B·DEBATE International Center for Scientific Debate BARCELONA

Sant Joan de Déu HOSPITAL MATERNOINFANTIL - UNIVERSITAT DE BARCELONA

Sant Joan de Déu Research Foundation

AURORA MARTÍNEZ

CV

PARTICIPANT AT:

CONNECTING THE GROWING BRAIN

UNDERSTANDING NEUROPAEDIATRIC DISEASES THROUGH SYNAPTIC COMMUNICATION

November, 26th-27th, 2015, Barcelona

Aurora Martínez, Professor, Department of Biochemistry, University of Bergen, Norway

PhD biochemistry, UPV/EHU (1988); postdoctor (1988-1994) at University of Bergen (UiB), Norway; Associate professor, 1995, and Full professor, 1997 at Department of Biomedicine, UiB. Martinez is the Leader of research group "Biorecognition", Dept. Biomedicine, UiB. Research interests: Development and application of biophysical methods in structural, functional and thermodynamic studies of protein-ligand and protein-membrane interactions. The research at present focuses on translational studies and search of novel therapeutic approaches for activation or inhibition of biomolecular networks of clinical relevance, using isolated proteins, cells and animal models. Special interest on genotype-phenotype correlations and investigation of genetic misfolding diseases, notably phenylketonuria (PKU) and THD. In this field Aurora Martinez has contributed with important publications characterizing molecular mechanisms behind tetrahydrobiopterin responsive PKU and the effect of pharmacological chaperones, which are compounds with therapeutic potential for correction of misfolding diseases. Member of the Norwegian Academy of Sciences and Letters since 2007. Partner of the K.B. Jebsen Center for neuropsychiatric diseases since 2011. President elect of the Norwegian Biochemical Society (2016-).

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ABSTRACT

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Chaperone Therapy for Synaptic Disorders

Tyrosine hydroxylase (TH) is a (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4)-dependent enzyme that catalyzes the rate-limiting enzyme in the synthesis of catecholamine neurotransmitters (dopamine, noradrenaline, adrenaline). Variants in the TH gene are responsible for the rare autosomal recessive disorder TH deficiency (THD) associated with defective catecholamine synthesis. The diagnosis of THD is based on clinical symptoms and measurement of the catecholamine metabolites HVA and MHPG in cerebrospinal fluid, which are present in lower concentrations in THD patients. THD phenotypes span from L-DOPA-responsive dystonia, with infantile onset (type A) or a more severe L-DOPA-non-responsive encephalopathy, with neonatal onset (type B), and suspected synaptic disorder. Most of the 40 reported mutations in THD appear to critically misfold TH and reduce the stability of the enzyme in vitro. The degree of misfolding correlates well with the severity of the patient phenotypes, underlying the relevance of searching for stabilizing compounds that correct misfolding and may protect from loss of protein and activity in vivo (pharmacological chaperones). A recent study with TH has revealed different mechanisms for the action of pharmacological chaperones and identifies a subtype of compounds that preserve TH activity by weak binding to the catalytic iron (Hole et al. (2015); BBA 1854: 1078-89). The stabilizing effect of these compounds has been established in vitro and in cells. A recent mice model of THD type B (Korner et al. (2015) Brain 138: 2948-63) represents an optimal frame for testing synergistic combinations of different pharmacological chaperones that could provide patient-tailored therapeutic options for THD.

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