SFB 35 Colloquia in Membrane Transport

Venue: Medical University Vienna, Center for Physiology and Pharmacology,

Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna,

"Leseraum - Hochparterre".

(Harald Sitte, Tel.: (01) 40160 31323, *harald.sitte@meduniwien.ac.at*,

Karl Kuchler, Tel.: (01) 4277 61807, *karl.kuchler@meduniwien.ac.at*)

Friday 19.06.2015 14:00 s.t. **Koen van de Wetering** (host: K. Kuchler)

Netherlands Cancer institute
BezoekadresPlesmanlaan 121
1066 CX Amsterdam
PostadresPostbus 90203
1006 BE Amsterdam

"Untargeted metabolomics uncovers N-lactoyl-amino acids and glutamate conjugates as substrates of ABCC5"

Koen van de Wetering (k.vd.wetering@nki.nl)

Abstract:
Our group studies ATP-binding cassette (ABC) efflux transporters using metabolomics-based approaches. ABC transporters are integral membrane proteins and use the energy provided by the hydrolysis of ATP to transport specific substrates across membranes. Despite the fact that ABC transporters have been extensively studied, their physiological function is incompletely understood. This is mainly due to a lack of knowledge about their *in vivo* substrate spectrum. ABCC5, for instance, is present at high levels in the blood-brain barrier, neurons and glia, but its preferred substrates are unknown. In my talk I will show how we used untargeted metabolomics to shed more light on the *in vivo* substrate spectrum of this ubiquitous efflux transporter. Using HEK293-ABCC5 cells we, for instance, found that N-lactoyl-amino acids are transported by ABCC5. N-lactoyl-amino acids are ubiquitous pseudo-dipeptides of lactic acid and amino acids and were not known to exist in mammals. Intriguingly, we found that N-lactoyl-amino acids are formed by CNDP2-mediated reverse proteolysis a process previously considered negligible *in vivo*. The function of N-lactoyl-amino acids, if any, is unknown.
We also applied our metabolomics screens to tissue extracts of *Abcc5*$^{-/-}$ and wild-type mice and uncovered ABCC5 as a general carrier for compounds containing a glutamate-moiety. Glutamate conjugates are of physiological relevance because they can affect the function of glutamate, the principal excitatory neurotransmitter in the brain. Interestingly, ABCC5 also transports exogenous glutamate analogs, like the classic excitotoxic neurotoxins kainic acid, domoic acid and N-methyl-D-aspartate (NMDA), and the therapeutic glutamate analog ZJ43.
In conclusion, in my presentation I will demonstrate the power of metabolomics to identify new substrates of (orphan) transporters. The presented methodology is not limited to ABC transporters but can be applied to any transporter of interest.