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Review

Pharmacology of cannabinoids in the treatment of epilepsy

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ABSTRACT

The use of *cannabis* products in the treatment of epilepsy has long been of interest to researchers and clinicians alike; however, until recently very little published data were available to support its use. This article summarizes the available scientific data of pharmacology from human and animal studies on the major cannabinoids which have been of interest in the treatment of epilepsy, including Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), Δ9-tetrahydrocannabivarin (Δ9-THCV), cannabidivarin (CBDV), and Δ9-tetrahydrocannabinolic acid (Δ9-THCA). It has long been known that Δ9-THC has partial agonist activity at the endocannabinoid receptors CB1 and CB2, though it also binds to other targets which may modulate neuronal excitability and neuroinflammation. The actions of Δ9-THCV and Δ9-THCA are less well understood. In contrast to Δ9-THC, CBD has low affinity for CB1 and CB2 receptors and other targets have been investigated to explain its anticonvulsant properties including TRPV1, voltage gated potassium and sodium channels, and GPR55, among others. We describe the absorption, distribution, metabolism, and excretion of each of the above mentioned compounds. Cannabinoids as a whole are very lipophilic, resulting in decreased bioavailability, which presents challenges in optimal drug delivery. Finally, we discuss the limited drug-drug interaction data available on THC and CBD. As cannabinoids and *cannabis*-based products are studied for efficacy as anticonvulsants, more investigation is needed regarding the specific targets of action, optimal drug delivery, and potential drug-drug interactions.

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1. Introduction

There has long been interest in the use of *cannabis* products in the treatment of various medical conditions, including epilepsy. After centuries of anecdotal reports of improvement with *cannabis* products but limited human data to support their use, there has been a vast expansion of research (including recent double-blinded, placebo controlled trials) investigating the pharmacologic potential of various cannabis products as anti-epileptic drugs (AEDs). The *cannabis* plant (*Cannabis sativa*) consists of around 100 compounds known as phytocannabinoids, and the vast majority of research on *cannabis* products in the treatment of epilepsy has been done on the main psychoactive component, Δ9-Tetrahydrocannabidiol (Δ9-THC). There has been more recent interest in investigating those compounds which do not have psychoactive properties as potential AEDs [1], namely cannabidiol (CBD), but also including Δ9-tetrahydrocannabivarin (Δ9-THCV), cannabidivarin (CBDV), and Δ9-tetrahydrocannabinolic acid (Δ9-THCA). These phytocannabinoids are structurally similar (see Fig. 1), but differ in regards to their pharmacology and actions by which they have anticonvulsant effect. Here, we summarize the literature to date on the mechanisms of action, metabolism, and interactions of the above listed major phytocannabinoids, in order to gain a better understanding of the proposed pharmacology of *cannabis* products which have potential for the treatment of epilepsy.

2. Mechanism of action

2.1. Δ9-THC

The pharmacology of Δ9-THC is perhaps the best understood of all the phytocannabinoids and has been studied extensively since its synthesis in 1964 [2]. The compound is responsible for the main psychotropic effects of *cannabis* and use of synthetic, high-affinity analogues led to the discovery of its CNS targets and identification of the

Abbreviations: (AED), Anti-epileptic drug; (THC), Δ9-Tetrahydrocannabidiol; (CBD), cannabidiol; (Δ9-THCV), Δ9-tetrahydrocannabivarin; (CBDV), cannabidivarin; (Δ9-THCA), Δ9-tetrahydrocannabinolic acid; (TRP), transient receptor potential; (VGCC), voltage gated calcium channel; (VGSC), voltage gated sodium channel; (VGKC), voltage gated potassium channel; (PPARγ), peroxisome proliferator-activated receptor gamma; (DLGα), diacylglycerol lipase alpha; (COX), cyclooxygenase.

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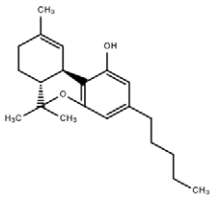
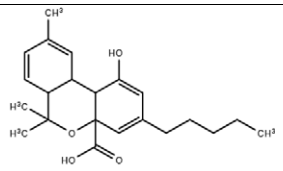
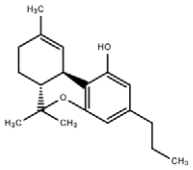
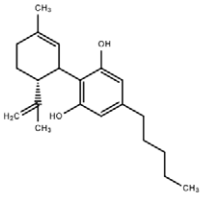
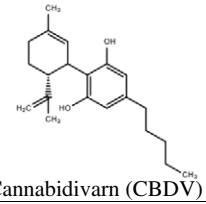
Chemical Structure	Potential Targets of Action in Epilepsy
 Δ9-tetrahydrocannabidiol (THC)	CB1 CB2 TRPA1 TPRV2 TRPM8 GPR55 5-HT_{3A} PPARγ μ- and δ-opioid receptors β-adrenoreceptors VGCC, VGKC, VGSC
 Δ9- tetrahydrocannabinolic acid (THCA)	TRPA1 TRPV4 TRPM8 DLGα COX 1, COX 2
 Δ9- Tetrahydrocannabivarin (THCV)	CB1 CB2 GPR55 TRPA1 TRPV1-4
 Cannabidiol (CBD)	TRPV1 VGCC, VGSC 5-HT_{1A}, 5-HT_{2A} GPR55 Adenosine receptors A_1 and A_2 VDAC1 TNFα
 Cannabidivarn (CBDV)	CB1 and CB2 – independent – more data needed

Fig. 1. Chemical structures of major phytocannabinoids and their possible targets by which they exert anticonvulsant effects.

endocannabinoid system [3,4]. The best studied targets of Δ9-THC are the endocannabinoid receptors, CB1R and CB2R, where it serves as a partial agonist at sub-micromolar concentrations [5]. Primarily found in the presynaptic terminals of CNS neurons, CB1 receptors are highly expressed in limbic structures (amygdala, hippocampus, cingulate), cerebral cortex, basal ganglia and select areas of the midbrain and medulla [6] and are a G-protein-coupled receptors which can modulate neurotransmitter release. Synaptic activity modulates the on-demand synthesis of anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), the endogenous ligands for the CB-receptors in the post-synaptic terminal and this signaling mechanism mediates several forms of short- and long-term synaptic plasticity [7]. The crystal structure of the CB1 receptor has recently been described, which may facilitate the design of the new CB1 receptor ligands for therapeutic use [8]. The major expression of CB2 receptors is in peripheral immune tissues such as the spleen, lymph nodes, and bone marrow as well as on B-cells, macrophages, and microglia where activation may lead to immunosuppressive responses [9]. There is also limited CB2-receptor expression in CNS neurons including in the brainstem [10] and hippocampus [11] where activation can affect neuronal excitability. In addition to its effects on the canonical endocannabinoid receptors, Δ9-THC binds to and modulates several other receptor targets in submicromolar or micromolar concentrations including the transient receptor potential (TRP) cation channels TRPA1, TRPV2, and TRPM8; the orphan G-coupled protein receptor GPR55; 5-HT_{3A} receptor; the peroxisome proliferator-activated receptor gamma (PPARγ); μ- and δ-opioid receptors, β-adrenoreceptors, some subtypes of *Ca*, K and Na channels [5]. The functional consequences of activation of these targets by Δ9-THC *in vivo* are not completely understood.

Even before the pharmacology of Δ9-THC was delineated, *in vivo* and *in vitro* studies demonstrated that the compound may have effects on experimental models of seizures. Many of the studies in acute seizure models demonstrated anticonvulsant effects of Δ9-THC or modulation of anticonvulsant effects of traditional anti-seizure drugs though others demonstrated no effects, mixed effects or proconvulsant effects [1]. There is CB1-receptor expression in human and experimental epilepsy