Activating LDL receptor-related protein 1 at the blood-brain barrier

Summary

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Supervisor:	Prof. Dr. Ute Panzenboeck
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Background:

Low-density lipoprotein receptor-related protein 1 (LRP1) is a cell surface receptor with multiple functions from lipoprotein endocytosis to mediating several signaling mechanisms. It is the major receptor responsible for Aβ clearance from the brain across the blood-brain barrier (BBB) (1). LRP1 consists of an α- (515 kDa) and a transmembrane β- (85 kDa) chain, which can be further cleaved by metalloproteinases, like ADAM10, and secretases, like BACE1, to generate soluble LRP1 (sLRP1) (2, 3). Circulating sLRP1 is the main carrier of Aβ in plasma and its release by vascular cells may be triggered by cholesterol (4). Recent results in our group show that LRP1 expression at the BBB is enhanced along with Aβ clearance *in vitro* and *in vivo* by simvastatin (5), and other treatments influencing cellular cholesterol metabolism (unpublished), while (insulin-resistant) 3xTG-AD mice exhibit LRP1-deficiency at the BBB (unpublished).

Hypothesis and Objectives:

LRP1 activity in pBCEC can be modulated to improve and recover Aβ clearance and/or insulin-mediated signaling at the BBB. We aim to investigate effects of (natural and synthetic) LXR- and other nuclear receptor (NR) agonists, on LRP1-mediated Aβ uptake and transport across the BBB and on regulating insulin receptor (IR) expression at the BBB.

Methodology:

Functions of LRP1 and regulatory effects of LXR activation, treatment with cholesterol, other NR agonists, and insulin/glucose, will be characterized using the established *in vitro* model of the BBB (5). The DK-MCD student will isolate pBCECs from pig brains and culture them on transwell filters to obtain a polarized and tight monolayer. The model allows access to the luminal ('blood' side) and abluminal ('brain' side) compartments. The tightness of the *in vitro* BBB will be monitored by measuring the transendothelial electrical resistance and [^{14}C]-sucrose paracellular permeability (5). The DK-MCD student will characterize effects of LXR/NR agonists, cholesterol, and insulin/glucose, on i) LRP1 mRNA and protein expression and posttranslational modification, ii) LRP1 activity in Aβ uptake and transcytosis, and iii) regulation of the IR-β/LRP1 axis including insulin-mediated signaling. Systemic effects of LXR/NR agonists on LRP1 activity will be assessed by employing mouse models such as C57BL/6 and 3xTg-AD animals on normal or high-fat diet (HFD). For this purpose, LRP1 expression will be analyzed in liver, brain, and isolated mBCEC by RTq-PCR, immunoblotting, and immunohistochemistry. Plasma lipids and sLRP1 will be determined using standard enzymatic kits and ELISA, respectively.

References:

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