Diuretics as treatment for lithium-induced nephrogenic diabetes insipidus

Clinical relevance

Lithium is the drug of choice for the treatment of bipolar disorders and is also regularly used to treat schizoaffective disorders and depression. Unfortunately, lithium has side effects, which include a decreased ability to concentrate urine. Approximately 20% of the patients develop symptomatic nephrogenic diabetes insipidus (NDI), characterized by excessive production of urine due to impairment of the antidiuretic effect of the hormone arginine-vasopressin (AVP). Patients with lithium-induced NDI are at risk for dehydration and prolonged lithium treatment might lead to cyst formation and end stage renal disease. However, cessation of lithium therapy is not an option for every patient with NDI, because the symptoms of the bipolar disorder have a larger impact on the patient's quality of life.

Background

The kidney is the main organ for regulating water homeostasis. In states of hypernatremia or hypovolemia, a hormone called AVP is released which triggers a signalling cascade that eventually leads in the redistribution of Aquaporin-2 (AQP2) water channels from intracellular vesicles to the apical membrane, resulting in the production of more concentrated urine. Besides this short-term regulation, AVP also exerts a long-term regulation by increasing AQP2 mRNA and protein expression.

From studies in rats, it became clear that the effects of lithium can be divided in two stages. At the short term (< 5 days), lithium-induced NDI results in AQP2 down regulation and increased excretion of sodium, without gross changes in renal morphology. Chronic lithium treatment (1-4 weeks), however, also leads to a severe loss of principal cells, which are essential for water reabsorption in the kidney.

Recent investigations demonstrated that diuretics can partially protect mice against the development of lithium-NDI. Mice treated with these compounds exhibited a reduced AQP2 downregulation upon lithium treatment compared to non-treated mice. It is unknown at present, whether lithium treatment of mice also results in a shift from principal to intercalated cells as is seen in rats and humans and whether diuretics can prevent this transition.

Goals

In this internship we want to answer the following questions:

- Does lithium treatment in mice result in remodelling of the collecting duct?
- Does treatment with diuretics prevent the remodelling of the collecting duct?
- Does lithium treatment lead to cell cycle arrest of principal cells? (In vivo model)
- How does lithium affect intracellular mechanisms / proteins involved in cell division? (In vivo model)

Techniquesc

This internship will allow you to learn and apply several techniques such as:

- Organizing and performing animal experiments
- Immunocytochemistry
- Westernblotting
- Molecular cloning
- Cell culture
- FACS analysis
- Writing & presentation skills

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