PPARdelta in hypothalamic microglial controls glucose metabolism and insulin sensitivity

F. Cázarez-Márquez, S. Guo, N.L. Korpel, A. Kalsbeek, C.X. Yi

Department of Endocrinology and Metabolism, Laboratory of Endocrinology, Amsterdam Gastroenterology and Metabolism, Amsterdam University Medical Centers (UMC), location AMC.

Background: Microglia are the brain innate immune cells essential for maintaining a local micro-environment optimal for neuronal function. Our previous study showed that lack of lipoprotein lipase (a key enzyme that gates lipid uptake) in microglia worsened glucose metabolism in high fat diet induced-obese (DIO) and insulin resistant mice. These effects are largely mediated by neurons located in the mediobasal hypothalamus (MBH) that control glucose metabolism and energy homeostasis. In the current study, we explored whether enhancing microglial fatty acid oxidation in the MBH by a peroxisome proliferator-activated receptor (PPAR)-δ agonist would exert beneficial effects on glucose metabolism in DIO rats.
Methods: To deliver the PPAR-δ agonist GW0742 specifically into microglia in the MBH, we developed polymer hybridized PLGA-PEG nanoparticles that can pack the GW0742 (NP-GW0742). Nanoparticles packed with vehicle were used as control (NP-Veh). We tested the efficacy of the NP-GW0742 in stimulating lipid utilization in microglial cells *in vitro*, by measuring the oxygen consumption rate (OCR). Subsequently, we infused the NPs into the MBH of DIO rats, and tested their effects on insulin sensitivity.
Results: We found that in a concentration of 5 μM NP-GW0742 increased the OCR by 52% in cultured microglial cells. In the *in vivo* study, after 12 days of NP-GW0742 infusions in the MBH, basal blood glucose levels in DIO rats were not different from the NP-Veh group. However, endogenous glucose production (EGP) was significantly higher in the NP-GW0742 infused rats as compared to the NP-Veh infused rats, indicating that rats received the NP-GW0742 also had a higher glucose uptake. Moreover, the NP-GW0742 induced increased EGP did not correlate with plasma insulin levels. In the insulin tolerance test, we found a significantly higher insulin sensitivity in the rats that had received NP-GW0742 as compared to those that had received NP-Veh.
Conclusion: Thus, administration of NP-GW0742 in the MBH resulted in an improvement in insulin sensitivity.