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Pro-psychotic effects of synthetic cannabinoids: interactions with central dopamine, serotonin and glutamate systems

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Abstract

An association between marijuana use and schizophrenia has been noted for decades, and the recent emergence of high-efficacy synthetic cannabinoids (SCBs) as drugs of abuse has lead to a growing number of clinical reports of persistent psychotic effects in users of these substances. The mechanisms underlying SCB-elicited pro-psychotic effects is unknown, but given the ubiquitous neuromodulatory functions of the endocannabinoid system, it seems likely that agonist actions at cannabinoid type-1 receptors (CB1Rs) might modulate the functions of other neurotransmitter systems known to be involved in schizophrenia. The present review surveys what is currently known about the interactions of CB1Rs with dopamine, serotonin and glutamate systems, because all three of those neurotransmitters are well-established in the pathophysiology of schizophrenia and psychosis. Identification of molecular mechanisms underlying the pro-psychotic effects of SCB drugs of abuse may establish certain classes of these substances as particularly dangerous, guiding regulations to control availability of these drugs. Likewise, an understanding of the pharmacological interactions which lead to schizophrenia and psychosis subsequent to SCB exposure might guide the development of novel therapies to treat afflicted users.

Introduction

The continuing emergence of novel “marijuana substitute” smoking blends such as *K2* and *Spice* frustrates regulatory efforts to curtail availability of the dangerous synthetic cannabinoids (SCBs) present in these products. These SCBs are often much more potent and efficacious at cannabinoid CB1 and CB2 receptors (CB1R/CB2R) than the main psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC), suggesting a capacity to induce more intense *in vivo* effects than cannabis. Epidemiological studies suggest that cannabis use, particularly in adolescence, increases risk for psychotic episodes later in life (D’Souza et al., 2009; Evins et al., 2012) and preclinical studies have also demonstrated pro-psychotic effects of Δ^9-THC in rodents treated during the adolescent period (Rubino and Parolaro, 2013). Fergusson and colleagues (2006) reviewed six prospective studies of cannabis users and found that all of them demonstrated increased risks

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of psychosis or psychotic symptoms with odds ratios ranging from 1.77 to 10.9. Alarmingly, reports of acute and lasting psychosis elicited by use of SCBs are rapidly accumulating in the clinical literature (Glue et al., 2013; Spaderna et al., 2013; Durand et al., 2013; Oluwabusi et al., 2013; Hermanns-Clausen et al., 2013; Peglow et al., 2012; Tung et al., 2012; Brakoulias, 2012; Hurst et al., 2011; Benford and Caplan, 2011; Every-Palmer, 2011; Every-Palmer, 2010; Müller et al., 2010; Monte et al., 2017; Vallersnes et al., 2016; Roberto et al., 2016), but the mechanism of psychosis remains poorly understood. Thus, in addition to other toxicities (Seely et al., 2012; Tai and Fantegrossi, 2017), SCB use may also elicit clinically relevant and persistent adverse mental health consequences. As growing numbers of young Americans are exposed to emerging SCB drugs of abuse, it is critical to understand the mechanisms by which SCBs induce a lasting vulnerability to psychosis and begin to define the molecular changes that underlie this effect so that efficacious therapies can be developed. Specifically, this review will focus on the role of CB1 receptors in the regulation of brain dopamine, serotonin and glutamate systems, because these neurotransmitters are al associated with schizophrenia and psychosis (Sawa and Snyder, 2003) and because their release is regulated by CB1 receptors (Howlett et al., 2004). Any or all of these neurotransmitters could therefore mediate the pro-psychotic effects of SCBs. The goal of this review is to address the current lack of knowledge regarding the persistent pro-psychotic effects of SCBs, and to highlight the unique public health challenges posed by these novel compounds. The data here reviewed will demonstrate that SCBs are not simply alternate forms of marijuana, but are dangerous drugs of abuse with persistent adverse neuropsychiatric sequelae arising from their use.

CB1 and CB2 Receptors

In the brain, there are two well-characterized cannabinoid receptors subtypes: cannabinoid type-1 receptors (CB1R; found on presynaptic neurons and densely expressed in the prefrontal cortex and in the hippocampus (Eggan and Lewis, 2007; Tsou et al., 1999)) and cannabinoid type-2 receptors (CB2R; highly-expressed in the peripheral tissues of the immune system, nervous system, and gastrointestinal system (Munro et al., 1993; Navarrete et al., 2013;Wright et al., 2005)). Although CB2R are also found in brain regions such as the prefrontal cortex, hippocampus and hypothalamus (reviewed in Demuth and Molleman, 2006; den Boon et al., 2012; Kim and Li, 2015; Onaivi et al., 2008; Wang et al., 2016), they are not thought to be involved in psychoactive effects of cannabis or SCBs (reviewed in Pertwee, 2006; Reggio, 2010; Caballero and Tseng, 2012). Therefore, this review will focus primarily on the role of CB1R in pro-psychotic effects of marijuana and SCBs.

Dopamine

Pharmacological treatment of schizophrenia (and arguably the entire field of psychopharmacology itself) began with the discovery that chlorpromazine was an efficacious therapeutic against mania and psychosis. The clinical efficacy of chlorpromazine was a serendipitous discovery, but its mechanism of action was eventually defined as antagonism of dopamine receptors (Carlsson and Lindquist, 1963), allowing for the rational design of antipsychotics and cementing dopamine hyperfunction as the most plausible pathophysiology underlying schizophrenia and psychosis. As the study of dopamine receptors matured, both D1-like and D2-like dopamine receptors have come to be associated

with primary psychotic symptoms (D2-like receptors) and cognitive dysfunctions (D1-like receptors) which accompany schizophrenia. Although other neurotransmitter systems are certainly implicated in the etiology of schizophrenia and psychosis (see below), dopamine systems remain the primary targets of antipsychotic medications, and disfunction of central dopamine circuits remains the predominant hypothesized mechanism underlying the illness.

First, second, and third generation synthetic cannabinoids (SCBS) have relatively higher binding affinity (*i.e.,* nanomolar inhibition constant [*Ki*] values) for cannabinoid CB1R and CB2R compared to the prototypical cannabinoid, Δ^9-THC. Once bound to the cannabinoid receptors, many SCBs function as full agonists that potently activate G-proteins and/or inhibit adenylyl cyclase activity leading to numerous changes in intracellular activities (for review of cannabinoid receptor physiology, Demuth & Molleman, 2006; for SCBs, Ford *et al.*, 2017). Although it is oftentimes convenient to limit the scope of experiments with SCBs to the endocannabinoid system and the intracellular signaling cascades initiated therein, it is well established that cannabinoid receptors affect functioning in other neurotransmitter systems such as the dopaminergic system (reviewed in El Khoury *et al.*, 2012). Indeed, SCBs produce downstream effects on dopaminergic functioning that are not predictable solely by their pharmacological actions at cannabinoid receptors. For example, SCBs are typically characterized as locomotor depressants in rodents (*e.g.,* Tai *et al.* 2015; Gatch & Forster 2014; 2016) and hypolocomotion serves as a primary endpoint in the cannabinomimetic-screening "tetrad" (Compton *et al.*, 1992). However, locomotor *stimulant* effects of SCBs occur within a relatively narrow dose range compared to prototypical psychostimulants. Ossato *et al.* (2017) reported that intraperitoneal injections of 0.3 mg/kg JWH-018 or 1 mg/kg AKB48 produced time-dependent increases in horizontal distance traveled in male CD-1 mice similar to, but, to a lesser extent than, 20 mg/kg cocaine or 10 mg/kg amphetamine. Moreover, these locomotor stimulant effects were attenuated by pretreatment with 1 mg/kg of the CB1R antagonist AM-251, or a combination of 0.1 mg/kg of the dopamine (DA) $D_{1\text{-like}}$ receptor antagonist SCH23390 and 0.05 mg/kg of the DA $D_{2\text{-like}}$ receptor antagonist haloperidol. However, unlike cocaine and amphetamine, JWH-018 and AKB48 display poor binding affinity (*i.e.*, >1000 nM Ki values) at the human dopamine transporter (DAT) expressed in CHO membranes (Ossato *et al.*, 2017). Whereas the psychostimulants cocaine and amphetamine increase extracellular concentrations of DA via direct actions at DAT and intracellular vesicles (with respect to the amphetamines), stimulation of CB receptors with nonselective and selective agonists does not appear to modulate DAT function, effect [^{3}H]-DA uptake in mouse striatal synaptosomes (Ossato *et al.*, 2017), or stimulate release or block reuptake of [^{3}H]-DA in rat striatal slices (Köfalvi *et al.*, 2005). Thus, the capacity of SCBs and psychostimulants to produce increases in locomotor activity appears to involve stimulation of DA receptors, but, as discussed below, the pharmacological mechanisms that mediate these effects differ between these drug classes.

Despite a lack of effect at DAT, SCBs produce increases in DA levels and firing activity of DA-expressing neurons. For example, the SCBs JWH-018, AKB48, and 5F-AKB48 stimulate dopamine release in nucleus accumbens of freely-moving mice (Canazza *et al.*, 2016; Ossata *et al.*, 2017), Δ^9-THC and WIN55212–2 increase extracellular concentrations of DA in the shell of the nucleus accumbens in Sprague-Dawley rats (Tanda *et al.*, 1997),

and intravenous injections of Δ^9-THC, WIN55212–2, and CP55940 increase the firing rate and bursting activity of A10 DA neurons in anesthetized and unanesthetized Sprague-Dawley rats (Gessaa *et al.*, 1998). However, instead of locally-mediated actions at DA targets (*e.g.,* DAT, DA receptors), previous research indicates that CB receptor stimulation may modulate the firing rate of DA-expressing neurons via inhibition of GABAergic and glutamatergic neurotransmission (see below), and/or endocannabinoids may directly stimulate TRPV1 receptors that are directly expressed on DA or glutamatergic neurons (reviewed in El Khoury *et al.*, 2015). For example, the nonselective CB receptor agonist WIN55212–2 and the selective CB1R agonist ACEA inhibits the release of electrically-evoked [^{3}H]-GABA in rat striatal slices, and the inhibitory effects of WIN55212–2 are blocked via coadministration of CB1R antagonists SR141716A and AM251, indicating a CB1R-dependent effect (Köfalvi *et al.*, 2005). In a later study, Morera-Herreras *et al.* (2008) reported that 0.25–2 mg/kg (iv) Δ^9-THC dose-dependently increased the firing rate of neurons in the *substania nigra pars compacta* (SNpc), a region rich with DA-expressing neurons, of anesthetized Sprague-Dawley rats. In addition, pretreatment with the CB1R antagonist/inverse agonist 0.5 mg/kg rimonabant (iv), pretreatment with the glutamate receptor antagonist kyuneric acid (0.5 μM, icv), or chemical lesion with ibotenic acid blocked Δ^9-THC's excitatory effect on the neurons in the SNpc (Morera-Herreras *et al.*, 2008). Thus, SCBs likely produce significant effects on dopaminergic functioning that results from the complex, multisynaptic interaction between endocannabinoid and other neurotransmitter systems. To add to this complexity, cannabinoid receptors have the capacity to dimerize with receptors from other protein families indicating the possibility of more direct effects of DA neurotransmission. For example, Kearn *et al.* (2005) observed that CB1R can form a heterooligomeric receptor complex (*i.e.,* dimerize) with dopamine D_2 receptors in HEK 293 cells. Interestingly, stimulation of either receptor *individually* results in activation of $G\alpha_{i/o}$ proteins, leading to inhibition of adenylyl cyclase and lower levels of cyclic AMP within the cell. However, co-stimulation of the CB1-D_2 receptors in the dimer results in preferential activation of $G\alpha_s$ proteins, resulting in an increase in cAMP (Kearn *et al.*, 2005). Thus, dimerizations of cannabinoid receptors with DA receptors produces neurochemical consequences that are distinct from the component receptors functioning alone. A better understanding of these interactions may profoundly modify predictions of *in vivo* pharmacological effects of SCBs based on *in vitro* or *ex vivo* experiments.

Although a full discussion of the complex interactions between CBs and DA receptors is beyond the scope of this review, it is clear from the foregoing discussion of selected examples from preclinical research, the popularity of the subject among literature reviews, and published case reports that SCBs are implicated in human activities, conditions, and bodily functions in which DA functioning is involved. Of particular relevance to the present section, the capacity of cannabinoid agonists to elicit increases in DA concentrations (*e.g.*, Tanda *et al.*, 1997; Canazza *et al.*, 2016; Ossata *et al.*, 2017), desynchronize the functioning of GABAergic interneurons in the hippocampus (*e.g.*, Hoffman & Lupica, 2000) to produce perturbations in learning and sensory processing, and the close interactions shared between the endocannabinoid system and pathways involved in stress and reward (reviewed in Volkow *et al.*, 2017) warrants rigorous investigation of the well-documented association between SCB consumption and psychosis (reviewed in van Amsterdam *et al.*, 2015).

Serotonin

Serotonin (5-HT) was isolated and identified in the late 1940s (Rapport et al., 1948; Rapport, 1949), and shortly thereafter it was proposed that it may play a vital role in cognition and the etiology of schizophrenia (Woolley and Shaw, 1954). Further cementing the relationship between 5-HT and schizophrenia is the fact that many efficacious antipsychotic agents including reserpine (Braun, 1960; Gore et al., 1957), clozapine, risperidone, and olanzapine all exhibit serotonergic mechanisms of action (Meltzer et al., 1989, Meltzer, 1991, 1999; Seeman, 2002). Specifically, atypical antipsychotics which block 5-HT_{2A} receptors with some selectivity over DA receptors exhibit lower incidence of extrapyramidal effects than do typical dopaminergic antipsychotics (Meltzer, 1999; Roth and Meltzer, 2000; Abi-Dargham and Krystal, 2000), which suggests that alterations of 5-HT_{2A} function may be involved in schizophrenia and psychosis. We will therefore focus this discussion on the regulation of 5-HT_{2A} by cannabinoid signaling.

5-HT_{2A} Receptors

The serotonin 2A receptor (5-HT_{2A}R) is found throughout the CNS, and is a $G_{q/11}$-coupled receptor (Raote et al., 2007; reviewed in Carhart-Harris and Nutt, 2017). It is mainly expressed in the pyramidal neurons of the prefrontal cortex (Jones et al., 2009). In the CNS, 5-HT_{2A} receptors may signal through numerous pathways. Under normal circumstances, 5-HT_{2A}Rs are involved in the regulation of many different functions, especially mood and impulse control (Higley and Linnoila, 1997; reviewed in Celada et al., 2004; Tsuang et al., 2013). Thus, alterations in 5-HT_{2A}R expression and function have been implicated in mental disorders (including schizophrenia) and drug addiction (reviewed in Meltzer et al., 2003; reviewed in Bubar and Cunningham, 2006). Importantly, abused 5-HT_{2A}R agonists, such as psilocybin or 2,5-dimethoxy-4-iodoamphetamine (DOI), cause users to experience altered perception and hallucinations, similar to the psychotic experienced by individuals with schizophrenia (reviewed in Nichols, 2004).

Recently, an indirect involvement modulation of 5-HT_{2A}R expression by SCBs has been proposed as a mechanism for causing psychosis. Interestingly, 5-HT_{2A}R upregulation by SCBs may be exclusively mediated by CB1R. For example, SCBs have been shown to increase the interaction of 5-HT_{2A}Rs and dopamine receptors in the prefrontal cortex; a finding which is also consistent with molecular interactions associated with schizophrenia (Franklin and Carrasco, 2012; reviewed in de Almeida et al., 2008). According to Franklin and Carrasco, activation of the ERK1/2 signaling pathway by selective CB2 receptor agonists seems to suggest a specific upregulation of 5-HT_{2A}Rs *in vitro* (2013).Thus, if certain antipsychotics like clozapine and risperidone function as 5-HT_{2A}R antagonists, while other psychotherapeutics like fluoxetine can be useful in psychosis via downregulation of 5-HT_{2A}Rs, then it may be the case that SCBs elicit pro-psychotic effects via upregulation of the 5-HT_{2A}Rs in a brain region-specific manner (Marek et al., 2005; reviewed in Gray and Roth, 2001; reviewed in Rogoz, 2013; Franklin et al., 2013). However, a recent study found that chronic exposure to JWH-018 prevents alterations in 5-HT_{2A}R expression (Elmore and Baumann, 2017), perhaps suggesting that the interaction between SCBs and brain serotonin systems may depend critically on dose, frequency of administration, or other procedural factors.

A useful behavioral assay sensitive to 5-HT_{2A}R agonists is the head-twitch response (HTR) (reviewed in Gonzalez-Maeso and Selfon, 2009; Martin et al., 1963). Synthetic cannabinoids can inhibit DOI-induced head twitches. For example, Darmani (2001) reported that pretreatment with structurally distinct classical synthetic cannabinoids HU-210, CP 55,940, or WIN 55,212–2 dose-dependently attenuated DOI-induced head twitches in mice. At the time of the writing of this review, synthetic cannabinoids have not been reported to elicit head twitches, however, there is evidence presented in the literature that demonstrates head twitch behavior can be induced by the CB1R antagonist/inverse agonist, rimonabant (Darmani and Pandya, 2000). Rimonabant can induce head twitching behavior in drug-naïve rodents, which can be attenuated by the selective 5-HT_{2A}R antagonist, SR46349B (Darmani and Pandya, 2000; Darmani, 2001; Janoyan et al., 2002). Additionally, DOI-induced head twitch behavior is inhibited when indirect-acting cannabinoid agonists, such as AM404 and URB597 are administered (Egashira et al. 2011). Taken together, these *in vivo* data imply that 5-HT_{2A}R agonists and antagonists produce the opposite psychosis-like effects observed in HTR compared to the cannabinoid receptor agonists and antagonists. The interaction between CB1R signaling an 5-HT_{2A}R expressions and function is an active area of research which may help to further identify the mechanisms of cannabinoid-induced psychosis in the future.

Glutamate

Glutamate (Glu) is the major excitatory neurotransmitter, and it binds to both ionotropic and metabotropic receptors. Metabotropic Glu receptors (mGluR) have at least eight subtypes classified into three groups based on sequence homology, signal transduction, and pharmacology. Maksymetz and colleagues (2017) have recently reviewed current strategies to target mGluR to treat schizophrenia, but there is scant data on interactions between mGluRs and CB receptors, so further discussion of this is largely outside the scope of this review. However, there are three currently recognized ionotropic Glu receptors (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors), and the NMDA receptors are most closely associated with neurological disorders, including schizophrenia and psychosis (Mechri et al., 2001; Maeng and Zarate, 2007). Importantly, administration of the noncompetitive NMDA antagonist phencyclidine (PCP) to healthy human subjects reliably induces psychosis-like effects (Davies and Beech 1960; Cohen et al. 1962), as does the structurally-related arylcyclohexylamine ketamine (Krystal et al. 1994; Malhotra et al. 1996). Accordingly, the remainder of this section will focus on interactions between CB1R and NMDA receptors.

Activation of NMDA receptors can elicit endocannabinoid released from postsynaptic neurons (Hashimotodani et al., 2007). Subsequently, endocannabinoids can decrease activity of NMDA receptors (Sánchez-Blázquez et al., 2014), perhaps analogous to the effects of PCP and ketamine. Indeed, alterations in NMDA receptor function induced by CB1R agonist actions has been demonstrated in mice (Derkinderen et al., 2003; Marsicano et al., 2003), in hippocampal slices (Khaspekov et al., 2004), and in cultured neurons (Kim et al., 2006). Multiple mechanisms may allow cannabinoids to modulate NMDA receptor activity, including CB1R-mediated attenuation of Glu release (Brown et al., 2003; Melis et al., 2004; Li et al., 2010) and events downstream from CB1R signaling which may attenuate NMDA

receptor signaling (Liu et al., 2009; Hampson et al., 2011). Thus, the high intrinsic efficacy of SCBs may allow for more dramatic regulation of NMDA receptor function than that of lower efficacy CB1R agonists like anandamide or Δ^9-THC.

At this time, it remains unclear whether or not SCBs interact directly with NMDA receptors, but given the dramatic structural diversity among the SCBs it seems unlikely that any general rule will emerge in this regard. There is perhaps some precedence for SCBs with relevant affinity for NMDA receptors, as the classical SCB HU-210 has a (+)-enantiomer referred to as HU-211 (or sometimes referred to as dexanabinol, dexanabinone, or sinnabidol) which exhibits affinity for NMDA receptors, but is also reported to be non-psychoactive (Feigenbaum et al., 1989). However, the first-generation aminoalkylindole SCB JWH-018 elicits interoceptive effects in nonhuman primates which are not occasioned by administration of ketamine up to doses which disrupted operant responding (Rodriguez and McMahon, 2014), likely suggesting that JWH-018 does not directly interact with NMDA receptors. Whether later-generation SCBs with different chemical structures are more similar to HU-211 or to JWH-018 in terms of NMDA affinity will likely have to be evaluated on a case-by-case basis, but it may be predicted that SCBs displaying significant antagonist affinity at the NMDA site would be more likely to induce pro-psychotic effects in human users.

Conclusions

The landscape of abused SCBs is constantly changing, with new compounds appearing as older drugs are regulated and controlled. Although the chemical scaffolds upon which these drugs are based has also changed over the years, there remains a relatively constant pharmacological truism – that the SCBs almost always exhibit higher efficacy at CB1Rs than Δ^9-THC. Because agonist actions at CB1Rs can regulate the function of DA, 5-HT and Glu systems implicated in schizophrenia and psychosis, higher efficacy CB1R agonists might alter the function of these three neurotransmitter systems to a greater degree than Δ^9-THC, although the role of intrinsic CB1R efficacy in this regard has never been parametrically studied. Furthermore, it may be the case that some SCBs might exhibit pharmacologically-relevant affinity for psychosis-associated receptors, including D2, 5-HT_{2A} or NMDA. Given the biotransformation of many SCBs to active metabolites (e.g., Brents et al., 2011), even if the parent drugs themselves do not interact with these receptors, it may be the case that a generated metabolite would do so. Although many studies have demonstrated the risk potential associated with excessive and prolonged SCB consumption, it will be important for policy makers and the general public to understand the major pharmacological and neurobiological consequences of consuming these compounds despite the current national emphasis on legalizing cannabis for medical and perhaps recreational use. Defining the behavioral and cellular mechanisms of SCB-induced pro-psychotic effects will provide critical scientific knowledge to further establish these drugs as public health risks, guide the development of new drug therapies, and perhaps identify novel effective therapies to treat acute SCB-induced psychosis.

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