannabinoid-induced impairments in working memory tasks are associated with neurochemical alterations in hippocampal areas (Inui et al., 2004; Nava et al., 2000).

In addition to the important role of the hippocampus, effective performance on working memory tasks may also involve prefrontal cortical functionality. Indeed, impairments in delayed working memory tasks for objects or spatial locations are seen following lesions or transient inactivation of both the hippocampal system (Floresco et al., 1997; Lee and Kesner, 2003a,b; Porter et al., 2000) and the prelimbic area of the PFC (Floresco et al., 1997; Izaki et al., 2001; Kesner et al., 1996; Lee and Kesner, 2003b; Porter et al., 2000). Prefrontal and hippocampal regions cooperate to control behaviour via a direct monosynaptic pathway which projects from the CA1 hippocampus and subiculum to medial and orbital prefrontal cortical areas (Floresco et al., 1997; Izaki et al., 2001; Kesner et al., 1996; Lee and Kesner, 2003b; Porter et al., 2000). The precise contributions of hippocampal and prefrontal areas to differential aspects of task performance are still under investigation (Eichenbaum et al., 1996; Floresco et al., 1996, 1997; Laroche et al., 2000; Newman and Grace, 1999; Seamans et al., 1998; Wall and Messier, 2001). In short, research suggests that the hippocampus may acquire, encode and consolidate new information in short-term memory. Working memory then provides a mechanism by which this information, present in short-term memory, may be represented and manipulated in the PFC, and used, together with motor plans, to direct behavioural response strategies (Doyere et al., 1993; Floresco et al., 1997; Fuster, 1991; Goldman-Rakic, 1987; Goldman-Rakic et al., 1992; Laroche et al., 2000; Lee and Kesner, 2003b; Newman and Grace, 1999; Wall and Messier, 2001). In this context, input from the hippocampus to the PFC may aid organized cortical representation of learned events (Laroche et al., 2000).

As cannabinoid-induced working memory impairments are largely delay-dependent (Hampson et al., 1998; Hill et al., 2004), it has been suggested that these compounds act in the hippocampus to particularly affect memory consolidation or storage (Hampson et al., 1998; Hill et al., 2004). However, lesions of the PFC particularly impair performance of tasks that include a delay-component, during which information must be held in working memory (Delatour and Gisquet-Verrier, 1999). Given the cooperation between hippocampal and prefrontal cortical areas necessary for effective performance of working memory tasks, it is possible that the deleterious effects of cannabinoids on working memory may additionally arise, at least in part, through disruption of prefrontal cortical transmission. In line with this hypothesis, Jentsch and colleagues have shown that Δ^9-THC-induced working memory deficits in a delayed alternation T-maze task are associated with altered dopamine and noradrenaline turnover in the rat PFC (Jentsch et al., 1997). Moreover, deficits in memory task performance detected in marijuana users are associated with a relative inability to activate prefrontal regions in response to task demands (Block et al., 2002). Further research is required in order to fully characterize the relative contribution of prefrontal cortical disruptions to the working memory impairments that follow administration of cannabinoids agonists.

3.3. Attention

In humans, studies have repeatedly demonstrated deficits in attentional capacity following Δ^9-THC intake (Block and Ghoneim, 1993; Bolla et al., 2002; Fletcher et al., 1996; Pope et al., 2001; Pope and Yurgelun-Todd, 1996; Solowij, 1995; Solowij et al., 1995, 2002). Early evidence for disruptive effects of cannabinoids on attentional processes in rats was detected in studies showing that the amplitudes of hippocampal synaptic potentials evoked by sensory stimuli in the DMTS task were reduced following cannabinoid administration, suggesting that cannabinoids may decrease the responsiveness of the hippocampus to sensory inputs (Campbell et al., 1986a,b; Heyser et al., 1993). Later, Presburger and Robinson (1999) investigated the effects of Δ^9-THC on visual attention in an operant signal detection task in rats. In this task, administration of Δ^9-THC decreased accuracy of stimulus detection and increased the number of response omissions (Presburger and Robinson, 1999). The authors concluded that Δ^9-THC produced attentional deficits, and suggested that the problems in encoding during the DMTS task employed by Heyser and colleagues (Campbell et al., 1986a,b; Heyser et al., 1993) may have resulted from an impaired ability to effectively attend to task-relevant stimuli (Presburger and Robinson, 1999).

Cannabinoid-induced disruption of attention has been more recently confirmed using the rat lateralized reaction time task (LRT) of visuospatial attention (Arguello and Jentsch, 2004; Verrico et al., 2004). In this task, rats must attend to apertures for the location of a visual stimulus over a number of trials. In the LRT, acute systemic administration of the cannabinoid agonist WIN55212-2 significantly impaired attentional performance in a CB_1-dependent manner (Arguello and Jentsch, 2004). Attentional deficits were also present following subchronic administration of Δ^9-THC in the rat, and persisted for at least 2 weeks following the final of 14 daily drug administrations (Verrico et al., 2004). Although SR141716A

reversed the WIN55212-2-induced impairments in attentional performance, this compound did not appear to produce any effects on attentional performance when administered alone (Arguello and Jentsch, 2004). As lesions of the medial PFC or striatum can produce attentional deficits similar to those observed following cannabinoid administration (Burk and Mair, 2001; Christakou et al., 2001) cannabinoid-induced attentional impairments might arise via CB_1 activation in the striatum or PFC (Arguello and Jentsch, 2004).

3.4. Behavioural flexibility

Impairments in cognitive flexibility have been reported in marijuana users after approximately 1 day (Pope and Yurgelun-Todd, 1996) and 28 days (Bolla et al., 2002) of abstinence from the drug. As this inflexibility in cognitive control may be deleterious to intellectual and social functioning (Pope and Yurgelun-Todd, 1996), we have recently investigated whether Δ^9-THC administration produces similar impairments in behavioural flexibility in rats (Egerton et al., 2005).

In the task employed, rats perform a series of discriminations during which they are required to shift behavioural strategies, by learning new stimulus-reward associations whilst inhibiting previously learned response tendencies (Birrell and Brown, 2000). Two types of behavioural flexibility are assessed during the task; for effective performance of extradimensional shifts, rats must shift attentional bias (or 'set') between different abstract features of stimuli, a process termed 'attentional set shifting'. In contrast, in order to perform reversal-learning discriminations, rats must update contingencies between stimuli and reward presentation when these are reversed. As shown in Fig. 2, acute administration of Δ^9-THC impairs performance on reversal learning stages of the task, whilst attentional set shifting ability is unaffected (Egerton et al., 2005). This profile of effects is similar to that observed following lesions of the orbitofrontal (McAlonan and Brown, 2003) but not the medial frontal (Birrell and Brown, 2000) division of the rat PFC, a dissociation that is also present in monkeys (Dias et al., 1996a,b, 1997; Jones and Mishkin, 1972) and humans (Fellows and Farah, 2003; Owen et al., 1991; Rolls et al., 1994). Indeed, the reversal learning deficits produced by Δ^9-THC administration correlates with alterations in IEG mRNA expression in orbitofrontal and striatal areas (Egerton et al., 2005).

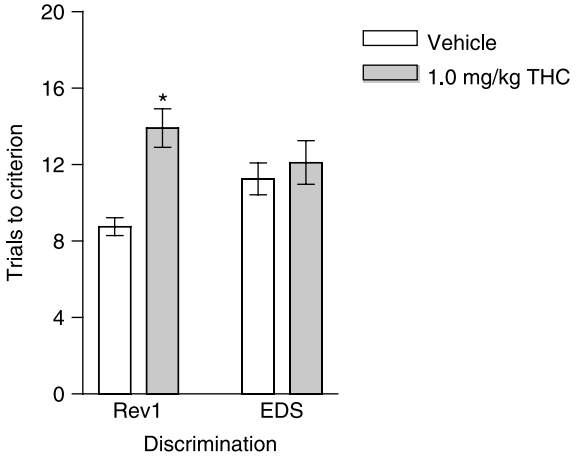

Fig. 2. Δ^9-THC significantly impairs reversal learning but does not affect attentional set-shifting ability. Following i.p. administration of Δ^9-THC (THC) rats were tested on a series of discriminations. THC-treated rats were particularly impaired on reversal learning discriminations (Rev1) but did not show impairments in ability to shift attentional set, as measured in the extradimensional shift (EDS) task stage compared to vehicle (saline)-treated control animals ($*p<0.05$) (This data is taken from Egerton et al., 2005).

These results, therefore, suggest that, at least on acute administration, cannabinoids do not affect ability to shift attentional set, but do impair ability to reverse stimulus-reward associations. Reversal learning deficits have been associated with increases in risk-taking and impulsive responding, and thus impairments on some decision-making tasks (see Clark et al., 2004). Furthermore, an inability to alter behaviour according to changing reinforcement contingencies may contribute towards continued drug use and, therefore, be of significance to continued marijuana intake in humans (Bolla et al., 2002; Jentsch and Taylor, 1999; Volkow and Fowler, 2000). We have preliminary evidence that on repeated administration reversal learning deficits are maintained, but that there appears to be an emerging deficit in ability to shift attentional set (Allison et al., 2004); therefore, additional deficits in attentional/higher cognitive flexibility may arise on chronic marijuana exposure.

3.5. The endocannabinoid system and cognition

As detailed above, several studies have demonstrated that cognitive impairments arise following administration of exogenous cannabinoid compounds. This interaction raises interesting questions regarding the possible contribution of the endogenous cannabinoid system to aspects of cognitive control. Specifically, research is beginning to address the mnemonic role of the endocannabinoid system under normal physiological conditions and the possible disruption of this system in pathological states associated with cognitive abnormalities. Further, this research has raised the possibility that potential therapeutic benefits may be achieved through pharmacological manipulation of the endocannabinoid system.

Initial evidence that antagonism of CB_1 receptors may improve certain memory processes was obtained using an olfactory recognition task (Terranova et al., 1996). As mature rodents normally spend more time investigating unfamiliar than familiar conspecific animals, the olfactory recognition task measures social short-term working memory capacity. In this task, administration of SR141716A alone improves olfactory recognition memory in both aged rats and mice (Terranova et al., 1996). In addition, SR141716A improves working memory performance on the 8-arm radial maze when long delay periods are included (Lichtman, 2000). These studies have therefore, suggested that SR141716A may exert nootropic effects when administered alone, and, by extension, indicate that the endocannabinoid system may negatively influence some mnemonic processes. Other studies using

different paradigms have not, however, demonstrated any effect of SR141716A on working memory performance (Brodkin and Moerschbaecher, 1997; Hampson and Deadwyler, 2000; Mallet and Beninger, 1998; Mansbach et al., 1996). Analysis of these results has led to the suggestion that the effects of SR141716A administration on working memory are dependent on temporal components of the task, and that CB_1 blockade may prolong the duration of memory rather than facilitating learning per se (Lichtman, 2000). Whilst these apparently nootropic effects of SR141716A may be interpreted in terms of a role for the endocannabinoid system in mnemonic function (Lichtman, 2000; Terranova et al., 1996), it has also been suggested that the observed effects may arise due to inverse agonist effects of SR141716A (Lichtman, 2000; Pan et al., 1998; Terranova et al., 1996), or an action of SR141716A at non- CB_1 receptors (Bukoski et al., 2002; Lichtman, 2000; Terranova et al., 1996). These possible confounds inherent to using a pharmacological antagonist to investigate endocannabinoid function are circumvented in the alternative approach of investigating cognitive function in mice lacking the CB_1 receptor. It should be noted, however, that the use of gene ablation strategies is also potentially subject to confounding effects, arising, for example, through developmental alterations and neuronal compensations (see Nelson and Young, 1998).

The availability of CB_1 receptor deficient mice has led to an elegant series of studies that further define the role of the endocannabinoid system in modulation of mnemonic processes. The first of these investigations showed that CB_1 receptor deficient mice exhibit better performance in an object-recognition memory task than wild-type control mice (Reibaud et al., 1999), in accordance with the improvement in memory produced by SR141716A on a similar task (Terranova et al., 1996). Subsequent studies showed that CB_1 receptor knock-out mice exhibit increased perseveration during reversal learning on a water maze task (Varvel and Lichtman, 2002). This observation led the authors to propose that the endocannabinoid system may aid 'forgetting' or memory extinction (Varvel and Lichtman, 2002); a theory further clarified by studies demonstrating that CB_1 deficient mice exhibit less extinction of contextual fear memory using foot-shock paradigms (Marsicano et al., 2002).

Further investigations, conducted in the water maze, have demonstrated that although both CB_1 receptor deficient mice and mice treated with SR141716A show deficits in extinction, these impairments crucially depend on the extinction procedure employed (Varvel et al., 2005). As inhibition of CB_1 receptor function appears to impair extinction when the extinction trials are spaced over long but not short periods, endocannabinoids may be involved in long- but not short-term extinction of learned behaviours (Varvel et al., 2005). As extinction learning, as assessed, for example, through fear conditioning paradigms in rodents, is also mediated by the medial frontal cortex, along with other areas (Morgan et al., 1993; Morrow et al., 1999), these mnemonic effects of cannabinoids may also arise, at least in part, through modulation of prefrontal cortical neurotransmission, as will be discussed in the following paragraphs.

In the above sections, we have shown that administration of CB_1 agonists may impair working memory, attentional function and behavioural flexibility in preclinical models. While the cognitive impairments that arise following acute cannabinoid administration are fairly well described, the effects of longer-term cannabinoid exposure warrant further investigation. Most of the effects of cannabinoid agonists on cognitive abilities appear to be dependent on CB_1 receptor activation, as they are absent in the presence of the CB_1 receptor antagonist SR141716A. In addition, studies that have investigated behaviours following administration of SR141716A alone or in CB_1 receptor-deficient mice have indicated that the endocannabinoid system may be tonically involved in extinction of learned behaviours. It is likely that neuromodulatory effects of cannabinoids in the PFC may contribute to alterations in cognitive performance.

4. Alterations in frontal neurochemical systems

4.1. Dopamine, GABA and glutamate

Several groups have investigated the effects of cannabinoids on neurotransmitter content in the PFC, as these alterations may underlie some of the cognitive deficits associated with marijuana use. Unsurprisingly, the focus of this attention has been directed towards dopamine (DA), as this neurotransmitter is critically implicated in neuromodulation of PFC transmission. The PFC receives major dopaminergic innervation from the mesocortical DA projection, which arises from cell bodies in the ventral tegmental area (VTA) (Morgan et al., 1993; Morrow et al., 1999, also see Seamans and Yang, 2004; Tzschentke, 2001 for review). In the PFC, DA exerts inhibitory control over the activity of glutamatergic pyramidal projection neurons (Gellman and Aghajanian, 1993; Gioanni et al., 1998; Law-Tho et al., 1994; Pirot et al., 1992). This interaction may occur by several mechanisms (for review see Goldman-Rakic, 1996; Seamans and Yang, 2004): Dopaminergic axons may modulate pyramidal neuron activity directly through synaptic contacts to the pyramidal neuron spines (Goldman-Rakic et al., 1989; van Eden et al., 1987), via the D_1 dopamine receptors that are localized to this area (Bergson et al., 1995), or, alternatively, inhibition may occur indirectly via activation of GABAergic (γ-amino butyric acid) inhibitory interneurons, (Gellman and Aghajanian, 1993; Retaux et al., 1991), possibly via a D_4 DA receptor-mediated mechanism (Goldman-Rakic, 1996; Mrzljak et al., 1996).

The involvement of DA in working memory performance is commonly accepted, but complex. Impairments in working memory function arise in situations where dopaminergic activity is either particularly high or low, (Murphy et al., 1996a,b; Stam et al., 1989; Zahrt et al., 1997), leading to an inverted 'U' (bell shaped) relationship between dopamine levels and working memory efficiency (see Goldman-Rakic, 1996; Robbins, 2000; Seamans and Yang, 2004). Prefrontal cortical dopamine levels contribute to other aspects of cognition, as manipulation of this system also affects

attentional performance (Granon et al., 2000), and attentional set shifting ability (Ragozzino, 2002; Roberts et al., 1994).

Several groups have reported increases in prefrontal cortical DA release or turnover following systemic cannabinoid administration (Chen et al., 1990; Diana et al., 1998; Jentsch et al., 1997, 1998a, b; Pistis et al., 2002; Tanda et al., 1997; Verrico et al., 2003). As the ability of cannabinoids to increase extracellular DA concentrations in the PFC is blocked by SR141716A (Pistis et al., 2002), this effect appears to be mediated by CB_1 receptor activation. In 1997, an important study performed by Jentsch and colleagues showed that increases in prefrontal cortical DA following cannabinoid administration were associated with impairments in working memory performance on a T-maze task, suggesting that working memory impairments produced by cannabinoid agonist administration may result from hyperstimulation of mesocortical dopaminergic transmission (Jentsch et al., 1997). This hypothesis was further clarified by studies showing that the cannabinoid-induced increase in prefrontal cortical DA turnover is sensitive to blockade by two compounds which modulate mesocortical dopaminergic neuron activity (Goldstein et al., 1994; Murphy et al., 1996a,b): the strychnine-insensitive glycine site partial agonist/NMDA receptor antagonist HA966 (Jentsch et al., 1997) and the α2-noradrenergic receptor agonist clonidine (Jentsch et al., 1998b). Therefore, cannabinoid-induced working memory deficits may result from increased mesocortical dopaminergic neuronal activity. Indeed, both Δ^9-THC and WIN55212-2 increase firing rate and burst firing of mesocortical dopaminergic neurons (Diana et al., 1998).

Later, Pistis and colleagues, (Pistis et al., 2001), further investigated the interaction of cannabinoid compounds with the mesocortical DA projection in the control of prefrontal neuronal responses, by characterizing the effects of cannabinoid administration on both the activity of pyramidal neurons projecting from the PFC to the VTA, and the inhibition of PFC neurons that occurs following VTA stimulation (Godbout et al., 1991; Pistis et al., 2001). As intravenous administration of Δ^9-THC and WIN55212-2 increased the firing rate of the pyramidal neurons projecting to the VTA and reversed the inhibition of pyramidal neurons produced by VTA stimulation, the authors concluded that cannabinoid agonists increase the excitability of PFC pyramidal neurons (Pistis et al., 2001). This effect was CB_1 receptor-mediated, as subsequent administration of SR141716A decreased the effects of cannabinoid agonist administration and restored the inhibitory PFC response to VTA stimulation (Pistis et al., 2001).

On the basis of these findings, Pistis and colleagues proposed important hypotheses relating to the action of cannabinoids on the mesocortical DA projection (Pistis et al., 2001). First, activation of mesocortical DA transmission by cannabinoids may arise, at least in part, from increases in the firing rate of pyramidal neurons projecting to the VTA. Second, as cannabinoids reduce the level of inhibition in the PFC produced by VTA stimulation, the authors suggest that cannabinoids may functionally counter mesocortical dopaminergic transmission, possibly by inhibiting the function of GABAergic neurons in the PFC (Pistis et al., 2001). This latter hypothesis is further qualified by studies showing that cannabinoids can decrease extracellular GABA and increase

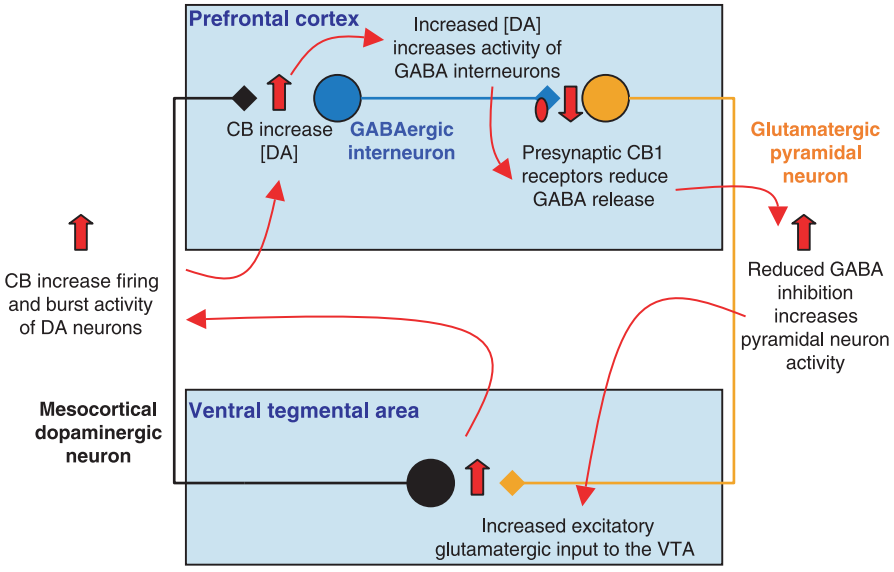

Fig. 3. Schematic diagram illustrating possible effects of cannabinoids on neurotransmission in the PFC. The diagram illustrates the mesocortical dopaminergic (DA) projection (black) from the ventral tegmental area (VTA) to the prefrontal cortex (PFC). Under normal conditions, dopamine release in the PFC increases activity of GABAergic interneurons (blue), which inhibits the activity of glutamatergic pyramidal projection neurons (orange) and, therefore, decreases excitatory input to dopamine neurons in the VTA providing a negative feedback loop. As shown by the red arrows, cannabinoid (CB) administration increases DA neuron activity (Diana et al., 1998) and augments dopaminergic transmission in the PFC (Jentsch et al., 1997; Tanda et al., 1997). This may increase dopamine-stimulated activity in GABAergic interneurons, however, GABA release is reduced (Pistis et al., 2002), possibly via presynaptic CB_1 receptors, which may underlie observed increases in pyramidal neuron activity (Pistis et al., 2001). It should be noted that this diagram is a simplification and in particular does not take into account CB_1-mediated effects in the VTA (e.g. Gessa et al., 1998a; Tanda et al., 1997) or other innervating structures, or the complex effects of DA on pyramidal neuron excitability in the PFC (Goldman-Rakic, 1996).

extracellular glutamate concentrations in the PFC (Ferraro et al., 2001; Pistis et al., 2001), effects which may occur via CB_1 receptors presynaptically located on GABAergic terminals (Marsicano and Lutz, 1999; Tsou et al., 1998). Indeed, in the auditory cortex, cannabinoids may suppress the inhibition of pyramidal neurons by depressing calcium-dependent GABA release from interneurons (Trettel and Levine, 2002). Together, these observations form the basis of the schematic diagram shown in Fig. 3, which illustrates possible mechanisms by which cannabinoids may alter activity in mesocortical dopaminergic and prefrontal pyramidal neurons.

Therefore, acute administration of cannabinoid agonists may modify PFC functionality by increasing the release of dopamine from mesocortical neurons and modifying the effects of dopamine on target neurons. This cannabinoid-induced hyperactivity in prefrontal dopaminergic transmission may contribute to working memory deficits (Diana et al., 1998; Jentsch et al., 1997); indeed, such deficits have been associated with increased PFC dopamine turnover (Jentsch et al., 1997).

In contrast to the increases in PFC DA release and turnover that follow acute cannabinoid administration (Jentsch et al., 1997; Tanda et al., 1997), repeated administration of Δ^9-THC and WIN55212-2 decreases DA turnover in the rat PFC, an effect which may persist for up to 2 weeks following discontinuation of treatment (Jentsch et al., 1998a; Verrico et al., 2003). Therefore, some form of adaptive change in the mesocortical dopaminergic projection may occur in response to repeated cannabinoid exposure (Verrico et al., 2003). As cognitive impairments may arise in situations where dopaminergic activity is either particularly high or low (see Robbins, 2000), PFC DA hypoactivity may underlie some of the cognitive impairments observed after chronic THC exposure (Verrico et al., 2003). In accordance with this hypothesis, the attentional impairments observed following repeated cannabinoid administration in the rat are transiently reversed by administration of amphetamine, suggesting that dopaminergic hypoactivity may contribute to some of the cognitive impairments that arise on, and persist after, chronic cannabinoid exposure (Verrico et al., 2004).

4.2. Acetylcholine

The PFC also receives cholinergic innervation from neurons originating in the basal forebrain and the reticular core of the brainstem (see Everitt and Robbins, 1997). Lesions of cholinergic neurons, which project from the nucleus basalis magnocellularis to the cortex, impair attentional performance on the 5-choice serial reaction task (5-CSRT) in rats, particularly when the attentional demand of the task is high (Lehmann et al., 2001; McGaughy et al., 2002). Moreover, performance of 5-CSRT is associated with increased release of acetylcholine (ACh) in the PFC (Dalley et al., 2001; McGaughy et al., 2002; Passetti et al., 2000). Therefore, prefrontal cortical ACh appears to play an important role in modulating attentional performance. Prefrontal cortical ACh is also implicated in working memory, as antagonists acting at muscarinic cholinergic receptors affect spatial working memory performance when infused to the prelimbic/infralimbic regions of the PFC (Kesner et al., 1996; Ragozzino and Kesner, 1998). Finally, prefrontal cholinergic depletion arising from lesions of the nucleus basalis also disrupts reversal learning but not attentional set shifting (Roberts et al., 1992). Decreased cholinergic function in the PFC, therefore, appears to result in deficits across several cognitive domains.

At low doses, cannabinoid administration increases extracellular ACh levels in the PFC (Acquas et al., 2001; Verrico et al., 2003). This effect is CB_1 receptor-dependent, (Acquas et al., 2001; Verrico et al., 2003), but does not appear to be mediated by CB_1 receptors on cholinergic terminals in the PFC as the increases in PFC ACh concentrations are observed after systemic but not intraprefrontal cannabinoid administration (Verrico et al., 2003). In contrast, administration of cannabinoids at higher doses decreases ACh concentrations in the PFC (Gessa et al., 1998b) and, accordingly, increases in ACh release have also been observed following CB_1 antagonist administration (Gessa et al., 1998b; Tzavara et al., 2003).

It is possible that some of the cognitive impairments associated with marijuana use may be associated with decreases in extracellular ACh concentrations in the PFC. As prefrontal ACh function correlates with performance on attentional, working memory and reversal learning tasks (Dalley et al., 2001; Kesner et al., 1996; Lehmann et al., 2001; McGaughy et al., 2002; Passetti et al., 2000; Ragozzino and Kesner, 1998; Roberts et al., 1992), by extension cannabinoid-induced decreases in PFC ACh (Gessa et al., 1998b) may contribute to the deficits across these cognitive domains that are observed following cannabinoid administration (Jentsch et al., 1997; Arguello and Jentsch, 2004; Egerton et al., 2005). However, these hypotheses have not been directly tested to date, and effects may be complex due to the mixed effects of cannabinoids on PFC ACh concentrations (Acquas et al., 2001; Verrico et al., 2003; Gessa et al., 1998b).

4.3. Serotonin

The effects of depleted serotonin (5-hydroxytryptamine, 5-HT) levels on cognitive function may be investigated by feeding humans or rats a diet deficient in tryptophan (see Robbins, 2000). Using this approach, Rogers et al. have demonstrated that low 5-HT levels may be associated with relatively selective impairments in reversal learning and decision-making in human volunteers (Rogers et al., 1999a,b). Similarly, 5,7-dihydroxytryptamine-induced prefrontal 5-HT lesions produce reversal-learning deficits in monkeys (Clarke et al., 2004, 2005), whilst attentional set shifting ability is preserved (Clarke et al., 2005).

As decreases in prefrontal 5-HT levels produce reversal learning deficits in monkeys (Clarke et al., 2004, 2005) similar to those observed following Δ^9-THC administration in rats (Egerton et al., 2005), this raises the possibility that cannabinoid-induced impairments in reversal learning may be mediated, at least in part, through disruption of serotonergic transmission in the PFC. Few studies have specifically investigated the effects of cannabinoids on prefrontal cortical

5-HT levels, but, in line with this hypothesis, increases in PFC 5-HT efflux and concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been reported to occur following blockade of CB_1 receptors (Tzavara et al., 2003) and stimulation of CB_1 receptors inhibits 5-HT release in mouse cortical slices (Nakazi et al., 2000). In contrast, however, administration of Δ^9-THC has been reported to have no effect on 5-HT turnover in the medial PFC in vivo (Jentsch et al., 1997). Given that reversal learning may more particularly involve 5-HT transmission in orbital than medial aspects of the PFC (see Clark et al., 2004; Clarke et al., 2004, 2005), and that Δ^9-THC-induced deficits in reversal learning were associated with altered activity in this area (Egerton et al., 2005), it is possible that investigation of the effects of cannabinoids on 5-HT content in more lateral PFC areas may reveal differential effects.

5. Summary and future directions

In conclusion, several lines of evidence suggest that cannabinoids may alter functionality of the PFC and thereby elicit impairments across several domains of complex cognitive function. Both cannabinoid receptors and endogenous cannabinoid compounds are present in the PFC (Bisogno et al., 1999; Di Marzo et al., 2000a,c; Tsou et al., 1998, 1999), from which position they may modulate neurotransmitter release and thereby the neural activity that underpins normal cognitive function. Several studies in both humans and rats have shown that cannabinoid exposure results in alterations in PFC activity (e.g. Block et al., 2002; Freedland et al., 2002; O'Leary et al., 2000; Whitlow et al., 2002), providing evidence that cannabinoid administration may affect the functionality of this brain area.

In accordance with the effects of marijuana intake in humans, several preclinical behavioural studies have demonstrated that acute administration of cannabinoid agonists produces impairments in working memory capacity (see Lichtman et al., 2002). Whilst working memory impairments have typically been assigned to disruption of hippocampal functioning (see Lichtman et al., 2002), some studies suggest that effects may arise from altered neurochemistry of the PFC (Jentsch et al., 1997). The relative contribution of hippocampal and prefrontal mechanisms to cannabinoid-induced working memory impairments warrants further investigation. Preclinical studies have additionally demonstrated cannabinoid-induced impairments in other cognitive domains, such as attentional function (Arguello and Jentsch, 2004) and reversal learning (Egerton et al., 2005). Together, these animal behavioural models of disordered cognition following cannabinoid exposure provide useful platforms for the future investigation of the neural mechanisms that underlie these effects. Indeed, administration of cannabinoid agonists such as Δ^9-THC may alter release of several neurochemicals in the PFC, such as DA (Jentsch et al., 1997), ACh (Gessa et al., 1998b) and 5-HT (Nakazi et al., 2000), that are heavily implicated in control of cognitive function (see Dalley et al., 2004; Robbins, 2000).

To date, few studies have addressed the impact of chronic cannabinoid exposure on cognitive function in rodents, and whether these impairments persist after periods of drug abstinence. This question forms an important clinical concern, as several studies in humans indicate long-term or prolonged effects of marijuana exposure on cognitive functioning (Bolla et al., 2002; Eldreth et al., 2004; Lundqvist, 2005; Pope et al., 2001; Schwartz et al., 1989; Solowij et al., 2002). Future preclinical investigation may aid characterization and understanding of the long-term cognitive effects of cannabinoid exposure, and the neural mechanisms that contribute to these impairments.

Studies in CB_1 receptor knock-out mice (Marsicano et al., 2002; Reibaud et al., 1999; Varvel et al., 2005; Varvel and Lichtman, 2002) or using the CB_1 antagonist SR141716A (Terranova et al., 1996) have also highlighted a possible role for the endogenous cannabinoid system in the negative regulation of some forms of cognition under normal physiological conditions. Prefrontal cortical pathological alterations in the endogenous cannabinoid system have also been associated with disorders of cognition such as schizophrenia (Dean et al., 2001) and depression (Hugund et al., 2004). The link between disordered cannabinoid signalling and cognitive impairment is certainly an important and exciting area of current research, as negative modulation of the endocannabinoid system may confer therapeutic benefit in treating impairments in some cognitive domains (Hugund et al., 2004; Marsicano et al., 2002; Terranova et al., 1996), although we are not aware of any published clinical studies to date.

In summary, although preclinical research has uncovered several interesting findings regarding the interaction of cannabinoids with the prefrontal cortex and the cognitive processes associated with this region, our understanding of these interactions is still relatively immature. Key areas for future research include identification of the mechanisms of the association between cannabinoid-induced alterations in neurotransmitter release in the PFC and resultant cognitive alterations, characterization of the effects of long-term cannabinoid exposure on these processes and the role of the endocannabinoid system in the PFC. No doubt, future preclinical research will further clarify neuroscientific understanding of the impact of cannabinoids on cognitive function in health and disease.

References

Acquas, E., Pisanu, A., Marrocu, P., Goldberg, S., Di Chiara, G., 2001. δ9-Tetrahydrocannabinol enhances cortical and hippocampal acetylcholine release in vivo: a microdialysis study. Eur. J. Pharmacol. 419, 155–161.

Allison, C., Brett, R., Pratt, J., 2004. Deficits in a rodent attentional set shift task induced by repeated THC administration. Program no 690.3. 2004 Abstract Viewer/Itinerary Planner. Society for Neuroscience.

Amen, D.G., Waugh, M., 1998. High resolution brain SPECT imaging of marijuana smokers with AD/HD. J. Psychoactive Drugs 30, 209–214.

Arguello, P.A., Jentsch, J.D., 2004. Cannabinoid CB1 receptor-mediated impairment of visuospatial attention in the rat. Psychopharmacology (Berl) 177, 141–150.

Beltramo, M., Piomelli, D., 2000. Carrier-mediated transport and enzymatic hydrolysis of the endogenous cannabinoid 2-arachidonylglycerol. Neuroreport 11, 1231–1235.

Bergson, C., Mrzljak, L., Smiley, J.F., Pappy, M., Levenson, R., Goldman-Rakic, P.S., 1995. Regional, cellular, and subcellular variations in the distribution of D1 and D5 dopamine receptors in primate brain. J. Neurosci. 15, 7821–7836.

Birrell, J.M., Brown, V.J., 2000. Medial prefrontal cortex mediates perceptual attention set shifting in the rat. J. Neurosci. 20, 4320–4324.

Bisogno, T., Berrendero, F., Ambrosino, G., Cebeira, M., Ramos, J.A., Fernandez-Ruiz, J.J., Di Marzo, V., 1999. Brain regional distribution of endocannabinoids: implications for their biosynthesis and biological function. Biochem. Biophys. Res. Commun. 256, 377–380.

Block, R.I., Ghoneim, M.M., 1993. Effects of chronic marijuana use on human cognition. Psychopharmacology (Berl) 110, 219–228.

Block, R.I., O'Leary, D.S., Hichwa, R.D., Augustinak, J.C., Boles Ponto, L.L., Ghoneim, M.M., Ardnt, S.V., Ehrhardt, J.C., Yuh, W.T.C., Hurtig, R.R., Watkins, G.L., Hall, J.A., Nathan, P.E., Maktabi, M.A., Smith, L.A., Andreasen, N.C., 1999. Effects of chronic marijuana use on regional cerebral blood flow during recall. Society for Neuroscience Abstracts 25, 831.812.

Block, R.I., O'Leary, D.S., Hichwa, R.D., Augustinack, J.C., Boles Ponto, L.L., Ghoneim, M.M., Arndt, S., Hurtig, R.R., Watkins, G.L., Hall, J.A., Nathan, P.E., Andreasen, N.C., 2002. Effects of frequent marijuana use on memory-related regional cerebral blood flow. Pharmacol. Biochem. Behav. 72, 237–250.

Bolla, K.I., Brown, K., Eldreth, D., Tate, K., Cadet, J.L., 2002. Dose-related neurocognitive effects of marijuana use. Neurology 59, 1337–1343.

Braida, D., Sala, M., 2000. Cannabinoid-induced working memory impairment is reversed by a second generation cholinesterase inhibitor in rats. Neuroreport 11, 2025–2029.

Brett, R., MacKenzie, F., Pratt, J., 2001. Delta 9-tetrahydrocannabinol-induced alterations in limbic system glucose use in the rat. Neuroreport 12, 3573–3577.

Brodkin, J., Moerschbaecher, J.M., 1997. SR141716A antagonizes the disruptive effects of cannabinoid ligands on learning in rats. J. Pharmacol. Exp. Ther. 282, 1526–1532.

Brown, V.J., Bowman, E.M., 2002. Rodent models of prefrontal cortical function. Trends Neurol. Sci. 25, 340–343.

Bukoski, R.D., Batkai, S., Jarai, Z., Wang, Y., Offertaler, L., Jackson, W.F., Kunos, G., 2002. CB(1) receptor antagonist SR141716A inhibits Ca(2+)-induced relaxation in CB(1) receptor-deficient mice. Hypertension 39, 251–257.

Burk, J.A., Mair, R.G., 2001. Effects of intralaminar thalamic lesions on sensory attention and motor intention in the rat: a comparison with lesions involving frontal cortex and hippocampus. Behav. Brain. Res. 123, 49–63.

Campbell, K.A., Foster, T.C., Hampson, R.E., Deadwyler, S.A., 1986a. delta 9-Tetrahydrocannabinol differentially affects sensory-evoked potentials in the rat dentate gyrus. J. Pharmacol. Exp. Ther. 239, 936–940.

Campbell, K.A., Foster, T.C., Hampson, R.E., Deadwyler, S.A., 1986b. Effects of delta 9-tetrahydrocannabinol on sensory-evoked discharges of granule cells in the dentate gyrus of behaving rats. J. Pharmacol. Exp. Ther. 239, 941–945.

Chen, J., Paredes, W., Lowinson, J.H., Gardner, E.L., 1990. D9-Tetrahydrocannabinol enhances presynaptic dopamine efflux in medial prefrontal cortex. Eur. J. Pharmacol. 190, 259–262.

Christakou, A., Robbins, T.W., Everitt, B.J., 2001. Functional disconnection of a prefrontal cortical-dorsal striatal system disrupts choice reaction time performance: implications for attentional function. Behav. Neurosci. 115, 812–825.

Chudasama, Y., Passetti, F., Rhodes, S.E., Lopian, D., Desai, A., Robbins, T.W., 2003. Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. Behav. Brain. Res. 146, 105–119.

Clark, L., Cools, R., Robbins, T.W., 2004. The neuropsychology of ventral prefrontal cortex: Decision making and reversal learning. Brain Cogn. 55, 41–53.

Clarke, H.F., Dalley, J.W., Crofts, H.S., Robbins, T.W., Roberts, A.C., 2004. Cognitive inflexibility after prefrontal serotonin depletion. Science 304, 878–880.

Clarke, H.F., Walker, S.C., Crofts, H.S., Dalley, J.W., Robbins, T.W., Roberts, A.C., 2005. Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. J. Neurosci. 25, 532–538.

Cravatt, B.F., Giang, D.K., Mayfield, S.P., Boger, D.L., Lerner, R.A., Gilula, N.B., 1996. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature 384, 83–87.

Dalley, J.W., McGaughy, J., O'Connell, M.T., Cardinal, R.N., Levita, L., Robbins, T.W., 2001. Distinct changes in cortical acetylcholine and noradrenaline efflux during contingent and noncontingent performance of a visual attention task. J. Neurosci. 21, 4908–4914.

Dalley, J.W., Cardinal, R.N., Robbins, T.W., 2004. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci. Biobehav. Rev. 28, 771–784.

Deadwyler, S.A., Heyser, C.J., Michaelis, R.C., Hampson, R.E., 1990. The effects of delta-9-THC on mechanisms of learning and memory. NIDA Res. Monogr. 97, 79–93.

Dean, B., Sundram, S., Bradbury, R., Scarr, E., Copolov, D., 2001. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience 103, 9–15.

Delatour, B., Gisquet-Verrier, P., 1999. Lesions of the prelimbic-infralimbic cortices in rats do not disrupt response selection processes but induce delay-dependent deficits: evidence for a role in working memory? Behav. Neurosci. 113, 941–955.

Devane, W.A., Dysarz, F.A., Johnson, M.R., Melvin, L.S., Howlett, A.C., 1988. Determination and characterisation of a cannabinoid receptor in the rat brain. Mol. Pharmacol. 34, 604–613.

Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., Mechoulam, R., 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258, 1946–1949.

Di Marzo, V., Berrendero, F., Bisogno, T., Gonzalez, S., Cavaliere, P., Romero, J., Cebeira, M., Ramos, J.A., Fernandez-Ruiz, J.J., 2000a. Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of delta 9-tetrahydrocannabinol-tolerant rats. J. Neurochem. 74, 1627–1635.

Di Marzo, V., Breivogel, C., Bisogono, T., Melck, D., Patrick, G., Tao, Q., Szallasi, A., Razdan, R.K., Martin, B.R., 2000b. Neurobehavioural activity of N-vanillyl-arachidonyl-amide. Eur. J. Pharmacol. 406, 363–374.

Di Marzo, V., Hill, M.P., Bisogno, T., Crossman, A.R., Brotchie, J.M., 2000c. Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. FASEB J. 14, 1432–1438.

Diana, M.A., Marty, A., 2004. Endocannabinoid-mediated short term synaptic plasticity:depolarisation-induced suppression of inhibition (DSI) and depolarisation-induced suppression of DSE. Br. J. Pharmacol. 142, 9–19.

Diana, M., Melis, M., Gessa, G.L., 1998. Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. Eur. J. Neurosci. 10, 2825–2830.

Dias, R., Robbins, T.W., Roberts, A.C., 1996a. Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380, 69–72.

Dias, R., Robbins, T.W., Roberts, A.C., 1996b. Primate analogue of the wisconsin card sorting test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. Behav. Neurosci. 110, 872–886.

Dias, R., Robbins, T.W., Roberts, A.C., 1997. Dissociable forms of inhibitory control within prefrontal cortex with an analog of the wisconsin card sort test: restriction to novel situations and independence from 'on-line' processing. J. Neurosci. 17, 9285–9297.

Doyere, V., Burette, F., Negro, C.R., Laroche, S., 1993. Long-term potentiation of hippocampal afferents and efferents to prefrontal cortex: implications for associative learning. Neuropsychologia 31, 1031–1053.

Egerton, A., Pratt, J.A., Brett, R., 2001. Differential dose effects of g-tetrahydrocannabinol on behaviour and gene expression. Behavioural pharmacology 12, s33.

Egerton, A., Brett, R.R., Pratt, J.A., 2005. Acute Delta(9)-Tetrahydrocannabinol-induced deficits in reversal learning: neural correlates of affective inflexibility. Neuropsychopharmacology 30 1895–1905.

Egertova, M., Cravatt, B.F., Elphick, M.R., 2003. Comparative analysis of fatty acid amide hydrolase and CB(1) cannabinoid receptor expression in the mouse brain: evidence of a widespread role for fatty acid amide hydrolase in regulation of endocannabinoid signaling. Neuroscience 119, 481–496.

Eichenbaum, H., Schoenbaum, G., Young, B., Bunsey, M., 1996. Functional organization of the hippocampal memory system. Proc. Natl Acad. Sci. USA 93, 13500–13507.

Eldreth, D.A., Matochik, J.A., Cadet, J.L., Bolla, K.I., 2004. Abnormal brain activity in prefrontal regions in abstinent marijuana users. Neuroimage 23, 914–920.

Everitt, B.J., Robbins, T.W., 1997. Central cholinergic systems and cognition. Ann. Rev. Psychol. 48, 649–684.

Fadda, P., Robinson, L., Fratta, W., Pertwee, R.G., Riedel, G., 2004. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. Neuropharmacology 47, 1170–1179.

Fellows, L.K., Farah, M.J., 2003. Ventromedial frontal cortex mediates affective shifting in humans: evidence from a reversal learning paradigm. Brain 126, 1830–1837.

Ferrari, F., Ottani, A., Vivoli, R., Giuliani, D., 1999. Learning impairment produced in rats by the cannabinoid agonist HU 210 in a water-maze task. Pharmacol. Biochem. Behav. 64, 555–561.

Ferraro, L., Tomasini, M.C., Gessa, G.L., Bebe, B.W., Tanganelli, S., Antonelli, T., 2001. The cannabinoid receptor agonist WIN 55,212-2 regulates glutamate transmission in rat cerebral cortex: an in vivo and in vitro study. Cereb. Cortex 11, 728–733.

Fletcher, J.M., Page, B., Francis, D.J., Copeland, K., Naus, M.J., Davis, C.M., Morris, R., Krauskopf, D., Satz, P., 1996. Cognitive correlates of long-term cannabis use in costa rican men. Arch. Gen. Psychiatry 53, 1051–1057.

Floresco, S.B., Seamans, J.K., Phillips, A.G., 1996. Differential effects of lidocaine infusions into the ventral CA1/subiculum or the nucleus accumbens on the acquisition and retention of spatial information. Behav. Brain. Res. 81, 163–171.

Floresco, S.B., Seamans, J.K., Phillips, A.G., 1997. Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. J. Neurosci. 17, 1880–1890.

Freedland, C.S., Whitlow, C.T., Miller, M.D., Porrino, L.J., 2002. Dose-dependent effects of delta9-tetrahydrocannabinol on rates of local cerebral glucose utilization in rat. Synapse 45, 134–142.

Fuster, J.M., 1991. The prefrontal cortex and its relation to behavior. Prog. Brain. Res. 87, 201–211.

Gellman, R.L., Aghajanian, G.K., 1993. Pyramidal cells in piriform cortex receive a convergence of inputs from monoamine activated GABAergic interneurons. Brain Res. 600, 63–73.

Gessa, G., Melis, M., Muntoni, A., Diana, M., 1998a. Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB1 receptors. Eur. J. Pharmacol. 341, 39–44.

Gessa, G.L., Casu, M.A., Carta, G., Mascia, M.S., 1998b. Cannabinoids decrease acetylcholine release in the medial-prefrontal cortex and hippocampus, reversal by SR 141716A. Eur. J. Pharmacol. 355, 119–124.

Gioanni, Y., Thierry, A.M., Glowinski, J., Tassin, J.P., 1998. Alpha1-adrenergic, D1, and D2 receptors interactions in the prefrontal cortex: implications for the modality of action of different types of neuroleptics. Synapse 30, 362–370.

Glass, M., Dragunow, M., Faull, R.L., 1997. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 77, 299–318.

Godbout, R., Mantz, J., Pirot, S., Thierry, A.M., 1991. Inhibitory influence of mesocortical dopaminegic neurons on their target cells: electrophysiological and pharmacological characterization. J. Pharmacol. Exp. Ther. 258, 728–738.

Goldman-Rakic, P.S., 1987. Motor control function of the prefrontal cortex. Ciba Found. Symp. 132, 187–200.

Goldman-Rakic, P.S., 1996. Regional and cellular fractionation of working memory. Proc. Natl Acad. Sci. USA 93, 13473–13480.

Goldman-Rakic, P.S., Leranth, C., Williams, S.M., Mons, N., Geffard, M., 1989. Dopamine synaptic complex with pyramidal neurons in primate cerebral cortex. Proc. Natl Acad. Sci. USA 86, 9015–9019.

Goldman-Rakic, P.S., Bates, J.F., Chafee, M.V., 1992. The prefrontal cortex and internally generated motor acts. Curr. Opin. Neurobiol. 2, 830–835.

Goldstein, L.E., Rasmusson, A.M., Bunney, B.S., Roth, R.H., 1994. The NMDA glycine site antagonist (+)-HA966 selectively regulates conditioned stress-induced metabolic activation of the mesoprefrontal dopamine but not serotonin systems: a behavioural, neuroendocrine and neurochemical study in the rat. J. Neurosci. 14, 4937–4950.

Granon, S., Passetti, F., Thomas, K.L., Dalley, J.W., Everitt, B.J., Robbins, T.W., 2000. Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. J. Neurosci. 20, 1208–1215.

Griffin, G., Atkinson, P.J., Showalter, V.M., Martin, B.R., Abood, M.E., 1998. Evaluation of cannabinoid receptor agonists and antagonists using the guanosine-5′-O-(3-[35S]thio)-triphosphate binding assay in rat cerebellar membranes. J. Pharmacol. Exp. Ther. 285, 553–560.

Groenewegen, H.J., Uylings, H.B.M., 2000. The prefrontal cortex and the integration of sensory, limbic and autonomic function. Prog. Brain Res. 126, 3–28.

Hajos, N., Freund, T.F., 2002. Distinct cannabinoid sensitive receptors regulate hippocampal excitation and inhibition. Chem. Phys. Lipids 121, 73–82.

Hampson, R.E., Deadwyler, S., 1999a. Role of cannabinoid receptors in memory storage. Neurobiol. Dis. 5, 474–482.

Hampson, R.E., Deadwyler, S.A., 1999b. Cannabinoids, hippocampal function and memory. Life Sci. 65, 715–723.

Hampson, R.E., Deadwyler, S.A., 2000. Cannabinoids reveal the necessity of hippocampal neural encoding for short term memory in rats. J. Neurosci. 20, 8932–8942.

Hampson, A.J., Bornheim, L.M., Scanziani, M., Yost, C.S., Gray, A.T., Hansen, B.M., Leonoudakis, D.J., Bickler, P.E., 1998. Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission. J. Neurochem. 70, 671–676.

Herkenham, M., 1992. Cannabinoid receptor localisation in brain: relationship to motor and reward systems. Ann. NY Acad. Sci. 654, 19–32.

Herkenham, M., Lynn, A.B., Little, M.D., Johnson, M.R., Melvin, L.S., de Costa, B.R., Rice, K.C., 1990. Cannabiniod receptor localisation in brain. Proc. Natl Acad. Sci. USA 87, 1932–1936.

Herkenham, M., Lynn, A.B., Johnson, M.R., Melvin, L.S., de Costa, B.R., Rice, K.C., 1991. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J. Neurosci. 11, 563–583.

Heyser, C.J., Hampson, R.E., Deadwyler, S.A., 1993. Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: alterations in short-term memory associated with changes in task-specific firing of hippocampal cells. J. Pharm. Exp. Ther. 264, 294–307.

Hill, M.N., Froc, D.J., Fox, C.J., Gorzalka, B.B., Christie, B.R., 2004. Prolonged cannabinoid treatment results in spatial working memory deficits and impaired long-term potentiation in the CA1 region of the hippocampus in vivo. Eur. J. Neurosci. 20, 859–863.

Howlett, A.C., Johnson, M.R., Melvin, L.S., Milne, G.M., 1988. Nonclassical cannabinoid analgetics inhibit adenylate cyclase: development of a cannabinoid receptor model. Mol. Pharmacol. 33, 297–302.

Hugund, B.L., Vinod, K.Y., Kassir, S.A., Basavarajappa, B.S., Yalamanchill, R., Cooper, T.B., Mann, J.J., Arango, V., 2004. Upregulation of CB1 receptors and agonist-stimulated [35S]GTPgS binding in the prefrontal cortex of depressed suicide victims. Mol. Psychiatry 9, 184–190.

Ilan, A.B., Smith, M.E., Gevins, A., 2004. Effects of marijuana on neurophysiological signals of working and episodic memory. Psychopharmacology (Berl) 176, 214–222.

Inui, K., Egashira, N., Mishima, K., Yano, A., Matsumoto, Y., Hasebe, N., Abe, K., Hayakawa, K., Ikeda, T., Iwasaki, K., Fujiwara, M., 2004. The serotonin1A receptor agonist 8-OHDPAT reverses delta 9-tetrahydrocannabinol-induced impairment of spatial memory and reduction of acetylcholine release in the dorsal hippocampus in rats. Neurotox. Res. 6, 153–158.

Izaki, Y., Maruki, K., Hori, K., Nomura, M., 2001. Effects of rat medial prefrontal cortex temporal inactivation on a delayed alternation task. Neurosci. Lett. 315, 129–132.

Jentsch, J.D., Taylor, J.R., 1999. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl) 146, 373–390.

Jentsch, J.D., Andrusiak, E., Tran, A., Bowers Jr., M.B., Roth, R.H., 1997. Delta 9-tetrahydrocannabinol increases prefrontal cortical catecholaminergic utilization and impairs spatial working memory in the rat: blockade of dopaminergic effects with HA966. Neuropsychopharmacology 16, 426–432.

Jentsch, J.D., Verrico, C.D., Le, D., Roth, R.H., 1998a. Repeated exposure to δ9-tetrahydrocannabinol reduces prefrontal cortical dopamine metabolism in the rat. Neurosci. Lett. 246, 169–172.

Jentsch, J.D., Wise, A., Katz, Z., Roth, R.H., 1998b. α-Noradrenergic receptor modulation of the phencyclidine- and δ9-tetrahydrocannabinol- induced increases in dopamine utilization in rat prefrontal cortex. Synapse 28, 21–26.

Jones, B., Mishkin, M., 1972. Limbic lesions and the problem of stimulus—reinforcement associations. Exp. Neurol. 36, 362–377.

Kanayama, G., Rogowska, J., Pope, H.G., Gruber, S.A., Yurgelun-Todd, D.A., 2004. Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. Psychopharmacology (Berl) 176, 239–247.

Katona, I., Sperlagh, B., Sik, A., Kafalvi, A., Vizi, E.S., Mackie, K., Freund, T.F., 1999. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J. Neurosci. 19, 4544–4558.

Kesner, R.P., Hunt, M.E., Williams, J.M., Long, J.M., 1996. Prefrontal cortex and working memory for spatial response, spatial location, and visual object information in the rat. Cereb. Cortex 6, 311–318.

Laroche, S., Davis, S., Jay, T.M., 2000. Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. Hippocampus 10, 438–446.

Law-Tho, D., Hirsch, J.C., Crepel, F., 1994. Dopamine modulation of synaptic transmission in rat prefrontal cortex: an in vitro electrophysiological study. Neurosci. Res. 21, 151–160.

Lee, I., Kesner, R.P., 2003a. Differential roles of dorsal hippocampal subregions in spatial working memory with short versus intermediate delay. Behav. Neurosci. 117, 1044–1053.

Lee, I., Kesner, R.P., 2003b. Time-dependent relationship between the dorsal hippocampus and the prefrontal cortex in spatial memory. J. Neurosci. 23, 1517–1523.

Lehmann, O., Grottick, A.J., Cassel, J.-C., Higgins, G.A., 2001. 192 IgG saporin-induced lesions of the basal forebrain: effects on attention as assessed by the 5-choice serial reaction time task. Behav. Pharmacol. 12, S58.

Lichtman, A.H., 2000. SR 141716A enhances spatial memory as assessed in a radial-arm maze task in rats. Eur. J. Pharmacol. 404, 175–179.

Lichtman, A.H., Martin, B.R., 1996. δ9-Tetrahydrocannabinol impairs spatial memory through a cannabinoid receptor mechanism. Psychopharmacology 126, 125–131.

Lichtman, A.H., Dimen, K.R., Martin, B.R., 1995. Systemic or intrahippocampal cannabinoid administration impairs spatial memory in rats. Psychopharmacology (Berl) 119, 282–290.

Lichtman, A.H., Varvel, S.A., Martin, B.R., 2002. Endocannabinoids in cognition and dependence. Prostaglandins Leukot. Essent. Fatty Acids 66, 269–285.

Lundqvist, T., 2005. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. Pharmacol. Biochem. Behav. 81, 319–330.

Lundqvist, T., Jonsson, S., Warkentin, S., 2001. Frontal lobe dysfunction in long-term cannabis users. Neurotoxicol. Teratol. 23, 437–443.

Macavoy, M.G., Marks, D.F., 1975. Divided attention performance of cannabis users and non-users following cannabis and alcohol. Psychopharmacologia 44, 147–152.

Mailleux, P., Vanderhaeghen, J., 1992. Distribution of neuronal cannabinoid receptors in the adult rat brain: a comparative receptor binding radioautography and in situ hybridisation histochemistry. Neuroscience 48, 655–668.

Mailleux, P., Verslype, M., Preud'homme, X., Vanderhaeghen, J., 1994. Activation of multiple transcription factor genes by tetrahydrocannabinol in rat forebrain. Neuroreport 5, 1265–1268.

Mallet, P.E., Beninger, R.J., 1998. The cannabinoid CB1 receptor antagonist SR141716A attenuates the memory impairment produced by delta9-tetrahydrocannabinol or anandamide. Psychopharmacology (Berl) 140, 11–19.

Mansbach, R.S., Rovetti, C.C., Winston, E.N., Lowe III., J.A., 1996. Effects of the cannabinoid CB1 receptor antagonist SR141716A on the behaviour of pigeons and rats. Psychopharmacology (Berl) 124, 315–322.

Margulies, J.E., Hammer, J.R.P., 1991. Tetrahydrocannabinol alters cerebral metabolism in a biphasic, dose-dependent manner in rat brain. J. Pharmacol. 202, 373–378.

Marsicano, G., Lutz, B., 1999. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations of the adult mouse forebrain. Eur. J. Neurosci 11, 4213–4225.

Marsicano, G., Wotjak, C.T., Azad, S.C., Bisogno, T., Rammes, G., Cascio, M.G., Hermann, H., Tang, J., Hofmann, C., Zieglgansberger, W., Di Marzo, V., Lutz, B., 2002. The endogenous cannabinoid system controls extinction of aversive memories. Nature 418, 530–534.

Mathew, R.J., Wilson, W.H., 1992. The effects of marijuana on cerebral blood flow and metabolism. In: Murphy, L., Bartke, A. (Eds.), Marijuana/Cannabinoids: Neurobiology and Neurophysiology. CRC Press, Boca Raton, FL.

Mathew, R.J., Wilson, W.H., 1993. Acute changes in cerebral blood flow after smoking marijuana. Life Sci. 52, 757–767.

Mathew, R.J., Wilson, W.H., Coleman, R.E., Turkington, T.G., DeGrado, T.R., 1997. Marijuana intoxication and brain activation in marijuana smokers. Life Sci. 60, 2075–2089.

Mathew, R.J., Wilson, W.H., Turkington, T.G., Hawk, T.C., Coleman, R.E., DeGrado, T.R., Provenzale, J., 2002. Time course of tetrahydrocannabinol-induced changes in regional cerebral blood flow measured with positron emission tomography. Psychiatry Res. 116, 173–185.

Mato, S., Pazos, A., 2004. Influence of age, postmortem delay and freezing storage period on cannabinoid receptor density and functionality in human brain. Neuropharmacology 46, 716–726.

Matsuda, L.A., Bonner, T.I., Lolait, S.J., 1993. Localization of cannabinoid receptor mRNA in rat brain. J. Comp. Neurol. 327, 535–550.

McAlonan, K., Brown, V.J., 2003. Orbital prefrontal cortex mediates reversal learning and not attentional set shifting in the rat. Behav. Brain. Res. 146, 97–103.

McGaughy, J., Dalley, J.W., Morrison, C.H., Everitt, B.J., Robbins, T.W., 2002. Selective behavioural and neurochemical effects of cholinergic lesions produced by intrabasalis infusions of 192 IgG-saporin on attentional performance in a five-choice serial treaction time task. J. Neurosci. 22, 1905–1913.

Mechoulam, R., Ben-Shabat, S., Hanus, L., Ligumsky, M., Kaminski, N.E., Schatz, A.R., Gopher, A., Almog, S., Martin, B.R., Compton, D.R., Pertwee, R.G., Griffin, G., Bayewitch, M., Barg, J., Vogel, Z., 1995. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem. Pharmacol. 50, 83–90.

Melis, M., Perra, S., Mutoni, A.L., Pillolla, G., Lutz, B., Marsicano, G., Di Marzo, V., Gessa, G.L., Pistis, M., 2004. Prefrontal cortex stimulation induces 2-arachidonoyl-glycerol-mediated suppression of excitation in dopamine neurones. J. Neurosci. 24, 10707–10715.

Miller, L.L., Branconnier, R.J., 1983. Cannabis: effects on memory and the cholinergic limbic system. Psychol. Bull. 93, 441–456.

Mishima, K., Egashira, N., Hirosawa, N., Fujii, M., Matsumoto, Y., Iwasaki, K., Fujiwara, M., 2001. Characteristics of learning and memory impairment induced by delta9-tetrahydrocannabinol in rats. Jpn. J. Pharmacol. 87, 297–308.

Mishima, K., Egashira, N., Matsumoto, Y., Iwasaki, K., Fujiwara, M., 2002. Involvement of reduced acetylcholine release in delta9-tetrahydrocannabinol-induced impairment of spatial memory in the 8-arm radial maze. Life Sci. 72, 397–407.

Misner, D.L., Sullivan, J.M., 1999. Mechanism of cannabinoid effects on long-term potentiation and depression in hippocampal CA1 neurons.. J. Neurosci. 19, 6795–6805.

Miyamoto, A., Yamamoto, T., Watanabe, S., 1995. Effect of repeated administration of delta 9-tetrahydrocannabinol on delayed matching-to-sample performance in rats. Neurosci. Lett. 201, 139–142.

Miyamoto, A., Yamamoto, T., Ohno, M., Watanabe, S., Tanaka, H., Morimoto, S., Shoyama, Y., 1996. Roles of dopamine D1 receptors in D9-tetrahydrocannabinol — induced expression of Fos protein in the rat brain. Brain Res. 710, 234–240.

Molina-Holgado, F., Gonzalez, M.I., Leret, M.L., 1995. Effect of delta 9-tetrahydrocannabinol on short-term memory in the rat. Physiol. Behav. 57, 177–179.

Morgan, J.I., Curran, T., 1989. Stimulus-transcription coupling: immediate-early genes. Trends Neurol. Sci. 12, 459–462.

Morgan, M.A., Romanski, L.M., LeDoux, J.E., 1993. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci. Lett. 163, 109–113.

Morris, R., 1984. Developments of a water-maze procedure for studying spatial learning in the rat. J. Neurosci. Methods 11, 47–60.

Morrow, B.A., Elsworth, J.D., Inglis, F.M., Roth, R.H., 1999. An antisense oligonucleotide reverses the footshock-induced expression of Fos in the rat medial prefrontal cortex and the subsequent expression of conditioned fear-induced immobility. J. Neurosci. 19, 5666–5673.

Mrzljak, L., Bergson, C., Pappy, M., Huff, R., Levenson, R., Goldman-Rakic, P.S., 1996. Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. Nature 381, 245–248.

Muir, J.L., Everitt, B.J., Robbins, T.W., 1996. The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. Cereb. Cortex 6, 470–481.

Murphy, B.L., Arnsten, A.F., Goldman-Rakic, P.S., Roth, R.H., 1996a. Increased dopamine turnover in the prefrontal cortex impairs spatial working memory in rats and monkeys. Proc. Natl Acad. Sci. USA 93, 1329.

Murphy, B.L., Arnsten, A.F., Jentsch, J.D., Roth, R.H., 1996b. Dopamine and spatial working memory in rats and monkeys: pharmacological reversal of stress-induced impairment. J. Neurosci. 93, 1325–1329.

Nakamura, E.M., da Silva, E.A., Concilio, G.V., Wilkinson, D.A., Masur, J., 1991. Reversible effects of acute and long-term administration of delta-9-tetrahydrocannabinol (THC) on memory in the rat. Drug Alcohol Depend. 28, 167–175.

Nakazi, M., Bauer, U., Nickel, T., Kathmann, M., Schlicker, E., 2000. Inhibition of serotonin release in the mouse brain via presynaptic cannabinoid CB1 receptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 361, 19–24.

Nava, F., Carta, G., Battasi, A.M., Gessa, G.L., 2000. D2 dopamine receptors enable δ9-tetrahydrocannabinol induced memory impairment and reduction of hippocampal extracellular acetylcholine concentration. Br. J. Pharmacol. 130, 1201–1210.

Nava, F., Carta, G., Colombo, G., Gessa, G.L., 2001. Effects of chronic Delta(9)-tetrahydrocannabinol treatment on hippocampal extracellular acetylcholine concentration and alternation performance in the T-maze. Neuropharmacology 41, 392–399.

Nelson, R.J., Young, K.A., 1998. Behavior in mice with targeted disruption of single genes. Neurosci. Biobeh. Rev. 22 (3), 453–462.

Newman, J., Grace, A.A., 1999. Binding across time: the selective gating of frontal and hippocampal systems modulating working memory and attentional states. Conscious. Cogn. 8, 196–212.

O'Leary, D.S., Block, R.I., Flaum, M., Schultz, S.K., Boles Ponto, L.L., Watkins, G.L., Hurtig, R.R., Andreasen, N.C., Hichwa, R.D., 2000. Acute marijuana effects on rCBF and cognition: a PET study. Neuroreport 11, 3835–3841.

O'Leary, D.S., Block, R.I., Koeppel, J.A., Flaum, M., Schultz, S.K., Andreasen, N.C., Ponto, L.B., Watkins, G.L., Hurtig, R.R., Hichwa, R.D., 2002. Effects of smoking marijuana on brain perfusion and cognition. Neuropsychopharmacology 26, 802–816.

Olton, D.S., 1987. The radial arm maze as a tool in behavioral pharmacology. Physiol. Behav. 40, 793–797.

Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219.

Owen, A.M., Roberts, A.C., Polkey, C.E., Sahakian, B.J., Robbins, T.W., 1991. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 29, 993–1006.

Pan, X., Ikeda, S.R., Lewis, D.L., 1998. SR 141716A acts as an inverse agonist to increase neuronal voltage-dependent Ca2+ currents by reversal of tonic CB1 cannabinoid receptor activity. Mol. Pharmacol. 54, 1064–1072.

Passetti, F., Dalley, J.W., O'Connell, M.T., Everitt, B.J., Robbins, T.W., 2000. Increased acetylcholine release in the rat medial prefrontal cortex during performance of a visual attention task. Eur. J. Neurosci. 12, 3051–3058.

Pirot, S., Godbout, R., Mantz, J., Tassin, J.P., Glowinski, J., Thierry, A.M., 1992. Inhibitory effects of ventral tegmental area stimulation on the activity of prefrontal cortical neurons: evidence for the involvement of both dopaminergic and GABAergic components. Neuroscience 49, 857–865.

Pistis, M., Porcu, G., Melis, M., Diana, M., Gessa, G.L., 2001. Effects of cannabinoids on prefrontal neuronal responses to ventral tegmental area stimulation. Eur. J. Neurosci. 14, 96–102.

Pistis, M., Ferraro, L., Pira, L., Flore, G., Tanganelli, S., Gessa, G.L., Devoto, P., 2002. Delta(9)-tetrahydrocannabinol decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex: an in vivo microdialysis study. Brain. Res. 948, 155–158.

Pope, H.G., Yurgelun-Todd, D., 1996. The residual cognitive effects of heavy marijuana use in college students. JAMA 275, 521–527.

Pope, H.G., Gruber, A.J., Hudson, J.I., Heustis, M.A., Yurgulen-Todd, D., 2001. Neuropsychological performance in long-term cannabis users. Arch. Gen. Psychiatry 58, 909–915.

Porcella, A., Gessa, G.L.P., Pani, L., 1998. δ9-Tetrahydrocannabinol increases sequence-specific AP-1 DNA-binding activity and Fos-related antigens in the rat brain. Eur. J. Neurosci. 10, 1743–1751.

Porter, M.C., Burk, J.A., Mair, R.G., 2000. A comparison of the effects of hippocampal or prefrontal cortical lesions on three versions of delayed non-matching-to-sample based on positional or spatial cues. Behav. Brain Res. 109, 69–81.

Presburger, G., Robinson, J.K., 1999. Spatial signal detection in rats is differentially disrupted by delta-9-tetrahydrocannabinol, scopolamine, and MK-801. Behav. Brain Res. 99, 27–34.

Preuss, T.M., 1995. Do rats have a prefrontal cortex? The Rose-Woolsey-Akert program reconsidered. J. Cogn. Res. 7, 1–24.

Ragozzino, M.E., 2002. The effects of dopamine D(1) receptor blockade in the prelimbic-infralimbic areas on behavioral flexibility. Learn. Mem. 9, 18–28.

Ragozzino, M.E., Kesner, R.P., 1998. The effects of muscarinic cholinergic receptor blockade in the rat anterior cingulate and prelimbic/infralimbic cortices on spatial working memory. Neurobiol. Learn. Mem. 113, 32–41.

Reibaud, M., Obinou, M.C., Ledent, C., Parmantier, M., Bohme, G.A., Castel-Barthe, M.N., Imperato, A., 1999. Enhancement of memory in CB1 receptor knock-out mice. Eur. J. Pharmacol. 379, R1–R2.

Retaux, S., Besson, M.J., Penit-Soria, J., 1991. Synergism between D1 and D2 dopamine receptors in the inhibition of the evoked release of [3H]GABA in the rat prefrontal cortex. Neuroscience 43, 323–329.

Rinaldi-Carmona, M., Barth, F., Heaulume, M., Shire, D., Calandra, B., Congy, C., Martinez, S., Maruani, J., Neliat, G., Caput, D., Ferrara, P., Soubrie, P., Breliere, J.C., Le Fur, G., 1994. SR 141716A, a potent and selective antagonist of the brian cannabinoid receptor. FEBS Lett. 350, 240–244.

Robbins, T.W., 2000. Chemical neuromodulation of frontal-executive functions in humans and other animals. Exp. Brain. Res. 133, 130–138.

Roberts, A.C., Robbins, T.W., Everitt, B.J., Muir, J.L., 1992. A specific form of cognitive rigidity following excitotoxic lesions of the basal forebrain in monkeys. Neuroscience 47, 251–264.

Roberts, A.C., De Salvia, M.A., Wilkinson, L.S., Collins, P., Muir, J.L., Everitt, B.J., Robbins, T.W., 1994. 6-Hydroxydopamine lesions of the

prefrontal cortex in monkeys enhance performance on an analog of the wisconin card sort test: possible interactions with subcortical dopamine. J. Neurosci. 14, 2531–2544.

Rogers, R.D., Blackshaw, A.J., Middleton, H.C., Matthews, K., Hawtin, K., Crowley, C., Hopwood, A., Wallace, C., Deakin, J.F., Sahakian, B.J., Robbins, T.W., 1999a. Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. Psychopharmacology (Berl) 146, 482–491.

Rogers, R.D., Everett, B.J., Baldaccio, A., Blackshaw, A.J., Swainson, R., Wynne, K., Baker, N.B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J.F.W., Sahakian, B.J., Robbins, T.W., 1999b. Dissociable deficits in decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan—depleted normal volunteers: Evidence for monoaminergic mechanisms. Neuropsychopharmacology 20, 322–339.

Rolls, E.T., Hornak, J., Wade, D., McGrath, J., 1994. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J. Neurol. Neurosurg. Psychiatry 57, 1518–1524.

Rose, J.E., Woolsey, C.N., 1948. The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep and cat. Res. Publ. Assoc. Nerv. Ment. Dis. 27, 210–232.

Sarter, M., 2004. Animal cognition: defining the issues. Neurosci. Biobehav. Rev. 28, 645–650.

Schulze, G.E., McMillan, D.E., Bailey, J.R., Scallet, A., Ali, S.F., Slikker Jr.., W., Paule, M.G., 1988. Acute effects of delta-9-tetrahydrocannabinol in rhesus monkeys as measured by performance in a battery of complex operant tests. J. Pharmacol. Exp. Ther. 245, 178–186.

Schwartz, R.H., Gruenewald, P.J., Kltzner, M., Fedio, P., 1989. Short-term memory impairment in cannabis-dependent adolescents. Am. J. Disord. Child. 143, 1214–1219.

Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 74, 1–58.

Seamans, J.K., Floresco, S.B., Phillips, A.G., 1998. D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. J. Neurosci. 18, 1613–1621.

Selley, D.E., Stark, S., Sim, L.J., Childers, S.R., 1996. Cannabinoid receptor stimulation of guanosine-5′-O-(3-[35S]thio)triphosphate binding in rat brain membranes. Life Sci. 59, 659–668.

Shah, Y.B., Prior, M.J.W., Dixon, A.L., Morris, P.G., Marsden, C.A., 2004. Detection of cannabinoid agonist evoked increase in BOLD contrast in rats using functional magnetic resonance imaging. Neuropharmacology 46, 379–387.

Shen, M., Piser, T.M., Seybold, V.S., Thayer, S.A., 1996. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J. Neurosci. 16, 4322–4334.

Solowij, N., 1995. Do cognitive impairments recover following cessation of cannabis use? Life Sci. 56, 2119–2126.

Solowij, N., Michie, P.T., Fox, A.M., 1995. Differential impairments of selective attention due to frequency and duration of cannabis use. Biol. Psychiatry 37, 731–739.

Solowij, N., Stephens, R., Roffman, R.A., Babor, T., 2002. Does marijuana use cause long-term cognitive deficits? JAMA 287, 2653–2654 (author reply 2654).

Stam, C.J., de Bruin, J.P., van Haelst, A.M., van der Gugten, J., Kalsbeek, A., 1989. Influence of the mesocortical dopaminergic system on activity, food hoarding, social-agonistic behavior, and spatial delayed alternation in male rats. Behav. Neurosci. 103, 24–35.

Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shinoda, A., Itoh, K., Yamashita, A., Waku, K., 1995. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem. Biophys. Res. Commun. 215, 89–97.

Tanda, G., Pontieri, F.E., Di Chiara, G., 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ1 opioid receptor mechanism. Science 276, 2048–2050.

Terranova, J.P., Storme, J.J., Perio, A., Rinaldi-Carmona, M., Le Fur, G., Soubrie, P., 1996. Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR141716. Psychopharmacology (Berl) 126, 165–172.

Thomas, E.A., Cravatt, B.F., Danielson, P.E., Gilula, N.B., Sutcliffe, J.G., 1997. Fatty acid amide hydrolase, the degradative enzyme for anandamide and oleamide, has selective distribution in neurons within the rat central nervous system. J. Neurosci. Res. 50, 1047–1052.

Trettel, J., Levine, E.S., 2002. Cannabinoids depress inhibitory synaptic inputs received by layer 2/3 pyramial neurons in the neocortex. J. Neurophysiol. 88, 534–539.

Tsou, K., Brown, S., Sanudo-Pena, M.C., Mackie, K., Walker, J.M., 1998. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 832, 393–411.

Tsou, K., Nogueron, M.I., Muthian, S., Sanudo-Pena, M.C., Hillard, C.J., Deutsch, D.G., Walker, J.M., 1999. Fatty acid amide hydrolase is located preferentially in large neurons in rat central nervous system as revealed by immunohistochemistry. Neurosci. Lett. 254, 137–140.

Tzavara, E.T., Davis, R.J., Perry, K.W., Li, X., Salhoff, C., Bymaster, F.P., Witkin, J.M., Nominkos, G.G., 2003. The CB1 receptor antagonist SR141716A selectively increases monoaminergic neurotransmission in the medial prefrontal cortex: implications for therapeutic actions. Br. J. Pharmacol. 138, 544–553.

Tzschentke, T.M., 2001. Pharmacology and behavioural pharmacology of the mesocortical dopamine system. Prog. Neurobiol. 63, 241–320.

Ueda, N., Goparaju, S.K., Katayama, K., Kurahashi, Y., Suzuki, H., Yamamoto, S., 1998. A hydrolase enzyme inactivating endogenous ligands for cannabinoid receptors. J. Med. Invest. 45, 27–36.

Uylings, H.B., van Eden, C.G., 1990. Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. Prog. Brain Res. 85, 31–62.

van Eden, C.G., Hoorneman, E.M., Buijs, R.M., Matthijssen, M.A., Geffard, M., Uylings, H.B., 1987. Immunocytochemical localization of dopamine in the prefrontal cortex of the rat at the light and electron microscopical level. Neuroscience 22, 849–862.

Varvel, S.A., Lichtman, A.H., 2002. Evaluation of CB1 receptor knockout mice in the morris water maze. J. Pharmacol. Exp. Ther. 301, 915–924.

Varvel, S.A., Hamm, R.J., Martin, B.R., Lichtman, A.H., 2001. Differential effects of delta 9-THC on spatial reference and working memory in mice. Psychopharmacology (Berl) 157, 142–150.

Varvel, S.A., Anum, E.A., Lichtman, A.H., 2005. Disruption of CB(1) receptor signaling impairs extinction of spatial memory in mice. Psychopharmacology (Berl) 179, 863–872.

Verrico, C.D., Jentsch, J.D., Roth, R.H., 2003. Persistent and anatomically selective reduction in prefrontal cortical dopamine metabolism after repeated, intermittent cannabinoid administration to rats. Synapse 49, 61–66.

Verrico, C.D., Jentsch, J.D., Roth, R.H., Taylor, J.R., 2004. Repeated, intermittent delta(9)-tetrahydrocannabinol administration to rats impairs acquisition and performance of a test of visuospatial divided attention. Neuropsychopharmacology 29, 522–529.

Volkow, N.D., Fowler, J.S., 2000. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb. Cortex 10, 318–325.

Volkow, N.D., Gillespie, H., Mullani, N., Tancredi, L., Grant, C., Valentine, A., Hollister, L., 1996. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. Psychiatry Res.: Neuroimaging 67, 29–38.

Wall, P.M., Messier, C., 2001. The hippocampal formation—orbitomedial prefrontal cortex circuit in the attentional control of active memory. Behav. Brain Res. 127, 99–117.

Whitlow, C.T., Freedland, C.S., Porrino, L.J., 2002. Metabolic mapping of the time-dependent effects of delta 9-tetrahydrocannabinol administration in the rat. Psychopharmacology (Berl) 161, 129–136.

Winsauer, P.J., Lambert, P., Moerschbaecher, J.M., 1999. Cannabinoid ligands and their effects on learning and performance in rhesus monkeys. Behav. Pharmacol. 10, 497–511.

Winstanley, C.A., Dalley, J.W., Theobald, D.E., Robbins, T.W., 2004. Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. Neuropsychopharmacology 29, 1331–1343.

Zahrt, J., Taylor, J.R., Mathew, R.G., Arnsten, A.F., 1997. Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. J. Neurosci. 17, 8528–8535.

Zimmerberg, B., Glick, S.D., Jarvik, M.E., 1971. Impairment of recent memory by marihuana and THC in rhesus monkeys. Nature 233, 343–345.