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Title of project: Targeting SIRT 1 signaling pathways in skeletal muscle to promote metabolic health

ABSTRACT

The overarching goal of this project is to specifically target sirtuin 1 (SIRT1) signaling pathways in insulin resistant skeletal muscle using nicotinamide riboside (NR) and pterostilbene (PT) to determine the putative metabolic health-promoting benefits. The deacetylase SIRT1 has recently stirred interest in the field of metabolism due to its role in energy homeostasis. SIRT1 is upregulated with calorie restriction and can ameliorate insulin resistance and chronic low-grade inflammation. NR is a precursor for NAD+, which is an essential co-substrate for SIRT1. Moreover, based on molecular docking studies and molecular resemblance to resveratrol, PT is thought to allosterically activate SIRT1. Our preliminary data from mouse muscle incubated with NR/PT suggest an ability to promote additive/synergistic metabolic effects. Moreover, we have developed a mouse model in which NAD+ levels in skeletal muscle *in vivo* can be acutely elevated by 70-80%. Thus, we hypothesize that the combined treatment with NR/PT will promote additive effects on SIRT1 activity and related down-stream signaling events. In addition, we hypothesize that an exercise-induced increase in blood flow in skeletal muscle will increase the bioavailability of NR/PT in this tissue and promote SIRT1-mediated beneficial effects.
To validate NR/PT as SIRT1 activators and assess potential off-target effects of the compounds, we will study C2C12 cells and *ex vivo* incubated skeletal muscle from wildtype and muscle-specific *Sirt1* knockout mice. Moreover, we will perform long-term NR/PT supplementation studies in mice of both genotypes, with/without access to running wheels, and employ gold-standard techniques to determine NR/PT-related effects on insulin sensitivity and mitochondrial function.
Our findings will provide novel insight into the physiological and molecular mechanisms of SIRT1-activation, and may have the potential to aid in improving health span of people with metabolic disorders.

ABSTRAKT

Det overordnede mål med projektet er specifikt at modulere sirtuin 1 (SIRT1) signalering i insulinresistente skeletmuskler ved benyttelse af nicotinamid riboside (NR) og pterostilbene (PT), for at bestemme de formodede fordele for metabolisk sundhed. Deacetylasen SIRT1 har nyligt vækket interesse indenfor metabolismefeltet på grund af dens rolle i energihomeostasen. SIRT1 bliver opreguleret under kalorierestriktion og kan mildne insulinresistens og kronisk inflammation. NR er en prækursor til NAD+, hvilket er et essentielt co-substrat for SIRT1. Derudover formodes PT, baseret på molekylære docking studier og molekylær lighed med resveratrol, at aktivere SIRT1 allosterisk. Vores præliminære data fra muskler fra mus inkuberet med NR/PT indikerer en evne til at promovere additive/synergistiske metaboliske effekter. Derudover har vi udviklet en forsøgsmodel i mus hvor vi akut kan øge NAD+ niveauerne i skeletmuskler med 70-80 %. Vores

hypotese er derfor at den kombinerede behandling med NR/PT vil promovere additive effekter på SIRT1 aktivitet og relateret nedstrøms signalering. Derudover er vores hypotese at en trænings-induceret stigning i blodgennemstrømningen i skeletmusklerne vil øge biotilgængeligheden af NR/PT i dette væv og promovere SIRT1-medierede fordelagtige effekter yderligere.

For at validere NR/PT som SIRT1 aktivatorer og undersøge potentielle uspecifikke effekter, vil vi udføre forsøg i C2C12 celler og i inkuberede skeletmuskler fra vildtype og muskelspecifikke SIRT1 knockout mus. Derudover vil vi udføre længerevarende NR/PT supplementeringsstudier i mus af begge genotyper, med/uden adgang til løbehjul og benytte state-of-the-art teknikker til at bestemme NR/PT-relaterede effekter på insulinfølsomhed og mitrokondriel funktion.

Vores fund vil give ny indsigt i de fysiologiske og molekylære mekanismer relateret til SIRT1 aktivering, og kan potentielt hjælpe med at forbedre sundheden hos folk med metaboliske problemer.