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Constant-moderate and high-intensity interval training induce contrasting metabolic effects in high-fat fed mice

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Obesity is highly associated with the development of metabolic disorders in insulin sensitive tissues (muscle, adipose tissue, liver). To determine if different exercise prescriptions could exert differential metabolic benefits on insulin sensitive tissues, we compared two isocaloric programs; constant-moderate endurance (END) and high intensity interval training (HIIT), in a mouse model of diet-induced obesity.

Ten week-old male C57BL/6 mice were fed a high fat diet (HFD;45% kcal fat) *ab libitum* for 10 weeks achieving 25% excess weight, and for a further 10 weeks they then underwent isocaloric END or HIIT (3×40 min sessions/week). Untrained HFD and chow-fed mice acted as controls. After 20 weeks mice were sacrificed and *quadriceps* muscle, subcutaneous adipose tissue (SAT) and liver were extracted for analysis.

Results showed that END and HIIT did not change the body weight or the fat/lean mass proportion in HFD groups ($p > 0.05$). Interestingly, after an insulin tolerance test (0.65 IU/kg*BW), only HIIT improved insulin sensitivity in HFD mice ($p < 0.05$ versus untrained). In *quadriceps*, HFD induced a down-regulation of muscle high-molecular weight (HMW) adiponectin which was similarly normalized by END and HIIT. However, only HIIT was able to reverse the HFD-driven downregulation of adiponectin receptor 1 (AdipoR1; $p < 0.05$). In SAT, both exercise programs tended to decrease collagen VI (protein; $p = 0.08$), whereas HIIT induced an upregulation in transcription (3-fold vs HFD untrained) and translation (2-fold vs untrained) of UCP1. In liver, only END was able to reverse collagen I accumulation (2-fold; $p < 0.05$) and downregulation of CTGF (0.5-fold; protein) seen in HFD untrained mice ($p < 0.05$).

In the light of these results, HIIT seems to promote better systemic metabolic effects, which could be explained by the normalization of muscle AdipoR1 and higher UCP1 induction in SAT. However, END was more effective in normalizing liver changes, suggesting differential metabolic effects of END and HIIT in an obesity-context.

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SGLT-2 inhibitor induced sympathoinhibition: a novel mechanism for cardiorenal protection

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Background: Sympathetic nervous system (SNS) activation is a common feature in obesity and type-2 diabetes and regulates glucose metabolism in organs including the kidneys. The sodium glucose co-transporter 2 (SGLT-2) mediates re-absorption of glucose from the renal proximal tubules in the kidney. SGLT-2 inhibitors have garnered attention due to their glucose lowering effects and associated improvement in both cardiovascular and renal outcomes. We hypothesized that SGLT-2 inhibitor-induced alterations of SNS activation may contribute to these favorable effects.

Aims: Firstly, to investigate the hypothesis that SGLT-2 is upregulated by norepinephrine (NE), the main neurotransmitter of the SNS. Secondly, to determine whether SGLT-2 inhibition may reduce SNS activity *in vivo*. Thirdly, to assess whether the SGLT-2 inhibitor induced blood pressure reduction is mediated by alterations in SNS activity *in vivo*.

Methods: Human renal proximal tubule cells (HK2) were treated with NE and SGLT-2 expression was determined. We determined the influence of SGLT-2 inhibition with dapagliflozin (DAPA) on blood pressure levels in normotensive and hypertensive mice and also the SNS activity *in vivo*. Expression of NE and the sympathetic nerve protein tyrosine hydroxylase was measured in the kidney and heart.

Results: A marked increase in SGLT-2 and IL-6 expression in HK2 cells and translocation of SGLT2 to the cell surface could be demonstrated in response to NE treatment. *In vivo*, DAPA treatment resulted in marked glucosuria in high fat diet fed mice. Importantly, SGLT-2 inhibition *in vivo* significantly reduced blood pressure and this was associated with reduced NE and tyrosine hydroxylase levels in the kidney and heart.

Conclusions: Our *in vitro* and *in vivo* studies provide first evidence for an important cross-talk between the SNS and SGLT-2 regulation, which may not only account for SNS-induced alterations of glucose metabolism but may potentially contribute to cardiovascular and renal protection observed with SGLT2 inhibitors.

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