Lithium therapy: from urine concentrating defect to chronic kidney disease

Clinical relevance

For 60 years, lithium solidified as the mainstay treatment for bipolar disorder and is prescribed to 0.1% of the population. Lithium, however, causes nephrogenic diabetes insipidus, a urinary concentrating defect on short term in 20% of patients. On the long term, it also increases development of chronic kidney disease (CKD), which may develop to end state renal disease (ESRD), when kidney transplantation or haemodialysis are the patient's only options. While NDI is clinically considered a nuisance, Li-CKD is clinically problematic. Due to the difficulty to follow Li-CKD in patients, however, its aetiology is unknown and, therewith, ways to prevent it are non-existing.

Background

Li-CKD is characterized by a reduced eGFR, interstitial fibrosis and tubular atrophy, with a suspected suppressed inflammatory response. While it is generally believed that Li-CKD is a consequence of Li-NDI, as the latter leads to hypovolemia, RAAS activation and increased (sodium and) lithium uptake, our recent studies in which we treated 28 mice strains with lithium revealed the contrary as several mice strains developed Li-CKD, but not Li-NDI. So, if not due to the effects of lithium on the collecting duct (Li-NDI), which segment is then involved in Li-CKD development?

Hypothesis and research questions

We hypothesize that Li-CKD originates in renal proximal tubules (PTs), because (1) PTs efficiently transport lithium via trans- and paracellular mechanisms, (2) acute administration of lithium to animals demonstrated direct (metabolic) modulation of PT function, (3) PT cells are very sensitive to various drugs (e.g. antibiotics, anti-cancer agents) leading to CKD and (4) the only urine marker that correlates with CKD in lithium-using patients is β2-microglobulin, which is only absorbed in PTs. Moreover, RNAseq analysis of PTs isolated from Li-treated rats indicated clear differences in gene expression. Within the project, we aim to answer the following research questions:

- Which pathways are changed in proximal tubules due to lithium treatment?
- Is the effect of lithium on the proximal tubule energy status mediated via the Na-H exchanger-3?

What do we offer?

The possibility to perform and present high-quality clinically-oriented interdisciplinary research in a professional, multicultural and highly-motivating working team. You will work on this project under the supervision of an enthusiastic PhD student/postdoc (Mol. Biol.) and you will have the opportunity to obtain a deep understanding of pathway analysis using bio-informatics (with group of Henk Stunnenberg, molecular biology) and techniques and skills, like culture of polarized cells, RNA isolation, RT-qPCR, immunoblotting, planning and performing experiments and writing & presentation skills.

What will you do?

Within the project, you will be responsible for your own research project. This project is interdepartmental. You will grow proximal tubule cells to polarization on semi-permeable membranes and test whether NHE3 blockers prevent lithium-induced cell stress. Moreover, supervised by the bio-informatics experts of FNWI Molecular Biology and using the available RNAseq data, you will deduce which pathways are changed in rat proximal tubules due to the influx of lithium. Accomplishment of these investigations and fitting of the data will lead to a co-authorship on a paper to come.

Contact:

Department:	Physiology
Supervisor:	Kim Neijman/ Prof. Peter Deen|Dr Joost Martens/Prof. Henk Stunnenberg
Contact person:	Kim Neijman
Telephone number:	+31 (0)24 3613684
Email address:	Anke.vanmil@radboudumc.nl
Website:	www.physiomics.eu