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Genetic dissection of the psychotomimetic effects of cannabinoid exposure

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ABSTRACT

Cannabis use is an established risk factor for the development of schizophrenia and related psychotic disorders. Factors that may mediate susceptibility to the psychosis-inducing effects of cannabis include the age at onset of first cannabis use, genetic predisposition, as well as interaction with other environmental risk variables. Clinical and preclinical genetic studies provide increasing evidence that, in particular, genes encoding proteins implicated in dopamine signalling are implicated in the cannabis–psychosis association. In the present review, we focus on both human and animal studies which have focused on identifying the neuronal basis of these interactions. We conclude that further studies are required to provide greater mechanistic insight into the long-term and neurodevelopmental effects of cannabis use, with implications for improved understanding of the cannabis–psychosis relationship.

1. Introduction

Case–control and longitudinal studies indicate that lifetime cannabis use increases risk for developing a psychotic disorder (see Moore et al., 2007, for a review of the clinical data). Specifically, cannabis use has been associated with a number of clinical variables related to psychosis, including higher relapse rates (Linszen and van Amelsvoort, 2007), poor treatment outcome and increased severity of symptoms (Grech et al., 2005), and accelerated loss of grey matter volume (Moore et al., 2007; Rais et al., 2008), even after adjusting for potential confounding factors. In a large-scale prospective study conducted in The Netherlands, a positive association was reported between cannabis use and self-reported psychotic symptoms; the risk was highest among subjects with greater baseline history of cannabis use, and those with a pre-established vulnerability to psychosis (van Os et al., 2002).

Several authors have questioned the directionality of the relationship between cannabis use and psychosis in longitudinal designs; for example, despite high prevalence of cannabis use in Western countries, only a minority of cannabis users develops subclinical symptoms or a clinical psychotic disorder (Decoster et al., 2012; van Os et al., 2009). This may be explained by potential amplification of cannabis risk when interacting with genetic and other environmental risk factors (van Winkel et al., 2011).

2. Neurobiology of cannabis use: overlap with psychosis

Cannabinoid CB1R receptors are expressed abundantly throughout the brain, notably brain areas implicated in psychosis such as the hippocampus, basal ganglia, cerebellum, and prefrontal cortex (Freund et al., 2003). CB1Rs are primarily localised at the presynaptic terminals of glutamate and GABA-ergic neurons (Eggan and Lewis, 2007; Eggan et al., 2010). Their endogenous transmitters (endocannabinoids) are released from dendritic spines and function as retrograde signalling molecules. In line with the retrograde signalling function of the endocannabinoid-CB1 receptor system, activation of CB1R receptors inhibits glutamatergic and GABA release (Eggan et al., 2010). As with most drugs of abuse, CB1R receptor stimulation also causes an increase in extracellular dopamine (DA); cannabinoids stimulate burst firing of midbrain DA neurons and increase DA release in the ventral striatum, which is likely attributable to activation of CB1R receptors on GABAergic interneurons that synapse with DA neurons (Pistis et al., 2002). Cannabinoid modulation of activity of dopaminergic projections from the brain stem to the striatum has been suggested to play a central role in the pathogenesis of cannabis-induced psychosis (Morrison and Murray, 2009).

Abbreviations: AKT1, V-akt murine thymoma viral oncogene homolog 1; BDNF, Brain-derived neurotrophic factor; CB1R, Cannabinoid receptor 1; COMT, Catechol-*o*-methyltransferase; CNV, Copy number variation; CPT, Continuous performance test; DA, Dopamine; DAT, Dopamine transporter; 5-HT2A, Serotonin 2A; GABA, Gamma-aminobutyric acid; GSK-3, Glycogen synthase kinase 3; G × E, Gene × environment; KO, Knockout; mGLUR5, Metabotropic glutamate receptor 5; NMDAR, N-methyl-D-aspartate receptor; NRG1, Neuregulin-1; PFC, Prefrontal cortex; PPI, Prepulse inhibition; PP2A, Protein phosphatase 2; Δ^9-THC, Delta-9-tetrahydrocannabinol; TM-domain, Transmembrane domain; WT, Wildtype.

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3. Cannabis and psychosis: experimental evidence

Cannabis contains greater than 60 cannabinoids, with Δ^9-tetrahydrocannabinol (THC), a partial agonist at the CB1R receptor, thought to be responsible for the principal psychotomimetic effects (Bossong et al., 2012; Casadio et al., 2011). Cannabidiol, another important constituent of cannabis, has been suggested to possess antipsychotic properties (Leweke et al., 2012; Schubart et al., 2011).

Several studies have shown that acute systemic administration of THC induces a transient increase in psychotic-like symptoms in both healthy volunteers (D'Souza et al., 2004, 2008; Morrison et al., 2009) and patients with schizophrenia (D'Souza et al., 2005). In a double-blind study, D'Souza et al. (2004) found that intravenous THC produced positive and negative symptoms, which peaked over the first 80 min after treatment, decreasing to baseline at 4 h. Bhattacharyya et al. (2012a) examined acute THC effects on salience attribution processing; aberrant salience processes have been linked with presence of positive symptoms such as delusions (Murray et al., 2008; Roiser et al., 2009). During a visual oddball task, THC reduced activation or augmented it in the right PFC during the processing of salient vs. non-salient stimuli, respectively. THC-related activation in the right caudate was negatively correlated with severity of drug-induced psychotic symptoms, as well as response latency in the task, suggesting that cannabis effects on psychosis may also involve modification of the neural substrate of attentional salience processing. Cannabidiol administration was associated with the opposite response to THC and enhanced the appropriate response to salient stimuli (Bhattacharyya et al., 2010, 2012a).

Imaging studies have indicated impairments in learning and memory following cannabinoids to be mediated by medial temporal, striatal, midbrain and PFC function (Bhattacharyya et al., 2009, 2012a; Bossong et al., 2012). Attentional deficits have also been reported following acute THC administration, as well as in chronic cannabis users (Solowij and Michie, 2007). Acute THC exposure also impaired attention and memory in schizophrenia patients and their unaffected siblings relative to healthy controls (D'Souza et al., 2005; Henquet et al., 2006).

Systematic reviews and meta-analyses indicated improved cognitive functioning in cannabis-using relative to non-cannabis-using patients (Løberg and Hugdahl, 2009; Rabin et al., 2011; Yücel et al., 2012). Furthermore, better cognitive functioning has been reported in cannabis-using patients relative to non-using patients on executive function tasks, visual memory, processing speed, global cognition and working memory (Coulston et al., 2007; Potvin et al., 2008; Yucel et al., 2012). It has been suggested that the cognition-improving properties of THC are probably due to stimulation of PFC neurotransmission (Potvin et al., 208; Cohen et al., 2008) or, alternatively, that psychotic patients with lifetime cannabis use may constitute a better functioning group of patients from the outset (de la Serna et al., 2010; Schnell et al., 2009).

4. Cannabis use and adolescence: increased liability for psychosis?

4.1. Human studies

Cannabis use is largely concentrated among young people (15–34 years), with highest prevalence being reported among 15–24 year olds (EMCDDA, 2010). Epidemiological studies have shown that risk to develop psychosis is highest among individuals who use cannabis during adolescence (Arseneault et al., 2002, 2004; Fergusson et al., 2003; McGrath et al., 2010). Prospective cohort studies indicated increased risk for psychosis among those who use cannabis in young adulthood, with heavy users more likely to develop psychosis during a 21-year follow-up period (McGrath et al., 2010). Schubart et al. (2011) underlined that early (under 12 years of age) and heavy cannabis use were each materially and independently associated with increased risk for psychiatric hospitalisation.

Adolescence is a critical period in brain development, with considerable maturation occurring in limbic structures, such as the hippocampus as well as PFC, which undergo synaptic pruning, myelination and receptor development during this age period (Andersen and Teicher, 2008; Spear, 2000). Interestingly, studies have reported long-term white matter changes in adolescent cannabis-using adults, in prefrontal fibre bundles of the corpus callosum (Arnone et al., 2008) and in fronto-parietal circuitry (Bava et al., 2009). However, other studies have reported no changes in white matter integrity (Delisi et al., 2006) or the hippocampus (Medina et al., 2007) relative to age-matched cannabis-naive subjects.

4.2. Rodent studies

Adolescent cannabinoid exposure in male rats produced changes across several schizophrenia-related endophenotypes, including deficits in prepulse inhibition (PPI; a measure of sensorimotor gating which is disrupted in schizophrenia), object recognition memory impairment and a deterioration in progressive ratio instrumental performance in adult animals (Schneider and Koch, 2003). These deficits were accompanied by abnormal basal neuronal activation across several brain regions (Wegener and Koch, 2009). Gleason et al. (2012) administered a CB1 receptor agonist during adolescence or adulthood to C57BL6 mice and evaluated long-term effects on fear conditioning, PPI, exploratory activity and social interaction. They reported long-lasting deficits in PPI and contextual fear conditioning in adolescent-treated mice, with no changes in social interaction and exploratory activity; these deficits were accompanied by normal CB1R receptor expression but reduced mGluR5 protein expression in the hippocampus.

Sex-specific (female only) deficits in working memory, as measured in the radial arm maze, were observed in adolescent THC-treated mice; these were accompanied by synaptic impairments in PFC (Rubino et al., 2009). Deficits in recognition memory were reported in THC-treated adolescent but not adult rats (Quinn et al., 2008; Renard et al., 2012), accompanied by proteomic alterations in the hippocampus related to degenerative and oxidative processes (Quinn et al., 2008). Other studies have reported structural changes in the hippocampus following adolescent THC treatment, including impairment in structural and functional plasticity of both neurons and glia in this region, alongside a reduction in dendrite length and complexity/number of dendritic spines in the dentate gyrus (Rubino et al., 2009).

5. Genetic architecture of psychosis

A continually evolving body of evidence suggested that schizophrenia involves the interaction of numerous common genetic risk factors, each with a small impact on risk liability, and/or the presence of a number of rare penetrant mutations which have a profound impact on brain development (Doherty et al., 2012). Specifically, rare structural genomic variants, including copy number variations (CNVs) and translocations have been described in schizophrenia (Moore et al., 2011).

Complex processes are likely to have an equally complex pathophysiology, with associated difficulties in conducting studies in human subjects that are able to isolate individual factors and quantify their clinical impact. The advance of molecular genetic technologies provides the capability to selectively delete, modify or introduce a target gene to create a mutant mouse: in a constitutive/developmental mutant, this modification is present from conception; in a conditional mutant, this modification is inducible in a temporally-specific or spatially-restricted manner (Tanaka et al., 2010). Applying a reverse genetic approach, specific disease-relevant genes of interest are mutated; numerous preclinical genetic models have been generated using such conventional gene targeting techniques (Table 1). Monogenetic preclinical models of psychosis should not be expected to recapitulate all aspects of a disease phenotype, particularly in light of evident clinical heterogeneity and diagnostic overlap with other disorders (Kvajo et al., 2012).