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# Kinetic characterization of clinically used GnRH peptide agonists

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Drug-target residence time is an important, yet often overlooked, factor in drug discovery. Multiple studies have proposed a long duration of action to be beneficial for prolonged drug efficacy and a once daily dosage schedule to increase patient compliance. Long duration of action for GnRH analogues is currently achieved by depot formulations for up to 6 months (leuprolide acetate and goserelin acetate) or even 12 months (histrelin acetate). However, the kinetic parameters of these commonly prescribed agonists for their interaction with the GnRH receptor have not yet been reported. Therefore, this project focused on determining the binding kinetics of clinically used GnRH agonists. A novel radioligand binding competition association assay was developed and optimized for the human GnRH receptor with the use of 125I-triptorelin, unlabeled triptorelin and CHOhGnRH membranes. Subsequently, the residence times of twelve unlabeled peptide GnRH agonists were determined. Of all tested ligands buserelin had the longest residence time on the receptor (131.0 ± 35.5 min), whereas goserelin had the shortest residence time (5.1 ± 0.71 min). All twelve agonists revealed good potencies and efficacies in functional luciferase reporter gene assays on CHOhGnRH-luc cells. A novel radioligand binding competition association assay was successfully applied to determine the kinetic binding characteristics of GnRH analogues. Our research provides new insights for the development of improved drugs targeting the GnRH receptor, i.e. combining long drug-target residence time with a depot formulation.

## Biography

Laura H Heitman, PhD. studied Biopharmaceutical Sciences at the University of Leiden, The Netherlands. Traineeships were performed at Medicinal Chemistry of the Leiden University, NL and at Pharmaceutical and Biological Chemistry of the School of Pharmacy in London, UK. In October 2004, she started as a PhD student on the project “Allosteric modulation of ‘reproductive’ GPCRs” at the Division of Medicinal Chemistry of Leiden University. In January 2009 she was appointed as assistant professor in this division. Her areas of interest include the molecular pharmacology of ligand-receptor interactions, and more specifically receptor residence time and allosteric modulation of GPCRs.

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