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Invited review

The endocannabinoid system as a target for addiction treatment: Trials and tribulations

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ABSTRACT

Addiction remains a major public health concern, and while pharmacotherapies can be effective, clinicians are limited by the paucity of existing interventions. Endocannabinoid signaling is involved in reward and addiction, which raises the possibility that drugs targeting this system could be used to treat substance use disorders. This review discusses findings from randomized controlled trials evaluating cannabinergic medications for addiction. Current evidence suggests that pharmacotherapies containing delta-9-tetrahydrocannabinol, such as dronabinol and nabiximols, are effective for cannabis withdrawal. Dronabinol may also reduce symptoms of opioid withdrawal. The cannabinoid receptor 1 (CB1) inverse agonist rimonabant showed promising effects for smoking cessation but also caused psychiatric side effects and currently lacks regulatory approval. Few trials have investigated cannabinergic medications for alcohol use disorder. Overall, the endocannabinoid system remains a promising target for addiction treatment. Development of novel medications such as fatty acid amide hydrolase inhibitors and neutral CB1 antagonists promises to extend the range of available interventions.

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1. Introduction

Despite the toll that addictions continue to take on public health (Forouzanfar et al., 2016; Rudd et al., 2016), only a small number of pharmacological treatment strategies are available. Although these treatments have been shown to reduce substance-related mortality (Degenhardt et al., 2009), existing pharmacotherapies are only effective for a subset of patients and several substance use disorders lack a single FDA-approved medication (Le Foll, 2016). Many existing pharmacotherapies function as either long-term or temporary substitution strategies, which replace the drug of abuse with a medication targeting the same receptor system that serves to reduce withdrawal and craving. There is an urgent need to develop pharmacotherapies with novel mechanisms of action for patients who are unresponsive to drugs targeting traditional receptor systems as well as for those who have substance use disorders which lack effective treatments.

Over the past three decades, the development of pharmacotherapies targeting the endocannabinoid system (Box 1) has produced a range of compounds that have been studied as treatments for substance use disorders. Many of these medications target cannabinoid receptor 1 (CB1), the primary cannabinoid receptor in the central nervous system (Box 2). CB1 is densely expressed in brain regions involved in the development and maintenance of addictive behaviors including the ventral striatum, the dorsal striatum, and the amygdala (Parsons and Hurd, 2015). Modulation of CB1 receptor activity in each of these regions leads to downstream behavioral effects. For example, CB1 receptor activity moderates alcohol consumption and alcohol-induced dopamine release in the ventral striatum (Caille et al., 2007; Hungund et al., 2003), gates habit formation in the dorsal striatum (Gremel et al., 2016), and regulates fear extinction in the amygdala (Gunduz-Cinar et al., 2013). Thus, pharmacological treatments which alter endocannabinoid signaling could be expected to change addictive behaviors across substance use disorders by directly impinging on the neurobiological underpinnings of addiction.

Pharmacotherapies targeting the endocannabinoid system may also have substance-specific effects. For cannabis use disorder, as delta-9-tetrahydrocannabinol (Δ^9-THC) is a partial CB1 agonist, CB1 agonists and partial agonists may serve as a substitution therapy analogous to methadone and buprenorphine for opioid use disorder or the nicotine patch for nicotine use disorder. For substances

Box 1
The Endocannabinoid System: Key Components

Cannabinoid Receptors:

CB1: A G-protein coupled cannabinoid receptor that is widely distributed in the human brain. Its activation is thought to be primarily responsible for the psychoactive effects of cannabinoids.

CB2: A cannabinoid receptor primarily expressed in peripheral immune cells, where it is thought to modulate immune function. Recent preclinical evidence suggests that it is also expressed in the central nervous system.

Endocannabinoid Neurotransmitters:

Anandamide: An endogenous cannabinoid neurotransmitter which functions as a cannabinoid receptor partial agonist.

2-arachidonoylgylcerol (2-AG): An endogenous cannabinoid neurotransmitter which functions as a full cannabinoid receptor agonist.

Cannabinoid metabolizing enzymes:

Fatty Acid Amide Hydrolase (FAAH): A membrane-bound serine hydrolase which inactivates anandamide by converting it to arachidonic acid and ethanolamine.

Monoacylglycerol Lipase (MAGL): A cytosolic serine hydrolase which inactivates 2-AG by converting it to arachidonic acid and glycerol.

Box 2
Selected Compounds Targeting the CB1 Receptor

Delta-9 Tetrahydrocannabinol (Δ^9-THC): Cannabinoid primarily responsible for the psychoactive effects of cannabis. Functions as a partial CB1 agonist.

Cannabidiol (CBD): Cannabinoid found in many strains of cannabis. Reduces CB1 activity, possibly through an allosteric mechanism, and has diverse pharmacodynamic effects on other receptor systems.

Dronabinol (Marinol®): Encapsulated oral formulation of Δ^9-THC. FDA-approved for the management of anorexia with weight loss in patients with AIDS and treatment-resistant nausea and vomiting associated with cancer chemotherapy.

Nabilone (Cesamet®): Synthetic analogue of Δ^9-THC. FDA-approved for the management of treatment-resistant nausea and vomiting associated with cancer chemotherapy.

Nabiximiols (Sativex®): An oromucosal spray containing both Δ^9-THC and cannabidiol (2.7 mg Δ^9-THC and 2.5 mg CBD per spray). Approved in Canada and the United Kingdom for adjunctive treatment of multiple sclerosis and in Canada for adjunctive treatment of pain associated with advanced cancer.

Rimonabant (Acomplia®): A CB1 receptor inverse agonist which was initially approved for the treatment of obesity in the European Union. Marketing approval was withdrawn in 2009 due to concerns about adverse psychiatric side effects.