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Review

Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection

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ABSTRACT

The isolation and identification of the discrete plant cannabinoids in marijuana revived interest in analyzing historical therapeutic claims made for cannabis in clinical case studies and anecdotes. In particular, sources as old as the 11th and 15th centuries claimed efficacy for crude marijuana extracts in the treatment of convulsive disorders, prompting a particularly active area of preclinical research into the therapeutic potential of plant cannabinoids in epilepsy. Since that time, a large body of literature has accumulated describing the effects of several of the >100 individual plant cannabinoids in preclinical models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection.

We surveyed the literature for relevant reports of such plant cannabinoid effects and critically reviewed their findings. We found that acute CB_1R agonism in simple models of acute seizures in rodents typically produces anti-convulsant effects whereas CB_1R antagonists exert converse effects in the same models. However, when the effects of such ligands are examined in more complex models of epilepsy, epileptogenesis and neuroprotection, a less simplistic narrative emerges. Here, the complex interactions between (i) brain regions involved in a given model, (ii) relative contributions of endocannabinoid signaling to modulation of synaptic transmission in such areas, (iii) multi-target effects, (iv) cannabinoid type 1 and type 2 receptor signaling interactions and, (v) timing, (vi) duration and (vii) localization of ligand administration suggest that there is both anti-epileptic therapeutic potential and a pro-epileptic risk in up- and down-regulation of endocannabinoid signaling in the central nervous system. Factors such receptor desensitization and specific pharmacology of ligands used (e.g. full vs partial agonists and neutral antagonists vs inverse agonists) also appear to play an important role in the effects reported. Furthermore, the effects of several plant cannabinoids, most notably cannabidiol (CBD) and cannabidavarin (CBDV), in models of seizures, epilepsy, epileptogenesis, and neuroprotection are less ambiguous, and consistent with reports of therapeutically beneficial effects of these compounds in clinical studies. However, continued paucity of firm information regarding the therapeutic molecular mechanism of CBD/CBDV highlights the continued need for research in this area in order to identify as yet under-exploited targets for drug development and raise our understanding of treatment-resistant epilepsies.

The recent reporting of positive results for cannabidiol treatment in two Phase III clinical trials in treatment-resistant epilepsies provides pivotal evidence of clinical efficacy for one plant cannabinoid in epilepsy. Moreover, risks and/or benefits associated with the use of unlicensed Δ^9-THC containing marijuana extracts in pediatric epilepsies remain poorly understood. Therefore, in light of these paradigm-changing clinical events, the present review's findings aim to drive future drug development for newly-identified targets and indications, identify important limitations of animal models in the investigation of plant cannabinoid effects in the epilepsies, and focuses future research in this area on specific, unanswered questions regarding the complexities of endocannabinoid signaling in epilepsy.

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Abbreviations: ABHD6, α-β-hydrolase domain 6; ACEA, arachidonyl-2′-chloroethylamide; AEA, anandamide; CBD, cannabidiol; CBDV, cannabidivarin; CB_1R, cannabinoid type 1 receptor; CB_2R, cannabinoid type 2 receptor; DAGL, diacylglycerol lipase; Δ^9-THC, Δ^9-tetrahydrocannabinol; DSE, depolarization-induced suppression of excitation; DSI, depolarization-induced suppression of inhibition; FAAH, fatty acid amide hydrolase; GABA, γ-Aminobutyric acid; GPR, G protein-coupled receptor; KA, kainic acid; KO, knock-out; MAGL, monoacylglycerol lipase; MDA, maximal dentate activation; MES, maximal electroshock; NAPE-PLD, N-acylphosphatidylethanolamine-hydrolyzing phospholipase D; PMSF, phenylmethane sulfonyl fluoride; PTZ, pentylenetetrazole; TLE, temporal lobe epilepsy; TRPV1, transient receptor potential vanilloid receptor (type 1); VDAC, voltage-dependent anion channel.

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1. Introduction

In order to understand the justification for modern, preclinical investigations of the effects of cannabinoids in animal models of epilepsy and its associated symptoms and features, some appreciation of the historical, anecdotal use of marijuana (cannabis) in convulsive disorders is required. There is general consensus that the origins of marijuana use in the treatment of convulsions lie in reports from the Middle East that were ascribed to the scholar al-Mayusi [1] in 1100 and the historian Ibn al-Badri in 1464 [2]. It was not until 1649 that Nicholas Culpeper translated the *Pharmacopoeia Londonensis* from Latin into English, and suggested marijuana as a treatment of "inflammation of the head" [3]. Thereafter, there appears to be no further mention of this therapeutic use of marijuana until its introduction to Western medicine in the 19th century by William O'Shaughnessy. Here, alongside other reports from the same period describing the control seizures with marijuana extracts [4–6], O'Shaughnessy described successful treatment of infantile seizures with a cannabis tincture [7]. Similarly, J. R. Reynolds described marijuana as '*the most useful agent with which I am acquainted*' in the treatment of '*attacks or violent convulsions …* (and) *…may be stopped with a full dose of hemp*' [6] while William Gowers commented that '*Cannabis indica…is sometimes, although not very frequently, useful. It is of small value as an adjunct to the bromide, but is sometimes of considerable service given separately*' [8].

Despite these admittedly anecdotal reports of efficacy in convulsive episodes, only very limited investigation of the anti-convulsant effects of marijuana were undertaken in animal models prior to the 1980s [9,10]. Arguably, it was the isolation, identification, and subsequent synthesis of the two most abundant cannabinoids derived from marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), in the 1960s [11,12] which has driven modern studies of their pharmacological effects in a variety of models of central nervous system disease, including those of epilepsy, seizures, epileptogenesis, and epilepsy-related neuroprotection reviewed here. Recent reports of positive effects in properly controlled human clinical trials of CBD in the treatment resistant epilepsies have provided the first definite evidence of clinical efficacy for one plant cannabinoid in epilepsy. Given the pivotal nature of these clinical findings, critical review of the preclinical literature associated with this topic is warranted and addressed herein.

2. Methods

To identify effects of cannabinoids in pre-clinical animal models of seizures, epilepsy, epileptogenesis, and neuroprotection, we searched for peer-reviewed, primary literature using a PubMed search. Results were obtained using the keywords "CB1R," "CB2R," "cannabinoid", "cannabidiol", "THC"/"Tetrahydrocannabinol", "anandamide", "2-AG", "FAAH"/"Fatty acid amide hydrolase", and "MAG lipase" plus the terms "seizures," "epilepsy," "epileptogenesis," and "neuroprotection." We excluded primarily in vitro studies and clinical studies in humans (clinical trials, case reports, observational studies). Studies were evaluated based on their scientific rigor and use of physiologically relevant drug concentrations to in vivo studies [13]. Summary details of all studies examined in the present review are presented in Supplemental Table 1.

3. Results

3.1. Pre-clinical models of seizures and epileptogenesis

Early studies from the 1970s–1980s demonstrated that plant cannabinoids ('phytocannabinoids') derived from cannabis exerted anti-convulsant effects in both acute animal models of seizures [14–18] and chronic models of epileptogenesis [19–23]. These studies initiated clinical and scientific inquiry into mechanisms mediating potential anti-seizure effects of cannabinoids, albeit using unstandardized animal models and variable routes of cannabinoid administration and doses. The isolation of the target receptors of the major phytocannabinoid, Δ^9-THC, (CB_1R [24]and CB_2R [25]) and the discovery of an endogenous "endocannabinoid" signaling network [26–28] inspired the use of synthetically derived compounds to specifically target cannabinoid receptors and modulate endocannabinoid function. Thus, within the past few decades, there has been a renewed interest in investigating which particular components of marijuana, target receptors, and endocannabinoids mediate potential pro- and anti-convulsant effects of cannabinoids in pre-clinical models. Adding to the complexity, differences in CB_1R expression patterns in different areas of the brain, as well as differential expression on excitatory vs inhibitory synaptic terminals [29] may mediate the variable responses in different seizure model studies. Additionally, a diversity of animal models of both acute and chronic epilepsy, as well as time, route, and frequency of drug administration produce complex and often contradictory results.

To address these concerns, we reviewed the current literature describing the use of modulators of endocannabinoid function, synthetic agonists and antagonists of CB_1R/CB_2Rs, and phytocannabinoids in both acute models of seizure and epilepsy (Section 3.3), chronic models of epileptogenesis (Section 3.4), and epilepsy-related neuroprotection (Section 3.5). We considered studies involving "epileptogenesis" as those in which drugs are administered during the "latent" phase following a trigger that mediates long-term, spontaneous recurrent seizure. In some cases (e.g. genetic animal models of seizure), clear divisions between acute seizures and epileptogenesis are somewhat ambiguous. Each pre-clinical model was evaluated for completeness and scientific rigor, and the resulting responses (pro-convulsive, anti-convulsive, mixed effect, or no significant effect) were tabulated (Suppl. Tables 1, 2) and summarized (Fig. 1), within "acute seizure" and "epileptogenesis" conditions.

3.2. The endocannabinoid system

The endocannabinoid system plays an important physiological role in modifying excitatory and inhibitory synaptic transmission in the brain. The canonical endocannabinoid system consists of two G protein coupled receptors, CB_1R and CB_2R, with endogenous ligands 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamide (anandamide or AEA), each with unique degradation machinery [30,31]. Of the two cannabinoid receptor subtypes, CB_1R is most widely expressed in the central nervous system, particularly in the mossy cell-granule cell synapses of the hippocampus. However, of relevance to epileptogenesis, CB_1Rs are also present, to a lesser extent, on microglia, astrocytes and oligodendrocytes [31]. Once thought to be exclusively expressed outside the central nervous system, current research suggests that CB_2Rs are also expressed in the brain [32], mediating neuronal excitability [33] and inflammation in microglia [34]. Importantly, in addition to acting via the canonical cannabinoid receptors, the endocannabinoids can also act via interactions with other receptor types such as the orphan G-protein coupled receptor, GPR55, and the transient receptor potential vanilloid receptor (type 1), TRPV1 [35].

Of importance in activity-dependent pathophysiological processes such as epileptogenesis and epilepsy, the synthesis of endocannabinoids typically occurs "on demand" from postsynaptic membrane phospholipids although pre-synthesized endocannabinoid reserves are also contained within intracellular storage organelles [36,37]. However, most commonly, postsynaptic neuronal depolarization triggers membrane phospholipid breakdown by the enzymes diacylglycerol lipase (DAGL) and N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) to form 2-AG and AEA respectively [38,39]. Following their synthesis, the endocannabinoids passively diffuse across the presynapse in a retrograde fashion to orthosterically bind to and activate presynaptically located CB_1R to inhibit the release of glutamate or GABA from principal or GABAergic neurons respectively [35,40]. The endocannabinoid-mediated inhibitions of excitatory