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Seeing through the smoke: Human and animal studies of cannabis use and endocannabinoid signalling in corticolimbic networks

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ABSTRACT

Public opinion surrounding the recreational use and therapeutic potential of cannabis is shifting. This review describes new work examining the behavioural and neural effects of cannabis and the endocannabinoid system, highlighting key regions within corticolimbic brain circuits. First, we consider the role of human genetic factors and cannabis strain chemotypic differences in contributing to interindividual variation in the response to cannabinoids, such as THC, and review studies demonstrating that THC-induced impairments in decision-making processes are mediated by actions at prefrontal CB_1 receptors. We further describe evidence that signalling through prefrontal or ventral hippocampal CB_1 receptors modulates mesolimbic dopamine activity, aberrations of which may contribute to emotional processing deficits in schizophrenia. Lastly, we review studies suggesting that endocannabinoid tone in the amygdala is a critical regulator of anxiety, and report new data showing that FAAH activity is integral to this response. Together, these findings underscore the importance of cannabinoid signalling in the regulation of cognitive and affective behaviours, and encourage further research given their social, political, and therapeutic implications.

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Contents

1. Introduction

In recent years, the social and political landscape surrounding cannabis use has been the focus of heightened scrutiny. Cannabis is the most widely used illicit drug with an estimated 180 million adults using the drug annually (SAMSHA, 2014; UNODC, 2015). However, a growing number of countries and jurisdictions have reformed cannabis laws so that personal consumption of the drug is no longer severely punishable (UNODC, 2015), while others have legalized its use for medicinal purposes. Recreationally, the drug is used for the "high" it produces, which includes feelings of relaxation and euphoria. However, these effects are biphasic, and in some individuals this high can manifest as anxiety, impaired cognition, and psychotic-like states such as in schizophrenia. Such adverse effects highlight the risks associated with cannabis exposure, with a number of studies showing that prolonged use may lead to adverse life outcomes and possible dependence in select users (American Psychiatric Association, 2013; Fergusson and Boden, 2008; Horwood et al., 2010). In contrast, for other individuals, cannabis use may provide therapeutic benefits for the relief of pain, spasticity, nausea and vomiting.

The psychoactive effects of cannabis are primarily mediated by Δ^9-tetrahydrocannabinol (THC), which is one of at least 70 phytocannabinoids found in the plant (Elsohly and Slade, 2005). THC binds to the presynaptic CB_1 receptor that, together with CB_2 receptors and the endogenous cannabinoids, 2-arachidonylglycerol (2-AG) and N-arachidonylethanolamine (anandamide; AEA), comprise the endocannabinoid system. CB_1 receptors are located in key regions throughout corticolimbic brain networks, such as the prefrontal cortex (PFC) and amygdala, which functionally interact with subcortical dopamine pathways (Tan et al., 2014). As such, aberrations of the endocannabinoid system are increasingly recognized as etiological factors in several neuropsychiatric syndromes, including schizophrenia, anxiety, and mood disorders (Bossong and Niesink, 2010; D'Souza et al., 2005; Hillard and Liu, 2014; Lutz et al., 2015; Papini et al., 2015; Passie et al., 2012; Saito et al., 2013; Semple et al., 2005; Smit et al., 2004; Tan et al., 2014). These conditions may involve deficits in executive function, emotional processing and social behaviours, and/or co-morbidities with affective or addiction-related phenomena—in essence, broad deficits in behavioural processes mediated by corticolimbic circuits. Indeed, growing evidence from clinical and preclinical research demonstrates that CB_1 receptor transmission within these networks strongly regulates the expression of cognitive and emotional behaviours (Arnold et al., 2012; Crane et al., 2013; Hajos and Freund, 2002; Hillard and Liu, 2014; Laviolette and Grace, 2006b; Lutz et al., 2015; Papini et al., 2015; Pattij et al., 2008; Tan et al., 2014).

In this review we will highlight key brain loci that are modulated by cannabinoid transmission, which may subserve the cognitive-impairing, pro-psychotic, and anxiety-regulating actions of cannabis. Given that not all individuals experience adverse effects, we will first describe factors that mediate interindividual variation in the behavioural response to cannabinoid drugs. This includes a number of identified gene variations, as well as different phytocannabinoids in the plant itself, which can modulate the neural and behavioural effects of THC. We will also review evidence suggesting that acute and/or regular THC exposure impairs frontal-cortical functioning, as evidenced by deficits in executive abilities following use. This section specifically focuses on the effects of cannabinoids in both clinical and preclinical models of decision-making, given that optimal cost/benefit decision-making is mediated by corticolimbic circuits. Focus will then shift to the endogenous cannabinoid system, and how CB_1 signalling in the PFC and ventral hippocampus (vHIPP) modulates mesolimbic dopamine activity, dysregulation of which may underlie the emotional processing deficits observed in psychotic disorders like schizophrenia. Lastly, we will review data suggesting that variations in amygdalar endocannabinoid signalling could contribute to vulnerability to anxiety-related disorders and trait anxiety. Each section reflects a symposium presentation at the 2015 International Behavioural Neuroscience Society meeting in Victoria, BC, Canada, and all include background literature and new data; readers are guided to more comprehensive reviews on the subject throughout each section.

2. Individual differences in response to cannabis: contribution of genetic factors and strain differences

It is clear from human research that there is great interindividual variation in response to cannabis and the cannabinoids. For some, cannabis use is pleasurable and enhances creative thinking, while for others it may provoke anxiety, panic, memory loss and, in rare instances, psychotic-like states. In this section we will review research that seeks to explain variation in response to cannabinoid exposure. One explanation for this variation is genetic disposition, with some individuals being genetically prone to the adverse actions of cannabinoids, while others may be resilient. We will examine clinical and preclinical evidence that demonstrates specific genes modulate the neurobehavioural actions of THC. Another explanation for divergent cannabinoid response centres on the type of cannabis people choose to smoke. Cannabis' psychoactive effects are primarily mediated by THC, but growing evidence highlights that other phytocannabinoids in the plant have unique properties that may modulate the actions of THC. Both human and clinical