Exploring how compartment-specific changes in NAD biosynthesis influence the response to endurance training

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Introduction: Nicotinamide adenine dinucleotide (NAD) plays a vital role in the maintenance of health – as an energy carrier and as a critical substrate for major systemic regulators such as the sirtuins and PARPs. NAD levels decline with ageing and with metabolic and chronic disease states. Lifestyle intervention through diet and exercise, as well as pharmaceutical intervention targeting the NAD biosynthetic pathways, have been shown to rescue declining NAD levels. Restoration of NAD levels in various organisms associates with increased longevity and a return to youthful and healthy physical function.

Methods: Examining two mouse models of genetic upregulation of the NAD biosynthetic enzyme nicotinamide mononucleotide adenylyl transferase (NMNAT) to target nuclear (NMNAT1) and mitochondrial (NMNAT3) NAD upregulation, our group has previously observed alterations in metabolic processes and in muscle morphology in these animals. NMNAT1 $^{Tg/+}$ mice have a marked reduction in muscle mass while NMNAT3 $^{Tg/+}$ mice have improved hepatic metabolism. In the present investigation, both NMNAT1 and NMNAT3 mice and their respective wildtype littermates were exposed to a six week progressive overload endurance training programme, with endurance capacity and oral glucose tolerance (oGTT) assessed before and after the training period.

Results: Despite substantially reduced muscle mass in the transgenic group, both absolute performance and the relative performance improvement in response to training were not different between NMNAT1$^{Tg/+}$ and WT mice (147.7 ± 40.08 % and 136.6 ± 28.61 % improvement above basal, respectively; mean ± SEM, n = 9). The NMNAT$^{1Tg/+}$ group also displayed signs of improved glucose handling and insulin sensitivity as compared to their WT littermates. Absolute performance was lower overall for NMNAT3$^{Tg/+}$ compared to WT mice, although relative improvement in response to training was not significantly different (98.37 ± 36.07 % and 72.29 ± 20.51 % improvement above basal, respectively; n = 8). All groups showed either significant or strong trends towards reduced peak blood glucose levels during oGTT after the training intervention. Both NMNAT1$^{Tg/+}$ and the respective WT mice post exercise intervention displayed elevated insulin release associated with the peak blood glucose time point. In contrast, the NMNAT3$^{Tg/+}$ mice exhibited a high peak insulin release associated with the peak blood glucose time point, irrespective of the training intervention.

Conclusions: Our results suggest that the reduction in lean mass in NMNAT1$^{Tg/+}$ mice, which appears to be due primarily to a shift towards oxidative fibres as previously observed, does not result in a performance deficit or an inability to adapt to endurance training. Despite differences in the underlying metabolic phenotypes, both NMNAT1$^{Tg/+}$ and NMNAT3$^{Tg/+}$ mice adapted to training in a similar manner.