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The Yin and Yang of Cannabis-induced Psychosis: the Actions of Δ^9-Tetrahydrocannabinol and Cannabidiol in Rodent Models of Schizophrenia

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Abstract: The link between cannabis and psychosis has often been debated with polarized views on the topic. There is substantial epidemiological evidence showing that cannabis increases the risk of psychosis, whereas other research suggests that schizophrenia patients self-medicate with the substance. These conflicting accounts may at least be partially explained by the two phytocannabinoids cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) and their opposing actions on schizophrenia-related symptoms. In the present review we will first focus on how traditional rodent models of schizophrenia have been used to improve our understanding of the propsychotic actions of THC and the antipsychotic actions of CBD. We will also review novel rodent models used to address genetic vulnerability to cannabis-induced schizophrenia and show that specific genes are being uncovered that modulate cannabinoid action (e.g. the schizophrenia susceptibility gene neuregulin 1). We will also review rodent studies that have addressed interactions between THC and CBD. These animal studies underscore great complexity with some studies showing that CBD antagonises the neurobehavioural effects of THC, while others show the opposite, that CBD potentiates the actions of THC. Various mechanisms are put forth to explain these divergent effects such as CBD antagonism at central CB1 receptors or that CBD inhibits proteins that regulate THC disposition and metabolism (e.g. the ABC transporter, P-glycoprotein).

Keywords: Δ^9-tetrahydrocannabinol, cannabidiol, schizophrenia, rodent model, CB1, CB2, neuregulin.

INTRODUCTION

It has been estimated that psychotic disorders affect 3% of the world's population [1]. Those diagnosed specifically with schizophrenia approaches 1%, although there exist a range of related diagnoses such as schizophreniform disorder, schizoaffective disorder, delusional disorder and drug-induced psychosis that can also be added to estimates of lifetime prevalence of psychosis. The onset of schizophrenia occurs normally in late adolescence/early adulthood and is characterized by negative symptoms (e.g. social withdrawal), cognitive dysfunction and positive symptoms (e.g. hallucinations and delusions). The chronic nature of schizophrenia makes it one of the leading forms of permanent disability. Since the discovery of typical antipsychotic drugs, the subsequent development of atypical compounds has provided marginal improvement in the treatment of schizophrenia. These agents are variably effective in dampening positive symptoms and 30% of patients remain treatment-resistant [2]. Importantly, antipsychotic drugs are poorly effective in treating cognitive dysfunction and negative symptoms in schizophrenia [3].

Although the exact causes of schizophrenia are still unknown, the role played by cannabis as a major risk factor has been widely debated with polarized views on the topic. For example, there is substantial epidemiological evidence showing that cannabis increases the risk of psychosis by at least 2-fold, whereas other research suggests that schizophrenia patients self-medicate with the substance to reduce schizophrenia symptoms or to alleviate the side effects of antipsychotic medication. These conflicting accounts may be partially explained by two phytocannabinoids cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) and their opposing actions on schizophrenia-related symptoms. Indeed much human and animal research is now focussing on these two constituents (see also other papers published in this issue). A growing body of evidence indicates that THC increases the risk of anxiety, psychotic symptoms and memory impairment in healthy individuals [4, 5] and those with an established psychotic disorder such as schizophrenia [6, 7]. In contrast, CBD, another major constituent of cannabis that lacks detectable intrinsic psychoactivity, has anxiolytic [8-10] and possibly antipsychotic properties [11, 12] and does not appear to impair memory or other cognitive functions. Furthermore, when co-administered, CBD can reduce the anxiogenic, memory-impairing and psychotomimetic effects induced by THC [13].

Other papers in the present issue will specifically address the neurobiological effects of cannabinoids on the brain. Functional neuroimaging studies directly comparing THC and CBD found distinct modulatory effects on regional neural responses to fearful faces [14]. Specifically, the authors observed a CBD-induced attenuation of neural responses to intensely fearful faces in the amygdala and cingulate cortex, which was correlated with an electrophysiological response and behavioural evidence for an anxiolytic effect. There was also a distinct effect for CBD on the brain connectivity linking these two regions [15]. In a subsequent fMRI study in the same cohort, THC and CBD had opposing effects on striatal activation during verbal recall, on hippocampal activation during response inhibition, on amygdalar activation in response to fearful faces, on temporal activation during an auditory task, and on occipital activation during visual processing [13]. A third experiment in the same study showed that pretreatment with CBD prevented acute induction of THC-induced psychotic symptoms compared to pretreatment with placebo, and suggested that THC and CBD can have opposing effects on regionally-specific brain activation, which may underlie their different symptomatic and behavioural effects. Thus, there is converging *in vivo* evidence supporting a differential neurobiological effect for different cannabinoids in the brain.

The present critical review aims at integrating the above evidence with findings from animal models. We will specifically focus on rodent studies that have been used to improve our understanding of the propsychotic actions of THC and the antipsychotic actions of CBD. Furthermore, we will carefully overview research that addresses interactions between these major cannabinoid constituents.

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We will then discuss how the study of cannabinoid action in animal models of schizophrenia may provide a deeper understanding of the underlying mechanisms responsible for cannabis-induced psychosis and provide insight on how cannabinoid-based therapies might be utilised to treat this chronic, disabling mental disorder.

CANNABIS, CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

Cannabis contains more than 60 molecules that belong to the class known as cannabinoids. The science of cannabis and the cannabinoids has progressed dramatically in the last two decades. An important factor in this has been the explosion of knowledge of the endocannabinoid system that exists within our brain and body. Cannabinoid CB1 and CB2 receptors have been cloned and their distribution in the brain and periphery mapped out [16, 17]. Further endocannabinoid agonists were discovered with the most characterized being arachidonic acid derivatives anandamide and 2-arachidonoylglycerol (2-AG) [18, 19]. The enzymes responsible for the biosynthesis of anandamide require complete characterization but a N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) has been implicated in the process [20]. The synthesis of 2-AG requires diacylglycerol lipase-α (DAGL-α) [21]. Metabolism of anandamide and 2-AG require fatty amide acid hydrolase (FAAH) and monoacylglycerol lipase (MAGL) respectively [20]. In neurons both anandamide and 2-AG behave as retrograde transmitters travelling backwards from the postsynaptic membrane to activate largely presynaptically located CB1 receptors to modulate the release of various neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, dopamine and serotonin [22]. They also mediate synaptic plasticity such as depolarization-induced suppression of inhibition [23]. These aspects of the cannabinoid system are fully described elsewhere in this issue.

The main psychoactive constituent of cannabis, THC, is a partial agonist at both CB1 and CB2 receptors. THC through its interaction with the CB1 receptor found on neurons is largely responsible for the distinctive effects of cannabis on mood, cognition and behaviour. CB2 receptors are expressed on microglia (the brain's macrophages) and perhaps even neurons, which opens up a whole new layer of complexity in the understanding of cannabinoid neuropsychopharmacology [16]. Furthermore, some of the actions of THC have been attributed to interfering with endocannabinoid-mediated synaptic plasticity [24, 25]. Although THC is the most abundant cannabinoid in the plant, another component, CBD, has also been extensively characterized but its mechanisms are more opaque. CBD is an isomer of THC but the subtle distinction in their chemical structures confers marked differences in their pharmacological activities. Early studies showed CBD had little affinity for cannabinoid receptors, likely explaining its lack of psychoactivity [26]. However, recent evidence suggests it may be an antagonist/inverse agonist at CB1 and CB2 receptors [27]. CBD also activates a myriad of receptor proteins dependent on concentration including transient receptor potential vanilloid type 1 (TRPV1) and 5-HT1A receptors [26]. Furthermore CBD inhibits FAAH, enhancing the levels of anandamide at the synapse.

RODENT MODELS OF SCHIZOPHRENIA: METHODOLOGICAL CONSIDERATIONS

It is impossible to model the uniquely human condition of schizophrenia in its entire complexity using rodent models. At best these models approximate aspects of the disorder and provide a means to improve our understanding of neurobiological processes that are related to schizophrenia symptoms. In addition they provide a platform to screen new therapeutic treatments for the disorder. At the core of compelling rodent models of schizophrenia are measures of behavioural deficits in animals that are also observed in schizophrenia patients. For example schizophrenia patients display deficits in various cognitive functions, with the most robust being in working memory [28]. Further, these patients have impaired sensorimotor gating as operationalised by prepulse inhibition (PPI) of startle or auditory evoked potentials [29-35]. All of these aforementioned phenomena have been reproduced in rodents. Negative symptoms like social withdrawal can also be measured in animals. Positive symptoms of the disorder such as hallucinations and delusions are - at least currently - impossible to measure in rodents. These symptoms are likely subserved by dopamine hyperactivity or glutamatergic hypoactivity in the brain of schizophrenia patients. Agents that increase dopamine levels or block N-methyl-D-aspartate (NMDA) receptors in the CNS trigger locomotor hyperactivity in rodents and so this behaviour is used to assess whether certain agents have antipsychotic potential by reversing such hyperactivity.

Schizophrenia arises due to genetic and environmental factors combining to negatively affect brain maturation at critical, early periods of development [36]. The translational power of rodent models will improve with the introduction of novel paradigms that combine genetic, environmental and neurodevelopmental factors to more faithfully approximate the underlying pathophysiology of the disorder. Current models are largely unidimensional, only recreating aspects of the disorder from single genetic or environmental factors that are related to schizophrenia [37]. Traditional rodent models of schizophrenia are based on dopamine hyperactivity and glutamate hypofunctioning theories of schizophrenia neurochemistry, replicating human evidence suggesting these are the core neurochemical alterations in the illness [38-40]. Agents that enhance dopamine (e.g. psychostimulants) or inhibit glutamate functioning in the CNS (NMDA receptor antagonists) trigger schizophrenia-like behaviours both in humans and animals. Sensitization of mesocorticolimbic dopaminergic circuits has also been suggested as important in the misattribution of salience to environmental stimuli, and may be involved in the positive symptoms of schizophrenia since its early phases [2, 38, 41, 42]. Therefore, rodent studies measuring behavioural and neurochemical sensitization to repeated psychoactive drug exposure have relevance to improving our understanding of the neurobiology of schizophrenia [43-45]. Early life stress has also been linked to increased risk of developing schizophrenia and animals exposed to neonatal stress (e.g. maternal deprivation or social isolation) display long-lasting schizophrenia-relevant deficits expressed in adulthood. With increasing knowledge of the genetic basis of schizophrenia newer genetic models have been developed where mutations in schizophrenia susceptibility genes [e.g. neuregulin 1 (*NRG1*)] promote schizophrenia-related behaviours. Many of these animal models have been used to examine the neural and genetic basis of the propsychotic and antipsychotic potential of THC and CBD.

The current review will specifically address rodent studies that examine the effects of cannabinoids: on schizophrenia-related neurobehavioural phenotypes; in adolescence; and in dopamine, glutamate, neonatal stress and genetic models of schizophrenia (for a summary of the effects of THC and CBD in these models see Tables **1** and **2** respectively). We will also assess rodent evidence of the potential therapeutic efficacy of cannabinoid receptor antagonist drugs as novel antipsychotics, as well as evaluating whether cannnabinoid receptor knockout mice display schizophrenia-relevant phenotypes. The final section of this review will be devoted to rodent studies addressing interactions between THC and CBD that might provide mechanistic insight into interactions between these agents that has been reported in the human literature (see Table **3**).

EFFECTS OF CANNABINOIDS ON SCHIZOPHRENIA-RELATED NEUROBEHAVIOURAL PHENOTYPES IN RODENTS

Acute THC administration transiently exacerbates core psychotic symptoms and cognitive deficits in schizophrenia patients

Table 1. The Effects of THC and Cannabinoid (CB) Agonists in Rodent Models of Schizophrenia

Model	CB	Species	CB Effect	Ref.
Dopamine	THC (adult, repeated dosing)	Rat	Potentiated ↑ locomotor activity and stereotypy (amphetamine)	[119, 120]
	THC and CP 55,940 (adult, repeated dosing)	Rat Mouse	No effect on ↑ locomotor activity (cocaine)	[47, 82]
Glutamate	WIN 55,212-2 (adult, acute dosing)	Rat	Exacerbated ↓ short-term memory deficits and hippocampal pyramidal cell firing (MK-801)	[133]
	THC (adolescent, repeated dosing)	Rat	Exacerbated ↓ recognition memory and GTPγS binding Blocked ↑ 2-AG levels in the prefrontal cortex (phenyclidine)	[134]
	WIN 55,212-2 (adult, repeated dosing)	Rat	Reversed ↓ PPI, recognition memory and social behaviour (phenyclidine)	[135]
Neonatal stress	THC (adult, acute dosing)	Rat	Potentiated ↓PPI	[68]
	CP 55,940 (adolescent, repeated dosing)	Rat	Stress or CB alone ↓ CB1 receptor expression and ↑ astrocytes no. in the hippocampus – combined stress and CB nullified these effects	[154]
	CP 55,940 (adolescent, repeated dosing)	Rat	No effect	[156]
	WIN 55,212 (neonatal, acute dosing)	Rat	Potentiated ↓ immune function Stress reversed and potentiated ↑ anxiety and serum corticosterone promoted by CB respectively (males only)	[157]
Genetic	THC (adult, acute dosing)	*Nrg1* HET mice	Enhanced behavioural effects of THC in *Nrg1* HET mice (e.g. *Nrg1*-specific ↑ PPI) *Nrg1*-specific ↑ brain activation pattern in stress circuitry (e.g. LSV)	[57, 172, 175]
	CP 55,940 (adult, repeated dosing)	*Nrg1* HET mice	*Nrg1* modulated CB tolerance; ↑ FosB/ΔFosB expression in LSV	[58]
	THC (adolescent, repeated dosing)	*Nrg1* HET mice	Exacerbated ↑ locomotor activity in *Nrg1* HET mice Promoted *Nrg1*-specific effects on CB1, 5-HT2A and NMDA receptor expression	[183]
	THC (adolescent, repeated dosing)	*COMT* KO mice	Induced *COMT*-specific ↑ locomotor activity, ↓ working memory and ↓ anxiety	[186]
	WIN 55,212-2 (adolescent, repeated dosing)	*COMT* KO mice	Promoted *COMT*-specific ↓ PPI, ↑ social behaviour and ↓ anxiety	[187]
	THC (adult, acute dosing)	*Mdr1a*/b and *Bcrp1* KO mice	↑ hypothermia, and ↑ brain and blood [THC] in *Mdr1a/b* and *Bcrp1* KO mice.	[195, 197]

Table 2. The Effects of CBD In Rodent Models of Schizophrenia

Model	Species	CB Effect	Ref.
Dopamine	Mouse (adult, repeated dosing)	Blocked ↑ locomotor activity (amphetamine)	[60]
	Mouse Rat (adult, acute dosing)	Blocked ↑ locomotor activity (amphetamine)	[123, 124]
	Rat (adult, repeated dosing)	No effect on ↑ locomotor activity (amphetamine)	[125]
Glutamate	Mouse (adult, acute dosing)	Inhibited ↑ locomotor activity (ketamine)	[123]
	Mouse (adult, acute dosing)	Reversed ↓PPI (MK-801)	[136]
	Rat (adult, acute dosing)	No effect on ↓PPI Blunted social withdrawal	[137]
Genetic	*Nrg1* HET mice (adult, repeated dosing)	No effect on ↓PPI, ↑ locomotor activity and ↓ 5-HT2A receptor expression in *Nrg1* HET mice. *Nrg1*-specific ↑ in social behaviour and GABAA receptor expression.	[198]

Table 3. Rodent Studies Examining Interactions between THC and CBD

	CB Effect	Species	CBD: THC Ratio	Proposed Mechanism	Admin Schedule	Ref.
CBD ↑ effect of THC	Antinociception	Mouse	100:1 (30 mg/kg CBD 0.3 mg/kg THC)	CBD ↑ blood but not brain [THC]	CBD pretreatment (10 min) i.v.	[101]
	↓ Spatial memory Hypothermia	Mouse	50:1 (50 mg/kg CBD 1 mg/kg THC)	↑ CB1 receptor in hippocampus and hypothalamus	Co-administration (simultaneous) i.p.	[90]
	↓ Locomotor activity	Mouse	10:1 & 50:1	↑ CB1 receptor in hippocampus and hypothalamus	Co-administration (simultaneous) i.p.	[90]
	↓ Social behaviour ↓ Locomotor activity	Rat	2:1 (20 mg/kg CBD 10 mg/kg THC) NDD	Not examined	CBD pretreatment (20 min) i.p.	[61]
	Weight loss ↑ Anxiety ↓ Social behaviour	Rat (adolescent)	1:1 (1-10 mg/kg CBD & THC)	CBD ↑ brain & blood [THC] No effect on CB1 or 5-HT_{1A} receptors.	CBD pretreatment (20 min) i.p., repeated, escalating	[246]
CBD ↓ effect of THC	Antinociception	Mouse	3.3:1 (10 mg/kg CBD 3 mg/kg THC) NDD	Not examined	CBD pretreatment (10 min) i.v.	[101]
	↓ Spatial working memory	Rat	12.5:1 (50 mg/kg CBD 4 mg/kg THC)	Not examined	Co-administration (simultaneous) i.p.	[89]
	↓ Social behaviour	Rat	20:1 (20 mg/kg CBD 1 mg/kg THC)	Not examined	CBD pretreatment (20 min) i.p.	[61]
	Place aversion	Mouse	1:10 & 1:1 (1 & 10 mg/kg CBD 10 mg/kg THC) NDD	Not examined	Co-administration (simultaneous) i.p.	[241]

NDD = non dose-dependent

[7]. Furthermore, THC administered to healthy participants mimics some of the core symptoms of schizophrenia – increasing positive and negative schizophrenia-like symptoms and cognitive deficits including impairment in working memory [4]. Similarly in rodents THC administration promotes an array of effects that are thought relevant to aspects of schizophrenia symptomology. Locomotor hyperactivity, presumably due to increased dopamine release in the brain, has been reported for THC and its synthetic analogues but only when using relatively low doses of these drugs [46-49]. Such locomotor activating effects of THC are consistent with studies showing that acute exposure to cannabinoids promote dopamine release in the nucleus accumbens and medial prefrontal cortex ([50-53] for a good review of this work see [54]). At high doses THC promotes dose-dependent locomotor suppression in rodents and catalepsy due to dense distribution of CB1 receptors in motor-related regions of the brain such as the globus pallidus, substantia nigra and cerebellum [55, 56].

Acute administration of THC and THC-like cannabinoid receptor agonists (e.g. CP 55,940 and WIN 55,212-2) also promotes deficits in behaviours relevant to negative symptoms of schizophrenia such as social withdrawal. Exposure to cannabinoids reduces social interaction of rodents following acute or repeated exposure which can be dissociated from the locomotor suppressant effects of these drugs [57-63]. Endocannabinoid neurotransmission may be involved in the mediation of prosocial behaviour as, unlike the administration of cannabinoid receptor agonists, the inhibitor of FAAH URB597 increased social interaction in adolescent rats [64]. Indeed the balance between social approach and withdrawal appears differentially regulated by CB1 receptors localised on GABAergic versus glutamatergic neurons. That is, CB1 receptor deletion from cortical and striatal GABA interneurons enhanced social and novel object exploration, whereas when CB1 receptors were removed from cortical glutamatergic neurons social and object exploration was reduced [65].

Acute administration of cannabinoid receptor agonists to rodents promotes a number of impairments in attention and cognitive function that are relevant to schizophrenia (see the specific paper released in the present issue). Cannabinoid receptor agonists including THC promote PPI deficits in rodents that can be reversed by atypical antipsychotic drugs [58, 66, 67]. However, only one study was able to show an acute cannabinoid-induced PPI deficit without the confounding influence of these agents on acoustic startle [67]. Other studies have shown that cannabinoid receptor agonists may augment PPI or have no effect [60, 68, 69]. Synthetic cannabinoid receptor agonists also disturb auditory evoked potentials. CP 55,940 disrupted both auditory evoked potentials and theta oscillations in the CA3 region of the hippocampus and entorhinal cortex that were mediated by CB1 receptors [70]. Further, CB1 receptor-mediated disruption of auditory gating by WIN 55,212 has also been demonstrated in the CA3, dentate gyrus and medial prefrontal cortex [71].

Acute systemic THC administration decreased working memory performance that correlated with reduced acetylcholine release in the hippocampus that were reversed by antipsychotic drugs [72, 73]. CB1 receptors in the hippocampus are vital to the memory impairing effects of THC as intrahippocampal injection of the CB1 receptor antagonist SR 141716 reversed working memory deficits of systemically administered THC [74]. Injection of THC directly into the medial prefrontal cortex also disrupts spatial working memory, which was reversed by the dopaminergic D1 receptor antagonist SCH23390 and the atypical antipsychotic drug clozapine [75]. The amnesic effects of THC in the hippocampus involve CB1 receptors localised on GABA interneurons that activate the mTOR pathway leading to a maladaptive increase in protein translation [76]. In addition, THC impairs cognitive flexibility and auditory discrimination performance that is mediated by CB1 receptors in rats [77]. Interestingly spatial learning impairments and cognitive inflexibility promoted by THC, unlike other effects of cannabinoids, are resistant to tolerance [78].

Behavioural sensitization is subserved by neurochemical sensitization in mesocorticolimbic circuits that might mediate the positive symptoms of schizophrenia [2, 41]. Behavioural sensitization in best characterized with repeated, intermittent dosing with psychostimulants where the initial enhancement in locomotion promoted by these drugs is progressively increased with repeated dosing. Early demonstrations of such behavioural sensitization to THC are questionable based on limitations in the experimental design implemented in these studies including a lack of tracing progressive changes in locomotor activity over days [79, 80]. The common design was to repeatedly administer vehicle or escalating THC doses and then challenge all animals with THC on a final test day 20 days after final pretreatment exposure [79, 80]. Arguing for "sensitization" the THC-challenged animals in the THC group had significantly higher locomotor activity or stereotyped behaviour scores than animals in the vehicle-pretreated group. However these studies lacked control groups critical to discerning sensitization (reverse tolerance) from tolerance. Without demonstrating that the THC-pretreatment group had significantly higher activity than a vehicle-vehicle or THC-vehicle group, the results reported might simply indicate lack of tolerance to the suppressant effects of THC in the vehicle-pretreated group compared to complete tolerance in the THC-pretreated animals. One more recent study implemented an identical test design to these early studies, included the critical experimental controls, and used both measures of locomotor activity and stereotyped behaviours. This study failed to demonstrate behavioural sensitization to THC [81]. Such findings are consistent with other work using designs typically utilised to demonstrate behavioural sensitization to psychostimulants where no such behavioural sensitization to cannabinoids could be demonstrated in animals of various age ranges [82-86].

While sensitization to repeated THC exposure is not expressed behaviourally it may be neurochemically due to various subtle neuroadaptive processes in the mesolimbic dopamine pathway. Repeated THC pretreatment reduced dopamine release in the shell and increased dopamine release in the core of the nucleus accumbens in response to THC challenge compared to animals pretreated with vehicle [87]. Repeated THC exposure also enhanced expression of ΔFosB in the nucleus accumbens and prefrontal cortex suggesting the drug triggers long-term neuroadaptive changes in mesocorticolimbic circuits [88]. In addition, repeated THC exposure promoted structural changes in neuronal morphology (increased dendritic branching and dendritic length) in medium spiny cells of the nucleus accumbens shell and in pyramidal cells of the medial prefrontal cortex [84]. Similar changes in ΔFosB and dendritic morphology have been observed following psychostimulant sensitization. Future studies are needed to better characterise the sensitizing neurobiological effects that repeated THC exposure might have on the mesocorticolimbic system.

Relative to THC, CBD appears largely behaviourally inert. CBD doesn't modulate social behaviour or learning and memory function in rodents following acute or repeated administration [60, 63, 89-92]. However, acute CBD exposure has anxiolytic effects in rodents that are mediated by 5-HT1A receptors and TRPV1 receptors [93-99]. Repeated CBD dosing promoted non dose-related anxiolytic effects in mice [60]. Contrasting with this a recent paper reported that repeated CBD dosing in rats promoted an anxiogenic effect [100]. Of particular relevance to schizophrenia is the finding that acute and repeated CBD administration enhances PPI in mice [60]. Acute CBD promoted a dose-related PPI facilitation (1 – 50 mg/kg), however following repeated exposure it was only the 1 mg/kg dose that retained the ability to facilitate PPI. This suggests that lower doses might be preferable to avoid tolerance to CBD-induced PPI facilitation. CBD does not modulate locomotor activity in male C57BL/6JArc mice following either acute of repeated in-

Table 4. Outstanding Research Questions

Examination of the effects of cannabinoids in novel multidimensional animals models of schizophrenia which reflect genetic, environmental and neurodevelopmental aspects of the disorder.
Better characterization of the sensitizing neurobiological effects that repeated THC exposure has on the mesocorticolimbic system.
Elucidation of the mechanism of action of CBD's antipsychotic efficacy in various animal models of schizophrenia.
Isolation of further genes involved in moderating cannabinoid action on schizophrenia-related phenotypes.
Further characterization of the role of CB1 and CB2 receptors in schizophrenia-relevant phenotypes.
Reconciliation of why in some cases CBD potentiates the effects of THC, while in others it inhibits THC's action.

traperitoneal dosing across a wide dose-range [60]. Although biphasic effects of intravenous CBD in ICR mice have been reported with locomotor stimulation at 10 mg/kg and suppression at 30 mg/kg [101]. It has been argued that because CBD doesn't promote catalepsy it might be better tolerated in patients than current prescribed therapies, which do have this sedative effect in rodents. It has also been suggested that CBD might engender neuropharmacological effects akin to the atypical antipsychotic clozapine rather than the typical drug haloperidol, as CBD and clozapine administration increased c-Fos expression, a marker of brain activation, only in the ventral striatum whereas haloperidol promoted c-Fos expression in both the ventral and dorsal striatum [102].

ADOLESCENCE – A PERIOD OF VULNERABILITY TO CANNABINOID EXPOSURE

Adolescence is a significant period of neurodevelopment in the pathophysiology of schizophrenia coinciding with the onset of the disorder and first experimentation with cannabis (for an excellent review see [103]). Animal studies have shown that this period offers particular vulnerability to the actions of cannabinoids leading to long-term neurobehavioural deficits in adulthood. Pubertal exposure to the synthetic cannabinoid receptor agonist WIN 55,212-2 promoted long-lasting deficits in PPI, social interaction, and social and object recognition that were reversed by treatment with antipsychotic drugs such as haloperidol and quetiapine [104-107]. Adolescent rats are less sensitive to the aversive effects of cannabinoids than adults, however they are more sensitive to the detrimental effects of cannabinoid receptor agonists including THC on object recognition memory and working memory [108-111]. Taken together, this suggests adolescent cannabis use provides a dangerous scenario where users may be less averse to the immediate effects of the drug and more likely to use it repeatedly thus exposing themselves to long-term cognitive impairment.

The neural basis of altered vulnerability to the effects of cannabinoids in adolescence shows that the adolescent brain may be more or less sensitive to the effects of cannabinoids than the adult brain, dependent on the proteins measured or the brain region analysed. Exposure to the potent synthetic analogue of THC, HU-210, has less effects on the adolescent brain than the adult CNS in terms of dopamine D2, GABAA, 5-HT1A and CB1 receptor expression in various brain regions [112-114]. Although a single dose of HU-210 was sufficient to promote increases in dopamine D1 receptor expression in nigrostriatal and mesolimbic brain regions of adolescent rats, this was only attained in adult animals after repeated dosing [115]. During adolescence there exist dynamic changes in the levels of endocannabinoids and CB1 expression level in the prefrontal cortex and nucleus accumbens, and repeated THC exposure enhanced anandamide levels in the nucleus accumbens selectively in adolescent animals [116].

Repeated THC exposure altered a greater number of proteins in the hippocampus of adolescent compared to adult rats (27 versus 10 respectively) [109]. Of note, proteins related to oxidative stress and protein folding were altered which could be related to greater degenerative changes and enhanced free radical damage in the hippocampus of adolescent animals. In addition, cytoskeletal and structural proteins were also affected indicating greater cytoarchitectural changes in the adolescent hippocampus. THC exposure selectively decreased levels of ubiquitin-conjugating enzyme E2 in adolescent rats. Interestingly, reduced levels of ubiquitin-conjugating enzymes have also been observed in the hippocampus of schizophrenia patients [117]. Repeated adolescent THC exposure also altered hippocampal dendritic morphology as well as reducing a number of synaptic markers including PSD-95 and expression levels of NMDA receptors [110]. Taken together hippocampal changes resulting from THC exposure in adolescence may contribute to lasting cognitive deficits that may have relevance to the pathophysiology of schizophrenia.

THE EFFECTS OF CANNABINOIDS IN DOPAMINE MODELS OF SCHIZOPHRENIA

Repeated THC treatment enhances the acute stimulatory effects of amphetamine and high doses of quinpirole (a D2 receptor agonist) on locomotor activity and stereotypy [118-120], suggesting that THC exposure sensitizes underlying mesocorticolimbic dopamine circuits. Prior studies have failed to demonstrate that THC or a 1:1 combination of THC and CBD modulates the hyperlocomotor effects of cocaine which is consistent with earlier studies utilising the cannabinoid receptor agonist CP 55,940 [47, 82]. Amphetamine promotes much greater levels of dopamine in the nucleus accumbens than cocaine [121, 122], therefore it is possible that only the action of potent psychostimulants like amphetamine is able to unmask subtle sensitizing changes in the mesocorticolimbic pathway triggered by repeated cannabinoid treatment.

The effect of CBD on neurobehavioural responses to psychostimulant drugs has been less comprehensively studied than that for THC and cannabinoid receptor agonists. Neuroadaptive changes in response to repeated CBD exposure might be necessary for demonstrating an antipsychotic action in dopamine models as repeated but not acute exposure to CBD (50 mg/kg) was effective in reversing amphetamine-induced hyperactivity in mice [60]. However, earlier studies have shown that acute CBD dose-dependently reduced amphetamine-induced hyperactivity in both mice and rats

[123, 124]. Another more recent study suggests that repeated CBD doesn't modulate locomotor hyperactivity in response to repeated exposure to amphetamine and behavioural sensitization [125]. This study utilized a study design that has been argued to model mania [126-128]. Two different treatment regimens were utilised in this study: 1) a "reversal" model where rats were pretreated with amphetamine twice daily for 7 days before CBD (15 – 60 mg/kg) was co-administered with amphetamine (2 mg/kg) on days 8-14 and 2) a "prevention" model rats where rats received CBD daily for 7 days before injection with amphetamine on days 8-14. In either case CBD did not influence the hyperlocomotor effects of amphetamine.

EFFECTS OF CANNABINOIDS IN GLUTAMATE MODELS OF SCHIZOPHRENIA

Phencyclidine, ketamine and MK-801, all glutamatergic NMDA receptor antagonists, have hallucinogenic effects in humans [129]. Administration of these agents to rodents promotes a number of different effects relevant to schizophrenia such as hypoactivation of the prefrontal cortex, deficits in PPI, cognitive dysfunction and social withdrawal [130-132]. Consistent with THC worsening cognitive deficits associated with schizophrenia, acute administration of WIN 55,212-2 exacerbated MK-801-induced deficits in short-term memory that correlated with an enhancement of the inhibitory effects of MK-801 on hippocampal pyramidal cell firing [133]. Another glutamate model utilized repeated, intermittent phencyclidine dosing over 4 weeks in adolescent rats before testing animals phenyclidine-free 3 days after the final dose. This schedule of phenyclidine treatment promoted a clozapine reversible impairment in recognition memory and alterations in the endocannabinoid system, notably in the prefrontal cortex, where phenyclidine reduced cannabinoid-stimulated GTPγS binding and enhanced 2-AG levels [134]. Repeated co-administration of THC with phencyclidine in this model exacerbated impairments in recognition memory and the reduction in cannabinoid-stimulated GTPγS binding but reversed the increase in 2-AG levels in the prefrontal cortex. Conflicting with this research, pre-exposure to the synthetic cannabinoid receptor agonist WIN 55,212-2 in adulthood reversed the usual deficits promoted by repeated phenyclidine such as PPI deficits, impaired recognition memory and social withdrawal [135]. Complicating interpretation of these data was that the "protective effects" of WIN 55,212-2 were on a background of the WIN 55,212-2 pre-treatment promoting deficits in PPI, recognition memory and social behaviour in control animals.

Unlike THC, CBD has an antipsychotic profile in glutamate models as it promoted a non dose-related inhibition of ketamine-induced hyperactivity (30 mg/kg was effective but not 15 or 60 mg/kg) in the absence of inhibiting motor activity on its own [123]. CBD also reversed acute MK-801-induced PPI deficits in mice [136] but not rats [137]. In addition, CBD blunted MK-801-induced social withdrawal in a non dose-dependent fashion as 3 and 10 mg/kg were effective, but not a higher 30 mg/kg dose [137]. The mechanism of action of CBD's antipsychotic action in glutamate models is unknown and its characterisation would be important to the development of this agent as an antipsychotic drug.

EFFECTS OF CANNABINOIDS ON NEONATAL STRESS MODELS OF SCHIZOPHRENIA

Early life stress is linked to an increased risk of psychosis, and childhood trauma may be involved in the pathogenesis of the disorder [138, 139]. Social isolation at weaning age has been used as an animal model of schizophrenia because it induces PPI deficits [140-142] and disrupts normal brain maturation [143, 144]. Acute THC exposure enhances PPI deficits promoted by post-weaning social isolation, an effect mediated by CB1 receptors [68]. Conflicting with this finding social isolation stress decreased CB1 receptor expression in the caudate putamen and amygdala [145]. It is possible that THC's exacerbation of social isolation-induced PPI deficits is mediated by disruption of endocannabinoid tone in the brain. Indeed, social isolation stress increased FAAH expression in the caudate putamen and the nucleus accumbens [145], and expression of MAGL in the caudate putamen and DAGLα and DAGLβ in the amygdala [146]. In addition, social isolation stress increased expression of NAPE-PLD and MAGL in the prefrontal cortex. Another stress-based and neurodevelopmental animal model of schizophrenia is the neonatal maternal stress deprivation model where rodents are separated from their mother at postnatal day 9 for 24 h. Adult animals that have undergone neonatal maternal deprivation display deficits in PPI, auditory sensory gating and startle habituation as well as reductions in levels of NR2A and NR2B NMDA receptor sub-units in the brain [147-151]. These animals display sexually dimorphic modulation of the endocannabinoid system – 13 day old male rats have increased levels of 2-AG and MAGL and decreased CB1 receptor expression in the hippocampus. Further both male and female animals display increased CB2 receptor and DAGLα expression in the hippocampus [152, 153].

Another promising approach combined two factors associated with increased risk of schizophrenia, neonatal stress and adolescent cannabinoid exposure, to observe whether there was any interaction following the sequential exposure to these factors [154]. Such an approach resonates with epidemiological evidence showing that childhood trauma and adolescent cannabis use increase the risk of schizophrenia by 3- and 2-fold respectively but when combined increase the risk by 21-fold [155]. Alone neonatal stress or repeated, adolescent exposure to the synthetic cannabinoid receptor agonist CP 55,940 reduced CB1 receptor expression and increased the number of GFAP-positive astrocytes in various regions of the hippocampus in male rats [154]. Somewhat surprisingly the combination of neonatal stress and adolescent cannabinoid exposure nullified these effects rather than potentiating them. Another study utilising the same paradigm observed no interactive effects on various schizophrenia-relevant behaviours in adulthood [156].

Neonatal maternal deprivation has protective effects against the anxiogenic effects of neonatal WIN 55,212-2 exposure in adolescent male but not female rats [157]. At odds with this finding is that neonatal maternal deprivation potentiated WIN 55,212-2-induced increases in serum corticosterone levels selectively in adolescent male rats [157]. This research shows that early neurodevelopmental stress and cannabinoid exposure may interact to modulate stress systems in the brain, that extends on prior research which has shown that the adult brain has a supra-additive response to stress and cannabinoid exposure [158-160]. Possibly as a consequence of altered HPA axis responsivity, neonatal stress and WIN 55,212-2 exposure additively reduced immune function as highlighted by reduced lymphocyte chemotaxis in the spleen and impaired lymphocyte proliferation in axillary nodes [157]. It would be of interest for future studies to continue with such an approach, possibly using other prenatal and neonatal stressors or immune challenges combined with adolescent exposure to the phytocannabinoid THC at doses more relevant to human consumption of cannabis.

GENETIC MOUSE MODELS OF VULNERABILITY TO CANNABIS-INDUCED SCHIZOPHRENIA

Genetic vulnerability to schizophrenia might explain why only a small proportion of the cannabis-using population develops schizophrenia. This is of great relevance to the clinical field of preventive psychiatry in human psychotic disorders. If the genes that confer genetic vulnerability to cannabis-induced psychosis were identified this would pave the way for preventative approaches where those at-high risk could be forewarned of the potential danger of experimentation with cannabis. In addition, one of the major impediments to the therapeutic development of cannabinoid medicines is the ability of these compounds to promote an increased risk of neuropsychiatric complications including psychosis. A pharmacogenetic approach would allow those at risk of psychiatric compli-

cations to be isolated leaving risk-free patients to benefit from cannabinoid-based therapy.

Early rodent studies attempting to model genetic vulnerability to the actions of cannabinoids compared the neurobehavioural responses of distinct inbred strains to cannabinoid exposure. Strain differences in the effects of cannabinoids were isolated on behaviour (e.g. reward and anxiety-related behaviours) [161, 162], brain activation patterns [163], and dopamine efflux in mesolimbic circuitry [52]. While these early studies lent credence to the idea that genetic disposition could moderate the actions of cannabinoids they did not provide any detail on the exact genes that were involved. The development of transgenic mice with targeted mutations has allowed identification of specific genes that moderate the CNS effects of cannabinoids, including those that modulate cannabinoid pharmacodynamics as well as the CNS disposition of these drugs.

We have utilized the heterozygous *Nrg1* mouse line (*Nrg1* HET mice) to develop an animal model of genetic vulnerability to cannabinoid-induced psychosis [164-167]. The neuregulin 1 gene (*NRG1*) - located on chromosome 8p12-p21 – was identified in 2002 as a schizophrenia-susceptibility gene [168]. The polypeptide influences key neurodevelopmental processes relevant to schizophrenia such as myelination, synaptogenesis, cell-cell signaling and neuronal migration, and regulates the expression/activation of NMDA receptors [169-171]. There are a number of ErbB receptors but ErbB4 is the only one that is bound and activated by NRG1 without forming a heterodimer. Alterations in the expression of *NRG1* mRNA have been found in the dorsolateral prefrontal cortex and hippocampus of patients with schizophrenia [169-171].

An initial study investigated the effects of THC on schizophrenia-relevant neurobehavioural parameters and demonstrated that adult male *Nrg1* mutant mice were more sensitive to the behavioural actions of THC compared to WT littermates [57]. The effects of THC on *Nrg1* HET mice were sex-specific as no increased behavioural sensitivity to acute THC challenge was detected in female *Nrg1* HET mice [172]. One striking finding was that unlike WT mice, male *Nrg1* HET mice showed improved PPI following THC exposure. Interestingly, nicotine and antipsychotic drugs increase PPI in rodents and reverse PPI deficits in patients with schizophrenia [173]. Following from our work recent human data support the idea that *NRG1* confers enhanced sensitivity to the actions of THC, however *NRG1* polymorphisms appear to worsen THC-induced information processing dysfunction rather than improve it. In healthy subjects THC-induced deficits in auditory mismatch negativity generation were only expressed in those with a specific *NRG1* variant [174]. These results suggest that variation in *NRG1* modulates CNS-effects of THC that can be related to dysfunctions observed in schizophrenia.

We also examined the neurobiological underpinnings of the increased behavioural susceptibility of *Nrg1* mutants to acute THC challenge by measuring THC-induced neuronal activation using c-Fos immunohistochemistry [175]. THC selectively increased c-Fos expression in the ventral part of the lateral septum (LSV) of *Nrg1* HET mice with no corresponding effect being observed in WT mice. Interestingly drugs which modulate sensorimotor gating, whether they are pro-psychotic drugs that impair PPI or anti-psychotic drugs that facilitate PPI, all increase c-Fos expression in the lateral septum [176]. In addition, our study showed that THC promoted a greater increase in c-Fos expression in *Nrg1* mutants compared to WT mice in an array of stress-related regions of the brain such as the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus. A 3-way interaction between *Nrg1* hypomorphism, THC exposure and stress appeared necessary to this Fos expression profile as it was only observed in animals that underwent the stress of behavioural testing with no such effects being observed in animals administered THC in their homecage. Therefore, future studies examining Nrg1-stress-cannabinoid interactions, particularly in a neurodevelopmental context, are warranted.

Chronic exposure to cannabinoids is more robustly associated with triggering psychosis than acute exposure so we examined how *Nrg1* HET mice responded to repeated cannabinoid administration [58]. Tolerance to CP 55,940-induced hypothermia and locomotor suppression developed more rapidly in adult, male *Nrg1* HET than WT mice. Conversely, only WT mice developed tolerance to the anxiogenic effect of CP 55,940 and *Nrg1* HET mice maintained consistent cannabinoid-induced anxiety throughout the repeated dosing period. Repeated cannabinoid exposure selectively increased FosB/ΔFosB expression, a marker of long-term neuroadaptive changes, in the LSV of *Nrg1* HET but not WT mice. Opposite effects of acute CP 55,940 treatment were observed on sensorimotor gating, as PPI was facilitated in *Nrg1* hypomorphs and impaired in WT mice. Irrespective of genotype, tolerance developed to the acute effects of CP 55,940 on PPI with repeated exposure to the drug. These results highlight that *Nrg1* also modulates neuroadaptive responses to repeated cannabinoid exposure and further reinforces the notion that the LSV is an important brain region dysregulated in *Nrg1*–cannabinoid interactions.

The role of the LSV in *Nrg1*-cannabinoid interactions is not surprising given its role in the integration of cognitive and emotional information. The lateral septum receives cognitive input from the hippocampus as well as from the prefrontal cortex [177]. It also shares reciprocal projections with the hypothalamus and the amygdala that support its role in relaying affective information. When directly injected in the lateral septum, nicotine and serotonin receptor agonists induced anxiogenic effects in rats [178, 179]. The LSV predominantly expresses estrogen [177], which has been shown to modulate cannabinoid-induced presynaptic inhibition of glutamate and GABA release in the hypothalamus [180]. Further, estrogen receptor gene variants have been linked to increased risk of schizophrenia and estrogen receptors and ErBB4 interact in the transcriptional control of estrogen receptor target gene expression [181, 182]. Future studies addressing the involvement of estrogen in *Nrg1*-cannabinoid interactions in the LSV would be of interest, as well as studies determining the exact role of the LSV in mediating the behavioural effects of cannabinoids on *Nrg1* HET mice we have observed in our studies.

We have also examined whether *Nrg1* hypomorphism confers vulnerability to the actions of acute or repeated THC exposure in adolescence [183]. THC exposure in adolescence exacerbated the hyperlocomotor phenotype of *Nrg1* HET mice expressed after withdrawal of the drug. Furthermore, adolescent *Nrg1* HET mice were more resistant to THC-induced suppression of investigative social behaviours than WT mice. Repeated adolescent THC administration also promoted differential effects on CB1 receptor expression in the substantia nigra, with THC decreasing binding in WT mice while increasing it in *Nrg1* HET mice. The mRNA for ErbB4 receptors that bind Nrg1 is localized on dopaminergic neurons in the substantia nigra [184] therefore it is possible that CB1 and ErbB4 receptors work in concert in this brain region to regulate the hyperactive phenotype of *Nrg1* HET mice. *Nrg1* hypomorphism also altered the effects of adolescent THC exposure on neurotransmitter receptors implicated in the pathophysiology of schizophrenia, that is, 5-HT2A and NMDA receptors. Notably in the insular cortex repeated adolescent THC exposure decreased 5-HT2A receptor expression in WT mice but increased it in *Nrg1* mutants. Adolescent THC exposure also selectively increased NMDA receptor expression in the cingulate cortex and hippocampus or *Nrg1* HET but not WT mice.

The first gene implicated in conferring vulnerability to cannabis-induced psychosis was *COMT*, which encodes for an enzyme important in the degradation of dopamine in the CNS. Adolescent cannabis use significantly enhances the risk of experiencing positive symptoms and diagnosis with schizophreniform disorder in

those with a specific single nucleotide polymorphism in *COMT* [185]. Recent animal studies support the notion that *COMT* moderates the neurobehavioural actions of cannabinoids. *COMT* knockout mice treated with repeated THC in adolescence but not adulthood displayed sexually dimorphic (males only) locomotor hyperactivity, working memory deficits and increased anxiety-like behaviour unlike WT mice treated with THC [186]. In a follow-up study it was shown that *COMT* knockout mice were similarly more vulnerable to the neurobehavioural effects of repeated WIN 55,212-2 exposure in adolescence, and that the mechanism for this interaction didn't involve cannabinoid-modulation of the enhanced dopamine levels found in *COMT* knockout mice [187].

Apart from genes that vary the pharmacodynamic effects of cannabinoids on the brain, it is also possible that genes which regulate the CNS disposition of cannabinoids confer vulnerability to cannabis-induced psychosis. ABC transporters are drug efflux pumps expressed at various pharmacological barriers in the body and regulate the disposition of substrate drugs [188]. Cannabinoids have affinity for members of the ABC transporter superfamily such as multidrug resistance associated protein 1, breast cancer resistance protein and P-glycoprotein [189-192]. The most characterized ABC transporter is P-glycoprotein, which is expressed at the blood brain barrier and helps determine the CNS accumulation of substrate drugs including atypical antipsychotic drugs such as olanzapine and risperidone [193, 194]. Mice with a targeted deletion of the mouse homologue of the gene that encodes P-glycoprotein, *Mdr1a*, showed increased plasma concentrations of THC compared to WT mice [195]. Further, a *MDR1* variant increases the risk of developing cannabis dependence [196]. We have recently found that *Mdr1a/b* and *Bcrp1* knockout mice show impaired excretion of THC from the brain and display a prolonged THC-induced hypothermia than WT mice [197]. Therefore P-glycoprotein and breast cancer resistance protein regulate the CNS disposition of THC and examination of whether variation in *MDR1* or *BCRP* confers increased risk to cannabis-induced schizophrenia may provide a fruitful avenue of future research.

Thus far only one study has examined the antipsychotic efficacy of CBD in a genetic animal model of schizophrenia [198]. This study investigated whether: 1) *Nrg1* HET mice displayed an altered neurobehavioural response to CBD and; 2) if CBD reversed schizophrenia-related phenotypes expressed by these mice. Repeated CBD (1 – 100 mg/kg) was ineffective in reversing locomotor hyperactivity, PPI deficits and reduced 5-HT2A receptor binding observed in *Nrg1* HET mice. However, repeated CBD (at 50 and 100 mg/kg) enhanced social interaction in *Nrg1* HET mice but not WT mice. Furthermore, acute CBD (100 mg/kg) selectively increased PPI in *Nrg1* HET mice, although tolerance to this effect was manifest upon repeated CBD exposure. Repeated CBD (50 mg/kg) also selectively increased GABAA receptor binding in the granular retrosplenial cortex in *Nrg1* HET mice. These results suggest that *Nrg1* facilitates the neurobehavioural actions of CBD, but that CBD was unable to reverse schizophrenia-related behaviour exhibited by *Nrg1* HET mice. Future studies could examine whether adolescent CBD exposure is effective in reversing schizophrenia-related behaviour by hindering the manifestation of neurobehavioural disturbances displayed by *Nrg1* HET mice in adulthood.

THE EFFICACY OF CANNABINOID RECEPTOR ANTAGONISTS IN ANIMAL MODELS OF PSYCHOSIS

Cannabinoid CB1 receptor antagonists show some promise as novel antipsychotic drugs in animal models of schizophrenia. Pretreatment with CB1 receptor antagonists SR141716 or AM251 reversed PPI deficits induced by acute apomorphine, phenyclidine and MK-801 in a similar fashion to the atypical antipsychotic drug clozapine [199]. This contrasted with an earlier finding where SR 141716 did not reverse PPI-deficits induced by apomorphine, amphetamine and MK-801 in rats [200]. These conflicting findings have been attributed to the different vehicle solutions, doses and PPI paradigms used between these studies. A novel cannabinoid CB1 receptor antagonist AVE1625 reversed MK-801 but not amphetamine induced abnormally persistent latent inhibition and improved working and recognition memory in mice [201]. This study suggested that AVE1625 might best be introduced as an adjunct therapy with conventional antipsychotic drugs because: 1) of its cognitive enhancing efficacy, 2) it did not alter the antipsychotic efficacy of haloperidol and olanzapine against phenyclidine and amphetamine-induced hyperactivity and 3) it ameliorated haloperidol and olanzapine-induced catalepsy and olanzapine-induced weight gain [201]. In a model where adolescent rats receive repeated, intermittent phenyclidine injections it was shown that coadministration with the CB1 receptor antagonist AM251 reversed phenyclidine-induced recognition memory deficits and enhancement of 2-AG levels in the prefrontal cortex [202].

Cannabinoid CB1 receptor antagonists inhibit behavioural sensitization promoted by psychostimulants [47, 203-206]. The literature contains conflicting findings on whether cannabinoid receptor antagonists hinder the induction versus expression of behavioural sensitization to psychostimulants that might be explained by the different cannabinoid CB1 receptor antagonists used in these studies and the differences in their selectivity [207]. AM 251 has been shown to impair induction [204-206] whereas SR 141716 has been shown to inhibit expression of behavioural sensitization to psychostimulants [47, 203]. Somewhat counterintuitive to these findings is that boosting endocannabinoid tone with URB 597, an inhibitor of FAAH, blocked the development of behavioural sensitization to amphetamine that was mediated by CB1 receptors [208]. The effectiveness of SR 141716 in reversing expression of behavioural sensitization to psychostimulants is also dependent on context, that is, SR 141716 only reversed established behavioural sensitization to cocaine when the drug was paired with the test chamber and not in mice receiving the drug in their homecage [47]. The VTA and nucleus accumbens have dissociable roles in mediating behavioural sensitization to psychostimulants, with the former being critical to induction and the latter to expression [209-211]. Interestingly, SR 141716 injected directly into the nucleus accumbens inhibited the expression but not the induction of behavioural sensitization to both cocaine [212] and methamphetamine [203]. Intra-VTA SR 141716 injection was ineffective in reversing induction of behavioural sensitisation to methamphetamine [203]. Methamphetamine-sensitized animals had reduced levels of CB1 receptors in the nucleus accumbens and these receptors were more sensitive to cannabinoid stimulation than animals treated with saline [203]. This further reinforces the notion that the endocannabinoid system is involved in contextual learning aspects of the expression of behavioural sensitization.

DO CANNABINOID RECEPTOR KNOCKOUT MICE DISPLAY SCHIZOPHRENIA-RELATED NEUROBEHAVIOURAL PHENOTYPES?

Human association studies have linked *CNR1*, the gene that encodes for the human cannabinoid receptor 1 gene, with an increased susceptibility to developing schizophrenia in various populations [213-216], although such positive associations have not always been replicated [217-219]. Lending weight to the notion that variation in *CNR1* is related to schizophrenia risk are observations that the brain of post-mortem schizophrenia patients contain increased CB1 receptor expression compared to healthy controls, particularly in areas of the brain that are distorted in schizophrenia patients such as the prefrontal cortex and cingulate cortex [220-223]. These studies suggest that increased CB1 expression or function may be involved in conferring susceptibility to schizophrenia.

CB1 receptor knockout mice do not display classic schizophrenia-like behaviour. Two separate CB1 receptor knockout mice have

been developed that were first described within months of each other [224, 225]. The CB1 receptor knockout mice developed by Ledent *et al*. (1999) bred on a CD1 background showed identical locomotor activity to WT animals, whereas the line developed by Zimmer *et al*. (1999) bred on a C57BL/6J background displayed locomotor hypoactivity. The Ledent line showed improved retention of novel object recognition memory function [226] and the Zimmer line exhibited disrupted reversal learning in the Morris water maze [227]. A follow up study confirmed that the deficit in reversal learning in these mice was due to an impairment in the extinction of spatial learning [228]. Consistent with the symptomology of schizophrenia, the Ledent line mice expressed reduced social behaviour dependent on being tested in an unfamiliar environment [229-231]. It would be of interest to observe whether mice overexpressing CB1 receptors provide a better animal model of schizophrenia given these findings with CB1 receptor knockout mice and that increased expression of the CB1 receptor is found in post-mortem schizophrenia brain [220-223].

It is possible that CB1 receptor loss might confer vulnerability to environmental factors that trigger psychosis in humans. CB1 receptor knockout mice display enhanced stereotypy promoted by phencyclidine administration consistent with an increased sensitivity to hyperdopaminergic function in these mice [230]. Consonant with this, SR141716 markedly increased stereotypies produced by simultaneous co-administration of both a D1 and D2 receptor agonists [232]. However, another study reported that CB1 receptor knockout mice were subsensitive to hyperlocomotion induced by cocaine and amphetamine [204]. In addition, CB1 receptor knockout hampered cocaine-induced c-Fos expression and phosphorylation of key proteins involved in the acute effects of cocaine in the striatum such as the GluR1 sub-unit of AMPA, DARPP-32 and extracellular-signal regulated kinase 2 (ERK2) [204]. CB1 receptors expressed in GABAergic medium spiny neurons of the striatum were critical to cocaine-induced ERK phosphorylation, which subserves the hyperlocomotor effects of cocaine. Research has also shown CB1 receptor deficiency bluntened the actions of 5-HT1A and 5HT2A/C agonists due to impaired 5-HT1A and 5-HT2A/C receptor function [233]. It would be of interest to observe whether CB1 receptor knockout mice are more susceptible to the adverse neurobehavioural actions of other environmental challenges implicated in the aetiology of schizophrenia.

CB2 receptors were once believed to be expressed solely in the periphery, however, there is a growing body of evidence supporting their localisation in the CNS. CB2 receptors are expressed on microglia and there also exists controversial evidence suggesting their expression on neurons [16]. Two recent studies show that polymorphisms in *CNR2* increase the risk of developing schizophrenia and bipolar disorder [234, 235]. Two polymorphisms in CB2 receptors were more prevalent in two independent samples of schizophrenia patients [234]. The risk allele for one of these SNPs was associated with low levels of *CNR2* in human postmortem brain tissue. CHO cells transfected with a missense allele of one of the SNPs displayed impaired cannabinoid-induced reductions in cAMP levels. Mouse studies also showed that the CB2 receptor antagonist AM630 potentiated MK-801 and methamphetamine-induced PPI deficits and locomotor activity stimulation [234]. CB2 receptor knockout mice have recently been shown to display schizophrenia-related behaviours such as PPI deficits and impairments in short and long-term memory consolidation [236]. These animals, while exhibiting reduced baseline locomotor activity, were more sensitive to cocaine-induced hyperactivity compared to WT mice. Furthermore, PPI deficits in these mice were reversed by administration of the atypical antipsychotic risperidone. CB2 knockout mice also expressed greater D2 receptor and less 5-HT2A receptor mRNA expression in the prefrontal cortex than WT mice.

PRECLINICAL STUDIES ON INTERACTIONS BETWEEN THC AND CBD

THC levels in cannabis have been steadily increasing over the last three decades and the ratio of CBD:THC is decreasing [237-240]. A recent US potency study reported that between 1993 and 2008 THC concentrations in cannabis preparations have more than doubled while CBD content has remained the same [238]. For example in 1993 cannabis contained on average 0.3% CBD and 3.4% THC (1:11 CBD:THC ratio), whereas in 2008 it contained 0.4% CBD and 8.8% THC (1:22 ratio). One of the most striking changes was reported for hashish or cannabis resin which is normally assumed to have a 1:1 CBD:THC concentration. In 1993 hashish contained 3.8% CBD and 6.6% THC (1:1.7 ratio) but by 2008 THC concentrations dramatically increased and the CBD level approximately halved with 2.1% CBD and 23.1% THC (1:11 ratio). Interestingly, in the early 80's hashish contained approximately 6% CBD and 3% THC (2:1 ratio) [237].

Animal and human data suggest that THC is responsible for the psychosis-inducing effects of cannabis and that CBD may have antipsychotic potential. Thus, rising THC levels without any increase in CBD concentration is of major concern. To be sure that increasing CBD concentrations in cannabis will be of benefit, more research is needed to better understand the nature and mechanisms subserving THC-CBD interactions. Preclinical studies may provide the experimental control to unequivocally address this issue, however the existing literature contains much conflicting data. Some studies show that CBD reverses the pharmacological actions of THC [61, 89, 241-243], while others report potentiating effects [61, 90, 101, 244-246] or no effect at all [101, 247] (see Table **3**).

One of most comprehensive studies on interactions between CBD and THC examined an array of dose combinations in the classic cannabinoid tetrad of tests in mice (locomotor activity, catalepsy, body temperature and nociception) [101]. Doses of CBD at a CBD:THC ratio between 30:1 and 1:1 had no effect on THC-induced locomotor suppression, catalepsy, hypothermia or antinociception. Only when the CBD:THC ratio was raised to 100:1 (ie 30 mg/kg CBD) was a potentiating action of CBD on antinociception promoted by a sub-threshold dose of THC realised (0.3 mg/kg). Interestingly the same 30 mg/kg CBD dose did not affect the antinociceptive actions of marijuana smoke suggesting other constituents in the plant might also modulate CBD-THC interactions. CBD (at 10 mg/kg but not 30 mg/kg) inhibited the analgesic actions of a maximal effective dose of THC (3.3:1 ratio). Taken together, pharmacological interactions between CBD and THC may not only rely on the ratio of THC:CBD used but also the actual doses of THC administered. It appears for any modulation to occur high doses of CBD are required and that low relative doses of THC favour potentiation and high doses antagonism. The fact that marijuana smoke also nullified THC-CBD interactions further highlights that a multitude of cannabinoid and non-cannabinoid constituents of the plant need to be taken into account when trying to simulate the complex pharmacology of cannabis use by humans.

Research has also attempted to address whether CBD modulates more complex psychological phenomena of relevance to schizophrenia and other mental disorders. Human users of cannabis low in CBD are more vulnerable to the memory impairing effects of THC [248]. Using THC-rich (high THC and low CBD and other phytocannabinoids) and CBD-rich extracts (high CBD and low THC etc), it was shown that CBD reversed the impairing effects of THC on spatial working memory as measured using a delayed-matching-to-place version of the open-field water maze in rats (only though if the ratio of CBD:THC was > 10:1; in this case 50 mg/kg CBD to 4 mg/kg THC) [89]. Conflicting with this finding using a more straightforward experimental design it was shown that 50 mg/kg CBD potentiated the impairing effects of 1 mg/kg THC on spatial memory as measured in an 8-arm radial arm maze in mice when the

drugs were co-administered simultaneously [90]. CBD also enhanced the hypothermic, cataleptic and motor suppressant actions of THC.

A number of recent studies have assessed whether CBD modulates social withdrawal and anxiety-related behaviour induced by THC. The social withdrawal induced by low dose THC (1 mg/kg) was reversed in animals pretreated with CBD (20 mg/kg administered 20 min before THC) [61]. However when a higher dose of THC (10 mg/kg) was administered significant social withdrawal and locomotor suppression was observed that was absent in animals treated with 10 mg/kg THC alone [61]. These findings conflict with the view that CBD is more likely to potentiate low THC doses and antagonise high ones, suggesting that CBD modulation of THC effects may vary from measure to measure. A more recent study assessed interactions between repeated co-administration of escalating doses of THC and CBD (CBD was administered 20 min before THC) on social behaviour and anxiety [246]. CBD enhanced the sedative and anxiogenic actions of THC including social withdrawal. It was also found that CBD exacerbated loss of body weight that is normally observed following repeated THC exposure [249].

Animal studies have investigated whether CBD modulates the subjective qualities of THC intoxication using place conditioning and drug discrimination paradigms. A particularly interesting observation that requires further investigation is that, while THC had no modulatory effect on place conditioning in adolescent rats, CBD and THC combined tended to promote a conditioned place preference [i.e. THC was more rewarding in the presence of CBD (1:1 ratio) [246]]. Using mice it was shown that CBD might hinder the aversive effects of THC on rodents as CBD (1 or 10 mg/kg but not 30 mg/kg) reversed conditioned place aversion induced by THC (10 mg/kg) (i.e. 1:10 and 1:1 ratios respectively) [241]. These findings are particularly important as they demonstrate interactions between CBD and THC at CBD:THC ratios relevant to those found in cannabis cultivated for recreational use today. The latter study used the drug discrimination procedure and also demonstrated that CBD doesn't modulate the subjective qualities of THC intoxication [241]. A prior study using much higher CBD:THC dosing ratios (30:1 and 100:1) showed CBD prolonged the discriminative stimulus properties of THC [245].

Interactions between CBD and THC are not adequately understood and may involve a multitude of both pharmacodynamic and pharmacokinetic mechanisms that require further investigation. CBD's ability to *hinder* THC effects might be more straightforwardly explained by CBD behaving as a potent antagonist at both CB1 and CB2 receptors [27]. Although CBD amelioration of THC effects often lacks dose dependence [61, 241] which might be due to non-selective effects of CBD being manifest at higher doses. CBD has a complex pharmacological profile and interacts with numerous non-cannabinoid receptor protein targets across a range of different concentrations (see [26]). For example, CBD activates 5-HT1A receptors at relatively high concentrations [250]. Future studies are required to delineate the exact pharmacodynamic mechanisms responsible for CBD inhibition of THC action.

Evidence supporting both pharmacodynamic and pharmacokinetic explanations of CBD-induced *augmentation* of THC effects has also been provided. First, combined THC and CBD exposure increased CB1 receptor expression in the hippocampus and the hypothalamus that correlated with greater memory-impairing and hypothermic effects of THC respectively [90]. Contrary to this finding CBD co-administration did not modify repeated THC-induced reductions in CB1 receptor expression in a more recent study [246]. The latter study did, however, provide a pharmacokinetic explanation consistent with earlier studies [251-253] which have demonstrated that CBD treatment increases brain and blood levels of THC. These effects have been attributed to CBD inactivation of cytochrome P450 enzymes involved in the metabolism of THC [254-256]. The drug efflux pumps P-glycoprotein and breast cancer resistance protein, which are expressed at the blood brain barrier, may also be involved as CBD inhibits these transporters [190, 192] and THC is a substrate for these transporters [195-197]. Thus, it is also possible that CBD blocks the excretion of THC from the brain.

CONCLUSION

Rodent studies assessing the actions of cannabinoids in animal models of schizophrenia have generated a wealth of information and a series of outstanding questions that could be addressed in future studies (see Table **4**). Modeling the neurobiological pathophysiology responsible for cannabis-induced schizophrenia using rodents is limited by the validity of the models used to address this issue. The vast majority of studies have assessed the effects of cannabinoids in models that manipulate a single factor implicated in the aetiology of the disorder such as exposure to a particular environmental factor (e.g. psychostimulant exposure). A few promising studies have utilized environmental challenges at critical neurodevelopmental periods of development (e.g. neonatal and adolescent stages). The vast majority of these studies highlight that THC is a propsychotic agent that exacerbates schizophrenia-related behaviours and neurobiology in these models. These studies collectively show that CB1 receptors mediate the schizophrenia-related actions of THC, however, new evidence showing CB2 receptor knockout mice display schizophrenia-related behaviours implies that a role of CB2 receptors should also be considered in future research. Research highlights that adolescence, a time where individuals begin to experiment with cannabis and manifest schizophrenia symptoms, is a particular period of vulnerability to the actions of THC and its synthetic analogues. Cannabis triggers schizophrenia in only those with a genetic vulnerability to the disorder and in the last 5 years animal studies have begun to isolate genes that might be involved. Transgenic mice studies suggest that variation in the schizophrenia susceptibility gene neuregulin 1 and the ABC transporter gene that encodes P-glycoprotein may contribute to cannabis-induced psychosis according to pharmacodynamic and pharmacokinetic mechanisms respectively. Further these studies reinforce human data demonstrating a role of *COMT* in this phenomenon. Future rodent studies could go one step further and examine the neurobehavioural consequences of combining genetic vulnerability (transgenic animals with mutations in schizophrenia susceptibility genes), with environmental challenges early in life (e.g. prenatal stress) and then adolescent cannabinoid exposure. Such an approach may more faithfully resemble the pathophysiological changes observed in schizophrenia patients and provide a better platform to test novel treatments.

While much research has been conducted assessing the propsychotic actions of THC and cannabinoid receptor agonists, few studies have assessed the antipsychotic potential of CBD and other novel cannabinoid-based therapies in animal models of schizophrenia. CBD does ameliorate schizophrenia-related behaviours induced by psychostimulant and NMDA receptor antagonist exposure, however the mechanisms responsible for CBD's antipsychotic profile have not been adequately explained. A repeated theme in many of these studies is that CBD's antipsychotic efficacy is not dose-dependent and in many cases follows an inverted U function. This likely reflects the complex pharmacology of CBD and it proclivity to affect many different proteins beyond simple CB1 receptor antagonism. Recent human data suggest that CBD hinders the propsychotic actions of THC and that the ratio of CBD:THC is decreasing in cannabis smoked by users. Rodent studies conducted over close to 40 years have attempted to model interactions between CBD and THC and have yielded more questions than providing unequivocal answers. Some of the literature reports that CBD reduces the pharmacological effects of THC, while other studies demonstrate the opposite, that CBD potentiates the actions of THC by increasing CB1 receptor expression levels in the brain and also augmenting THC concentrations in the brain and the blood. Future research is

needed to reconcile these discordant findings including studies that also assess modulating actions of other phytocannabinoids.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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