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A Personal Retrospective: Elevating Anandamide (AEA) by Targeting Fatty Acid Amide Hydrolase (FAAH) and the Fatty Acid Binding Proteins (FABPs).

Deutsch DG[1].

Author information

1 Department of Biochemistry and Cell Biology, Stony Brook University Stony Brook, NY, USA.

Abstract

This perspective was adapted from a Career Achievement Award talk given at the International Cannabinoid Research Society Symposium in Bukovina, Poland on June 27, 2016. As a biochemist working in the neurosciences, I was always fascinated with neurotransmitter inactivation. In 1993 we identified an enzyme activity that breaks down anandamide. We called the enzyme anandamide amidase, now called FAAH. We and other laboratories developed FAAH inhibitors that were useful reagents that also proved to have beneficial physiological effects and until recently, new generations of inhibitors were in clinical trials. Nearly all neurotransmitters are water soluble and as such, require a transmembrane protein transporter to pass through the lipid membrane for inactivation inside the cell. However, using model systems, we and others have shown that this is unnecessary for anandamide, an uncharged hydrophobic molecule that readily diffuses across the cellular membrane. Interestingly, its uptake is driven by the concentration gradient resulting from its breakdown mainly by FAAH localized in the endoplasmic reticulum. We identified the FABPs as intracellular carriers that "solubilize" anandamide, transporting anandamide to FAAH. Compounds that bind to FABPs block AEA breakdown, raising its level. The cannabinoids (THC and CBD) also were discovered to bind FABPs and this may be one of the mechanisms by which CBD works in childhood epilepsy, raising anandamide levels. Targeting FABPs may be advantageous since they have some tissue specificity and do not require reactive serine hydrolase inhibitors, as does FAAH, with potential for off-target reactions. At the International Cannabis Research Society Symposium in 1992, Raphe Mechoulam revealed that his laboratory isolated an endogenous lipid molecule that binds to the CB1 receptor (cannabinoid receptor type 1) and this became the milestone paper published in December of that year describing anandamide (AEA, Devane et al., 1992). As to be expected, this discovery raised the issues of AEA's synthesis and breakdown.

KEYWORDS: AEA; FAAH inhibitors; FABP inhibitors; anandamide; anandamide synthesis; anandamide transporter; fatty acid amide hydrolase (FAAH); fatty acid binding protein (FABP)

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