Prolyl oligopeptidase alters cortical glutamate and function of metabotropic glutamate receptor mGluR5 in mice and in cells

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Background
Prolyl oligopeptidase (PREP) is a serine-protease that hydrolyses proline-containing peptides shorter than 30 amino acids. Alteration in PREP activity has been connected to neurodegenerative diseases, schizophrenia and depression. PREP inhibitors have shown neuroprotective, anti-amnesic and cognition-enhancing properties. PREP is widely distributed in different tissues of the mammalian body but the highest activities have been measured in the brain. PREP localizes in GABAergic and cholinergic interneurons of the thalamus and cortex, in short glutamatergic projection neurons between cortex and thalamus, and also in GABAergic neurons of nigrostriatal tract but in lower extent in dopaminergic neurons. High levels of PREP have been found in glutamatergic cortical spiny pyramidal cells and hippocampal CA1 pyramidal neurons indicating that PREP could participate in glutamatergic neurotransmission.

Methods
Aim of the study was to study further the role of PREP in glutamatergic neurotransmission. Concentration of glutamate, dopamine and GABA in the motor cortex and prefrontal cortex of PREP knock-out mice was measured by tissue HPLC analysis. Metabotropic glutamate receptor 5 (mGluR5) and NMDA receptor 1 (NMDA R1) in motor cortex were investigated by Western blotting. Glutamate receptor function was measured in mGluR5 transfected HEK-293 cells and stable PREP knock-out cells by Western blotting and glutamate binding assay.

Results
Tissue concentration of glutamate was significantly decreased in the motor cortex and the prefrontal cortex in PREP knock-out mice. However, dopamine and GABA were unchanged in the cortical tissue. Metabotropic glutamate receptor mGluR5 was decreased in the cortical tissue but the level of NMDA R1 was similar in PREP knock-out mice and in wild-type littermates. Glutamate binding and mGluR5 expression were decreased in PREP knock-out cells compared to wild-type HEK-293 cells.

Conclusions
Our results suggest that PREP participates on glutamatergic neurotransmission. PREP regulates cortical glutamate and mGluR5 receptor in the mouse brain and in the HEK-293 cells. Decreased mGluR5 in the brain of PREP knock-out mice and in the mGluR5 transfected PREP knock-out cells is probably caused by increased recycling of the receptors. PREP could be possible target in treatment of neurological diseases connected on altered glutamatergic neurotransmission.