M.J.W. Hanssen, PhD

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Maastricht University,
Maastricht

Promotores:
Prof. W.D. van Marken Lichtenbelt, PhD
Prof. P. Schrauwen, PhD
Prof. F.M. Mottaghy, MD, PhD

Cold cure for type 2 diabetes: role of brown adipose tissue and skeletal muscle in glucose metabolism

Background

The prevalence of type 2 diabetes has increased dramatically in recent decades, especially due to a strong increase in the number of people suffering from obesity. Currently, ~6.4% of the world population is affected by type 2 diabetes and this number is still growing rapidly. Type 2 diabetes is generally caused by a reduced sensitivity for insulin (i.e. insulin resistance) and is characterised by elevated blood glucose levels. The health impact of diabetes is substantial, and it is a major risk factor for the development of other comorbidities, especially cardiovascular complications.

Brown adipose tissue

Brown adipose tissue (BAT) is an attractive target tissue that can potentially be exploited in the fight against obesity and type 2 diabetes. BAT has the unique capacity to dissipate energy from glucose and fat oxidation as heat. This heat generating capacity of BAT becomes particularly apparent when individuals are exposed to cold, when BAT thermogenesis is activated to help maintain a constant core body temperature. The surplus of energy that is expended this way contributes to increased whole-body energy expenditure, may therefore be very beneficial to create a negative energy balance and hence induce weight loss. In addition, upon activation BAT oxidises large amounts of glucose, which leads to enhanced glucose clearance from the circulation. This may be especially beneficial in a diabetic situation. In my thesis, we explored the role of human BAT in the pathophysiology and treatment of type 2 diabetes.

The current gold standard for assessing BAT activity/glucose uptake in humans is by means of ^{18}F-FDG PET/CT scanning upon acute cold exposure. For this purpose, individuals are gradually cooled, using a water-perfused suit, until they experience shivering and are then slightly re-heated until shivering disappears. As such, maximal non-shivering thermogenic conditions are achieved. Hereafter, ^{18}F-FDG is injected followed by either a dynamic (60 minutes, supraclavicular BAT area) or a static (6 to 7 bed positions covering skull to abdomen, 4 min/bed position) PET/CT scanning protocol. By using this protocol, we previously showed that cold-induced BAT activity is present in nearly 100% of young, healthy adults (1).

To address whether insulin resistance may hamper the capacity of BAT to internalise glucose upon cold exposure, we employed a prolonged-fasting (54 hours) model in young healthy individuals. Prolonged fasting is known to induce insulin resistance in peripheral tissues, such as BAT, in order to spare glucose for the brain. This approach was chosen to eliminate the confounding effects of obesity and high age (which are present in most type 2 diabetes patients) on BAT glucose uptake capacity, as had been shown previously (2, 3). We showed that fasting-induced insulin resistance markedly reduced cold-induced glucose uptake in BAT. Two-tissue compartment modelling revealed that this reduction was due to decreased cellular glucose uptake in BAT, and not due to decreased glucose supply (4). Based on these results it might be expected that in other insulin resistant conditions, cold-stimulated glucose uptake into BAT is impaired as well.

If BAT activity is indeed impaired in type 2 diabetes, increasing its presence and activity may result in improved metabolic health, due to greater glucose clearance capacity by BAT. We therefore investigated whether BAT could be recruited in obese individuals and type 2 diabetes patients by means of prolonged intermittent mild cold exposure (10 days, 6 h/day, 15°C; i.e. cold acclimation), as had previously been shown in young, lean subjects (5), and whether this would subsequently impact glucose metabolism. Indeed, cold acclimation led to significant BAT recruitment in both obese subjects and type 2 diabetes patients, although even after cold acclimation BAT activity was still relatively low in the type 2 diabetes patients (see figure).

Skeletal muscle

Surprisingly, ten days of cold acclimation led to a very marked ~40% increase in insulin sensitivity, as assessed by

hyperinsulinemic-euglycemic clamps, in the type 2 diabetes patients. Although the increase in BAT may have contributed to these effects, it is likely that changes in skeletal muscle glucose handling accounted for the major portion of these improvements, as skeletal muscle is the major site for glucose disposal under insulin stimulated conditions. Indeed, in skeletal muscle biopsies we discovered a very pronounced increase in basal GLUT4 translocation from the cytosol to the sarcolemma in order to facilitate glucose uptake. As a consequence, we also noticed that acute cold-induced ^{18}F-FDG uptake into skeletal muscle was increased after the cold acclimation period (6). These findings in type 2 diabetes patients were also confirmed in biopsies and ^{18}F-FDG PET scans in the obese subjects (7).

The studies described in this thesis provide important insight into the role of BAT and skeletal muscle in glucose metabolism upon cold exposure. Prolonged mild cold exposure impacts metabolic activity of both tissues and subsequently improves metabolic health. These findings open up a new therapeutic window for the prevention and treatment of type 2 diabetes and associated metabolic conditions.

mjw.hanssen@maastrichtuniversity.nl

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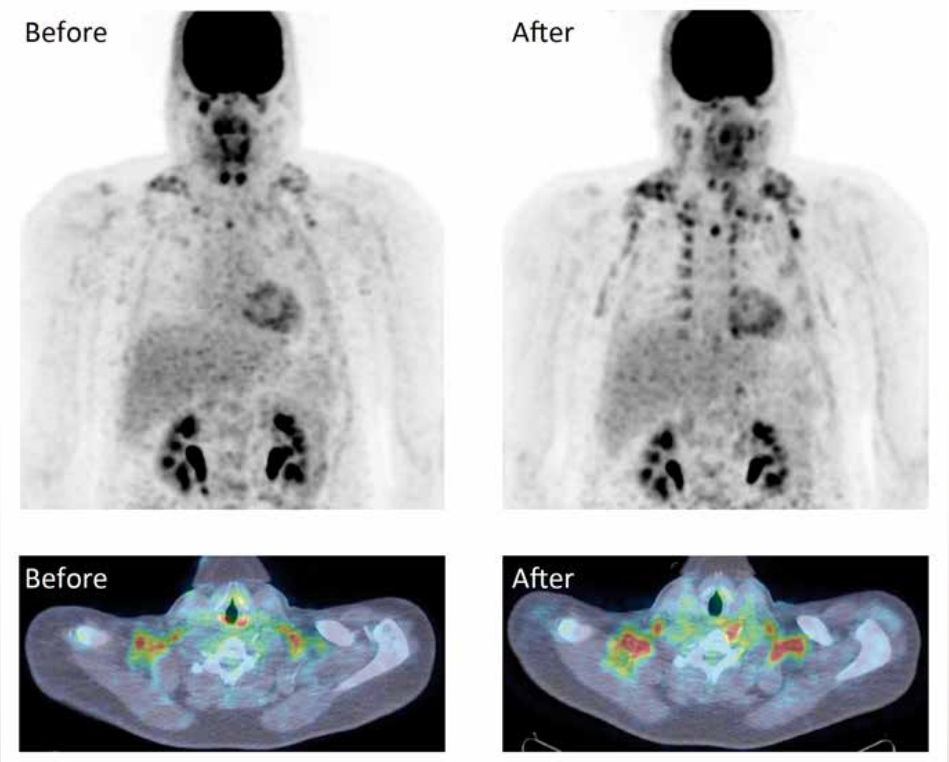

Top: upper-body ^{18}F-FDG PET/CT image of an obese subject exposed to mild cold, before (left) and after (right) ten days of cold acclimation; Bottom: transverse PET/CT fusion slices of the supraclavicular region showing ^{18}F-FDG uptake in BAT locations upon exposure to mild cold, before (left) and after (right) ten days of cold acclimation.