## Increasing nuclear $NAD^+$ biosynthesis alters skeletal muscle size and metabolism

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Nicotinamide adenine dinucleotide ($NAD^+$) is a ubiquitous metabolite involved in a multitude of reactions throughout the cell. The recent recognition that $NAD^+$ levels influence many processes in obesity and ageing has sparked a surge in interest in NAD biology. Nicotinamide mononucleotide adenylyltransferase (NMNAT) is a key enzyme of the $NAD^+$ salvage pathway, that catalyses the conversion of $NAD^+$ precursors to $NAD^+$, thus playing a major role in maintaining cellular $NAD^+$ concentrations. However little is known about the metabolic role of NMNATs or how changing $NAD^+$ levels *via* NMNAT manipulation alters metabolism.

In the current study we have examined transgenic mice overexpressing NMNAT1 (a NMNAT isoform residing in the nuclear compartment). Transgenic mice (NMNAT1Tg) and their wild-type littermates (WT) were administered a chow or high-fat diet (HFD) for 8 weeks, with NMNAT1Tg mice exhibiting no difference in fat accumulation, but a decreased lean mass on both diets, primarily as a result of a pronounced reduction (30-40%, $P<0.001$) in skeletal muscle mass. Immunohistochemical analysis of laminin-stained sections showed the reduced muscle size in NMNAT1Tg mice was due to smaller individual muscle fibres. Assessment of the mRNA expression of myosin heavy chain (MHC) isoforms indicated an oxidative shift in skeletal muscle, with a significant increase ($P<0.05$) in more oxidative MHC isoforms (MHC1, MHC2a), accompanied by a decrease ($P<0.01$) in fast MHC2b expression.

At the whole-body level, NMNAT1Tg mice displayed higher energy expenditure and improved glucose tolerance (ipGTT $p<0.01$) on both diets. When subjected to hyperinsulinaemic-euglycaemic clamps, NMNAT1Tg mice showed an increased whole-body glucose infusion rate ($P<0.05$), with a significantly elevated (40-80%, $P<0.05$) clearance of glucose into various skeletal muscles.

Overall our findings suggest that increasing $NAD^+$ biosynthesis in the nucleus has a profound influence on muscle size and metabolism, with further studies required to understand the molecular pathways and mechanisms involved.