

Endocrine regulation of lipid mobilization in human obesity

Citation for published version (APA):

Verboven, K. (2017). *Endocrine regulation of lipid mobilization in human obesity: unraveling the role of atrial natriuretic peptide*. [Doctoral Thesis, Maastricht University]. Universiteit Hasselt en Maastricht University. <https://doi.org/10.26481/dis.20170703kv>

Document status and date:

Published: 01/01/2017

DOI:

[10.26481/dis.20170703kv](https://doi.org/10.26481/dis.20170703kv)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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ADDENDUM

Valorisation

The present thesis describes the potential of targeting the endocrine regulation of adipocyte lipolysis in human obesity treatment and prevention. An appropriate adipose tissue lipid metabolism is imperative to maintain normal adipose tissue function in human metabolically compromised conditions like obesity or type 2 diabetes mellitus. The valorization potential of the current results will be described in terms of social and economic relevance and implications for specific target groups and future innovative development.

Social and economic relevance of the obesity epidemic

Currently, our society is facing an alarming increase of overweight and obesity prevalence, which even extends to developing countries. According to latest statistics of the World Health Organisation (2014), Europe had the second highest proportion of individuals with overweight or obesity, preceded by the Americas. In Belgium and the Netherlands, 67% and 49% of the adult population deals with overweight and even 22% and 14% are diagnosed with obesity, respectively. The future perspectives on the development of obesity are disconcerting since it is predicted that the number of individuals with obesity will increase even more in the next two decades. This is a perplexing trend as individuals with obesity are more prone to develop metabolic diseases, cardiovascular diseases, mental disorders and certain types of cancer. Moreover, obesity (together with obesity-related complications) will further hamper efforts for healthcare cost management and thus not only affects public health but also has major socio-economic consequences. Therefore, new or optimized strategies for treatment and prevention are warranted to counteract this global obesity epidemic. Obtaining more insights into the adipose tissue physiology, and in particular adipose tissue lipid metabolism, is crucial with respect to treatment optimization and therefore was the main focus of the current thesis.

Development of obesity and obesity-related health complications

Obesity results from a chronic positive energy balance in which energy intake exceeds energy expenditure. Consequently, the energy surplus is stored within the adipose tissue, which gradually expands and may result in adipose tissue dysfunction. The main pillars of restoring the energy balance are reducing energy intake in relation to energy expenditure and increasing energy

expenditure. However, despite diet intervention being one of the most studied interventions in obesity treatment, many people often cannot maintain their initial weight loss due to a high relapse (weight regain) rate in this type of interventions. Contrarily, stimulating energy expenditure could be a suitable alternative to restore or even create a negative energy balance, in which increased physical activity or exercise is a common used strategy. Despite the efficacy of exercise, with respect to induce weight loss and promote healthier metabolic outcomes, many people often have difficulties maintaining regular physical activity regimes in their everyday life, ultimately limiting weight loss and in particular limiting weight maintenance after weight loss. Furthermore, the observed biomechanical anomalies often present in the obese state frequently hamper the ability to perform physical exercise. Developing alternative (combinational) strategies to improve clinical efficacy (i.e. maximizing weight loss and restoring metabolic complications) in the obese state are therefore imperative. With respect to weight loss, the stimulation of adipocyte lipolysis, a physiological process that is tightly regulated in an endocrine manner, is essential to reduce adipose tissue mass in the context of a negative energy balance.

Long-term regulation and control of body weight (body composition) relies upon a large regulatory network integrating different metabolic organs, in which the white adipose tissue is the major place for long-term energy storage in the form of triacylglycerol in adipocytes. In obesity, the chronic positive energy balance enlarges the adipocytes which may lead to an impaired lipid buffering capacity of the adipose tissue, which together with intrinsic lipolytic impairments may be identified as putative key factors in the pathophysiology of obesity and obesity-related metabolic and cardiometabolic complications. Gaining better insight into the role of these anomalies in obesity pathophysiology as well as lipolytic endocrine regulation is warranted in human metabolically compromised conditions. Therefore, in this thesis we explored whether natriuretic peptides, and in particular atrial natriuretic peptide (ANP), are substantially involved in the physiological regulation of adipocyte lipolysis in the obese insulin resistant state. Moreover, another goal was to explore the effect(s) of combined exercise intervention on this endocrine regulation system. As confirmed in the present thesis, there is now significant evidence that ANP is involved in the regulation of

adipocyte lipolysis, especially in the abdominal subcutaneous adipose tissue. However, in the obese insulin resistant or obese diabetic state, adipose tissue lipolysis displays a catecholamine- and ANP-resistant phenotype, which was not improved upon exercise intervention in the obese insulin resistant state. Therefore, finding appropriate strategies to alleviate the observed lipolytic impairments in the obese insulin resistant state are of major importance for body weight control and to improve adipose tissue function and metabolic profile in humans with obesity and thus more research in humans is required.

Target groups

Given the development of obesity associated metabolic disease affecting millions of people in our current societies, finding strategies to prevent and treat overweight, obesity and obesity-related health risks are crucial to improve global health and to counteract exploding healthcare costs. Indeed, in the obese state, even modest weight loss might lead to substantial beneficial health effects. Therefore, optimizing clinical efficacy of intervention programs, in terms of adipose tissue mass reduction and metabolic health, are of primary interest. In this respect, developing strategies, which are able to restore known lipolytic impairments present in the obese insulin resistant adipose tissue could be of major interest. To develop targeted exercise interventions or better pharmacological therapies should include fundamental as well as clinical work in human individuals with obesity and/or obesity-related metabolic complications.

In order to tackle obesity development, and in particular the development of its associated metabolic diseases like type 2 diabetes mellitus and cardiovascular disease, health care professionals, health institutions (including hospital settings, rehabilitation and sports centers), governments and general society need to be informed about these targeted exercise or combinational treatment (e.g. lifestyle intervention including exercise, diet and/or pharmaceutical treatments) strategies. In science, the aim is to make results available for the scientific community and health professionals through publication in international peer-reviewed journals and presentation on (inter)national scientific meetings. However, translation of scientific knowledge to society is essential. Beyond academia and scientific journals and meetings, our research

has been published in newspapers which enabled us to reach a broader audience to take notice of our findings. In this thesis, by performing in vitro work and clinical intervention studies with human subjects, we demonstrated a pronounced attenuation of ANP-mediated lipolysis in the abdominal subcutaneous adipocytes of obese individuals. The physiological relevance of this pathway in adipose tissue lipolysis was confirmed in the obese state as well, although exercise intervention could not restore the observed anomaly. Yet, exercise training in individuals with obesity or its combination with partial pharmacological inhibition of adipose tissue lipolysis in patients with type 2 diabetes was shown to modulate whole-body insulin sensitivity. Thus, the results presented in this thesis are of clinical relevance for a large number of people and therefore may be used by health care professionals to optimize lifestyle programs for individuals with overweight or obesity. In order to stimulate the translation of these findings to society and obtain awareness and support from the general public or policy makers, communicating these observations outside science is of considerable importance. Of interest, next to lifestyle and behavioral intervention to target obesity or its metabolic complications, pharmacological (co)interventions may be an alternative to alleviate adipose tissue function in the obese state. Targeting adipose tissue lipid metabolism or adipocyte function via pharmaceutical agents requires a good understanding and collaboration between universities and the pharmaceutical industry.

Activities and products

The research described in this thesis has been conducted at the department of Human Biology (Maastricht University), the Rehabilitation Research Center (Hasselt University) in collaboration with Heart Center Hasselt and Abdominal Surgery of Jessa Hospital and Hospital East-Limburg (Belgium). This unique collaboration between Universities and hospitals is a good example of how basic science can be performed in a hospital setting, combining knowledge of scientists and medical specialists across borders. The collaboration between basic scientists and professionals involved in obesity management is essential given that the current applied physical activity modalities in obesity rehabilitation, which are applied very frequent at both aforementioned hospital departments, might not be appropriate to restore adipose tissue function in

these patients. In order to increase the knowledge on white adipose tissue function and thereby improve prevention and/or treatment of human metabolically compromised conditions, strong national and international collaboration between different disciplines is of utmost importance.

The results described in this thesis are published or will be published in original research articles in scientific journals in the field of obesity and diabetes. Accordingly, these articles can be found online (accessible to those interested). The present results help to understand white adipose tissue physiology in humans and can be used for future studies on exploring optimized strategies to combat the obesity epidemic. The key role of adipose tissue function in metabolic health is currently subject of debate in the field of obesity research. The main outcomes of this thesis provide evidence for recommending the importance of a proper regulation of adipose tissue lipid metabolism in order to maintain a 'healthy' adipose tissue function. Moreover, this thesis showed that exercise training was not able to improve adipose tissue lipolysis despite improvements in metabolic disturbances, indicating the need for substantial weight loss to further restore adipose tissue function. However, the repercussions of adipose tissue depot- and sex-specific effects on adipocyte function, as well as the relationship to cardiometabolic health and the efficacy of diet/exercise intervention are important aspects, which require further research. This might also imply that stratification of individuals with obesity based on metabolic health characteristics is necessary to optimize and create tailored prevention and treatment strategies.

Innovation

By combining state-of-the-art *in vivo* clinical research and laboratory analyses, we were able to investigate for the first time the contribution of ANP in the regulation of adipocyte lipolysis in individuals with obesity. Moreover, the use of exercise intervention was shown to be insufficient to restore the observed impaired adipocyte lipolysis regulation in the obese insulin resistant state, leaving some opportunities for future research (as described in Chapter 6 and 7 of this thesis).

The current findings indicate a possible important role of non-adrenergically mediated lipolysis, most likely (partly) mediated by ANP, especially during physical activity or exercise. Together with the observations of the presence of a putative natriuretic deficiency in metabolic disease (as described in Chapter 2), this might indicate that the natriuretic peptide system or some of their components (*e.g.* their receptors or downstream mediators at the level of the adipose tissue) are candidate drug targets with therapeutic potential in obesity and type 2 diabetes, population in which poor adherence to lifestyle intervention is frequently observed. However, the therapeutic potential should be explored guardedly in future research, with special attention to cardiovascular complications. Of interest, efficient and selective (*i.e.* adipose tissue specific) ANP receptor agonists and antagonists are warranted to firmly delineate the physiological relative contribution of the different lipolytic agents in adipocyte lipolysis.