Hypothalamic regulation of metabolism
Zhang, Z.

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Thyroid hormone and estrogen both play an essential role in energy metabolism. The current thesis investigated the possible central effects of these hormones in the control of energy metabolism by administrating triiodothyronine (T3), estradiol (E2) and thyrotropin-releasing hormone (TRH) in distinct hypothalamic nuclei. We evaluated various aspects of metabolic alterations including glucose and lipid metabolism, food intake, body weight, body temperature, locomotor activity, energy expenditure and bone remodelling, from gene expression to behavioural changes. For these experiments, we used different experimental techniques. For example, we used slow-releasing pellets for chronic T3 or E2 administration and microdialysis for acute TRH or E2 administration into hypothalamus. We used metabolic cages to monitor caloric parameters including energy expenditure, carbohydrate oxidation and locomotor activity. We used positron emission tomography (PET) and micro computed tomography (μ-CT) scans to examine brown adipose tissue (BAT) activation and bone morphology, respectively. A number of different surgeries have been applied such as ovariectomy, liver denervation, and jugular vein catheterization, to help explicating specific research questions. We present new findings that not only extend our physiological understanding, but also indicate potential therapeutic possibilities for metabolic diseases.

Chapter 1 gives a brief introduction to the (neuro)endocrine system, as well as the hormones or neuropeptides that are studied in this thesis, including thyroid hormones, estrogen and TRH. An overview of their functions, especially their metabolic functions via the central nervous system (CNS), is provided.

Chapter 2 introduces a chronic animal model for selective prolonged T3 administration in the paraventricular nucleus of the hypothalamus (PVN) and the ventromedial nucleus of the hypothalamus (VMH) by T3-containing pellets. The T3 released from these pellets was validated by determining T3 concentrations in vitro as well as in the targeted and neighbouring brain areas and biologically validated by determining selective T3 responsive gene expression in the targeted and neighbouring brain areas. The model was further validated by the differential responses of the hypothalamus-pituitary-thyroid (HPT) axis upon T3 administration into the PVN or VMH.

Chapter 3 shows the metabolic consequences of chronic (7 and 28 days) T3 administration in the PVN or the VMH using the animal model developed in Chapter 2. The study shows limited metabolic changes by the chronic hypothalamic T3 challenge,
Summary

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suggesting different mechanisms are involved in the acute and chronic hypothalamic T3 regulation of metabolism.

In Chapter 4 we studied the acute and chronic rescuing effects of E2 in ovariectomized rats on white adipose tissue (WAT) and bone metabolism via the CNS. We first showed significant rescuing effects on body weight, fat distribution and bone remodeling by intracerebroventricular (ICV) E2 administration for four weeks. We then demonstrated that the central E2 effect on WAT is partly mediated via the VMH as both acute and chronic E2 administration in the VMH affects WAT metabolism. Importantly, our study also indicates that the central effect of E2 on bone metabolism is not mediated via the VMH.

Chapter 5 shows a key role for TRH release in the PVN in regulating glucose and body temperature during cold. Both TRH administration in the PVN and cold exposure show increased glucose production, locomotor activity, corticosterone concentration and body temperature. In addition, by using selective liver denervations we demonstrated that the effects of TRH in the PVN on glucose metabolism are partly mediated by both sympathetic and parasympathetic nervous system.

Chapter 6 demonstrates the stimulatory effect of TRH on BAT in humans. Intravenous administration of TRH increases BAT activity in cold pre-exposed subjects without significant changes in circulation thyroid hormones, heart rate and blood pressure. Our study extends the findings from animal studies where TRH administration induces a cold-defence response, suggesting a critical role of TRH on cold adaptation, also in humans.
Samenvatting

Naast een scala van andere functies hebben zowel schildklierhormoon (T3) als oestrogeen (E2) ook belangrijke metabole effecten. In dit proefschrift onderzochten wij of metabole effecten van deze hormonen op energiemetabolisme deels via het centraal zenuwstelsel tot stand kunnen komen door de effecten te bestuderen van toediening van schildklierhormoon, oestrogeen of TRH in specifieke hypothalamische nuceli. We onderzochten verschillende aspecten van het energiemetabolisme, zoals glucose en lipidenmetabolisme, eetgedrag, lichaamsgewicht, lichaamstemperatuur, bewegingsactiviteit, energieverbruik en botmetabolisme. De effecten werden bestudeerd zowel op moleculair als op functioneel niveau. Voor deze experimenten maakten we dan ook gebruik van verschillende experimentele technieken. We gebruikten bijvoorbeeld tabletten met een langzame afgifte van T3 en E2 om deze hormonen lokaal gedurende weken te kunnen toedienen in hypothalamische kerngebieden. Daarnaast gebruikten we microdialyse om TRH en E2 acuut (uren) lokaal in de hypothalamus toe te dienen. We maakten gebruik van calorimetrische kooien om verschillende metabole parameters, zoals energieverbruik, koolhydraten oxidatie en bewegingsactiviteit te meten. We maakten gebruik van positron emissie tommografie (PET) en micro computer tommografie (μ-CT) scans om respectievelijk de activiteit van bruin vetweefsel en de botmorfoogie te bestuderen. Ook maakten we gebruik van een aantal chirurgische ingrepen, zoals ovariektomie, lever denervatie en catheterisatie van de vena jugularis om specifieke onderzoeksvragen te beantwoorden. De verkregen resultaten vergroten niet alleen ons begrip van de neuroendocrinologie, maar geven ook preliminaire aanwijzingen voor therapeutische modaliteiten bij de behandeling van metabole ziekten.

In Hoofdstuk 2 introberen we een diermodel voor de chronische en selectieve toediening van T3 in de paraventriculaire (PVN) en ventromediale (VMH) kern van de hypothalamus van de rat middels T3-bevattende tabletten. De afgifte van T3 door deze tabletten werd gevalideerd door het meten van T3 concentraties zowel in vitro als in vivo in de doelgebieden en nabij gelegen hersengebieden. De biologische activiteit van het afgegeven T3 werd gevalideerd door het meten van de expressie van T3 afhankelijke genen in de doelgebieden en in nabij gelegen hersengebieden. De specificiteit van ons model werd verder aangetoond door de verschillende responsen van de hypothalamus-hypofyse-schildklier (HPT) as na toediening van T3 in de PVN dan wel VMH.
Chapter 8

In Hoofdstuk 3 presenteren we de metabole consequenties van chronische (7 en 28 dagen) T3 toediening in de PVN en VMH gebruik makend van het diermodel zoals besproken in Hoofdstuk 2. De resultaten van deze studie laten zien dat de metabole consequenties van chronische toediening zeer beperkt zijn, hetgeen suggereert dat er verschillende mechanismen betrokken zijn bij de (eerder gerapporteerde) acute en chronische effecten van T3 op metabolisme.

In Hoofdstuk 4 onderzochten we de effecten van acute en chronische toediening van E2 in het centraal zenuwstelsel op vet- en botmetabolisme in vrouwelijke ratten na ovariectomie. Na toediening van E2 in de laterale hersenventrikel gedurende 4 weken vonden we een significant herstel van het toegenomen lichaamsgewicht en van de veranderingen in vetdistributie en botmetabolisme. Vervolgens konden we aantonen dat de centrale effecten van E2 op het vetweefsel voor een deel gemedieerd worden via de VMH, zowel na acute als chronische toediening. Dezelfde studie liet echter ook zien dat de centrale effecten van E2 op botmetabolisme niet gemedieerd worden via de VMH.

De resultaten in Hoofdstuk 5 laten een belangrijke rol zien voor TRH in de PVN bij de regulatie van glucosemetabolisme en lichaamstemperatuur tijdens blootstelling aan koude (4°C). Zowel de toediening van TRH in de PVN als blootstelling aan kou resulteerde in een toegenomen glucoseproductie, bewegingsactiviteit, plasma corticosteron concentratie en lichaamstemperatuur. Middels selectieve denervatie van de autonome leverinput konden we aantonen dat de effecten van TRH in de PVN op glucosemetabolisme voor een deel gemedieerd worden via zowel de parasympathische als sympathische lever innervatie.

In Hoofdstuk 6 toonden we een stimulerend effect aan van TRH op de activiteit van bruin vetweefsel in gezonde proefpersonen gemeten aan de hand van FDG PET/CT. Intraveneuze toediening van TRH resulteerde in een toegenomen activiteit van bruin vetweefsel in een aantal proefpersonen na voorafgaande blootstelling aan een koele (17°C) omgeving. Deze toename kon niet worden verklaard door een stijging van de plasma schildklierhormoonconcentraties, en ook de hartfrequentie en bloeddruk bleven ongewijzigd. De resultaten van deze studie zijn globaal in overeenstemming met de resultaten van onze dierexperimentele studies waarin TRH toediening resulteerde in een fysiologische adaptatie aan kou, en wijzen op een belangrijke rol voor TRH in de adaptatie aan kou niet alleen bij knaagdieren maar ook bij mensen.

Acknowledgements

Time flies! Four years ago, in a cold sunset winter, I was sitting in Peter's car and watching out side of Amsterdam for my first sight: maze- like land cut by numerous cannels. Up ahead in the distance, splendid golden radiation reflected from the frozen Amstel River was heating my blood, exciting my nerves and illuminating my dream. Every time I recall, I am delighted and grateful for those knowledge I learnt here, for those people I know here and for those friendship I make here. I will never forget these beautiful and precious memories here.

My first gratitude goes to Prof. Eric Fliers. Dear Eric, thank you for having me here for my PhD training. I am particularly fascinated by your elegant presentations and graceful manner in dealing with problems. Your profound knowledge, intellectual scientific intuition and confidence immensely inspire me and nourish my growth as an independent researcher. Thank you for your taking care of my projects and warm help for my living. When I am in trouble, it is your encouragement and firmly support that secure me and motivate me to move on.

My great mentor Prof. Andries Kalsbeek, thank you for your motivation and guidance during my PhD trip. I am very grateful for your always opening door, providing me endless scientific resources and precious daily supervision. You are definitely a great chronobiologist because you even behave yourself as a "clock". I learn from you not only your extensive knowledge in science but also your prominent time management, creative perspective and enthusiastic science spirit.

Dear Peter, thank you for your patience, motivation and most importantly friendship. Your excellent coaching on how to manager my projects, to make good slides, to compose a convincing rebuttal, always inspire me and benefit me a million.

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Prof. Swaab, you are a great scientist and you are a great grandfather. Your kindly smile and humorous remark impress me every time. Dear Susanne, thank you for your inspiration and friendly help in both my research and personal life. Chunxia, thank you
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Chapter 8

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Life will not be colourful without my lovely friends - within and outside of academic field. Mehran, more than four years’ friendship makes us brothers. I thank you deeply for your personal advices and generous help in every facet. Your dedication and enthusiasm to science set a role model for me to become a scientist. Pawan, we had
Acknowledgements

good time of being eating, drinking and debating together. I greatly appreciate your Guru philosophy and those joyous memories with you. Ruben, it is really lucky to meet you. Thank you for your precious help to me and my family. Dear Bart, living in Amsterdam will not be easier without you. I only need to move to five places in four years. I admire your every joke and am very grateful for your help with housing and my life. Juan, thank you for your sweet help. I still remember you led me the way from NIN to Wibaustraat on my first day here. Thank you to my other dear friends in the NIN: Sebastian, Daniel, Prem and Maike for the happy time with you guys together. Thank you lovely girls in the NIN: Dan, Xueyan, Lei and Lin for your kindness and support. I am very grateful to have 师兄们: Zhonglin, Cheng, Ji and Shangfeng for helping me out in science and life. Yongjie, Brother Qing, Ting, Meichen, Chun, Junhui and Liang, thank you for sharing those delicious food and cheerful game time with me and my family. I thank my basketball mates: Zemin, Zongliang, Xiaolin and Yuanjie to bring me the joyful time after work.

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PhD portfolio

Name PhD student: Zhi Zhang
PhD period: 02. 2012 – 01. 2017

Name PhD supervisor: Prof. dr. E. Fliers
Prof. dr. A. Kalsbeek
Dr. P.H.L.T. Bisschop
Dr. A. Boelen

Courses

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<td>- Practical biostatistics</td>
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<td>- Functional neuroanatomy</td>
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<td>- Functional Imaging and Super Resolution</td>
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<td>- Grant writing</td>
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Specific courses

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<th>Year</th>
<th>Workload (Hours/ECTS)</th>
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<tr>
<td>- Article 9 Laboratory Animal Science</td>
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<td>- Radiation Protection (deskundigheidsniveau 5B)</td>
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<tr>
<td>- ESE Basic Science course on Neuroendocrinology</td>
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<td>- Leadership in Science</td>
<td>2016</td>
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Seminars, workshops and master classes

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<th>Seminars, workshops and master classes</th>
<th>Year</th>
<th>Workload (Hours/ECTS)</th>
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<tr>
<td>- Weekly research meeting Endocrinology</td>
<td>2012-2016</td>
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<td>- Weekly symposium NIN</td>
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<td>- Master course Endocrinology UvA</td>
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<td>- Symposium: UvA Meets China</td>
<td>2013</td>
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<td>- Annual PhD Meeting ACM/MDL</td>
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<td>- Annual PhD-meeting ONWAR and BCRM</td>
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<td>- Swammerdam Lectures</td>
<td>2012-2015</td>
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Chapter 8

Presentations

Poster presentation
- Nutrition, Metabolism and the Brain (NMB) meeting 2013
- Annual PhD-meeting ONWAR and BCRM 2013-2014
- ESE Basic Science course on Neuroendocrinology 2014
- Annual meeting of Society for Neuroscience (SFN) 2015

Oral presentation
- Annual PhD Meeting ACM/MDL 2013
- Annual meeting of European thyroid association 2014
- Dutch Endocrine Meeting (NVE) 2015
- Annual meeting of Young active research in endocrinology 2015 (YARE)
- Masters course in the NIN 2016
- Annual meeting of NVCB 2016

(International) national conferences
- Annual symposium of Dutch Thyroid Research Foundation 2013-2016
- Metabolism and the Brain (NMB) meeting 2013
- Annual meeting of European thyroid association 2014-2015
- Annual meeting of NVCB 2014, 2016
- Dutch Endocrine Meeting (NVE) 2015
- Annual meeting of Society for Neuroscience (SFN) 2015
- Annual meeting of Young active research in endocrinology 2015 (YARE)

Grants
- AUF Spinoza Fund for mobility
- Travel grant for 38th ETA

List of publications


Z. Zhang, A. Boelen, P.H. Bisschop, A. Kalsbeek, E. Fliers. Hypothalamic effects of thyroid hormone, Molecular and Cellular Endocrinology (2016), in press


Z. Zhang, E. Foppen, Y. Su, P.H. Bisschop, A. Kalsbeek, E. Fliers, A. Boelen. Metabolic effects of chronic T3 administration in the hypothalamic para-ventricular and ventromedial nucleus in male rats, Endocrinology (2016) en20161397


Meng FT, Zhao J, Ni RJ, Fang H, Zhang LF, Zhang Z, Liu YJ. Beneficial effects of enriched environment on behaviors were correlated with decreased estrogen and increased BDNF in the hippocampus of male mice. Neuro Endocrinol Lett. 2015; 36(5):490-7


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Zhi Zhang (张智) was born on 10th of June 1987 in a village in the north of Anhui province, where he grew up along with the wild beautiful natural greens in the field. When six years old, he walked every day three kilometres with his little friends to the primary school. When he was fourteen, he went for high-school education in a neighborhood town, twenty kilometres away from his home. In 2005, he started his undergraduate training in bioengineering at the China University of Mining and Technology (CUMT) in Xuzhou, a city about a hundred kilometres away from his hometown. Four years later, he was recommended to the laboratory of Prof. J-N Zhou for his master study at the University of Science and Technology of China (USTC) in Hefei, the capital city of his mother province, which is about three hundred and fifty kilometres away from his hometown. At this university, he met his wife, Wenjing Cai, who is now studying Innovation Management at the Free University in Amsterdam. In 2012, Zhi came to the Netherlands for his PhD study in the department of Endocrinology and Metabolism of the Academic Medical Centre (Prof. E. Fliers and Prof. A. Kalsbeek) in Amsterdam, about eight thousand kilometres from his hometown. His PhD project focused on the central effects of thyroid hormone and estrogen on bone and energy metabolism. In 2015, his daughter, Elisa (Bozhen) Zhang, was born in Amsterdam on 11th May.
About the author

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