Role of ABHD6 in 2-AG Signaling

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Country

USA

Title of project or programme

Role of ABHD6 in 2-AG Signaling

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,572,063.30

Start date of award

01/04/2009

Total duration of award in years

3

The project/programme is most relevant to:

Huntington's disease

Keywords

ABHD6 gene, 2-arachidonylglycerol, Huntington Disease, endocannabinoid signaling, Seizures

Research Abstract
DESCRIPTION (provided by applicant): Compounds that target endocannabinoid (eCB) signaling in the brain represent powerful pharmacological tools to probe the basic biological function of this signaling system in healthy and diseased brain and may represent novel therapeutic venues to treat neurological diseases such as Huntington’s disease (HD). During the funding cycle of this RO1, our laboratory studied the function of ABHD6 in neurons and glia,

as well as the therapeutic potential of ABHD6 inhibitors in R6/2 mice, an early-onset mouse model of HD. We leveraged functional proteomics and shRNA technology and identified ABHD6 as a candidate enzyme for 2-AG hydrolysis in brain. We then developed new ABHD6 inhibitors and showed that ABHD6 activity tightly controls the levels and efficacy of 2-AG at cannabinoid receptors. Together, these studies demonstrated that ABHD6 belongs to the eCB signaling system. Recently we found that in vivo ABHD6 inhibition greatly reduces seizure incidence and attenuates hippocampal neuropathology in R6/2 mice. In this grant, we will test the following hypothesis: The novel enzyme, ABHD6, controls both the level and efficacy of 2-arachidonoylglycerol (2-AG) at cannabinoid CB1 receptors. ABHD6 inhibitors reduce seizure activity in two HD mouse models (R6/2 and HDQ200) and may represent a novel class of therapeutics to treat seizures in general. To test this hypothesis, we propose 3 Aims: AIM 1: Development, validation, and mechanism of action of 3rd generation ABHD6 inhibitors that exhibit superior in vivo selectivity and efficacy. AIM 2: Determine to what extent ABHD6 in vivo inhibition and genetic deletion reduces seizure incidence in HD and chemically-induced seizures mouse models. AIM 3: Why do HD mice seize, and how does ABHD6 prevent this process? Thus we will characterize newly optimized inhibitors of ABHD6, an eCB-hydrolyzing enzyme that we identified during the previous funding period. Coupled to genetic approaches, we will use ABHD6 inhibitors to determine the molecular and cellular details of how this enzyme controls seizure incidence in HD mice models. Completion of the studies outlined above will provide a comprehensive understanding of the role of ABHD6 in healthy and HD mouse brain within the context of epileptic activity. Our long-term goal is to increase our understanding of th role played by ABHD6 in healthy and diseased brain, and help develop novel therapeutics that lack the potential for abuse and adverse effects produced by classic cannabinoid agonists.

Lay Summary
PUBLIC HEALTH RELEVANCE: Compounds that target the endocannabinoid (eCB) signaling in brain represent powerful tools to discover the basic biological function of this signaling syste and represent promising therapeutics to treat neurological diseases such as Huntington’s disease (HD). Here we will use newly optimized inhibitors of the eCB hydrolyzing enzyme, ABHD6, in combination with genetics to determine how this enzyme controls seizure incidence in HD and chemically-induced seizures mouse models. This research will provide a comprehensive understanding of the expression, activity and role of ABHD6 in healthy and HD brain within the context of epileptic activity, with the potential of developing novel therapeutics that will benefit patients with HD while avoiding the abuse liability and adverse effects produced by cannabinoid agonists.

Further information available at:

Types:
Investments > €500k

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United States of America

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Huntington's disease

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2016

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