Receptomics to identify the targets for plant-based anti-obesity compounds

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Background

With 2.3 billion overweight and 700 million obese adults worldwide in 2015 (WHO), obesity and consequently diabetes type II are among the biggest global health problems. Even though dietary and lifestyle changes may eventually reduce obesity for some individuals, new safe and more effective drugs are required for successful weight reduction and treatment of type 2 diabetes in a large proportion of obese individuals. It has been shown that various G-protein coupled receptors (GPCRs) expressed in various tissues such as liver, muscle, pancreatic islets, immune cells and the central nervous system are involved. GPCRs are important targets for food components. The members of this large family of membrane proteins are involved in virtually every physiological process. This study will focus on the interaction between food ligands and GPCRs.

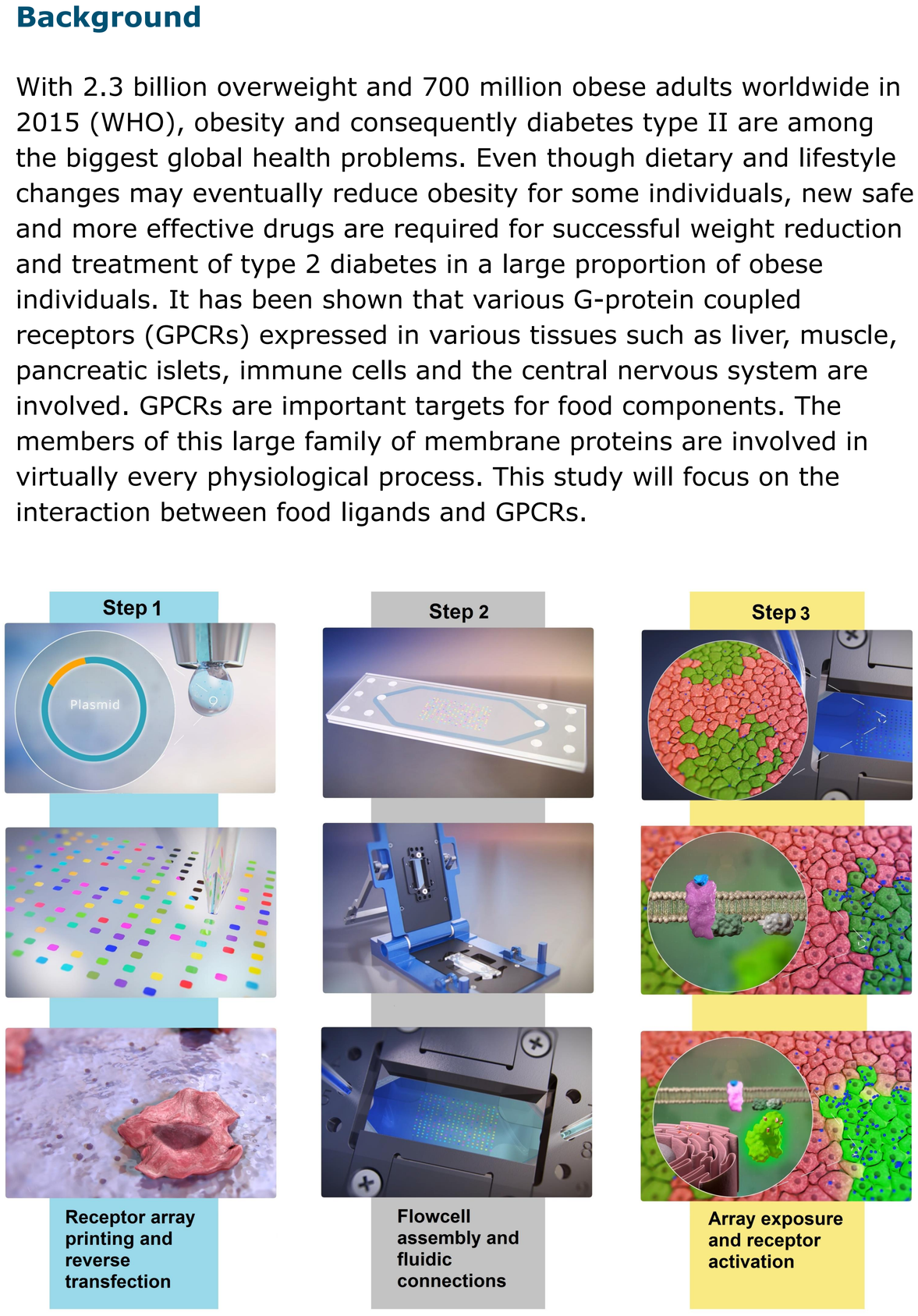


Figure 1. Schematic overview of receptor array preparation and measurement in the microfluidic system. This microfluidic biosensor enables direct detection of G-protein coupled receptor (GPCR) activation by monitoring dynamics in cytosolic calcium ion concentration.

Aim and strategy

Our group has recently published about a microfluidic biosensor array enabling direct detection of GPCR activation using a genetically encoded calcium ion sensor (Roelse et al., 2018). This biosensor platform is generic for all GPCR receptors, including bitter receptors, which use or can be made to use calcium as secondary messenger in their signalling pathway. The biosensor array or receptomics chip can detect activating substances in sequential series of analytes every 5 min.

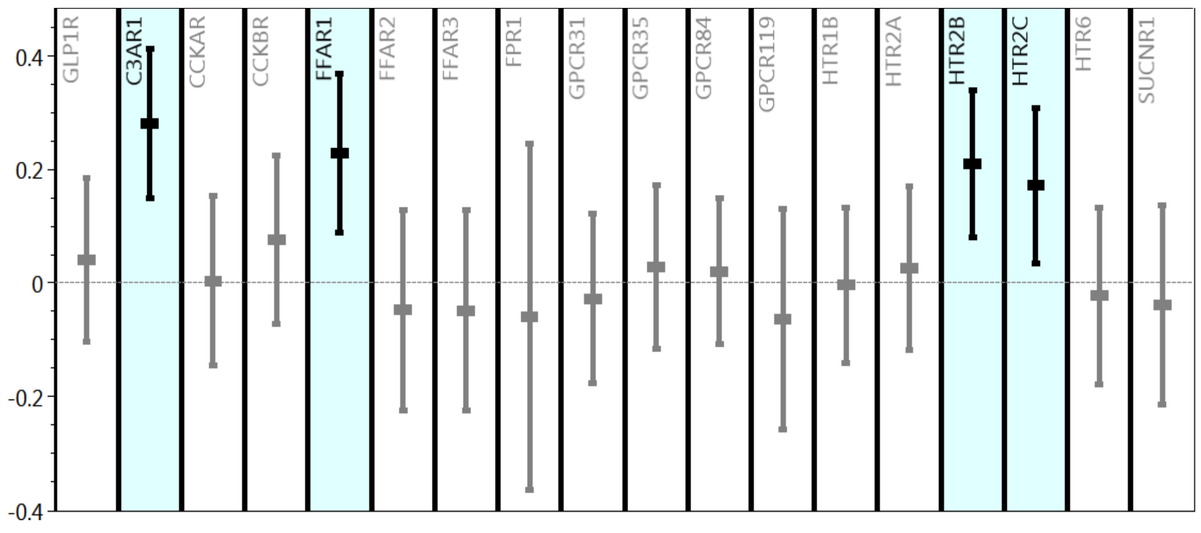
In this project, we are establishing the influence of receptor-ligand interactions on the development of obesity and correlated type 2 diabetes mellitus. Next to this, we aim to identify food-related compounds that can prevent or intervene in these chronic diseases on a receptor level.

Method

- Identify food related compounds and receptors involved in obesity and related diseases
- Screen food & plant extracts or compounds for receptor binding
- Confirm results in *in vivo* assays with high-fat diet (HFD) fed mice

Results

Figure 2. *Right:* Picture of bitter gourd fruit (adapted from indianmart.com) *Bottom:* Example of preliminary receptor analysis with bitter gourd leaves *(Momordica charantia)* extract using receptors known to be involved in obesity and related diseases. Response differences between blank and *M. charantia* extract injections compared to the mock. Various receptors show a clear increased response towards the *M. charantia* extract.



Status and future experiments

A selection of 26 receptors based on literature and expression data was made. Initial receptor binding experiments using *Momordica charantia* leaf extract show specific receptor responses to serotonin (HTR2B, HTR2C), fatty acid receptor (FFAR1) and to the complement component 3a receptor 1 (C3AR1) (Figure 2). More compounds and extracts will be analyzed for receptor binding and activation this year. Furthermore, compounds and extracts will also be tested in cell assays for metabolic activity and immune responses in various cell assays.

References

Roelse et al., Calcium Imaging of GPCR Activation Using Arrays of Reverse Transfected HEK293 Cells in a Microfluidic System. Sensors Feb 2018

Henquet M.G.L. *et al.*, Metabolomics meets functional assays: coupling LC–MS and microfluidic cell-based receptor-ligand analyses. Metabolomics Jun 2016.

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