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Invited review

New vistas on cannabis use disorder

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ABSTRACT

Cannabis sativa preparations are the most consumed illicit drugs for recreational purposes worldwide, and the number of people seeking treatment for cannabis use disorder has dramatically increased in the last decades. Due to the recent decriminalization or legalization of cannabis use in the Western Countries, we may predict that the number of people suffering from cannabis use disorder will increase. Despite the increasing number of cannabis studies over the past two decades, we have gaps of scientific knowledge pertaining to the neurobiological consequences of long-term cannabis use. Moreover, no specific treatments for cannabis use disorders are currently available.

In this review, we explore new research that may help fill these gaps. We discuss and provide a solution to the experimental limitation of a lack of rodent models of THC self-administration, and the importance this model can play in understanding the neurobiology of relapse and in providing a biological rationale for potential therapeutic targets. We also focus our attention on glial cells, commenting on recent preclinical evidence suggesting that alterations in microglia and astrocytes might contribute to the detrimental effects associated with cannabis abuse. Finally, due to the worrisome prevalence rates of cannabis use during pregnancy, we highlight the associations between cannabis use disorders during pregnancy and congenital disorders, describing the possible neuronal basis of vulnerability at molecular and circuit level.

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1. Introduction

Social debate on mental health consequences of cannabis use has intensified in the last years due to the high rates of recreational cannabis use and the changing legal status of cannabis in several Western countries. As a consequence of this higher use, demand for therapeutic treatments for cannabis use disorders (CUD) has increased worldwide since 2003 (World Drug Report, 2016). CUD is associated with a broad range of health-related problems, such as cognitive decline, respiratory and cardiovascular diseases, psychiatric symptoms, and risk of addiction or substance use disorders (SUD; Volkow et al., 2014). Despite the high prevalence of CUD and the increasing number of cannabis users seeking treatment (World Drug Report, 2016), to date no specific pharmacotherapy has been approved by any national regulatory authority. Current therapies are aimed at alleviating symptoms of cannabis withdrawal and include compounds that directly affect endogenous cannabinoid signaling or drugs efficacious in treating psychiatric conditions associated with other drugs of abuse (Gorelick, 2016). However, none of these medications has been proven broadly and consistently effective. Thus, an in-depth understanding of the neurobiological underpinnings of CUD is needed to provide potential new therapeutic targets.

In this review, we address some interesting findings that have been recently described regarding CUD. These novel insights into the neurobiological basis of CUD may help pave the way for new therapeutic approaches.

2. Why do we still lack a rodent model of cannabis self-administration?

Although cannabis is the most widely used illegal drug in the world (Borgelt et al., 2013), there is relatively little understanding of the neurobiological consequences of long-term cannabis use. The primary reason for our poor knowledge of CUD is the lack of experimental paradigms that model cardinal characteristics of addiction. Specifically, it has been difficult to establish a model of cannabis use in rodents that involves self-administration and drug seeking initiated by cues or contexts associated with cannabis delivery. Noncontingent (experimenter delivered) administration of the psychoactive ingredient of cannabis, Δ9-tetrahydrocannabinol (THC), is the currently used model, and provides understanding of the acute pharmacology of the drug and the neurobiological adaptations to repeated drug use. However, key to understanding relapse in particular is the integration between drug pharmacology and environmental or interoceptive stimuli that become associated with drug delivery (Shaham et al., 2003; Spencer et al., 2016). Thus, the lack of ability to produce learned associations with cannabis delivery in available animal models severely limits their utility in understanding the neurobiology of voluntary relapse to cannabis use. Even more critical, the lack of a model of voluntary use and highly motivated drug seeking limits the ability to use animal models in developing pharmacotherapies that might limit the motivation to relapse to cannabis use. The rodent model of cue- or context-induced relapse has proven successful in identifying novel biological targets for possibly treating other addictive drugs (Brown et al., 2013). Accordingly, the inability to model the neurobiology of relapse and to develop treatments for relapse is likely to be an expanding deficit as cannabis becomes decriminalized, legalized or medically legalized throughout the Western Countries.

2.1. Problems modeling cannabis self-administration and relapse

The majority of drugs abused by humans are also self-administered by rodents, lending strong face validity to this model. The standard model of drug self-administration varies in terms of time and dose of self-administration (Zernig et al., 2007). The period of self-administration ranges from weeks to months with a goal of either establishing stable intake in short 1–2 h daily sessions or establishing escalated intake in extended 4–8 h daily sessions of self-administration. To study relapse, the self-administration sessions are typically conducted daily in the same environment to create a contextual association. Also, many studies incorporate a Pavlovian discrete cue(s) that is associated with drug delivery. Irrespective of the precise self-administration protocol, relapse is evaluated after a period of withdrawal. The withdrawal period varies from 24 h to many weeks and is either a period of forced abstinence, or a period of daily exposure to the drug-paired context in order to “extinguish” the association the animal makes between drug and context (Shaham et al., 2003). Context extinction training is used to isolate the discrete drug associated cue as a trigger for reinstating drug-seeking. In the forced abstinence model, the animal is simply placed into the drug-paired context to initiate drug-seeking, although discrete cues may also be present. Initiating drug-seeking without drug access by either a drug-paired context or discrete cue is considered a model of high face validity since both types of stimuli can elicit craving and highly motivated drug-seeking in humans. Perhaps more importantly, these models of relapse may have predictive validity since compounds that successfully suppress relapse in these animal models are also successful at suppressing craving in clinical trials (Shaham et al., 2003; Spencer et al., 2016). Indeed, understanding the neurobiology underpinning this model of relapse for some drugs has provided rationales for introducing new compounds into clinical trials, specifically *N*-acetylcysteine for treating cocaine craving (Kalivas and Volkow, 2011; Brown et al., 2013).

The models outlined above have been successfully applied to most drugs that are addictive in humans, in particular amphetamine-like psychostimulants such as cocaine, opioids such as heroin, nicotine and alcohol. For the first three drug classes intravenous drug delivery is by far the most common route of administration, while for alcohol oral drug delivery is most common. The lack of a rodent model of THC self-administration and drug-seeking arises largely from four facts that taken together distinguish cannabis from other addictive drugs.

a) Cannabis self-administration delivery systems are more difficult to establish than for most other addictive drugs. Human cannabis use is via inhalation or ingestion. Rodent models of voluntary drug inhalation are notoriously difficult to establish, as is revealed by the relatively few publications in the preclinical literature employing voluntary inhalation of tobacco smoke as a means of drug delivery (Harris et al., 2010). An alternative is intravenous (i.v.) drug self-administration, and i.v. self-administration of nicotine, the main psychoactive component of tobacco, has become the accepted model for studying tobacco addiction (Caille et al., 2012). Thus i.v. administration is the preferred model of self-administration for most addictive drugs but it has been difficult to establish for cannabis in rodents.

b) Cannabis, like nicotine, contains a number of psychoactive constituents, making the i.v. delivery of cannabis uncertain in terms of which constituent(s) to use. The primary psychoactive constituent of cannabis is THC, which is a partial agonist at both the cannabinoid CB1 and CB2 receptors (Pertwee, 2008). However, CB1 receptors are generally thought to be the primary site of action in brain contributing to the addictive properties of cannabis; although see (Zhang et al., 2014). With the exception of a series of publications in squirrel monkeys by Steve Goldberg's group (Tanda et al., 2000; Justinova et al., 2003, 2008), there is a paucity of literature on the successful de novo i.v. self-administration of THC in rodents. Rats previously trained to self-administer the CB1 receptor agonist

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