European Journal of Internal Medicine 49 (2018) 30–36

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Narrative Review

Cannabinoids and cancer pain: A new hope or a false dawn?

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ARTICLE INFO

Keywords:
Endocannabinoids
CB1 receptor
CB2 receptor
Fatty acid amide hydrolase
Analgesia
Malignancy

ABSTRACT

The endocannabinoid system is involved in many areas of physiological function and homeostasis. Cannabinoid receptors are expressed in the peripheral and central nervous system and on immune cells, all areas ideally suited to modulation of pain processing. There are a wealth of preclinical data in a number of acute, chronic, neuropathic and cancer pain models that have demonstrated a potent analgesic potential for cannabinoids, especially in patients with cancer. However, although there are some positive results in pain of cancer patients, the clinical evidence for cannabinoids as analgesics has not been convincing and their use can only be weakly recommended. The efficacy of cannabinoids seems to have been 'lost in translation' which may in part be related to using extracts of herbal cannabis rather than targeted selective full agonists at the cannabinoid CB1 and CB2 receptors.

1. Introduction

The subtle and continuous interplay between the numerous physiological processes required to maintain homeostasis is controlled by a number of regulatory systems, perhaps none more ubiquitous than the endocannabinoid system. This complex biological overseer presents both huge potential for pharmacological manipulation but also huge challenges due to the sheer diversity of its physiological influences. Humans have ingested phytochemical substances which interact with the endocannabinoid system for millennia in the attempt to treat myriad symptoms, but it is only recently that the complex pharmacology of the system and the means to produce synthetic ligands has been realised. To date a significant proportion of research work has focused on the therapeutic potential of harnessing the endocannabinoid system to manage pain, a field of medicine embodied by unmet clinical need and clear requirements for novel therapeutic options. This narrative review provides a germane and current summary of the phytochemistry, pharmacology and physiology of the cannabinoids and the endocannabinoid system and delineates the latest evidence for the use of cannabinoids to attempt to manage pain states especially in cancer patients, a cohort in which pain represents a significant challenge [1]. The pharmacological potential of the endocannabinoid system on potential future directions of preclinical research and the use of novel moieties in the clinical environment is also considered. The methodology of this narrative review comprised a PubMed literature search and Google Scholar search for all types of articles using the search terms 'cannabinoids & pain', 'cannabinoids & cancer pain', 'cannabinoids & neuropathic pain', 'CB1 & pain', 'cannabinoids & phytochemistry', 'cannabinoid receptors', 'cannabinoids & sensory nerves', 'CB1 receptors', 'CB2 receptors', 'cannabinoid pharmacology', 'endocannabinoid system', 'cannabinoids & cancer', 'cannabinoids & tumorigenesis', 'cannabinoids & metastases', 'cannabinoids & GVHD', published between January 1980 and November 2017. Additional articles were identified by manually searching the references of previously identified publications. Articles not written in English were disregarded.

2. Historical perspectives

Cannabis sativa, Cannabis indica and *Cannabis ruderalis* (Family: Cannabaceae) have been cultivated widely since antiquity for use in the production of fibres for rope and fabric, as a food source for both animals and humans and for medicinal applications [2]. Descriptions of its use to treat a broad range of medical conditions reach back millennia, with evidence of the therapeutic consumption of cannabis in ancient Egypt, in Indian *aruvyedic* medicine and in classical Greece and Rome [3]. Over successive centuries, the beneficial effects of the plant and its extracts continue to be mentioned in medical texts including Culpeper's Complete Herbal of 1653 in which it is stated that "The decoction of the root eases the pains of the gout, the hard humours of knots in the joints, the pains and shrinking of the sinews, and the pains of the hips" [4]. By the latter half of the nineteenth century the popularity of medicinal cannabis had reached its peak, with its use advocated by leading medical authorities in patients suffering from a range of conditions including epilepsy, rheumatological complaints, hysteria and 'neuralgia' [5]. The popularity of medicinal cannabis waned in the early 20th

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https://doi.org/10.1016/j.ejim.2018.01.020
Received 20 December 2017; Received in revised form 11 January 2018; Accepted 14 January 2018

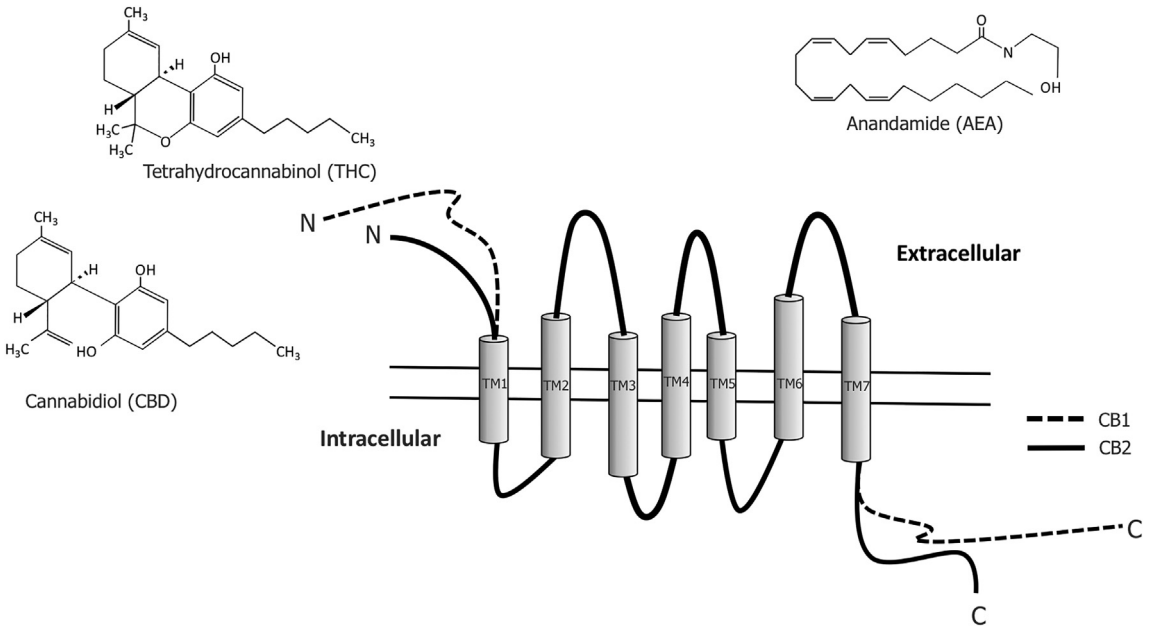

Fig. 1. Schematic showing the CB1 and CB2 cannabinoid receptors and the chemical form of 3 predominant cannabinoids. Cannabinoid receptors are metabotropic G protein-linked structures and comprise 7 transmembrane domains with an extracellular N-terminal and an intracellular C-terminal. Binding of a ligand results in G protein activation, which leads to the inhibition of adenylate cyclase and voltage-gated calcium channels, the activation of mitogen-activated protein kinase and of inwardly rectifying potassium channels.

century (Cannabis was removed from the British Pharmacopeia in 1932 and the American Pharmacopeia in 1941) as a result of a better understanding of the pathophysiology of disease and an expansion in the number of effective therapeutic options available [6].

These advances coincided with a greater governmental awareness of the illicit use of cannabis and the subsequent introduction of laws which criminalised its cultivation, refinement and consumption. This process was exemplified by the adoption of emotive language such as "Marijuana is the most violence-causing drug in the history of mankind" voiced during testimony to the United States Congress, and the subsequent levy in 1937 of a $100 per ounce tax that effectively outlawed cannabis in the United States [7]. In 1970 cannabis was classified as a class I drug, legislation indicating a high potential for abuse but also stating that it had no accepted medical use.

The story of medicinal cannabis may easily have finished at this point, however in recent times the combination of an improved understanding of the neurobiology of pain and a requirement for the development of novel analgesic agents has triggered a burgeoning interest in the use of cannabis for therapeutic purposes. This has led to a situation where in some legislative domains, illicitly consumed cannabis remains illegal, whilst purified extracts (or industrially synthesised analogues) are permitted when used medicinally.

3. Phytochemistry of *Cannabis sativa*

The phytochemical profile of the various strains of *cannabis* is complex; with many hundreds of substances produced, some of which, namely the terpenophenolic cannabinoid compounds, are unique to *Cannabis sativa* [8]. Of the > 70 cannabinoids produced within the plant, the most bountiful are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [9]. These substances differ in their pharmacological effects, with THC acting as a potent psychoactive agent and CBD possessing anxiolytic and analgesic properties [10]. There is great variability in the levels of differing cannabinoids between distinct subspecies and cultivars (termed chemotypes) of *Cannabis sativa*. Drug forms of cannabis (marijuana and hashish) have high levels of THC, a situation established through a process of selective breeding and refined cultivation techniques, whilst cannabis grown for industrial and agricultural purposes (hemp) has a low THC content [11].

4. Pharmacology of cannabinoid receptors

The pharmacological effects of ingested cannabinoid compounds are predominantly mediated via interaction with the endocannabinoid system. The endocannabinoid system is a physiologically omnipresent regulatory system which comprises endogenous cannabinoids (endocannabinoids), cannabinoid receptors and the enzymes involved in synthesising and metabolising endocannabinoids [12]. The system plays an important role in neuro- and immunomodulatory effects which impact upon the homeostasis of processes relating to appetite [13], motor function [14], fertility [15] and pain sensation [16].

The majority of cannabinoid and endocannabinoid effects are mediated by two G protein-coupled cannabinoid receptors, termed the CB1 and CB2 receptors. These receptors are found widely throughout the body but with some differences in their distribution; CB1 receptors are found abundantly in the central and peripheral nervous system, whilst CB2 receptors are predominantly expressed on immune cells where they modulate cytokine release [17]. The ubiquity of expression of cannabinoid receptors in multiple areas of the central and peripheral nervous system explains the apparent potential utility for exogenous cannabinoids in a number of different human physiology and pathologies including, but not limited to, the modulation of memory, appetite, development of multiple sclerosis and different types of shock [18].

Cannabinoid receptors are metabotropic in nature, linked to their downstream effectors by G-protein mediated signal transduction. Structurally both CB1 and CB2 comprise seven transmembrane protein domains [19] (Fig. 1), which predominantly couple to the inhibitory G proteins Gi and Go [20]. The intracellular consequences of G protein activation include the inhibition of adenylate cyclase and certain voltage-gated calcium channels, the activation of mitogen-activated protein kinase (MAP kinase) and of inwardly rectifying potassium channels [21]. In the central and peripheral nervous system, the net effect of these processes is to dampen neuronal excitability and to negatively modulate neurotransmission. Interestingly there is also evidence that CB1 receptors may induce morphological changes in neurones including inhibition of synapse formation and retraction of neurites [22]. In immune cells, CB2 receptor activation results in a slew of suppressive effects including impaired antigen presentation, reduced cytokine release and disruption of immunocyte migration [23].