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Title of project: Effect of repeated cold exposure on human brown adipose tissue function – can obesity induced whitening of brown fat be reversed to counteract type II diabetes ?

ABSTRACT

Brown adipose tissue (BAT) has the potential to counteract obesity and the metabolic complications associated herewith including type II diabetes in rodents and probably also humans. Knowledge of the molecular mechanisms associated with human brown fat recruitment is however currently lacking, and is essential to obtain if human BAT is to be targeted in future treatment strategies. We have recently observed that supraclavicular brown fat attains a more 'white fat- like' RNA profile in obese compared to lean individuals. With the current project our overall objective is to leverage the understanding of BAT whitening and recruitment in the context of human obesity and T2DM by performing a randomized repeated cooling trial of patients undergoing neck surgery. Specifically, we wish to investigate whether this obesity-induced whitening of BAT can be counteracted through repeated cold exposure (CE) and subsequent BAT stimulation, as well as the cellular mechanisms driving these processes. We also wish to explore the effect of repeated CE on the thermogenic function of the brown adipocytes and investigate the involved thermogenic pathways, including potential non-uncoupling protein 1 (UCP-1)-dependent pathways. We furthermore wish to investigate the potential epigenetic changes in human brown adipocytes associated with repeated cold exposure. We will address this by including 20 normal weight and 20 obese individuals scheduled for thyroid surgery and randomize them to daily cold exposure or control conditions in the window from booking of surgery to operation. We will obtain supraclavicular and subcutaneous fat biopsies during surgery and perform RNA sequencing, histology and isolation of both pre- and mature adipocytes. The study will provide completely novel insights into the regulation of human brown fat recruitment at the transcriptional level, thereby revealing potential pathways which can be targeted in future medical treatment strategies.

ABSTRAKT

Brunt fedtvæv (BAT) er et energiforbrugende væv med potentiale til at modvirke overvægt og hermed associerede sygdomme, herunder type II diabetes (T2DM). En medicinsk udnyttelse af disse egenskaber forudsætter dog en indsigt i humant BAT's egenskaber og regulering, som for nuværende er mangelfuld. Brunt fedtvæv aktiveres og kan rekrutteres ved kuldestimulering. Denne kuldeaktivering af BAT er nedsat i svært overvægtige individer samt patienter med T2DM, men de bagvedliggende mekanismer er uafklarede. Vi har for nyligt observeret at brunt fedtvæv antager en hvid fedtvævslignende RNA-signatur i svært overvægtige individer, mens de brune præ-fedt cellers funktion og tilstedeværelser er bevaret.
Det overordnede formål med dette projekt er således at undersøge reguleringen af humant brunt fedtvævsaktivitet i association med fedme og metabolisk sygdom ved at gennemføre et randomiseret kuldeforsøg i patienter, som er planlagt til en halskirurgisk procedure.

Vi ønsker specifikt at undersøge om den hvide fedtvævs-lignende profil observeret i BAT ved svær overvægt kan modvirkes ved gentagen kuldestimulering samt at identificere de underliggende cellulære mekanismer. Vi vil undersøge effekten af gentagen kuldestimulering på de brune adipocytters thermo-genetiske funktion og de involverede signalveje, herunder uncoupling protein 1 (UCP1)-uafhængige signaleringsveje og kuldeinducerede epigenestiske forandringer. Vi vil undersøge dette ved at indkludere 20 normalvægtige og 20 svært overvægtige patienter, som er planlagt til at gennemgå operation grundet benign thyroidea sygdom og randomisere dem til daglig kuldeeksponering eller en kontrolgruppe i tidsvinduet frem til selve operationen. Under operationen vil vi udtage supraklavikulære og subkutane fedtbiopsier, som skal karakteriseres ved hjælp af RNA-sekventering, immunhistokemi og etablering af cellekulturer fra både præ-adipocytter og modne adipocytter. Resultaterne vil give en unik og essentiel indsigt i reguleringen af humant brunt fedtvæv, hvilket kan bidraget til udnyttelse af vævet som et mål for fremtidige medicinske interventioner.