Neurochemical Actions of Psychotropic Drugs

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Country

USA

Title of project or programme

Neurochemical Actions of Psychotropic Drugs

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 3,959,481.65

Start date of award

01/09/1985

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

serine racemase, Cysteine Desulfhydrase, Psychotropic Drugs, stargazin, Cysteine

Research Abstract
DESCRIPTION (provided by applicant): Our research, supported by this grant over the years, has focused on identifying and characterizing novel neural messenger molecules and their roles in psychotropic drug actions. We propose new studies based on recent advances in this area involving, in particular, gasotransmitters and D-amino acids. Based on our earlier work on NO and CO, we have recently identified hydrogen sulfide (H2S) as a notable signaling molecule.

We established its biosynthesis by cystathionine-gamma-lyase (CSE) and cystathionine- beta-synthase (CBS) by demonstrating its depletion with CSE and CBS knockout. We showed that H2S signals by sulfhydrating cysteines in target proteins, analogous to NO acting by nitrosylation. We will map CBS/CSE and their catalytic activity via a novel histochemical stain for H2S generation from cysteine. We will characterize new sulfhydrated targets. Based on our findings regarding CSE's transcriptional induction, we will elucidate the enzyme's turnover under diverse conditions. Recently we discovered a profound depletion of CSE in Huntington's Disease (HD) reflecting mutant huntingtin affecting the CSE transcription factor SP1. Pathophysiologic relevance was evident in the alleviation of the HD phenotype by rescue in cultures and intact mice by cysteine supplementation. We will further characterize cysteine/H2S dynamics in HD mice and neural cultures. The cysteine depletion may also account for the inanition of HD patients. Accordingly, we will also investigate the regulation by CSE of adiposity. We established D-serine as an endogenous agonist for glutamate-NMDA receptors, identifying, cloning and characterizing its biosynthetic enzyme serine racemase (SR). Recently, we discovered that SR can link AMPA and NMDA glutamate transmission. SR binds the AMPA receptor accessory protein stargazin leading to membrane association and SR inhibition. SR also binds PSD-95 from which it is dissociated by NMDA treatment. We will elucidate the physiologic significance of SR in an apparent cross-talk between AMPA and NMDA receptor systems. We recently identified substantial levels of D-cysteine in mammalian brain and other tissues. We have developed a novel sensitive and specific assay for tissue D-cysteine. We will monitor D-cysteine levels in diverse tissues under varying circumstances. We will seek biosynthetic mechanisms for D-cysteine via known or hitherto unidentified enzymes.

Lay Summary
PUBLIC HEALTH RELEVANCE: Our research under this grant addresses synaptic and other signaling systems that mediate psychotropic drug influences. We propose work on hydrogen sulfide, D-serine, and D-cysteine and their impact on neuropsychiatric disorders.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A