Proceedings of the 37th European Peptide Symposium
Michal Lebl, Editor
European Peptide Society, 2024 *http://doi.org/10.17952/37EPS.2024.P1138*

Impaired metabolic phenotyping in mice with deletions of GPR10 and NPFFR2 receptors: Implications for lipidized PrRP analog therapy in obesity

Veronika Strnadová[1], Magdalena Škrlová[1], Jaroslav Kuneš[1,2], Lenka Maletínská[1]

[1] *Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, 16600 Prague, Czech Republic*
[2] *Institute of Physiology of the Czech Academy of Sciences, 14200 Prague, Czech Republic*

Scientific background: Obesity is a growing global health concern with limited treatment options. Prolactin-releasing peptide (PrRP) is a neuropeptide that can reduce food intake when administered centrally but loses this effect when given peripherally. However, lipidization of peptides can enhance their stability and efficacy after peripheral administration. Our previous work showed that lipidized PrRP analogs effectively reduced food intake and body weight in mice[1]. PrRP binds to its GPR10 receptor and with high affinity to neuropeptide FF receptor type 2 (NPFFR2)[2], both of which are involved in regulating food intake and energy homeostasis.

Palmitoylated analog of PrRP31, palm^{11}-PrRP31 improved its binding and agonist activity for both receptors[3,6,7]. We have previously shown that deletion of GPR10 resulted in increased food intake, elevated insulin levels, impaired glucose tolerance, and altered lipid metabolism gene expression[4]. NPFFR2 knockout mice showed severe glucose intolerance, which worsened with a high-fat diet (HFD), and developed hypothalamic insulin resistance due to reduced insulin pathway signaling proteins[5]. Deletion of both GPR10 and NPFFR2 caused sex-specific and diet-dependent metabolic changes, including impaired glucose tolerance and hyperglycemia on a high-fat diet.

Methods: In this study, we examined the effect of palm^{11}-PrRP31 on mice with deletion of either GPR10 or NPFFR2 or both receptors (GPR10/NPFFR2 KO or dKO mice). Male mice were fed a HFD starting at 8 weeks of age for a duration of 5 months. During the final month, they received a 4-week subcutaneous treatment with either saline or palm^{11}-PrRP31 (5 mg/kg) administered twice daily. An oral glucose tolerance test (OGTT) was performed in the third week of the interventions, and fasting plasma was collected to measure insulin levels. Finally, the mice were euthanized by decapitation, and organs (brain, liver, adipose tissue) were collected for further analysis.

Results and discussion: The palmitoylated palm11-PrRP31 analog demonstrated strong appetite-suppressing and glucose-lowering effects in obese wild-type (WT) mice. Treatment with palm11-PrRP31 led to a significant reduction in body weight and food intake in GPR10 KO mice, whereas in NPFFR2 KO mice, the reduction in body weight was less pronounced and food intake was only slightly reduced. In dKO mice, which lack both GPR10 and NPFFR2 receptors, there was no reduction in body weight or food intake.

 http://doi.org/10.17952/37EPS.2024.P1138

Palm^{11}-PrRP31 significantly improved glucose tolerance in WT mice, but had no effect in any of the KO models, suggesting that the activation of both GPR10 and NPFFR2 receptors is essential for its anti-obesity and anti-diabetic effects.

Previous studies have shown that the GPR10 and NPFFR2 receptors are involved in regulating energy balance, food intake, and glucose homeostasis. The dual agonism of these receptors by palm^{11}-PrRP31 may enhance anorectic signaling pathways, reduce insulin resistance, and promote glucose uptake in peripheral tissues, which are critical mechanisms for weight loss and improved metabolic control. Moreover, lipidization of PrRP analogs, such as palm^{11}-PrRP31, increases their stability and prolongs their half-life, enhancing their therapeutic efficacy. Therefore, targeting both GPR10 and NPFFR2 receptors with lipidized PrRP analogs could offer a promising strategy for treating obesity and related metabolic disorders by addressing both appetite regulation and glucose metabolism, potentially overcoming the limitations of current therapies that target only a single pathway.

Dedication:
This research was supported by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104) - Funded by the European Union - Next Generation EU, by grant 21-03691S Czech Science Foundation of the GACR and by RVO: 61388963 and RVO:67985823 of the CAS.

References:

1. Maletínská L. et al., Int J Obes (2015), 39, 986–993
2. Engström M. et al., J Pharmacol Exp Ther (2003), 305(3):825-32
3. Pražienková V., Holubová M. et al.,PLoS ONE 12(8): e0183449
4. PražienkováV. et al., Gene (2021), 774-145427
5. Karnošová A., Strnadová V. et al., Clin Sci (2023), 137 847–862
6. Strnadová V. et al., Neuropeptides 98 (2023), 102319
7. Karnošová A. et al., Int J Mol Sci (2021), 22, 8904