Mechanisms of cold-induced improvements in glucose homeostasis

Impact

What is the main aim of the research described in the thesis and what are the most important results and conclusions?

Repeated cold exposure (or cold acclimation as it is called in science) has presented itself as a new way to help patients with type 2 diabetes mellitus (T2DM) maintain their blood glucose levels within normal boundaries. This glucose homeostasis appears to be primarily caused by an increased glucose uptake from the blood by skeletal muscle, as was shown by (clinical) studies performed by our own research group, as well as by others (**Chapter 2**). To this day, it is unknown how cold exposure enhances glucose uptake by skeletal muscle. The main aim of this thesis was to investigate two potential mechanisms how repeated exposure to cold enhances skeletal muscle glucose uptake and improves glucose homeostasis.

One potential mechanism through which cold could have its beneficial metabolic effects, is via activation of a specific part of the nervous system named the sympathetic nervous system, which also controls the well-known fight-or-flight response. Cold exposure is known to stimulate this part of the nervous system, in order to defend core body temperature. Activation of the sympathetic nervous system causes the release of the hormone norepinephrine onto skeletal muscle cells, which can stimulate specific receptors better known as the β_2-adrenergic receptors (β_2-ARs). In cultured muscle cells, it has previously been shown that compounds with the ability to activate these receptors (so-called β_2-agonists), can stimulate glucose uptake. However, it was unknown whether this effect could also occur *in vivo*. In **Chapter 3**, we therefore treated obese, insulin-resistant mice, with the β_2-agonist clenbuterol and investigated skeletal muscle glucose uptake, as well as whole-body glucose homeostasis. Interestingly, we found that clenbuterol treatment improved skeletal muscle glucose uptake and also whole-body glucose homeostasis in these mice.

Although clenbuterol mainly activates β_2-ARs, it also has some affinity for β_1- and β_3-ARs. As these receptors are present on several other tissues influencing blood glucose levels, the possibility exists that other tissues than muscle contribute to the improvements in whole-body glucose homeostasis described in **Chapter 3**. An important tissue in this context is the brown adipose tissue (BAT), which is capable of taking up large amounts of glucose from the blood once it is activated upon cold, via β_1- and β_3-ARs. In contrast to rodents however, it is known that (especially obese) humans have low amounts of BAT. It is therefore important to investigate if the results described in **Chapter 3** are dependent on BAT, as otherwise similar effects might not be achieved in humans. In **Chapter 4**, we therefore investigated the effects of clenbuterol treatment in obese mice that have non-

functional BAT. Also in these mice, clenbuterol was able to improve glucose homeostasis, suggesting that BAT is not essential for these beneficial effects.

After these studies in mice, we next investigated if activation of the β_2-AR could also improve skeletal muscle glucose uptake in humans (**Chapter 5**). For this study, we treated healthy, young, male subjects with clenbuterol for two weeks and subsequently measured insulin-stimulated skeletal muscle glucose uptake. In line with the results found in mice (**Chapter 3** and **Chapter 4**), clenbuterol could also enhance insulin-stimulated skeletal muscle glucose uptake in humans, although it remains unknown how this exactly works inside the skeletal muscle. Combined, the animal and human studies described in this thesis demonstrate that activation of β_2-AR could potentially be used as a therapy to improve glucose homeostasis in patients diagnosed with T2DM. However, future studies in T2DM patients are required to further explore the therapeutic potential of β_2-agonist treatment.

The second potential mechanism for the improved glucose regulation upon cold exposure is the occurrence of shivering. When the body loses a lot of heat during cold exposure, it will start to produce extra heat via involuntary muscle contractions, a phenomenon known as shivering. Muscle contractions are known to enhance skeletal muscle glucose uptake and hence, some level of (mild) shivering or muscle activity may be involved in improving glucose homeostasis upon repeated cold exposure. However, it has never been directly tested whether cold exposure with shivering can improve glucose homeostasis in humans. In **Chapter 6** of this thesis, we therefore exposed overweight/obese individuals to shivering via cold exposure for 10 days, with at least 1 hour of shivering per day. Interestingly, the 10 days of cold exposure with shivering not only led to improvements in glucose tolerance, but also in blood lipid content and blood pressure. However, the exact mechanisms responsible for these effects are still not known. Nevertheless, the results of this study indicate that shivering could potentially be a way by which cold exposure improves glucose homeostasis.

What is the contribution of the results from this research to science and social challenges?

The number of people diagnosed with T2DM has increased tremendously over the past few decades. As T2DM is well-known to increase the risk for the development of other diseases, the latter creates an extraordinary economic burden for health care funds and society itself, as well as reduces the quality of life of millions of people. Finding new ways to treat patients with T2DM is therefore highly important to improve the global quality of life, alleviate the immense pressure currently experienced by the health care system, and help lower ever-increasing costs of health care.

This thesis contributes to this search for new ways to improve glucose homeostasis and highlights an alternative lifestyle strategy for people at risk for, or patients with, T2DM. It is however important for future research to determine the frequency and intensity by which patients should be exposed to cold to maximally improve glucose homeostasis. The outcomes of the research described in this thesis also shed some light on the potential physiological mechanisms through which cold exposure improves skeletal muscle glucose uptake and glucose homeostasis in humans. Since not all relevant target groups could be studied in the context of this thesis and since not all findings could be mechanistically explained, this thesis also provides a foundation for other researchers to further investigate the effects of cold exposure or activation of β_2-ARs on glucose homeostasis.

To whom are the research results interesting and/or relevant?

The outcomes of the studies described in this thesis are primarily interesting for other researchers within the field of metabolism and/or diabetes, as this newly generated knowledge provides additional information with respect to the effects of cold exposure on glucose homeostasis. The results described in this thesis will be published in scientific journals in order for this information to become available to these researchers. In addition, the research results will be highlighted at various national and international congresses within the field of metabolism, which are visited by researchers all over the globe. Individuals that participated in these clinical studies will also be informed about the results by means of special participant events, as well as internet and social media.

Besides other researchers, these results could also be interesting for the pharmaceutical industry, as future research within this field could potentially identify new targets for drug development. The development of these drugs could provide T2DM patients with a whole new class of medication to improve their disease state. In addition, the outcomes of the studies described in this thesis could potentially lead to the foundation of new companies providing cold exposure therapy to T2DM patients. The results are also interesting for individuals with prediabetes or T2DM patients, as it could provide them with additional knowledge on how to improve their disease state. The outcomes of the studies described in this thesis could also potentially contribute to new lifestyle advices for T2DM patients, thereby also making these results interesting for general practitioners or lifestyle coaches. Finally, these results may also be of interest for policy makers, as it may indicate that lowering ambient temperature (e.g. in offices) may not only be favourable to minimize energy consumption, but may also have beneficial health effects.