Treatment of inherited forms of hypercalcemia: the use of calcimimetic drugs

Clinical relevance

The disorders familial hypocalciuric hypercalcemia (FHH) and neonatal severe hyperparathyroidism (NSHPT) are caused by inactivating mutations in respectively a single or both alleles of the CaSR gene. These disorders demonstrate characteristic abnormalities in calcium homeostasis and regulation of renal and parathyroid function, exhibiting phenotypes ranging from no symptoms at all in some patients, to gallstones, osteopenia and chondrocalcinosis in others. The devastating disorder NSHPT shows a more severe phenotype and typically results in death of the neonatal patient within 2 years. Symptomatic FHH/NSHPT patients are usually subjected to surgical intervention in the form of parathyroidectomy. Although this treatment initially corrects the patient's serum Ca^{2+} levels, it has many disadvantages as the patient will keep having occasional unbalanced serum Ca^{2+} levels.

Background

The calcium-sensing receptor (CaSR) is a G-protein coupled receptor (GPCR) that, as the name implies, has a key role in calcium homeostasis. This receptor is the driving force behind bone resorption, renal calcium reabsorption and intestinal calcium uptake. Calcium homeostasis is of great importance, since perturbation of the overall calcium balance could result in disturbed vital physiological functions.
Interestingly, the clinically-approved cell-permeable allosteric modulator cinacalcet has been shown to relieve FHH in some patients. However, this compounds mechanism of action has not yet been fully elucidated.

Goals

In this internship we want to answer the following questions:

- What is the influence of mutations found in FHN/NSHPT patients on CaSR function and localization?
- Can cinacalcet rescue the CaSR mutants found in FHN/NSHPT patients?

Techniques

This internship will allow you to learn and apply several techniques such as:
Immunocytochemistry
Westernblotting
Live cell imaging techniques

Contact:

Department:	Physiology, Osmoregulation
Contact person:	Tim Schreuder
Telephone number:	0243614222
Email address:	tim.schreuder@radboudumc.nl
Website:	www.physiomics.eu