

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/32582> holds various files of this Leiden University dissertation

**Author:** Wijngaarden, Marjolein A.

**Title:** Metabolic and endocrine adaptations to fasting in lean and obese individuals

**Issue Date:** 2015-03-26

# **Metabolic and endocrine adaptations to fasting in lean and obese individuals**

Marjolein A. Wijngaarden

---

Cover design: I.C. Wijngaarden

Lay-out and print: F&N Boekservice – Castricum

The research described in this thesis was financially supported by The Center for Medical Systems Biology (CMSB), within the framework of the Netherlands Genomics Initiative (NGI/NOW). Printing of this thesis was financially supported by Boehringer Ingelheim, Goodlife Pharma, Ipsen Farmaceutica, Novartis Pharma B.V., Novo Nordisk B.V., Pfizer BV.

© Marjolein A. Wijngaarden, Leiden, The Netherlands.

The copyright of the articles published or submitted for publication has been transferred to the respective journals. No part of this thesis may be reproduced or transmitted in any form, by any means, without prior written permission of the author.

---

ISBN: 978949109879 6

# **Metabolic and endocrine adaptations to fasting in lean and obese individuals**

## **Proefschrift**

ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker  
volgens besluit van het College voor Promoties  
te verdedigen op  
donderdag 26 maart 2015  
klokke 16.15 uur

door

Marjolein A. Wijngaarden  
geboren in 1983  
te Amsterdam

# Promotiecommissie

**Promotores:** Prof. dr. H. Pijl  
Prof. dr. K. Willems van Dijk

**Co-promotor:** Dr. B. Guigas

**Overige leden:** Dr. J. van der Grond  
Prof. dr. E.J.M. Feskens, Universiteit Wageningen  
Prof. dr. W.H.M. Saris, Universiteit Maastricht

# Contents

<b>List of abbreviations</b>	7
<b>Chapter 1</b> General Introduction	11
<b>Chapter 2</b> Effects of prolonged fasting on AMPK signaling, gene expression and mitochondrial respiratory-chain content in skeletal muscle from lean and obese individuals	23
<b>Chapter 3</b> Obesity is associated with an altered autonomic nervous system response to nutrient restriction	51
<b>Chapter 4</b> Obesity is marked by distinct functional connectivity in neural networks involved in the control of food reward and salience	63
<b>Chapter 5</b> Regulation of skeletal muscle energy/nutrient-sensing pathways during metabolic adaptation to fasting in healthy humans	85
<b>Chapter 6</b> Food cues do not modulate the neuroendocrine response to a prolonged fast in healthy men	149
<b>Chapter 7</b> Discussion	173
<b>Chapter 8</b> Nederlandse Samenvatting	183
<b>List of publications</b>	193
<b>Curriculum Vitae</b>	195
<b>Dankwoord / Acknowledgements</b>	197

---

---

# List of abbreviations

ACC	acetyl-coA carboxylase
ACOX1	peroxisomal acyl-coenzyme A oxidase 1
ADA	American Diabetes Association
ALT	alanine aminotransferase
AMPK	adenosine monophosphate-activated kinase
AMPKKs	AMPK kinases
AST	aspartate aminotransferase
AS160	akt substrate of 160kDa
BMI	body mass index
BOLD	blood-oxygen level dependent
CAMKK $\beta$	Ca <sup>2+</sup> /calmodulin-dependent protein kinase kinase $\beta$
CPT1B	carnitine-palmitoyl transferase 1B
CR	calorie restriction
CREB	cAMP response element-binding protein
CRP	C-reactive protein
CS	citrate synthase
DEGs	differentially expressed genes
4EBP1	eukaryotic initiation factor 4E binding protein;
ECG	electrocardiogram
EF2	eukaryotic elongation factor 2
EGP	endogenous glucose production
ELISA	enzyme-linked immunosorbent assay
ERK	extracellular signal-regulated kinase;
FAT/CD36	fatty acid transporter CD36
FA/FFA	free fatty acid
FFM	fat-free mass
fMRI	functional magnetic resonance imaging
FM	fat mass
FOXO	forkhead box protein O
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
FT4	free thyroxine

GLM	general linear model
GLUT4	glucose transporter isoform 4
GO	gene ontology
GS	glycogen synthase
GSK3	glycogen synthase kinase 3
G6Pase	glucose-6-phosphatase catalytic subunit
HADHA	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, alpha subunit
Hb	hemoglobin
HDAC	histone deacetylase
HDL	high-density lipoprotein
HRV	heart rate variability
MRS	magnetic resonance spectroscopy
HOMA-IR	homeostatic model assessment of insulin resistance
HPLC	high-performance liquid chromatography
hsCRP	high sensitive c-reactive protein
IGF-1	insulin-like growth factor 1
IGT	impaired glucose tolerant
IL	interleukin
IFNy	interferon gamma
IR	insulin receptor
IR $\beta$	insulin receptor $\beta$
IRS	insulin receptor substrate
LBM	lean body mass
LC-CoA	long chain fatty acid-CoA
LDL	low density lipoprotein
LH	luteinizing hormone
LKB1	liver kinase B1
LPL	lipoprotein lipase
LUMC	leiden university medical center
MRI	magnetic resonance imaging
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
mTORC1	mammalian target of rapamycin complex 1
OGTT	oral glucose tolerance test

---

## List of abbreviations

---

PI3K	phosphatidylinositol 3-kinase
PDK	phosphatidylinositol dependent protein kinase
PGC-1 $\alpha$	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PKB(Akt)	protein kinase B (also known as Akt)
PKC	protein kinase C
PPAR- $\delta$	peroxisome proliferator-activated receptor delta
ppm	parts per million
PRAS40	proline rich Akt substrate of 40 kDa
REE	resting energy expenditure
RQ	respiratory quotient
S6	ribosomal protein S6
S6K	ribosomal protein S6 kinase
SHBG	sex-hormone binding globulin
SIRT1	sirtuin 1
SEM	standard error of the mean
Ser	serine
T3	triiodothyronine
TC	total cholesterol
TE	echo time
TG	triglyceride
Thr	threonine
TR	repetition time
TRH	thyrotropin releasing hormone
TSC2	tuberous sclerosis protein 2
TSH	thyroid-stimulating hormone
Tyr	tyrosine
T2DM	type 2 diabetes mellitus
VLCD	very low calorie diet
VLDL	very low density lipoprotein
WHO	world health organization

