Nutritional Ketosis, Aquaporins, and Energy Homeostasis

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Objectives: Ketogenic diets (KDs), promoting nutritional ketosis, profoundly impact energetic metabolism, and are being widely used for weight loss purposes. Aquaporins (AQPs) are transmembrane channels that facilitate water and glycerol transport across cell membranes and are critical players in energy homeostasis. The axis of adipose AQP7/hepatic AQP9 assures the body's glycerol homeostasis. Studies investigating the relation between KD, aquaporins, and energy homeostasis are scarce.

Methods: *ApoE−/−* mice were fed *ad libitum* a KD (Kcal%: 1/81/18, carbohydrate/fat/protein; n = 8) or a control diet (Kcal%: 70/11/18, carbohydrate/fat/protein; n = 7) for 12 weeks. Food consumption and body weight were determined weekly, and plasma was collected every 4 weeks for biochemical analyses. Upon euthanasia, the tissues involved in energy homeostasis, the liver, white adipose tissue (WAT), and brown adipose tissue (BAT), were collected for gene expression analysis.

Results: Bodyweight gain (% to the initial weight) was similar in both groups (4.0 ± 1.1, KD-mice vs. 3.3 ± 1.3, controls), in spite of the profoundly different diet fat content, thus confirming the anti-obesogenic effect of the diet. The plasma concentration of the major ketone body, ß-hydroxybutyrate, was significantly elevated in KD (2,019 ± 87 vs. control, 418 ± 72 nM, mean ± SEM), confirming the presence of nutritional ketosis under this dietary condition. The transcript level for uncoupling protein 1 (*Ucp1*) gene in BAT of KD-fed mice was upregulated by 400%, compared to control-fed mice, unveiling a thermogenic effect of KD. Lastly, mice subjected to KD exhibited: in BAT, a significant KD-induced upregulation of *Aqp9* transcripts suggesting the participation in the influx of excess plasma glycerol to fuel thermogenesis; in WAT, a downregulation of *Aqp7*, suggesting the non-utilization of adipocyte lipid droplets as fuel; in the liver, an *Aqp7* up-regulation suggesting its participation in glycerol influx into hepatocytes.

Conclusions: The anti-obesogenic effect of KD was associated with the upregulation of thermogenic genes in BAT and with the modulation of AQPs expression patterns in BAT, WAT, and the liver

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