ABSTRACT

Obesity is a worldwide health problem and an effective treatment is still scarce. Anorexigenic neuropeptides, such as prolactin-releasing peptide (PrRP), have a potential for the treatment of obesity and its complications, but in their natural form they have several limitations such as poor bioavailability, low stability and inability to cross the blood-brain barrier after peripheral administration. Recently we have designed lipidized analogs of PrRP. Lipidization makes this peptide more stable and able to act centrally after peripheral administration.

The aim of this study was to investigate the chronic effect of PrRP palmitoylated at position 11 (palm^{11}-PrRP31) on obesity and obesity-related metabolic parameters and to clarify mechanisms of its action. We used three rodent models of obesity: Wistar Kyoto (WKY) rats with high-fat diet-induced obesity (DIO) having intact leptin and leptin receptor as well as rodents with disrupted leptin function: leptin deficient *ob/ob* mice and *fa/fa* rats with a disturbed leptin signaling.

Consumption of a high-fat diet in DIO WKY rats increased their body weight, caused strong glucose intolerance and increased liver mRNA expression of enzymes of *de nov*o lipogenesis. Palm^{11}-PrRP31 treatment significantly decreased cumulative food intake, body weight, plasma leptin level, attenuated glucose intolerance as well as expression of liver lipogenesis enzymes. In leptin deficient *ob/ob* mice, palm^{11}-PrRP31 and leptin showed a synergistic effect in chronic treatment at a younger age on attenuating hyperglycemia and liver weight. At an older age it showed a decrease in body weight, cholesterol level and an increase in body temperature. On the other hand, there was a beneficial effect on obesity and related disturbances occurred in *fa/fa* rats with leptin signaling disruption after palm^{11}-PrRP31 treatment.

Our data suggest a good efficacy of palm^{11}-PrRP31 with diet-induced obesity with intact leptin and leptin receptor. Through the rodents with disturbed leptin signaling, we showed that leptin signaling is necessary for palm^{11}-PrRP31 anorexigenic and related effects. Thus, palmitoylated PrRP analogs are attractive candidates for treatment of humans with high energy diet-induced obesity and derived disturbances.