Bioorganic & Medicinal Chemistry 22 (2014) 2830–2843

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Review

The cannabinoid acids, analogs and endogenous counterparts

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ARTICLE INFO

Article history:
Received 7 February 2014
Revised 15 March 2014
Accepted 24 March 2014
Available online 1 April 2014

Keywords:
Cannabinoid
Δ^9-THC-11-oic acid
Ajulemic acid
NAgly
Lipoamino acid
Prostaglandin
Lipoxin

ABSTRACT

The cannabinoid acids are a structurally heterogeneous group of compounds some of which are endogenous molecules and others that are metabolites of phytocannabinoids. The prototypic endogenous substance is N-arachidonoyl glycine (NAgly) that is closely related in structure to the cannabinoid agonist anandamide. The most studied phytocannabinoid is Δ^9-THC-11-oic acid, the principal metabolite of Δ^9-THC. Both types of acids have in common several biological actions such as low affinity for CB1 anti-inflammatory activity and analgesic properties. This suggests that there may be similarities in their mechanism of action, a point that is discussed in this review. Also presented are reports on analogs of the acids that provide opportunities for the development of novel therapeutic agents, such as ajulemic acid.

Contents

Abbreviations: NAgly, N-arachidonoyl glycine; AJA, ajulemic acid; THC, tetrahydrocannabinol; CBD, cannabidiol; CBN, cannabinol.

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http://dx.doi.org/10.1016/j.bmc.2014.03.038
0968-0896/

1. Introduction

Since an earlier review on this topic published in 1999,[1] there have been a considerable number of new research findings. This paper represents an update of the field and also gives a more detailed and comprehensive treatment of this subject. The present review includes not only phytocannabinoid-derived acids, but also their synthetic analogs and lipoamino acid counterparts, sometimes called elmiric acids. In contrast to earlier beliefs, the cannabinoid acids have a number of biological activities that are of potential therapeutic interest and will be discussed here.

2. Cannabinoid acids as plant constituents

The penultimate intermediates in the biosynthesis of Δ^9-THC are two molecules, tetrahydrocannabinolic acid A and tetrahydrocannabinolic acid B, containing a carboxyl group at either the 2 or 4 positions on the aromatic ring (Fig. 1).[2–4] These compounds are readily decarboxylated when heated to give Δ^9-THC especially when the plant material is consumed by smoking. It is possible that some of the oral preparations of Cannabis such as Bhang and Majun may contain these acids. Little is known about their pharmacology, however, several reports suggest that these compounds may have biological activities.[5–8] Similar acids of the other phytocannabinoid acids such as Cannabidiolic acid, Cannabigerolic acid, Cannabidivarinic acid, Cannabichromenic acid, (5a*S*,6*S*,9*R*,9a*R*)-Cannabielsoic acid A, (5a*S*,6*S*,9*R*,9a*R*)-Cannabielsoic acid B, (1a*S*,3a*R*,8b*R*,8c*R*)-Cannabicyclolic acid, and Cannabinolic acid have all been isolated from plant extracts.[3]

3. Acid metabolites of the phytocannabinoids

The earliest report suggesting the existence of acid metabolites of Δ^9-THC was made by a Swedish group.[9] They observed that observed that a large proportion of the urinary metabolites in the rabbit were acidic in nature. However, no structural assignments were made. Subsequently, in a scaled up repetition of this study, large enough samples of two metabolites were isolated to allow identifications by proton NMR and low-resolution mass spectrometry.[10] The structures were shown to be the 1′ hydroxy and 2′ hydroxy derivatives of Δ^9-THC-11-oic acid (Fig. 2D). The occurrence of Δ^9-THC-11-oic acid itself as a urinary metabolite was reported in a subsequent study that also described its synthesis and lack of psychotropic activity.[11] Apparently, the possibility of other activities was not investigated by them or any other researchers until some years later (see Section 3.3). Figure 3 shows examples of metabolites of Δ^9-THC.

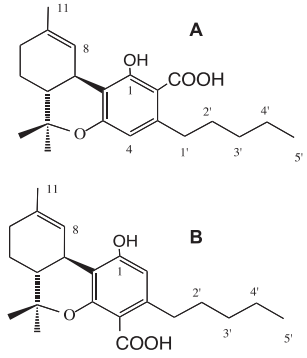

Figure 1. Cannabinoid acids as plant constituents. (A) Tetrahydrocannabinolic acid A. (B) Tetrahydrocannabinolic acid B.

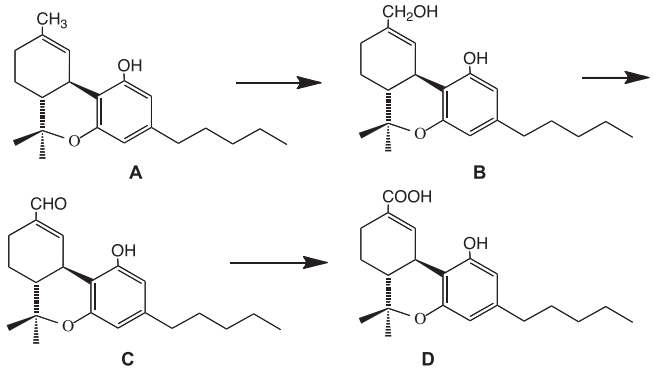

Figure 2. Principal route of metabolism for Δ^9-THC in most species. Compounds **A** (Δ^9-THC), **B** and **C** all showed similar biological activities. While devoid of psychotropic activity in mice and humans, compound **D**, the terminal carboxy metabolite showed NSAID-like action in several animal models, albeit at low potency. This prompted the synthesis of a more potent analog, ajulemic acid (vide infra).

3.1. Acid metabolites from in vivo metabolism

The most widely studied cannabinoid acid is Δ^9-THC-11-oic acid (Fig. 2D). It is the terminal metabolite of Δ^9-THC (Fig. 2A) that is generated in a three-stage process going through the hydroxyl (Fig. 2B) and aldehyde (Fig. 2C) intermediates. This route occurs in humans and in every other species thus far examined.[11,12] In contrast to its precursors, it is devoid of psychotropic activity, however, it does have biological actions described in Section 3.3 that may contribute to the pharmacological profile of Δ^9-THC. There