ABSTRACT

Prolactin-releasing peptide (PrRP) is a member of the family of RF-amide peptides. These peptides have typical C-terminal sequence –Arg-Phe-NH_2 and similar biological effects. PrRP was discovered as an endogenous ligand of an orphan receptor GPR10 while searching for a factor responsible for a prolactin secretion. This effect was not later confirmed and nowadays, PrRP is mainly considered as an anorexigenic peptide. This is supported by a fact that PrRP and GPR10 deficient mice suffer from hyperphagia and late-onset obesity. Besides GPR10, PrRP is bound to $NPFF_2$ receptor whose endogenous ligand is neuropeptide FF (NPFF).

In this study, the PrRP's analogues modified at the N-terminus with fatty acids of different lenghts were tested *in vitro* on binding and activation MAPK/ERK1/2 signalling pathway. In *in vivo* experiments on food intake, the central anorexigenic effects of lipidized PrRP-analogues were tested provided their crossing blood brain barrier.

Binding studies showed that all analogues bound to rat pituitary RC-4B/C cells with high affinity, analogues containing fatty acid with K_i of one order of magnitude lower than native PrRP. High affinity was also confirmed for binding to cells overexpressing GPR10 receptor and cell membranes with overexpressed $NPFF_2$ receptor. All tested analogues activated MAPK/ERK1/2 signalling cascade with EC_{50} in 10^{-9} M range.

In vivo experiments confirmed that PrRP had no effect on food intake after peripheral administration. On the contrary, all analogues with 14-carbon fatty acid or longer attenuated food intake, probably because of a higher lipophilicity of the analogues that could facilitate transport over the blood-brain barrier. Tested analogues didn't shown any sedative or analgetic effect. In conclusion, analogues palm-PrRP31 a myr-PrRP20 are proposed as potential antiobesitic agents for further studies. (In Czech)