Valorisation
Social relevance – obesity epidemic

Currently, the world is facing an alarming increase of obesity prevalence, which extents to developing countries and obesity is thus not longer regarded as a typical Western disease. Obesity prevalence has nearly doubled since 1980, and in 2008 more than 1.4 billion adults were overweight of whom 200 million men and 300 million women were obese. Strikingly, more than 40 million children under the age of five are obese. In the Netherlands, 48.5% of the people (19 years and older) are overweight and 12.7% are obese. The future perspectives on the development of obesity are disturbing since it is predicted that obesity prevalence will increase with 33% (in the United States) in the next two decades. This is an alarming trend as obesity is related to metabolic diseases such as type 2 diabetes, cardiovascular diseases, and certain forms of cancer. Furthermore, this will further hinder efforts for healthcare cost containment. Therefore, strategies are warranted to counteract this global obesity epidemic. The overall aim of brown adipose tissue (BAT) research is to explore its role in the development, prevention, and treatment of obesity. This thesis investigated possible strategies to activate BAT in humans and examine its role in energy expenditure.

Scientific background – development of obesity

Obesity develops as a consequence of a positive energy balance in which energy intake exceeds energy expenditure. To restore and/or maintain a healthy energy balance, one could reduce energy intake or increase energy expenditure. Reduction of energy intake by diet is one of the most studied interventions, however this type of intervention has a high relapse rate and people thus often cannot maintain their initial weight loss. On the other hand, stimulating energy expenditure could be a plausible alternative to restore a healthy energy balance. Physical activity or exercise is one of the most used strategies to induce weight loss by increasing energy expenditure. Again, even though exercise promotes healthier outcomes in relation to the metabolic syndrome, people often have difficulties maintaining regular exercise regimes and its role on weight loss is therefore limited. Moreover, in certain circumstances people are not able to perform physical exercise. Finding alternative strategies to increase energy expenditure are therefore important. Notably, even slight increases in energy expenditure can have effects on energy balance in the long run. One way to increase energy expenditure is cold exposure. Slight reductions in ambient temperature can already increase energy expenditure with 5-30% in humans without inducing shivering. An important tissue in mediating this is BAT.

In small mammals, BAT is the most important organ to maintain body temperature, and moreover, it has been suggested that it is directly involved in energy balance regulation. Interestingly, mice without BAT tend to become obese. The recent
observations that BAT is still present in considerable amounts in humans, has driven human BAT research in the last 5 years. Findings thus far demonstrate that there is a negative relationship between BAT and adiposity, indicating overweight and obese people to have less active BAT. Thus BAT might play a role in weight regulation in humans as well. In this thesis we explored whether human BAT is involved in burning excessive caloric intake. The other goal was to find ways to activate BAT in humans and explore its relationship with energy expenditure. There is now strong evidence that BAT contributes to cold-induced energy expenditure, as confirmed in the present thesis. Therefore, BAT might have potential in targeting the current obesity problem, and therefore more research in humans is required.

**Target groups**

Finding strategies to prevent and treat obesity are crucial given the development of associated metabolic diseases affecting millions of people worldwide leading to exploding healthcare costs. Therefore, the search for novel strategies to counteract obesity is important for the general public, especially for people that have an increased risk in developing overweight and obesity. Stimulating energy expenditure by activating and recruitment of BAT could be one such strategy.

In order to tackle overweight and obesity, health institutions, health care professionals, and general society need to be informed about possible strategies. Translation of scientific knowledge to society is therefore essential. In this thesis we clearly demonstrate that cold exposure increases energy expenditure and BAT activity. This activation of BAT thermogenesis occurs at relatively low temperatures when shivering is absent. Recent research demonstrates that mild reductions in temperature can already activate BAT. This means that lowering ambient temperature in houses and offices might be one way to burn calories. Clearly, more research is needed to generate conclusive results about the potential of this intervention in stimulating weight loss. Nevertheless, in order to stimulate the translation of science to society and obtain awareness and support from the general public, communicating these observations outside science is important.

Next to this behavioural intervention to target overweight and obesity, pharmaceutical interventions stimulating energy expenditure and BAT activity are important. Targeting BAT via pharmaceutical agents requires a good understanding of BAT physiology and the molecular pathways that lead to BAT stimulation. Human BAT research is therefore essential, as well as a good collaboration between universities and the pharmaceutical industry. This thesis contributes to a better understanding of human BAT physiology and strategies to pharmaceutically target human BAT.
Activities and products

All research described in this thesis has been conducted at the department of Human Biology in collaboration with Nuclear Medicine of Maastricht University Medical Center+. This collaboration between the University and a hospital is a good example of how basic science can be performed in a hospital setting, combining knowledge of scientists and medical specialists. This collaboration is essential given that the current technique to measure human BAT requires the knowledge of nuclear medical specialists. BAT is currently measured by means of $^{18}$F-fluorodeoxyglucose-positron emission tomography-computed tomography ($^{18}$F-FDG-PET-CT)-scanning. In order to increase the knowledge on human BAT, good collaboration between hospital and university setting is essential.

In order to use BAT as a possible treatment for overweight and obesity, more extensive knowledge is required. The present findings do indicate that the most effective way to activate BAT in humans is by exposure to mild cold. As explained previously, reduction of ambient temperature in houses and offices is therefore a strategy to increase energy expenditure via BAT. With respect to the pharmaceutical approach, this thesis clearly demonstrated that systemic, non-selective adrenergic stimulation of BAT is ineffective in humans. Furthermore, the associated cardiovascular stress (i.e. increased heart rate and systolic blood pressure) is problematic using these types of stimulants. Therefore, future studies should investigate more selective $\beta$-AR agonists that could target BAT, such as the $\beta_3$-AR, without causing these side effects. Moreover, non-adrenergic agents and agents that are able to stimulate BAT centrally (i.e. via the brain) instead of systemically (i.e. via the blood) might be more effective. Recent studies in rodents indicate the potential ways to stimulate this tissue and should be investigated in humans.

The results described in this thesis are written in original articles that have been published or submitted to scientific journals in the field of obesity and diabetes. Moreover, these articles can be found online and are accessible to scientists who are interested in this topic. In addition to this, results have been presented on international conferences and some have been published in a national newspaper. The present results help to understand BAT physiology in humans and can be used for future studies on exploring strategies to stimulate BAT in humans.

Innovation

The work described in this thesis is mostly new in the field of BAT research. Prof. dr. W.D. van Marken Lichtenbelt was among the first researchers to rediscover BAT in human adults in 2009, and more BAT researchers joined his group from then onwards.
This thesis confirms the experiments in 2009 showing that cold exposure is an effective strategy to activate human BAT. The innovative part of this thesis was to explore other strategies to activate human BAT. The experiment on β-AR stimulation of BAT in humans was the first to investigate a possible role for BAT in the well-known adrenergic stimulation of thermogenesis. Furthermore, it was the first to explore the role of the sympathetic nervous system and the adrenergic receptors in stimulating human BAT in vivo.

Moreover, in this thesis we explored whether human BAT is involved in weight regulation by burning excessive caloric intake. That BAT could play a role in weight regulation has been demonstrated in animals. In this thesis it appeared that BAT was indeed activated upon a single high calorie meal, although no direct relationship between postprandial BAT activity and diet-induced thermogenesis was found. These findings suggest that BAT might be activated after excessive food intake, but whether it actively burns calories and to what extent remains to be found out. Clearly, more evidence is needed to confirm whether BAT can burn excessive caloric intake.

Animal studies have provided several strategies to recruit BAT in white adipose tissue, as explained in chapter 2. We here tested one of these promising strategies in humans, namely endurance exercise. The finding in mice that endurance exercise can recruit BAT via the hormone irisin was not confirmed in human adults. Regular endurance training was not associated with increased browning of white adipose tissue and seems to result in even less BAT activity.

Planning and realization

In this thesis we measured BAT activity in humans during several interventions by means of [18F]FDG-PET-CT-scanning. We have clearly demonstrated that cold exposure is the most effective way to activate BAT in humans. Recently our lab has demonstrated that BAT can also be recruited upon longer periods of cold exposure in healthy human adults with a concomitant increase in the capacity for nonshivering thermogenesis. This effect of cold acclimatization on BAT and nonshivering thermogenesis is now being explored in obese and type 2 diabetic people by the research team of Prof. dr. W.D. van Marken Lichtenbelt. As explained before, finding alternative ways to activate and recruit human BAT are important. Currently the effects of bile acids on human BAT are being conducted at the department of Human Biology and Nuclear Medicine. Another important step will be to further explore the role of BAT during situations of overfeeding.

From a methodological point of view, it will be important to find alternatives to [18F]FDG-PET-CT-scanning for BAT measurement in the future. First, because it is a very expensive technique, and second, it is associated with a radioactive burden for the study participants, which also limits the amount of scans that can be used per subject.
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For longitudinal studies on human BAT, it will be important to find less invasive methods. Another important aspect is that $^{18}$F-FDG-PET-CT solely measures glucose uptake and not oxidative metabolism in BAT. An important future step is to gain more knowledge about the heat producing capacity of BAT during several conditions of stimulation. Therefore measuring oxidative metabolism in BAT will be important. Such a measurement provides more information to what extent full BAT activation can contribute to total daily metabolism and ultimately weight loss.

Finally, future research should also examine the effects of long term BAT stimulation on energy balance and measure whether or not the human body adapts to this continuous stimulation of energy expenditure, for instance by increase energy intake.