ABSTRACT

This work focuses on anorexigenic neuropeptides, cocaine- and amphetamine-regulated transcript (CART) and prolactin-releasing peptide (PrRP), which decrease food intake and body weight.

CART peptide is an anorexigenic neuropeptide and, despite many efforts, its receptor has not yet been identified. We found CART peptide specific binding sites in pheochromocytoma PC12 cells. Cells differentiated to neurons increased significantly the number of binding sites. On the other hand, after differentiation to chromaffin cells the number of binding sites was so low that it was impossible to determine their density. To clarify the importance of each of the three disulfide bridges in the CART molecule, analogs with one or two disulfide bridges were synthetized. The biological activity was maintained in analog with two disulfide bridges in positions 74-94 and 88-101. Moreover, we demonstrated the stimulation of JNK and subsequently c-Jun activation in PC12 cells.

Neuropeptide PrRP belongs to the RF-amide peptide family and has anorexigenic properties. PrPR has a high affinity to GPR10 and neuropeptide FF (NPFF2) receptor. In our laboratory lipidized analogs of PrRP were synthesized, which are able to decrease food intake after peripheral administration and may cross the blood-brain barrier.

We tested biological activity of novel lipidized analogs of PrRP with myristic or palmitic acid on the N-terminus of the chain and with C-terminal modification of Phe^{31} by non-coded amino acids *in vitro* and *in vivo*. Lipidized PrRP analogs have a high affinity to RC-4B/C cells and to both GPR10 and NPFF2 receptors. Moreover, lipidized PrRP analogs, in contrast to native PrRP, have a high affinity to neuropeptide Y receptor – Y5, which shows homology to GPR10.

Lipidized analogs showed a significant and long-term effect on decreasing food intake. Palm-PrRP31, myr-PrRP20 and analog with $PheCl_2^{31}$ were tested for two weeks on diet-induced obese mice. They decreased food intake and body weight significantly and improved some metabolic parameters related to the obesity. Research on biological activity of lipidized PrRP analogs and the understanding of its transportation mechanism is important because of their potential use as treatment of obesity.