Distinct metabolic effects of elevated NAD biosynthesis in the nuclear or mitochondrial compartments

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NAD is an important cofactor for many biochemical reactions, and serves as an essential substrate for several classes of enzymes, including sirtuins. Synthesis of NAD occurs through de novo synthesis and a salvage pathway. In the salvage pathway the conversion of nicotinamide mononucleotide (NMN) to NAD is facilitated by the enzyme nicotinamide mononucleotide adenylyltransferase (NMNAT), which exists as 3 separate isoforms spread across different sub-cellular compartments. Pharmacologically increasing NAD biosynthesis improves the metabolic profile of obese and aged rodents, in part, by enhancing mitochondrial function. We have examined the metabolic phenotype of mice overexpressing the nuclear and mitochondrial NMNAT isoforms, NMNAT1 and NMNAT3 respectively, to determine if increasing rates of NAD biosynthesis in specific compartments confers any metabolic benefits.

Wildtype (WT) or transgenic (NMNAT1-TG or NMNAT3-TG) mice were maintained on a regular chow diet or fed a high-fat diet for 8-14 weeks. Overexpression of both NMNAT isoforms was confirmed by qPCR and Western blot across multiple tissues (*e.g.* muscle, kidney, liver, heart, brain). In nuclear and mitochondrial fractions, there was a substantial increase in NMNAT1 and NMNAT3 activity respectively, which correlated with an ~2-fold elevation in NAD^+ levels in these organelles. Compared to WT counterparts, NMNAT1-TG mice displayed a significant reduction in muscle mass on both diets, with a tendency for increased adiposity as measured by EchoMRI. Surprisingly, despite these alterations in body composition, NMNAT1-Tg mice exhibited improved glucose tolerance. In contrast, NMNAT3-TG mice had significantly reduced fat mass compared to WT mice on both a chow and high-fat diet. NMNAT3-TG mice also displayed significantly ($P<0.05$) improved glucose tolerance. NMNAT1 overexpression had limited impact on measures of oxidative metabolism in tissues, while respiration in isolated liver mitochondria and primary hepatocytes was increased by 40-60% in NMNAT3-TG mice compared to WT. Collectively, our findings reveal disparate whole-body and tissue-specific metabolic effects resulting from specific increases in NAD biosynthesis in the nucleus or mitochondria.