Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Obesity and Metabolic flexibility: the key to metabolic health?

Ellen E Blaak

Professor in physiology of fat metabolism
Department of Human Biology
NUTRIM School for Nutrition, Toxicology and Metabolism
Maastricht University Medical Centre
NUGO week 2015 Barcelona

Maastricht University Leading on Learning!

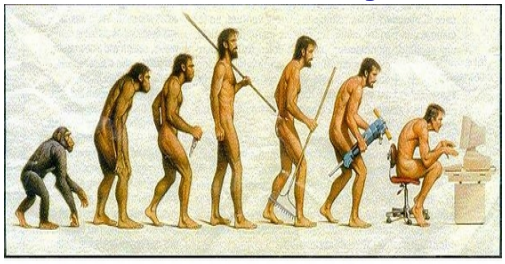
NUTRIM School for Nutrition, Toxicology and Metabolism

Overview

- Prevalence Diabesity
- Insulin resistance, Interorgan cross talk and metabolic inflexibility
- Muscle lipid accumulation/lipid turnover
- Gut-host metabolism crosstalk: SCFA
- Dietary polyphenols and metabolic inflexibility

Maastricht University Leading on Learning!

The prevalence of obesity and type 2 diabetes mellitus is increasing

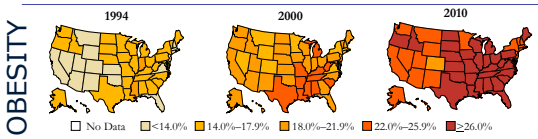


Somewhere, something went terribly wrong

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Age-adjusted prevalence of obesity among U.S. adults



Overweight: >50% (>1 billion) adults
Obesity: 12% (475 million) adults

In every region of the world, 2-fold increase in obesity since 1980

WHO Factsheet 311

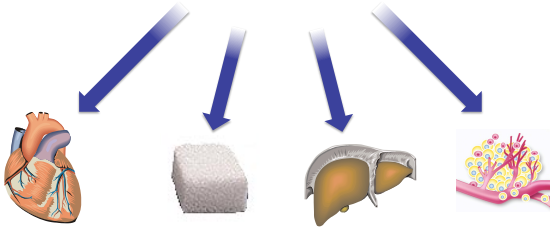
Source: www.cdc.gov

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Obesity: a major risk factor for chronic diseases

OBESITY



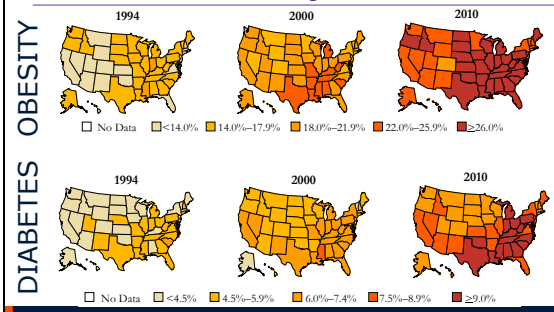
Cardiovascular disease | Type 2 diabetes | Liver steatosis | Cancer

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Age-adjusted prevalence of obesity and diabetes among U.S. adults



Department of Human Biology

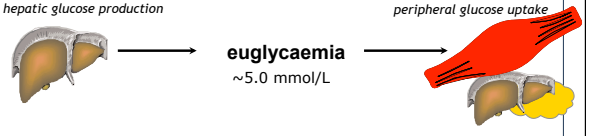
Source: www.cdc.gov

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Importance of insulin in glucose homeostasis

hepatic glucose production → **euglycaemia** ~5.0 mmol/L → *peripheral glucose uptake*



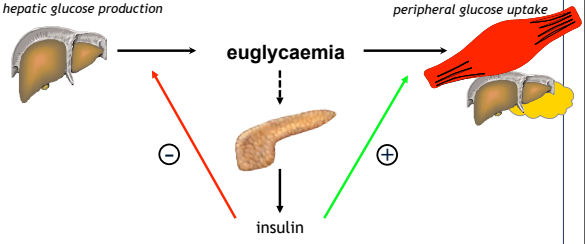
Department of Human Biology

Maastricht University Leading on Learning!

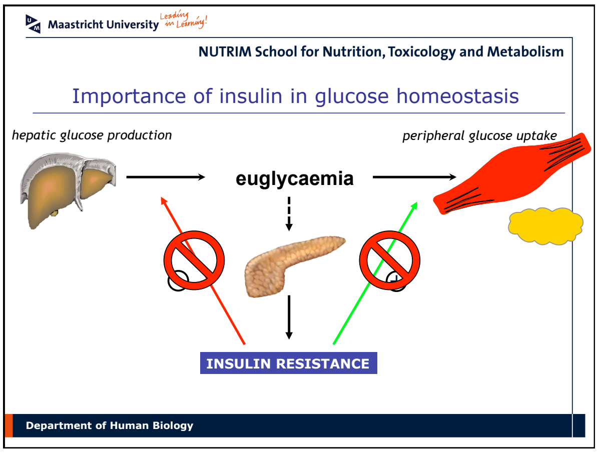
NUTRIM School for Nutrition, Toxicology and Metabolism

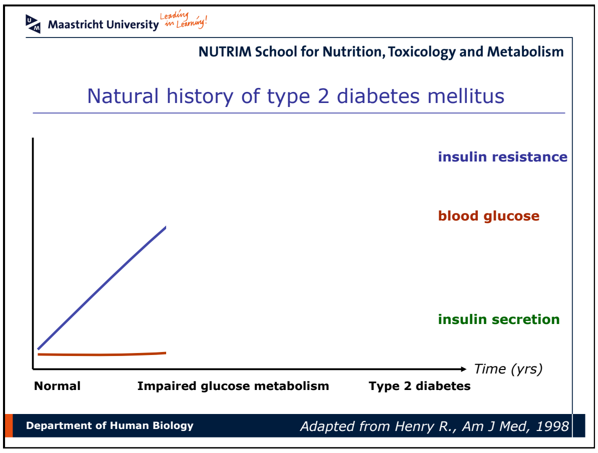
Importance of insulin in glucose homeostasis

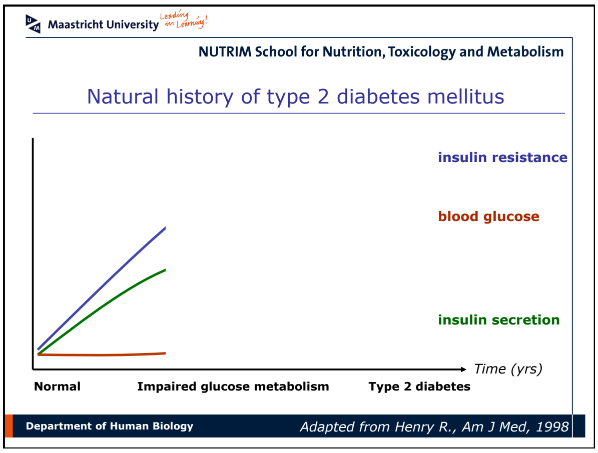
hepatic glucose production → **euglycaemia** → *peripheral glucose uptake*

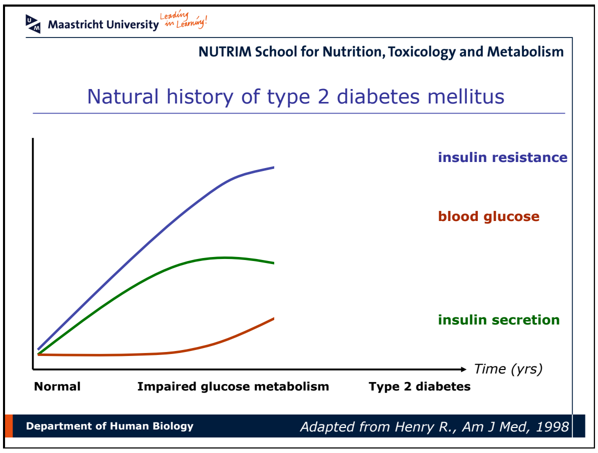


Department of Human Biology


Maastricht University Leading in Learning!
NUTRIM School for Nutrition, Toxicology and Metabolism
Importance of insulin in glucose homeostasis
hepatic glucose production
peripheral glucose uptake
euglycaemia
INSULIN RESISTANCE
Department of Human Biology


Maastricht University Leading in Learning!
NUTRIM School for Nutrition, Toxicology and Metabolism
Natural history of type 2 diabetes mellitus
insulin resistance
blood glucose
insulin secretion
Time (yrs)
Normal
Impaired glucose metabolism
Type 2 diabetes
Department of Human Biology
Adapted from Henry R., Am J Med, 1998

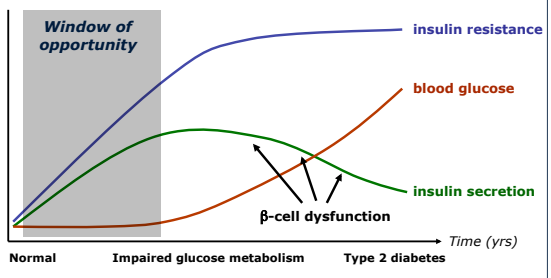

Maastricht University Leading in Learning!
NUTRIM School for Nutrition, Toxicology and Metabolism
Natural history of type 2 diabetes mellitus
insulin resistance
blood glucose
insulin secretion
Time (yrs)
Normal
Impaired glucose metabolism
Type 2 diabetes
Department of Human Biology
Adapted from Henry R., Am J Med, 1998


Maastricht University Leading in Learning!
NUTRIM School for Nutrition, Toxicology and Metabolism
Natural history of type 2 diabetes mellitus
insulin resistance
blood glucose
insulin secretion
Time (yrs)
Normal
Impaired glucose metabolism
Type 2 diabetes
Department of Human Biology
Adapted from Henry R., Am J Med, 1998

Maastricht University

NUTRIM School for Nutrition, Toxicology and Metabolism

Natural history of type 2 diabetes mellitus



Department of Human Biology

Adapted from Henry R., Am J Med, 1998

Maastricht University

NUTRIM School for Nutrition, Toxicology and Metabolism

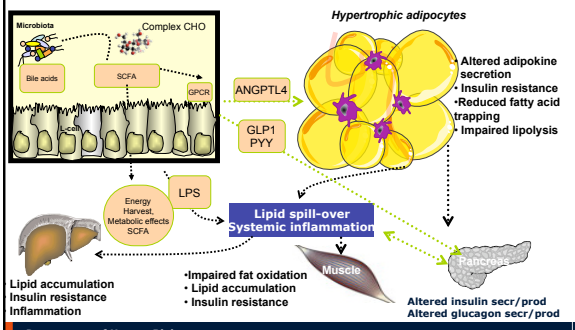
Overview

- Prevalence Diabesity
- Insulin resistance, Interorgan cross talk and metabolic inflexibility
- Muscle lipid accumulation/lipid turnover
- Gut-host metabolism crosstalk: SCFA
- Dietary polyphenols and metabolic inflexibility

Department of Human Biology

Maastricht University

Disturbed interorgan cross-talk in insulin resistance



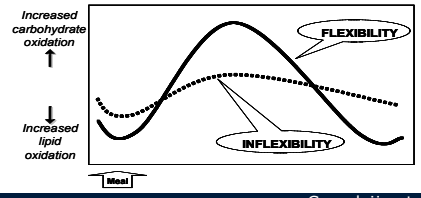
Department of Human Biology

Maastricht University

NUTRIM School for Nutrition, Toxicology and Metabolism

Metabolic inflexibility in regulating skeletal muscle substrate utilization in obese insulin resistant / T2DM subjects

- Impaired capacity to decrease muscle fat oxidation during insulin-stimulated conditions
- Impaired capacity to increase muscle fat oxidation during fasting, β-adrenergic stimulation, and exercise.



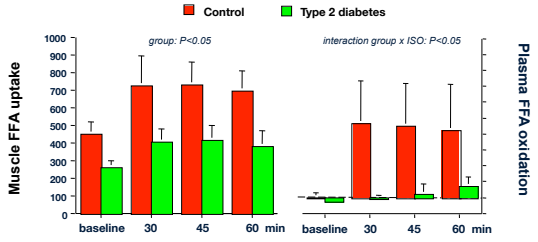
Department of Human Biology

Corpeleijn et al, 2009

Maastricht University

NUTRIM School for Nutrition, Toxicology and Metabolism

Impaired capacity to increase fat oxidation during ß-adrenergic stimulation in T2DM



Comparable findings in obese and type 2 diabetic subjects

(Blaak et al. 1994, Kelley et al. 1994, Colberg et al. 1995, Mensink et al 2001)

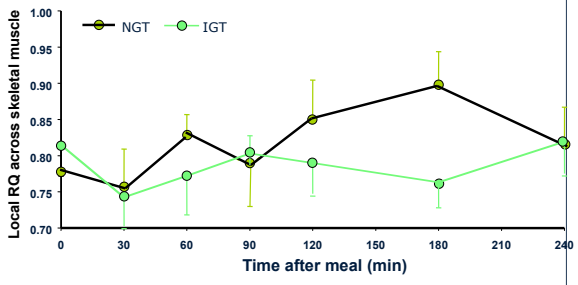
Department

Blaak et al. 2000

Maastricht University

NUTRIM School for Nutrition, Toxicology and Metabolism

Skeletal muscle fatty acid handling is disturbed in IGT subjects



Postprandial iAUC: *P*<0.05 *vs.* NGT

Corpeleijn et al., 2009

Maastricht University

NUTRIM School for Nutrition, Toxicology and Metabolism

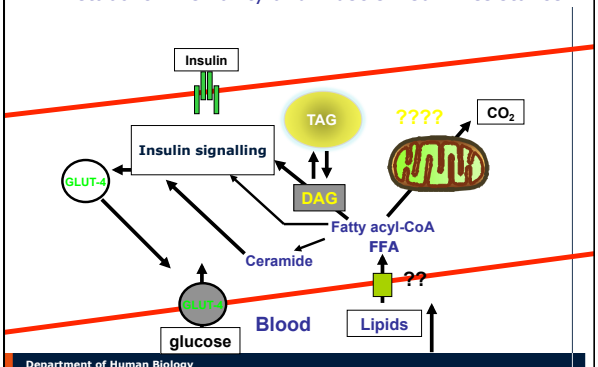
Overview

- Prevalence Diabesity
- Insulin resistance, Interorgan cross talk and metabolic inflexibility
- Muscle lipid accumulation/lipid turnover
- Gut-host metabolism crosstalk: SCFA
- Dietary polyphenols and metabolic inflexibility

Department of Human Biology

Maastricht University

Metabolic inflexibility and muscle insulin resistance

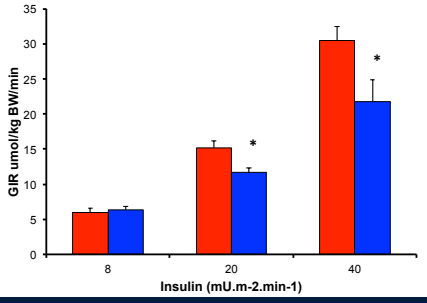


Department of Human Biology

Maastricht University Leading on Learning!

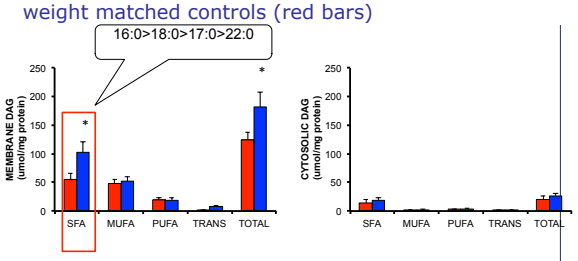
NUTRIM School for Nutrition, Toxicology and Metabolism

Reduced peripheral glucose disposal in T2DM (blue bars)



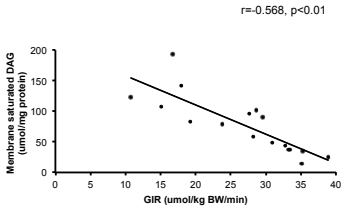
Maastricht University Leading on Learning!

Higher saturated DAG in the muscle membrane of obese T2D men (blue bars) as compared to body weight matched controls (red bars)

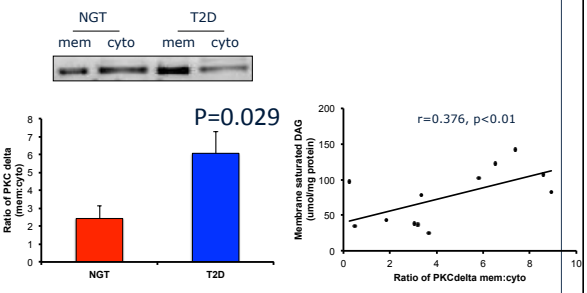


No differences were observed in total or subcellular TAG, phospholipid or FA composition between groups

Inverse relationship between muscle membrane saturated DAG and insulin sensitivity



Increased ratio PKCδ membrane:cytosol in muscle of T2D men



Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Accumulation of saturated DAG in the muscle membrane

↓

PKC activation

↓

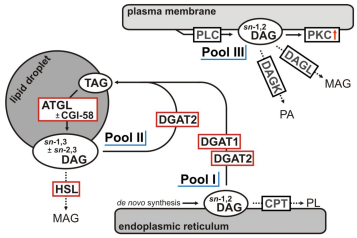
Reduced glucose disposal

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Cellular localization and composition of DAG might be of importance



Eichmann et al. JBC 2012
Bergman et al. Diabetologia 2012
Jocken et al. JCEM 2010

Department of Human Biology

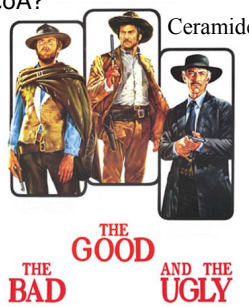
Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Fatty acyl CoA?

DAG?

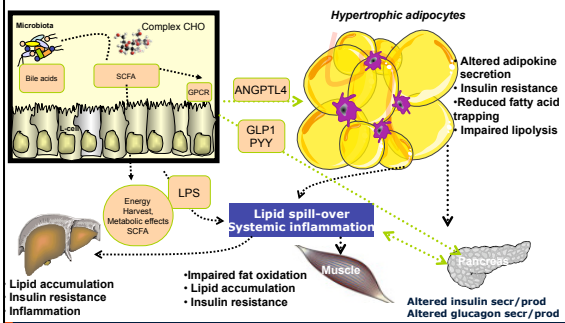
Ceramides?



Department of Human Biology

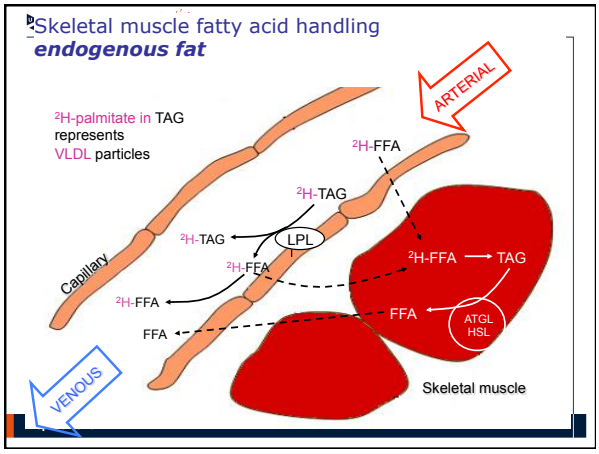
Maastricht University Leading on Learning!

Disturbed interorgan cross-talk in insulin resistance

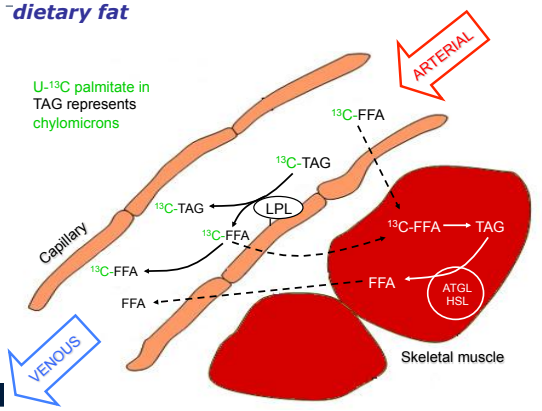


Department of Human Biology

Skeletal muscle fatty acid handling
endogenous fat



Skeletal muscle fatty acid handling
dietary fat

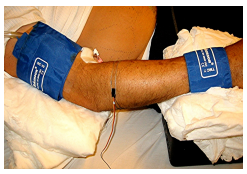


Maastricht University *Leading on Learning!*

NUTRIM School for Nutrition, Toxicology and Metabolism

Skeletal muscle fatty acid handling

- High fat mixed meal (2.6 MJ: 62.3 en% fat, 32.6 en% CHO, 5.1 en% proteins)
- Arterio-venous differences across forearm muscle
- Forearm blood flow using venous occlusion plethysmography



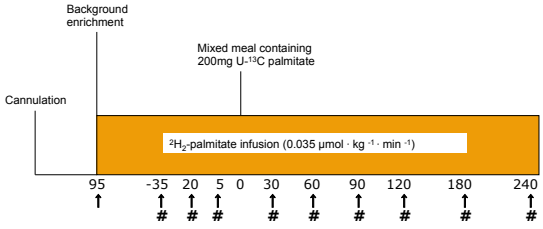
Net flux = plasma flow x (arterio-venous difference)
Positive: Net uptake from plasma
Negative: Net release from tissue

Department of Human Biology

Maastricht University *Leading on Learning!*

NUTRIM School for Nutrition, Toxicology and Metabolism

Stable Isotope Study
Study design

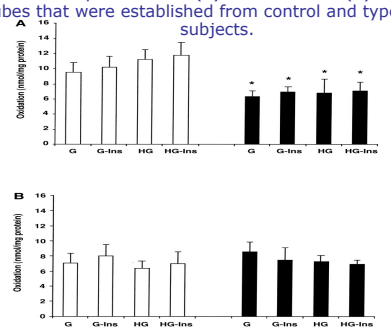


↑ simultaneous arterial and deep venous blood sampling
forearm blood flow

Department of Human Biology

Maastricht University Leading on Learning!

Oxidation of palmitic acid (A) and oleic acid (B) to CO2 in myotubes that were established from control and type 2 diabetic subjects.



Gaster M et al. Diabetes 2005;54:648-656

Maastricht University Leading on Learning!

Intervention

Dietary fat quality and muscle fatty acid Handling in obese insulin resistant subjects

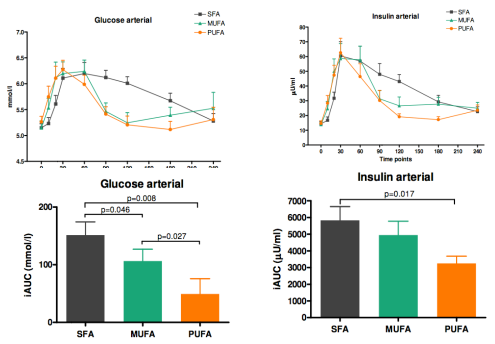
3 postprandial high fat meals (2,6 MJ), randomized order

	SFA	MUFA	PUFA
Protein (en%)	6.3	6.5	6.5
Carbohydrate (en%)	32.6	32.3	32.3
Fat (en%)	61.2	61.2	61.2
SFA (en%)	**35.5**	12.9	18.6
MUFA (en%)	18.8	**42.7**	12.4
PUFA (en%)	1.7	8.1	**34.8**

MUFA: Olive oil

PUFA: n-6 safflower oil and n-3 fish oil (Ratio 1:1)

Higher postprandial insulin sensitivity with PUFA meal in in obese IR subjects

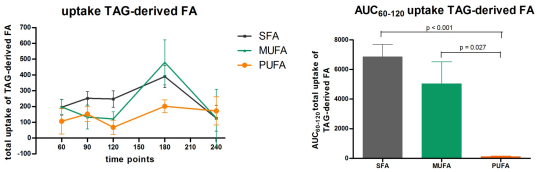


Jans et al, AJCN, 2012

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Reduced muscle TAG-derived FA uptake with PUFA meal

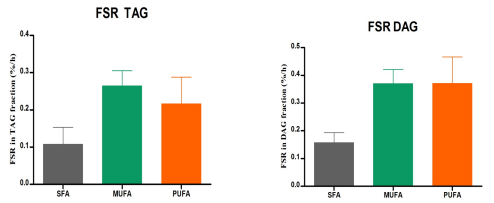


Maastricht University Leading on Learning!

Results

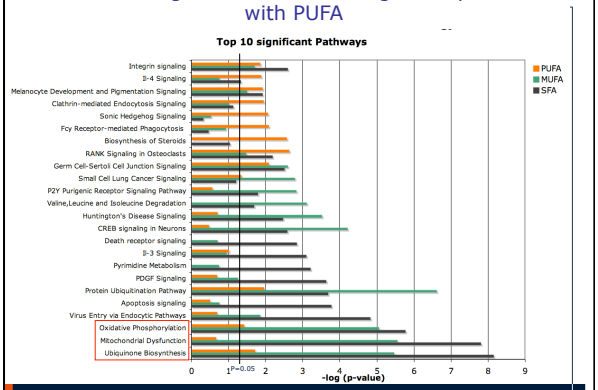
NUTRIM School for Nutrition, Toxicology and Metabolism

Higher TAG and DAG synthesis (FSR) with PUFA and MUFA



Department of Human Biology

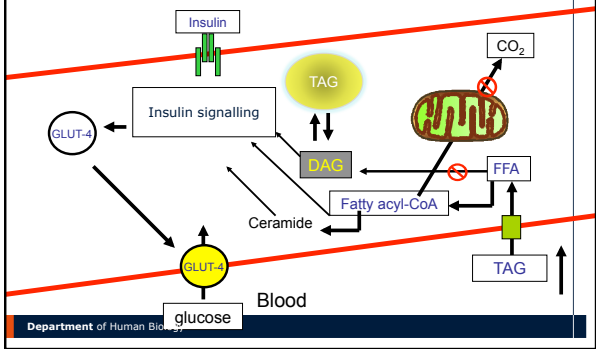
Less downregulation of oxidative gene expression with PUFA



Department of Human Biology

Maastricht University Leading on Learning!

Impaired turnover of SFA in insulin resistance



Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Fatty acyl CoA? DAG? Ceramides?

The insulin resistant muscle may be characterised by a reduced lipid turnover of in particular saturated fatty acids

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

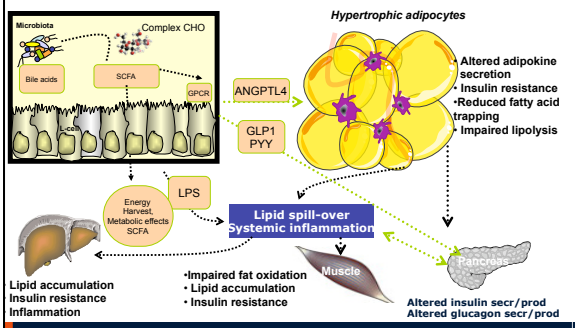
Overview

- Prevalence Diabesity
- Insulin resistance, Interorgan cross talk and metabolic inflexibility
- Muscle lipid accumulation/lipid turnover
- Gut-host metabolism crosstalk: SCFA
- Dietary polyphenols and metabolic inflexibility

Department of Human Biology

Maastricht University Leading on Learning!

Disturbed interorgan cross-talk in insulin resistance

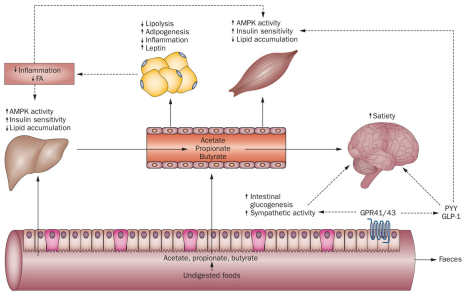


Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

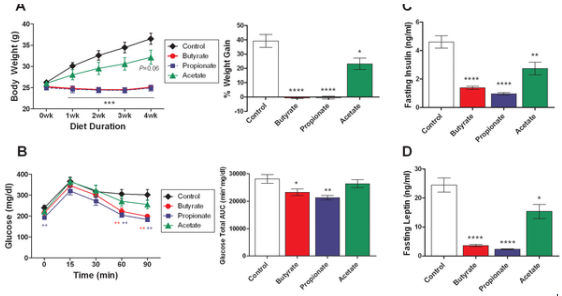
SCFA and interorgan crosstalk



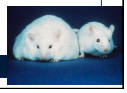
Nature Reviews | Endocrinology

Department of Human Biology

Dietary SCFAs affect body weight and glucose homeostasis in mice.



Lin HV, Frassetto A, Kowalik Jr EJ, Nawrocki AR, et al. (2012). PLoS ONE 7(4): e35240.



Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Colonic SCFA administration and metabolism: acetate study

Aim:

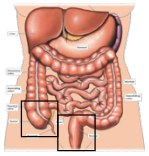
To investigate differential effects of proximal and distal colonic infusions with sodium acetate on human substrate and energy metabolism

Study design

- Double blind, placebo controlled, randomized crossover study
- 6 healthy overweight males (BMI 25 – 34.9 kg/m^2)
  - Aged 20 – 50 years;
  - Caucasian;
  - Weight stable for at least 3 months (± 2 kg)
  - No use of antibiotics, pre- or probiotics

Intervention

1. Sodium acetate 100mM in 120mL
2. Sodium acetate 180mM in 120mL
3. Placebo (0.9 NaCl) 120mL

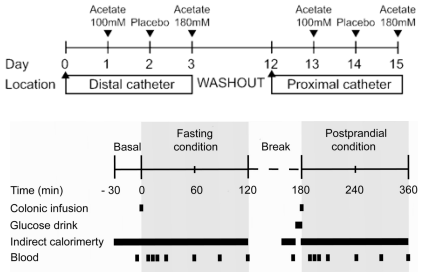


Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology an

Intervention protocol

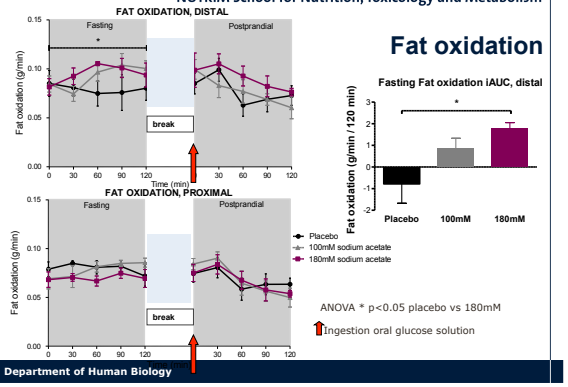


Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Fat oxidation



ANOVA * p<0.05 placebo vs 180mM

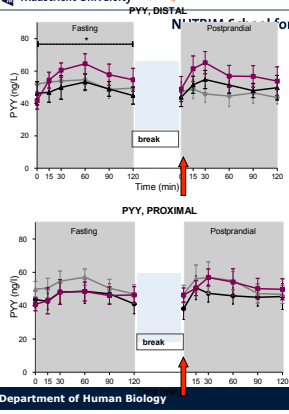
Ingestion oral glucose solution

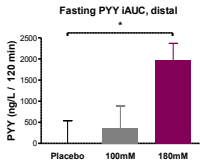
Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

PYY





ANOVA * p<0.05 placebo vs 180mM

Ingestion oral glucose solution

Department of Human Biology

Conclusion

- Distal acetate infusions increase fat oxidation, plasma PYY, and decrease TNF-α
- Relevant mixtures of SCFAs all increase fat oxidation and plasma PYY after distal colonic administration

Improved metabolic profile and reduced systemic inflammatory state after colonic SCFA infusions

→ *Modulating colonic SCFAs may yield new mechanisms for treating or preventing obesity and T2DM: link with dietary fibres*

Overview

- Prevalence Diabesity
- Insulin resistance, Interorgan cross talk and metabolic inflexibility
- Muscle lipid accumulation/lipid turnover
- Gut-host metabolism crosstalk: SCFA
- Dietary polyphenols and metabolic inflexibility

Polyphenols and metabolic health

- Epigallocatechin-gallate (EGCG)
  - Benefits on body weight management & risk for T2DM
    Hursel '09, Phung '10, Thavanesan '11, Jing'09
  - Human studies on RQ & fat oxidation data inconclusive
    Boschmann '07, Dulloo '99, Ichinose '10, Gosselin '13 vs Berube-Parent '05, Gregersen '09, Basu '11, Lonac '11 van Can, 2015
- Resveratrol (RSV)
  - Improved mitochondrial function & insulin sensitivity in rodents
    Lagouge '06, Baur '06, Andersen '11, Chen '11, Momken '11
  - Benefits on energy metabolism & metabolic profile in humans
    Timmers & Konings '11, Brasnyo '11 vs. Yoshino '12, Poulsen '12; Liu '14 (meta-analysis on glucose homeostasis)

Short term study

International Journal of Obesity (2014), 1–9

www.nature.com/ijo

ORIGINAL ARTICLE

Short-term supplementation with a specific combination of dietary polyphenols increases energy expenditure and alters substrate metabolism in overweight subjects

J Most, GH Goossens, JWE Jocken and EE Blaak


Epigallocatechin-gallate (EGCG)


Resveratrol (RSV)


Soy Isoflavones (SI)

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Short-term study (3d)

Complete picture of the combined short term effects of EGCG either in combination with RSV or with RSV and SI on lipolysis and fat oxidation

A) Placebo

B) EGCG+RSV

C) EGCG+RSV+SI

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Subject characteristics

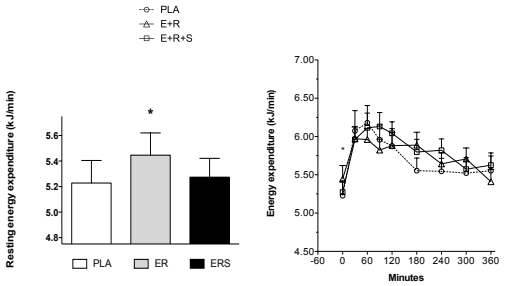
Subjects	18		(9/9)
Age (years)	34	+/-	2.57
BMI (kg/m^2)	28.9	+/-	0.42
Body fat (%)	28.0	+/-	1.88
WHR	0.83	+/-	0.02
Fasting Glucose (mmol/l)	5.02	+/-	0.08
Fasting Insulin (mU/l)	15.05	+/-	1.40
HOMA-IR	3.44	+/-	0.32

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Energy Expenditure

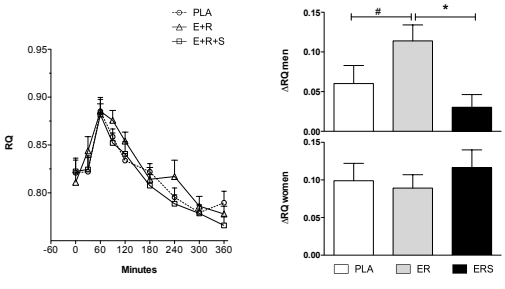


Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Respiratory quotient & metabolic flexibility



Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Conclusion

Combination of EGCG and RSV seems to be most effective in

increasing energy expenditure &

improving metabolic flexibility (in men)

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Hypothesis

Epigallocatechin-gallate (EGCG)

Resveratrol (RSV)

12 wk-supplementation with EGCG+RSV may improve

insulin sensitivity

which is accompanied by improvements in

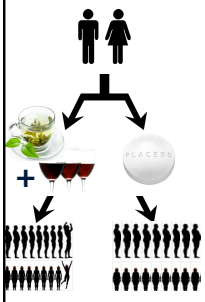
fat oxidation, lipolysis & mitochondrial function

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Long-term effects of the more effective polyphenol combination



	Meal test Indirect calorimetry	Lipid handling Substrate Oxidation
	Microdialysis (men)	Local lipolysis & blood flow in SM & AT
	Hyperinsulinemic euglycemic clamp (10 & 40mU/m²/min) Indirect Calorimetry	Hepatic & systemic insulin sensitivity Substrate oxidation in response to insulin
	Skeletal muscle biopsy	Mitochondrial function RNA expression, microarray analysis Protein levels & activity
	Adipose tissue biopsy	Adipocyte size RNA expression, microarray analysis Protein levels & activity
	Fasting blood & urin sample	Oxidative stress Inflammation & Adipokines
	Feces sample	Microbial composition Energy content Short-chain fatty acid composition
	DEXA-scan	Body composition Adipose tissue depots

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Subject characteristics

	PLA (n=20)	E+R (n=18)	P
Age (years)	38.7 ± 2.2	36.1 ± 2.2	0.43
BMI (kg/m²)	29.5 ± 0.7	29.9 ± 0.6	0.67
Waist-Hip-ratio	0.87 ± 0.02	0.87 ± 0.02	0.78
Systolic blood pressure (mmHg)	114 ± 2	117 ± 2	0.27
Diastolic blood pressure (mmHg)	76 ± 2	76 ± 2	0.86
Fasting plasma glucose (mmol/l)	5.10 ± 0.08	5.19 ± 0.09	0.44
2h-Plasma Glucose (mmol/l)	5.38 ± 0.21	5.34 ± 0.24	0.92
HbA1c (%)	5.15 ± 0.06	5.12 ± 0.06	0.76
Hemoglobine (mmol/l)	8.9 ± 0.1	8.6 ± 0.2	0.22
Hematocrit (L/L)	0.43 ± 0.01	0.39 ± 0.02	0.18
Creatinin (µmol/l)	79.5 ± 3.7	74.2 ± 2.7	0.29
ALAT (U/l)	27.9 ± 4.4	26.9 ± 2.2	0.86

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Plasma profile

	PLA (n=20)		E+R (n=18)		
	Week 0	Week 12	Week 0	Week 12	P
E (ng/ml)	0 ± 0	0 ± 0	0 ± 0	15 ± 6	0.011
R (ng/ml)	0 ± 0	0 ± 0	10 ± 10	274 ± 51	<0.001
DHR (ng/ml)	2 ± 2	0 ± 0	12 ± 12	192 ± 28	<0.001
Fasting plasma glucose (mmol/l)	5.0 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	0.690
Fasting plasma insulin (mU/l)	10.1 ± 1.5	10.0 ± 1.0	8.1 ± 1.0	7.4 ± 0.6	0.667
HOMA-IR	2.3 ± 0.4	2.2 ± 0.2	1.8 ± 0.2	1.7 ± 0.1	0.740
FFA (umol/l)	553 ± 33	533 ± 43	523 ± 24	555 ± 35	0.367
TAG (mmol/l)	1.3 ± 0.2	1.5 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	0.182
Cholesterol (mmol/l)	5.9 ± 0.3	5.8 ± 0.3	6.0 ± 0.2	5.8 ± 0.2	0.489
HDL-C (mmol/)	1.23 ± 0.07	1.20 ± 0.07	1.27 ± 0.08	1.29 ± 0.09	0.142
LDC-L (mmol/l)	4.40 ± 0.27	4.30 ± 0.27	4.45 ± 0.22	4.20 ± 0.16	0.385
Cholesterol/HDL-C	5.09 ± 0.34	5.27 ± 0.43	5.16 ± 0.42	4.94 ± 0.42	**0.027**

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Body composition – DXA scan

PLA (n=20) E+R (n=18)

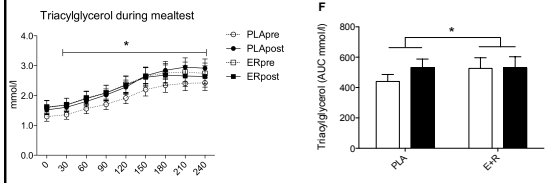
	Week 0	Week 12	Week 0	Week 12	P
Body weight (kg)	88.3 ± 2.8	88.6 ± 2.9	92.4 ± 3.6	92.0 ± 3.8	0.413
Body fat (kg)	26.7 ± 1.9	26.5 ± 1.9	29.4 ± 1.4	29.1 ± 1.6	0.848
Body fat (%)	30.1 ± 1.9	29.9 ± 1.8	31.9 ± 1.4	31.5 ± 1.4	0.840
Lean mass (kg)	59.5 ± 2.5	59.6 ± 2.5	61.2 ± 3.0	61.1 ± 3.2	0.734
Upper body fat (kg)	13.1 ± 1.0	12.9 ± 1.0	14.0 ± 0.7	13.8 ± 0.7	0.925
Lower body fat (kg)	9.4 ± 0.9	9.4 ± 0.9	11.0 ± 0.8	10.8 ± 0.9	0.512
Visceral fat (kg)	0.48 ± 0.04	0.50 ± 0.05	0.44 ± 0.05	0.41 ± 0.04	**0.088**

Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

High-fat mixed-meal test: circulating metabolites

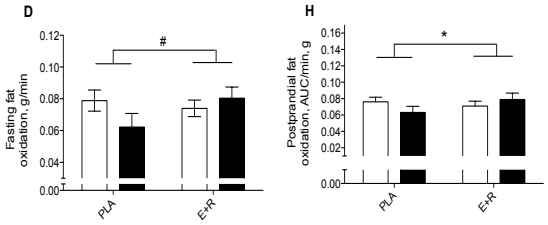


Department of Human Biology

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Fat oxidation, fasting and postprandial

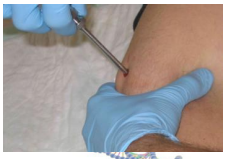


Department of Human Biology

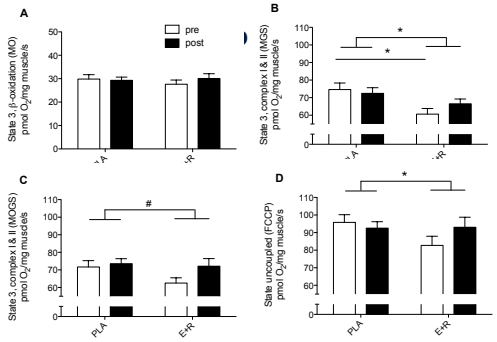
Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

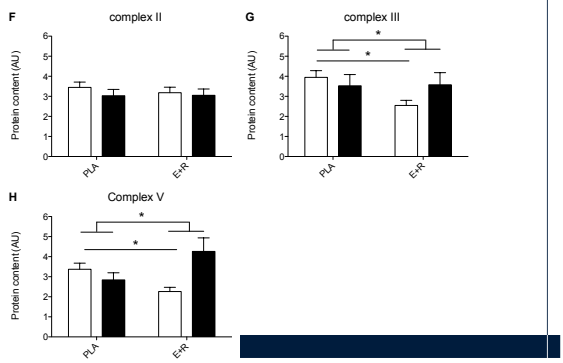
Adipose tissue and Skeletal muscle biopsies



Mitochondrial capacity



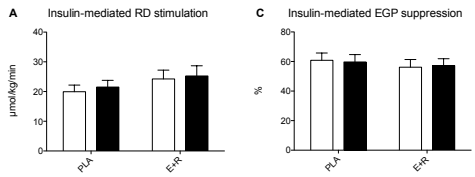
Proteins of oxidative phosphorylation



Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Peripheral and hepatic insulin sensitivity



Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Conclusion

12 wk-supplementation EGCG+RSV…
- Tended to reduce visceral fat
- Reduced triglyceride concentrations
- Increased fat oxidation
- Improved mitochondrial oxidative capacity

…did not affect
- Insulin sensitivity
- Body mass/composition

in overweight men and women

Department

Maastricht University Leading on Learning!

NUTRIM School for Nutrition, Toxicology and Metabolism

Summary

- The insulin resistant muscle is characterized by a reduced lipid turnover of in particular saturated fatty acids
- Manipulation of diet or dietary components may improve metabolic flexibility and metabolic profile
  - -via SCFA (dietary fibre)
  - -polyphenols
- Towards an optimised lifestyle intervention?

Department of Human Biology

Maastricht University Leading on Learning! ZonMw

NUTRIM School for Nutrition, Toxicology and Metabolism

Collaborations/Acknowledgements

- Gijs Goossens
- Johan Jocken
- Dorien Reijnders
- Emanuel Canfora
- Rudi Stinkens
- Max Vogel
- Jasper Most
- Kenneth Verboven
- Kirsten vander Beek
- Kees Dejong
- Ad Masclee
- Freddy Troost

Dept Human Biology, general Surgery, gastroenterology, MUMC

And external Collaborations
Top Institute Food and Nutrition (project GH003, microbiota, energy balance and metabolism)
Max Nieuwdorp, AMC
EU consortia: EU-Lipgene, MIRdiet

Diabetes Fonds

EFSD European Foundation for the Study of Diabetes