Pharmacology, Biochemistry and Behavior 190 (2020) 172840

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

In vivo evaluation of the CB_1 allosteric modulator LDK1258 reveals CB_1-receptor independent behavioral effects

Mohammed Mustafa[a], Giulia Donvito[a], Lauren Moncayo[a], Amelia Swafford[a], Justin Poklis[a], Ralph Grauer[a], Teresa Olszewska[c], Bogna Ignatowska-Jankowska[c], Debra A. Kendall[b], Dai Lu[c], Aron H. Lichtman[a,d,*]

[a] Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA
[b] Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, USA
[c] Rangel College of Pharmacy, Health Science Center, Texas A&M University, Kingsville, TX, USA
[d] Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA, USA

ARTICLE INFO

Keywords:
CB_1 receptor
Cannabinoid
Allosteric modulator
Anandamide
CP55;940
Rimonabant
Neuropathic pain
Drug discrimination

ABSTRACT

In the present study, we examined whether LDK1258, which produces strong CB_1 receptor allosteric effects in *in vitro* assays, would elicit *in vivo* effects consistent with allosteric activity. In initial studies, LDK1258 reduced food consumption and elicited delayed antinociceptive effects in the chronic constrictive injury of the sciatic nerve (CCI) model of neuropathic pain, which unexpectedly emerged 4 h post-injection. UPLC-MS/MS analysis quantified significant levels of LDK1258 in both blood and brain tissue at 30 min post-administration that remained stable up to 4 h. The observation that LDK1258 also produced respective antinociceptive and anorectic effects in rimonabant-treated wild type mice and CB_1 (−/−) mice suggests an off-target mechanism of action. Likewise, LDK1258 produced a partial array of common cannabimimetic effects in the tetrad assay, which were not CB_1 receptor mediated. Additionally, LDK1258 did not substitute for the CB_1 receptor orthosteric agonists CP55,940 or anandamide in the drug discrimination paradigm. In other *in vivo* assays sensitive to CB_1 receptor allosteric modulators, LDK1258 failed to shift the dose-response curves of either CP55,940 or anandamide in producing thermal antinociception, catalepsy, or hypothermia, and did not alter the generalization curve of either drug in the drug discrimination assay. Thus, this battery of tests yielded results demonstrating that LDK1258 produces antinociceptive effects in the CCI model of neuropathic pain, anorectic effects, and other *in vivo* pharmacological effects in a manner inconsistent with CB_1 receptor allosterism. More generally, this study offers a straightforward screening assay to determine whether newly synthesized CB_1 receptor allosteric modulators translate to the whole animal.

1. Introduction

Δ^9-tetrahydrocannabinol (THC) and other psychoactive cannabimimetic agents bind and activate CB_1 and CB_2 receptors (Devane et al., 1988; Matsuda et al., 1990; Munro et al., 1993), which lead to myriad pharmacological effects. In addition, the endogenous cannabinoids *N*-arachidonylethanolamine (anandamide; Devane et al., 1992) and 2-arachidonoylglycerol (2-AG; Mechoulam et al., 1995; Sugiura et al., 1995) bind these receptors, though their rapid metabolic hydrolysis result in a short-lived duration of action (Cravatt et al., 2001; Dinh et al., 2002). These receptors and endogenous ligands comprise the endogenous cannabinoid system, which modulates many physiological processes including feeding behavior and energy storage (Wiley et al., 2005), memory impairment (Lichtman et al., 1995), reward (Chen et al., 1991; Gardner et al., 1988; Lepore et al., 1996), stress responses (Patel et al., 2017), and pain and inflammation (Guindon and Hohmann, 2009). CB_1 receptor agonists reduce cancer chemotherapy elicited nausea and vomiting (Sallan et al., 1975; Poster et al., 1981) as well as stimulate appetite in patients afflicted with AIDS-related cachexia (Gorter et al., 1992). Although these drugs also possess promise to treat many other conditions, they also elicit psychomimetic intoxicating effects, impair cognitive function, and are associated with a variety of psychiatric illnesses (*i.e.* schizophrenia, acute anxiety, and cannabis use disorder) (Ramaekers et al., 2009; Renard et al., 2018;

* Corresponding author at: P.O. Box 980613, Dept. of Pharmacology & Toxicology, Dept. of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23298-0613, USA.
E-mail address: aron.lichtman@vcuhealth.org (A.H. Lichtman).

https://doi.org/10.1016/j.pbb.2019.172840
Received 4 June 2019; Received in revised form 24 November 2019; Accepted 21 December 2019
Available online 30 December 2019