

COLLOQUIA IN MEMBRANE TRANSPORT

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna, "Leseraum".

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Monday	17.03.2014 14:30 s.t.	Anika Hartz (host: K. Kuchler)
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"Blood-Brain Barrier P-glycoprotein: A New Target for Alzheimer's disease?"

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Abstract.

One hallmark of Alzheimer's disease is accumulation of neurotoxic amyloid-beta (Abeta) in the brain. The mechanistic basis for this pathology is unknown, but reports indicate that elevated Abeta brain levels are in part due to a failure in clearing Abeta from the brain. Abeta brain clearance is a two-step process: Abeta must first pass through the abluminal plasma membrane and then through the luminal membrane of the brain capillary endothelium. Since Abeta is a peptide, both steps must be facilitated. At the abluminal membrane, LRP appears to be responsible for the first step of Abeta uptake. Our data indicate that the second step in clearing Abeta from the brain is mediated by P-glycoprotein, suggesting that this transporter plays an important role in AD pathology.

We show that P-glycoprotein transports Abeta from brain capillaries into the vascular space. We also demonstrate in a transgenic mouse model of Alzheimer's disease (Tg2576; Abeta-overproducing mice) that P-glycoprotein expression and transport activity are substantially reduced in brain capillaries, suggesting a link between high Abeta levels and reduced brain capillary P-glycoprotein in Alzheimer's disease. Using this Alzheimer's disease mouse model we show that restoring P-glycoprotein expression and transport activity in brain capillaries significantly reduces Abeta brain levels within one week. We also found that blocking P-glycoprotein reduction by inhibiting the proteasome reduces Abeta brain levels. Thus, restoring blood-brain barrier P-glycoprotein and preventing its proteasomal degradation both have the potential to increase Abeta clearance and reduce Abeta brain accumulation. This mechanism could potentially be used as a new therapeutic strategy in Alzheimer's disease.