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Mechanisms Contributing to Cognitive Deficits in Cannabis Users

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Abstract

Studies from preclinical animal models indicate that sustained activation of CB1 receptor signaling is a major contributing factor for the onset of cognitive deficits associated to chronic cannabis use, in particular within the working memory and decision-making domains. Yet, very few studies have been designed to directly assess the role of CB1 receptors in mediating the effects of cannabis on human brain function. This perspective review article provides an overview of current state of knowledge on possible neurobiological mechanisms accounting for the detrimental effects of chronic cannabis use on cognition and related changes in brain structure and functional connectivity.

Introduction

The endogenous cannabinoid system is comprised by the cannabinoid receptors (e.g., CB1 and CB2), the endocannabinoids (eCB) anandamide (AEA) and 2-arachydonylglycerol (2-AG), and the enzymes that regulate their production and degradation (Freund et al., 2003; Regehr et al., 2009). Both AEA and 2-AG are postsynaptically-produced fatty acid-derived retrograde ligands that diffuse presynaptically to limit the strength of both excitatory and inhibitory transmission by acting onto presynaptic CB1 receptors (Freund et al., 2003; Regehr et al., 2009). The CB1 receptor is widely expressed in the brain (Glass et al., 1997; Freund et al., 2003) and is coupled to a pertussis-sensitive Gi/o protein-dependent signaling mechanism (Vogel et al., 1993), which in turn leads to reduction of cAMP levels and inhibition of presynaptic calcium currents (Freund et al., 2003; Regehr et al., 2009). It is through this generic mode of action that the CB1 receptor signaling is responsible for the

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psychoactive effects of cannabis, Δ9-tetrahydrocannabinol (Δ9-THC) (Devane et al., 1988), and of modulating the release of a broad range of neurotransmitters including GABA, glutamate as well as serotonin and acetylcholine (Freund et al., 2003; Regehr et al., 2009).

Investigation of the eCB system in human cognition is limited by tools available to manipulate and measure eCB targets that can safely be used in clinical trials. These include selective and specific drugs targeting cannabinoid CB1 and CB2 receptors as well as eCB metabolizing enzymes. In this regard, tetrahydrocannabivarin (THCv) is a promising candidate, although further studies are needed to elucidate its pharmacology *in vivo*. Radioligands for PET are also available for *in vivo* imaging of CB1 receptors ([^{11}C]OMAR and [^{18}F]MK9470) and FAAH ([^{11}C]CURB), but selective probes for each of these targets are required in order to provide a complete picture of the eCB system in health and disease. On the other hand, acute pharmacological studies using Δ9-THC are quite variable due to its poor oral bioavailability/pharmacokinetics and partial agonism of CB1 receptors, which likely differs from the effects of full CB1 receptor agonists (Fantegrossi et al., 2014). Moreover, the primary eCBs and synthetic CB1 receptor full agonists, mainstays of preclinical investigation, are expected to exhibit a more potent profile than Δ9-THC in humans (Fantegrossi et al., 2014). Finally, a better standardization for cannabinoid research in humans is currently needed (Broyd et al., 2016; Curran et al., 2016; Lorenzetti et al., 2016). High heterogeneity of dependent variables across studies include (i) the study design and its sample size, (ii) the route of Δ9-THC/cannabis and cannabinoid administration, (iii) the delay period between drug administration and behavioral testing, (iv) and the poor characterization of participants' drug history (e.g., age of onset and frequency) and exposure to stimulants such as caffeine, alcohol and nicotine.

Of particular interest is the negative impact of chronic cannabis use on cognitive functions within the working memory and decision-making domains (Solowij et al., 2002; Kanayama et al., 2004; Schweinsburg et al., 2008; Meier et al., 2012). Similar cognitive deficits have been observed in rodent models of chronic cannabinoid exposure (Schneider and Koch, 2003; O'Shea et al., 2004; Schneider et al., 2008; Raver et al., 2013; Renard et al., 2013), indicating that sustained activation of CB1 receptor signaling is a major contributing factor for the onset of cognitive deficits in chronic cannabis users (Caballero and Tseng, 2012). However, the neural substrates accounting for such detrimental effects remain unclear despite the fact that major changes in brain structure have been repeatedly reported in chronic cannabis users (Lorenzetti et al., 2016). The goal of this review is to provide an overview of current state of knowledge on possible neurobiological mechanisms contributing to the development of cognitive deficits following chronic cannabis use/abuse.

Role of CB1 receptor signaling in mediating the effects of cannabis on human cognition

It is well established from pre-clinical animal studies that most of the disrupting effects of Δ9-THC in the brain are mediated by activation of CB1 receptor signaling (Devane et al., 1988; Mallet and Beninger, 1998; Raver and Keller, 2014; Colizzi et al., 2016). However, very few studies have been designed to directly assess the role of CB1 receptors in mediating the effects of Δ9-THC on human brain function, or more broadly the role of CB1 receptors in cognition (Colizzi et al., 2016). In humans, Δ9-THC-induced subjective effects

were blocked by a high dose of the CB1 receptor antagonist AVE1625 (Zuurman et al., 2010), whereas the subjective effects of smoked cannabis were only partially blocked by the CB1 receptor antagonists rimonabant and surinabant (Huestis et al., 2001; Gorelick et al., 2006). Existing data linking CB1 receptors to cognition are largely limited clinical trials of rimonabant that were halted upon its withdrawal from the market in 2008. For example, the increased number of intrusions in verbal recall tasks observed following administration of Δ9-THC (D'Souza et al., 2004) was significantly attenuated in individuals treated with rimonabant as revealed by fewer intrusions of positive self-relevant words and overall of non-self-relevant words (Horder et al., 2012). More recently, the phytocannabinoid THCv has emerged as a putative neutral CB1 receptor antagonist (Thomas et al., 2005; Pertwee, 2008; McPartland et al., 2015). Accordingly, Δ9-THC-induced impairment of delayed recall can be markedly diminished with THCv treatment, suggesting a role for CB1 receptor signaling in mediating the effects of Δ9-THC on verbal memory (Englund et al., 2016).

In addition to the acute effects of cannabis, studies from chronic cannabis users also indicate that changes in CB1 receptor signaling contribute to the development of cognitive deficits resulting from chronic exposure to cannabis. Typically, cognitive impairments observed in chronic users do not persist beyond 4–6 weeks after cannabis abstinence (Pope et al., 2001; Schreiner and Dunn, 2012). Similarly, the density of cortical CB1 receptors becomes downregulated with years of cannabis use, but it begins to recover within days of abstinence (D'Souza et al., 2016) and returns to control levels within4 weeks of abstinence (Hirvonen et al., 2012). Of note, the level of CB1 receptor availability was not correlated with the duration of cannabis use or the age of onset of cannabis use (Ceccarini et al., 2015). Yet, subjects with the lowest cannabis use showed the smallest global CB1 receptor decrease whereas the magnitude of CB1 receptor downregulation was the highest among heavy cannabis users (Hirvonen et al., 2012; Ceccarini et al., 2015). Thus, the degree of cognitive deficits observed in chronic cannabis users may be associated with the extent of CB1 receptor stimulation in a dose-dependent manner. To our knowledge, the relationship between the recoveries of CB1 receptors and of cognitive performance or task-related brain activity has not been tested directly.

Disruption of brain regional architecture and connectivity

Changes in regional brain architecture (Lorenzetti et al., 2016) and resting state functional connectivity (Wetherill et al., 2015; Blanco-Hinojo et al., 2016) associated with chronic cannabis use often map onto CB1 receptor-enriched cortical networks and neural pathways involved in cognitive functions (Glass et al., 1997; Freund et al., 2003). However, major anatomical abnormalities associated with higher levels of cannabis use (age of onset, duration, dosage) were primarily found within the prefrontal cortex and the hippocampus (Lorenzetti et al., 2016), two interconnected brain regions critically implicated in the execution of cognitive outcomes (Floresco et al., 2009). Thus, any disruption that compromises the functional integrity of the prefrontal-hippocampal pathway will negatively impact cognitive functions such as working memory, decision-making and inhibitory control (Floresco et al., 1997; Floresco et al., 2009).

In addition to the duration and intensity of exposure, there is evidence indicating that the onset of cannabis use during adolescence contributes to disrupt cognitive functions and aspects of frontal cortical connectivity more severely (Ashtari et al., 2009; Cheetham et al., 2012; Batalla et al., 2013; Filbey and Dunlop, 2014; Lorenzetti et al., 2014; Jakabek et al., 2016). Consistent with this view, a recent resting-state fMRI study found that early-onset chronic cannabis use can lead to reduced functional connectivity between the anterior cingulate/medial frontal cortex and the striatum (Blanco-Hinojo et al., 2016). Such a disruption of the corticostriatal connectivity could result from excessive stimulation of CB1 receptors given the fact that the distinct resting-state connectivity observed between cannabis users and controls was not longer apparent after a 28-days period of abstinence (Blanco-Hinojo et al., 2016), precisely when the density of CB1 receptors returns to control levels (Hirvonen et al., 2012).

Relative to non-user controls, chronic cannabis users generally exhibit lower resting-state functional connectivity across different cortical networks with the exception between the posterior cingulate cortex and the anterior insular cortex (Wetherill et al., 2015). In contrast, opposite changes in connectivity appear in response to acute administration of Δ9-THC in healthy volunteers (Klumpers et al., 2012). Typically, Acute Δ9-THC exposure is associated with a global increase in functional connectivity, mainly across cortical regions involved in sensorimotor-visual processing, although a reduction in the dorsal visual network occurred to a lesser extent (Klumpers et al., 2012). Together, these findings suggest that the chronicity/duration of cannabis use can elicit changes in resting-state connectivity that is opposite to those seen with acute Δ9-THC. Future studies are needed to improve our understanding on the neural mechanisms contributing to the different effects of cannabis.

Disruption of cognition function and cortical network activity

A single dose of cannabis or Δ9-THC robustly impairs working and episodic memory (Curran et al., 2002; Crane et al., 2013). Such disruption of working memory processes is associated with a loss of the normal load-associated increase in prefrontal cortex activity (Bossong et al., 2012). Similarly, the most consistently reported long-term effects/case-control studies of non-acute effects of cannabis are impairments in the encoding of new episodic memories, with some studies finding persistent deficits in the first few days of abstinence, but little evidence of persisting deficits after 28 days of abstinence (Crane et al., 2013).

On the other hand, chronic cannabis use is associated with modest impairments in cognitive performance, with the most reliable and marked effects on prospective memory, verbal learning, verbal immediate and delayed recall, and recognition memory (Ranganathan and D'Souza, 2006; Solowij and Battisti, 2008; Broyd et al., 2016; Schoeler et al., 2016). Impairments of working memory are less reliably observed in chronic cannabis users, perhaps because such deficits are detected only at higher cognitive loads or in tasks requiring manipulation rather than mere repetition of information (Bossong et al., 2014). Typically, working memory recruits network activity across regions of the posterior and superior parietal cortex, the prefrontal cortex, and the anterior cingulate cortex (Cabeza and Nyberg, 2000). Network activity within these brain regions increases linearly with increases

in working memory load. Interestingly, the reduced task accuracy following acute Δ9-THC exposure parallels the elevated working memory network activity at low working memory load with no further changes in network activity with increases in working memory load (Bossong et al., 2012). Similarly, chronic cannabis users often exhibit weaker associations between task-related brain activity and task performance, that is, recruitment of brain regions that are typically not activated in non-users (Kanayama et al., 2004; Chang et al., 2006) and alterations in brain activity of network nodes associated with increasing load.

Practice over trials of the Sternberg item recognition task is also associated with task-related deactivation of the superior parietal cortex, reflecting decreasing load. Such load-related deactivation of the parietal cortex was absent in chronic users tested at one week of cannabis abstinence (Jager et al., 2006). Chronic cannabis users with a shorter period of abstinence (6–36h) also showed greater task-related activation of the frontal and superior temporal gyrus with further activation of the anterior cingulate cortex during a spatial working memory task (Kanayama et al., 2004). Similar studies from adolescent cannabis users also revealed a pattern of compensatory-like activation of frontal cortical regions associated with task-related processing during a working memory task (Jager et al., 2010; Jacobus and Tapert, 2014).

Relative to non-user controls, individuals with a history of chronic cannabis use also showed less activation of the attention network regions (e.g., right frontal, dorsal parietal, medial cerebellum) during a visual attention task (Chang et al., 2006). While non-users exhibit load-dependent changes in large clusters within the parietal cortex and the frontal lobe, chronic cannabis users instead exhibited elevated effects of attentional load spread across a larger number of small areas across several nuclei (Chang et al., 2006; Jager et al., 2006). For a simple visual attention task, this fragmented activation pattern persisted for a long period of abstinence (Chang et al., 2006). In contrast, the fragmented activation pattern during a visual-auditory selective attention task was no longer observed following one week of abstinence (Jager et al., 2006). It remains unclear whether these divergent results are reflective of differences in the task demands or due to differences in study design and power.

It should be considered that studies measuring task-related brain activity are often designed to detect changes in brain activity between groups at comparable levels of performance, and are typically not designed or powered to detect group differences in task performance per se (Curran et al., 2016). Complementary studies designed and powered to detect differences in performance (i.e., working memory load) are needed to elucidate the practical impact of the abnormalities in functional activity associated with acute or chronic cannabis use.

Overall, chronic cannabis users tend to exhibit (i) changes in task-related activity that in nonusers would be associated with poor performance, (ii) a weakening or loss of associations between task-related brain activity and task performances, (iii) alterations in brain activity in network nodes that are associated with increasing load or learning-related reductions of activity, (iv) and recruitment of additional brain regions that may or may not be typically considered part of the same functional network. To what extent these changes are mechanistically linked to the global decrease in resting-state connectivity remain unclear.

Concluding Remarks

It is well known that activation of the frontal cortex increases with working memory load following an inverted-U relationship such that a shift towards the left of the load-activity curve emerges when the demand exceeds the functional capacity and cortical activation decreases (Manoach, 2003; Lew and Tseng, 2014). In this regard, the pattern of activation observed in cannabis users may reflect a leftward shift of the load-activity curve, that is, higher activation at low loads and weaker load-related changes in activity. In addition, recruitment of additional brain regions in cannabis users may reflect a compensatory mechanism as the load pushes activity in task-related areas towards the descending arm of the curve. Interestingly, the abnormalities in cognitive task-related brain activity in chronic cannabis users can be reversed with abstinence, paralleling the time courses for recovery of task performance and CB1 receptor density. However, other deficits and alterations in task-associated brain activity seem to persist beyond the period of normalization of CB1 receptor levels. Together, these findings indicate that different mechanisms of neuroadaptations may occur in response to chronic cannabis use/abuse. In summary, more work is needed to link cannabis-associated alterations in brain activity and performance with alterations of the brain eCB system and its impact on synaptic transmission.

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