Cold cure for type 2 diabetes

Valorization

Relevance

The worldwide prevalence of overweight and obesity has reached epidemic proportions in recent decades. According to the World Health Organization, more than 1.9 billion adults are currently considered overweight, and 600 million of these are obese. This equals 39% and 13%, respectively, of the world's adult population. In the Netherlands, these numbers are slightly higher, with ~48% of the Dutch adult population being overweight, and ~13% being obese. Several other western countries show even more dramatic records: In the US, over two third of the population is considered overweight, while over a third suffers from obesity. This high obesity prevalence is the main cause for a dramatically increased incidence and prevalence of type 2 diabetes during the past decades. Currently, ~6.4% of the world's population is affected by this disease. Until a couple of decades ago, type 2 diabetes was especially known as "diabetes of the elderly", since high age was the main risk factor for developing this condition. However, rising (childhood-)obesity rates have caused increased type 2 diabetes incidence in all age categories, and is now even ever more diagnosed in teenagers and young adults. This is especially worrisome, since diabetes may cause several other long-term complications such as end-stage renal disease, myocardial infarction and cerebrovascular stroke, reduction of quality of life and reduced overall life expectancy with 5-10 years. Thus, increased diabetes prevalence inevitably impacts health care systems around the globe. As a consequence of this increased health care burden, the economic costs of type 2 diabetes are rising as well. In the US alone, it was estimated that the total economic costs of diagnosed diabetes in 2012 were $245 billion, which represents a staggering increase of 41% compared to estimations of these costs in 2007. In other words, 1 in 5 health care dollars in the US are currently spend on diabetes care. Since similar trends are ongoing globally, it is projected that type 2 diabetes-related health care costs will continue to grow in the coming years as well.

Successful strategies to counteract obesity and type 2 diabetes include diet and exercise programs. However, despite their proven efficacy, these lifestyle interventions remain very challenging to implement in the general population. Therefore, therapeutic alternatives need to be evaluated. In this thesis, we explored the role of brown adipose tissue (BAT) in the pathophysiology of type 2 diabetes and determined whether cold-induced BAT activation can be exploited as

novel means to increase energy expenditure and glucose disposal, and thereby counteract obesity and type 2 diabetes.

Target group

The main target groups that may benefit from novel BAT-centered therapies are subjects that are currently being overweight/obese or diagnosed with type 2 diabetes or associated metabolic conditions. In addition, individuals that are at increased risk for the development of type 2 diabetes (e.g. through genetic predisposition) may benefits from such therapies. As such, it is essential to translate our scientific knowledge to the general population. In this thesis, we clearly demonstrated that lowering ambient temperature results in enhanced energy expenditure. In addition, prolonged exposure to such lower ambient temperatures greatly improved insulin sensitivity, which may translate into lower blood glucose levels in type 2 diabetes patients on the long term. Thus, lowering housing and office temperatures may represent a simple, but very effective means to improve metabolic health in the general population. At this moment, more research is required in other population groups and it should be determined whether compliance and metabolic improvements persist during more long-term intervention periods. Nonetheless, it is essential to communicate these observations to the general public outside science, in order to create general awareness and support and to achieve our desired health effects.

Pharmaceutical and food companies could also play a major role in the development of BAT-centered therapies to combat obesity and type 2 diabetes. In this thesis, we determined that serum FGF21 concentrations were positively correlated to BAT activity in young, healthy individuals. Thus, FGF21 analogs may in fact be able to stimulate BAT and thereby have favorable effects on metabolic health, which has also been suggested from rodent studies, Such positive effects of FGF21 analogue drugs may also be achieved in humans.
We also studied the effect of 6-weeks L-arginine (an α-amino acid) supplementation on BAT activity, but found to changes herein. Some food components, notably capsaicin-related compounds found in chili peppers, have been suggested to activate BAT in previous studies. It is highly relevant to evaluate whether other food component exert similar stimulatory effects on BAT; these can subsequently be included in dietary regimens to provide additional metabolic

benefits through the activation of BAT.

Activities and products

All studies described in this thesis were conducted at the Department of Human Biology and Human Movement Sciences in close collaboration with the Department of Nuclear Medicine of Maastricht University Medical Center. Their expertise with respect to [^{18}F]FDG-PET/CT scanning was essential for us in order to visualize and quantify BAT activity in vivo. This collaboration between basic physiologists from the university and medical specialist from the academic hospital is a good example of how basic science can be performed in the clinic. In addition, such a collaborative, multi-disciplinary approach opens up the doors for an effective translational medicine working environment.
The results presented in this thesis are described in original articles that have been published or submitted to peer-reviewed scientific medical journals. Importantly, these articles can be accesses online and can be used by other researchers in this field and others who are interested in this topic. Furthermore, our results have been presented to the scientific community at several (inter)national conferences and have been communicated to the general public through several national mass media (newspapers, radio, tv).

Innovation

Since the 'rediscovery' of BAT in adult humans in 2009, scientific interest in BAT as a novel tool to combat obesity and type 2 diabetes has increased exponentially. Our research group was among the first to show that young, lean adults possessed significant amounts of functionally active BAT, by exposing individuals to mild cold temperatures and subsequently visualizing BAT activity by means of [^{18}F]FDG-PET/CT scanning. In addition, our group has shown that prolonged intermittent cold exposure (i.e. cold acclimation) is an effective method to enhance BAT quantity and activity in young, lean adults. In this thesis, we now show that also in obese subjects, BAT can be recruited by means of cold acclimation. In addition, we show for the first time that cold acclimation results in very remarkable improvements in insulin sensitivity in patients with type 2 diabetes, although it is unlikely that these improvements can be attributed to the minimal increase in BAT activity that we observed in these patients. However, we did find very pronounced

effects of cold acclimation on skeletal muscle GLUT4 protein localization, which may explain the remarkable effects on insulin sensitivity. We were the first to describe such effects in humans, and these findings represent a solid base for future studies investigating the effects of mild cold on skeletal muscle glucose metabolism.

Furthermore, in this thesis we explored alternative methods to expand the BAT depot in individuals of Caucasian and South Asian descent. Specifically, we tested whether L-arginine supplementation would lead to BAT recruitment. Unfortunately, we did not observe any significant effects of L-arginine on BAT in either ethnicity. However, we did observe an interesting other phenomenon during this study, again residing in skeletal muscle: muscle oxidative capacity was significantly lower in South Asians than in Caucasians. Such functional skeletal muscle mitochondrial impairments had never been reported yet, but could play a vital role in the enhanced susceptibility of South Asians to develop obesity and type 2 diabetes compared to Caucasians. These results also raise the question whether improving muscle mitochondrial function specifically in South Asians could subsequently lead to improvements in their metabolic profile. This could be subject of future studies.

In this thesis we also explored the role FGF21 in BAT activity, and observed a positive relationship between circulating FGF21 levels and BAT activity in young, healthy subjects. Thus, increasing FGF21 levels or enhancing FGF21 sensitivity may represent a novel means to enhance BAT activity. Whether this is indeed the case, and whether this may subsequently impact metabolic health, could be subject of future studies.

Planning and realization

In this thesis we clearly demonstrated that short-term cold acclimation can have a major impact on metabolic health. It remains to be elucidates, however, to what extent BAT contributed to these metabolic improvements, as we noticed only a relatively small effect of cold acclimation on BAT in type 2 diabetes patients, whereas they showed very pronounced improvements in whole-body insulin sensitivity. Our data strongly suggests that skeletal muscle plays a major in these improvements. Our research group is currently investigating in more detail how skeletal muscle glucose metabolism is affected by cold exposure and cold acclimation, and whether cold acclimation also affects lipid metabolism. In

addition, it is being explored whether the positive effects on insulin sensitivity persist several weeks after the cold acclimation period.

As stated above, it is highly important to quantify in more detail to what extent BAT actually contributes to whole body energy expenditure and glucose and lipid metabolism. To study this, alternative radioactive tracers, such as ^{15}O and [^{18}F]FTHA, may be used to study oxygen metabolism and free fatty acid uptake, respectively, in BAT upon activation. In addition, novel tracers may be developed to measure incorporation of free fatty acids from circulation triglycerides into brown adipocytes. Ideally, a combination of such tracers is used in each individual under similar cold-exposed circumstances, in combination with whole-body energy expenditure measurements, to get a complete picture of BAT metabolism in relation to whole-body metabolism. However, this poses several insurmountable practical issues, as well as increased radioactive exposure for test subjects. The latter point may be partly overcome by using alternative methods to visualize BAT. In this respect, our research group has investigated the potential use of MRI to identify BAT. Although the initial results were promising, more research is necessary at this point in order for MRI to compete with the current "golden standard" [^{18}F]FDG-PET/CT scanning to quantify BAT presence and activity.

Another important aspect in BAT research at this moment is the identification of other strategies, besides cold exposure, to activate BAT in humans. Our research group recently showed that the bile acid CDCA may activate BAT, although to a much lesser extent than cold exposure. Other studies have shown that the β_3-agonistic drug Mirabegron activates BAT to a similar extent as cold exposure. However, such drugs may have substantial cardiovascular side effects, especially in individuals at increased risk for such comorbidities (i.e. obese or type 2 diabetes patients). It is therefore crucial to identify other ways to activate BAT in humans, and to determine whether these strategies impact metabolic health, without imposing other negative side effects.

Finally, future studies should also focus on the effects of long term BAT stimulation on energy and substrate metabolism. The cold acclimation periods that we used in our studies were relatively short and intense (10 days, 6 hours/day), and it would thus be interesting to investigate the effects of longer, less intense intervention periods. Such studies are necessary to determine how the human body adapts to a continuous cold stimulus, both physiologically and psychologically, and whether compensation mechanisms, such as increasing energy intake, may take place.