Abstract

Chronic protein-restrictive diet (low protein/high carbohydrate (LPHC) diet) and exercise training independently extends health- and life-span in rodents but the efficacy of periodized LPHC (pLPHC) diet and the potential synergy between pLPHC diet and exercise training is unexplored. To explore the efficacy and mechanisms of pLPHC diet and its potential synergy with exercise, this PhD thesis project set up a proof-of-concept study involving a mouse intervention study of control high fat diet (HFD) vs. pLPHC combined with exercise in middle-aged retired breeder mice. A chronic LPHC and high protein/low carbohydrate (HPLC) diet vs. chow diet was conducted in parallel to confirm the previous reported effects of these diets and to specifically study the effects on whole-body and muscle-specific insulin action.

We found that pLPHC diet provided in 14 days on/off cycles protected mice against weight gain on a HFD, such that they had no net weight gain after 3 full cycles ending on a LPHC diet cycle. This was despite higher total calorie intake and could be explained molecularly by the pLPHC diet-stimulated release of FGF21 from liver to increase adaptive thermogenesis in brown adipose tissue. Furthermore, marked improvements in whole-body insulin sensitivity measured as HOMA2-IR and in a modified glucose tolerance test were seen on the pLPHC diet. The protective effects were highly transient and nullified by 14 days on a control HFD. Interestingly, repeated pLPHC diet cycles increased, and exercise training decreased liver Fgf21 mRNA expression and plasma FGF21. The changes in FGF21 correlated tightly with the expression of the liver integrated stress response (ISR)-marker Nupr1, suggesting that repeated pLPHC diet cycles increase and dampen the liver ISR respectively. The control study with chronic LPHC and HPLC diets showed increased and decreased whole-body insulin sensitivity. However, neither basal skeletal muscle cell signaling in situ nor insulin action in skeletal muscle ex vivo was altered, suggesting that skeletal muscle is not involved in the effects of these diets seen at the whole-body level.

In conclusion, this thesis provided the first data showing that periodized low protein diet confers considerable and remarkable health benefits in mice. Whether these effects are translatable into humans should now be determined.