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Review article

The endocannabinoid system as a target for novel anxiolytic drugs

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ABSTRACT

The endocannabinoid (eCB) system has attracted attention for its role in various behavioral and brain functions, and as a therapeutic target in neuropsychiatric disease states, including anxiety disorders and other conditions resulting from dysfunctional responses to stress. In this mini-review, we highlight components of the eCB system that offer potential 'druggable' targets for new anxiolytic medications, emphasizing some of the less well-discussed options. We discuss how selectively amplifying eCBs recruitment by interfering with eCB-degradation, via fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), has been linked to reductions in anxiety-like behaviors in rodents and variation in human anxiety symptoms. We also discuss a non-canonical route to regulate eCB degradation that involves interfering with cyclooxygenase-2 (COX-2). Next, we discuss approaches to targeting eCB receptor-signaling in ways that do not involve the cannabinoid receptor subtype 1 (CB1R); by targeting the CB2R subtype and the transient receptor potential vanilloid type 1 (TRPV1). Finally, we review evidence that cannabidiol (CBD), while representing a less specific pharmacological approach, may be another way to modulate eCBs and interacting neurotransmitter systems to alleviate anxiety. Taken together, these various approaches provide a range of plausible paths to developing novel compounds that could prove useful for treating trauma-related and anxiety disorders.

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1. Introduction

The eCB system and drugs that act on it continues to attract enormous attention from the scientific community and general public for its contribution to behavioral and brain functions, and for its potential as a therapeutic target across an array of peripheral and neuropsychiatric disease states. This trend is evident against a background of an ever developing understanding of the biology of cannabinoidergic actions, as well as public policy shifts towards greater acceptance of eCB-acting drugs for both recreational and medicinal purposes. In fact, interest in the therapeutic properties of the *Cannabis sativa* plant for all manner of ailments has a history that dates back millennia. In more recent times, the era of studying the plant for its medicinal properties can be traced to the identification of Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as the plant's main active constituents and to the discovery of cannabinoid receptors and the endogenous substances (eCBs) acting on them, throughout the brain and body (Mechoulam and Parker, 2013).

The intervening half-century has seen important advances in medicinal exploitation of the eCB system, such that there are now a number of cannabinoid-acting compounds which are clinically approved to treat low appetite, nausea, vomiting, pain, and spasticity in cancer, AIDS and multiple-sclerosis, among other indications, with active research into developing drugs for a variety of other conditions. One area of particular interest to preclinical and clinical research on the eCB system is that relating to fear, anxiety and stress, and their associated psychiatric conditions, including the Anxiety Disorders and Posttraumatic Stress Disorder (PTSD, now diagnostically categorized as Trauma and Stress-related Conditions (DSM-5, 2013). These disorders represent by far the most common mental health problems, are often intertwined with other problems, such as alcohol and substance abuse. Unfortunately, they remain inadequately served by existing therapeutic, particularly pharmaceutical, options (Griebel and Holmes, 2013).

Several clinical observations have pointed to a link between stress-related disorders and cannabis use. For example, PTSD patients are more likely to exhibit cannabis dependence (Bonn-Miller et al., 2007; Kessler et al., 1995; Stewart et al., 1998), suggesting a degree of co-morbidity between PTSD and cannabis use. Epidemiology data such as these cannot clarify whether this link reflects shared etiological factors or cannabis use as a form of self-medication, though it is worth noting that symptom severity correlates with the reported motivation to use cannabis in order to cope with emotional distress (Bonn-Miller et al., 2007). There is also preliminary data indicating that cannabis and related compounds can manage PTSD symptoms related to hyperarousal, anxiety responses to exteroceptive triggers and situational trauma-reminders (Bremner et al., 1996; Jetly et al., 2015). While these clinical observations need to be substantiated in larger, replicate populations, they do hint at stress and anxiety-alleviating effects of cannabis. In fact, cannabis has long been anecdotally noted for its ability to reduce anxiety and elevate mood in non-clinical populations and, in part because of this, eCBs have attracted considerable interest in recent years as a target for a new class of drugs to treat anxiety and stress-related conditions (Fig. 1).

Comprehensive overviews of the large literature that has now built up around the potential clinical utility of eCB-targeting drugs can be found in previously published reviews from our groups and others (Gunduz-Cinar et al., 2013a; Lee et al., 2016; Micale et al., 2013; Morena et al., 2016b; Zlebnik and Cheer, 2016). Our aim in this mini-review is to highlight various components of the eCB system that offer 'druggable' targets for new anxiolytic and antidepressant medications, and to emphasize some of the less well-discussed options that nonetheless represent exciting possibilities for drug development (Fig. 2). We begin with the intriguing

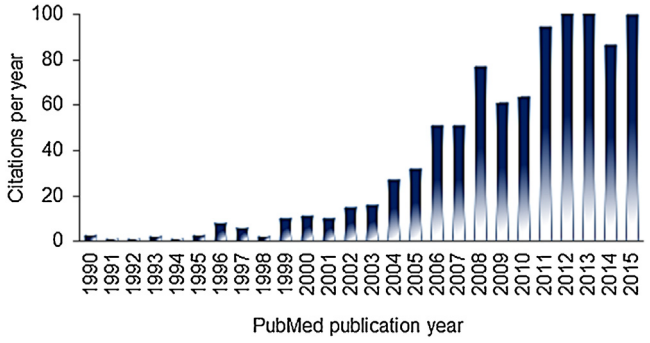

Fig. 1. The burgeoning literature linking the eCB system and anxiety. PubMed citation results for 'cannabinoid and anxiety' from 1990 to 2015.

concept of selectively amplifying recruitment of eCBs by interfering with the molecular machinery responsible for eCB-degradation. We discuss this approach with reference to the two canonical eCB hydrolyzing enzymes, fatty acid amide hydrolyze (FAAH) and monoacylglycerol lipase (MAGL), but also in terms of the less well-known mechanism mediated by cyclooxygenase-2 (COX-2). We then turn to eCB receptor-signaling with a view to drawing focus away from the vast literature on the cannabinoid receptor subtype 1 (CB1R) to other important receptors, most notably the transient receptor potential vanilloid receptor type 1 (TRPV1). Finally, we consider the nascent but interesting potential for modulating eCBs and interacting neurotransmitter systems via a major constituent of cannabis, cannabidiol (CBD).

2. FAAH and MAGL: the Yin and the Yang of eCB hydrolysis

While the biosynthesis of AEA has remained enigmatic for some time, the canonical pathways of AEA metabolism have been well described for over a decade. First characterized by Cravatt and colleagues as an enzyme which metabolizes oleamide (Cravatt et al., 1996), FAAH is a membrane-bound serine hydrolase which hydrolyzes a large class of fatty acid amides, including AEA. FAAH is primarily tethered to the membrane of the endoplasmic reticulum and is widely distributed throughout the brain, with prominent expression in the post-synaptic compartment of large pyramidal-like neurons (Gulyas et al., 2004; Thomas et al., 1997; Tsou et al., 1998). As genetic or pharmacological inactivation of FAAH results in a dramatic elevation in tissue levels of AEA, but not 2-AG, FAAH is considered as the primary metabolic enzyme of AEA.

It has been well established that inhibition of FAAH, and elevation of AEA signaling, can significantly attenuate behavioral indices of fear and anxiety-related behavior in rodents. Following the characterization of the first relatively selective FAAH inhibitor, URB597, Piomelli's group established over a decade ago that inhibition of AEA hydrolysis produces anxiolytic-like effects in rats (Kathuria et al., 2003). Follow-up studies over the following several years demonstrated that there was an intriguing degree of specificity to these effects, such that gene deletion or selective pharmacological inhibition of FAAH, produced anxiolytic-like effects more reliably under conditions of high environmental aversiveness (Bluett et al., 2014; Carnevali et al., 2015; Duan et al., 2017; Gray et al., 2015; Haller et al., 2014; Haller et al., 2009; Hill et al., 2013b; Lomazzo et al., 2015; Naidu et al., 2007; Patel and Hillard, 2006; Rossi et al., 2010).

While a mechanistic explanation of why FAAH inhibition only exerts anxiolytic effects under highly aversive conditions remains elusive, the current working model posits that rather than directly producing frank anxiolytic-like effects, AEA signaling acts to restore homeostasis in anxiety-mediating circuits following stress-challenge. Specifically, under conditions of stress, FAAH activity has