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Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

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Abstract

Δ(9)-Tetrahydrocannabinol (THC) and cannabidiol (CBD) occur naturally in marijuana (Cannabis) and may be formulated, individually or in combination in pharmaceuticals such as Marinol or Sativex. Although it is known that these hydrophobic compounds can be transported in blood by albumin or lipoproteins, the intracellular carrier has not been identified. Recent reports suggest that CBD and THC elevate the levels of the endocannabinoid anandamide (AEA) when administered to humans, suggesting that phytocannabinoids target cellular proteins involved in endocannabinoid clearance. Fatty acid-binding proteins (FABPs) are intracellular proteins that mediate AEA transport to its catabolic enzyme fatty acid amide hydrolase (FAAH). By computational analysis and ligand displacement assays, we show that at least three human FABPs bind THC and CBD and demonstrate that THC and CBD inhibit the cellular uptake and catabolism of AEA by targeting FABPs. Furthermore, we show that in contrast to rodent FAAH, CBD does not inhibit the enzymatic actions of human FAAH, and thus FAAH inhibition cannot account for the observed increase in circulating AEA in humans following CBD consumption. Using computational molecular docking and site-directed mutagenesis we identify key residues within the active site of FAAH that confer the species-specific sensitivity to inhibition by CBD. Competition for FABPs may in part or wholly explain the increased circulating levels of endocannabinoids reported after consumption of cannabinoids. These data shed light on the mechanism of action of CBD in modulating the endocannabinoid tone in vivo and may explain, in part, its reported efficacy toward epilepsy and other neurological disorders.

KEYWORDS: Anandamide (N-Arachidonoylethanolamine) (AEA); Cannabidiol (CBD); Cannabinoid; Cannabinoid Transporters; Endocannabinoid; Fatty Acid Amide Hydrolase (FAAH); Fatty Acid Binding Protein; Lipid Trafficking; Lipid Transport; Δ-tetrahydrocannabinol (THC)