PPARs are major regulators of glucose and lipid metabolism. Furthermore, PPARs are also involved in the regulation of inflammation and angiogenesis. PPARs were originally named for their ability to induce hepatic peroxisome proliferation in mice in response to xenobiotic stimuli. The expression of three PPAR isoforms, alpha, beta/delta, and gamma, has been described. They share 60%-80% homology in their ligand-binding and DNA-binding domains. Nuclear receptors, to which PPARs belong, are promising targets for T2DM treatment strategies because they act as transcription factors and may produce selective alterations in downstream gene expression. PPAR agonists are used therapeutically in patients with T2DM, but unfortunately, PPAR agonists can have long-term adverse effects, such as increased body weight, fluid retention and increased risk of heart failure. The goal of our screening strategy is to find PPAR agonists that are more selective and have less adverse affects compared to the present PPAR drugs.

Taken together, new drugs to treat T2DM should be more selective with fever adverse effects. Screening strategies and initial results will be presented.

MECHANISM OF ACTION OF ANTIMICROBIAL PEPTIDES ISOLATED FROM INVERTEBRATES

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Antimicrobial peptides (AMPs) use several different strategies to inhibit bacterial growth. While many AMPs are responsible for membrane pore formation and cell lysis, other AMPs manage to permeabilize the membrane without membrane disruption. The aim of our studies is to characterize membrane non-disruptive AMPs, which act by targeting intracellular molecules and thereby inhibit processes vital for bacterial survival. Arasin 1 is a 37 amino acid long proline-rich antimicrobial peptide isolated from the spider crab, *Hyas araneus*. We report the localization of the pharmacophore of arasin 1 to be the proline/arginine-rich NH_2 terminus, whereas the C-terminal cysteine containing part does not seem to have any antimicrobial property. A kinetic killing study of *Escherichia coli* by using a synthetic peptide made of the first 23 NH_2 terminus amino acids, named arasin 1(1–23), revealed that this peptide acts as a bacteriostatic agent. The study implies that arasin 1(1–23) has a different mode of action than membrane lytic peptides like cecropin P1. An *in vivo* bacterial membrane integrity assay, using an *E. coli* strain expressing luciferase, showed that arasin 1(1–23) did not render the cells leaky, indicating that arasin 1(1–23) has intracellular target molecules and inhibits bacterial growth without lysing the cells. Transmission electron microscopy in combination with immunogold staining showed intracellular localization of arasin 1, which could be due to arasin 1 targeting intracellular molecules. Strategies involving peptide tagging together with chromatographic separation and mass spectroscopy identification of intracellular peptide targets will also be presented.