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Does cannabidiol have a role in the treatment of schizophrenia?

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ABSTRACT

Schizophrenia is a debilitating psychiatric disorder which places a significant emotional and economic strain on the individual and society-at-large. Unfortunately, currently available therapeutic strategies do not provide adequate relief and some patients are treatment-resistant. In this regard, cannabidiol (CBD), a non-psychoactive constituent of *Cannabis sativa*, has shown significant promise as a potential antipsychotic for the treatment of schizophrenia. However, there is still considerable uncertainty about the mechanism of action of CBD as well as the brain regions which are thought to mediate its putative antipsychotic effects. We argue that further research on CBD is required to fast-track its progress to the clinic and in doing so, we may generate novel insights into the neurobiology of schizophrenia.

1. Introduction

Schizophrenia is one of the top 25 causes of global disease burden in terms of years lived with disability and the emotional and economic strain it imposes on society (Kooyman et al., 2007; Mangalore and Knapp, 2007; Vos et al., 2015; Wu et al., 2005). The symptomatology of schizophrenia is multifaceted with positive symptoms such as delusions and hallucinations, negative symptoms including avolition and social withdrawal and cognitive deficits such as impairments in working memory. At a time when studies like CUTLASS, CATIE and EUFEST have shown limited efficacy of atypical over typical antipsychotics (Davidson et al., 2009; Lewis and Lieberman, 2008) and newer, synthetic drugs are essentially 'me-too' drugs or do not meet expectations (Carpenter and Koenig, 2008; Conn and Roth, 2008), there is an urgent need to accelerate research into finding more efficacious antipsychotics.

In this regard, there is now wide-spread recognition of the existence of therapeutic strategies for the treatment of schizophrenia that extend beyond the dopamine hypothesis of schizophrenia (Dunlop and Brandon, 2015). These strategies are based on alternative hypotheses for the aetiology of schizophrenia, one of which involves dysfunction of the endocannabinoid system. The endocannabinoid system in the brain has been implicated in mediating several important functions including appetite and mood regulation as well as reward processing (Di Marzo et al., 2004). Evidence for an endocannabinoid hypothesis of schizophrenia comes from a range of studies linking the abuse of cannabis to the increased risk of developing schizophrenia (Gururajan et al., 2012a; Malone et al., 2010), and from observations that patients with schizophrenia showed elevated levels of the endogenous cannabinoid anandamide (AEA) and alterations in the expression of cannabinoid receptors in several brain regions (Zamberletti et al., 2012). This evidence provides the basis for the development of pharmacotherapies to treat schizophrenia by targeting the endocannabinoid system (Pacher et al., 2006).

Given the above mentioned epidemiological link, l it is perhaps ironic that a derivative of the cannabis plant known as cannabidiol (CBD) has shown promise as an antipsychotic. This was first reported nearly two decades ago by Zuardi et al. (1995) in a small case report and it has been three years since the last major clinical trial of CBD in patients with schizophrenia by Leweke et al. (2012). In the intervening years, there have been clinical and preclinical studies which have provided evidence to support its use for the treatment of schizophrenia. However, the number of studies is relatively few compared to investigations of other pharmacotherapies such as clozapine or even aripiprazole. Furthermore, as discussed later in this review, the lack of a consistent approach between research groups has resulted in inconsistent findings.

There have been several recent reviews on the antipsychotic potential of CBD. But in addition to critiquing the clinical and preclinical studies that have been performed to date, in this review we have extended the discussion to include the neuropharmacology of CBD, potential mechanisms of antipsychotic action as well as the pharmacokinetic and metabolic considerations associated with its use. We will finally discuss possible experimental avenues which could be followed to further tap into its potential, fast-tracking its progress to the clinic.

2. Neuropharmacology

CBD belongs to a group of naturally occurring phytocannabinoids derived from the *Cannabis sativa* plant of which there are approximately 100, and is exemplified by the archetypal cannabinoid, delta-9-

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tetrahydrocannabinol (THC) (Mechoulam et al., 2014). The human body also produces its own endogenous cannabinoids which include AEA and 2-acyl-glycerol (2AG) (Di Marzo et al., 2004). Phytocannabinoids and endogenous cannabinoids exert their effects by binding to canonical cannabinoid receptors, CB1 and CB2 (Howlett et al., 2004). These are G-protein-coupled receptors (GPCR) which are linked to numerous mechanisms including enhancing inwardly rectifying potassium currents, inhibiting voltage-gated calcium channels (VGCC), inhibiting the adenylate cyclase transduction pathway and activating the mitogen activated kinase pathway (Pertwee, 1997). However there is evidence to suggest that some of the actions of cannabinoids are mediated by non-CB1/CB2 receptors such as the vanilloid TRPV1 (Caterina and Julius, 2001) and GPR55 receptors (Nevalainen and Irving, 2010). Furthermore, CB1 receptors in particular can also exist as heterodimers with other GPCRs which have different functional profiles (Hudson et al., 2010).

First isolated over 75 years ago from the Minnesota hemp (Adams et al., 1940), CBD is unlike the vast majority of cannabinoids in that it is not adversely psychoactive and has a neuropharmacological profile that goes beyond acting as a ligand at the CB1 and CB2 receptors. In fact, the affinity for CBD at these receptors is poor (e.g. rat CB1 receptor, THC Ki:42.6 ± 5 vs CBD Ki:2210.5 ± 558.08) (McPartland et al., 2007). The first set of studies investigating the neuropharmacology of CBD examined its effects using in vitro synaptosomal preparations. These studies showed that CBD was able to inhibit reuptake of radiolabelled dopamine, serotonin, noradrenaline and GABA in synaptosomal preparations of the striatum and hypothalamus (Banerjee et al., 1975; Poddar and Dewey, 1980). However, these studies were in contrast to work which showed that tail vein injections of CBD induced an increase in synaptic reuptake of dopamine, albeit with much less potency than THC (Hershkowitz and Szechtman, 1979). Other studies have shown that CBD inhibited metabolism of acetylcholine in the striatum (Revuelta et al., 1978) and inhibited depolarisation-dependent calcium uptake in synaptosomal preparations from whole brain regions (Harris and Stokes, 1982).

One of the first studies to report the effects of CBD on cannabinoid receptors utilised rat cerebellar membranes and reported that CBD had no agonist activity by itself but acted as a weak antagonist, shifting the concentration response curve for $GTP_{\gamma}S$ binding (a measure of intrinsic cellular GPCR activity) of the cannabinoid receptor agonist, CP-55,940, rightwards (Petitet et al., 1998). As a follow-up to these findings, another study used whole mouse brain membrane preparations and CHO cells expressing human CB1 and CB2 receptors (Thomas et al., 2007). Results showed firstly that in the mouse brain preparations, CBD inhibited CP-55,940-induced $GTP_{\gamma}S$ binding. However, this effect occurred at affinities much lower than the value required for the displacement of CP-55,940 from the CB1 receptor (79 nM vs 4.9 μM), suggesting that it was not involved. This was further supported by evidence from similar observations in experiments with membrane preparations from CB1 receptor knockout mice. Secondly, this study showed in CHO cells expressing CB1 receptors that CBD had inverse agonist effects but again this was also observed in experiments with membrane preparations from CB1 receptor knockout mice. CBD also had high affinity for CHO cells expressing CB2 receptors and also showed inverse agonist activity at this receptor.

In 2001, an important paper that provided insight into a mechanism of action of CBD at the intracellular vanilloid TRPV1 receptor was published (Bisogno et al., 2001). While showing negligible affinity for CB1 in synaptosomal preparations and in COS-7 cells expressing CB2 receptors, CBD showed agonist activity similar to capsaicin in HEK cells transfected to over-express the human variant of the TRPV1 receptor as observed by an increase in cytosolic calcium concentration. Furthermore, the effect of CBD was inhibited by pretreatment with the TRPV1 receptor antagonist capsazepine and CBD displayed competitive binding in the presence of the radiolabelled TRPV1 agonist resinferatoxin. Interestingly, this study also showed that CBD was able to inhibit the reuptake of AEA in RBL-2H3 cells and inhibit hydrolysis of AEA by the enzyme, fatty acid amide hydrolase (FAAH). This is consistent with evidence in support of the existence of a so-called endocannabinoid transporter which facilitates cellular uptake followed by chaperoning by carrier proteins to intracellular targets such as FAAH (Fowler, 2013). Following on from these findings, another study showed that the CBD-induced increase in cytosolic calcium was dependent on both external sources of calcium (mediated by opening of voltage-gated channels) and also the activation of intracellular calcium stores (Drysdale et al., 2006). However, in contrast to the suggested role of the TRPV1 receptor as a receptor for CBD, these authors observed that this specific effect of CBD was potentiated in the presence of capsazepine suggesting that this receptor was negatively coupled to the effects of CBD via a non-TRPV1 based mechanism. More recently, it has been reported that CBD activates TRPV1, TRPV2 and TRPA1 channels, which is followed by rapid desensitisation of these ion channels (Iannotti et al., 2014).

As reported above, CBD is a putative inhibitor of AEA reuptake and hydrolysis, however it remains to be determined whether this effect is mediated by the vanilloid receptor or via another mechanism (Bisogno et al., 2001). Incidentally, endocannabinoid tone was reported to influence the effects of CBD in vitro (Ryan et al., 2007). Under basal conditions, the effect of CBD on cytosolic calcium levels was intact but a stimulus induced increase in endocannabinoid levels inhibited the effects of CBD. In contrast, pretreatment with THC increased the effects of CBD. Furthermore, the phospholipase C inhibitor U73122 potentiated the CBD response which led to the conclusion that the effect of CBD was negatively coupled to the activation of an uncharacterised $G_{q/11}$ coupled cannabinoid receptor (Ryan et al., 2007). It has been hypothesized that the potentiating effects of CBD on AEA levels, which activate both TRPV1 and CB1 receptors, are crucial to the effects of CBD on glutamate-mediated activation of the prefrontal cortex (Zuardi et al., 2012). As TRPV1 and CB1 receptor activation is largely thought to have opposing effects in neurons (activation versus inhibition respectively), the relative activity of AEA at each receptor may be responsible for the often reported biphasic effects of CBD (Zuardi et al., 2012).

In vitro work using CHO cells expressing serotonin 5HT1A receptors showed that CBD dose-dependently displaced the radiolabelled 5HT1A receptor agonist, 8-OH-DPAT, increased $GTP_{\gamma}S$ binding to a similar extent to serotonin and also inhibited forskolin-induced cAMP production in a manner sensitive to the 5HT1A receptor antagonist, NAN-190 (Russo et al., 2005). In experiments in NIH-3T3 cells expressing serotonin 5HT2A receptors, CBD also showed dose-dependent displacement of the radiolabelled agonist, ketanserin, but with much less potency than at the 5HT1A receptor. These results suggested that CBD could also be a ligand for 5HT1A and 5HT2A receptors.

As mentioned earlier, GPR55 is purportedly a non-CB receptor via which cannabinoids such as CBD may exert their effects. Analysis of mouse, rat and human brains revealed high levels of GPR55 expression in several brain regions (Sawzdargo et al., 1999). Using HEK293 cells transfected with the human variant of this orphan receptor, CBD antagonised CP-55,940-induced $GTP_{\gamma}S$ binding at a concentration considerably lower than that required to observe a similar effect in CB1/CB2-receptor preparations (445 nM vs >30.000 nM) (Ryberg et al., 2007). This concentration was also approximately 5 orders of magnitude higher than what was required to displace CP-55,940 from CHO cells expressing CB1 (79 nM) (Petitet et al., 1998). The authors of this study also observed that CBD inhibited AEA-induced activation of GPR55 and its downstream signaling proteins rhoA, cdc42 and rac1 which are involved in cell morphology (Ryberg et al., 2007).

A recent in vitro study has suggested another mechanism of action of CBD could involve negative allosteric modulation (NAM) at the CB1 receptor (Laprairie et al., 2015) but we have not been able to observe NAM effects at CB1 receptors when investigating CB1 receptor agonists with other NAMs (Khajehali et al., 2015). Importantly, this mechanism has not been validated in vivo.

Overall, consensus as to the precise neuropharmacology of CBD has not yet been reached partly due to the disparate experimental

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