Allosteric modulation by sodium ions and amilorides of G protein-coupled receptors : a closer look at the sodium ion site of the adenosine A2a receptor and development of a mass spectrometry ligand binding assay for adenosine A1 and A2a receptors

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Stellingen

bij het proefschrift

Allosteric modulation by sodium ions and amilorides of G protein-coupled receptors
A closer look at the sodium ion site of the adenosine A_{2A} receptor
Development of a mass spectrometry ligand binding assay for adenosine A_1 and A_{2A} receptors

1. Understanding allosteric mechanisms of GPCRs on a molecular level is important for drug development.
   Keov P, et al. Neuropharmacology, 2011. 60(1): 24-35.

2. The sodium ion site is a versatile allosteric site that can exert various allosteric effects, even if it is well conserved amongst Class A GPCRs.
   Chapter 2, this thesis.

3. At physiological concentrations sodium ions are important regulators of GPCR activity; in particular adenosine A_{2A} receptor activity is down-regulated significantly.
   Chapter 3, this thesis.

4. The sodium ion site has a vital role in the activation mechanism of the adenosine A_{2A} receptor and of GPCRs in general.
   Chapter 4, this thesis.

5. The proximity of the allosteric sodium ion site and the orthosteric site allows the synthesis of a bitopic ligand binding at both sites, which may provide more information on allosteric mechanisms of GPCRs.
   Chapter 5, this thesis; Guo D, et al. Br J Pharmacol, 2014. 171(23): 5295-312.

6. Computational biology is vital to understand biochemical processes on a molecular level but still needs a firm foundation of 'wet lab' work.
   Chapters 3 and 4, this thesis.

7. Even if the "snapshot" structural information provided by X-ray crystallization of GPCRs has given a substantial boost to the field, the next step to better understand GPCR allosteric and activation mechanisms will be pushed by time-resolved methods that can follow structural dynamics at an atomic scale.
   Isogai S, et al. Nature, 2016. 530(7589): 237-41; Deupi X. Biochim Biophys Acta, 2014. 1837(5): 674-82.

8. As well researched targets adenosine receptors are excellent model systems to evaluate new methods.
   Fredholm BB, et al. Pharmacol Rev, 2011. 63(1): 1-34.

9. The ongoing development of label-free assays for GPCRs greatly expands the possibilities to study protein-ligand interactions.
   Jacobson KA. Biochem Pharmacol, 2015. 98(4): 541-55.

10. Mass spectrometry provides an excellent label-free alternative for the quantification of ligand binding to radiolabeled and fluorescently labeled ligands.
    Chapter 6, this thesis; Neiens P, et al. ChemMedChem, 2015. 10(11): 1924-31.

11. Research is the process of going up alleys to see if they're blind.
    Barstow Bates.

12. Doing a PhD comes with interesting time-dilation effects: four years seem plenty of time in the beginning, but appear to be nothing in the end.