Neurotransmitter synthesis disorders: towards a therapeutic correction

Results in Brief

Neurotransmitters and neurodegenerative diseases

Several neurodegenerative disorders, including Parkinson’s disease, are associated with dysfunctions of the dopamine system. Understanding dopamine synthesis regulation will facilitate exploration of new therapeutic options for such diseases, affecting millions of people worldwide.

The symptoms of Parkinson’s disease result from the death of dopamine-generating cells in the brain and a decline in the enzyme tyrosine hydroxylase (TH). TH is a key enzyme, catalysing the conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA). L-DOPA is in turn converted to dopamine, a precursor for the other catecholamine neurotransmitters and hormones in the brain and neuroendocrine tissues. Decrease in TH is also associated with other neuropsychiatric diseases such as manic depressive illness, schizophrenia or L-DOPA-responsive dystonia.

Funded by the EU, the project THERAPY OPTIONS THD (Neurotransmitter synthesis disorders: Towards a therapeutic correction) was dedicated to further understand TH regulation. Scientists focused on the effect of TH phosphorylation and its binding to partner proteins and membranes. Phosphorylation of TH is a complex
process, affecting four different residues. To understand the roles of each phosphorylation site, cellular localisation of different phosphorylated forms of TH was characterised.

Confocal microscopy analysis revealed co-distribution of each phosphorylated form with different partner proteins in neuroendocrine and neuroblastoma cell line cultures as well as in human dopaminergic neurons. The project identified specific and clear differences in the subcellular localisation of each TH species. In addition, using biophysical approaches such as cell-substrate impedance and flow cytometry allowed analysis of the effect of TH on the synthetic membranes.

Finally, the screening a library of pharmacological compounds by differential scanning fluorimetry led to the identification of 17 compounds interacting with TH. These compounds were studied in wild-type TH and as well as in TH mutants associated with the neurological disorder TH deficiency (THD). In all cases the compounds protected from time-dependent loss of activity. Two of the identified compounds resulted in increased TH activity in the cells transfected with either wild-type TH or THD-associated mutants without affecting steady-state TH protein levels.

Advancing understanding of the mechanisms affecting TH and dopamine synthesis regulation is an important step to address the diseases caused by TH dysfunction.

**Keywords**

Neurotransmitters, neurodegenerative, Parkinson’s, dopamine, tyrosine hydroxylase

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**Project Information**

**THERAPY OPTIONS THD**

Grant agreement ID: 299972

**Closed project**

<table>
<thead>
<tr>
<th>Start date</th>
<th>End date</th>
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<tr>
<td>1 October 2012</td>
<td>30 September 2014</td>
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**Funded under**

FP7-PEOPLE

**Overall budget**

€ 208 353,60

**EU contribution**

€ 208 353,60

**Coordinated by**

UNIVERSITETET I BERGEN

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Last update: 14 August 2015
Record number: 169457
