Optimizing Blood Sugar and Fat Burning Machinery Through the Leptin-Gut Metabolic Axis

by Mike Mutzel, MS

Disclaimer

- i.The information, comments, and opinions expressed in this presentation are those of the speaker based on their own clinical experience and interpretation of the literature and for educational purposes only. Practitioners should evaluate the information, comments, and opinions using their own expertise coupled with an assessment for each patient.

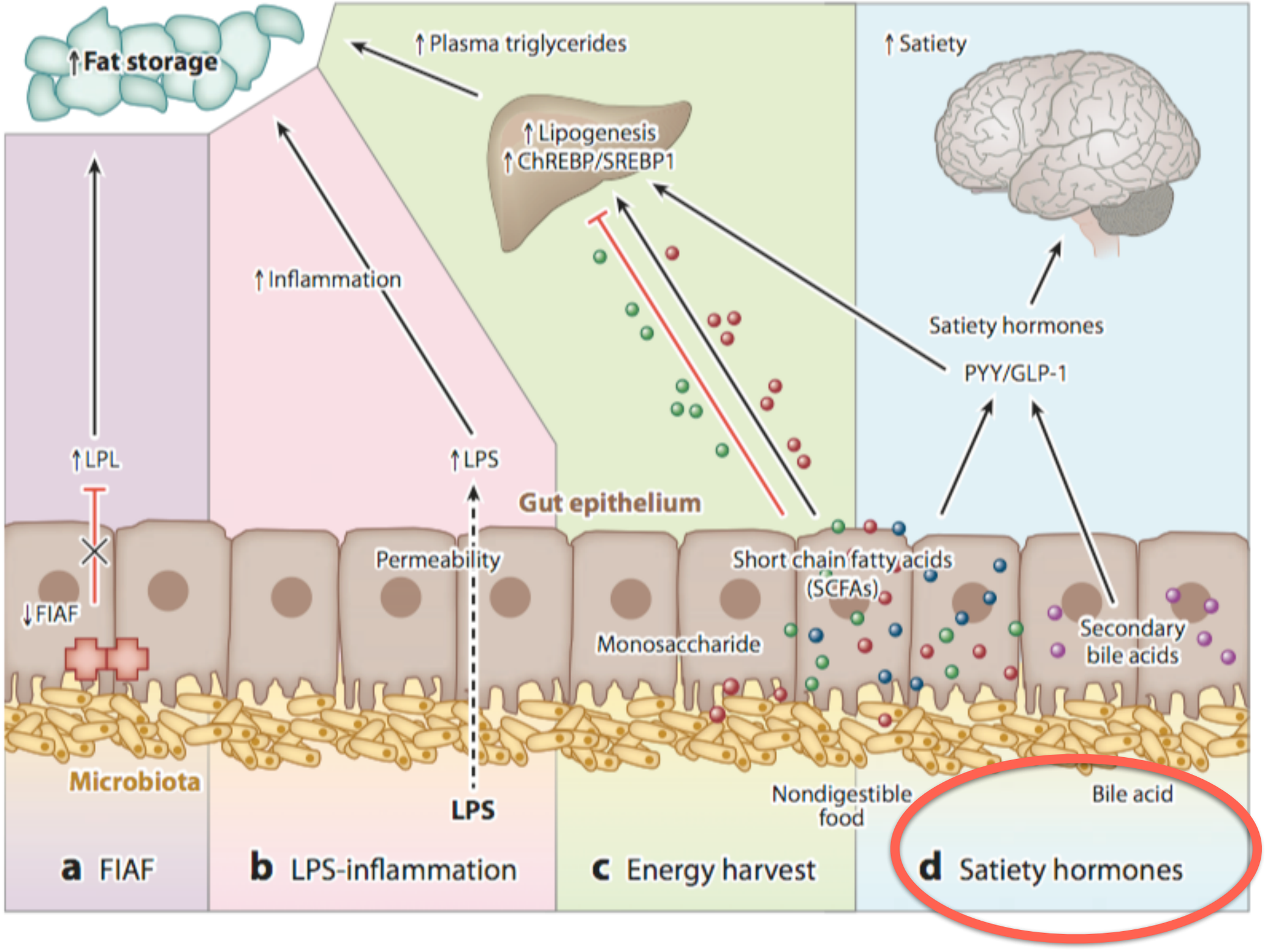
- ii. The information in this presentation is neither approved nor endorsed by SHINE. The content herein does not necessarily represent the views or brand of SHINE or Dr. Rita Marie. None of the content herein has been evaluated by the Food and Drug Administration.

Disclosure

- I am a not being paid for this talk.
- I am a consultant for XYMOGEN
- I am selling Belly Fat Effect books on amazon.com and through other book retailers

THREE BIG IDEAS FROM OUR DISCUSSION

- Overview of the metabolic switches of the gastrointestinal tract—that are highly modifiable
- Nutritional interventions to improve the gut-metabolic axis
- Leptin 2.0: Exploring gut-induced leptin resistance and the extra-metabolic roles of leptin


↑Fat storage
↑Plasma triglycerides
↑Satiety
↑Lipogenesis
↑ChREBP/SREBP1
↑Inflammation
Satiety hormones
PYY/GLP-1
↑LPL
↑LPS
Gut epithelium
Permeability
Short chain fatty acids
(SCFAs)
↓FIAF
Monosaccharide
Secondary
bile acids
Microbiota
LPS
Nondigestible
food
Bile acid
a FIAF
b LPS-inflammation
c Energy harvest
d Satiety hormones
Butyrate
Acetate
Propionate
Secondary
bile acids

Cephalic Phase: preparing the body for food

Salivary amylase

Digestive secretions

Vagal Nerve

Liver

Gall bladder

Bile duct

Pyloric sphincter

Stomach

HCl

Incretin Hormones

CCK, GLP-1, GLP-2, GIP, PPY

Secretin ← Acidic chyme

Small intestine

BELLY FAT EFFECT™

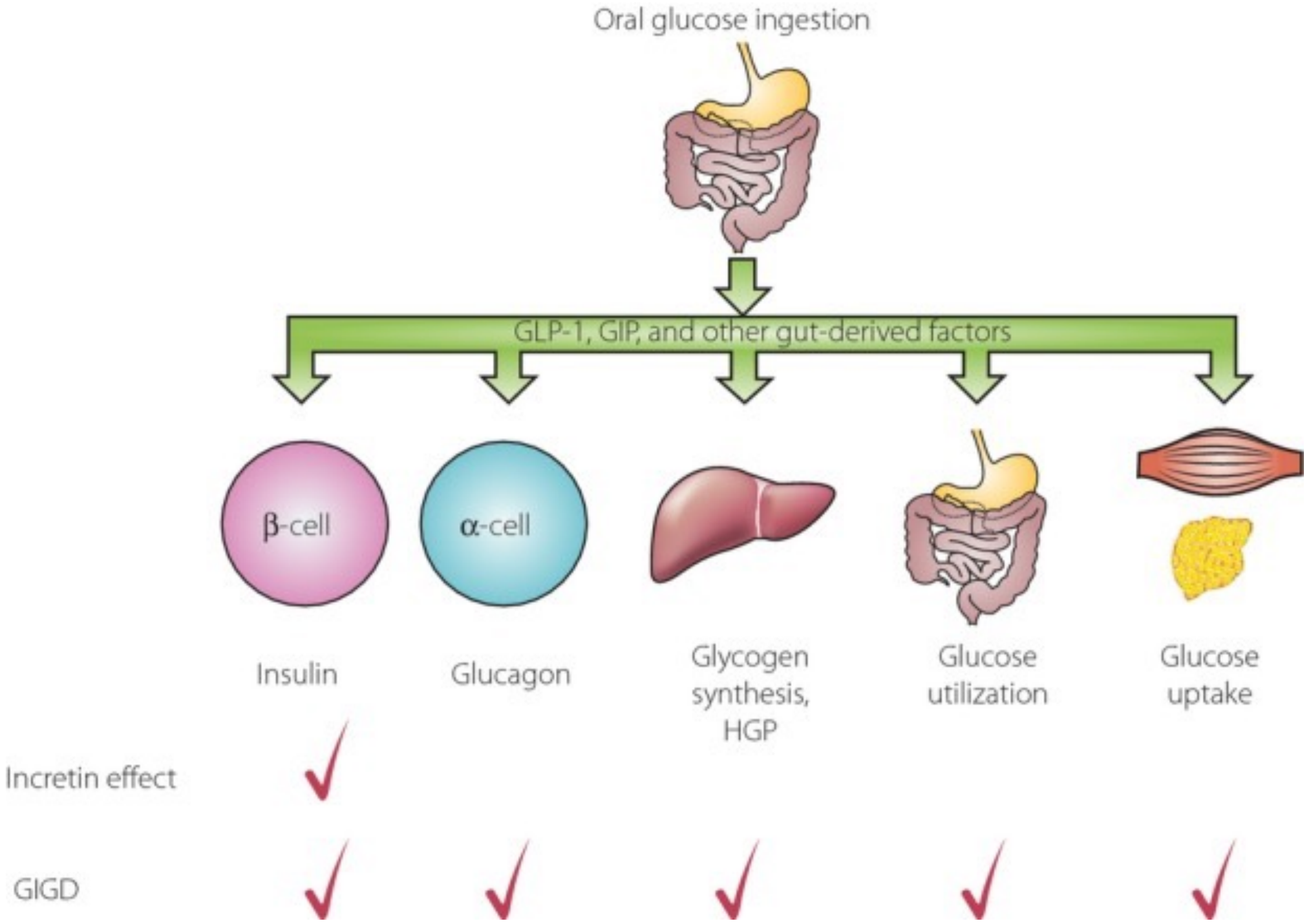
What is the incretin effect?

"….a humoral substance is released from the **jejunal wall** (small intestine) during glucose absorption which acts by **stimulating the release of insulin** from the pancreatic islet cells."

–Neil McIntyrre 1965

McINTYRE, N., HOLDSWORTH, C. D., & TURNER, D. S. (1965). Intestinal Factors in the Control of Insulin Secretion. The Journal of Clinical Endocrinology and Metabolism.

The **Incretin Effect** and the **Gastrointestinally-Mediated Glucose Disposal (GIGD)**



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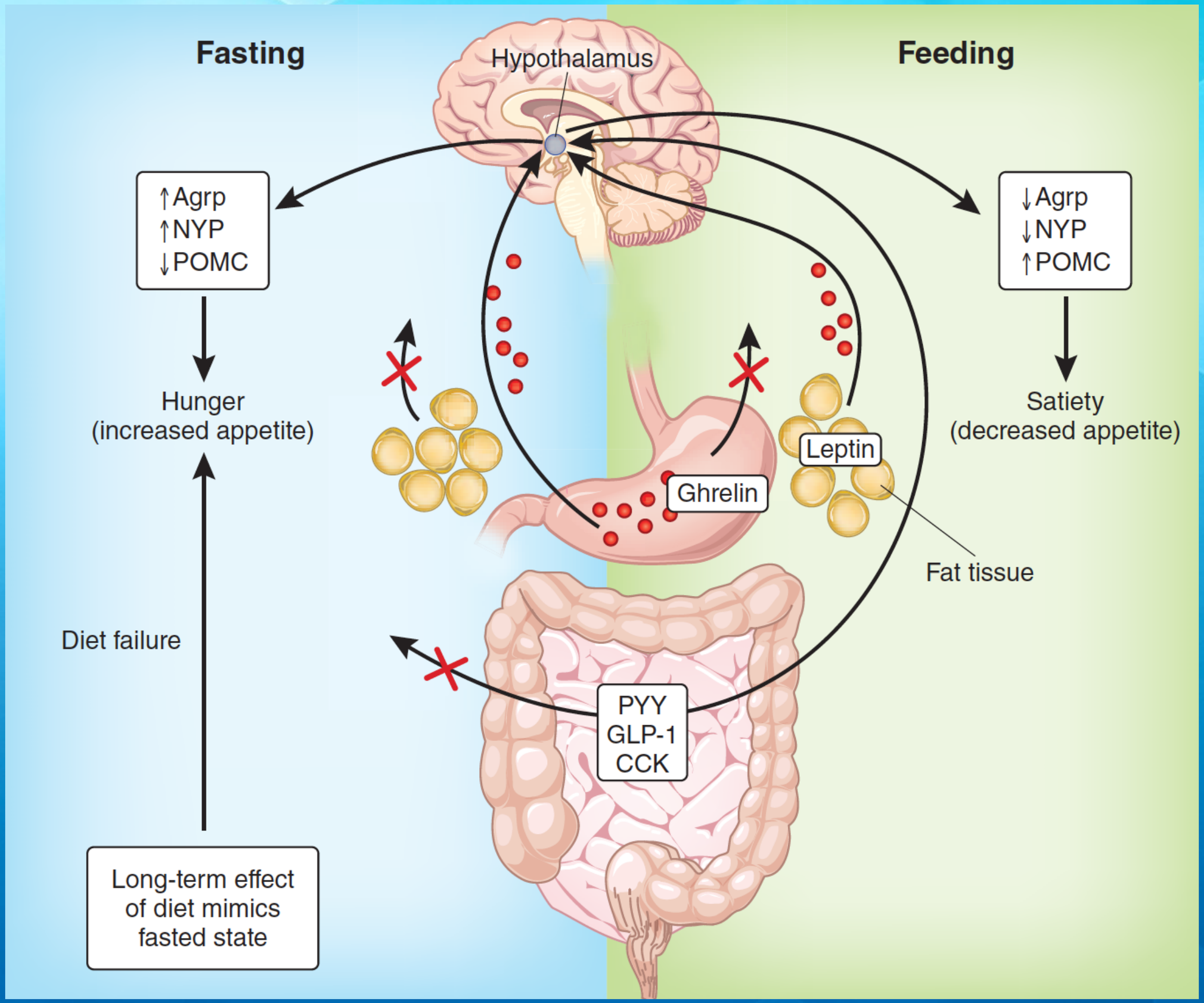


Larder, R., & O'Rahilly, S. (2012). Guts over glory—why diets fail. Nature Medicine, 18(5), 666–667. http://doi.org/10.1038/nm.2747

Diabetologia
DOI 10.1007/s00125-012-2561-x

THEN AND NOW

The incretin hormones: from scientific discovery to practical therapeutics

S. Mudaliar · R. R. Henry

Received: 23 December 2011 / Accepted: 21 February 2012

Abstract The incretins are gut hormones secreted in re-

and treating clinicians. In this edition of 'Then and Now,' it is useful to look back 25 years and reflect upon the developments in this field since Nauck and colleagues published two seminal papers. In 1986 they first documented a reduced incretin effect in patients with type 2 diabetes (*Diabetologia* 29:46–52), and then in 1993 they demonstrated that, in patients with poorly controlled type 2 diabetes, a single exogenous infusion of an incretin (GLP-1) increased insulin levels in a glucose-dependent manner and normalised fasting hyperglycaemia (*Diabetologia* 36:741–744). In the ensuing 26 years, progress in the field of incretin hormones has resulted in a greater understanding of the relative roles of GLP-1 and glucose-dependent insulinotropic polypeptide secretion and activity in the pathogenesis of type 2 diabetes and the important recognition that native GLP-1 is quickly degraded by the ubiquitous protease DPP-4. This has led to

extra-glycaemic effects that could translate into potential cardiovascular and other benefits.

“In 1986 Nauck and colleagues were the first to report **reduced signaling of GLP-1 and CCK in type-2 diabetes**….26 years later and we know now have an expanded understanding about how to optimize these **gut-derived metabolic hormones**, through a **nutritional perspective**.”

Keywords GIP · GLP-1 · Incretin hormones

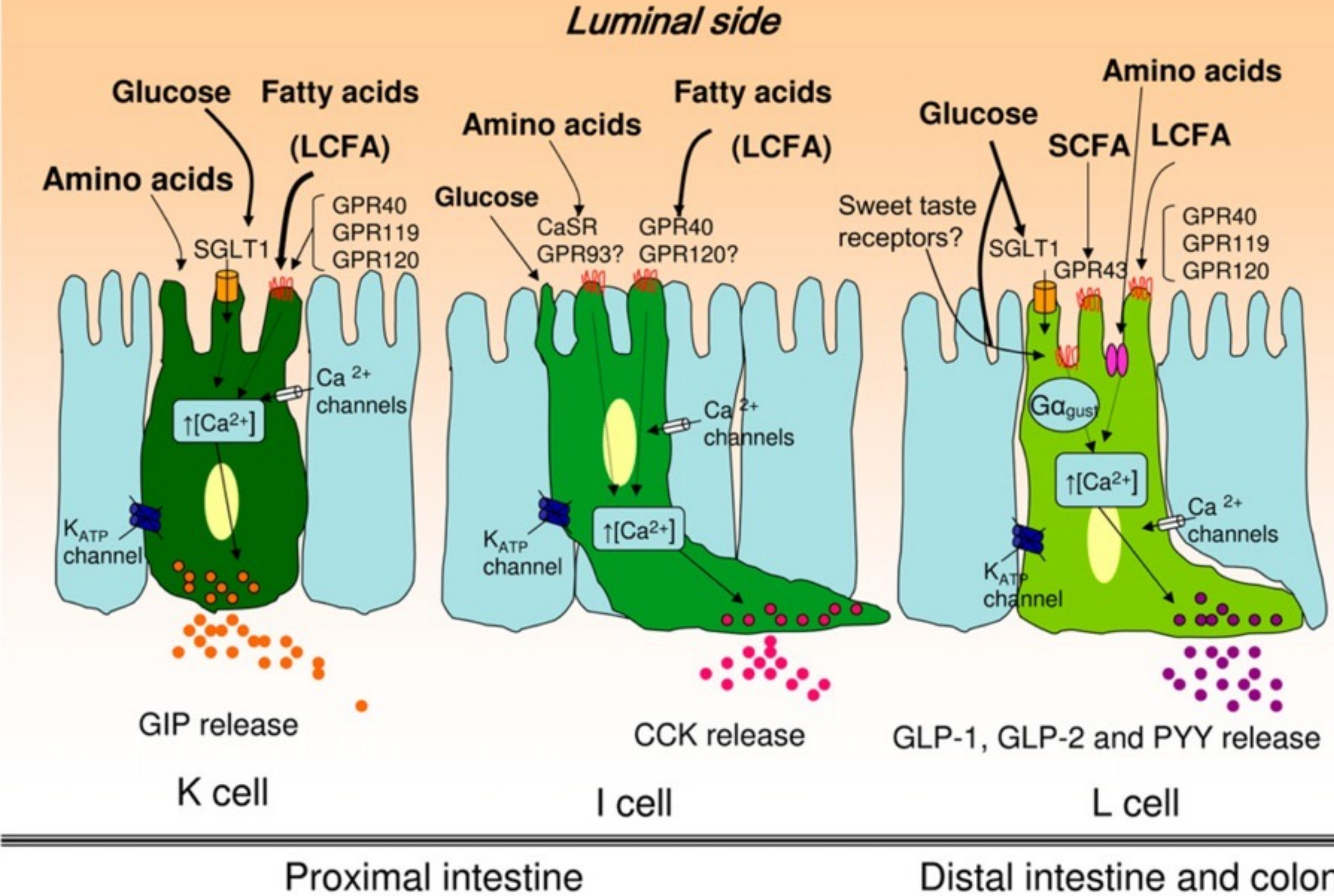
Abbreviations

CNS	Central nervous system
DPP-4	Dipeptidyl peptidase IV
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1

Then

In their 1986 *Diabetologia* paper [1], Nauck et al described

Mudaliar, S., & Henry, R. R. (2012). The incretin hormones: from scientific discovery to practical therapeutics. *Diabetologia*, *55*(7), 1865–1868. http://doi.org/10.1007/s00125-012-2561-x



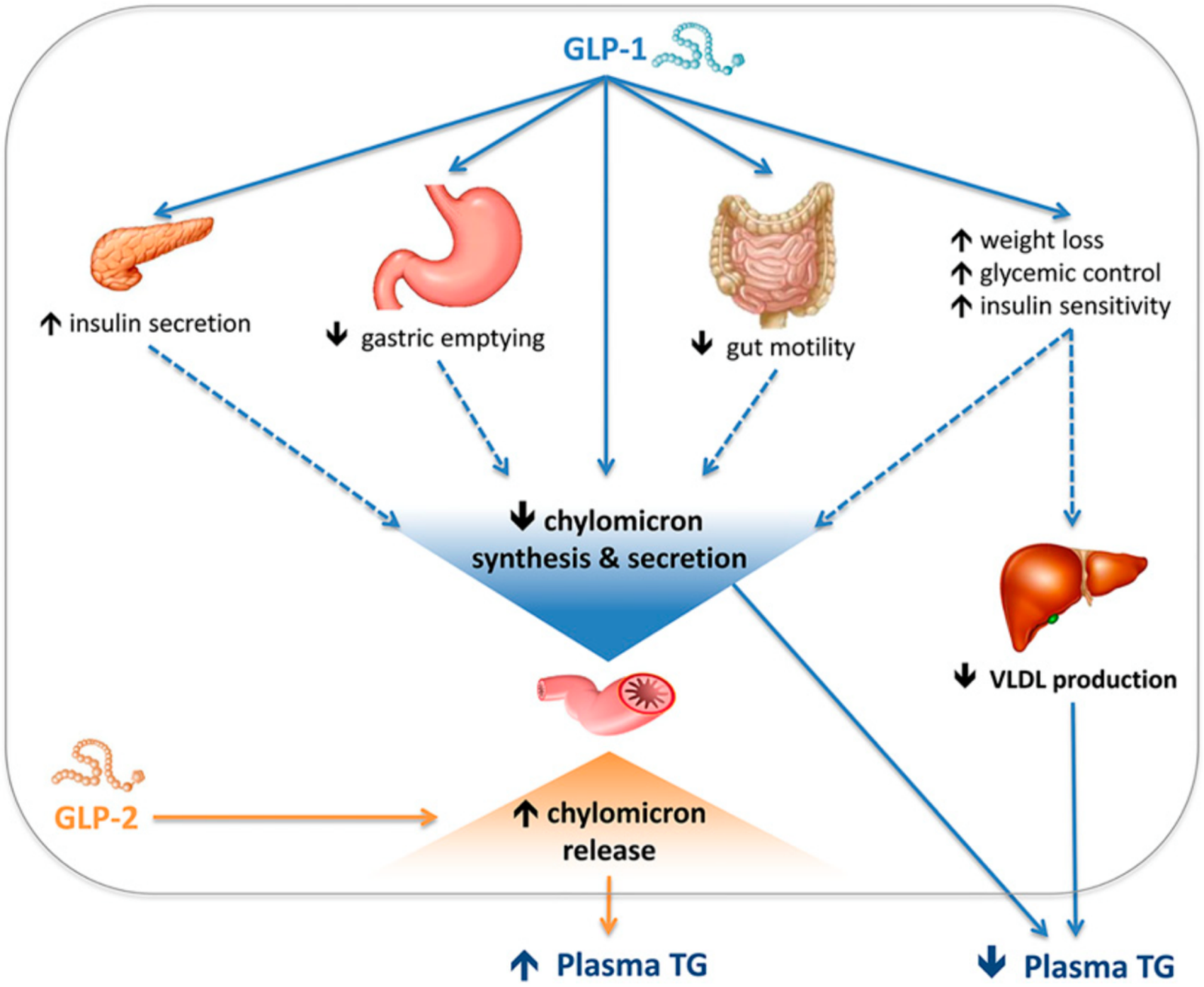
Moran-Ramos, S., Tovar, A. R., & Torres, N. (2012). Diet: friend or foe of enteroendocrine cells--how it interacts with enteroendocrine cells. Adv Nutr, 3(1), 8–20. doi:10.3945/an.111.000976

Changting Xiao,[1] Satya Dash,[1] Cecilia Morgantini,[1] Khosrow Adeli,[2] and Gary F. Lewis[1]

Gut Peptides Are Novel Regulators of Intestinal Lipoprotein Secretion: Experimental and Pharmacological Manipulation of Lipoprotein Metabolism

Diabetes 2015;64:2310–2318 | DOI: 10.2337/db14-1706

Individuals with metabolic syndrome and frar diabetes are at increased risk of atherosclerotic vascular disease, partially due to the presenc and lipoprotein abnormalities. In these condit liver and intestine overproduce lipoprotein exacerbating the hyperlipidemia of fasting a prandial states. Incretin-based, antidiabetes (i.e., glucagon-like peptide [GLP]-1 receptor and dipeptidyl peptidase-4 inhibitors) have pro cacy for the treatment of hyperglycemia. Evi accumulating that these agents also improv and postprandial lipemia, the latter more sig than the former. In contrast, the gut-derivec GLP-2, cosecreted from intestinal L cells wit has recently been demonstrated to enhance lipoprotein release. Understanding the roles emerging regulators of intestinal lipoprotein may offer new insights into the regulation of lipoprotein assembly and secretion and prov opportunities for devising novel strategies to hyperlipidemia, with the potential for cardio disease reduction.



Individuals with metabolic syndrome or fran diabetes (T2D) are at increased risk for cardi disease (CVD) contributed to by the atherogeni demia that frequently accompanies these c (1,2). The typical lipid abnormalities in these c include elevated plasma triglycerides (TG)

Diabetologia (2015) 58:1745–1750
DOI 10.1007/s00125-015-3608-6

COMMENTARY

Incretin-based therapies: where will we be 50 years from now?

Juris J. Meier[1] · **Michael A. Nauck**[1]

Received: 4 February 2015 / Accepted: 17 March 2015 / Published online: 21 May 2015

Abstract The development of incretin-based therapies (glucagon-like peptide 1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) has changed the landscape of type 2 diabetes management over the past decade. Current developments include longer-acting GLP-1 receptor agonists, fixed-ratio combinations of GLP-1 analogues and basal insulin, as well as implantable osmotic minipumps for long-term delivery of GLP-1 receptor agonists. In longer terms, oral or inhaled GLP-1 analogues may become a reality. In addition, oral enhancers of GLP-1 secretion (e.g. via G-protein-coupled receptors, nuclear farnesoid-receptor X and the G-protein-coupled bile acid-activated receptor [TGR5]) are currently being explored in experimental studies. Combination of GLP-1 with other gut hormones (e.g. peptide YY, glucagon, gastrin, glucose-dependent insulinotropic polypeptide [GIP], secretin, cholecystokinin, vasoactive intestinal polypeptide and pituitary adenylate cyclase-activating polypeptide) may enhance the glucose- and weight-lowering effect of GLP-1 alone, and dual or triple hormone receptor agonists may even exploit the properties of different peptides with just one molecule. There is also an increasing interest in employing incretin-based therapies in other areas, such as type 1 diabetes, impaired glucose metabolism, obesity, polycystic ovary syndrome, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), psoriasis or even neurodegeneration. Thus, incretin-based therapies may continue to broaden the therapeutic spectrum for type 2 diabetes and for various other indication
commentaries
personal opinio
brate the 50th a

Keywords GIP

Abbreviations
DPP-4 Dipep
GIP Gluco
GLP-1 Gluca
IFG Impai
IGT Impai
PYY Peptid

Where are we

The developme
unique exampl
glucose-lowerin
ings from acad
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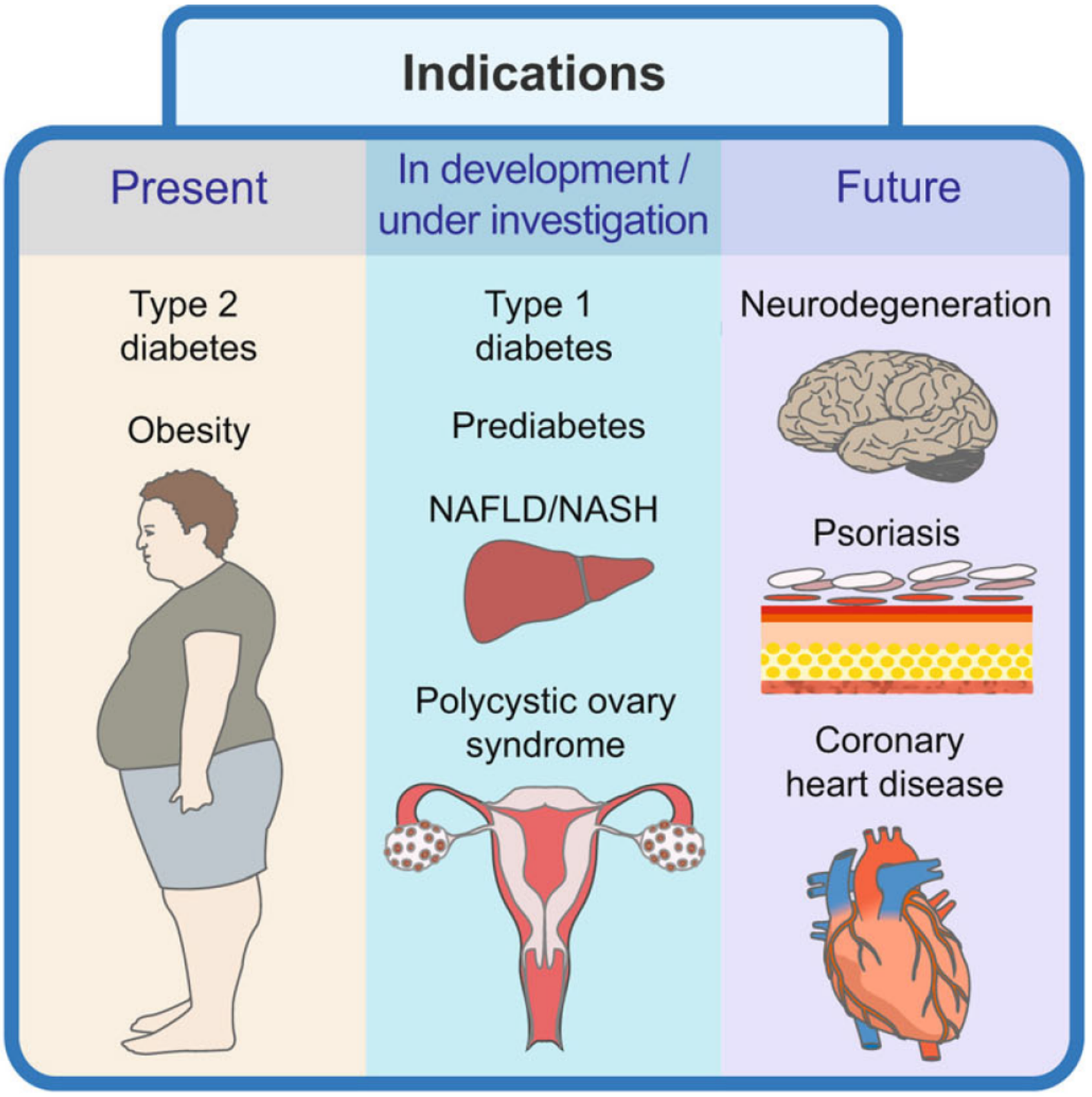
tide (GIP) and glucagon-like peptide-1 (GLP-1) [1]. These peptide hormones were later synthesised and prepared for in-



Bowels control brain: gut hormones and obesity

Benjamin C. T. Field, Owais B. Chaudhri and Stephen R. Bloom

Abstract | Food intake and energy expenditure are tightly regulated by the brain, in a homeostatic process that integrates diverse hormonal, neuronal and metabolic signals. The gastrointestinal tract is an important source of such signals, which include several hormones released by specialized enteroendocrine cells. These hormones exert powerful effects on appetite and energy expenditure. This Review addresses the physiological roles of peptide YY, pancreatic polypeptide, islet amyloid polypeptide, glucagon-like peptide 1, glucagon, oxyntomodulin, cholecystokinin and ghrelin and discusses their potential as targets for the development of novel treatments for obesity.

Field, B. C. T. *et al. Nat. Rev. Endocrinol.* advance online publication 29 June 2010; doi:10.1038/nrendo.2010.93

Gut Sensors:
Enteroendocrine Cells

"A potential therapy for obesity might be based on the concept of pharmacological mimicry of the hormonal milieu after bariatric surgery."

Introduction

Energy intake and expenditure are regulated by a homeostatic mechanism; in healthy adults, body weight thus remains relatively constant over decades despite large short-term fluctuations in food intake and physical activity. This remarkable feat is achieved by a complex and nucleus accumbens, where reward is assigned to them in a process involving dopaminergic, opioid and 5-hydroxytryptamine signaling. Inputs from these pathways are integrated with circulating signals of nutritional state, such as fatty acids and the adipocyte hormone

toxic substances in the blood; the volume, composition and satiating effect of nutrients in the gastrointestinal tract; and the appearance, aroma and taste of potential foodstuffs. This information is integrated with neuronal contributions from pleasure and reward pathways, as well as higher cognitive functions, such as an awareness of social context. Efferent signals from the homeostatic network are directed to the neuroendocrine axes, autonomic nervous system and diverse regions of the CNS. The result is a finely controlled, continuous adaptation to, and alteration of, a fluctuating energy requirement.

Neuronal control of energy homeostasis

Meal-related hormonal and neuronal signals from the gastrointestinal tract are received via the blood in the area postrema and through vagal afferent fibers in the nucleus of the tractus solitarius (Figure 1). These sensory inputs are transmitted via the parabrachial nucleus and ventral tegmental area to other centers, including the amygdala

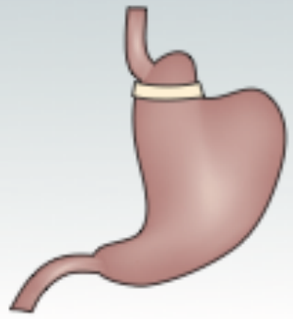
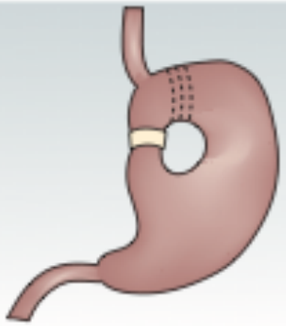
is inhibited. Axons from both types of neurons project in parallel to the paraventricular nucleus and lateral hypothalamic area. Release of α-melanocyte-stimulating hormone by POMC-expressing neurons leads to activation of the melanocortin receptor 4 (MC4R), which results in the reduction of food intake and an increased energy expenditure. By contrast, release of NPY activates Y_1 and Y_5 receptors, which increases food intake and reduces energy expenditure. NPY-expressing neurons also release agouti-related peptide, an endogenous antagonist of the MC4R. The response to this dual innervation within the paraventricular nucleus leads to modulation of energy expenditure via the thyroid and adrenal axes and the sympathetic nervous system.

Within the lateral hypothalamic area, second order neurons that express melanin-concentrating hormone and orexins are of importance in modulating food intake. In the ventromedial nucleus, neurons that express brain-derived neurotrophic factor regulate palatable food ingestion via interactions with the amygdala and nucleus accumbens. Motivation and cognition influence energy homeostasis and are influenced in turn by nutritional

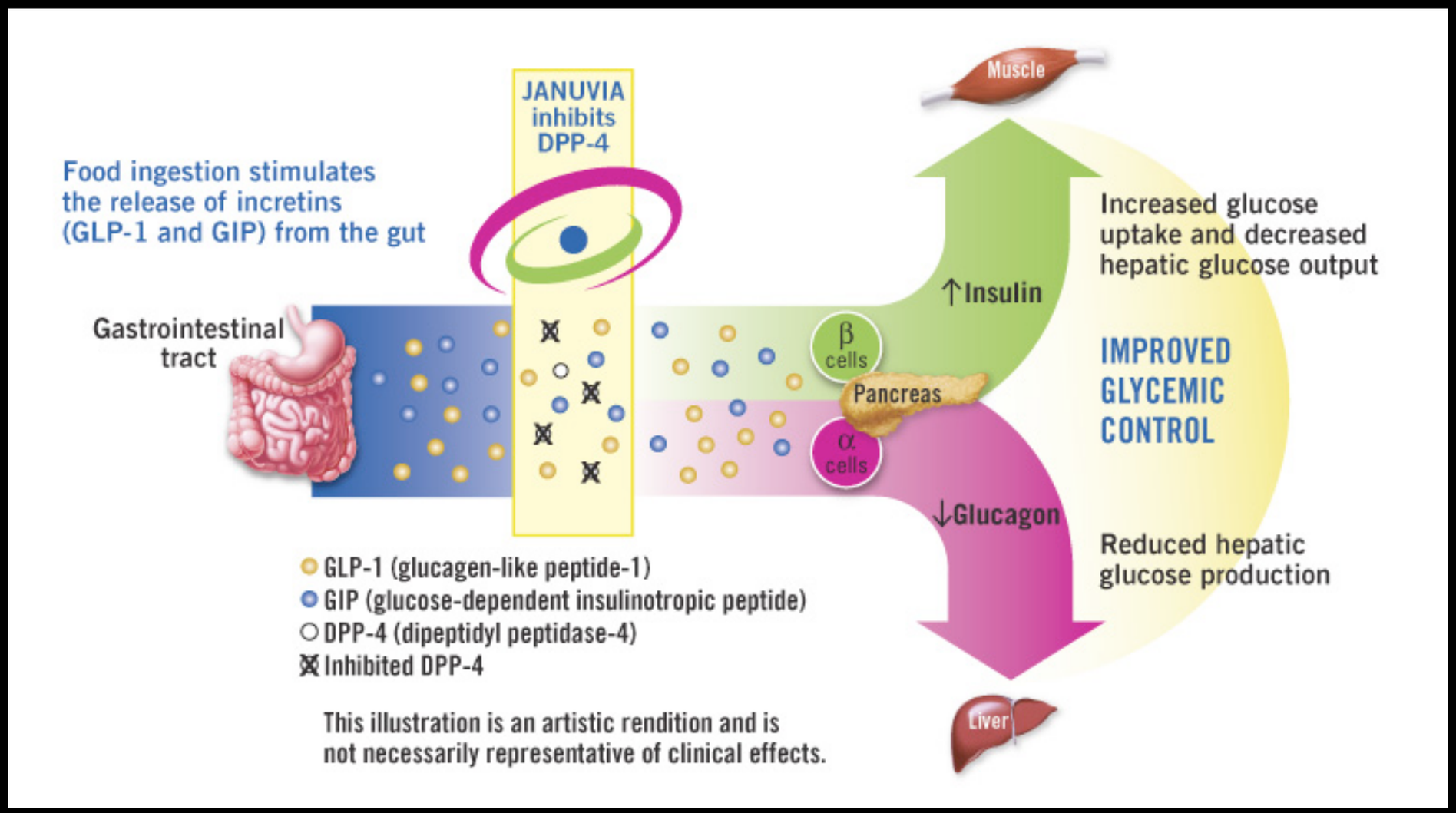
Competing interests

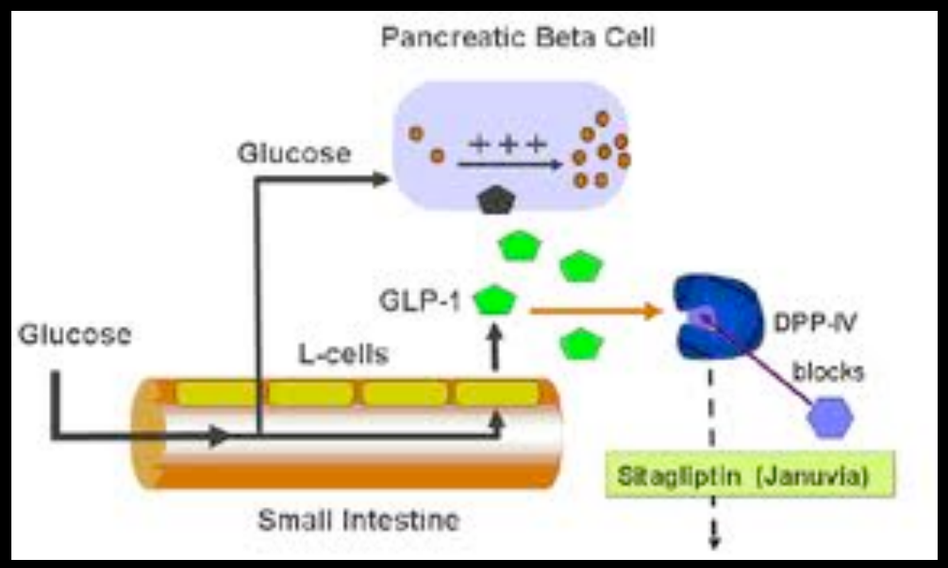
Division of Diabetes, Endocrinology and Metabolism, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK
(**B. C. T. Field, O. B. Chaudhri, S. R. Bloom**)

Increase in Gut peptides with bariatric surgical procedures

Procedure	Anatomy	Malabsorption	Hormone effect	Diabetes resolution	Weight loss
Adjustable gastric banding		–	Ghrelin ↑ PYY No change GLP-1 No change	With weight loss	+
Vertical banded gastroplasty		–	Ghrelin ↑ PYY No change GLP-1 No change	With weight loss	+
Sleeve gastrectomy		–	Ghrelin ↓ PYY ↑ GLP-1 ↑	With weight loss	++
Roux-en-Y gastric bypass		–	Ghrelin ↑ or no change PYY ↑↑ GLP-1 ↑↑	Rapid	++

The new wave of diabetic drugs modulate intestinal endocrine signaling peptides GLP-1 and DPP-4





Januvia is a DPP-4 inhibitor, blocking the breakdown of insulin-sensitizing GLP-1

**GI-side effects, expensive

DIAB-6125; No. of Pages 4

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DIABETES RESEARCH AND CLINICAL PRACTICE XXX (2014) XXX.E1–XXX.E4

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ELSEVIER

International Diabetes Federation

Mechanism of increase in plasma intact GLP-1 by metformin in type 2 diabetes: Stimulation of GLP-1 secretion or reduction in plasma DPP-4 activity?

Tongzhi Wu [a,b], *Sony S. Thazhath* [a,b], *Michelle J. Bound* [a,b], *Karen L. Jones* [a,b], *Michael Horowitz* [a,b], *Christopher K. Rayner* [a,b,*]

[a] *Discipline of Medicine, The University of Adelaide, Adelaide, South Australia 5000, Australia*

[b] *Centre of Research Excellence in Translating Nutritional Science to Good Health, South Australia 5000, Australia*

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Dipeptidyl peptidase-4
Metformin
Enteral nutrition

ABSTRACT

Metformin was reported to incr
trations in type 2 diabetes. Th
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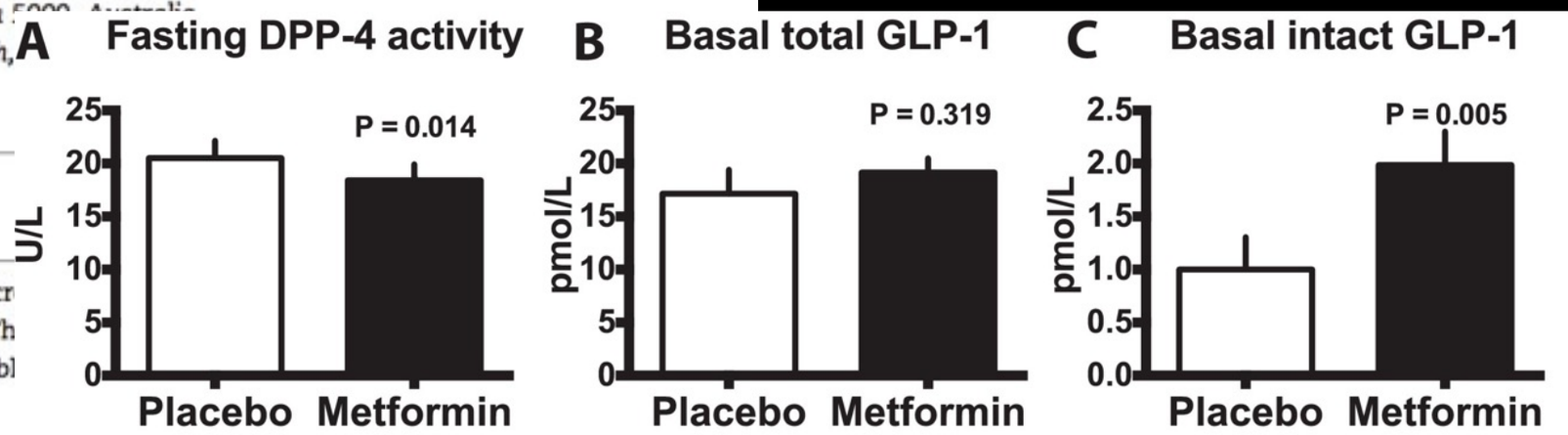
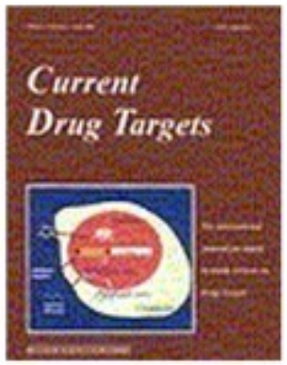
contribution.





Dipeptidyl Peptidase IV Inhibitors: A New Paradigm in Type 2 Diabetes Treatment

Authors: Janardhan, Sridhara; Narahari Sastry, G.

Source: Current Drug Targets, Volume 15, Number 6, June 2014, pp. 600-621(22)

Publisher: Bentham Science Publishers

Abstract:

Dipeptidyl peptidase IV (DPP4) is a promising target for the treatment of chronic metabolic type 2 diabetes mellitus (T2D). DPP4 is a highly specific serine protease involved in the regulation and cleavage of two incretin hormones, glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These incretin hormones are released by the gastrointestinal tract in response to ingestion of food and stimulate insulin secretion and thereby regulate glucose homeostasis with a low risk of hypoglycemia and glucagon secretion. Currently different chemical classes of DPP4 inhibitors are in last-stage of clinical trials and few of them such as sitagliptin, vildagliptin, saxagliptin alogliptin and linagliptin have already been successfully released into market. These drugs have been approved as either monotherapy or combination therapy with other oral hypoglycemic agents such as metformin, pioglitazone, sulfonylurea, glyburide and glibenclamide for the treatment of T2D. Though several clinical trial compounds were discontinued because of severe adverse toxic effects that are associated with other prolyldipeptidases include DPP8 and DPP9. The current review provides an overview of DPP4 and its inhibitors with emphasis on the structure, expression, activity, selectivity and pharmacokinetics information. This review further dwells upon the issues relating to the rational design and development of selective DPP4 inhibitors for the treatment of T2D.

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REVIEW

Dipeptidyl peptidase-4: A key player in chronic liver disease

Minoru Itou, Takumi Kawaguchi, Eitaro Taniguchi, Michio Sata

Minoru Itou, Eitaro Taniguchi, Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume 830-0011, Japan
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Author contributions: Itou M and Kawaguchi T collected the materials and wrote the manuscript; Taniguchi E discussed the topic; Sata M supervised the manuscript.
Correspondence to: Takumi Kawaguchi, MD, PhD, Division of Gastroenterology, Department of Medicine and Department of Digestive Disease Information and Research, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. takumi@med.kurume-u.ac.jp
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Key words: Incretin; Viral hepatitis; Insulin resistance; Steatohepatitis; (
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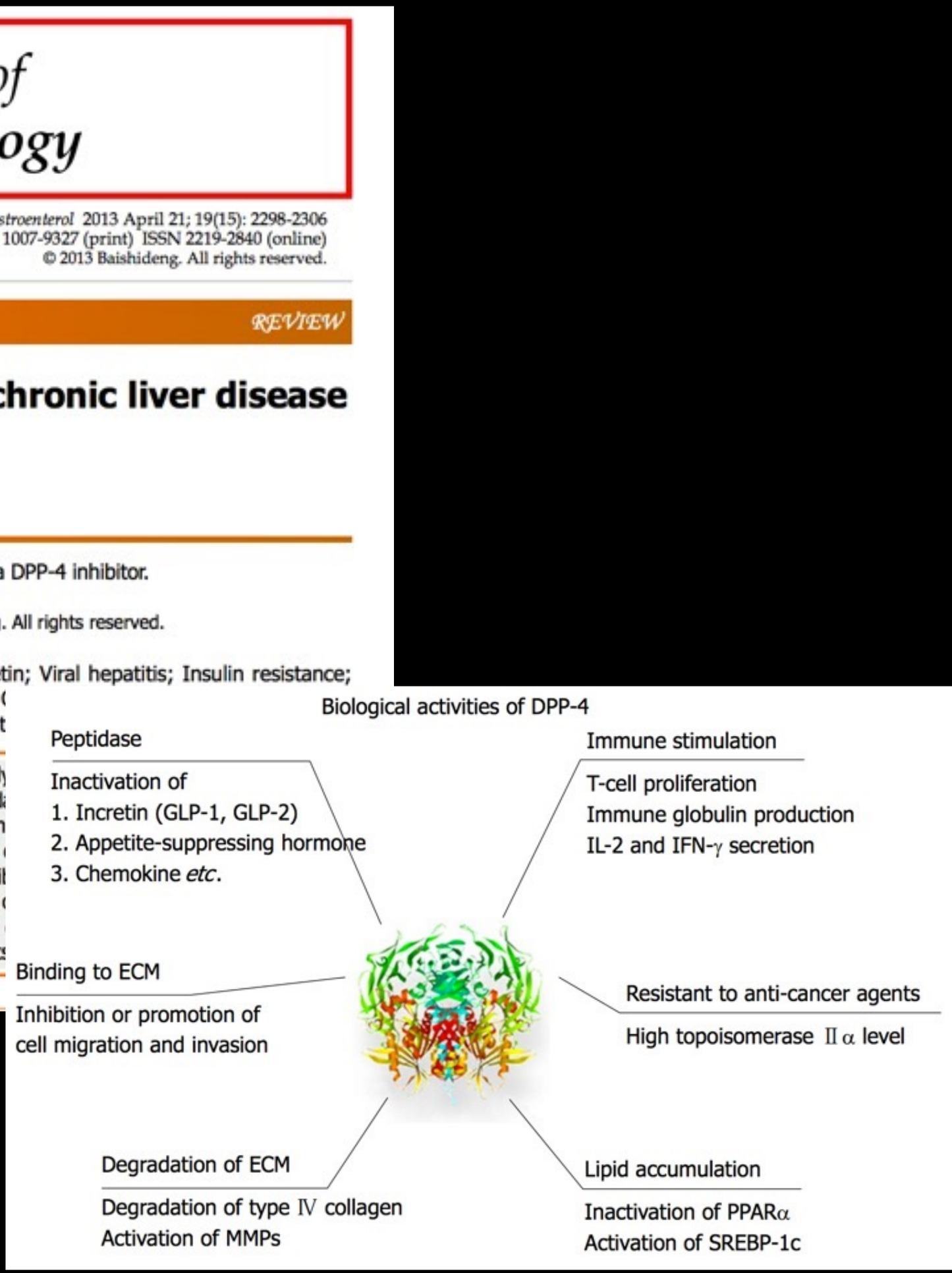

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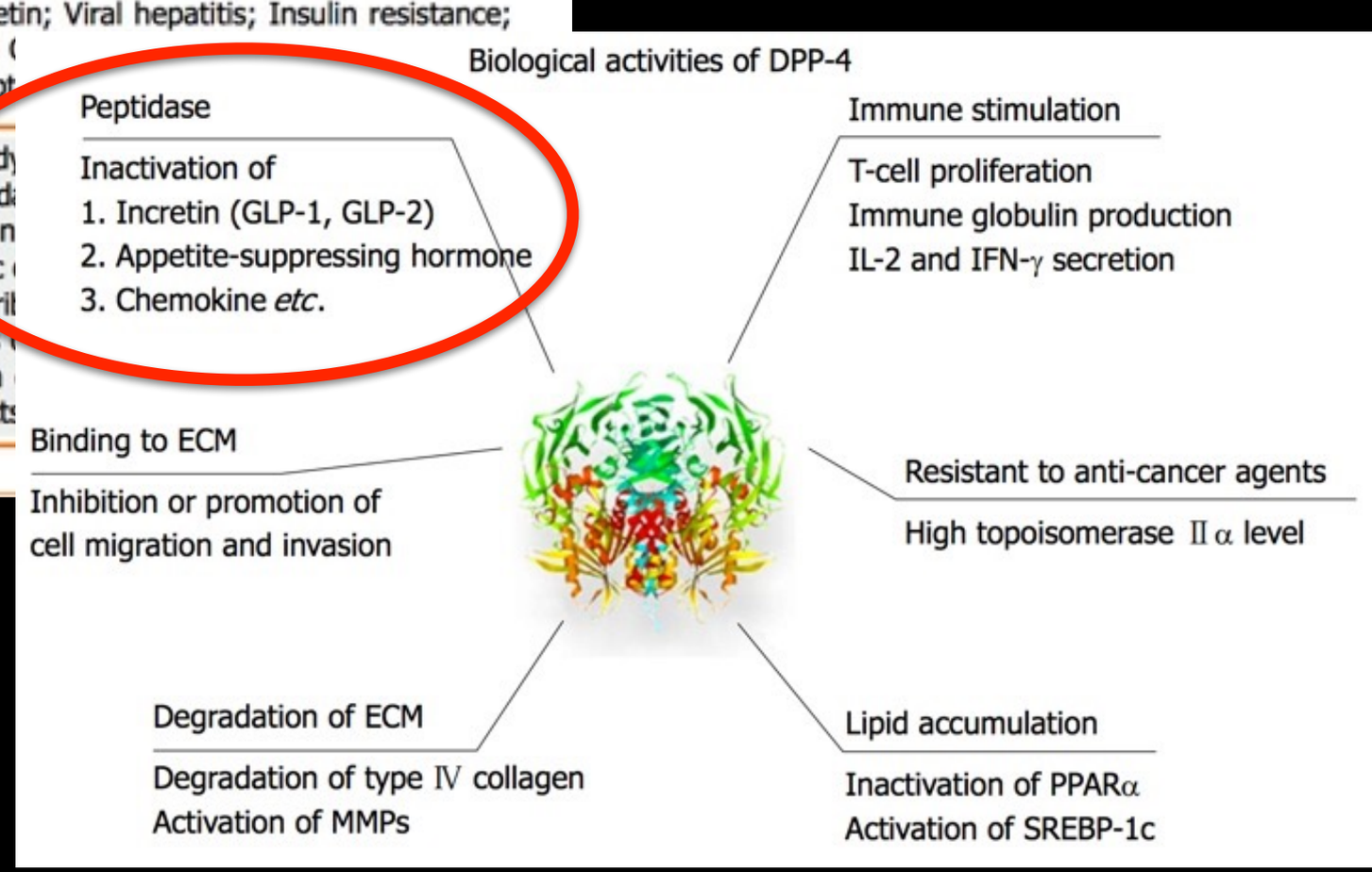

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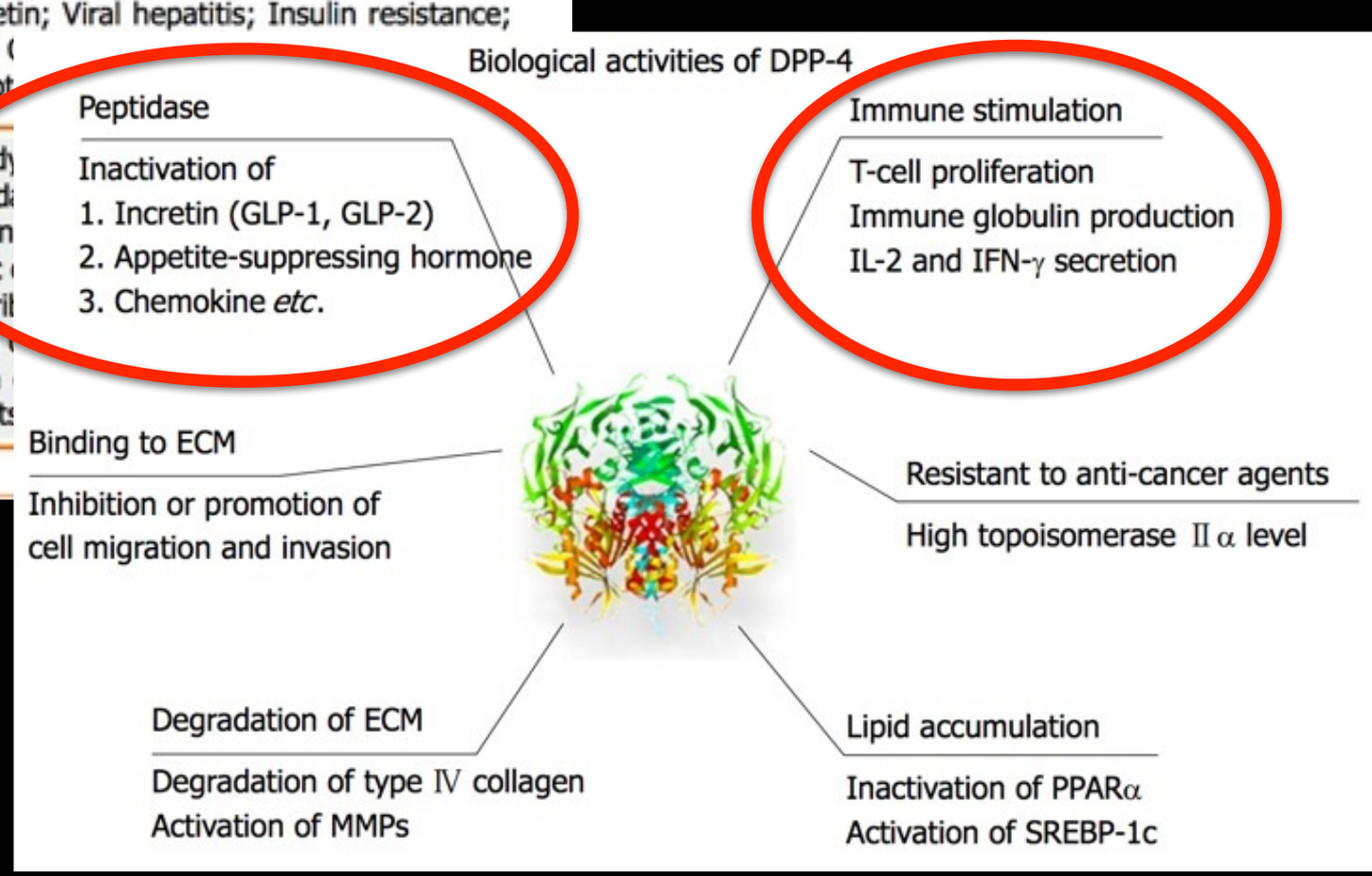

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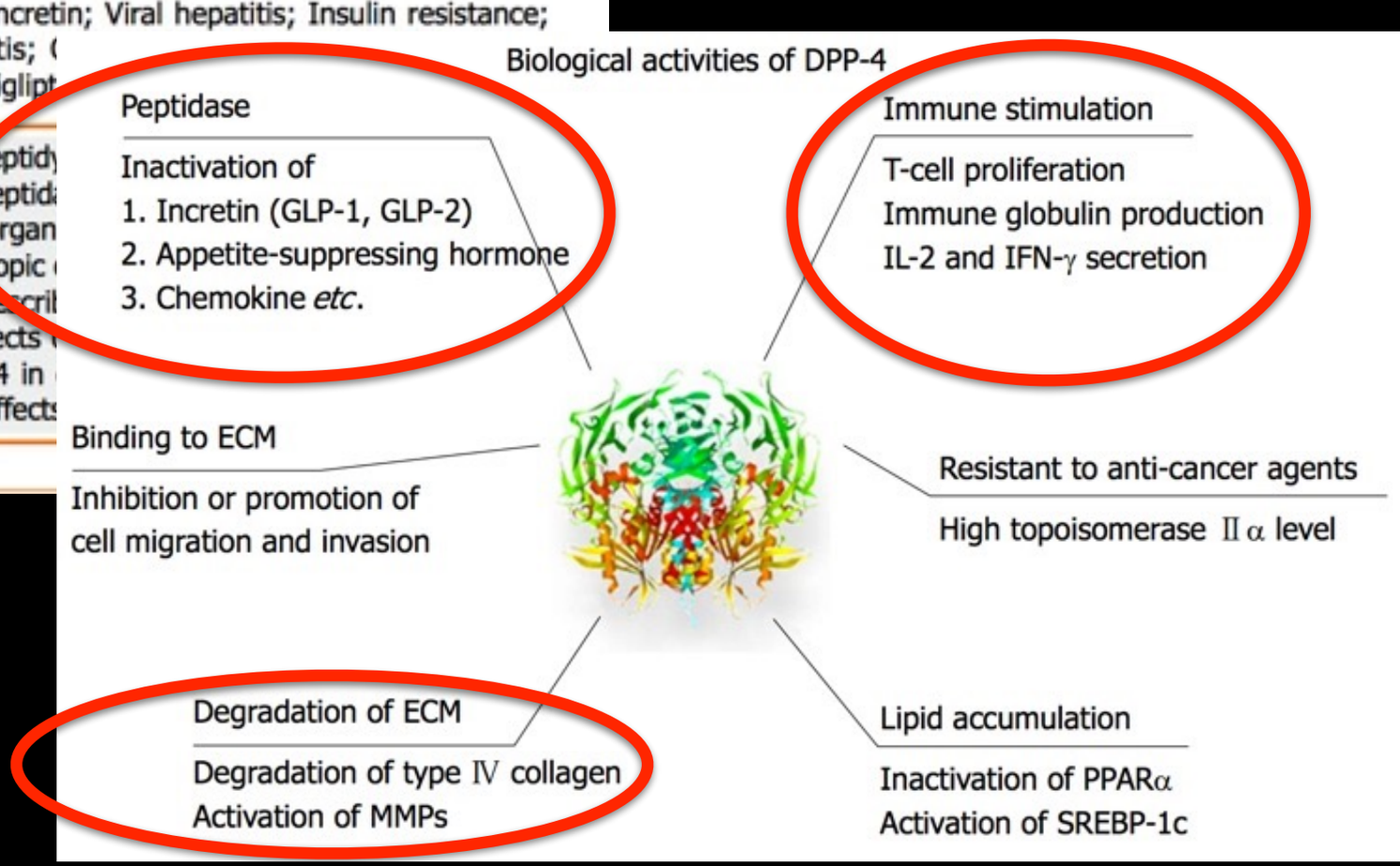

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REVIEW

Dipeptidyl peptidase-4: A key player in chronic liver disease

Minoru Itou, Takumi Kawaguchi, Eitaro Taniguchi, Michio Sata

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Takumi Kawaguchi, Michio Sata, Division of Gastroenterology, Department of Medicine and Department of Digestive Disease Information and Research, Kurume University School of Medicine, Kurume 830-0011, Japan
Author contributions: Itou M and Kawaguchi T collected the materials and wrote the manuscript; Taniguchi E discussed the topic; Sata M supervised the manuscript.
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Telephone: +81-942-317902 Fax: +81-942-317820
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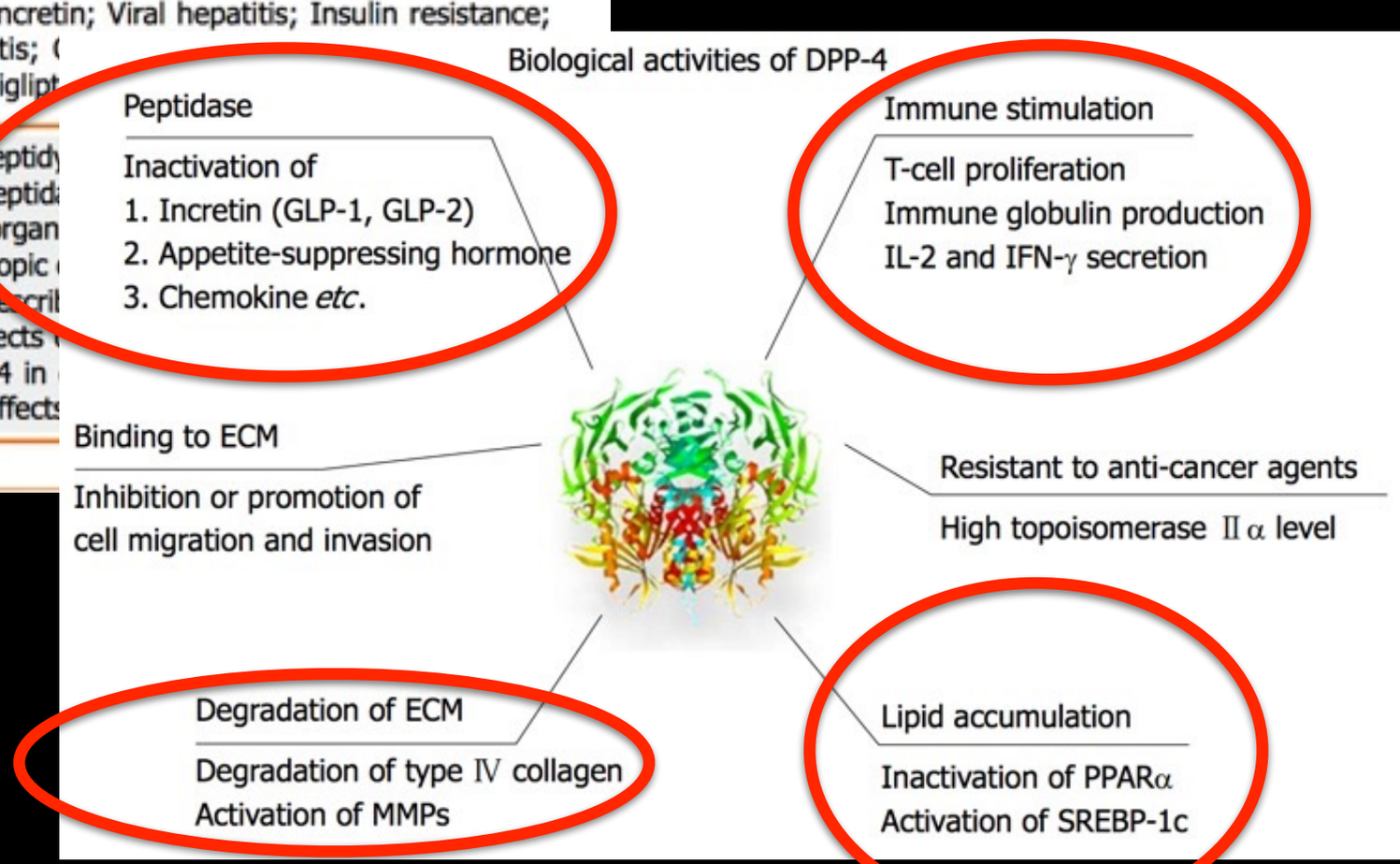


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Persistence of Hormonal Adaptations to Weight Loss

Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D., Elizabeth Delbridge, Ph.D., Katrina Purcell, B.Sc., Arthur Shulkes, Sc.D., Adamandia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.

ABSTRACT

BACKGROUND

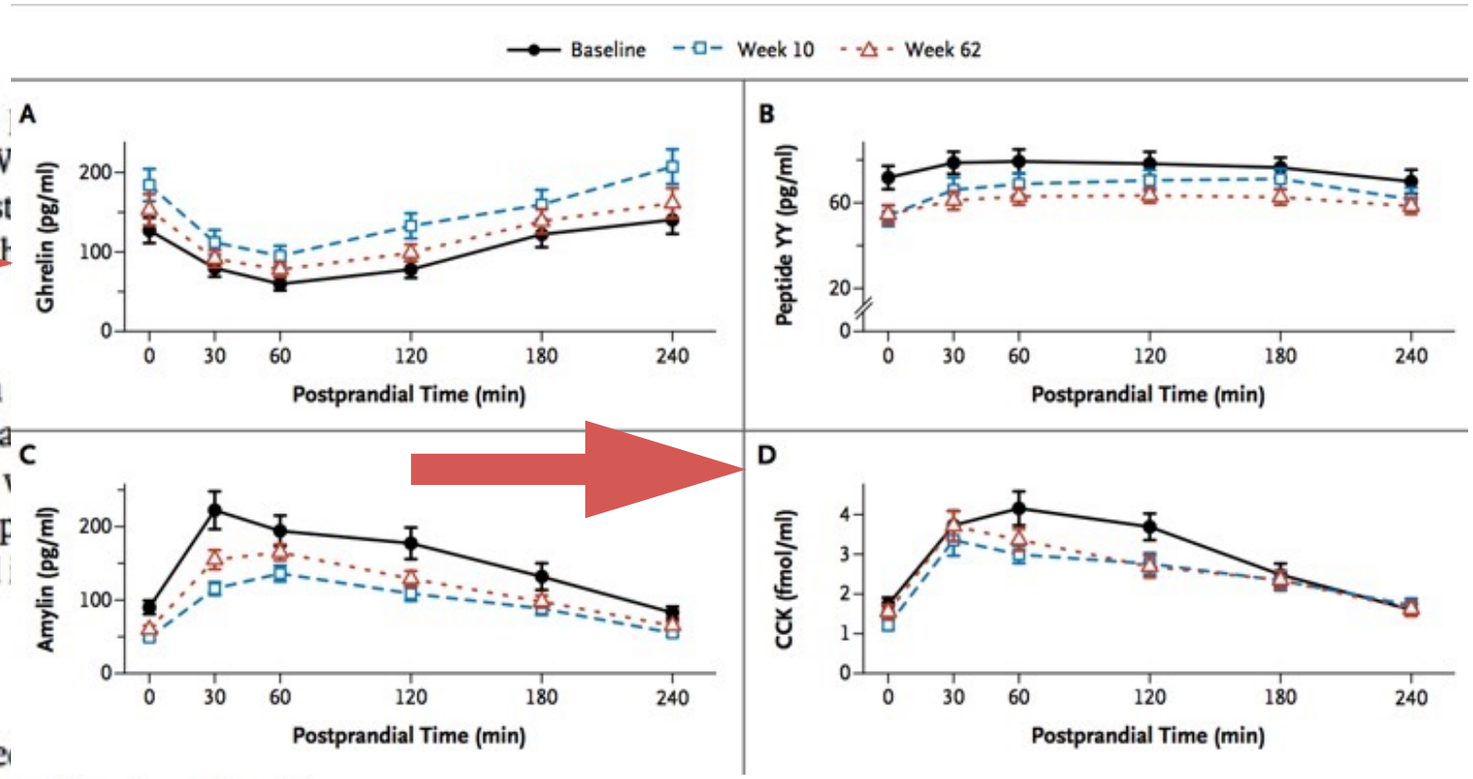
After weight loss, changes in the circulating levels of several involved in the homeostatic regulation of body weight occur. W are transient or persist over time may be important for an underst behind the high rate of weight regain af

METHODS

We enrolled 50 overweight or obese patients without diabetes in program for which a very-low-energy diet was prescribed. At ba loss), at 10 weeks (after program completion), and at 62 weeks, ing levels of leptin, ghrelin, peptide YY, gastric inhibitory polyp peptide 1, amylin, pancreatic polypeptide, cholecystokinin, and ratings of appetite.

RESULTS

Weight loss (mean [±SE], 13.5±0.5 kg) led to significant re leptin, peptide YY, cholecystokinin, insulin (P<0.001 for all comparisons), and amylin (P=0.002) and to increases in levels of ghrelin (P<0.001), gastric inhibitory polypeptide (P=0.004), and pancreatic polypeptide (P=0.008). There was also a significant increase in subjective appetite (P<0.001). One year after the initial weight loss, there were still significant differences from baseline in the mean levels of leptin (P<0.001),



Sumithran, P., Prendergast, L. A., Delbridge, E., Purcell, K., Shulkes, A., Kriketos, A., & Proietto, J. (2011). Long-term persistence of hormonal adaptations to weight loss. N Engl J Med, 365(17), 1597–1604. doi:10.1056/NEJMoa1105816

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Persistence of Hormonal Adaptations to Weight Loss

"One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss did not revert to the levels recorded before weight loss."

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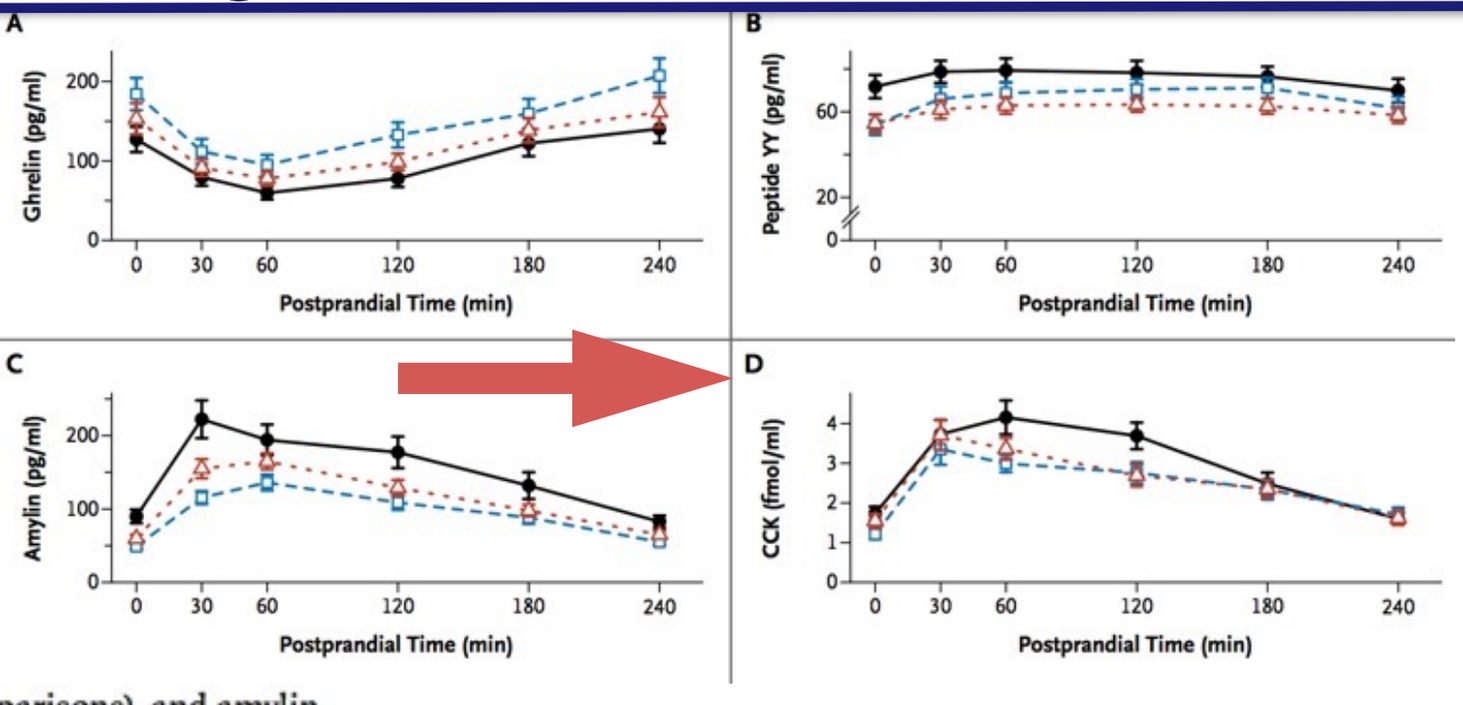

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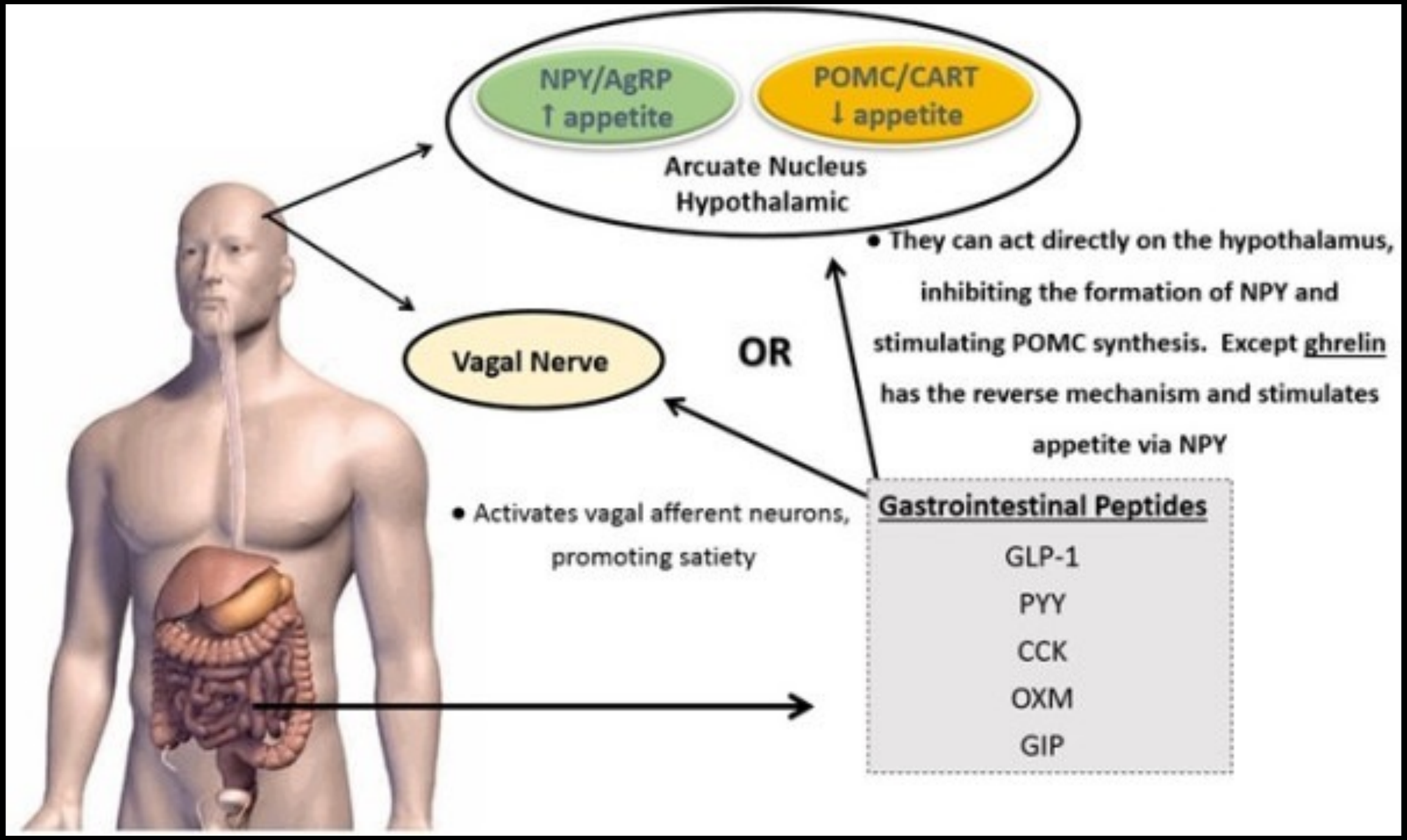


Sala, P., Torrinhas, R., Giannella-Neto, D., & Waitzberg, D. (2014). Relationship between gut hormones and glucose homeostasis after bariatric surgery. Diabetology & Metabolic Syndrome, 6(1), 87. doi:10.1186/1758-5996-6-87

Sympathetic
Fight or flight

Vagal Nerve Inhibited

Dilates pupils

Inhibits salivation

Increases heart rate

Bronchial dilation

Inhibits digestion

Stimulates glucose release

Inhibits intestine activity

Secretes epinephrine, norepinephrine

Relaxes bladder

Orgasm

Ejaculation

Peripheral vasoconstriction

Parasympathetic
Rest and digest

Vagal Nerve Activated

Consticts pupils

Stimulates salivation

Decrease heart rate

Bronchial constriction

Stimulates digestion

Stimulates gallbladder

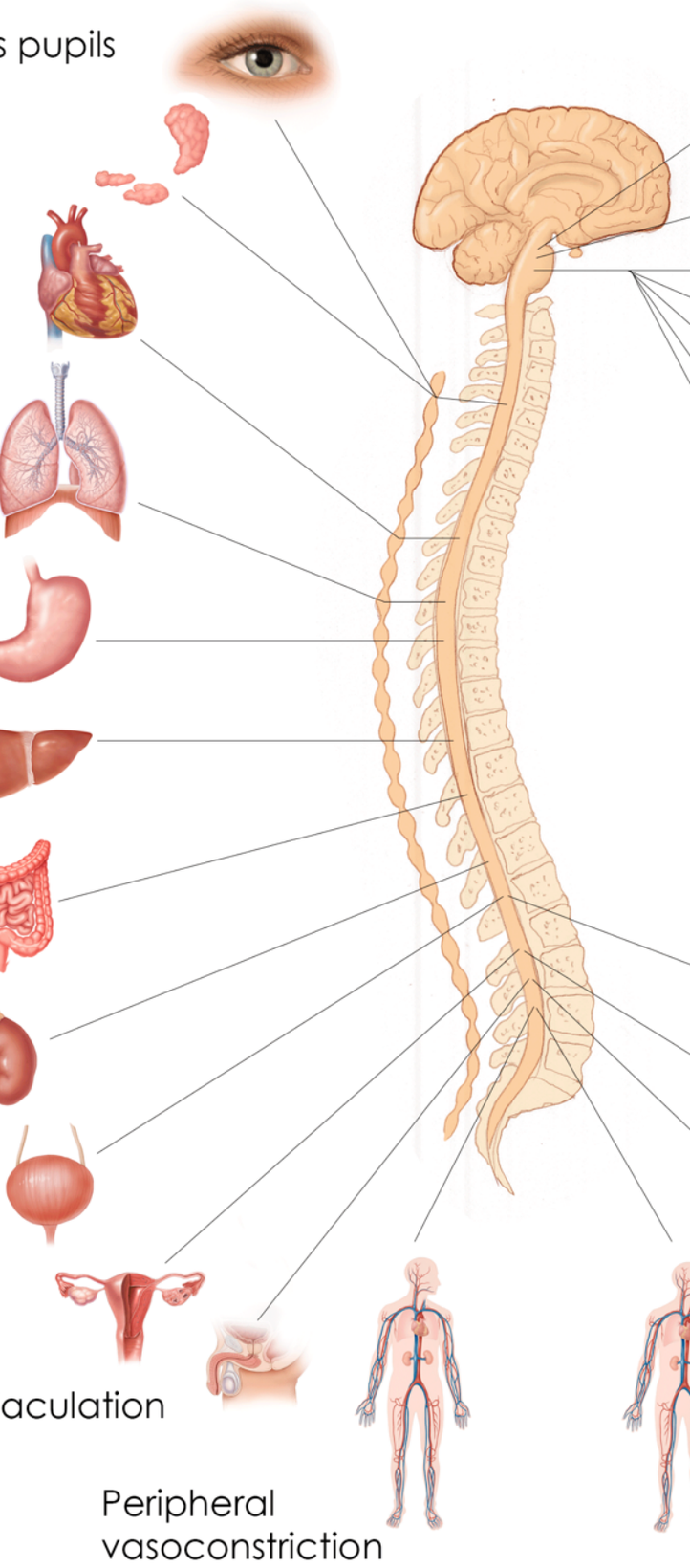
Stimulates intestine activity

Contracts bladder

Vaginal lubrication

Erection

Peripheral vasodilation



Comparable effects of moderate intensity exercise on changes in anorectic gut hormone levels and energy intake to high intensity exercise

Shin-ya Ueda, Takahiro Yoshikawa, Yoshihiro Katsura, Tatsuya Usui and **Shigeo Fujimoto**

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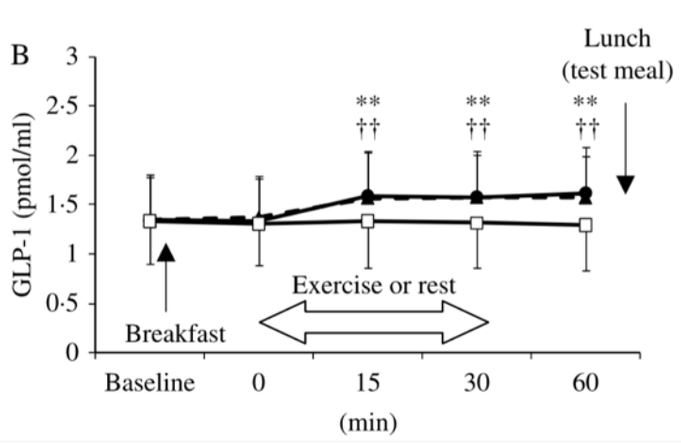
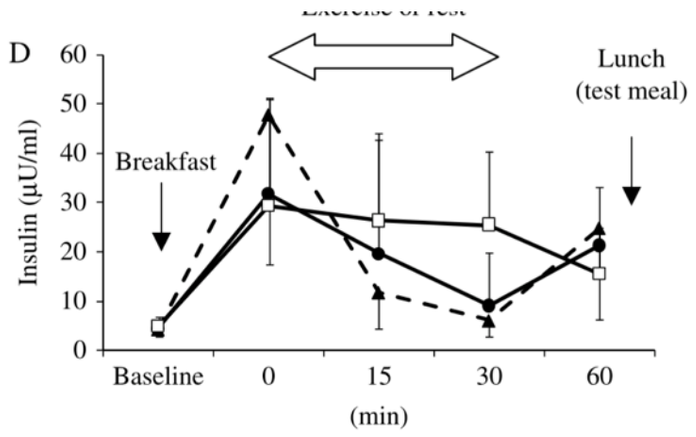
Abstract

There is growing interest in the effects of exercise on plasma gut hormone levels and subsequent energy intake (EI) but the effects of mode and exercise intensity on anorectic hormone profiles on subsequent EI remain to be elucidated. We aimed to investigate whether circulating peptide $YY_{3–36}$ ($PYY_{3–36}$) and glucagon-like peptide-1 (GLP-1 or GCG as listed in the HUGO Database) levels depend on exercise intensity, which could affect subsequent EI. Ten young male subjects (mean ±S.D., age: 23·4±4·3 years, body mass index: 22·5 ±1·0 kg/m^2, and maximum oxygen uptake ($VO_{2\ max}$): 45·9±8·5 ml/kg per min) received a standardized breakfast, which was followed by constant cycling exercise at 75% $VO_{2\ max}$ (high intensity session), 50% $VO_{2\ max}$ (moderate intensity session), or rest (resting session) for 30 min. At lunch, a test meal was presented, and EI was calculated. Blood samples were obtained during three sessions for measurements of glucose, insulin, $PYY_{3–36}$, and GLP-1, which includes GLP-1 (7–36) amide and GLP-1 (9–36) amide. Increases in blood $PYY_{3–36}$ levels were dependent on the exercise intensity (effect of session: $P<0·001$ by two-way ANOVA), whereas those in GLP-1 levels were similar between two different exercise sessions. Of note, increase in area under the curve values for GLP-1 levels was negatively correlated with decrease in the EI in each exercise session (high: $P<0·001$, moderate: $P=0·002$). The present findings raise the possibility that each gut hormone exhibits its specific blood kinetics in response to two different intensities of exercise stimuli and might play differential roles in regulation of EI after exercise.

Journal of Endocrinology (2009) **203,** 357–364





Comparable effects of moderate intensity exercise on changes in anorectic gut hormone levels and energy intake to high intensity exercise. (2009). Comparable effects of moderate intensity exercise on changes in anorectic gut hormone levels and energy intake to high intensity exercise. *Journal of Endocrinology*, 1–8. http://doi.org/10.1677/JOE-09-0190

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Nutrition, Metabolism & Cardiovascular Diseases (2012) xx, 1–7

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Nutrition, Metabolism & Cardiovascular Diseases

Eating rate is associated with cardiometabolic risk factors in Korean adults

K.S. Lee [a], D.H. Kim [b,*], J.S. Jang [c], G.E. Nam [b], Y.N. Shin [b], A.R. Bok [b], M.J. Kim [b], K.H. Cho [b]

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[b] *Department of Family Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 516 Gojan-dong, Danwon-gu, Ansan-si, Gyeonggi-do 425-707, Republic of Korea*
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KEYWORDS
Eating rate;
Satiety;
Cardiometabolic risks;
Cardiovascular diseases;
Obesity

Summary *Background and Aim:* Eating slowly is a crucial concept in behavioural nutrition and is recommended for weight management as it is believed to have an important effect on satiety control. This study aimed to determine whether or not eating rate is associated with cardiometabolic risk factors.
Methods and results: This was a cross-sectional study involving 8775 Korean adults, who visited the Center for Health Promotion of Korea University Anam Hospital in Seoul, Korea. In male study participants, weight and body mass index (BMI) were found to depend on eating rate after adjusting for age, alcohol consumption, smoking, exercise and total energy intake. When adjusted for age, alcohol consumption, smoking, exercise and BMI, differences were found between the eating rate groups with respect to high-density lipoprotein (HDL)-cholesterol, alanine aminotransferase (ALT) and alkaline phosphatase (ALP) values, white blood cell (WBC) count and total energy intake. Female participants were found to be different from males in that diastolic blood pressure and low-density lipoprotein (LDL)- and HDL-cholesterol values were significantly different between each eating rate group, while ALT and ALP values, WBC count and total energy intake were not. Compared with the slow eating rate group (>15 min), the fastest eating rate group (<5 min) had significantly increased odds ratios for cardiometabolic risk factors such as high glucose and low HDL-cholesterol levels in males, even after adjusting for BMI.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; ANOVA, analysis of variance; AST, aspartate aminotransferase; BMI, body mass index; γ-GT, gamma glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitive C-reactive protein; LDL, low-density lipoprotein; TSH, thyroid stimulating hormone; WBC, white blood cell; NTS, the nucleus of the solitary tract; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY; CPRs, cephalic phase responses; CHD, coronary heart disease.

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Int J Obes (Lond). 2013 February ; 37(2): 309–316. doi:10.1038/ijo.2012.39.

Acute stress potentiates brain response to milkshake as a function of body weight and chronic stress

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[2]The John B Pierce Laboratory, 290 Congress Ave, New Haven, CT 06519 USA

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Abstract

Objective—Stress is associated with increased intake of palatable foods and with weight gain, particularly in overweight women. Stress, food, and body mass index (BMI) have been separately shown to impact amygdala activity. However, it is not known whether stress influences amygdala responses to palatable foods, and whether this response is associated with chronic stress or BMI.

Design—Fourteen overweight and obese women participated in a functional magnetic resonance imaging (fMRI) scan as they consumed a palatable milkshake during script-driven autobiographical guided imagery of stressful and neutral-relaxing scenarios.

Results—We report that a network including insula, somatomotor mouth area, ventral striatum, and thalamus responds to milkshake receipt, but none of these areas are impacted by stress. In contrast, while the left amygdala responds to milkshake irrespective of condition, the right amygdala responds to milkshake only under stressful conditions. Moreover, this right amygdala response is positively associated with basal cortisol levels, an objective measure of chronic stress. We also found a positive relationship between BMI and stress related increased response to milkshake in the orbitofrontal cortex.

Conclusions—These results demonstrate that acute stress potentiates response to food in the right amygdala and orbitofrontal cortex as a function of chronic stress and body weight, respectively. This suggests that the influence of acute stress in potentiating amygdala and OFC responses to food is dependent upon individual factors like BMI and chronic stress. We conclude that BMI and chronic stress play a significant role in brain response to food and in stress-related eating.

Keywords

Stress potentiates brain response to food in obese with chronic stress; Risk factors for obesity; Obesity and the brain; neuroimaging

Correspondence to be sent to: Dr. Dana M Small, The John B Pierce Laboratory, 290 Congress Ave, New Haven, CT 06520, USA. dsmall@jbpierce.org; phone: 203-562-9901 ext 210; fax: (203) 624-4950.

Conflict of Interest
The authors declare that they have no competing financial conflicts of interest.

Behaviour, Appetite and Obesity

Increasing the number of masticatory cycles is associated with reduced appetite and altered postprandial plasma concentrations of gut hormones, insulin and glucose

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Abstract

To determine the influence of masticatory efficiency on postprandial satiety and glycaemic response, twenty-one healthy males were recruited for this randomised cross-over trial. The participants consumed a fixed amount of pizza provided in equal-sized portions by chewing each portion either fifteen or forty times before swallowing. Subjective appetite was measured by appetite questionnaires at regular intervals for 3 h after the meal and plasma samples were collected for the measurement of selected satiety-related hormones, glucose, insulin and glucose-dependent insulinotropic peptide (GIP) concentrations. An *ad libitum* meal was provided shortly after the last blood sample was drawn and the amount eaten recorded. Compared with fifteen chews, chewing forty times per portion resulted in lower hunger (P= 0·009), preoccupation with food (P= 0·005) and desire to eat (P= 0·002). Meanwhile, plasma concentrations of glucose (P= 0·024), insulin (P< 0·001) and GIP (P< 0·001) were higher following the forty-chews meal. Chewing forty times before swallowing also resulted in a higher plasma cholecystokinin concentration (P= 0·045) and a trend towards a lower ghrelin concentration (P= 0·051). However, food intake at the subsequent test meal did not differ (P= 0·851). The results suggest that a higher number of masticatory cycles before swallowing may provide beneficial effects on satiety and facilitate glucose absorption.

Mindful Chewing Activates Vagal Nerve and Gut Hormones

Zhu, Y., Hsu, W. H., & Hollis, J. H. (2012). Increasing the number of masticatory cycles is associated with reduced appetite and altered postprandial plasma concentrations of gut hormones, insulin and glucose. British Journal of Nutrition, 1–7. doi:10.1017/S0007114512005053

Physiology & Behavior 151 (2015) 88–96

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Review

Effects of chewing on appetite, food intake and gut hormones: A systematic review and meta-analysis

Sophie Miquel-Kergoat [a,*], Veronique Azais-Braesco [b], Britt Burton-Freeman [c], Marion M. Hetherington [d]

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[b] VAB Nutrition, 1 Rue Claude Danziger, 63100 Clermont-Ferrand, France
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[d] School of Psychology, University of Leeds, Leeds LS2 9JT, United Kingdom

Reference	Participants		Intervention	Results		
	N	BMI	Design	Effect on appetite	Effect on energy intake	Hormones & metabolites
Cassady et al. [19]	13	HW	Fixed weight almonds (11 × 5-g portions) chewed 10, 25 or 40 times; within subjects	Yes, (40-chew condition differs from 25 chews, but not from 10-chews)	NA	No. But trend (p = 0055) for GLP-1 to be ↑ when chewing increases
Li et al. [25] Study 1 (observational, not reported here)	30	16 HW 14 OB	Fixed amount of pork pie (300 g in 10-g pieces) chewed 15 or 40 times; 12 h later breakfast intake measured; within subjects	No effect on appetite ratings	Yes, ↓ energy intake when food is chewed longer	No effect on glucose or insulin Ghrelin ↓, GLP-1 ↑, CCK ↑ with more chews
Zhu et al. [32]	21	HW and OW	Fixed breakfast of pizza "bites" chewed 15 or 40 times; 3 h later ad libitum pasta intake recorded; within subjects	Yes; hunger, desire to eat and preoccupation with food were ↓ after longer chewing (no effect on fullness ratings)	No effect on energy intake	Yes more chews ↑ glucose, insulin and GIP and ↑ CCK; tend to ↓ decrease ghrelin

Miquel-Kergoat, S., Azais-Braesco, V., Burton-Freeman, B., & Hetherington, M. M. (2015). Physiology & Behavior. Physiology and Behavior, 151(C), 88–96. http://doi.org/10.1016/j.physbeh.2015.07.017

Annals of Nutrition & Metabolism

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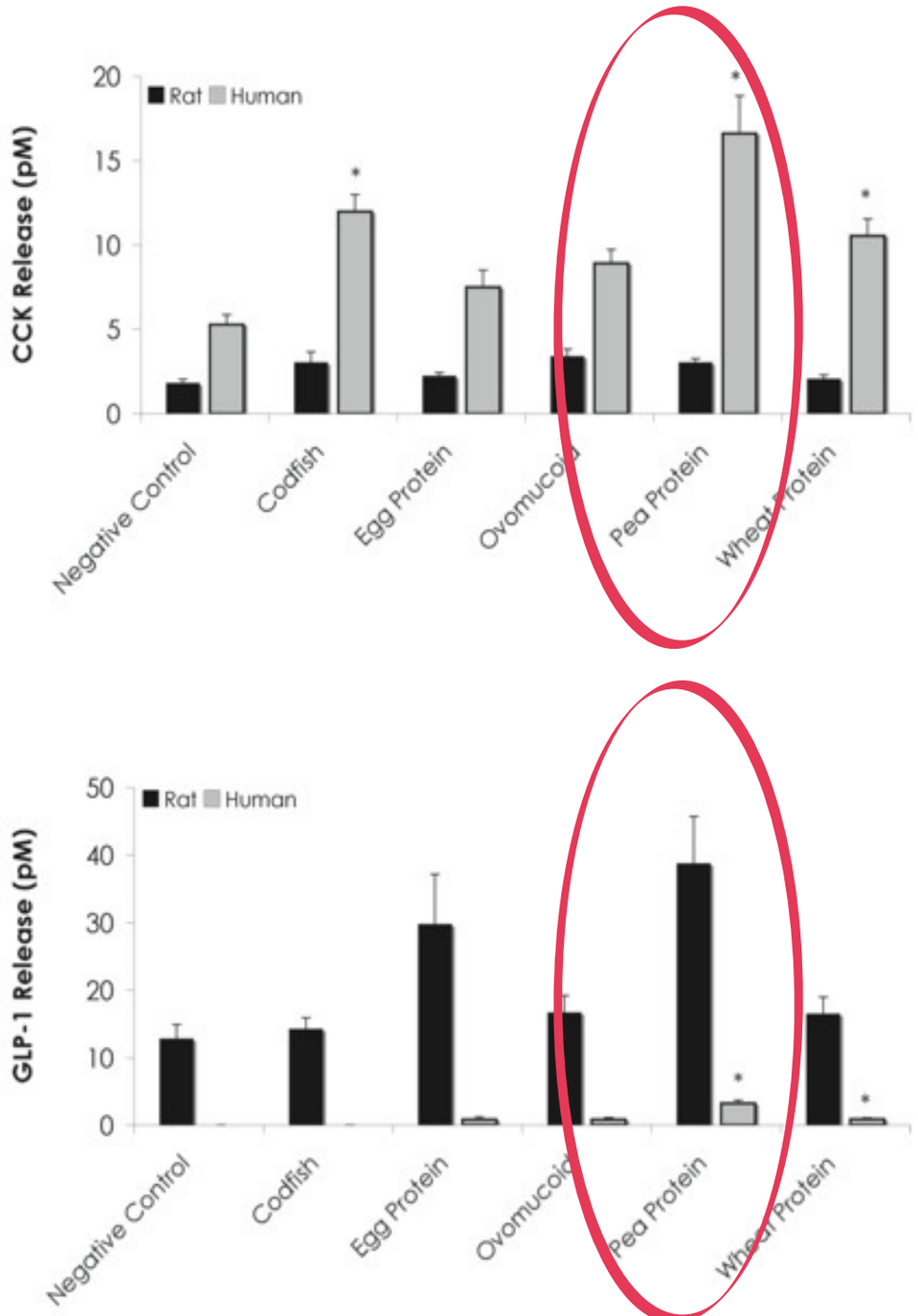
Issue release date: June 2010

Release of Satiety Hormones in Response to Specific Dietary Proteins Is Different between Human and Murine Small Intestinal Mucosa

Geraedts M.C.P. · Troost F.J. · Tinnemans R. · Söderholm J.D. · Brummer R.-J. · Saris W.H.M.

Ann Nutr Metab 2010;56:308–313 (DOI:10.1159/000312664)



OPEN ACCESS Freely available online

PLoS one

Intraduodenal Administration of Intact Pea Protein Effectively Reduces Food Intake in Both Lean and Obese Male Subjects

Maartje C. P. Geraedts[1,3]*, Freddy J. Troost[2,3], Marjet J. M. Munsters[1,3], Jos H. C. H. Stegen[1,3], Rogier J. de Ridder[2,3], Jose M. Conchillo[2,3], Joanna W. Kruimel[2,3], Ad A. M. Masclee[2,3], Wim H. M. Saris[1,3]

1 Department of Human Biology, Maastricht University Medical Center, Maastricht, The Netherlands, **2** Department of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, The Netherlands, **3** Nutrition and Toxicology Research Institute Maastricht, Maastricht, The Netherlands

Abstract

Background: Human duodenal mucosa secretes increased levels of satiety signals upon exposure to intact protein. However, after oral protein ingestion, gastric digestion leaves little intact proteins to enter the duodenum. This study investigated whether bypassing the stomach, through intraduodenal administration, affects hormone release and food-intake to a larger extent than orally administered protein in both lean and obese subjects.

Methods: Ten lean (BMI:23.0±0.7 kg/m^2) and ten obese (BMI:33.4±1.4 kg/m^2) healthy male subjects were included. All subjects randomly received either pea protein solutions (250 mg/kg bodyweight in 0.4 ml/kg bodyweight of water) or placebo (0.4 ml/kg bodyweight of water), either orally or intraduodenally via a naso-duodenal tube. Appetite-profile, plasma GLP-1, CCK, and PYY concentrations were determined over a 2 h period. After 2 h, subjects received an *ad-libitum* meal and food-intake was recorded.

Results: CCK levels were increased at 10($p<0.02$) and 20($p<0.01$) minutes after intraduodenal protein administration (IPA), in obese subjects, compared to lean subjects, but also compared to oral protein administration (OPA)($p<0.04$). GLP-1 levels increased after IPA in obese subjects after 90($p<0.02$) to 120($p<0.01$) minutes, compared to OPA. Food-intake was reduced after IPA both in lean and obese subjects (-168.9±40 kcal ($p<0.01$) and −298.2±44 kcal ($p<0.01$), respectively), compared to placebo. Also, in obese subjects, food-intake was decreased after IPA (−132.6±42 kcal; $p<0.01$), compared to OPA.

Conclusions: Prevention of gastric proteolysis through bypassing the stomach effectively reduces food intake, and seems to affect obese subjects to a greater extent than lean subjects. Enteric coating of intact protein supplements may provide an effective dietary strategy in the prevention/treatment of obesity.

Citation: Geraedts MCP, Troost FJ, Munsters MJM, Stegen JHCH, de Ridder RJ, et al. (2011) Intraduodenal Administration of Intact Pea Protein Effectively Reduces Food Intake in Both Lean and Obese Male Subjects. PLoS ONE 6(9): e24878. doi:10.1371/journal.pone.0024878

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Funding: Th
publish, or

Competing

* E-mail: M.G

Pea protein in humans modifies gut-endocrine hormones GLP-1, CCK and PYY

Introduction

Food ingestion triggers a number of stimuli, such as the release of the gastrointestinal hormones cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1) and peptide YY (PYY). These hormones are known to be involved in the modulation of appetite sensations. CCK is produced by I-cells in the duodenal and jejunal mucosa, and is secreted in response to luminal food compounds, especially lipids and proteins [1]. GLP-1 and PYY are produced primarily by the L-cells in the more distal small intestine and colon. Ingested nutrients stimulate CCK-, GLP-1-, and PYY secretion indirectly by neurohumoral mechanisms, e.g. feedback mechanisms of hormones from a more distal part of the small intestine, as well as by direct sensing mechanisms at the intestinal mucosa [2,3].

Previously, it was demonstrated that the plasma levels of GLP-1 [illegible] compared to lean children [5]. Also, PYY levels are lower in obese subjects compared to lean subjects [6]. These data indicate that there are significant differences between lean and obese subjects with respect to hormone release, and that the gut may respond different to ingested nutrients in obese subjects, compared to lean subjects.

Among all properties of food, the total energy content and the macronutrient composition appears to be one of the major determinants of the control of food intake. Recent literature points to the effect of dietary protein in reducing food intake by improving satiety sensations [7,8]. It seems that proteins have the highest satiating effect when compared to carbohydrates and in particular fats in humans and rats [9,10], although the nature of the protein can influence its satiating effects. In most cases, high-protein meals increase feelings of satiety and decrease subsequent energy intake

Review

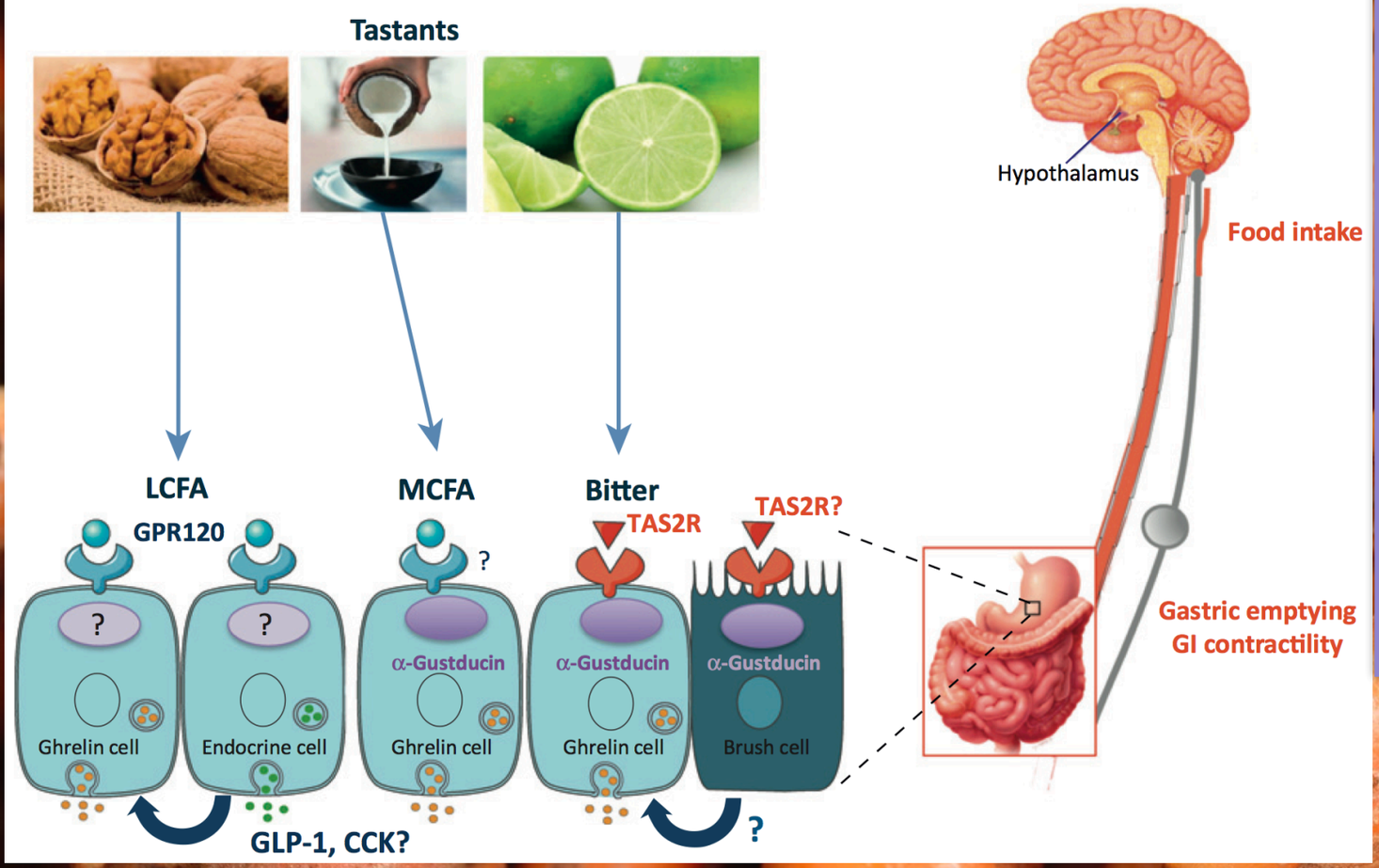
Cell PRESS

Special Issue: Neuroendocrine control of appetite

Nutrient sensing in the gut: new roads to therapeutics?

Sara Janssen and Inge Depoortere

Translational Research Center for Gastrointestinal Disorders, Gut Peptide Research Lab, Catholic University of Leuven, 3000 Leuven, Belgium



Best Natural Ways to Increase Incretin Activity

- Vagal nerve activation (heart math)
- Pea and whey protein
- Mindful eating
- Eat phytochemical rich foods
- Chewing food thoroughly

EAT MORE COLOR

Journal of Agricultural and Food Chemistry, 60(36), 2013

FUELING YOU MICROBIOME

Food

Non-digestible nutrients

ITF – GOS – AX – XOS

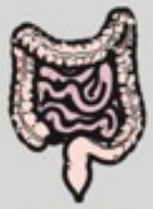
Chitin-glucan

Phenolic compounds

Changes in gut microbiota

↑ *Bifidobacterium* spp. ↑ *Lactobacillus* spp. ↑ *Collinsenlla* spp. ↑ *Roseburia* spp.
↑ *Akkermansia muciniphila* ↑ *Faecalibacterium prausnitzii* ↑ *Bacteroides-Prevotella* spp.

Targeted organs



Molecular targets

↑ L cells
↑ Tight junctions (barrier)
↑ GLP-1, GLP-2, PYY
Regulation of eCB system tone

↓ Lipogenesis
↓ Inflammatory markers

↓ PPARg/GPR43
↓ Inflammatory markers
Regulate eCB system tone
Change apelinergic system tone

↑ Insulin sensitivity
↓ Inflammatory markers

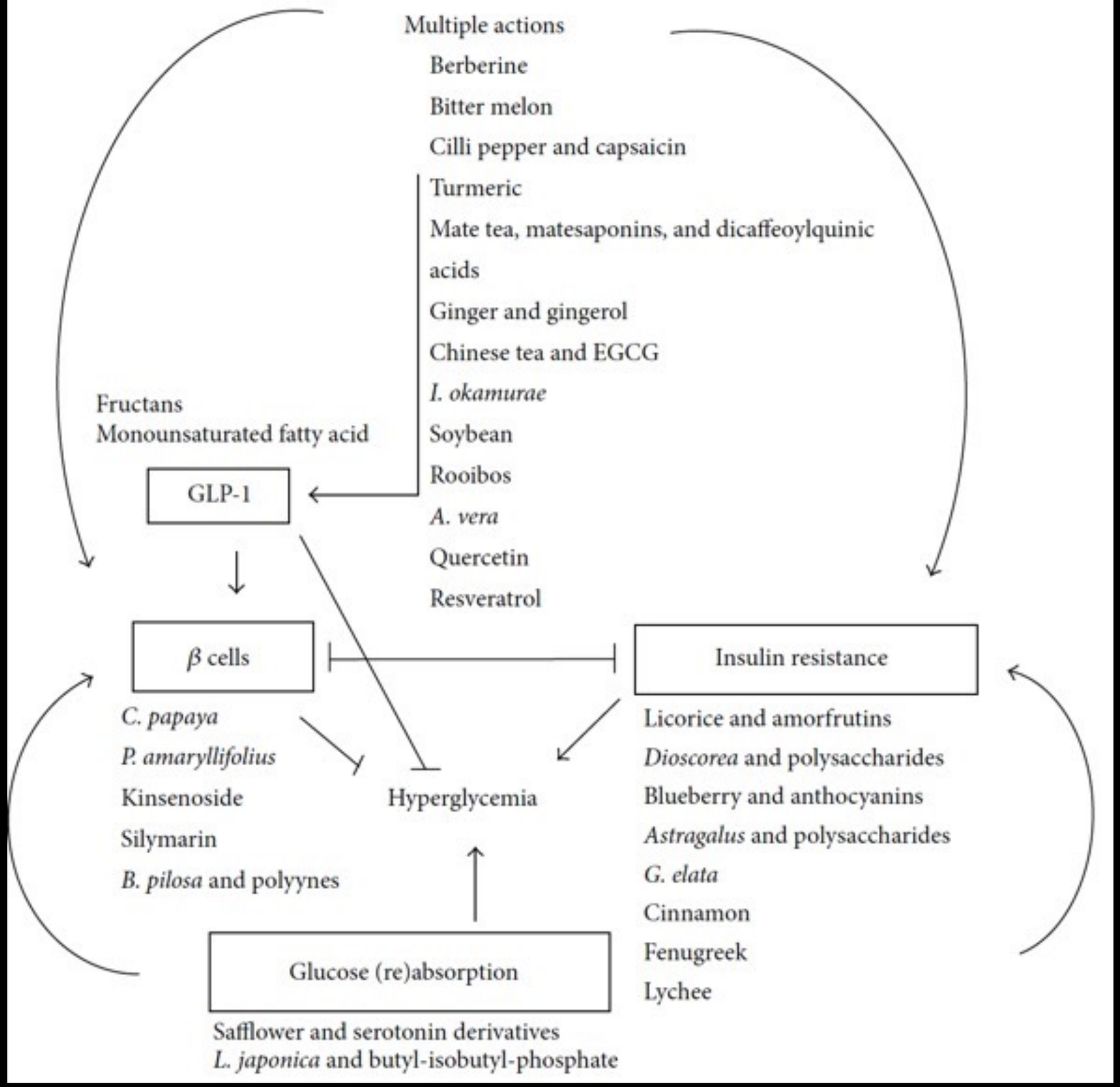
Metabolic consequences related to obesity

↓ Glycemia ↓ Fat mass ↓ Steatosis ↓ Appetite ↓ Lipemia
↓ Insulin resistance ↑ Glucose tolerance ↓ Inflammation ↓ Metabolic endotoxemia

Modulation of the endocannabinoid and the apelinergic system tone

2013. Beneficial Microbes, 1(-1), 1–15.

(a)



Chang, C. L. T., Lin, Y., Bartolome, A. P., Chen, Y.-C., Chiu, S.-C., & Yang, W.-C. (2013). Herbal Therapies for Type 2 Diabetes Mellitus: Chemistry, Biology, and Potential Application of Selected Plants and Compounds. Evidence-Based Complementary and Alternative Medicine, 2013(1), 1–33. doi:10.1001/jama.294.1.97

Table 1. Effects of polyphenols on neuropeptides/neurohormones that may have an effect on the central nervous system in obesity

Polyphenol	Neuropeptide	Observed results	Refrences
Cinnamon polyphenol	Insulin	Improved insulin sensitivity in subjects with type-2 diabetes, metabolic syndrome, and in women with PCOS; anti-oxidant effects in obese subjects; improves insulin sensitivity in an animal model of metabolic syndrome;	[6, 124–127]
	GLP-1	Increased postprandial serum GLP-1 in healthy subjects (Hlebowicz et al. 2009)	[128]
Curcumin	IGF-1	Increases IGF-1 levels in the rat brain in an animal model of insulin resistance	[129]
Resveratrol	NPY, AgRP	Downregulation of NPY and Agrp activities in N29-4 mouse hypothalamic cells.	[130]
	Insulin	Improved insulin resistance in fructose-fed insulin-resistant rats; attenuated abnormal insulin secretion from islets of high-fat fed mice; improved insulin sensitivity in normal lemurs without affecting insulin secretion; improved insulin tolerance in KKA(y) insulin-resistant mice	[131–134]
	Amylin	Inhibits amylin fibril formation in INS-1E rat insulinoma cells	[135]
	GLP-1	Increased GLP-1 content in high-fat fed diabetic mice	[136]
Grape-seed Extract	Insulin	Improved insulin resistance in high-fructose fed rats; no significant effect on insulin resistance in type-2 diabetic subjects; displayed insulin-mimetic activity in L6E9 myoblasts and 3T3-L1 adipocytes	[137–139]
Apigenin	POMC, CART	Decreased food intake in mice fed a high-fat diet; increased POMC and CART gene expression in N29-2 and SH-SY-5Y neuronal cell lines	[140]
Adlay seed water Extract	NPY, leptin	Decrease in hypothalamic NPY and leptin mRNA and antiobesity effects in rats	[141]
Soy isoflavone	PYY	Plasma PYY increased in healthy postmenopausal women	[142]
	Insulin,	Improved insulin sensitivity in postmenopausal leptin women but did not change serum leptin; possible effect on reducing serum leptin in obese postmenopausal women	[143, 144]
	IGF-1	Increased circulating levels of IGF-1 in postmenopausal women	[145]
Oleuropein Aglycone	amylin	Atenuated aggregation of amylin in RIN-5F pancreatic cells	[146]
EGCG	amylin	Inhibits amylin fibril formation in vitro	[147]
	IGF-1	Inhibitory effect of EGCG mediated by IGF-1 in human glioblastoma cell lines.	[148]
Carob pulp Polyphenol	ghrelin	Decreased acyclated ghrelin in healthy subjects and enhanced lipid oxidation	[149]
Green tea polyphenol	ghrelin	Decreased ghrelin prepropeptide mRNA in the liver in rats fed a high-fat diet	[150]
	IGF-1, leptin	Decreased serum IGF-1 and leptin levels in obese rats	[151]
	Insulin	Maternal feeding of green tea ameliorates insulin resistance in offspring; improves insulin secretion in obese mice	[152, 153]
Berries	GLP-1	Modest response of GLP-1 response in the venous blood of healthy subjects with improved glycemic profile	[154]
Chocolate	Orexin	Context-dependent expectation of chocolate increased orexin-A neuronal activation in rat hypothalamus	[155]
	Insulin	Decreased insulin resistance and increased insulin sensitivity in hypertensive subjects with impaired glucose tolerance	[156]
	Ghrelin	Olfactory stimulation with chocolate induced a satiation response in 12 women that inversely correlated with plasma ghrelin levels	[157]
Cocoa	Insulin	Meta-analysis report shows that cocoa improved insulin resistance in subjects; no significant difference in fasting plasma insulin levels in obese/diabetic rats	[158, 159]

Panickar, K. S. (2013). Effects of dietary polyphenols on neuroregulatory factors and pathways that mediate food intake and energy regulation in obesity. Molecular Nutrition & Food Research, 57(1), 34–47. doi:10.1002/mnfr.201200431

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PLoS one

Resveratrol Increases Glucose Induced GLP-1 Secretion in Mice: A Mechanism which Contributes to the Glycemic Control

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Abstract

Resveratrol (RSV) is a potent anti-diabetic agent when used at high doses. However, the direct targets primarily responsible for the beneficial actions of RSV remain unclear. We used a formulation that increases oral bioavailability to assess the mechanisms involved in the glucoregulatory action of RSV in high-fat diet (HFD)-fed diabetic wild type mice. Administration of RSV for 5 weeks reduced the development of glucose intolerance, and increased portal vein concentrations of both Glucagon-like peptid-1 (GLP-1) and insulin, and intestinal content of active GLP-1. This was associated with increased levels of colonic proglucagon mRNA transcripts. RSV-mediated glucoregulation required a functional GLP-1 receptor (Glp1r) as neither glucose nor insulin levels were modulated in Glp1r-/- mice. Conversely, levels of active GLP-1 and control of glycemia were further improved when the Dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin was co-administered with RSV. In addition, RSV treatment modified gut microbiota and decreased the inflammatory status of mice. Our data suggest that RSV exerts its actions in part through modulation of the enteroendocrine axis *in vivo*.

Citation: Dao T-MA, Waget A, Klopp P, Serino M, Vachoux C, et al. (2011) Resveratrol Increases Glucose Induced GLP-1 Secretion in Mice: A Mechanism which Contributes to the Glycemic Control. PLoS ONE 6(6): e20700. doi:10.1371/journal.pone.0020700

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Competing Interests: The authors have read the journal's policy and have the following conflicts: Laurent Pechere and Sylvain Barthelemy have a duality of interest with ENTERONOVA and YVERY Cosmetics, because they are employed by the above mentioned companies. Rémy Burcelin and Eric Sérée have a duality of interest with ENTERONOVA as they have a consultancy mission. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials.

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Meet Berberine

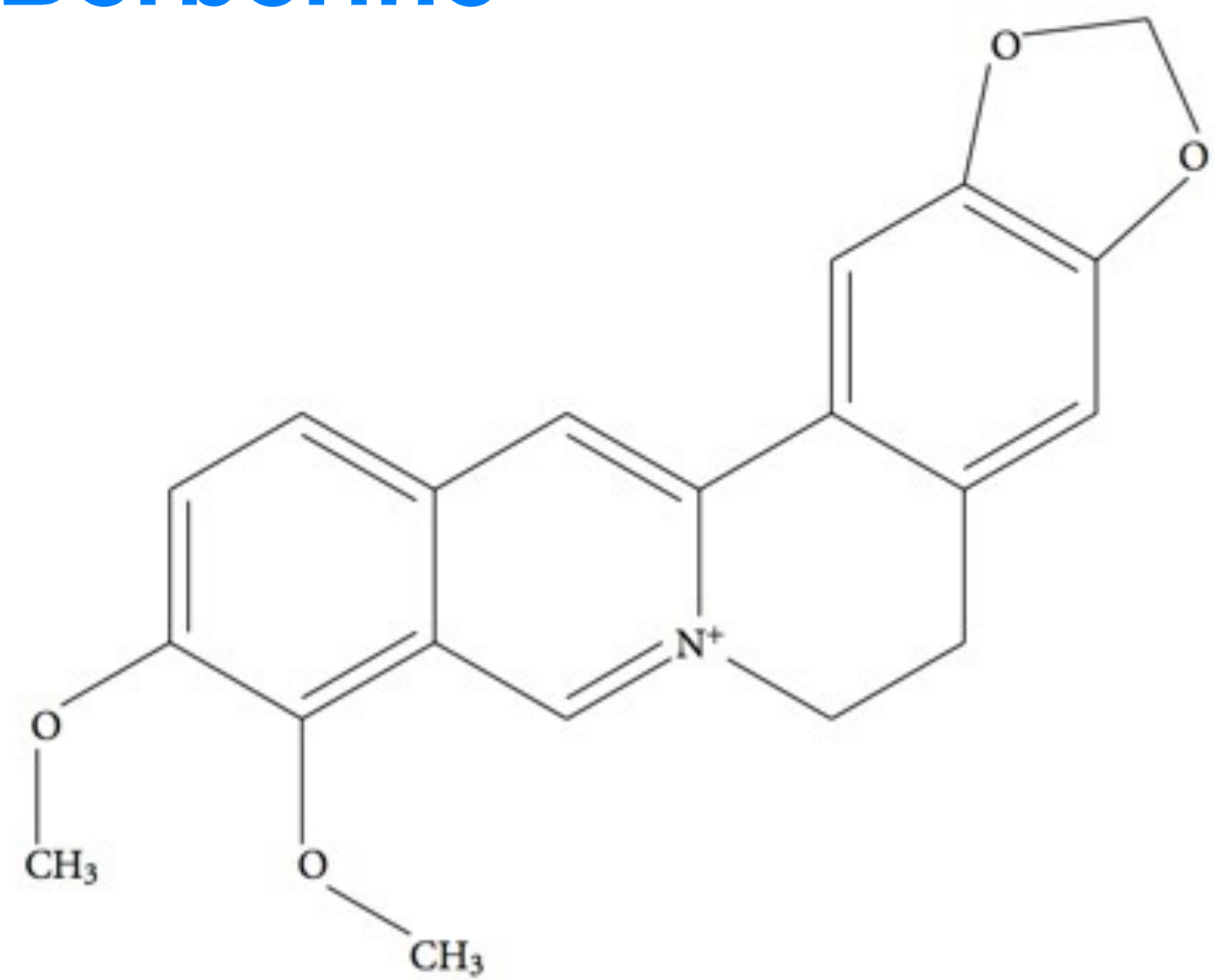

FIGURE 1: Chemical structure of berberine.

Yu, Y., Liu, L., Wang, X., Liu, X., Liu, X., Xie, L., & Wang, G. (2010). Modulation of glucagon-like peptide-1 release by berberine: In vivo and in vitro studies. Biochemical Pharmacology, 79(7), 1000–1006. doi:10.1016/j.bcp.2009.11.017

Table 6: Comparison of clinical studies of berberine in diabetes patients.

Study type	Study subjects	Berberine dosage	Control treatment	Major findings	Side effects	Reference
Randomised, double-blind, placebo-controlled, multiple-center	Type 2 diabetes and dyslipidemia ($n = 116$)	0.5 g, b.i.d for 3 months	Placebo	Significantly reduced fasting and postload plasma glucose, HbA_{1c} Significantly reduced triglyceride, total cholesterol, and LDL-cholesterol	Mild to moderate constipation in 5 patients	[61]
Randomised, blinded, placebo-controlled	Type 2 diabetes ($n = 36$)	0.5 g, t.i.d for 3 months	Metformin (0.5 g t.i.d)	Significantly reduced FBG, PBG, and HbA_{1c} Significantly reduced plasma triglycerides	Transient gastrointestinal adverse effects. No liver or kidney damage	[14]
	Type 2 diabetes poorly controlled ($n = 48$)	0.5 g, t.i.d for 3 months	Existing anti-diabetic treatment	Lowered FBG and PBG Significantly decreased HbA_{1c} Significantly reduced fasting plasma insulin and HOMA-IR		
Randomised	Type 2 diabetes ($n = 97$)	1 g/day for 2 months	Metformin (1.5 g/day); rosiglitazone (4 mg/day)	Significantly reduced FBG, HbA_{1c}, and triglycerides Serum insulin level was declined significantly ($P < 0.01$), increased insulin sensitivity in peripheral tissues. Significantly elevated surface expression of InsR by 3.6-fold	No adverse events	[62]
	Type 2 diabetes with chronic hepatitis C virus infection ($n = 35$)	1 g/day for 2 months	N/A	Significantly reduced FBG and triglyceride levels Reduced the elevated ALT and aspartate aminotransferase levels		

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Original article

Berberine improves reproductive features in obese Caucasian women with polycystic ovary syndrome independently of changes of insulin sensitivity

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[b] Endocrinology of Fertile Age, University Hospital "S. Giovanni di Dio e Ruggi d'Aragona" Salerno, Italy
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[e] Faculty of Medicine and Surgery, University of Salerno, Italy
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[h] Laboratory ASL Salerno, Italy
[i] University "Parthenope" Naples, Italy
[j] Outpatient Diabetic Clinic, "San Gerardo" Hospital, Monza, Italy

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PCOS
Insulin resistance
FAI
Testosterone
BMI

ABSTRACT

Background and aims: Berberine (BBR) is an isoquinoline derivative alkaloid isolated from Rhizoma Coptidis traditionally used as anti diarrheic and, more recently, as hypolipidemic and insulin sensitizer agent. Thus, BBR could represent a potential therapeutic option for patients with polycystic ovary syndrome (PCOS). The aim of this study was to evaluate the clinical, metabolic and hormonal effects of BBR in PCOS women.

Methods: Fifty oligoamenorrheic PCOS obese women and 50 age and Body Mass Index (BMI) matched healthy controls were enrolled. PCOS women received BBR treatment (500 mg, 2 times daily) for 6 months. Clinical and biochemical parameters were assessed before and after the treatment period.

Results: Total testosterone ($p < 0.01$), free androgen index ($p < 0.01$), androstenedione ($p < 0.01$), sex hormone binding globulin ($p < 0.01$), progesterone ($p < 0.01$), total cholesterol ($p = 0.01$), low density lipoprotein cholesterol ($p < 0.01$), triglycerides ($p < 0.01$), area under the curve of insulin ($p < 0.01$), menses frequency ($p < 0.01$) and Waist Circumference ($p = 0.04$) significantly ($p < 0.05$) improved after BBR treatment. No correlation was found between variations of insulin sensitivity and hormonal changes.

Conclusions: BBR improves clinical, metabolic and reproductive features in PCOS women. Its mechanism of actions need to be elucidated in further studies.

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Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 591654, 12 pages
doi:10.1155/2012/591654

Research Article

Berberine in the Treatment of Type 2 Diabetes Mellitus: A Systemic Review and Meta-Analysis

Hui Dong,[1] Nan Wang,[2] Li Zhao,[1] and Fuer Lu[1]

[1] *Institute of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China*
[2] *Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China*

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Academic Editor: Pierre Kamtchouing

"Based on the existing evidence reviewed, berberine has beneficial effects on blood glucose control in the treatment of type 2 diabetic patients and exhibits efficacy comparable with that of conventional oral hypoglycaemics."

number of trials, and unidentified risks of bias.

1. Introduction

The prevalence of diabetes mellitus (DM) has continued to increase globally. According to the latest figures from the International Diabetes Federation (IDF), the number of individuals with diabetes in 2011 has reached a staggering 366 million, causing 4.6 million deaths each year. Type 2 diabetes mellitus (T2DM) is the most common form of diabetes. Initial therapy for treating T2DM includes diet and exercise, followed by the use of oral hypoglycemic agents and potentially subcutaneous insulin injections [1, 2]. Evidence from many multicenter trials has demonstrated that the adverse effects limit their widespread use in clinical practice [4].

Consequently, many diabetic patients are also suggested to receive complementary and alternative medicine therapies. This is particularly true in China [5]. DM is referred to as "Xiao Ke" disease (which means emaciation and thirst) in Chinese medicine, which is a consequence of over-intake of greasy food and sedentary lifestyle [6]. There is a long history of using herbal medications to treat diabetes in China. Numerous researches also suggest that some herbal therapies may have a role in the treatment of this complex disease [7].

Zhang et al. BMC Complementary and Alternative Medicine 2014, 14:188
http://www.biomedcentral.com/1472-6882/14/188

BMC
Complementary & Alternative Medicine

RESEARCH ARTICLE Open Access

Berberine moderates glucose metabolism through the GnRH-GLP-1 and MAPK pathways in the intestine

Qian Zhang, Xinhua Xiao*, Ming Li, Wenhui Li, Miao Yu, Huabing Zhang, Fan Ping, Zhixin Wang and Jia Zheng

Abstract

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"Rhuzima Coptidis was recorded as an anti-diabetes medication approximately **1500 years ago** in a book titled "Note of Elite Physicians" by Hongjing Tao"

Results: We found that 8 weeks of treatment with berberine significantly decreased fasting blood glucose levels. An oral glucose tolerance test (OGTT) showed that blood glucose was significantly reduced in the BerL and BerH groups before and at 30 min, 60 min and 120 min after oral glucose administration. Plasma postprandial glucagon-like peptide-1 (GLP-1) levels were increased in the berberine-treated groups. The ileum from the BerH group had 2112 genes with significantly changed expression (780 increased, 1332 decreased). KEGG pathway analyses indicated that all differentially expressed genes included 9 KEGG pathways. The top two pathways were the MAPK signaling pathway and the GnRH signaling pathway. Q-RT-PCR and immunohistochemistry verified that glucagon-like peptide 1 receptor (Glp1r) and mitogen activated protein kinase 10 (Mapk10) were significantly up-regulated, in contrast, gonadotropin releasing hormone receptor (Gnrhr) and gonadotropin-releasing hormone 1 (Gnrh1) were down-regulated in the BerH group.

Conclusion: Our data suggest that berberine can improve blood glucose levels in diabetic rats. The mechanisms involved may be in the MAPK and GnRh-Glp-1 pathways in the ileum.

Keywords: Diabetes, Digestive tract, Gene expression, GnRH

Zhang et al. BMC Complementary and Alternative Medicine 2014, 14:188
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BMC
Complementary & Alternative Medicine

RESEARCH ARTICLE Open Access

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Keywords: Diabetes, Digestive tract, Gene expression, GnRH

Absorption??

Biochemical Pharmacology 79 (2010) 1000–1006

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Modulation of glucagon-like peptide-1 release by berberine: In vivo and in vitro studies

Yunli Yu, Li Liu, Xinting Wang, Xiang Liu, Xiaodong Liu *, Lin Xie, Guangji Wang

Key Laboratory of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing 210009, PR China

ARTICLE INFO

ABSTRACTS

"**AMPK** is a major intermediate in facilitating the beneficial effects of berberine (Several reports showed that **AMPK lay on upstream** of **MAPK** pathway… involved in **GLP-1 secretion**.)

mediated GLP-1 secretion. Compound C (inhibitor of AMPK) also inhibited berberine-mediated GLP-1 secretion. But only low concentrations of H89 (inhibitor of PKA) showed inhibitory effects on berberine-mediated GLP-1 release. The present results demonstrated that berberine showed its modulation on GLP-1 via promoting GLP-1 secretion and GLP-1 biosynthesis. Some signal pathways

The main finding in the present study was that **berberine modulated GLP-1 release** and **biosynthesis**…"

Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal[1–3]

Patrice D Cani, Elodie Lecourt, Evelyne M Dewulf, Florence M Sohet, Barbara D Pachikian, Damien Naslain, Fabienne De Backer, Audrey M Neyrinck, and Nathalie M Delzenne

ABSTRACT

Background: We have previously shown that gut microbial fermentation of prebiotics promotes satiety and lowers hunger and energy intake in humans. In rodents, these effects are associated with an increase in plasma gut peptide concentrations, which are involved in appetite regulation and glucose homeostasis.

Objective: Our aim was to examine the effects of prebiotic supplementation on satiety and related hormones during a test meal for human volunteers by using a noninvasive micromethod for blood sampling to measure plasma gut peptide concentrations.

Design: This study was a randomized, double-blind, parallel, placebo-controlled trial. A total of 10 healthy adults (5 men and 5 women) were randomly assigned to groups that received either 16 g prebiotics/d or 16 g dextrin maltose/d for 2 wk. Meal tolerance tests were performed in the morning to measure the following: hydrogen breath test, satiety, glucose homeostasis, and related hormone response.

Results: We show that the prebiotic treatment increased breath-hydrogen excretion (a marker of gut microbiota fermentation) by ≈3-fold and lowered hunger rates. Prebiotics increased plasma glucagon-like peptide 1 and peptide YY concentrations, whereas postprandial plasma glucose responses decreased after the standardized meal. The areas under the curve for plasma glucagon-like peptide 1 and breath-hydrogen excretion measured after the meal (0–60 min) were significantly correlated ($r = 0.85$, $P = 0.007$). The glucose response was inversely correlated with the breath-hydrogen excretion areas under the curve (0–180 min; $r = -0.73$, $P = 0.02$).

Conclusion: Prebiotic supplementation was associated with an increase in plasma gut peptide concentrations (glucagon-like peptide 1 and peptide YY), which may contribute in part to changes in appetite sensation and glucose excursion responses after a meal in healthy subjects. *Am J Clin Nutr* 2009;90:1236–43.

associated risk factors for cardiovascular disease (3). A number of recent studies provide novel insights that might help establish a link between dietary nondigestible carbohydrate that changes the composition of gut microbiota and obesity and
(4–8). These compounds are called prebiotics
mote the growth of certain bacteria (eg, bifi
number correlates with an improvement of s
metabolic syndrome (9). In the search to dete
prebiotics in the control of body weight and fat n
a recent study showed that supplementation wi
a significant benefit for the maintenance of an
mass index and fat mass in primarily nonobese y
in addition to its benefit in bone mineralizatic
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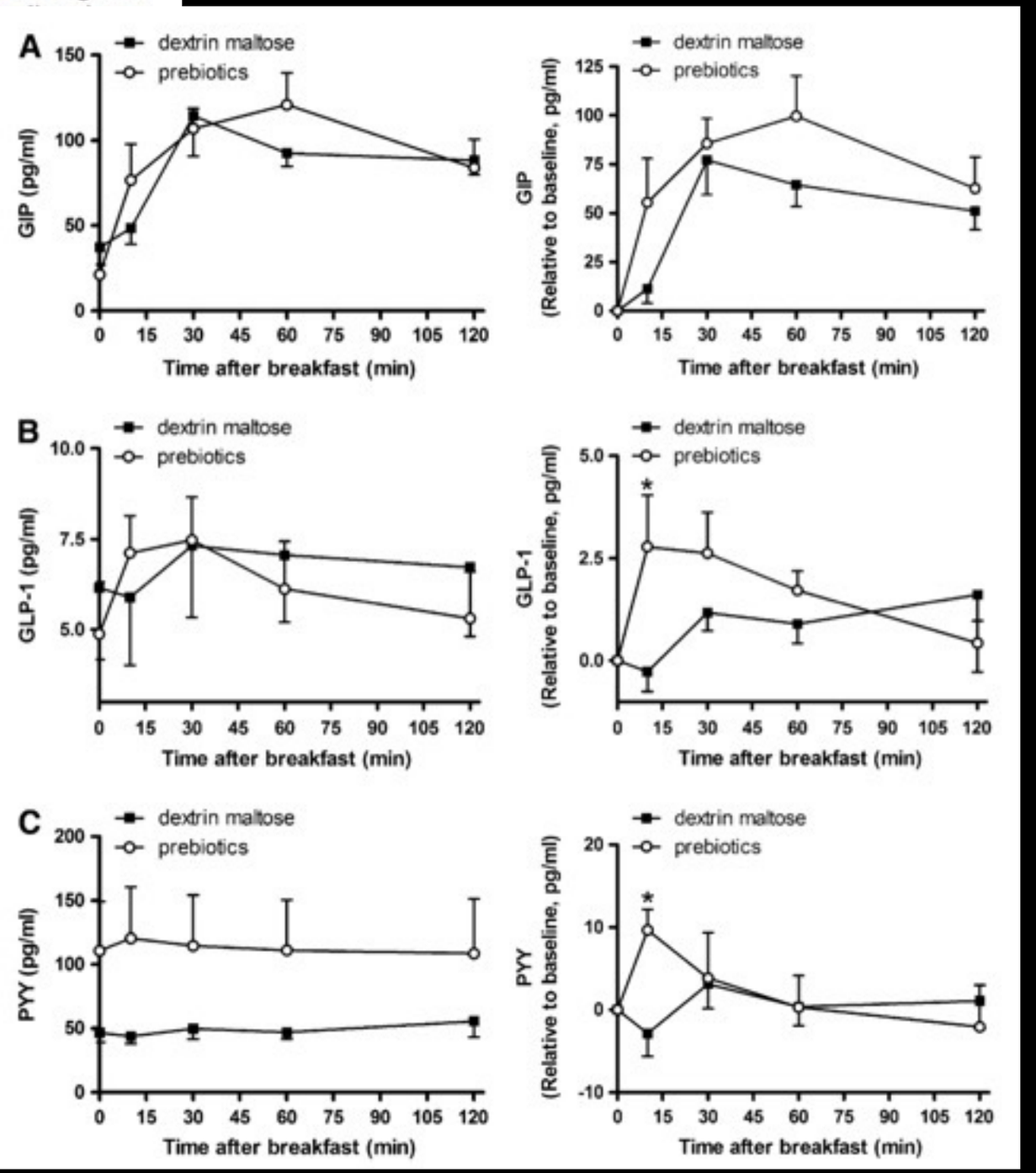
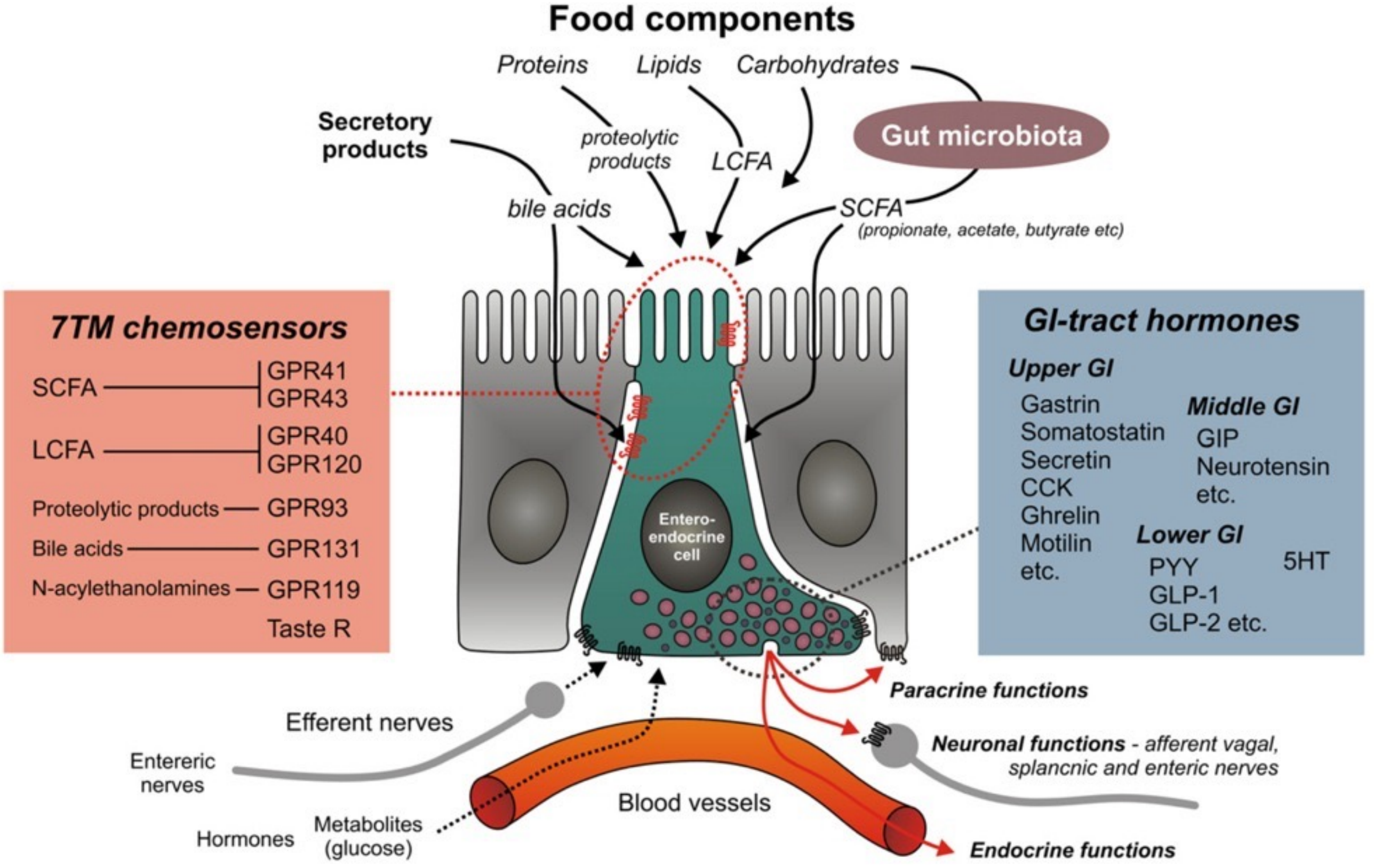
of gut microbiota by using prebiotics affects er
and body weight gain. However, few data a
mechanisms involved in these effects are provi
ers have previously published experimental
the modulation of gut peptide secretion [gluc
1 (GLP-1), glucose-dependent insulinotropic p
peptide YY (PYY), and/or ghrelin] in rodents
fermentable dietary fibers could constitute a
outcome of microbial fermentation in the low
and metabolic consequences (eg, decreased f
weight and fat mass development, and improved i
(11–20).

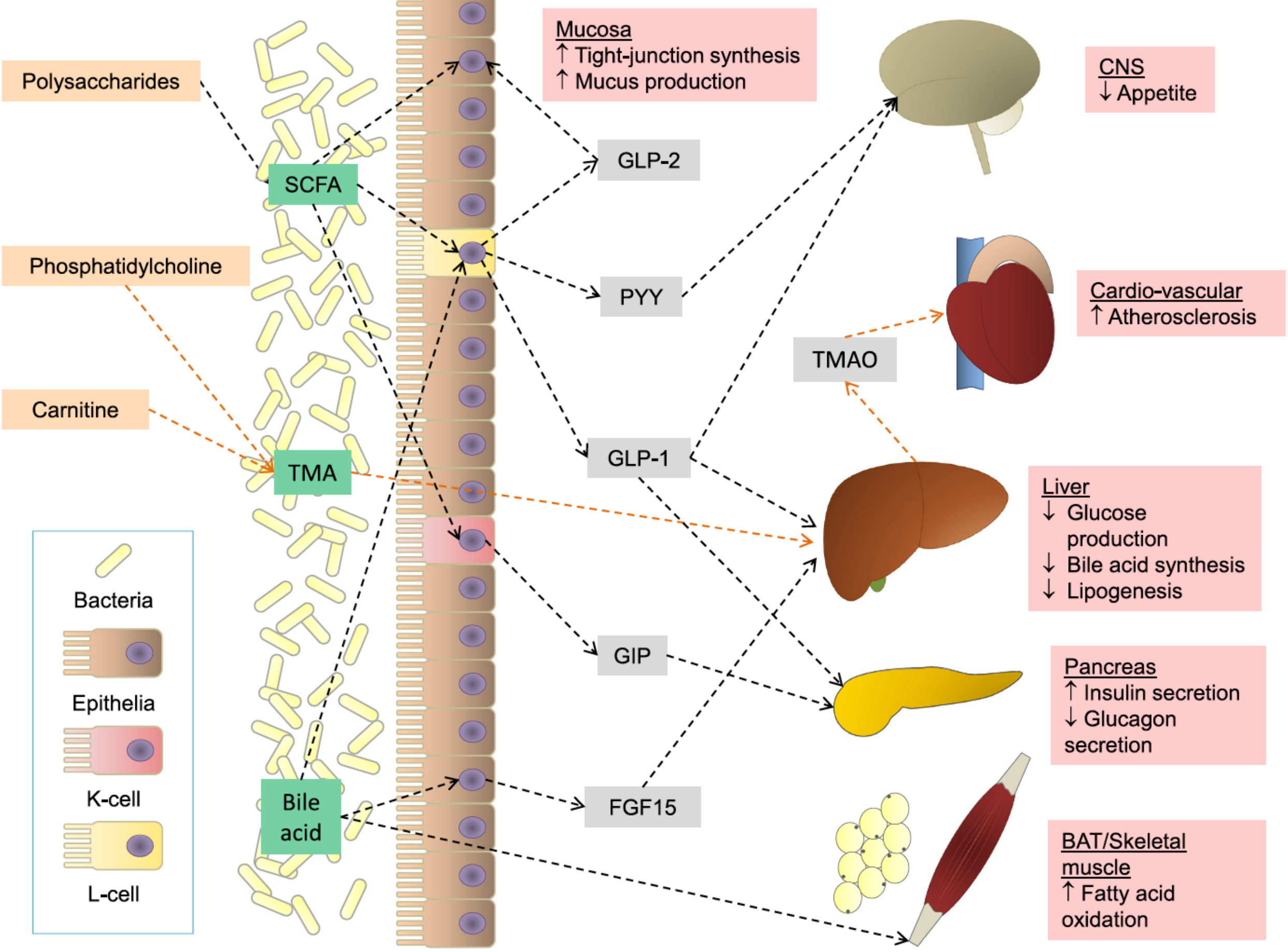
Several results support the relevance of preb
in appetite management in healthy and obese hu
date, few data are available that concomitantl
fluence of prebiotics on appetite sensation, gut
and metabolism in humans. Interestingly, one



Cani, P. D., Lecourt, E., Dewulf, E. M., Sohet, F. M., Pachikian, B. D., Naslain, D., et al. (2009). Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. American Journal of Clinical Nutrition, 90(5), 1236–1243. doi:10.3945/ajcn.2009.28095



Engelstoft, M. S., Egerod, K. L., Holst, B., & Schwartz, T. W. (2008). A Gut Feeling for Obesity: 7TM Sensors on Enteroendocrine Cells. Cell Metab., 8(6), 447–449. doi:10.1016/j.cmet.2008.11.004



Hansen, T. H. (2015). The gut microbiome in cardio-metabolic health, 1–16. http://doi.org/10.1186/s13073-015-0157-z

The Journal of Nutrition
Nutrition and Disease

Including Indigestible Carbohydrates in the Evening Meal of Healthy Subjects Improves Glucose Tolerance, Lowers Inflammatory Markers, and Increases Satiety after a Subsequent Standardized Breakfast[1,2]

Anne C. Nilsson,[3]* Elin M. Östman,[3] Jens J. Holst,[4] and Inger M. E. Björck[3]

[3]Division of Applied Nutrition and Food Chemistry, Department of Food Technology, Engineering and Nutrition, Lund University, SE-22100 Lund, Sweden and [4]Department of Biomedical Sciences, University of Copenhagen, the Panum Institute, DK-2200 Copenhagen, Denmark

Abstract

Low-glycemic index (GI) foods and foods rich in whole grain are associated with reduced risk of type 2 diabetes and cardiovascular disease. We studied the effect of cereal-based bread evening meals (50 g available starch), varying in GI and content of indigestible carbohydrates, on glucose tolerance and related variables after a subsequent standardized breakfast in healthy subjects ($n = 15$). At breakfast, blood was sampled for 3 h for analysis of blood glucose, serum insulin, serum FFA, serum triacylglycerides, plasma glucagon, plasma gastric-inhibitory peptide, plasma glucagon-like peptide-1 (GLP-1), serum interleukin (IL)-6, serum IL-8, and plasma adiponectin. Satiety was subjectively rated after breakfast and the gastric emptying rate (GER) was determined using paracetamol as a marker. Breath hydrogen was measured as an indicator of colonic fermentation. Evening meals with barley kernel based bread (ordinary, high-amylose- or β-glucan-rich genotypes) or an evening meal with white wheat flour bread (WWB) enriched with a mixture of barley fiber and resistant starch improved glucose tolerance at the subsequent breakfast compared with unsupplemented WWB ($P < 0.05$). At breakfast, the glucose response was inversely correlated with colonic fermentation ($r = -0.25$; $P < 0.05$) and GLP-1 ($r = -0.26$; $P < 0.05$) and positively correlated with FFA ($r = 0.37$; $P < 0.001$). IL-6 was lower ($P < 0.01$) and adiponectin

Nilsson, A. C., Ostman, E. M., Holst, J. J., & rck, I. M. E. B. (2008). Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. The Journal of Nutrition, 138(4), 732–739.

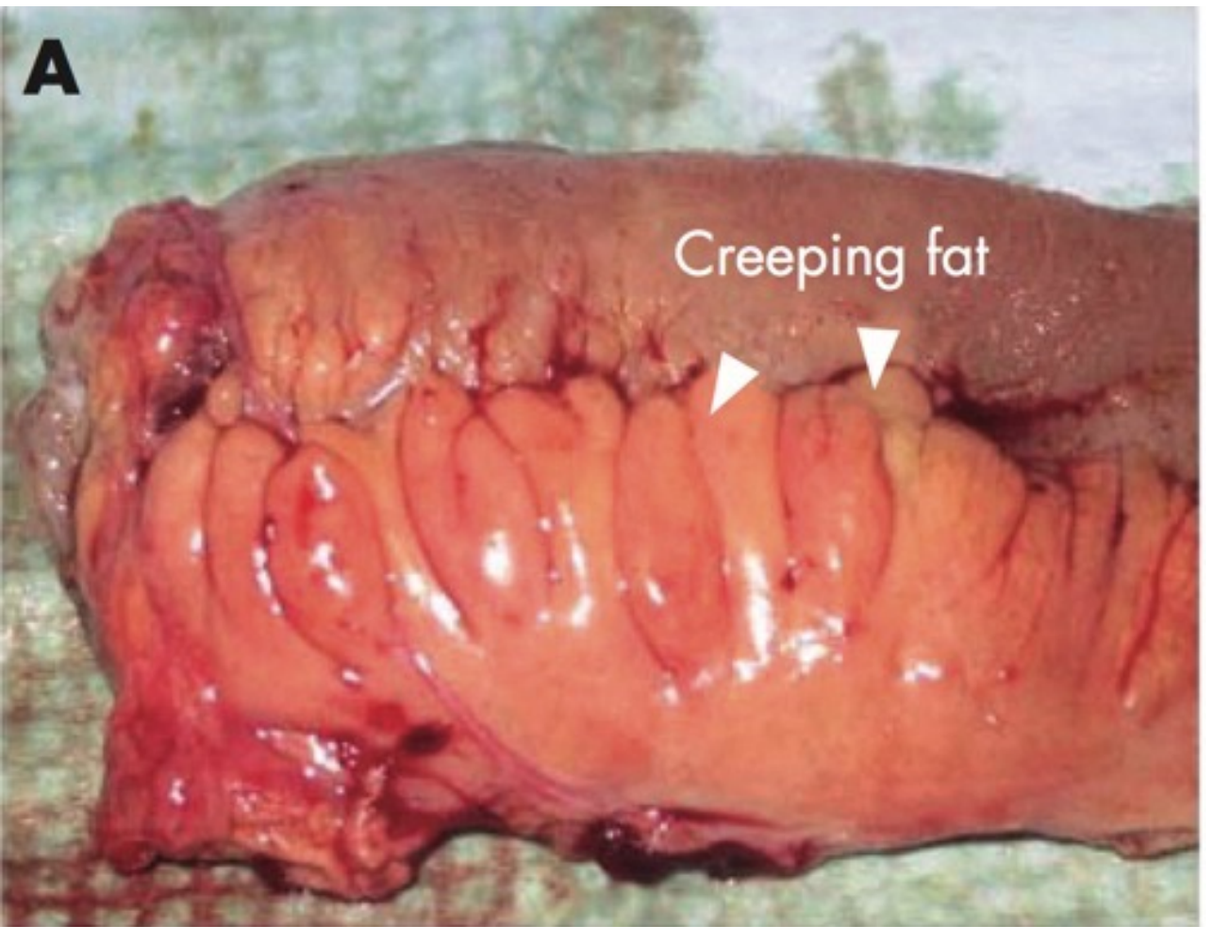
Summary of Gut Hormones

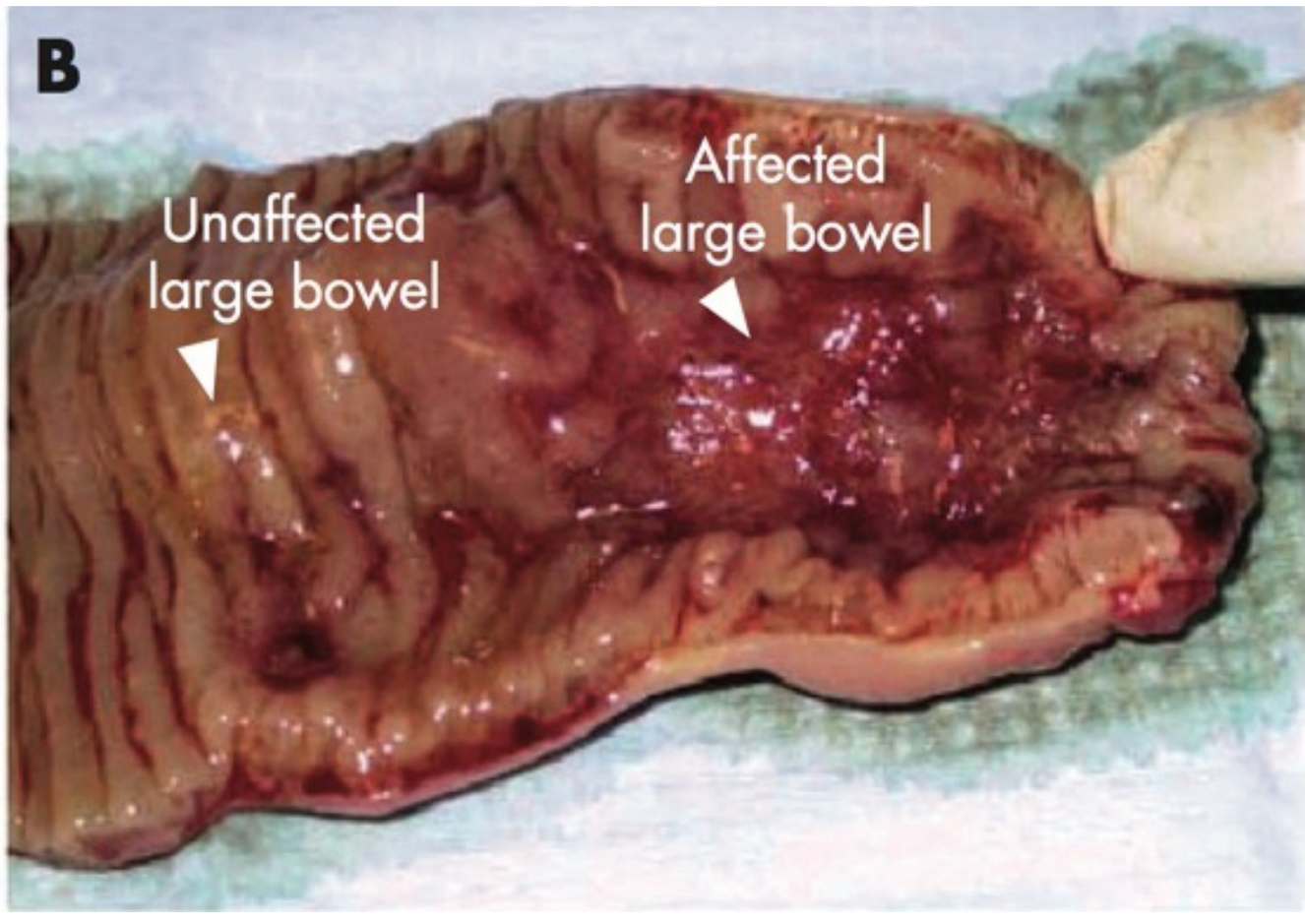
- DPPIV enzyme digests gut hormones, avoid it
- Eating breakfast, mindfully and thorough chews increase gut hormones
- Pea protein has unique amino acids that increase gut hormone release
- Fiber and phytonutrients (especially Berberine) increase gut hormone release

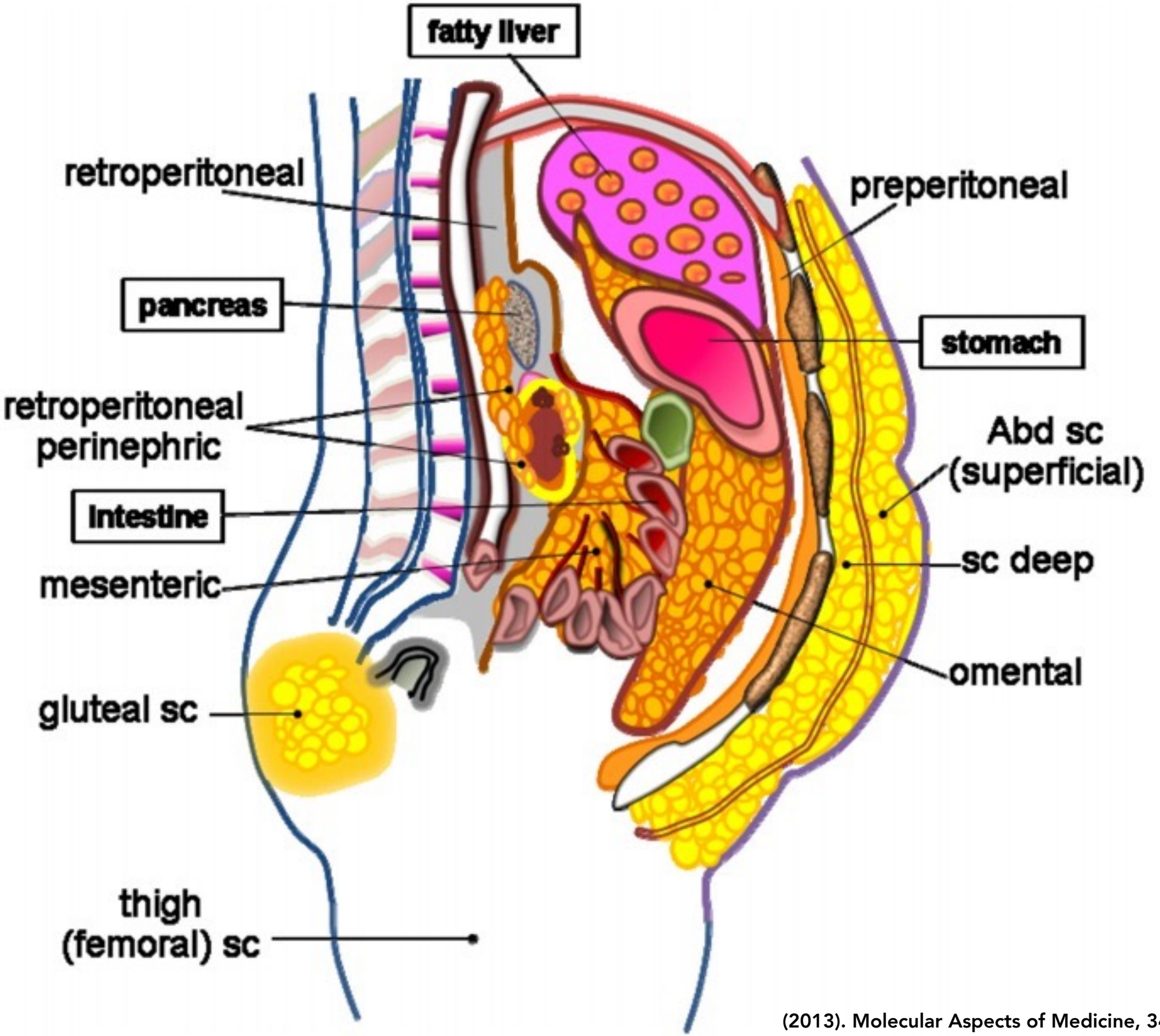
MESENTERIC FAT IN CROHN'S DISEASE: A PATHOGENETIC HALLMARK OR AN INNOCENT BYSTANDER?

Laurent Peyrin-Biroulet, Mathias Chamaillard, Florent Gonzalez, Elodie Beclin, Cecilia Decourcelle, Laurent Antunes, Jérôme Gay, Christel Neut, Jean-Frédéric Colombel, Pierre Desreumaux

Gut 2007;**56**:577–583. doi: 10.1136/gut.2005.082925







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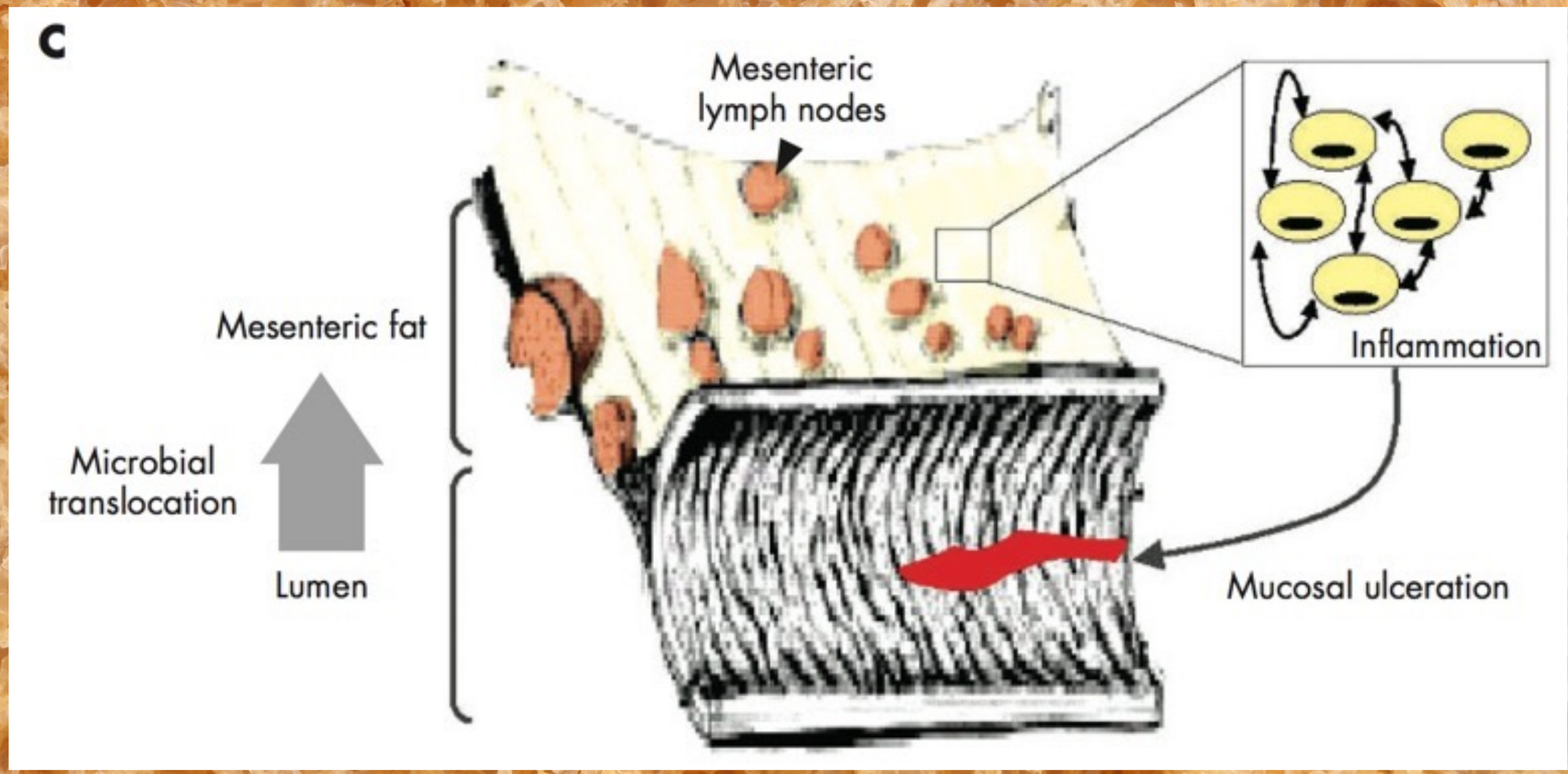
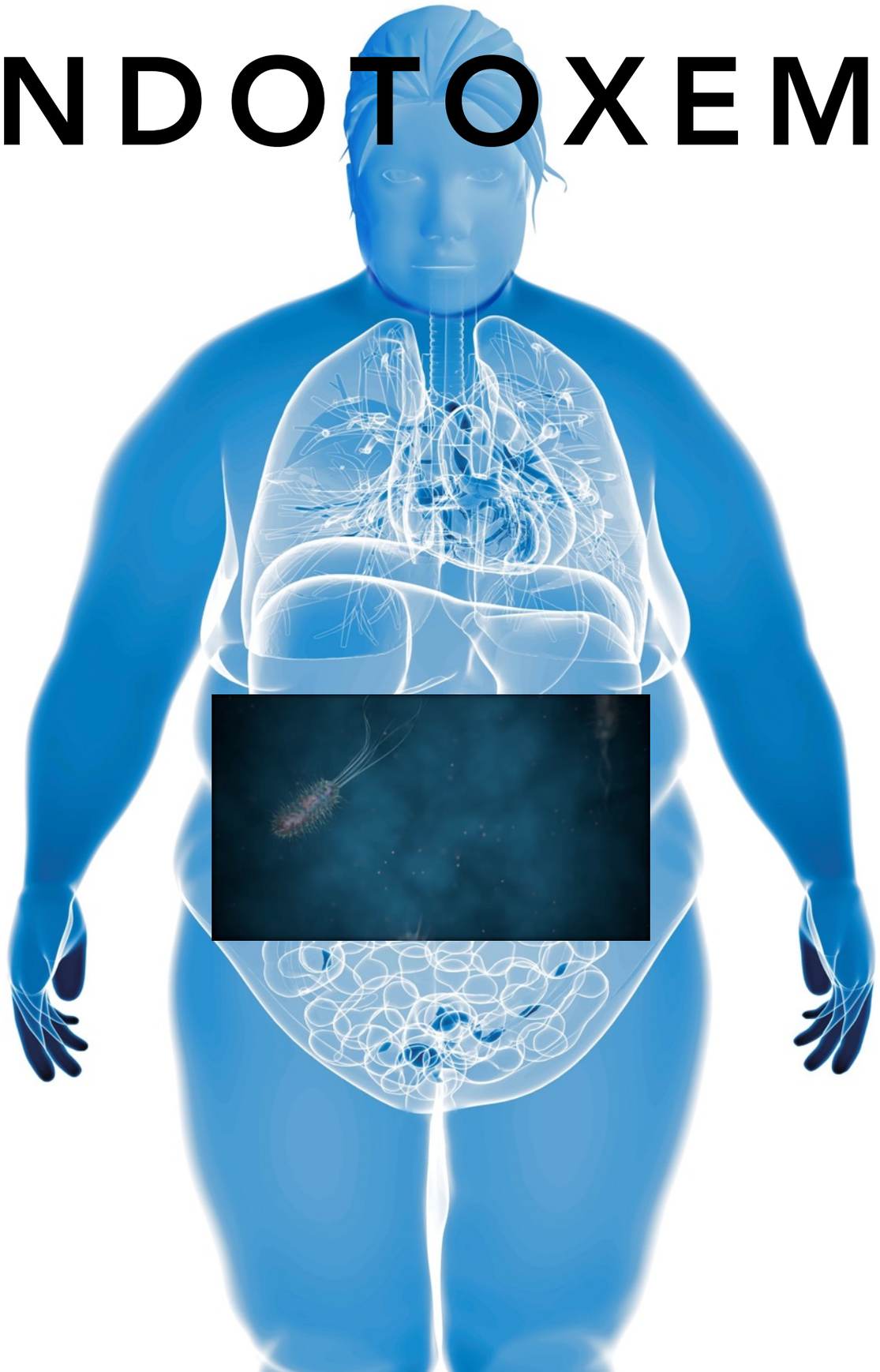


(2007). Gut, 56(4), 577–583.

OBESITY IS LINKED WITH ENDOTOXEMIA



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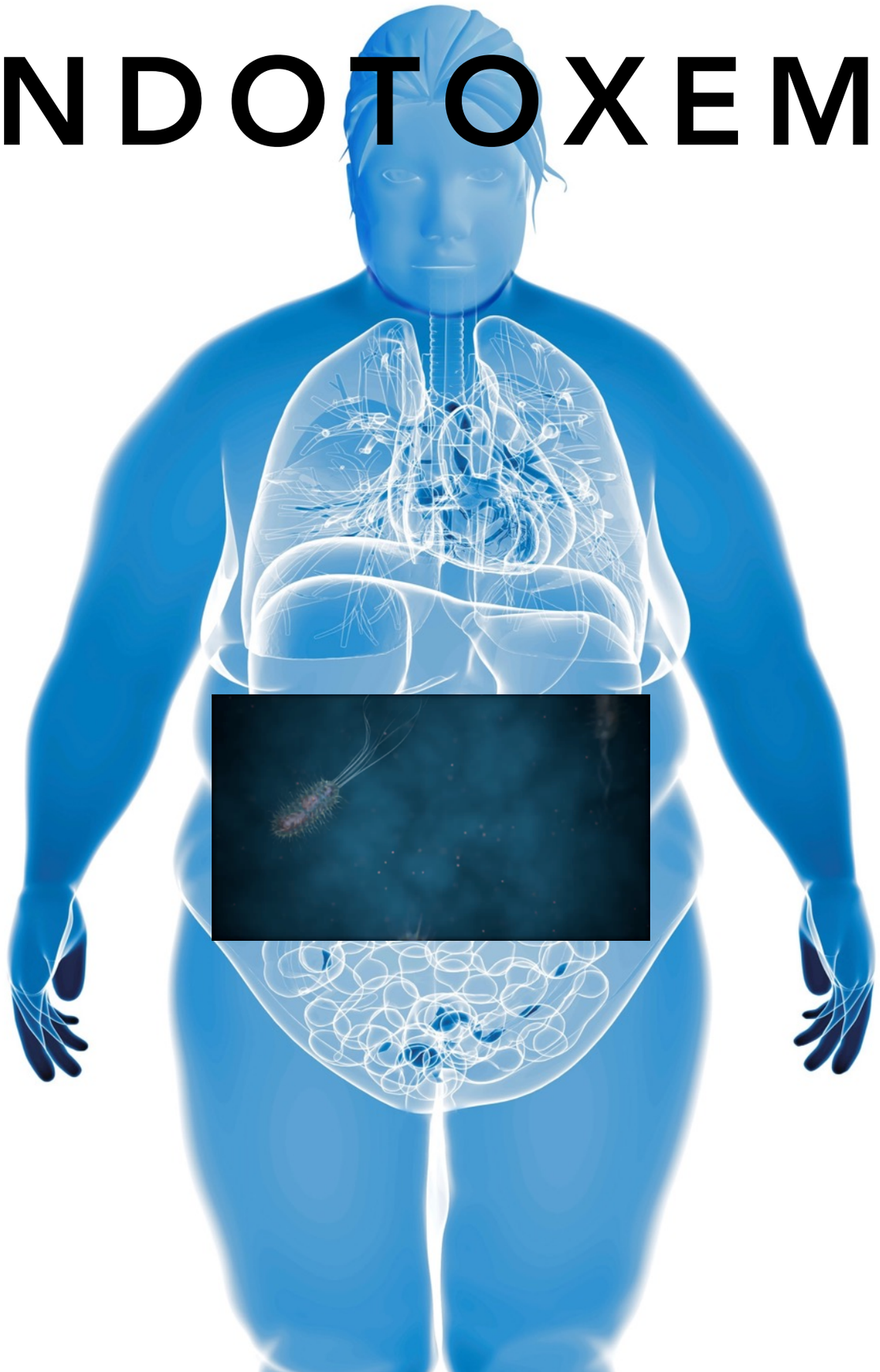

High-fat diet
Low fibres

↗ Lipogenesis
↗ Inflammation
↗ Steatosis
↘ Insulin sensitivity

↗ Inflammation
↗ Macrophages infiltration

1 Modulation of gut microbiota

2 ↘ *Bifidobacterium* spp.

3 ↗ LPS

Macrophages

↗ Inflammation
↘ Insulin sensitivity

Gut epithelium

Blood

Legend

LPS : lipopolysaccharides

mCD14 TLR4 LPS

(2009). Current Pharmaceutical Design, 15(13), 1546–1558.

Invited Review

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Of Microbes and Meals: The Health Consequences of Dietary Endotoxemia

Caleb J. Kelly, MS, RD [1]; Sean P. Colgan, PhD [1]; and Daniel N. Frank, PhD[2,3]

Abstract

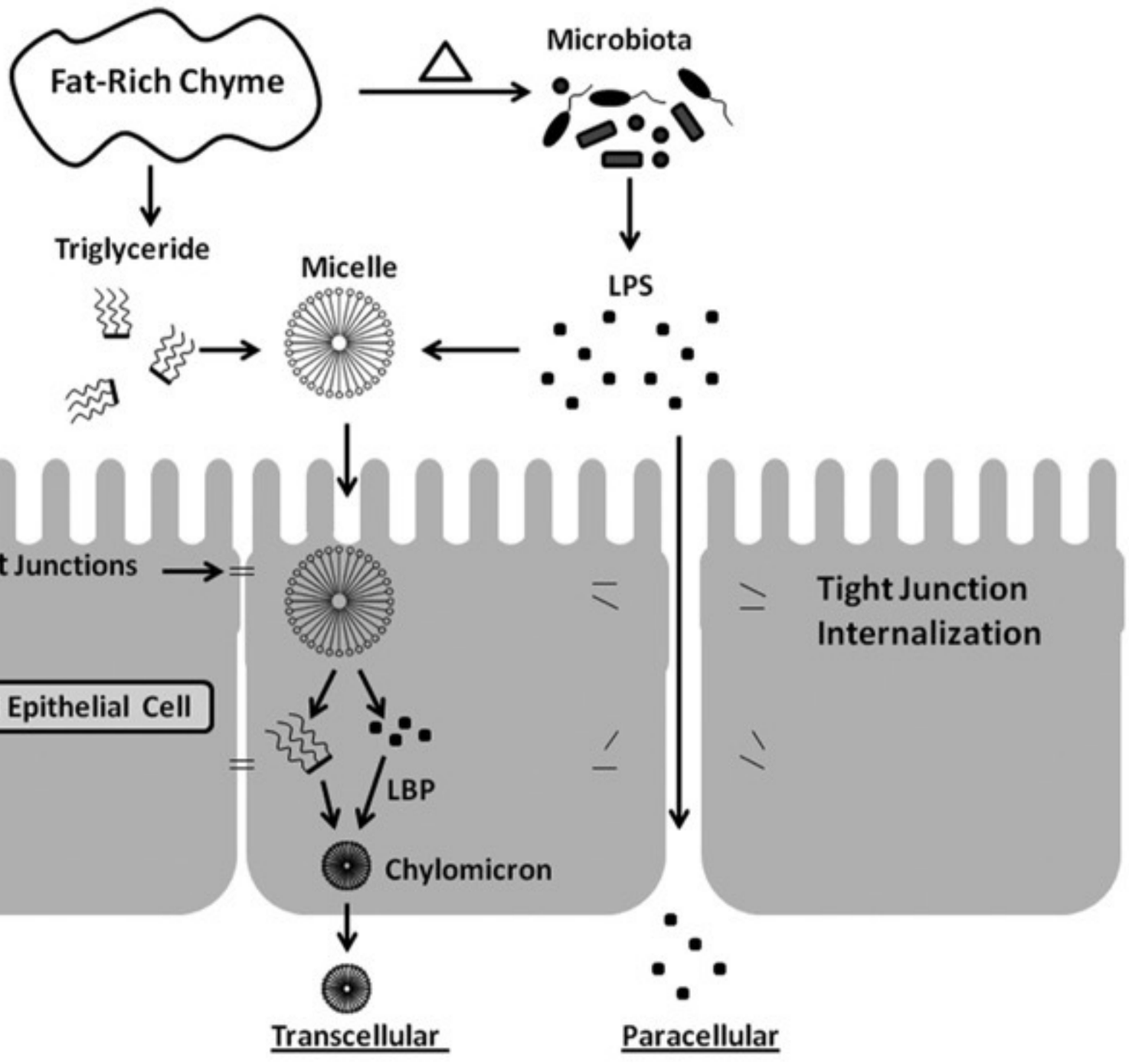
The human intestinal tract comprises a rich and complex microbial eco
of potentially toxic molecules, including bacterial endotoxin (ie, lipop
detectable in the circulation of healthy individuals, and levels transientl
exposure to circulating endotoxin has been associated with obesity, diabe
LPS translocation and by this mechanism may contribute to the pathogene
evolved mechanisms to detoxify endotoxin and neutralize the potentially
interest to clinicians is evidence that acute postprandial elevation of circ
review, the authors present an overview of the biochemical and cellular
interplay between microbial and nutrition determinants of this condition. Th
microbiota raise the possibility that dietary interventions can, at least in pa
Clin Pract. XXXX;xx:xx-xx)

Keywords

intestines; metagenome; inflammation; postprandial period; endotoxins; e

The gastrointestinal tracts of humans and other mammals are
complex bioreactors that have evolved to extract nutrients from diverse natural products. Critical to the functions of these systems are dynamic communities of microorganisms that likely have coevolved with their hosts to provide myriad beneficial services, including nutrient provision.[1] The high-carbohydrate diets ingested by omnivores and herbivores typically contain plant polysaccharides that cannot be directly hydrolyzed by the mammalian gut. Instead, the intestinal microbiota, which in adults is dominated by diverse members of the bacterial phyla Firmicutes (eg, clostridia) and Bacteroidetes,[2-4] encodes a variety of hydrolytic enzymes that can convert otherwise indigestible polysaccharides into relatively simple compounds such as short-chain fatty acids (SCFAs), which are more readily absorbed by the mammalian intestines.[1] In this way, the microbiota collectively provides genomic coding capacity—the "microbiome"[5,6]—that supplements the function of the host genome. That mammalian breast milk is composed of many types of oligosaccharide that both direct the early development of the intestinal microbiota and are fermented by this microbiota into compounds that nourish the developing infant is testament to the deeply interlinked relationships between host and microbiota.[7,8]

The intimate association of numerically rich and diverse microbial communities with the human host potentially comes



LIPOPROTEINS BIND TO ENDOTOXIN

commentary

The role of HDL in innate immunity[1]

Kenneth R. Feingold[2] and Carl Grunfeld

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HDL has anti-atherogenic properties that are primarily attributed to its key role in reverse cholesterol transport. The ability of HDL to inhibit the oxidation of LDL, decrease inflammation, inhibit thrombosis, stimulate fibrinolysis, and favorably affect endothelial cell function may also contribute to the anti-atherogenic effects of HDL (1, 2). Not well recognized is the role HDL plays in innate immunity (3).

Numerous studies have shown that lipoproteins bind microorganisms or compounds derived from microorganisms (3). When either endotoxin (LPS), from gram negative bacteria, or lipoteichoic acid (LTA), from gram positive bacteria, are incubated with whole blood from

globin-related protein also inhibit infection by Leishmania (14). Finally, low levels of HDL and apolipoprotein A-I are associated with an increase in mortality in patients admitted to intensive care units (15–17). Taken together, these observations indicate that HDL plays a role in protecting the host from the toxic effects of microorganisms and is part of the innate immune system.

The structural basis for the protective effects of HDL has been studied most intensively for LPS. Both the lipid and proteins that comprise HDL contribute to the neutralization of LPS. Apolipoprotein A-I alone can neutralize LPS and this interaction can be altered by changing the structure of apolipoprotein A-I (18). For example, serine

"Numerous studies have shown that **lipoproteins bind** to microorganisms or compounds derived from microbes...the majority of LPS and LTA are bound to HDL...inhibits the ability of LPS and LTA to interact with toll-like receptors (TLR). "

Similarly, several studies have shown that infusion of HDL or apolipoprotein A-I mimetic peptides into animals with experimental sepsis improves survival (3, 8, 9). Conversely, reducing serum lipoprotein levels increases the ability of LPS administration to induce death and this increased susceptibility can be reversed by providing exogenous lipoproteins (10). Humans with low HDL levels have a more robust inflammatory response to LPS administration (11). Furthermore, the administration of reconstituted HDL to humans blunts the deleterious effects of LPS administration (12). In addition to binding bacterial products, HDL also binds a wide variety of viruses and neutralizes their activity (3). Moreover, HDL also plays a protective role in parasitic infections (3). The lysis of trypanosomes is mediated by HDL particles that contain apolipoprotein L1 and

both apolipoproteins and phospholipids can play important roles in the ability of HDL to neutralize LPS (3).

In this issue, Hara et al. (19) explore the effect of endothelial lipase deficiency on the function of HDL particles. They report that HDL isolated from endothelial lipase knockout mice is similar to HDL isolated from wild-type mice in the ability to facilitate cholesterol efflux, protect from oxidation, and inhibit the ability of cytokines to activate endothelial cells. However, they demonstrate that HDL from endothelial lipase knockout mice are more potent in neutralizing LPS than control HDL in vitro and in vivo. Specifically, they show that *1*) HDL from endothelial lipase knockout mice is more effective than control HDL in inhibiting the ability of LPS to stimulate tumor necrosis factor secretion by macrophages in vitro, *2*) Endothelial

ORIGINAL ARTICLE

Endotoxemia Is Associated With an Increased Risk of Incident Diabetes

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MARKKU LEHTO, PHD[3,4]
JOUKO SUNDVALL, MSC[2]
VEIKKO SALOMAA, MD[2]

OBJECTIVE—Diabetes is accompanied with a chronic low-grade inflammation, which may in part be mediated by endotoxins derived from Gram-negative bacteria.

RESEARCH DESIGN AND METHODS—We investigated in a population-based cohort whether endotoxemia is associated with clinically incident diabetes. The serum endotoxin activity was measured by limulus assay from the FINRISK97 cohort comprising 7,169 subjects aged 25–74 years and followed up for 10 years.

RESULTS—Both the subjects with prevalent diabetes ($n = 537$) and those with incident diabetes ($n = 462$) had higher endotoxin activity than the nondiabetic individuals ($P < 0.001$). The endotoxin activity was significantly associated with increased risk for incident diabetes with a hazard ratio 1.004 (95% CI 1.001–1.007; $P = 0.019$) per unit increase resulting in a 52% increased risk ($P = 0.013$) in the highest quartile compared with the lowest one. The association was independent of diabetes risk factors: serum lipids, γ-glutamyl transferase, C-reactive protein, BMI, and blood glucose. Furthermore, the association of endotoxemia with an increased risk of incident diabetes was independent of the metabolic syndrome as defined either by the National Cholesterol Educational Program-Adult Treatment Panel III or the International Diabetes Federation. Endotoxin activity was linearly related ($P < 0.001$) to the number of components of the metabolic syndrome.

CONCLUSIONS—Both prevalent and incident diabetes were associated with endotoxemia, which may link metabolic disorders to inflammation. The results suggest that microbes play a role in the pathogenesis of diabetes.

Diabetes Care 34:392–397, 2011

Endotoxin (lipopolysaccharide [LPS]) is one of the potent virulence factors of Gram-negative bacterial species and has a major role in both acute and chronic infections. This unique glycolipid is located at the outer membrane of the bacteria, but in the circulation system 80–97% of it is bound to the lipoproteins (1). LPS may be cleared from the circulation system mainly by HDLs, which also neutralize its activity effectively.

Circulating endotoxin may derive from bacteria causing either overt acute infections or common chronic conditions. Additionally, endotoxin is believed to translocate from microbiota in the gut. Experiments in animal models kept in germ-free environments have shown that endotoxin is associated with cardiometabolic abnormalities including obesity, insulin resistance, and diabetes (2). Endotoxin activates both adaptive and innate immune systems characterized by a release of antibodies, cytokines, and other inflammatory mediators, which may promote hepatic insulin resistance. Treatment of rats with an antibiotic specifically targeted against Gram-negative bacteria reduces macrophage tumor necrosis factor-α expression and hepatic steatosis (3).

In humans, energy-enriched diets increasing weight gain and insulin resistance associate with absorption of endotoxin from the gastrointestinal track (4–6). This "metabolic endotoxemia" (7) resulting from the increased intestinal permeability/motility may lead to low-grade inflammation. Severity of inflammation may depend on a complex interplay between specific proteins, receptors, and lipoproteins that mediate the endotoxin bioactivity and metabolic fate.

In two small case-control studies, circulating LPS was higher in both type 1 and type 2 diabetic subjects compared with nondiabetic subjects (8,9). High serum LPS activity also associates with the development of diabetic nephropathy in patients with type 1 diabetes (10). It has been hypothesized that bacterial endotoxins can act as triggers, linking inflammation to metabolic syndrome and thereby diabetes (4,11,12). Studies of this association in humans, however, are scarce as a result of the methodological challenges. Therefore, we investigated in a large population-based cohort followed up for 10 years, if endotoxemia is associated with clinically incident diabetes.

RESEARCH DESIGN AND METHODS

The FINRISK97 involved a population-based sample ($n = 7,169$) of 25- to 74-year-old participants of the survey, which was conducted in five geographical areas in Finland (13). The survey included a self-administered questionnaire and a clinical examination with weight, height, and blood pressure measurements as well as blood drawing. The study was approved by the Ethics Committee of the National Public Health Institute and conducted according to the Helsinki Declaration. All subjects gave written informed consent.

Laboratory analyses

Before blood sampling, the participants were asked to fast for 4 h and to avoid heavy meals earlier during the day. The median fasting time was 5 (interquartile range 3–7) hours. All laboratory measurements, except serum glucose (14), were carried out at the Disease Risk Unit in the National Institute for Health and Welfare, Helsinki. Lipids and

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Received 30 August 2010 and accepted 9 November 2010.
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ORIGINAL ARTICLE

Endotoxemia Is Associated With an Increased Risk of Incident Diabetes

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Aki S. Havulinna, msc[2]
Markku Lehto, phd[3,4]
Jouko Sundvall, msc[2]
Veikko Salomaa, md[2]

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The American Journal of Clinical Nutrition

Energy intake is associated with endotoxemia in apparently healthy men[1–4]

Jacques Amar, Rémy Burcelin, Jean Bernard Ruidavets, Patrice D Cani, Josette Fauvel, Marie Christine Alessi, Bernard Chamontin, and Jean Ferriéres

ABSTRACT
Background: The bridge between food intake and weight is not fully understood. Recently, the role of gut microbiota and bacterial lipopolysacharides (LPS) in weight has been noted.
Objective: The objective was to evaluate the relation between plasma LPS concentration and food intake.
Design: A dietary survey was conducted in 1015 subjects randomly recruited in France. The participants were given oral and written instructions on how to keep a consecutive 3-d food record. Plasma LPS was measured in a subsample of 201 men. To assess, under controlled conditions, the differential impact of various high-energy diets, plasma LPS concentrations were measured in mice fed a high-fat or a high-carbohydrate diet over a 4-wk period.
Results: In humans, no significant relation was observed between cardiovascular disease risk factors, carbohydrate and protein intakes, and plasma LPS concentration. Conversely, positive correlations were observed with fat and energy intakes. In a multivariate analysis, endotoxemia was independently associated with energy intake. Compared with the control mice, mice fed a high-energy diet showed an increase in plasma LPS. However, in mice fed a high-carbohydrate diet, the increase in plasma LPS was blunted compared with mice fed a high-fat diet.
Conclusions: In this large sample of healthy men from a population-based sample, we found a link between food intake and plasma LPS. Experimental data suggest that fat was more efficient in transporting bacterial LPS from the gut lumen into the bloodstream. The results of this study add to the knowledge of mechanisms responsible for relations between food intake and metabolic diseases. *Am J Clin Nutr* 2008;87:1219–23.

INTRODUCTION

Obesity has reached epidemic proportions globally. More than 1 billion adults are overweight, at least 300 million of whom are clinically obese. Obesity and overweight pose a major risk of chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension, and stroke. The key causes are an increased consumption of energy-dense foods high in saturated fats and sugars (1). However, the bridge between food intake and weight is not fully understood. The hypothesis that gut microbiota influences weight gain was posited recently. An original observation reported that young adult mice have 40% more total body fat

high-fat obesitogenic diet did not gain weight, which suggests that, indeed, a bacterially related factor is responsible for obesity induced by a high-fat diet (4). The authors suggested that gut microbiota from obese mice allows energy to be salvaged from otherwise indigestible dietary polysaccharides (5). Recently, we reported in mice the role of bacterial lipopolysaccharide (LPS) from the gram-negative intestine (6). We first showed that metabolic concentrations of plasma LPS are modulated by food content: the higher the fat food content, the higher the concentration of plasma LPS. Second, we found that the metabolic concentration of plasma LPS is a sufficient molecular mechanism for triggering the high-fat diet–induced metabolic diseases such as obesity and diabetes. Whether these experimental results are relevant in humans deserves to be studied. We sought to evaluate in healthy men the relation between plasma LPS concentration and food intake.

SUBJECTS AND METHODS

Population

Subjects ($n = 1015$) randomly selected from polling lists were recruited between 1995 and 1997 by the Toulouse MONICA Center in Haute Garonne, a region of southwestern France. Authorization from the appropriate ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Lille) was obtained, and each subject signed an informed consent form (7). The examination was performed in the morning, and a blood sample was drawn after the subjects fasted overnight. With the help of medical staff, each subject filled in a questionnaire about his or her medical history, drug intake, smoking habits, and alcohol consumption. The dietary survey

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[2] JA, RB, and JBR contributed equally to this work.
[3] Supported by grants from the Délégation Régionale à la Recherche Clinique des Hôpitaux de Toulouse 2003, the Institut National de la Santé et de la Recherche Médicale (INSERM), the Fondation de France, and the Fédération Française de Cardiologie.
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High Fat Intake Leads to Acute Postprandial Exposure to Circulating Endotoxin in Type 2 Diabetic Subjects

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Sudhesh Kumar, md[1]
Philip G. McTernan, phd[1]

OBJECTIVE—To evaluate the changes in circulating endotoxin after a high–saturated fat meal to determine whether these effects depend on metabolic disease state.

RESEARCH DESIGN AND METHODS—Subjects ($n = 54$) were given a high-fat meal (75 g fat, 5 g carbohydrate, 6 g protein) after an overnight fast (nonobese control [NOC]: age 39.9 ± 11.8 years [mean ± SD], BMI 24.9 ± 3.2 kg/m^2, $n = 9$; obese: age 43.8 ± 9.5 years, BMI 33.3 ± 2.5 kg/m^2, $n = 15$; impaired glucose tolerance [IGT]: age 41.7 ± 11.3 years, BMI 32.0 ± 4.5 kg/m^2, $n = 12$; type 2 diabetic: age 45.4 ± 10.1 years, BMI 30.3 ± 4.5 kg/m^2, $n = 18$). Blood was collected before (0 h) and after the meal (1–4 h) for analysis.

RESULTS—Baseline endotoxin was significantly higher in the type 2 diabetic and IGT subjects than in NOC subjects, with baseline circulating endotoxin levels 60.6% higher in type 2 diabetic subjects than in NOC subjects ($P < 0.05$). Ingestion of a high-fat meal led to a significant rise in endotoxin levels in type 2 diabetic, IGT, and obese subjects over the 4-h time period ($P < 0.05$). These findings also showed that, at 4 h after a meal, type 2 diabetic subjects had higher circulating endotoxin levels (125.4%↑) than NOC subjects ($P < 0.05$).

CONCLUSIONS—These studies have highlighted that exposure to a high-fat meal elevates circulating endotoxin irrespective of metabolic state, as early as 1 h after a meal. However, this increase is substantial in IGT and type 2 diabetic subjects, suggesting that metabolic endotoxinemia is exacerbated after high fat intake. In conclusion, our data suggest that, in a compromised metabolic state such as type 2 diabetes, a continual snacking routine will cumulatively promote their condition more rapidly than in other individuals because of the greater exposure to endotoxin.

Diabetes Care 35:375–382, 2012

Studies examining the interrelationships between adipose tissue, inflammation, and insulin resistance appear key to understanding type 2 diabetes risk (1,2). It is known that low-grade chronic systemic inflammation contributes to this risk, which appears altered by several factors such as increasing age, sex, ethnicity, genetics, and dietary influences. However, systemic inflammation appears to persist in type 2 diabetic subjects, despite medication, while the mechanisms and mediators of this continual inflammation appear less clear. Evidently, adipose tissue accumulation has a significant impact on disease risk and inflammation in type 2 diabetes but may merely act in response to systemic primary insults (3–9).

One potential cellular mechanism for increased inflammation may arise through activation of the innate immune system in human adipose tissue (10–13). Previous studies have shown that increased activation of the innate immune pathway may arise through excess circulating gut-derived bacteria, known as lipopolysaccharide (LPS) or endotoxin, which represents the outer cell wall membrane of gram-negative bacteria (10,11,14–17). Our previous work has shown that endotoxin has an immediate impact on the innate immune pathway in human adipose tissue, acting via key receptors known as the Toll-like receptors, which recognize antigens, such as the LPS component, to initiate an acute-phase response to infection (8,10). Stimulation of the Toll-like receptors leads to intracellular activation of nuclear factor-κB (NF-κB), a key transcription factor in the inflammatory cascade that regulates the transcription of numerous proinflammatory adipokines (9,10). Therefore, in vitro endotoxin may act as a mediator of inflammation through activation of NF-κB, leading to a rapid response within adipose tissue that may be exacerbated by increased adipose tissue mass (18–22).

However, clinical studies have also implicated gut-derived endotoxin as a "primary insult" to activate the inflammatory state, contributing to metabolic disease, with current cross-sectional data showing elevated systemic endotoxin levels in conditions of obesity, type 2 diabetes, coronary artery disease, and fatty liver disease (8,10,11,14–17). Within these studies, circulating endotoxin is observed to be positively associated with waist circumference, waist-to-hip ratio, insulin levels, inflammatory cytokines and lipids, including total cholesterol, triglycerides (TGs), and LDL cholesterol, and negatively associated with HDL cholesterol (8,10,11,14–17). The combined importance of dietary lipids and LPS in determining inflammatory risk may arise, since endotoxin has a strong affinity for chylomicrons (lipoproteins that transport dietary long-chain saturated fatty acids [SFAs] through the gut wall) as endotoxin crosses the gastrointestinal mucosa (23–25). As such, atherogenic and inflammatory risk may arise through a

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The American Journal of Clinical Nutrition

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Conclusions: In this large sample of healthy men from a population-based sample, we found a link between food intake and plasma LPS. Experimental data suggest that fat was more efficient in transporting bacterial LPS from the gut lumen into the bloodstream. The results of this study add to the knowledge of mechanisms responsible for relations between food intake and metabolic diseases. *Am J Clin Nutr* 2008;87:1219–23.

INTRODUCTION

Obesity has reached epidemic proportions globally. More than 1 billion adults are overweight, at least 300 million of whom are clinically obese. Obesity and overweight pose a major risk of chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension, and stroke. The key causes are an increased consumption of energy-dense foods high in saturated fats and sugars (1). However, the bridge between food intake and weight is not fully understood. The hypothesis that gut microbiota influences weight gain was posited recently. An original observation reported that young adult mice have 40% more total body fat

high-fat obesitogenic diet did not gain weight, which suggests that, indeed, a bacterially related factor is responsible for obesity induced by a high-fat diet (4). The authors suggested that gut microbiota from obese mice allows energy to be salvaged from otherwise indigestible dietary polysaccharides (5). Recently, we reported in mice the role of bacterial lipopolysaccharide (LPS) from the gram-negative intestine (6). We first showed that metabolic concentrations of plasma LPS are modulated by food content: the higher the fat food content, the higher the concentration of plasma LPS. Second, we found that the metabolic concentration of plasma LPS is a sufficient molecular mechanism for triggering the high-fat diet–induced metabolic diseases such as obesity and diabetes. Whether these experimental results are relevant in humans deserves to be studied. We sought to evaluate in healthy men the relation between plasma LPS concentration and food intake.

SUBJECTS AND METHODS

Population

Subjects ($n = 1015$) randomly selected from polling lists were recruited between 1995 and 1997 by the Toulouse MONICA Center in Haute Garonne, a region of southwestern France. Authorization from the appropriate ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Lille) was obtained, and each subject signed an informed consent form (7). The examination was performed in the morning, and a blood sample was drawn after the subjects fasted overnight. With the help of medical staff, each subject filled in a questionnaire about his or her medical history, drug intake, smoking habits, and alcohol consumption. The dietary survey

[1] From INSERM 558, Toulouse, France (JA, JBR, BC, and JF); the Institute of Molecular Medicine, I2MR, IFR 31, Toulouse, France (RB and PDC); the Service de Biochimie, INSERM U 563, CHU Toulouse, France (JF); and INSERM U 626, Marseille, France (MCA).
[2] JA, RB, and JBR contributed equally to this work.
[3] Supported by grants from the Délégation Régionale à la Recherche Clinique des Hôpitaux de Toulouse 2003, the Institut National de la Santé et de la Recherche Médicale (INSERM), the Fondation de France, and the Fédération Française de Cardiologie.
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were carried out at the Disease Risk Unit in the National Institute for Health and Welfare, Helsinki. Lipids and

Energy intake is associated with endotoxemia in apparently healthy

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Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

Differential Effects of Cream, Glucose, and Orange Juice on Inflammation, Endotoxin, and the Expression of Toll-Like Receptor-4 and Suppressor of Cytokine Signaling-3

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HUSAM GHANIM, PHD
JAY FRIEDMAN, PHD
SANAA ABUAYSHEH, BSC
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PRABHAKAR VISWANATHAN, PHD
AJAY CHAUDHURI, MD
PARESH DANDONA, MD, PHD

OBJECTIVE — We have recently shown that a high-fat high-carbohydrate (HFHC) meal induces an increase in plasma concentrations of endotoxin (lipopolysaccharide [LPS]) and the expression of Toll-like receptor-4 (TLR-4) and suppresser of cytokine signaling-3 (SOCS3) in mononuclear cells (MNCs) in addition to oxidative stress and cellular inflammation. Saturated fat and carbohydrates, components of the HFHC meal, known to induce oxidative stress and inflammation, also induce an increase in LPS, TLR-4, and SOCS3.

RESEARCH DESIGN AND METHODS — Fasting normal subjects were given 300-calorie drinks of either glucose, saturated fat as cream, orange juice, or only water to ingest. Blood samples were obtained at 0, 1, 3, and 5 h for analysis.

RESULTS — Indexes of inflammation including nuclear factor-κB (NF-κB) binding, and the expression of SOCS3, tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β in MNCs, increased significantly after glucose and cream intake, but TLR-4 expression and plasma LPS concentrations increased only after cream intake. The intake of orange juice or water did not induce any change in any of the indexes measured.

CONCLUSIONS — Although both glucose and cream induce NF-κB binding and an increase in the expression of SOCS3, TNF-α, and IL-1β in MNCs, only cream caused an increase in LPS concentration and TLR-4 expression. Equicaloric amounts of orange juice or water did not induce a change in any of these indexes. These changes are relevant to the pathogenesis of atherosclerosis and insulin resistance.

Diabetes Care 33:991–997, 2010

Our recent work has shown that a high-fat high-cholesterol (HFHC) meal induces oxidative and inflammatory stress in addition to inducing an increase in plasma endotoxin (lipopolysaccharide [LPS]) levels and the expression of Toll-like receptor (TLR)-4, the specific receptor for LPS (1). In contrast, a high-fiber and fruit meal does not induce any of these changes. These data are of great interest because the content of LPS in these meals is not significantly different, and, thus, it would appear that the inflammatory nature of the meal may lead to a partial breakdown of the intestinal barrier that normally protects the body from invasion of bacteria and the entry of LPS from the gut. The concept of this immunological barrier of the gut has developed rapidly over the past few years and is vital to the protection from bacterial toxins and immunological responses to the commensal and pathogenic intestinal bacteria.

In this context, we wanted to analyze which macronutrient was responsible for the induction of oxidative stress and inflammation, on the one hand, and the increase in LPS concentrations and the expression of TLR-4 and suppresser of cytokine signaling (SOCS)-3 on the other. To elucidate this, we investigated the effect of glucose, the most important carbohydrate, cream, a saturated fat, and orange juice, a carbohydrate-containing food product, which does not induce either oxidative stress or inflammation.

SOCS3 is a protein that has been shown to interfere with insulin and leptin signal transduction (2–5). Our recent work has shown that SOCS3 expression in the circulating mononuclear cells (MNCs) of the obese human is markedly increased when compared with that in normal subjects (6). In addition, our work demonstrated that SOCS3 expression in MNCs is inversely related to the tyrosine phosphorylation of the insulin receptor and directly related to BMI and insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]), consistent with its role in the pathogenesis of insulin resistance. Leptin resistance in human obesity leads to the inability of leptin to cause satiety and weight loss, whereas insulin resistance makes the obese vulnerable to diabetes. Human obesity is also a state of chronic inflammation characterized by an increase in inflammatory mediators in plasma, in adipose tissue, and in circulating mononuclear cells (7,8). Because SOCS3 is induced in animal models by proinflammatory stimuli like the cytokines, TNF-α, IL-6, and IL-1β (3,4,9) and because macronutrient intake causes oxidative stress (10,11) and inflammation (12,13), it is possible that the intake of glucose and saturated fat (cream) induces an increase in the expression of SOCS3 as a part of macronutrient-induced inflam-

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R.D., H.G., and J.F. contributed equally to this study.

Pathophysiology/Complications

ORIGINAL ARTICLE

High Fat Intake Lead
Postprandial Exposu
Endotoxin in Type 2

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SUDHESH KUMAR, MD[1]
PHILIP G. MCTERNAN,

OBJECTIVE—To evaluate the changes in circulating endotoxin after a h
to determine whether these effects depend on metabolic disease state.

RESEARCH DESIGN AND METHODS—Subjects ($n = 54$) were
(75 g fat, 5 g carbohydrate, 6 g protein) after an overnight fast (nonobe
39.9 ± 11.8 years [mean ± SD], BMI 24.9 ± 3.2 kg/m^2, $n = 9$; obese: age
33.3 ± 2.5 kg/m^2, $n = 15$; impaired glucose tolerance [IGT]: age 41.7 ± 1
4.5 kg/m^2, $n = 12$; type 2 diabetic: age 45.4 ± 10.1 years, BMI 30.3 ± 4.5
was collected before (0 h) and after the meal (1–4 h) for analysis.

RESULTS—Baseline endotoxin was significantly higher in the type 2 dia
than in NOC subjects, with baseline circulating endotoxin levels 60.6% hi
subjects than in NOC subjects ($P < 0.05$). Ingestion of a high-fat meal led
endotoxin levels in type 2 diabetic, IGT, and obese subjects over the 4-h t
These findings also showed that, at 4 h after a meal, type 2 diabetic subjects
endotoxin levels (125.4%[]) than NOC subjects ($P < 0.05$).

CONCLUSIONS—These studies have highlighted that exposure to a
circulating endotoxin irrespective of metabolic state, as early as 1 h after
increase is substantial in IGT and type 2 diabetic subjects, suggesting that ma
is exacerbated after high fat intake. In conclusion, our data suggest that, in a c
state such as type 2 diabetes, a continual snacking routine will cumulatively p
more rapidly than in other individuals because of the greater exposure to e

Diabetes Ca

Studies examining the interrelationships between adipose tissue, inflammation, and insulin resistance appear key to understanding type 2 diabetes risk (1,2). It is known that low-grade chronic systemic inflammation contributes to this risk, which appears altered by several factors such as increasing age, sex, ethnicity, genetics, and dietary influences. However, systemic inflammation appears to persist in type 2 diabetic subj
tion, while the mecha
of this continual infla
clear. Evidently, adip
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and inflammation in
may merely act in resp
mary insults (3–9).

One potential cel
increased inflammatio

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Science, Biomarkers Research Programme and Center of Excellence in Biochem
University, Riyadh, Saudi Arabia; the [3]Institut d'Investigacions Biomèdiques Aug
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Energy intake is associated with endotoxemia in apparently healthy

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Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

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mpared with that in
6). In addition, our
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versely related to the
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with its role in the
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to cause satiety and
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High Fat I
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ALISON L. HARTE, PHD[1]
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OBJECTIVE—To evaluate the c
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systemic inflammation contribu
risk, which appears altered by s
tors such as increasing age, sex
genetics, and dietary influences
systemic inflammation appears

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Research report

Increased IgA and IgM responses against gut commensals in chronic depression: Further evidence for increased bacterial translocation or leaky gut

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ABSTRACT

Background: Recently, we discovered that depression is accompanied by increased IgM and IgA responses directed against gram negative gut commensals. The aim of this study was to replicate these findings in a larger study group of depressed patients and to examine the associations between the IgA and IgM responses to gut commensals and staging of depression as well as the fatigue and somatic (F&S) symptoms of depression.

Methods: We measured serum concentrations of IgM and IgA against the LPS of gram-negative enterobacteria, i.e. *Hafnia alvei*, *Pseudomonas aeruginosa*, Morganella morganii, *Pseudomonas putida*, *Citrobacter koseri*, and *Klebsiella pneumoniae* in 112 depressed patients and 28 normal controls. The severity of F&S symptoms was measured using the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale.

Results: The prevalences and median values of serum IgM and IgA against LPS of these commensals were significantly higher in depressed patients than in controls. The IgM levels directed against the LPS of these commensal bacteria were significantly higher in patients with chronic depression than in those without. The immune responses directed against LPS were not associated with melancholia or recurrent depression. There was a significant correlation between the IgA response directed against LPS and gastro-intestinal symptoms.

Discussion: The results indicate that increased bacterial translocation with immune responses to the LPS of commensal bacteria may play a role in the pathophysiology of depression, particularly chronic depression. Bacterial translocation may a) occur secondary to systemic inflammation in depression and intensify and perpetuate the primary inflammatory response once the commensals are translocated; or b) be a primary trigger factor associated with the onset of depression in some vulnerable individuals. The findings suggest that "translocated" gut commensal bacteria activate immune cells to elicit IgA and IgM responses and that this phenomenon may play a role in the pathophysiology of (chronic) depression by causing progres-

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Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

Pathophysiology/Complications

ORIGINAL ARTICLE

Bacterial Endotoxin Activity in Human Serum Is Associated With Dyslipidemia, Insulin Resistance, Obesity, and Chronic Inflammation

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Markku Lehto, phd[1,2]
on behalf of the FinnDiane Study Group*

OBJECTIVE—To investigate whether bacterial lipopolysaccharide (LPS) activity in human serum is associated with the components of the metabolic syndrome (MetS) in type 1 diabetic patients with various degrees of kidney disease and patients with IgA glomerulonephritis (IgAGN).

RESEARCH DESIGN AND METHODS—Serum LPS activity was determined with the Limulus Amoebocyte Lysate chromogenic end point assay in type 1 diabetic patients with a normal albumin excretion rate ($n = 587$), microalbuminuria ($n = 144$), macroalbuminuria ($n = 173$); patients with IgAGN ($n = 98$); and in nondiabetic control subjects ($n = 345$). The relationships of the LPS/HDL ratio and MetS-associated variables were evaluated with Pearson correlation.

RESULTS—The MetS was more prevalent in type 1 diabetic patients (48%) than in patients with IgAGN (15%). Diabetic patients with macroalbuminuria had a significantly higher serum LPS/HDL ratio than patients with IgAGN. In the normoalbuminuric type 1 diabetic group, patients in the highest LPS/HDL quartile were diagnosed as having the MetS three times more frequently than patients in the lowest quartile (69 vs. 22%; $P < 0.001$). High LPS activity was associated with higher serum triglyceride concentration, earlier onset of diabetes, increased diastolic blood pressure, and elevated urinary excretion of monocyte chemoattractant protein-1.

CONCLUSIONS—High serum LPS activity is strongly associated with the components of the MetS. Diabetic patients with kidney disease seem to be more susceptible to metabolic endotoxemia than patients with IgAGN. Bacterial endotoxins may thus play an important role in the development of the metabolic and vascular abnormalities commonly seen in obesity and diabetes-related diseases.

Diabetes Care 34:1809–1815, 2011

In patients with type 1 diabetes, long duration of the disease and poor glycemic control increase the risk for micro- and macrovascular complications. A significant proportion of type 1 diabetic patients who develop these complications exhibit clinical features commonly seen in subjects with the metabolic syndrome (MetS), including dyslipidemia, insulin resistance, obesity, hypertension, and chronic inflammation (1,2). Vascular diseases are also common in patients with IgA glomerulonephritis (IgAGN), and those with a progressive form of the disease run a significantly elevated risk of developing different cardiovascular sequela (3). Whether the MetS is independently associated with the progression of IgAGN is currently unclear, but at least several related factors, including hyperuricemia, hypertriglyceridemia, weight, insulin resistance, and inflammation, seem to associate with the development of kidney dysfunction in IgAGN (4,5).

Many of these clinical subphenotypes likely emerge from the complex interactions between a genetic background, lifestyle, and environmental factors. Recent studies have highlighted the role of the innate immune system in the developmental process of these metabolic abnormalities (6). Our living environment is inhabited with commensal and pathogenic bacteria, which have both beneficial and detrimental effects on human health. If the immune defense functions properly, these microorganisms rarely cause any serious infections in healthy individuals. The situation is different in immunocompromised patients—local infections, use of antibiotics, and even diet may lead to the colonization of opportunistic bacteria in various sites of the body. In diabetic patients, long duration of the disease and poor glycemic control increase the risk for urinary tract, pulmonary, oral, and skin infections (6,7).

Lipopolysaccharides (LPS) are unique glycolipids in the cell wall of gram-negative bacteria. LPS molecules, also known as bacterial endotoxins, may trigger acute and

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*A complete list of participating centers in the FinnDiane Collection can be found in the Supplementary Data.

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ELSEVIER

Research report

Increased I... depression:... leaky gut

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b Department of Experim...
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ARTICLE I...

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Cytokines
Chronic fatigue
Oxidative stress
Leaky gut

Pathophysiology/...

ORIGINAL AR...

High Fat I... Postprand... Endotoxi...

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Kirsty C. McGee, phd[1]
Nasser M. Al-Daghri, phd[2]
Omar S. Al-Attas, phd[2]

OBJECTIVE—To evaluate the ch... to determine whether these effects...

RESEARCH DESIGN AND ...

RESULTS—Baseline endotoxin...

CONCLUSIONS—These studi...

Studies examining the ... ships between adipose tis... mation, and insulin resista... key to understanding type 2 di... (1,2). It is known that low-gra... systemic inflammation contrib... risk, which appears altered by... tors such as increasing age, sex... genetics, and dietary influences... systemic inflammation appear...

OPEN

Citation: Nutrition & Diabetes (2013) 3, e83; doi:10.1038/nutd.2013.24

www.nature.com/nutd

ORIGINAL ARTICLE

Evidence for metabolic endotoxemia in obese and diabetic Gambian women

S Hawkesworth[1], SE Moore[1,2], AJC Fulford[1,2], GR Barclay[3], AA Darboe[2], H Mark[2], OA Nyan[4] and AM Prentice[1,2]

OBJECTIVE: Emerging evidence from animal models suggests that translocation of bacterial debris across a leaky gut may trigger low-grade inflammation, which in turn drives insulin resistance. The current study set out to investigate this phenomenon, termed 'metabolic endotoxemia', in Gambian women.

METHODS: In a cross-sectional study, we recruited 93 age-matched middle-aged urban Gambian women into three groups: lean (body mass index (BMI): 18.5–22.9 kg m^{-2}), obese non-diabetic (BMI: ⩾30.0 kg m^{-2}) and obese diabetic (BMI: ⩾30.0 kg m^{-2} and attending a diabetic clinic). We measured serum bacterial lipopolysaccharide (LPS) and endotoxin-core IgM and IgG antibodies (EndoCAb) as measures of endotoxin exposure and interleukin-6 (IL-6) as a marker of inflammation.

RESULTS: Inflammation (IL-6) was independently and positively associated with both obesity and diabetes ($F = 12.7$, $P < 0.001$). LPS levels were highest in the obese-diabetic group compared with the other two groups ($F = 4.4$, $P < 0.02$). IgM EndoCAb (but not total IgM) was highly significantly reduced in the obese (55% of lean value) and obese diabetic women (30% of lean; $F = 21.7$, $P < 0.0001$ for trend) compared with lean women.

CONCLUSION: These data support the hypothesis that gut-derived inflammatory products are associated with obesity and diabetes. Confirmation of these findings and elucidation of the role of the microbiota, gut damage and the pathways for translocation of bacterial debris, could open new avenues for prevention and treatment of type 2 diabetes.

Nutrition & Diabetes (2013) **3,** e83; doi:10.1038/nutd.2013.24; published online 26 August 2013

Keywords: type 2 diabetes; bacteria; metabolic endotoxemia; The Gambia

INTRODUCTION

Although obesity is the leading risk factor for metabolic syndrome, insulin resistance and type 2 diabetes, not all obese individuals go on to develop disease.[1] Type 2 diabetes is a heterogeneous condition with aetiologies reflecting a complex interaction between genes and environment, including diet, physical activity and factors operating in early life. Among these exposures, low-grade inflammation (assessed by a range of markers including C-reactive protein, sialic acid, tumour necrosis factor (TNF) and interleukin-6 (IL-6)) has emerged as a consistent correlate of metabolic syndrome[2–4] and a strong predictor of progression to incident type 2 diabetes among at-risk individuals.[5,6] Macrophage infiltration of adipose tissue, driven by adipocyte-secreted macrophage chemotractant protein-1, has hitherto been considered the most likely source of such inflammation and could explain the correlations with adipose tissue mass.[7] However, recent research suggests an alternate or additional explanation by which bacterial products are translocated across the gut, either in association with a high-fat diet or due to gut damage, and thereby drive the inflammation, so-called 'metabolic endotoxemia' (ME).[8–10]

Animal and human data have suggested that the composition of the gut microflora may be an important mediator of the risk of obesity and diabetes.[10,11] Germ-free mice are protected

microbiota from obese animals results in adiposity in those who are born germ-free.[13] One suggested mechanism is through a more efficient energy harvest.[14] Additional evidence suggests that the microbiota can influence metabolic disease through a separate mechanism. Bacterial lipopolysaccharide (LPS, also termed endotoxin) is released from dead Gram-negative bacteria in the gut and under conditions of gut damage can translocate into the circulation (as can whole bacteria) where it triggers an inflammatory response.[15] Using mouse models, Cani and colleagues have demonstrated that exposure to a high-fat diet increases systemic endotoxin concentration, a phenomenon they termed 'ME' in recognition of the fact that levels are much lower than those observed in septic shock.[9] In addition, mice infused with similarly low levels of LPS demonstrate raised glucose mimicking the levels observed for mice fed a high-fat diet.[9]

Few studies have investigated the association between endotoxemia and obesity in humans. A study in Saudi Arabian patients reported a positive association between endotoxin levels and various components of the metabolic syndrome,[16] whereas another study in healthy French men reported a positive association between energy intake and endotoxemia.[17]

The inner-core of LPS molecules is relatively conserved across species and antibodies to this are therefore the most cross-reactive.[18] Anti-endotoxin core antibodies (EndoCAb)[19]

Open

The ISME Journal (2012), 1–5

www.nature.com/ismej

SHORT COMMUNICATION

An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice

Na Fei[1] and Liping Zhao[1,2]

[1]State Key Laboratory of Microbial Metabolism and School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai, China and [2]Shanghai Centre for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China

Lipopolysaccharide endotoxin is the only known bacterial product which, when subcutaneously infused into mice in its purified form, can induce obesity and insulin resistance via an inflammation-mediated pathway. Here we show that one endotoxin-producing bacterium isolated from a morbidly obese human's gut induced obesity and insulin resistance in germfree mice. The endotoxin-producing *Enterobacter* decreased in relative abundance from 35% of the volunteer's gut bacteria to non-detectable, during which time the volunteer lost 51.4 kg of 174.8 kg initial weight and recovered from hyperglycemia and hypertension after 23 weeks on a diet of whole grains, traditional Chinese medicinal foods and prebiotics. A decreased abundance of endotoxin biosynthetic genes in the gut of the volunteer was correlated with a decreased circulating endotoxin load and alleviated inflammation. Mono-association of germfree C57BL/6J mice with strain *Enterobacter cloacae* B29 isolated from the volunteer's gut induced fully developed obesity and insulin resistance on a high-fat diet but not on normal chow diet, whereas the germfree control mice on a high-fat diet did not exhibit the same disease phenotypes. The *Enterobacter*-induced obese mice showed increased serum endotoxin load and aggravated inflammatory conditions. The obesity-inducing capacity of this human-derived endotoxin producer in gnotobiotic mice suggests that it may causatively contribute to the development of obesity in its human host.

The ISME Journal advance online publication, 13 December 2012; doi:10.1038/ismej.2012.153

Subject Category: microbe-microbe and microbe-host interactions

Keywords: gut microbiota; germfree mice; endotoxin-producing bacterium; obesity; insulin resistance; high-fat diet

The role of the gut microbiota in the pathogenesis of obesity has emerged into an important research area (Backhed *et al.*, 2004). Gram-negative opportunistic pathogens in the gut may be pivotal in obesity (Schumann *et al.*, 1990; Zhang *et al.*, 2010, 2012). Lipopolysaccharide (LPS) endotoxin purified from *Escherichia coli* induced obese and insulin-resistant phenotypes when subcutaneously infused into mice at a concentration comparable to what can be found in a mouse model of high-fat diet (HFD)-induced obesity (Cani *et al.*, 2007). Endotoxin-induced inflammation seems to be essential for the development of obese and insulin-resistant phenotypes in the mouse model involving LPS infusion, as CD14-knockout mice did not develop these phenotypes after endotoxin infusion (Cani *et al.*, 2007).

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Received 1 August 2012; revised 24 October 2012; accepted 28 October 2012

Epidemiological studies show increased population of endotoxin producers and elevated endotoxin load in various obese cohorts (Lepper *et al.*, 2007; Ruiz *et al.*, 2007; Moreno-Navarrete *et al.*, 2011), but experimental evidence of endotoxin producers having a causative role in human obesity is lacking.

During our clinical studies, we found that *Enterobacter*, a genus of opportunistic, endotoxin-producing pathogens (Sanders and Sanders, 1997), made up 35% of the gut bacteria in a morbidly obese volunteer (weight 174.8 kg, body mass index 58.8 kg m^{-2}) suffering from diabetes, hypertension and other serious metabolic deteriorations (Table 1). The volunteer lost 30.1 kg after 9 weeks, and 51.4 kg after 23 weeks, on a diet composed of whole grains, traditional Chinese medicinal foods and prebiotics (WTP diet, Supplementary Information; Supplementary Figure 1), with continued amelioration of hyperinsulinemia, hyperglycemia and hypertension until most metabolic parameters improved to normal ranges (Table 1). After 9 weeks on the WTP diet, this *Enterobacter* population in the volunteer's gut reduced to 1.8%, and became undetectable by the end of the 23-week trial, as

Citation: Nutrition & Diabetes (2013) **3**, e83; doi:10.1038/nutd.2013.24

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endotoxemia in obese and diabetic

GR Barclay[3], AA Darboe[2], H Mark[2], OA Nyan[4] and AM Prentice[1,2]

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cruited 93 age-matched middle-aged urban Gambian women into three groups: lean obese non-diabetic (BMI: ⩾30.0 kg m^{-2}) and obese diabetic (BMI: ⩾30.0 kg m^{-2} and rum bacterial lipopolysaccharide (LPS) and endotoxin-core IgM and IgG antibodies re and interleukin-6 (IL-6) as a marker of inflammation.

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thesis that gut-derived inflammatory products are associated with obesity and elucidation of the role of the microbiota, gut damage and the pathways for new avenues for prevention and treatment of type 2 diabetes.

8/nutd.2013.24; published online 26 August 2013

olic endotoxemia; The Gambia

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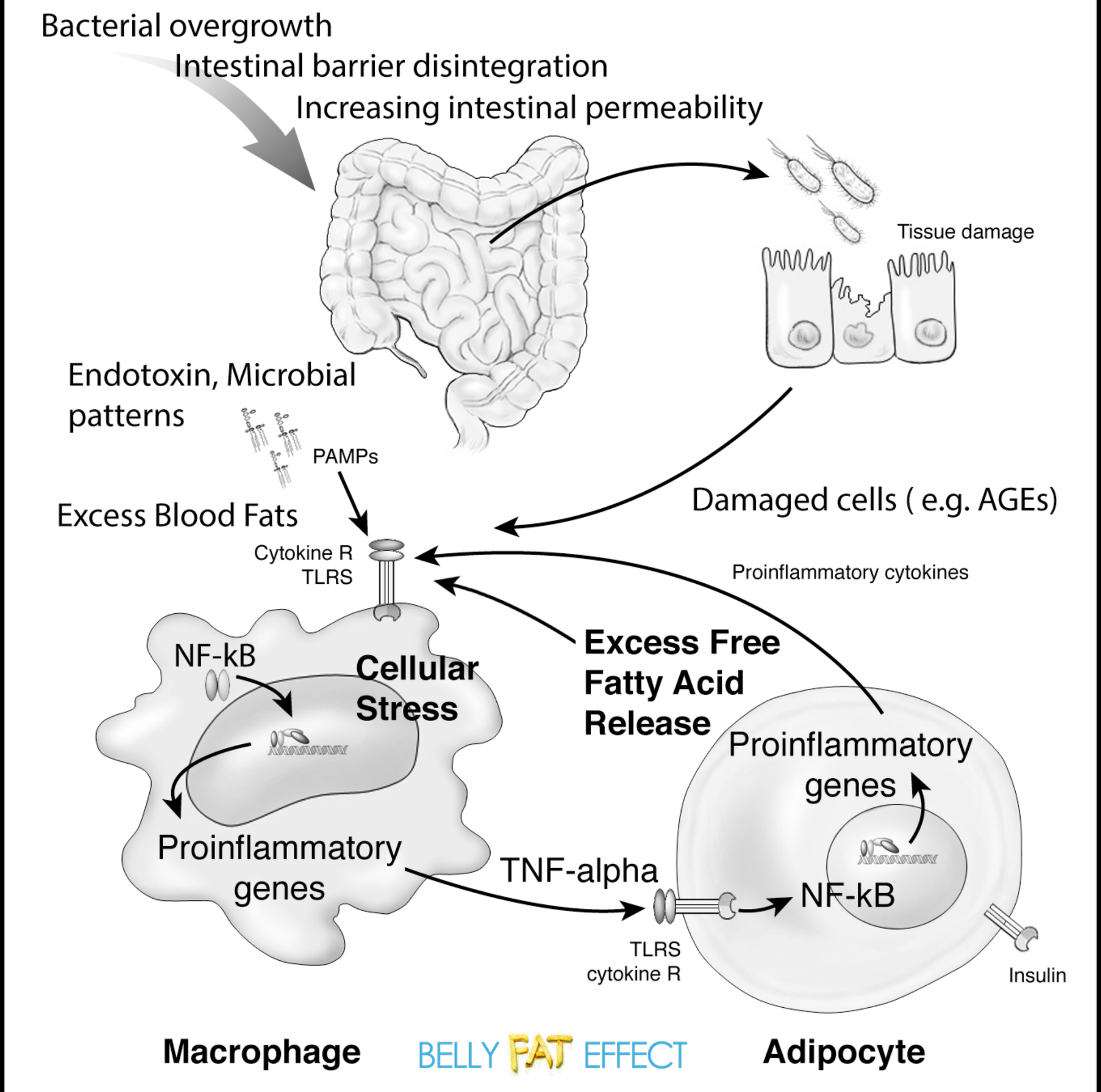
The inner-core of LPS molecules is relatively conserved across species and antibodies to this are therefore the most cross-reactive.[18] Anti-endotoxin core antibodies (EndoCAb)[19]


Bacterial overgrowth
Intestinal barrier disintegration
Increasing intestinal permeability
Tissue damage
Endotoxin, Microbial patterns
PAMPs
Excess Blood Fats
Damaged cells (e.g. AGEs)
Cytokine R
TLRS
Proinflammatory cytokines
NF-kB
Cellular Stress
Excess Free Fatty Acid Release
Proinflammatory genes
TNF-alpha
NF-kB
TLRS
cytokine R
Insulin
Macrophage
BELLY FAT EFFECT
Adipocyte

AP&T Alimentary Pharmacology and Therapeutics

Combat-training increases intestinal permeability, immune activation and gastrointestinal symptoms in soldiers

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EV Pub Online 24 February 2013

SUMMARY

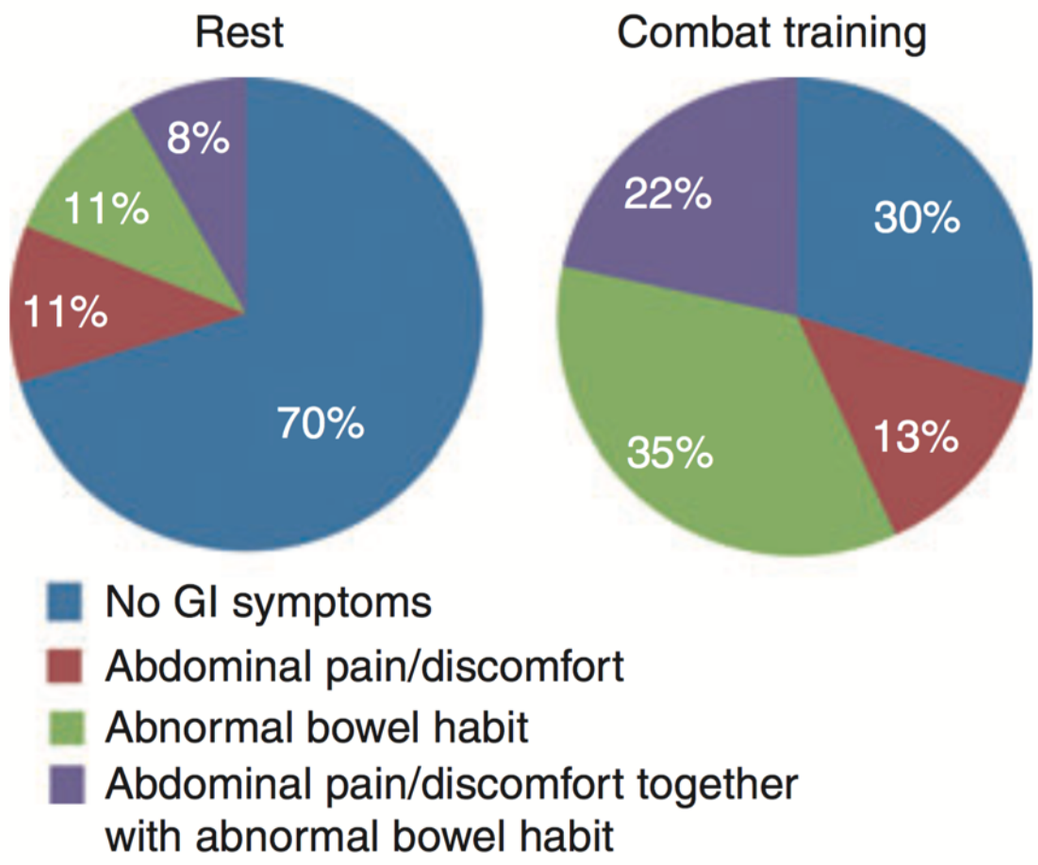
Background
Gastrointestinal (GI) symptoms are common in soldiers in combat or high-pressure operational situations and often lead to compromised performance. Underlying mechanisms are unclear, but neuroendocrine dysregulation, immune activation and increased intestinal permeability may be involved in stress-related GI dysfunction.

Aim
To study the effects of prolonged, intense, mixed psychological and physical stress on intestinal permeability, systemic inflammatory and stress markers in soldiers during high-intensity combat-training.

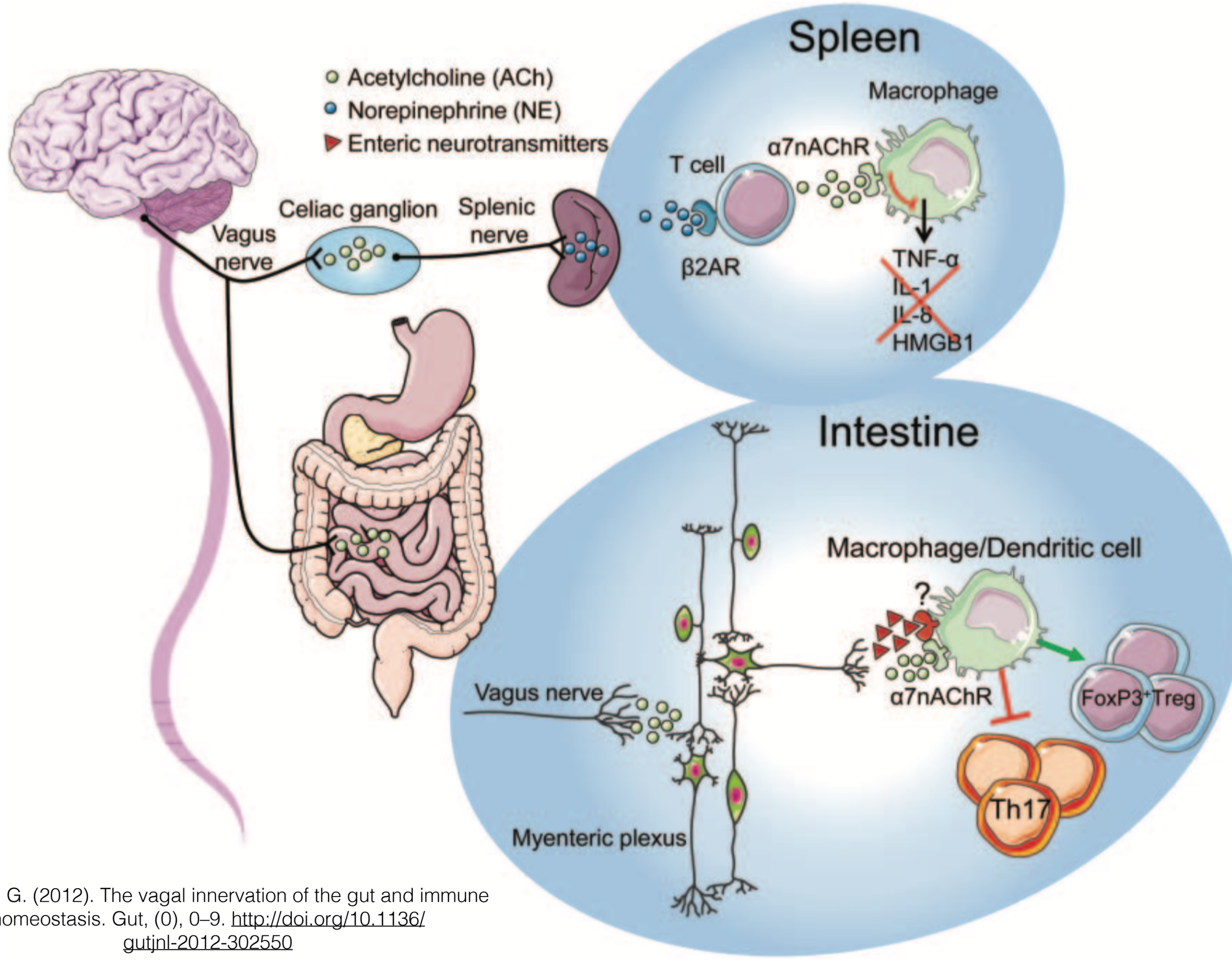
Methods
In 37 male army medical rapid response troops, GI symptoms, stress markers, segmental intestinal permeability using the 4-sugar test (sucrose, lactulose, mannitol and sucralose) and immune activation were assessed during the 4th week of an intense combat-training and a rest period.

Results
Combat-training elicited higher stress, anxiety and depression scores (all $P < 0.01$) as well as greater incidence and severity of GI symptoms [irritable bowel syndrome symptom severity score (IBS-SSS), $P < 0.05$] compared with rest. The IBS-SSS correlated with depression ($r = 0.41$, $P < 0.01$) and stress ($r = 0.40$, $P < 0.01$) ratings. Serum levels of cortisol, interleukin-6, and tumour necrosis factor-α, and segmental GI permeability increased during combat-training compared with rest (all $P < 0.05$). The lactulose:mannitol ratio was higher in soldiers with GI symptoms (IBS-SSS ≥ 75) during combat-training than those without (IBS-SSS <75) ($P < 0.05$).

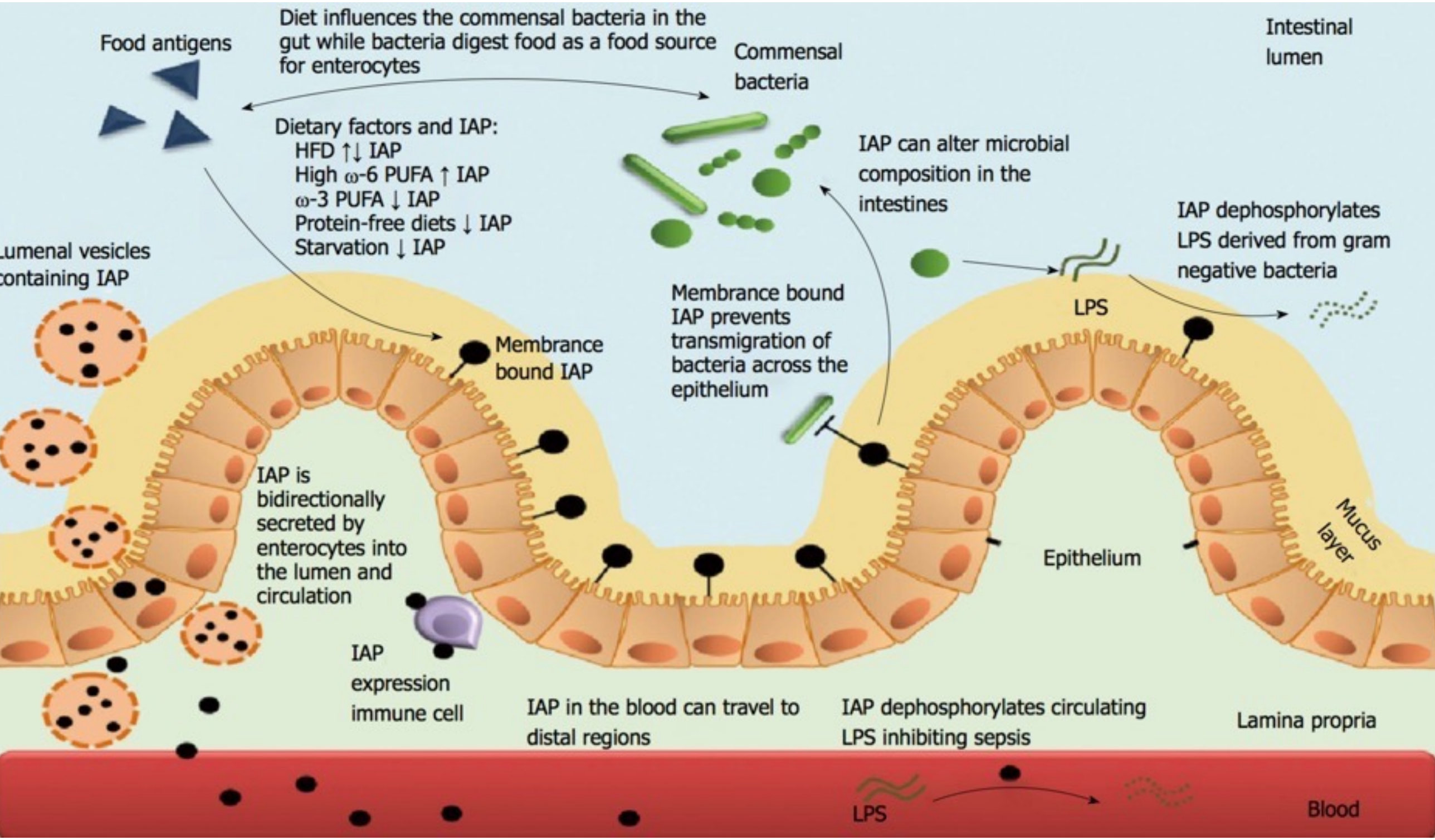
Conclusions
Prolonged combat-training not only induces the expected increases in stress, anxiety and depression, but also GI symptoms, pro-inflammatory immune activation and increased intestinal permeability. Identification of subgroups of individuals at high-risk of GI compromise and of long-term deleterious effects of operational stress as well as the development of protective measures will be the focus of future studies.



Li, X., Kan, E. M., Lu, J., Cao, Y., Wong, R. K., Keshavarzian, A., & Wilder-Smith, C. H. (2013). Combat-training increases intestinal permeability, immune activation and gastrointestinal symptoms in soldiers. Alimentary Pharmacology & Therapeutics, 37(8), 799–809. http://doi.org/10.1111/apt.12269



Matteoli, G. (2012). The vagal innervation of the gut and immune homeostasis. Gut, (0), 0–9. http://doi.org/10.1136/gutjnl-2012-302550



Estaki, M. (2014). Interplay between intestinal alkaline phosphatase, diet, gut microbes and immunity. *World Journal of Gastroenterology*, *20*(42), 15650. doi:10.3748/wjg.v20.i42.15650

ORIGINAL ARTICLE

Differential Effects of Cream, Glucose, and Orange Juice on Inflammation, Endotoxin, and the Expression of Toll-Like Receptor-4 and Suppressor of Cytokine Signaling-3

RUPALI DEOPURKAR, PHD
HUSAM GHANIM, PHD
JAY FRIEDMAN, PHD
SANAA ABUAYSHEH, BSC
CHANG LING SIA, BSC
PRIYA MOHANTY, MD
PRABHAKAR VISWANATHAN, PHD
AJAY CHAUDHURI, MD
PARESH DANDONA, MD, PHD

OBJECTIVE — We have recently shown that a high-fat high-carbohydrate (HFHC) meal induces an increase in plasma concentrations of endotoxin (lipopolysaccharide [LPS]) and the expression of Toll-like receptor-4 (TLR-4) and suppresser of cytokine signaling-3 (SOCS3) in mononuclear cells (MNCs) in addition to oxidative stress and cellular inflammation. Saturated fat and carbohydrates, components of the HFHC meal, known to induce oxidative stress and inflammation, also induce an increase in LPS, TLR-4, and SOCS3.

RESEARCH DESIGN AND METHODS — Fasting normal subjects were given 300-calorie drinks of either glucose, saturated fat as cream, orange juice, or only water to ingest. Blood samples were obtained at 0, 1, 3, and 5 h for analysis.

RESULTS — Indexes of inflammation including nuclear factor-κB (NF-κB) binding, and the expression of SOCS3, tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β in MNCs, increased significantly after glucose and cream intake, but TLR-4 expression and plasma LPS concentrations increased only after cream intake. The intake of orange juice or water did not induce any change in any of the indexes measured.

CONCLUSIONS — Although both glucose and cream induce NF-κB binding and an increase in the expression of SOCS3, TNF-α, and IL-1β in MNCs, only cream caused an increase in LPS concentration and TLR-4 expression. Equicaloric amounts of orange juice or water did not induce a change in any of these indexes. These changes are relevant to the pathogenesis of atherosclerosis and insulin resistance.

Diabetes Care 33:991–997, 2010

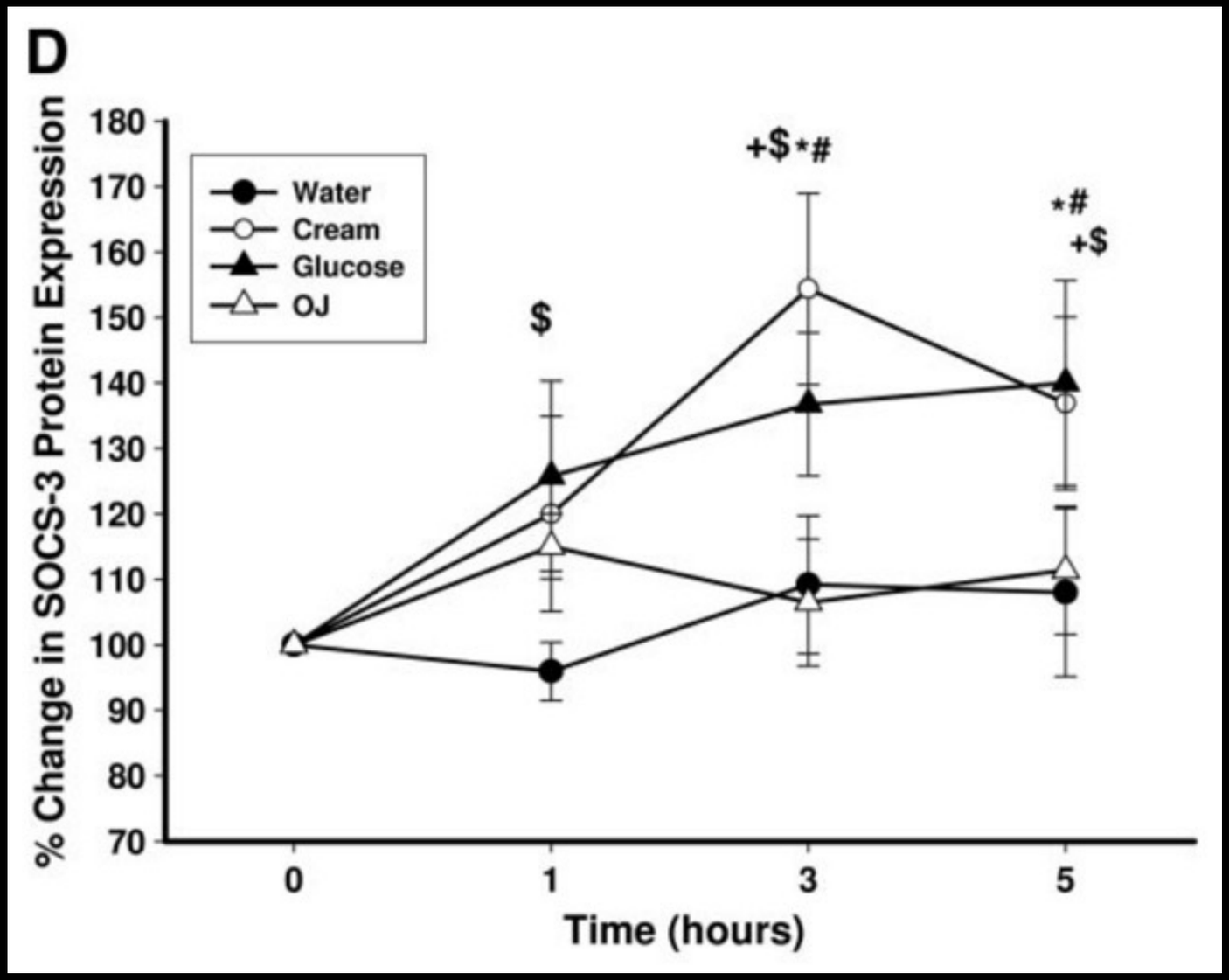
vital to the protection from bacterial toxins and immunological responses to the commensal and pathogenic intestinal bacteria.

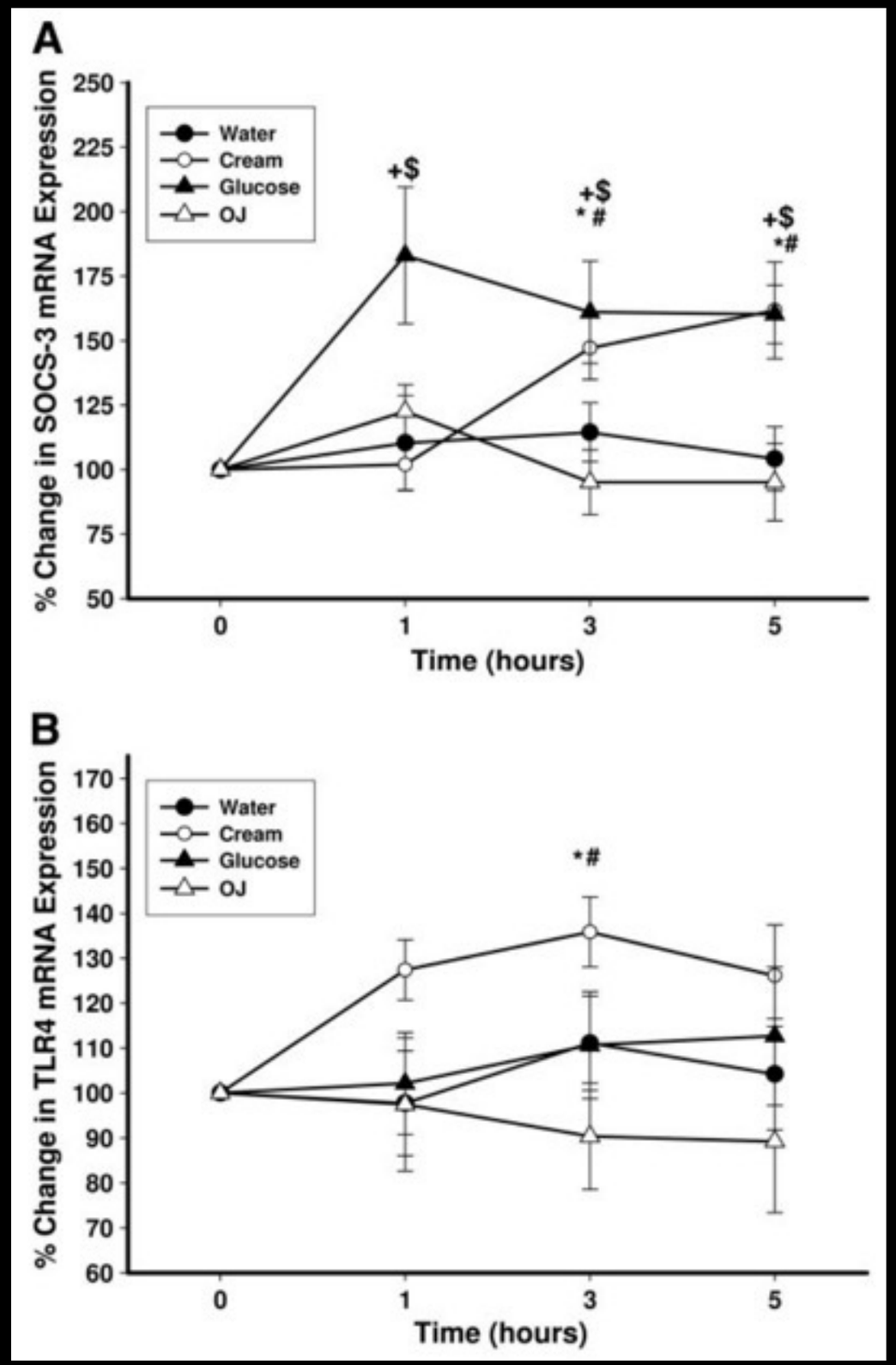
In this context, we wanted to analyze which macronutrient was responsible for the induction of oxidative stress and inflammation, on the one hand, and the increase in LPS concentrations and the expression of TLR-4 and suppresser of cytokine signaling (SOCS)-3 on the other. To elucidate this, we investigated the effect of glucose, the most important carbohydrate, cream, a saturated fat, and orange juice, a carbohydrate-containing food product, which does not induce either oxidative stress or inflammation.

SOCS3 is a protein that has been shown to interfere with insulin and leptin signal transduction (2–5). Our recent work has shown that SOCS3 expression in the circulating mononuclear cells (MNCs) of the obese human is markedly increased when compared with that in normal subjects (6). In addition, our work demonstrated that SOCS3 expression in MNCs is inversely related to the tyrosine phosphorylation of the insulin receptor and directly related to BMI and insulin resistance (homeostasis model as-

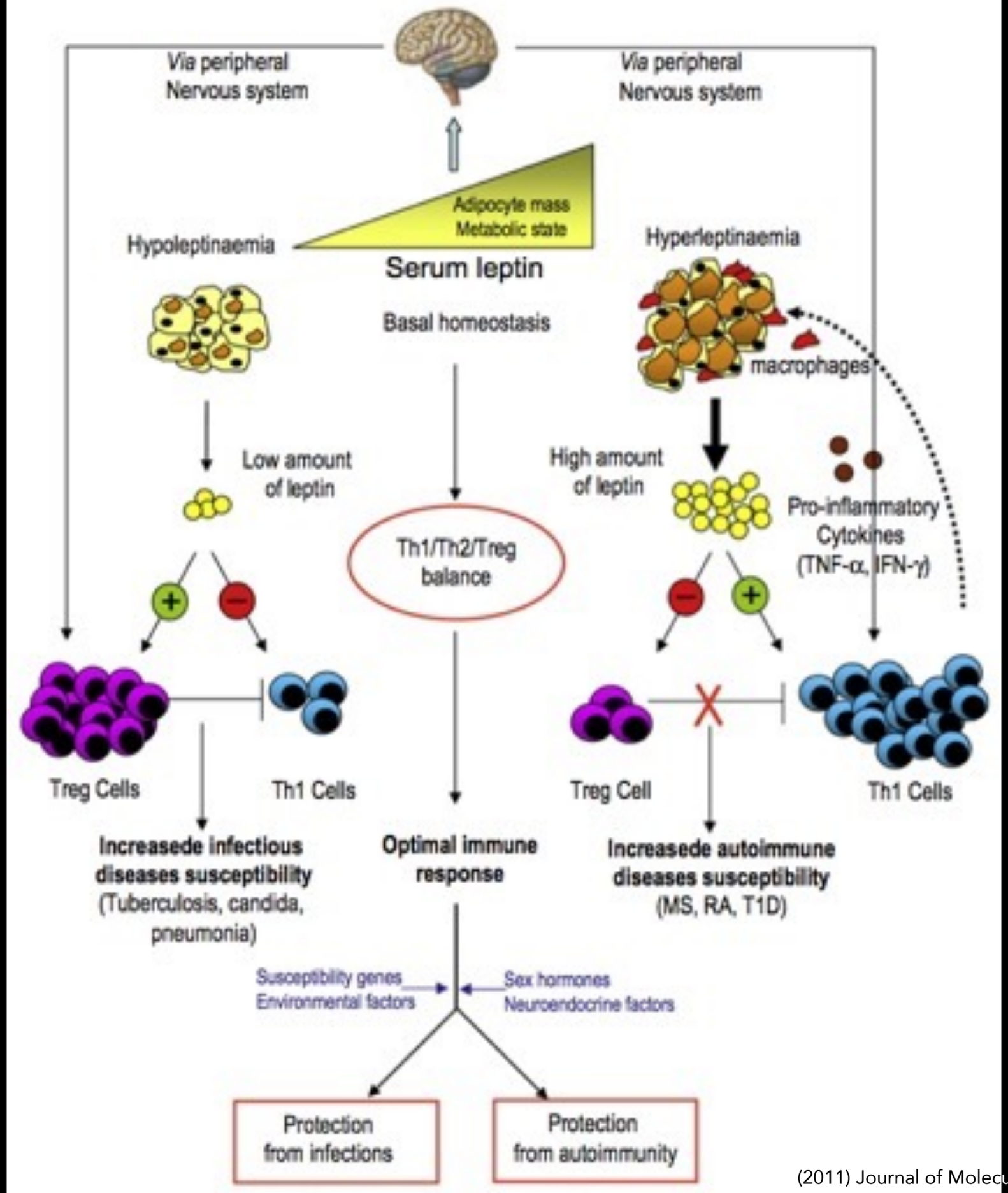
ENDOTOXIN

SOCS-3





2010. Diabetes Care, 33(5), 991–997.



(2011) Journal of Molecular Aspects of Medicine, 1–11.

Review

Cell PRESS

Regulatory T cells in obesity: the leptin connection

Giuseppe Matarese[1], Claudio Procaccini[1], Veronica De Rosa[1], Tamas L. Horvath[2] and Antonio La Cava[3]

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[2] Program on Cell and Neurobiology of Energy Metabolism, Section of Comparative Medicine, Yale University School of Medicine, New Haven, CT, USA
[3] Department of Medicine, David Geffen School of Medicine, University California Los Angeles, Los Angeles, CA, USA

Studies to understand the pathogenesis of obesity have revealed mediators that are responsible for the control of food intake and metabolism at the hypothalamic level. However, molecular insight explaining the link between obesity and low-degree chronic inflammation remains elusive. The adipocyte-derived hormone leptin, and thereby the nutritional status, could control immune self-tolerance by affecting regulatory T (Treg) cell responsiveness and function. Furthermore, resident Treg cells, which are capable of modulating metabolism and glucose homeostasis, are abundant in adipose tissue. Here, we provide an update on recent findings relating Treg cells to obesity and discuss how the intricate network of interactions among leptin, Treg cells and adipose tissue might provide new strategies for therapeutic interventions.

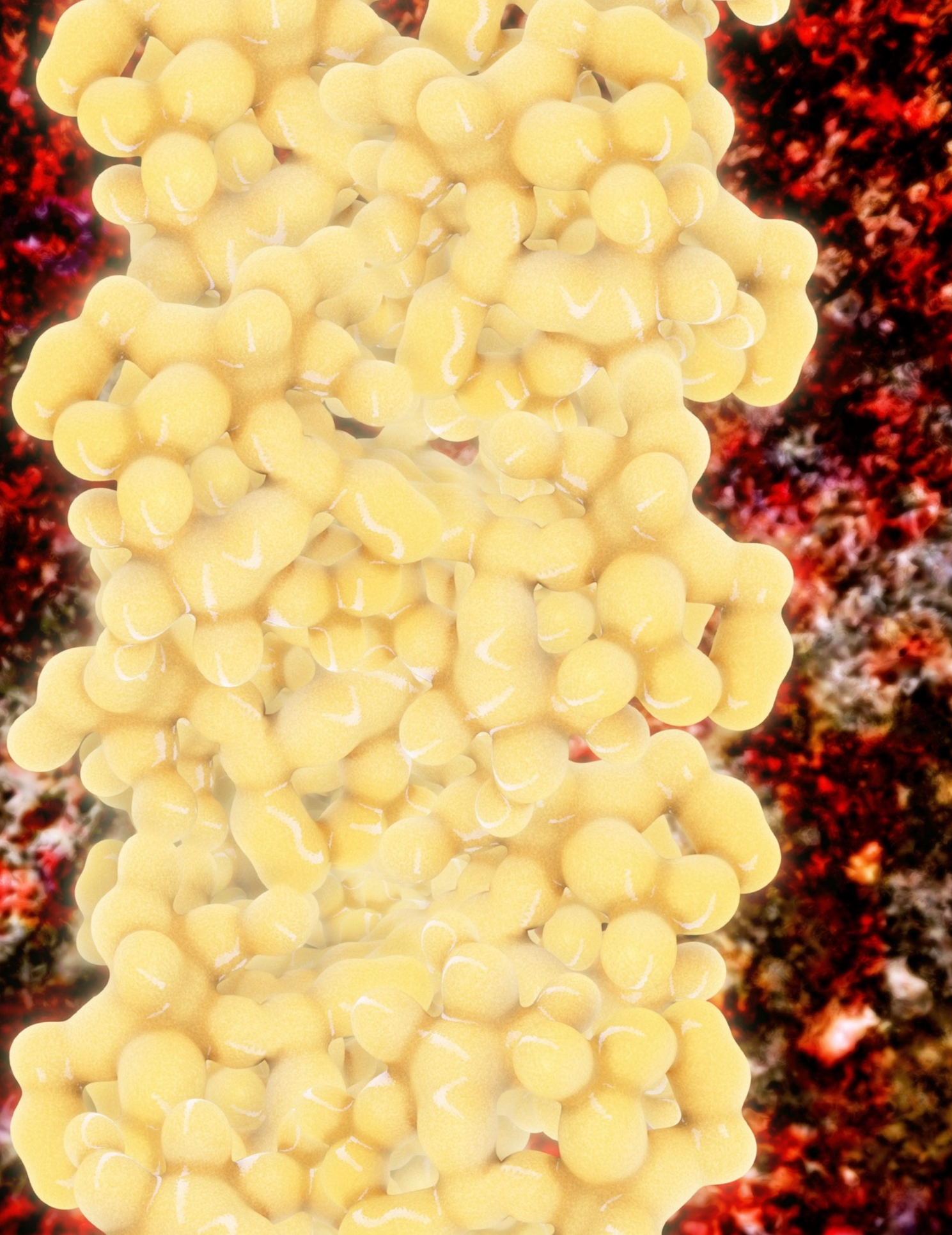
Here, we review the most recent findings relating Treg cell biology with obesity and discuss how the modulation of leptin secretion, Treg cell function and adipose tissue activity might provide new strategies for therapeutic interventions in obesity and its metabolic consequences.

Treg cells: a renaissance

Treg cells are a small subset of T cells, usually constituting only 5–15% of the peripheral $CD4^+$ T cell compartment in mice and humans [18–20]. Treg cells are important in the control of the inappropriate immune responses that characterize autoimmunity and allergy. In general, Treg cells control effector T cell responses and also influence the activities of cells of the innate immune system [18–20]. Treg cells display several surface markers, none of which are unique, and express the master gene that encodes the forkhead/winged-helix transcription factor Foxp3 [21,22].

(2010). Trends in Molecular Medicine, 16(6), 247–256.

- 4-5 fold increase macrophages in VAT
- Reduced Treg cells
- Increased quantities of every type of immune cell possible



LEPTIN IS AT THE CORE

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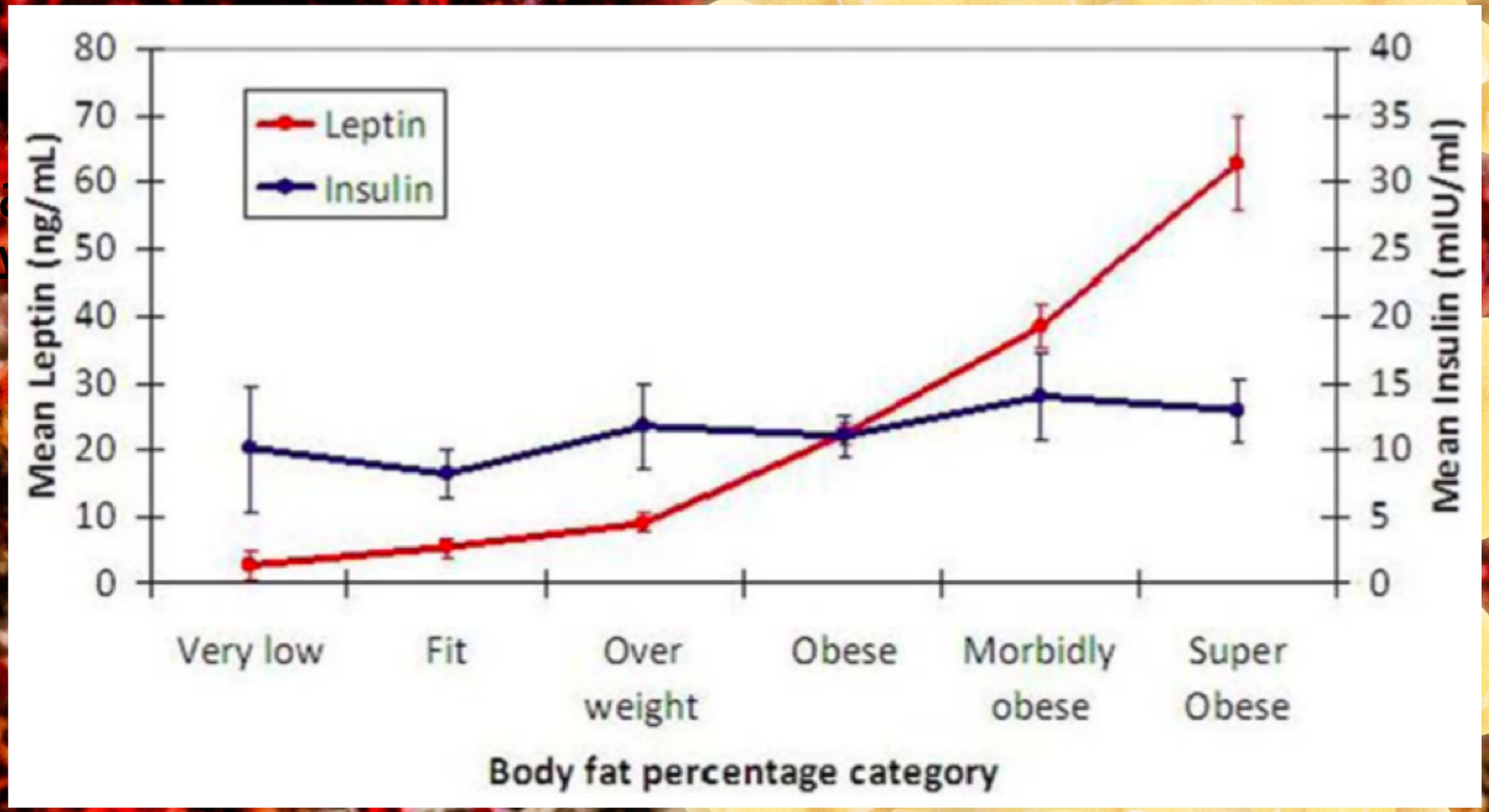
  ma
  VA



Shah, N. R., & Braverman, E. R. (2012) *PLoS ONE*, *7*(4), e33308. doi:10.1371/journal.pone.0033308.t004

FAT ON FIRE

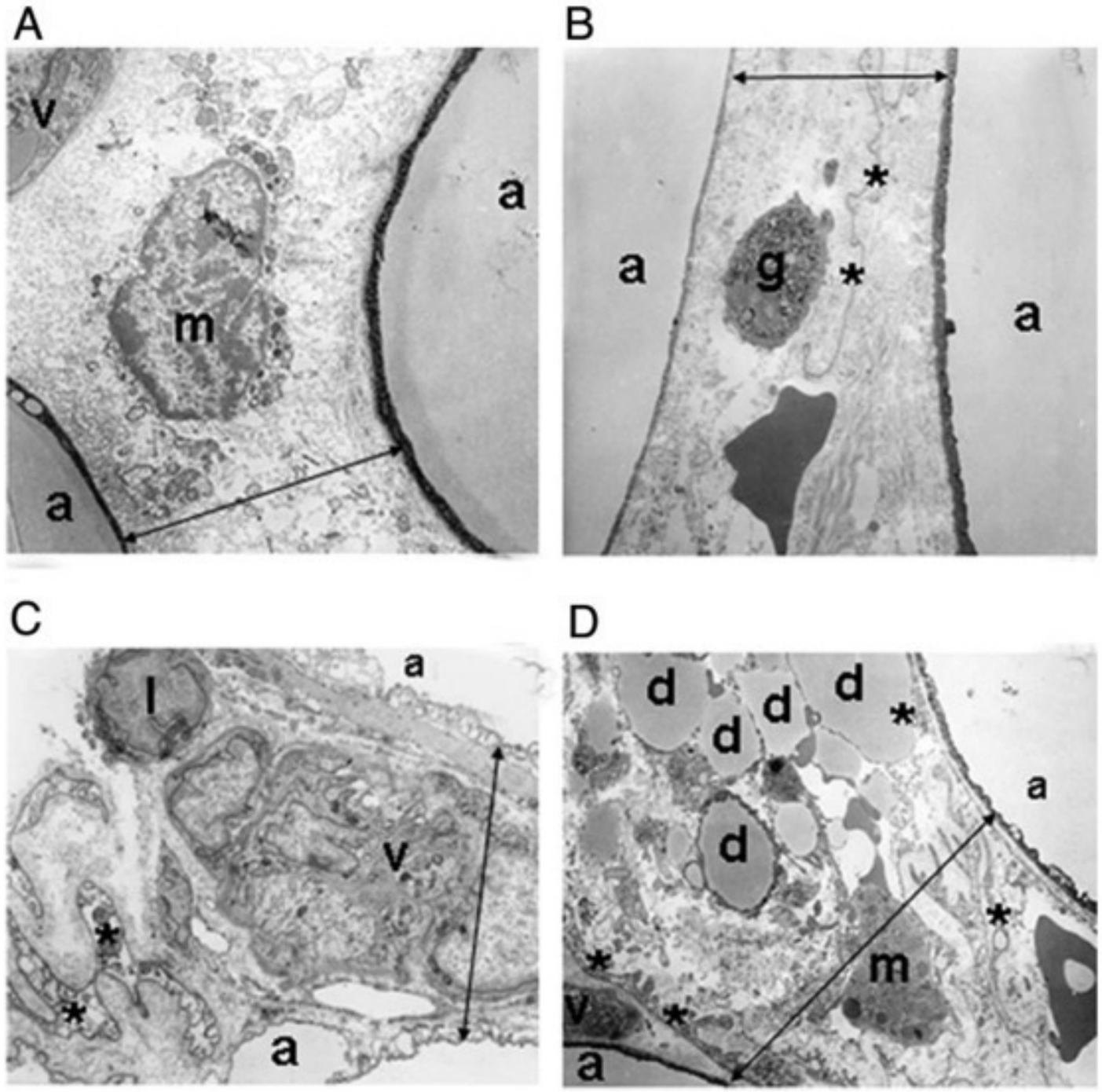
PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Obesity and Inflammation: Evidence for an Elementary Lesion

Andrea Sbarbati, Francesco Osculati, Davide Silvagni, Donatella Benati, Mirco Galiè, Francesco Saverio Camoglio, Gino Rigotti and Claudio Maffeis

Pediatrics 2006;117;220
DOI: 10.1542/peds.2004-2854

"ELECTRON MICROSCOPY OF ADIPOSE TISSUE IN CHILDREN OF OBESE 11 YEAR OLD"



PEDIATRICOBESITY

ORIGINALARTICLE

doi:10.1111/j.2047-6310.2013.00160.x

ORIGINALARTICLE

Increased serum IgG and IgA in overweight children relate to a less favourable metabolic phenotype

J. Bassols[1], A. Prats-Puig[1], M. Gispert-Saüch[1], M. Crehuet-Almirall[2], G. Carreras-Badosa[1], F. Díaz-Roldán[1], M. Montesinos-Costa[3], F. de Zegher[4], L. Ibáñez[5,6] and A. López-Bermejo[1,7]

[1]Pediatrics, Dr. Josep Trueta Hospital, and Girona Institute for Biomedical Research, Girona, Spain; [2]Primary Care Pediatrics, Catalan Institute of Health, Girona, Spain; [3]Clinical Laboratory, Dr. Josep Trueta Hospital, Girona, Spain; [4]Department of Woman & Child, University of Leuven, Leuven, Belgium; [5]Pediatric Endocrinology, Sant Joan de Déu Children's Hospital, Barcelona, Spain; [6]CIBERDEM (Spanish Biomedical Research Centre in Diabetes and Associated Metabolic Disorders), ISCIII, Barcelona, Spain; [7]TransLab Research Group, Department of Medical Sciences, Faculty of Medicine, University of Girona, Girona, Spain

Received 30 November 2012; revised 5 February 2013; accepted 20 February 2013

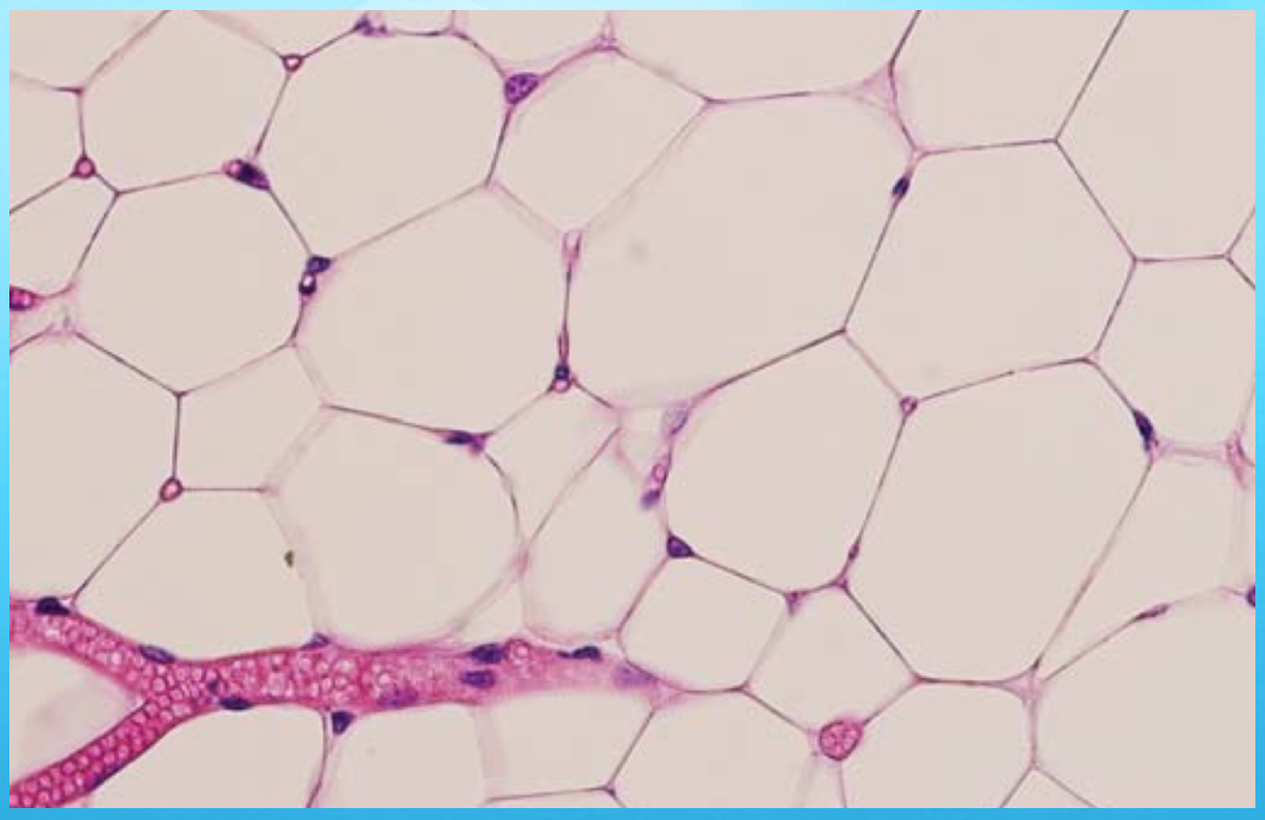
What is already known about this subject

- The adaptive immune system has been shown to be a novel modulator of insulin resistance.
- Increased activation of B lymphocytes has been described in obese mice and in obese and type 2 diabetic patients.
- B lymphocytes promote insulin resistance by accumulating in adipose tissue and producing pathogenic antibodies.

What this study adds

- Increased serum concentrations of IgG and IgA were found in overweight pre-pubertal children.
- Increasing concentrations of IgG and IgA were in obese, but not in lean pre-pubertal children, associated with a less favourable metabolic phenotype, consisting of increased insulin resistance and a more adverse lipid profile.

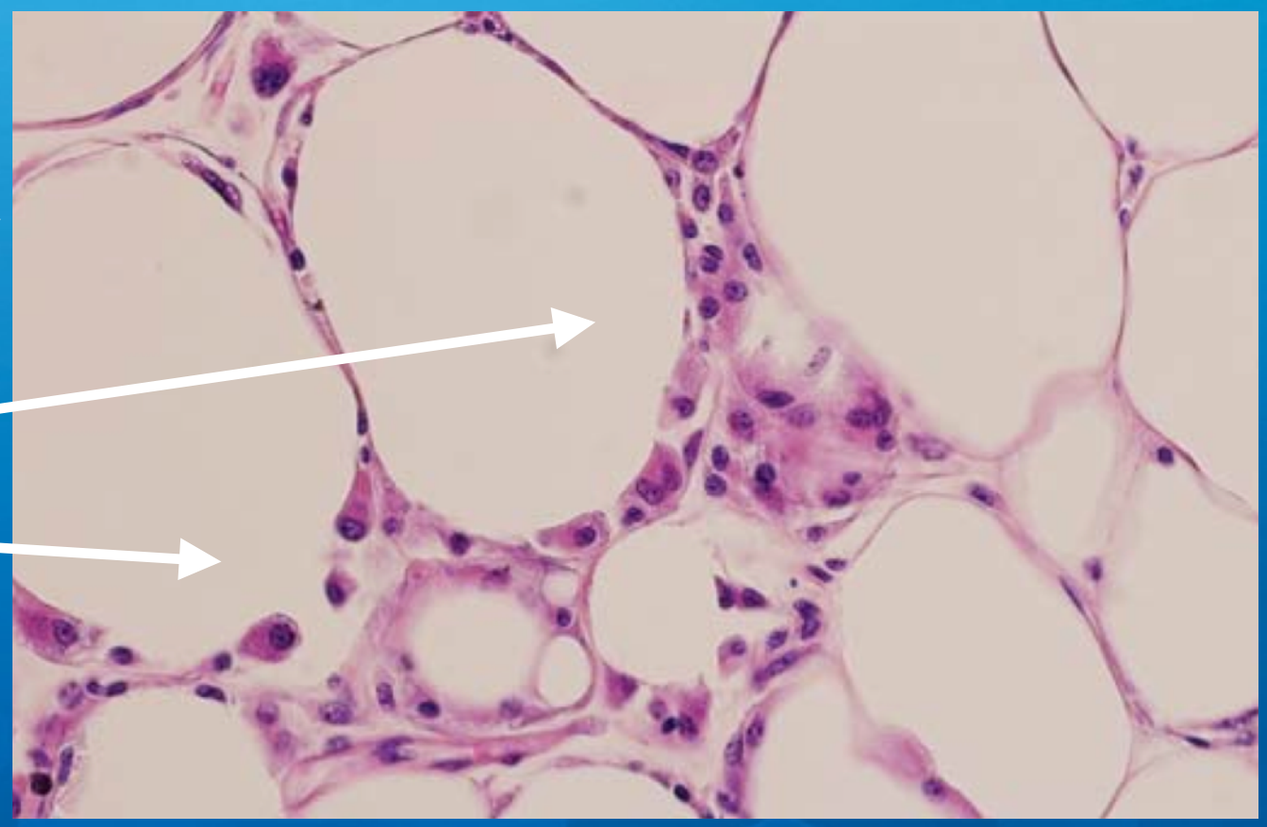
Adipose tissue is dynamic



Adipocytes from obese

Adipocytes from lean mice

- Enlarged Adipocytes
- Immune Cells



Gudrias, E. (2008, October 22). DECODING DIABETES. *Harvard Magazine*, (November-December), 50–58.

Short term overfeeding creates rapid changes in fat cell physiology

JCEM ONLINE

Hot Topics in Translational Endocrinology—Endocrine Research

Subcutaneous Adipose Tissue Remodeling during the Initial Phase of Weight Gain Induced by Overfeeding in Humans

M. Alligier, E. Meugnier, C. Debard, S. Lambert-Porcheron, E. Chanseaume, M. Sothier, E. Loizon, A. Ait Hssain, J. Brozek, J.-Y. Scoazec, B. Morio, H. Vidal,* and M. Laville*

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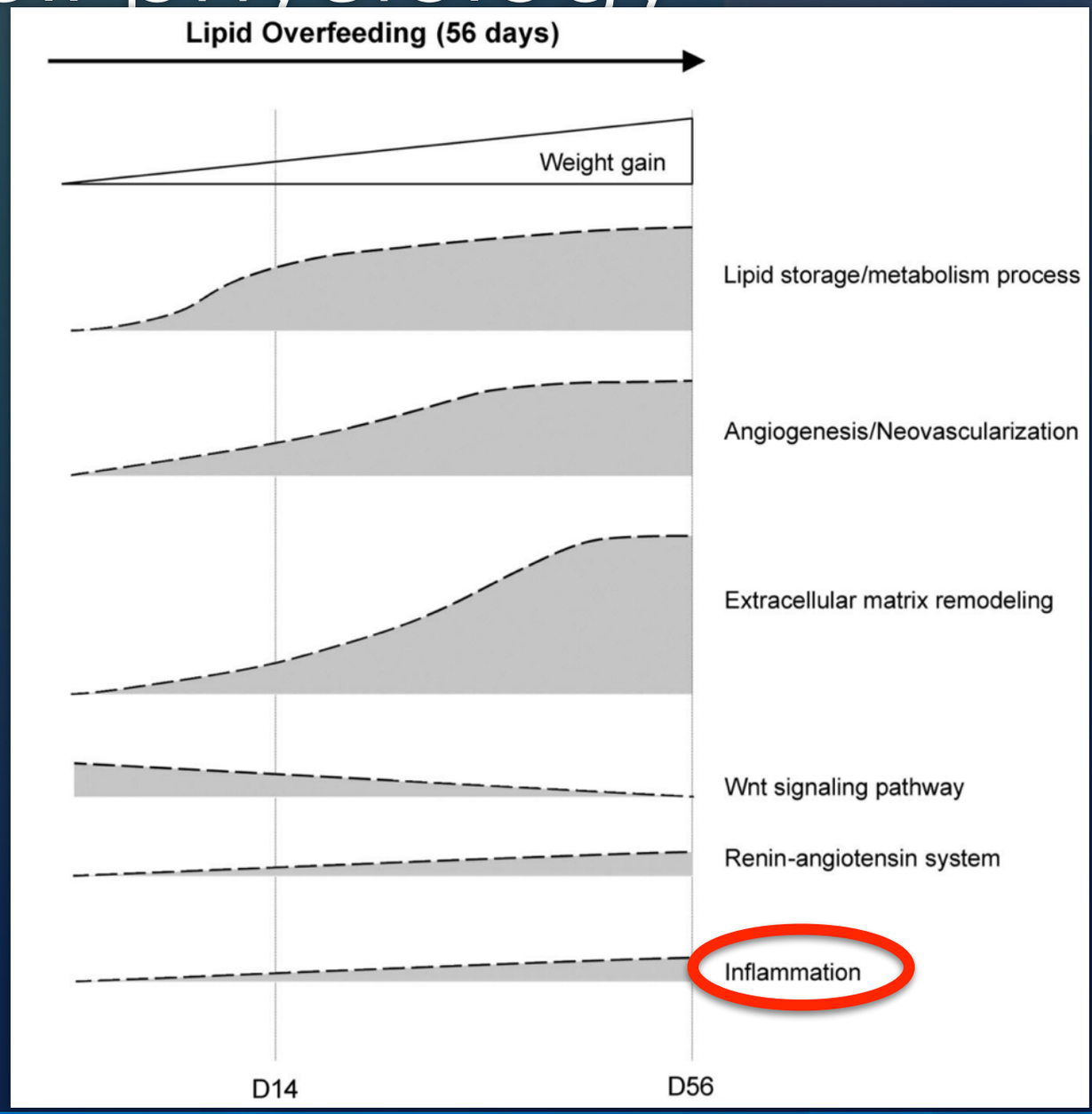
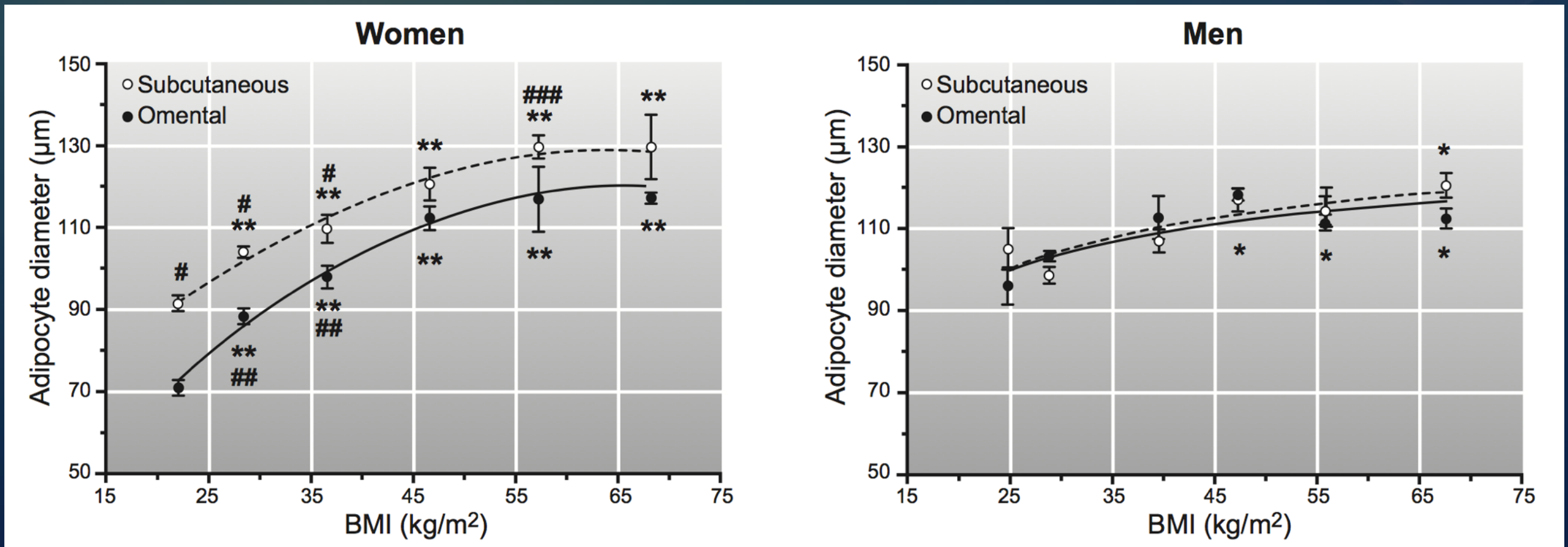
Context: Deciphering the early processes occurring in adipose tissue during weight gain is a major issue for understanding the development of fat mass and obesity. Experimental overfeeding in humans is a unique situation to tackle these events.

Objective: Our aim was to identify the pathways involved in sc adipose tissue remodeling during the initial phase of weight gain.

Research Design and Methods: Forty-four healthy men were involved in an overfeeding protocol with a lipid-enriched diet (+760 kcal/d) for 2 months. Subcutaneous abdominal adipose tissue biopsies were taken for histology, transcriptomics, and Western blotting in the basal state, after 14 d, and at the end of the protocol.

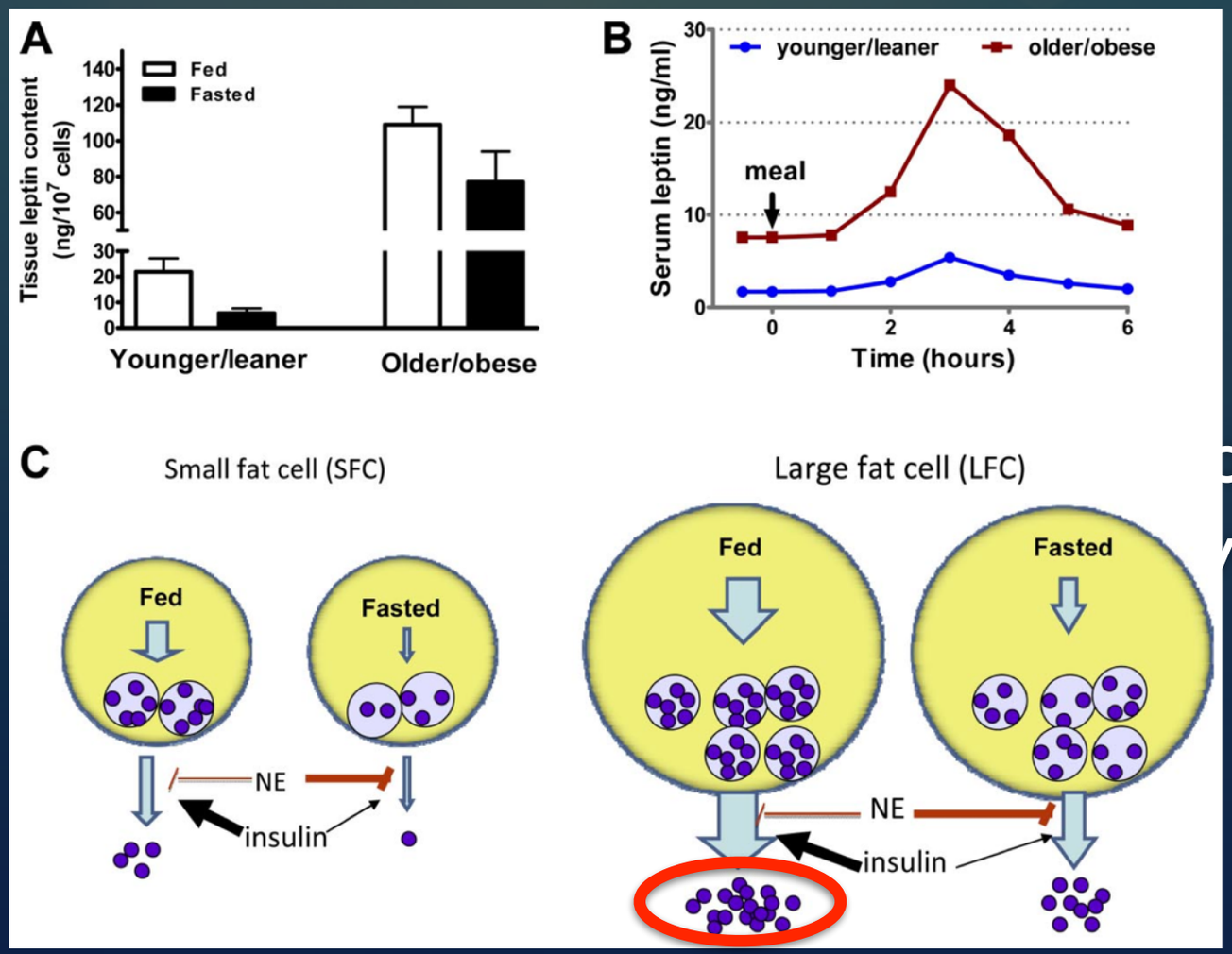


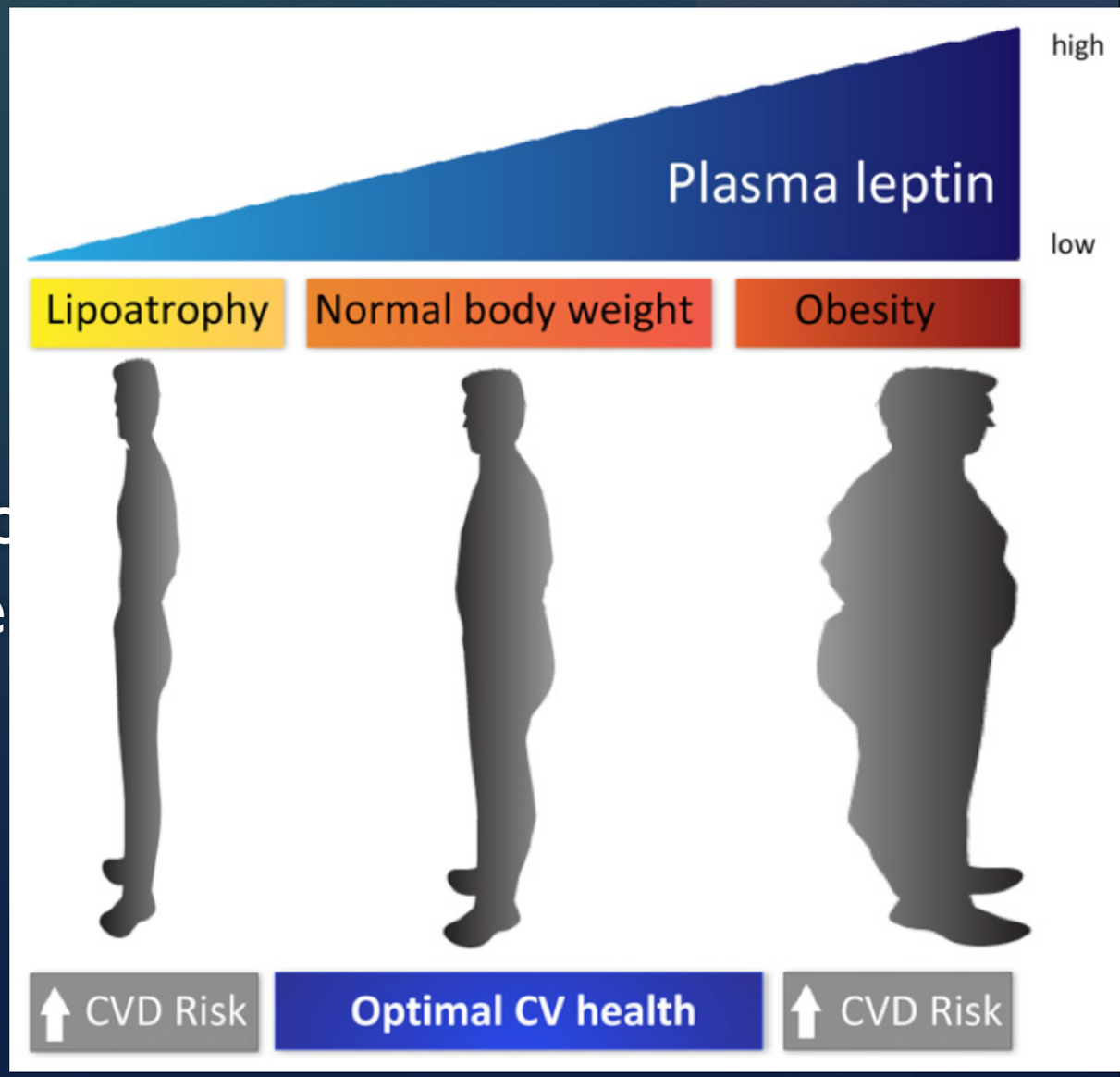
weight gain proportionally increases fat cell size and number



Tchernof, A., & Despres, J. P. (2013). Pathophysiology of Human Visceral Obesity: An Update. *Physiological Reviews*, *93*(1), 359–404. doi:10.1152/physrev.00033.2011

Enlarged fat cells release more leptin





Integration of hormonal and nutrient signals that regulate leptin synthesis and secretion. (2009). Integration of hormonal and nutrient signals that regulate leptin synthesis and secretion, 1–9. doi:10.1152/ajpendo.90927.2008

Abel, E. D., & Sweeney, G. (2012). Modulation of the cardiovascular system by leptin. *Biochimie*, *94*(10), 2097–2103. doi:10.1016/j.biochi.2012.03.019

BELLY FAT EFFECT

Geriatrics & Gerontology INTERNATIONAL

Original Article: Biology

Age-related changes of leptin and leptin receptor variants in healthy elderly and long-lived adults

Malgorzata Roszkowska-Gancarz[1], Marta Jonas[2], Magdalena Owczarz[3], Alina Kurylowicz[2], Jacek Polosak[1,2], Edward Franek[2], Przemyslaw Slusarczyk[3], Malgorzata Mossakowska[3] and Monika Puzianowska-Kuznicka[1,2,*]

Article first published online: 26 FEB 2014

DOI: 10.1111/ggi.12267

Issue

Geriatrics & Gerontology International

Early View (Online Version of Record published before inclusion in an issue)

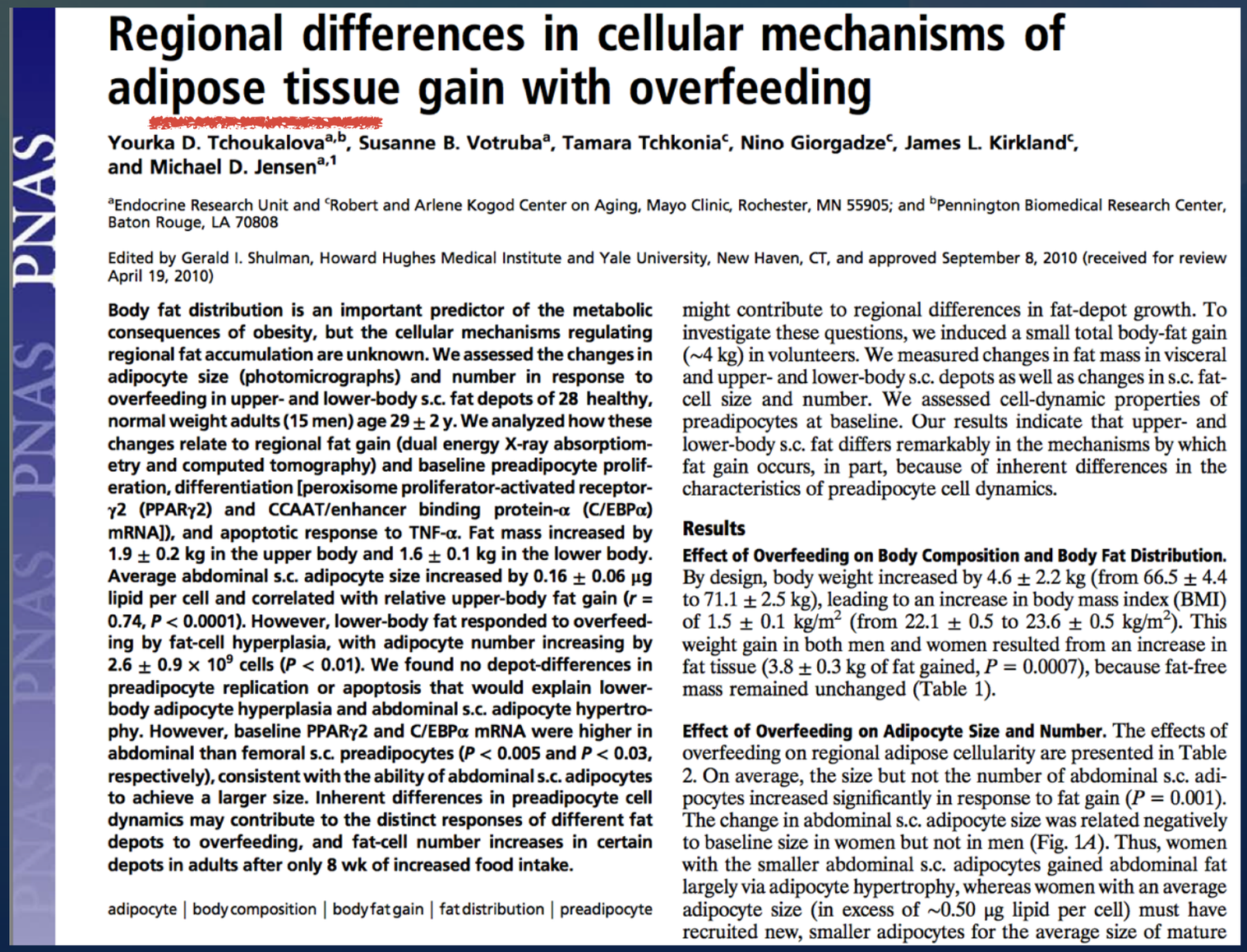
"In elderly men, the median concentration of leptin and the median FLI (free leptin index) were significantly higher than in young men."

"In healthy, non-obese individuals, only some elements of the leptin axis slightly change with age."

Roszkowska-Gancarz, M., Jonas, M., Owczarz, M., Kurylowicz, A., Polosak, J., Franek, E., et al. (2014). Age-related changes of leptin and leptin receptor variants in healthy elderly and long-lived adults. Geriatrics & Gerontology International, n/a–n/a. doi: 10.1111/ggi.12267

Proof of concept in humans

- As the bodies main storage tissue, fat **rapidly expands** (hypertrophy)
- Adipocytes also rapidly differentiate, creating new fat cells (hyperplasia)
- A 1.6 kg gain in body weight lead to **2.6 billion new adipocytes** in just 8 weeks



PNAS PNAS PNAS

Regional differences in cellular mechanisms of adipose tissue gain with overfeeding

Yourka D. Tchoukalova[a,b], Susanne B. Votruba[a], Tamara Tchkonia[c], Nino Giorgadze[c], James L. Kirkland[c], and Michael D. Jensen[a,1]

[a]Endocrine Research Unit and [c]Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN 55905; and [b]Pennington Biomedical Research Center, Baton Rouge, LA 70808

Edited by Gerald I. Shulman, Howard Hughes Medical Institute and Yale University, New Haven, CT, and approved September 8, 2010 (received for review April 19, 2010)

Body fat distribution is an important predictor of the metabolic consequences of obesity, but the cellular mechanisms regulating regional fat accumulation are unknown. We assessed the changes in adipocyte size (photomicrographs) and number in response to overfeeding in upper- and lower-body s.c. fat depots of 28 healthy, normal weight adults (15 men) age 29 ± 2 y. We analyzed how these changes relate to regional fat gain (dual energy X-ray absorptiometry and computed tomography) and baseline preadipocyte proliferation, differentiation [peroxisome proliferator-activated receptor-γ2 (PPARγ2) and CCAAT/enhancer binding protein-α (C/EBPα) mRNA]), and apoptotic response to TNF-α. Fat mass increased by 1.9 ± 0.2 kg in the upper body and 1.6 ± 0.1 kg in the lower body. Average abdominal s.c. adipocyte size increased by 0.16 ± 0.06 μg lipid per cell and correlated with relative upper-body fat gain (r = 0.74, P < 0.0001). However, lower-body fat responded to overfeeding by fat-cell hyperplasia, with adipocyte number increasing by 2.6 ± 0.9 × 10^9 cells (P < 0.01). We found no depot-differences in preadipocyte replication or apoptosis that would explain lower-body adipocyte hyperplasia and abdominal s.c. adipocyte hypertrophy. However, baseline PPARγ2 and C/EBPα mRNA were higher in abdominal than femoral s.c. preadipocytes (P < 0.005 and P < 0.03, respectively), consistent with the ability of abdominal s.c. adipocytes to achieve a larger size. Inherent differences in preadipocyte cell dynamics may contribute to the distinct responses of different fat depots to overfeeding, and fat-cell number increases in certain depots in adults after only 8 wk of increased food intake.

adipocyte | body composition | body fat gain | fat distribution | preadipocyte

might contribute to regional differences in fat-depot growth. To investigate these questions, we induced a small total body-fat gain (~4 kg) in volunteers. We measured changes in fat mass in visceral and upper- and lower-body s.c. depots as well as changes in s.c. fat-cell size and number. We assessed cell-dynamic properties of preadipocytes at baseline. Our results indicate that upper- and lower-body s.c. fat differs remarkably in the mechanisms by which fat gain occurs, in part, because of inherent differences in the characteristics of preadipocyte cell dynamics.

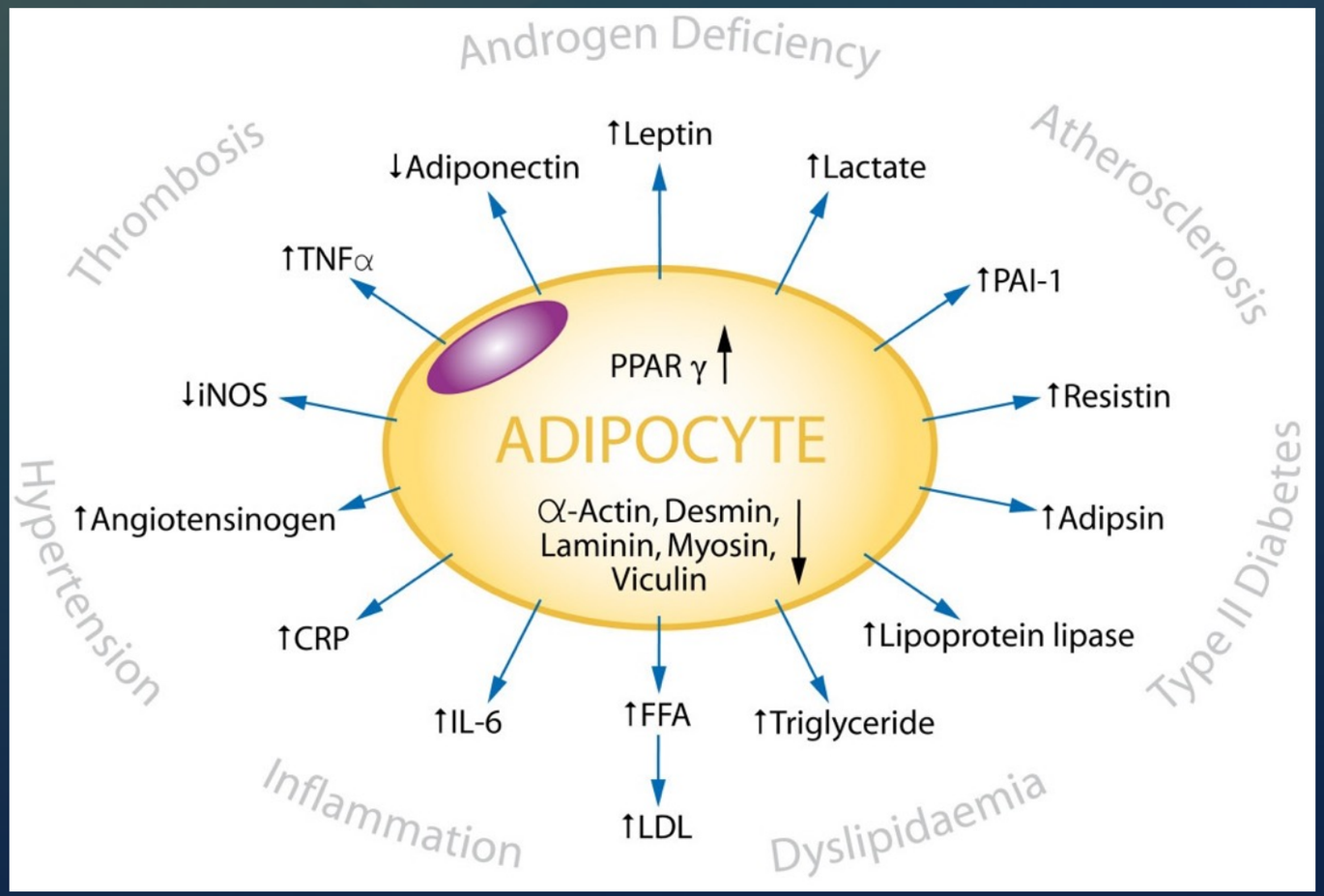
Results

Effect of Overfeeding on Body Composition and Body Fat Distribution. By design, body weight increased by 4.6 ± 2.2 kg (from 66.5 ± 4.4 to 71.1 ± 2.5 kg), leading to an increase in body mass index (BMI) of 1.5 ± 0.1 kg/m^2 (from 22.1 ± 0.5 to 23.6 ± 0.5 kg/m^2). This weight gain in both men and women resulted from an increase in fat tissue (3.8 ± 0.3 kg of fat gained, P = 0.0007), because fat-free mass remained unchanged (Table 1).

Effect of Overfeeding on Adipocyte Size and Number. The effects of overfeeding on regional adipose cellularity are presented in Table 2. On average, the size but not the number of abdominal s.c. adipocytes increased significantly in response to fat gain (P = 0.001). The change in abdominal s.c. adipocyte size was related negatively to baseline size in women but not in men (Fig. 1*A*). Thus, women with the smaller abdominal s.c. adipocytes gained abdominal fat largely via adipocyte hypertrophy, whereas women with an average adipocyte size (in excess of ~0.50 μg lipid per cell) must have recruited new, smaller adipocytes for the average size of mature

Tchoukalova, Y. D., Votruba, S. B., Tchkonia, T., Giorgadze, N., Kirkland, J. L., & Jensen, M. D. (2010). Regional differences in cellular mechanisms of adipose tissue gain with overfeeding. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(42), 18226–18231. doi:10.1073/pnas.1005259107

The Problem:
fat cells are not inert



The adipocyte as the 'Axis of Evil' – PPARγ agonists such as the glitazones stimulate the adipocyte to produce adipocytokines and cause insulin resistance, dyslipidaemias, hypertension, and impaired immunological responses, which together can have the adverse clinical consequences shown. Carruthers et al. Cardiovascular Diabetology 2008 7:30 doi: 10.1186/1475-2840-7-30

Adipose tissue is both an **immune** and **endocrine organ**

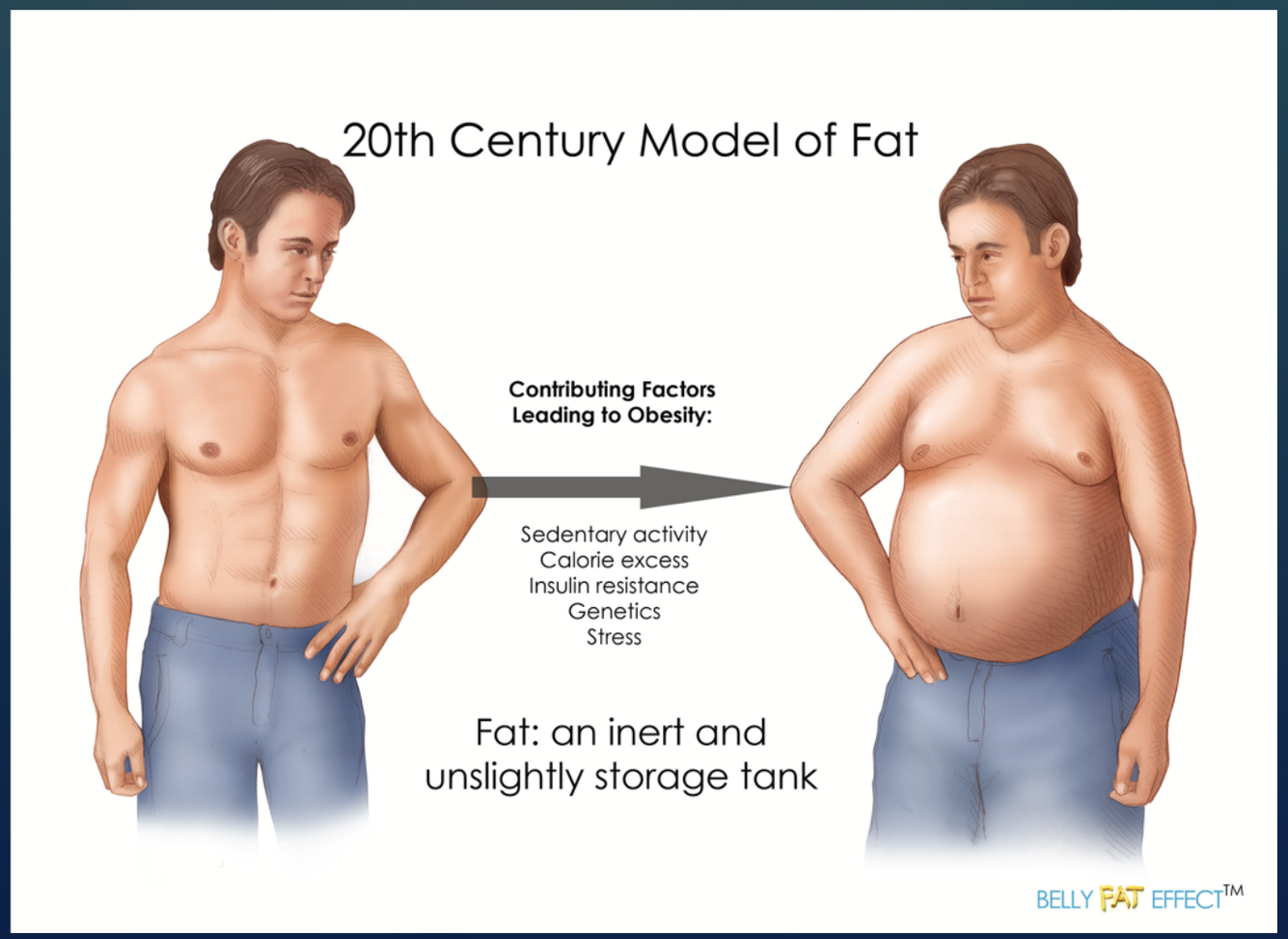


TABLE 1. Examples of adipocyte-derived proteins with endocrine functions

Cytokines and cytokine-related proteins	Leptin
	TNFα
	IL-6
Other immune-related proteins	MCP-1
Proteins involved in the fibrinolytic system	PAI-1
	Tissue factor
Complement and complement-related proteins	Adipsin (complement factor D)
	Complement factor B
	ASP
	Adiponectin
Lipids and proteins for lipid metabolism or transport	Lipoprotein lipase (LPL)
	Cholesterol ester transfer protein (CETP)
	Apolipoprotein E
	NEFAs
Enzymes involved in steroid metabolism	Cytochrome P450-dependent aromatase
	17βHSD
	11βHSD1
Proteins of the RAS	AGT
Other proteins	Resistin

Kershaw, E. E., & Flier, J. S. (2004). Adipose tissue as an endocrine organ. *Journal of Clinical Endocrinology & Metabolism*, *89*(6), 2548–2556. doi:10.1210/jc.2004-0395

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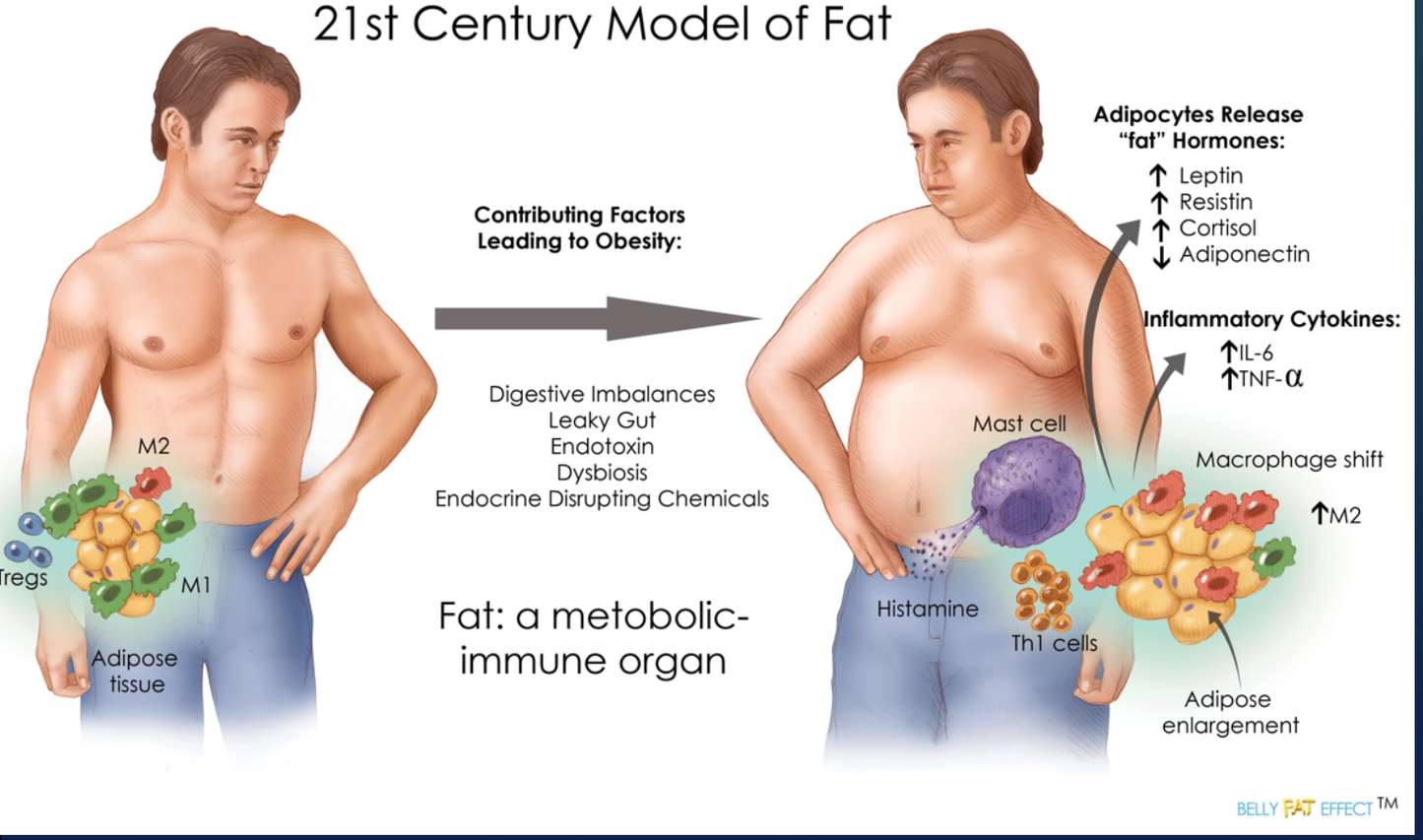

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Lipids and proteins for lipid metabolism or transport	Lipoprotein lipase (LPL)
	Cholesterol ester transfer protein (CETP)
	Apolipoprotein E
	NEFAs
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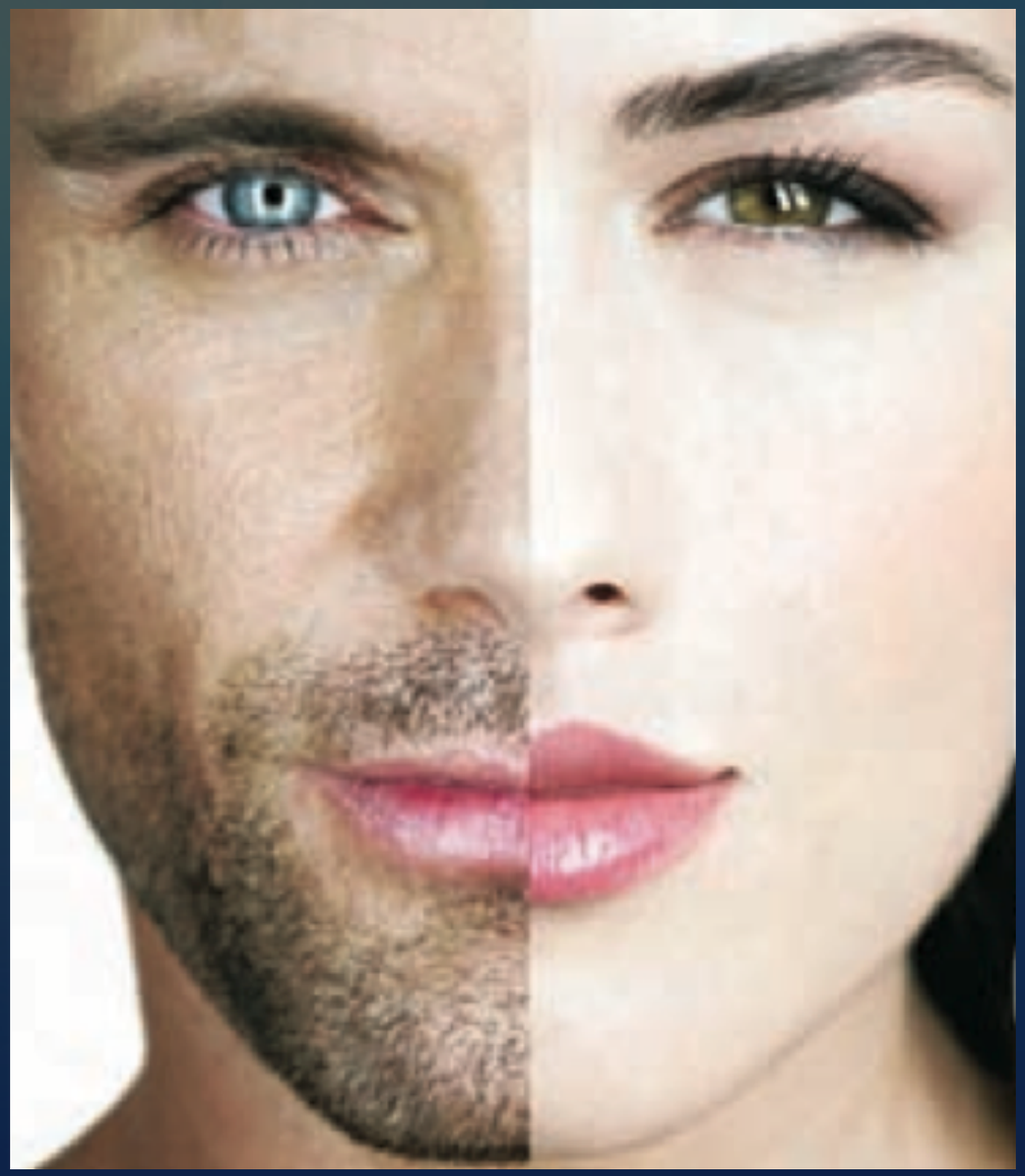
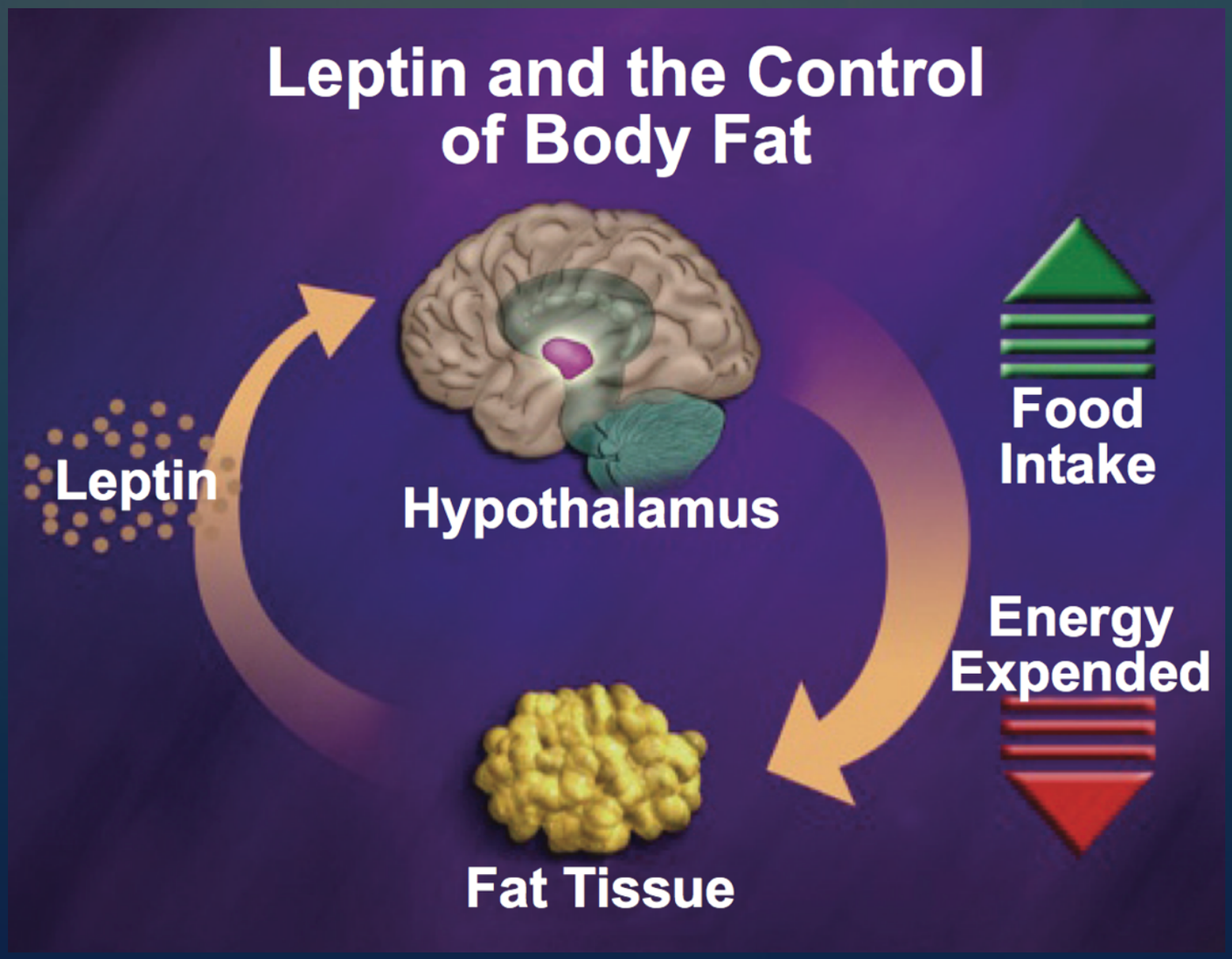
Leptin has two personalities

Metabolic



Immune

On the metabolic side, leptin functions as an energy sensor



The circadian rhythm of leptin

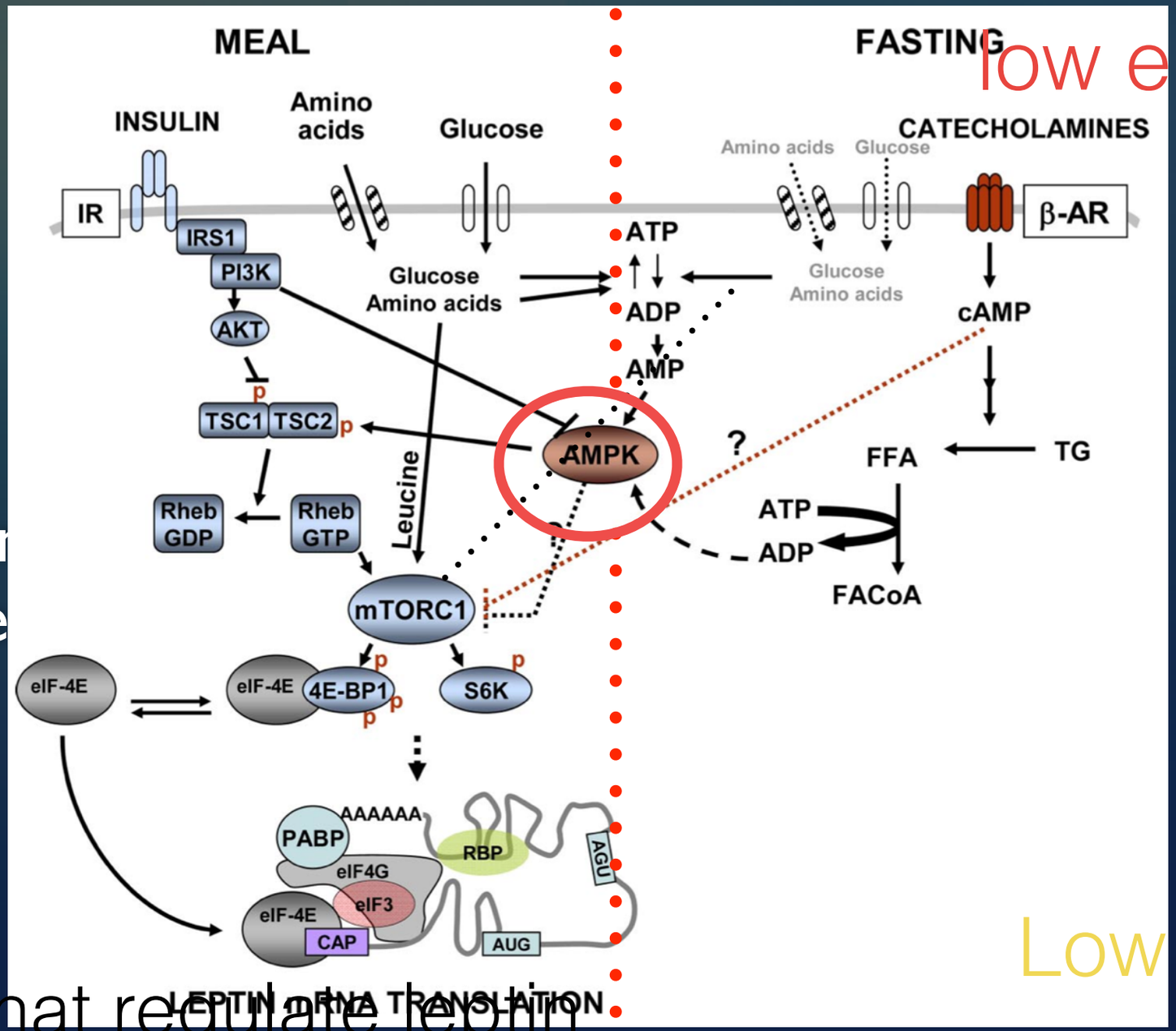
- **Lowest** in the **morning**, thus stimulating appetite and feeding
- Progressively **increases** as the day goes on, reducing appetite and increasing energy expenditure

f Body Weight. *Journal of Medical Sciences*, *3*(3), 131–135.

leptin lies at the core of cellular nutrient state

energy

low energy



Leptin

Is the

leptin

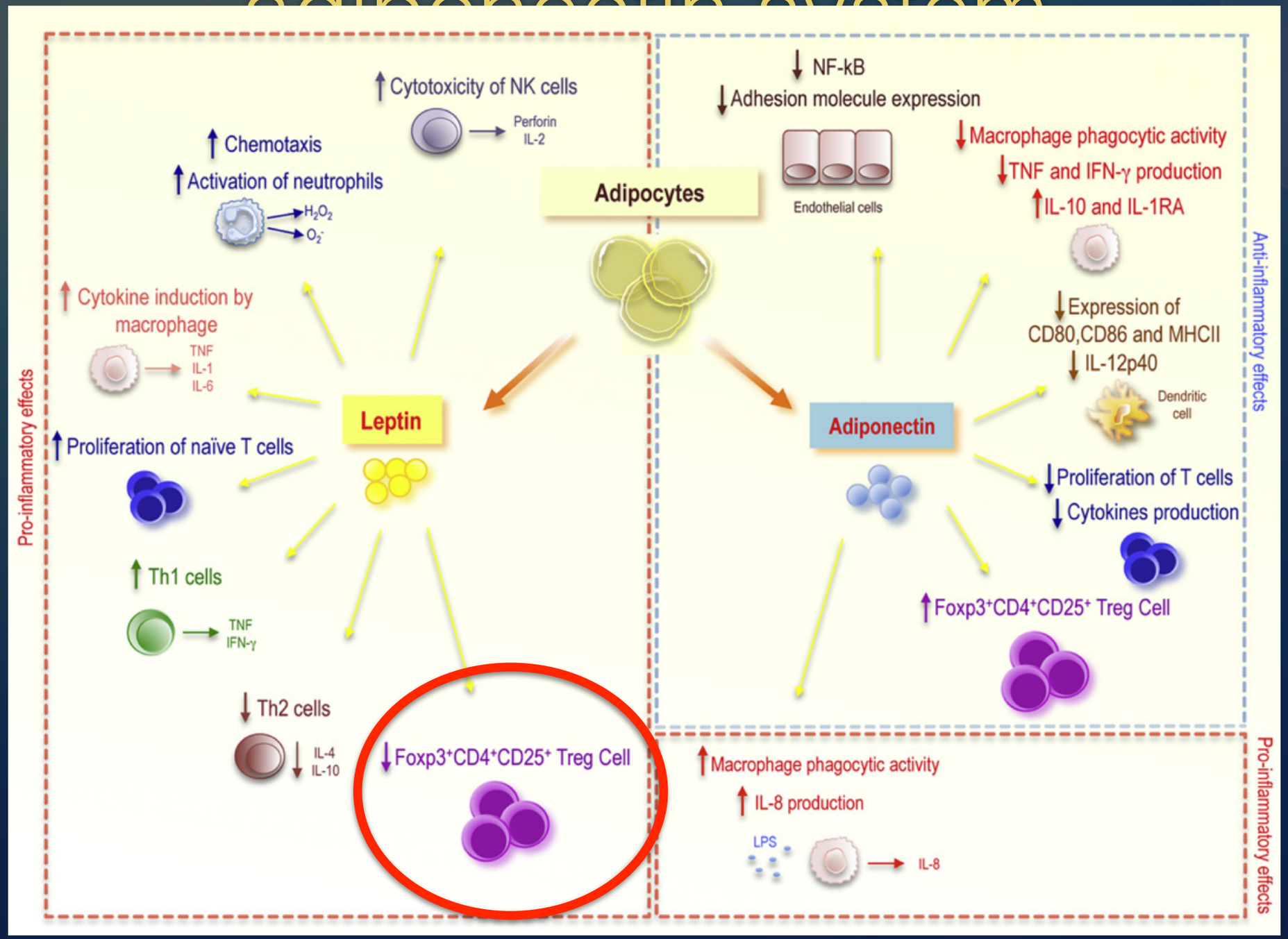
Low leptin

trient signals that regulate leptin

9). Integration of hormonal and

ptin synthesis and secretion, 1–

the yin and yang of leptin and adiponectin system



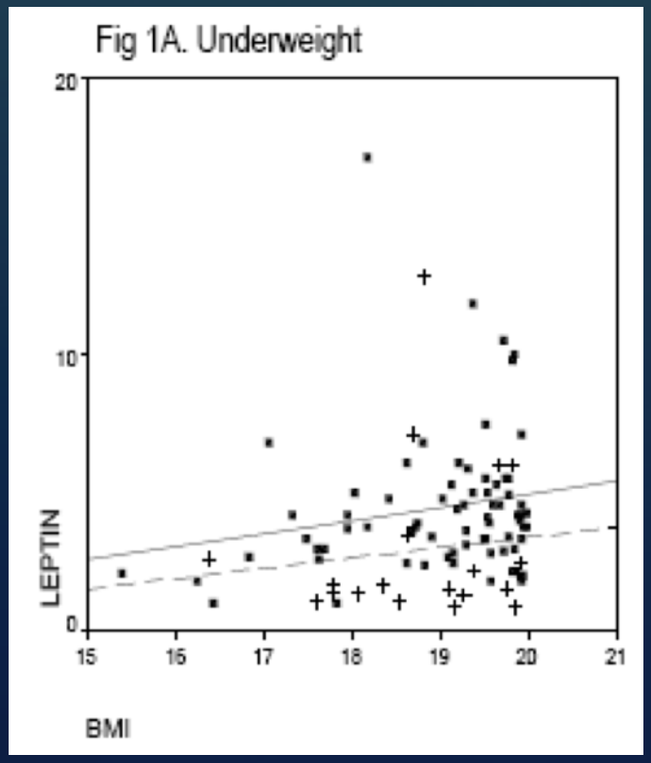
body mass index (BMI) and leptin

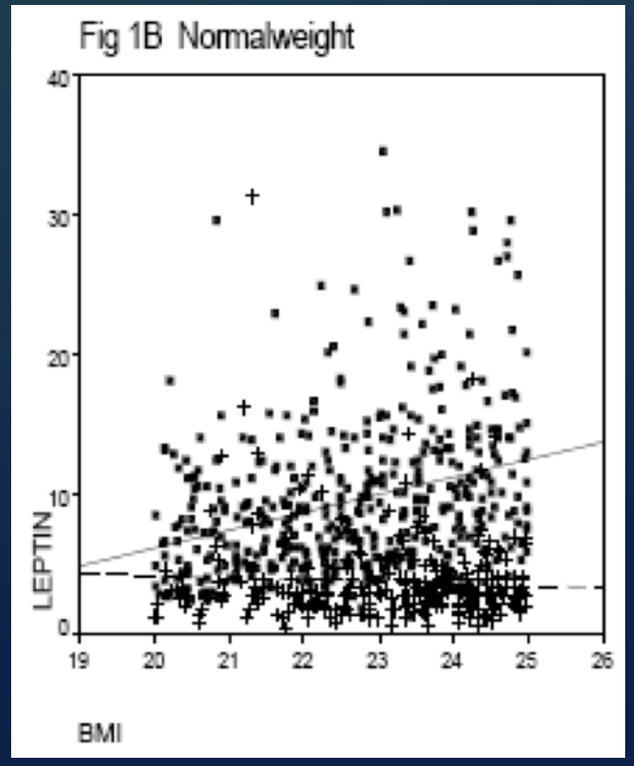
The Open Behavioral Science Journal, 2011, *5*, 8-15

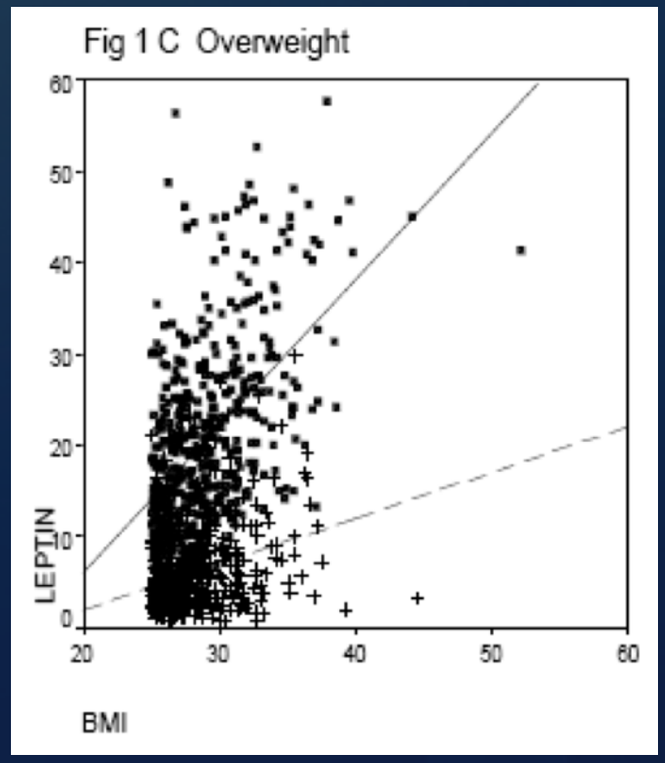
Open Access

Leptin in the General Population, Differences in Sex Hormones, Blood Lipids, Gender and Life Style Characteristics

Reidun Olstad[1,5], Jon Florholmen[2,5], Johan Svartberg[3,5], Jan H. Rosenvinge[4] and Grethe Støa Birketvedt[*,6]



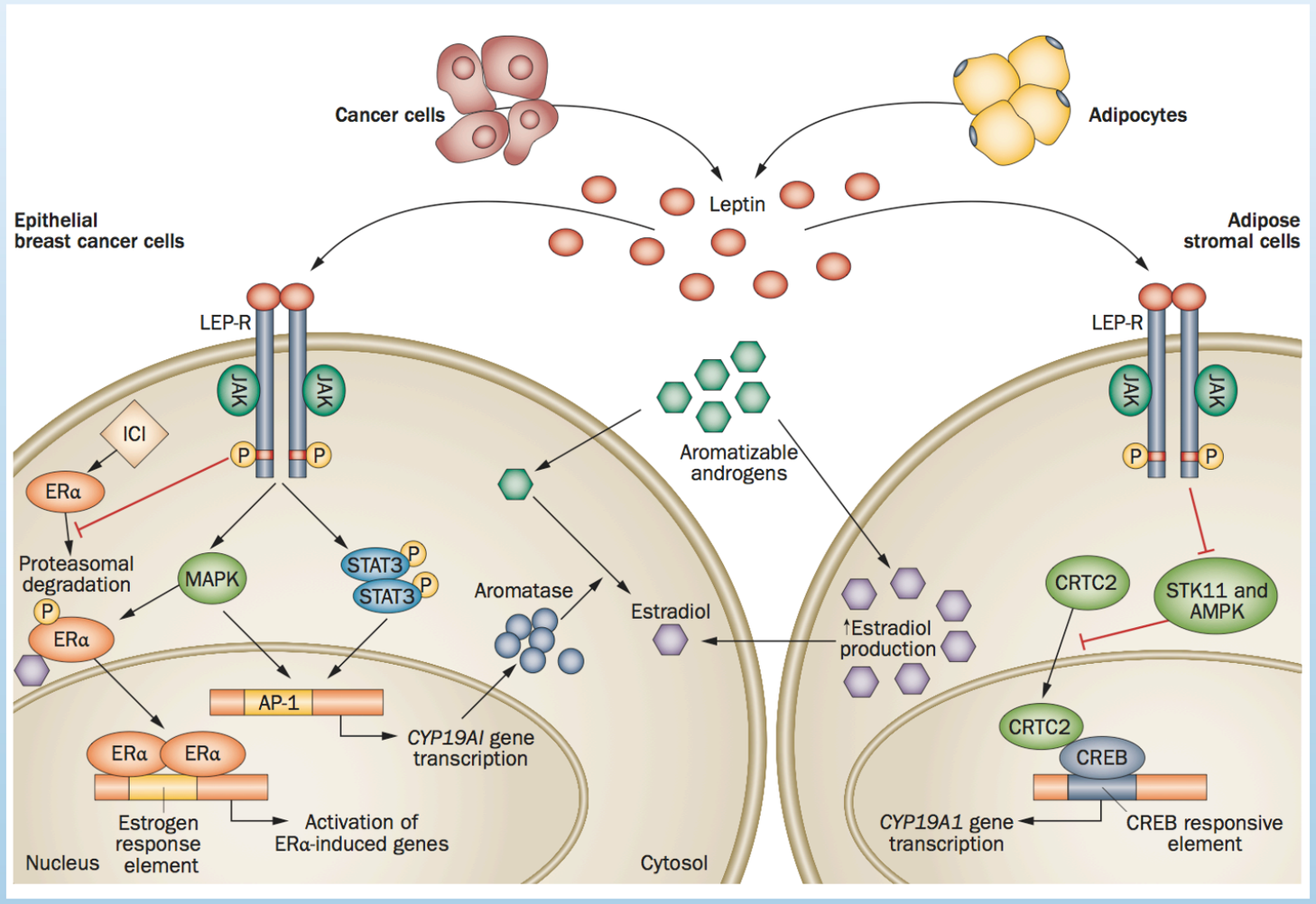




Leptin in the General Population, Differences in Sex Hormones, Blood Lipids, Gender and Life Style Characteristics. (2011). Leptin in the General Population, Differences in Sex Hormones, Blood Lipids, Gender and Life Style Characteristics, 1–8.

BELLY FAT EFFECT

Leptin may increase the local production of estrogens by driving aromatase activity



Andò, S., & Catalano, S. (2011). The multifactorial role of leptin in driving the breast cancer microenvironment. *Nature Reviews | Endocrinology*, *8*(5), 263–275. doi:10.1038/nrendo.2011.184

BELLY FAT EFFECT

Human studies link leptin with breast tumor size

J Mol Med (2010) 88:677–686
DOI 10.1007/s00109-010-0611-8

ORIGINAL ARTICLE

Correlation of body mass index and leptin with tumor size and stage of disease in hormone-dependent postmenopausal breast cancer: preliminary results and therapeutic implications

Antonio Macciò · Clelia Madeddu · Giulia Gramignano · Carlo Mulas · Carlo Floris · Daniela Massa · Giorgio Astara · Paola Chessa · Giovanni Mantovani

Received: 5 January 2010 / Revised: 1 March 2010 / Accepted: 1 March 2010 / Published online: 26 March 2010

"…leptin reflects the total amount of fat mass, which correlates to aromatase activity and subsequent estrogens levels."

breast cancer risk and its prognosis. The present prospective observational study aims to investigate the relationship between body mass index (BMI), serum levels of leptin and proinflammatory cytokines, and breast cancer prognostic factors. In the study, 98 postmenopausal and 82 premenopausal patients with ER-positive breast cancer participated.

…rs were …inflam- …g blood …ts, BMI, …ed with pathological tumor classification (pT) and TNM stage. Multivariate regression analysis showed that BMI and leptin, but not interleukin-6, were independent predictive variables of pT and TNM stage. Our results seem to suggest a twofold role of leptin in the etiopathogenesis of postmenopausal estrogen-positive breast cancer. Indeed, leptin

"Our results seem to suggest a twofold role of leptin in the etiopathogenesis of postmenopausal estrogen-positive breast cancer."

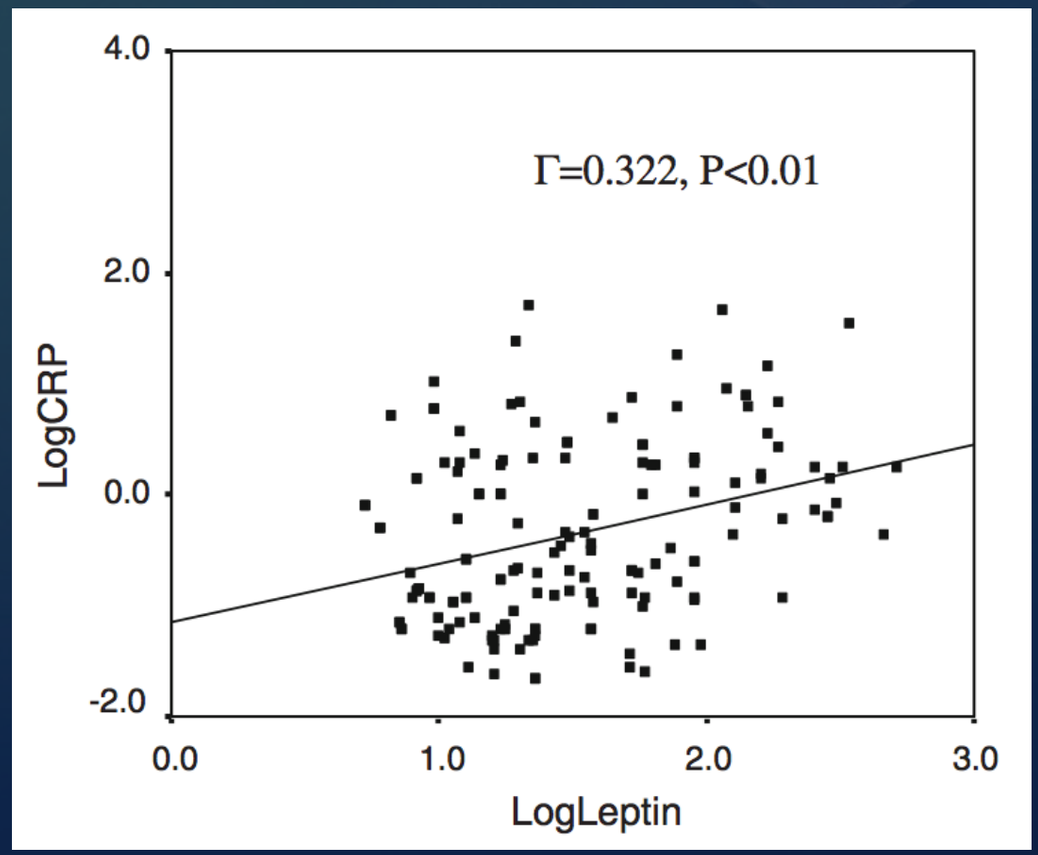
leptin, Belly Fat, and inflammation

Acta Diabetol (2010) 47:113–118
DOI 10.1007/s00592-009-0125-4

ORIGINAL ARTICLE

Visceral adiposity and leptin are independently associated with C-reactive protein in Korean type 2 diabetic patients

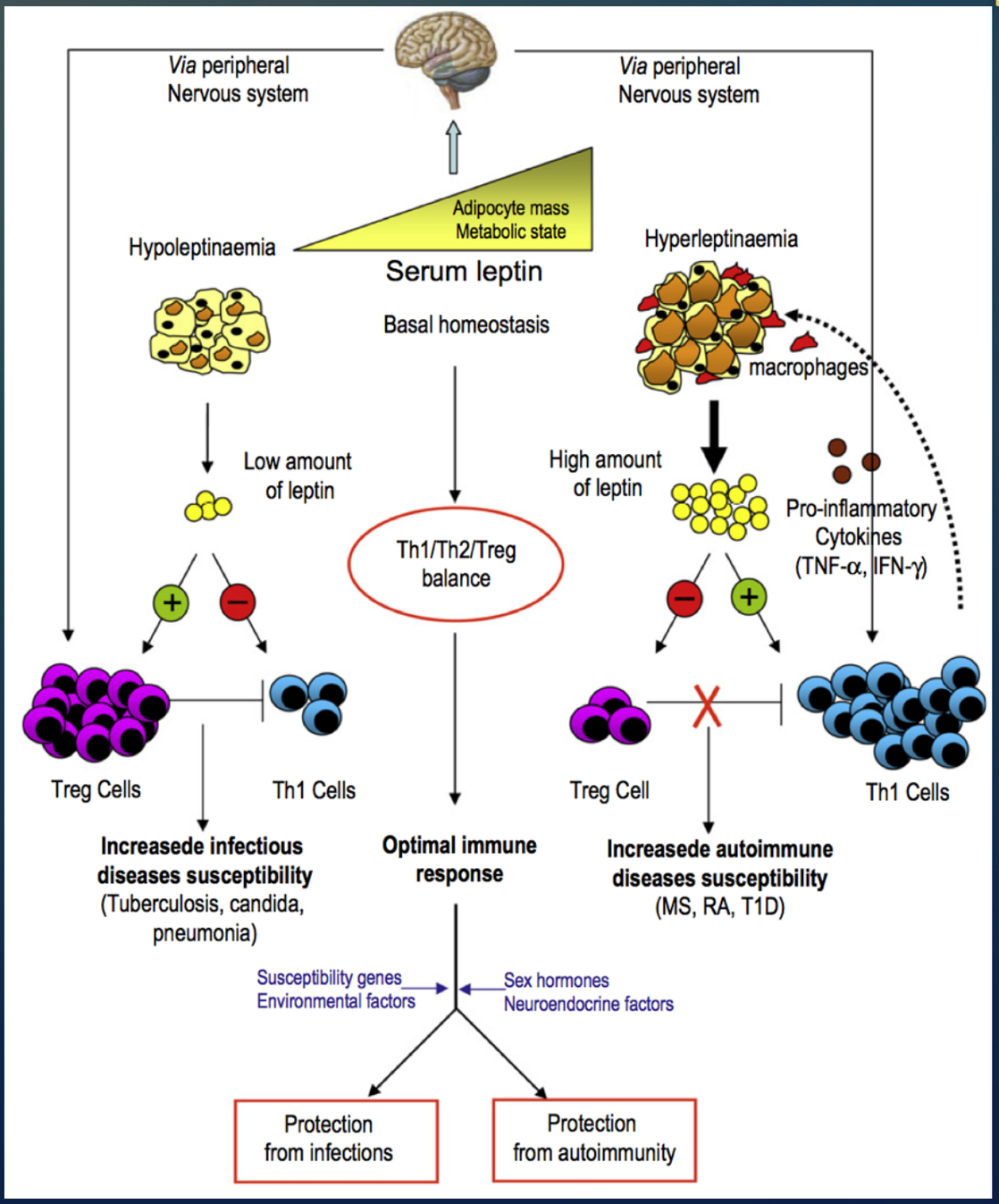
Jong Suk Park · Min Ho Cho · Ji Sun Nam · Chul Woo Ahn · Bong Soo Cha · Eun Jig Lee · Sung Kil Lim · Kyung Rae Kim · Hyun Chul Lee



"We found a significant correlation between leptin and CRP…Serum leptin is an important independent factor associated with CRP in Korean type 2 diabetic patients."

Park, J. S., Cho, M. H., Nam, J. S., Ahn, C. W., Cha, B. S., Lee, E. J., et al. (2009). Visceral adiposity and leptin are independently associated with C-reactive protein in Korean type 2 diabetic patients. *Acta Diabetologica*, *47*(2), 113–118. doi:10.1007/s00592-009-0125-4

leptin and the immune system



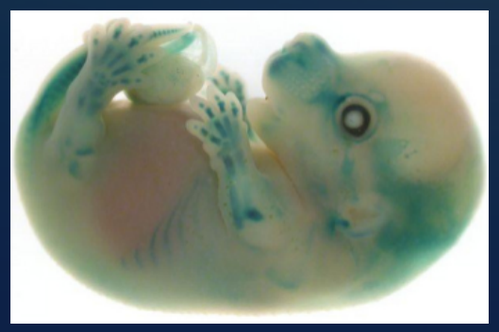
Procaccini, C., Jirillo, E., & Matarese, G. (2011). Leptin as an immunomodulator. *Journal of Molecular Aspects of Medicine*, 1–11. doi:10.1016/j.mam.2011.10.012

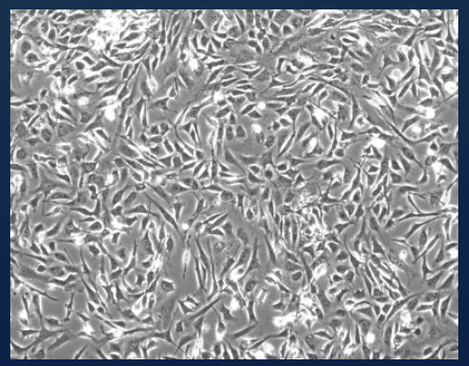
the answer:

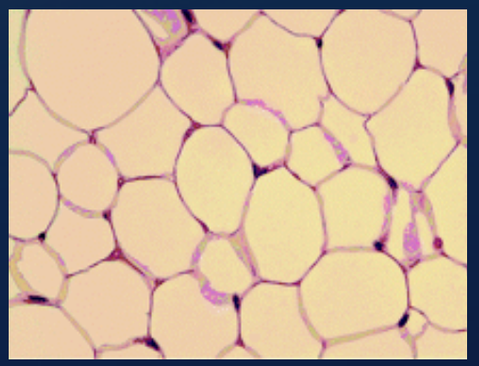
european researchers have discovered
a natural extract that prevents adipogenesis

IN VITRO STUDIES

Inhibition of adipogenesis





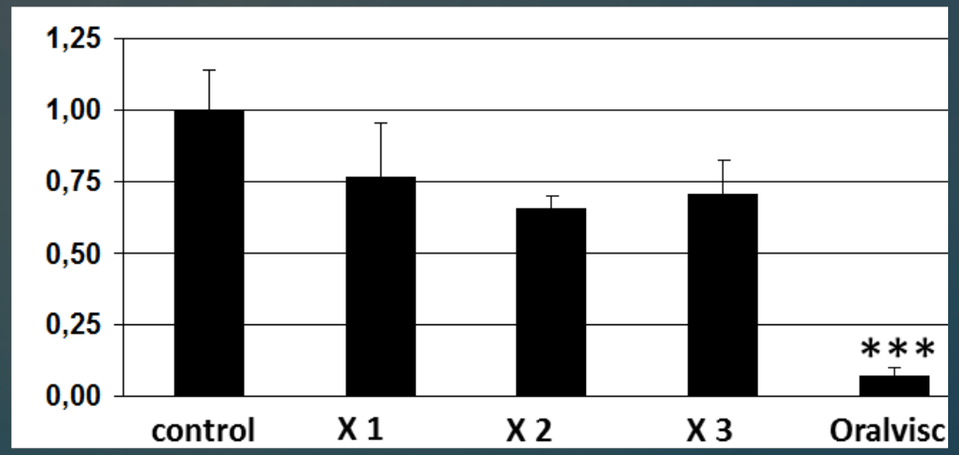


Prominent cellular metabolites involved in adipocyte differentiation

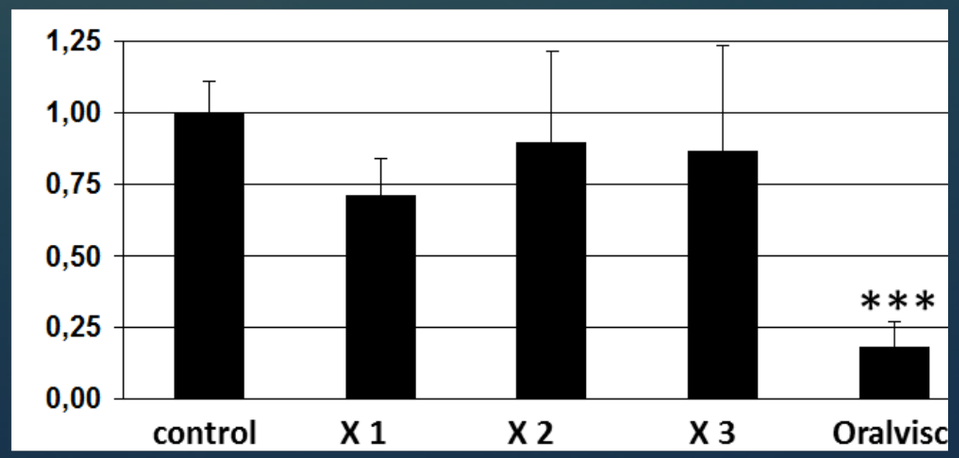
Agent	Effect	Comments
Insulin	+	Accelerates lipid accumulation
IGF-1	+	Stimulates adipocyte differentiation
Glucocorticoids	+	Stimulate adipocyte differentiation
Growth hormone	+/-	Induces adipogenesis in preadipose cell lines, inhibits adipogenesis in primary cultures
Retinoic acid	+/-	Concentration dependent
Thyroid hormone	+/no effect	Inducing effect on adipogenesis restricted to a preadipose cell line
Prostaglandins	+/-	Varied effects depending on model system
EGF, TGF-α	-	Inhibit adipocyte differentiation
TGF-β	-	Potent inhibitor of adipogenesis
aFGF, bFGF	+/-	Conflicting results
IL-1, interferon-γ, TNF-α	-	Inhibit adipocyte differentiation
PDGF	+/-	Conflicting results
cAMP	+	Induces adipocyte differentiation
Vitamin D	+/-	Conflicting results
Oestrogen, progesterone	+/no effect	

Cellular pathways driving new adipocytes are reduced

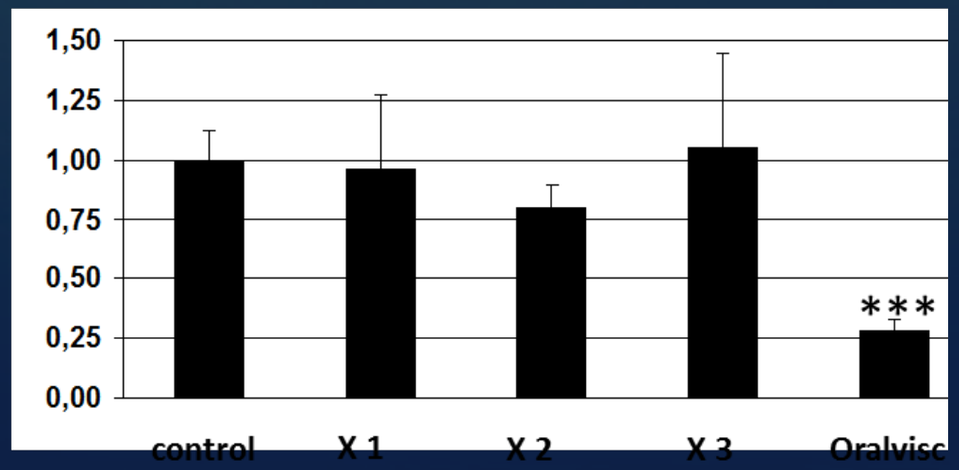
A)



B)

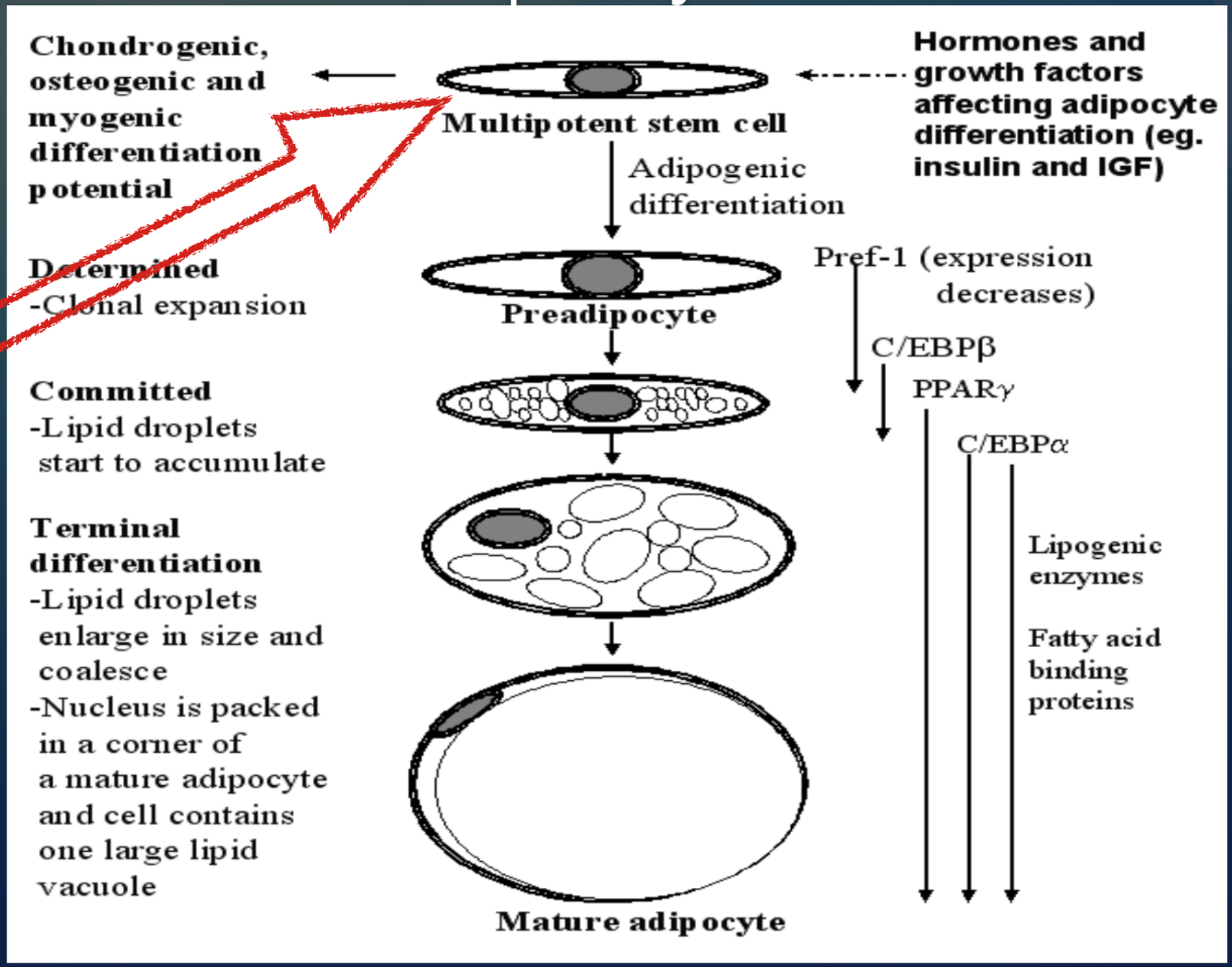


C)

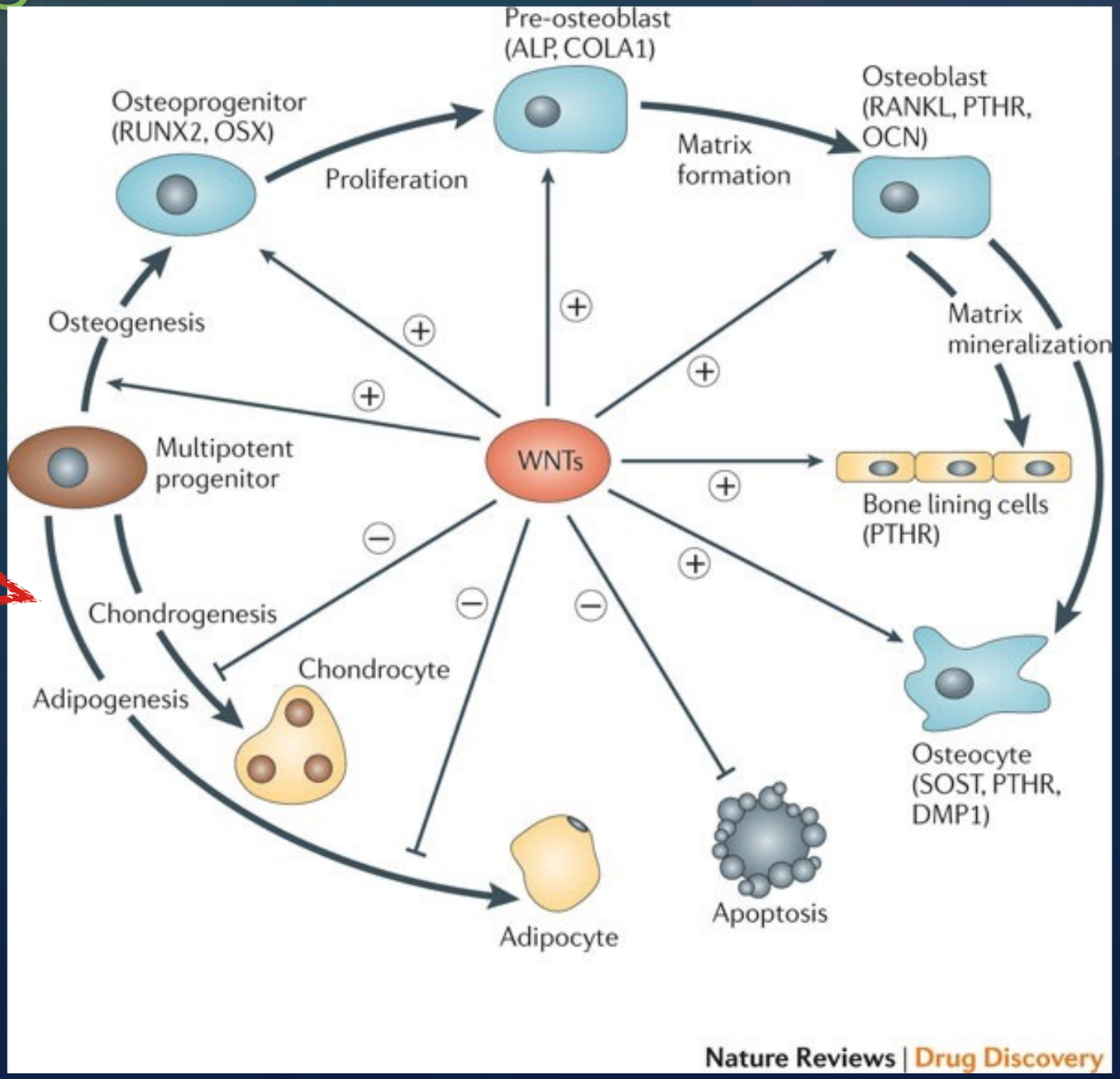


Overview of adipocyte differentiation

key point



proposed mechanism of action:
favoring chondrogenesis



Masanobu Kawai. Emerging therapeutic opportunities for skeletal restoration. Nature Reviews Drug Discovery 10, 141-156 (February 2011) | doi:10.1038/nrd3299

The effects of an oral preparation containing hyaluronic acid (Oralvisc®) on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses

F. R. Nelson · R. A. Zvirbulis · B. Zonca · K. W. Li · S. M. Turner · M. Pasierb · P. Wilton · D. Martinez-Puig · W. Wu

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Abstract The purpose of this study was to determine the effects of an oral preparation containing hyaluronic acid on osteoarthritic knee joint pain and function as well as changes in inflammatory cytokines, bradykinin, and leptin. We also used heavy water to determine the turnover rates of glycosaminoglycans in synovial fluid. This was a double-blind, randomized, placebo-controlled study of 40 subjects over a period of 3 months. Visual analog scale, Western Ontario McMaster pain, and WOMAC function scores water analyses revealed a significant decrease in hyaluronic acid turnover in the synovial fluid of the treatment group. A preparation containing hyaluronic acid and other glycosaminoglycans holds promise for a safe and effective agent for the treatment for patients with knee osteoarthritis and who are overweight. Further studies will be required to see whether this is a disease-modifying agent.

Keywords Osteoarthritis · Clinical Outcomes Research ·

"A preparation containing hyaluronic acid and other glycosaminoglycans…both **serum** and **synovial fluid** samples showed significant decreases for a majority of inflammatory **cytokines**, **leptin**, and **bradykinin** in the oral **hyaluronic acid** preparation group."

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Role of cholinergic anti-inflammatory pathway in regulating host response and its interventional strategy for inflammatory diseases

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The cholinergic anti-inflammatory pathway (CAP) is a neurophysiological mechanism that regulates the immune system. The CAP inhibits inflammation by suppressing cytokine synthesis via release of acetylcholine in organs of the reticuloendothelial system, including the lungs, spleen, liver, kidneys and gastrointestinal tract. Acetylcholine can interact with α7 nicotinic acetylcholine receptors (α7 nAchR) expressed by macrophages and other cytokine producing cells, down-regulate pro-inflammatory cytokine synthesis and prevent tissue damage. Herein is a review of the neurophysiological mechanism in which the CAP regulates inflammatory response, as well as its potential interventional strategy for inflammatory diseases.

Key words: ***Cholinergic agents; Vagus nerve; Inflammation; Alpha-bungarotoxin receptor***

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Adequate inflammatory response initiated by infection and injury can eradicate the invading pathogen and enhance wound healing. If the inflammatory response is excessive, it will cause cytokine overproduction which induces general tissue damage and organ dysfunction. Excessive cytokine production and release are characteristics of chronic or uncontrolled inflammatory responses and primarily related to the pathology of many diseases, including sepsis, rheumatoid arthritis, Crohn's disease and other autoimmune diseases.[1] Thus, inhibiting pro-inflammatory cytokines is beneficial to prevent the occurrence and progress of uncontrolled inflammatory responses. For instance, experimental therapies that neutralize pro-inflammatory cytokines, including monoclonal anti-tumor necrosis factor (TNF) antibodies, interleukin (IL)-1 receptor antagonists and TNF-receptor fusion proteins, are successfully used in rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriasis. Recent studies have identified high mobility group box 1 protein (HMGB1) as an important late inflammatory mediator in sepsis and several inflammatory disorders. Anti-HMGB1 therapeutics are successful in reducing multi-organ injuries and improving survival in inflammatory disease models.[2]

Anti-inflammatory mechanisms include the release of glucocorticoids, anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β), and soluble receptors which neutralize the activity of cytokines. Recent studies found that vagus nerve-mediated cholinergic anti-inflammatory pathway (CAP) can effectively regulate systemic inflammatory response. This article reviewed the neurophysiological mechanism in which the CAP regulates inflammatory response, as well as its potential interventional strategy for inflammatory diseases.

Cholinergic anti-inflammatory pathway

The vagus nerve, in addition to its classically assigned function of controlling heart rate, hormone secretion, gastrointestinal peristalsis and digestion, may also be involved in regulating pro-inflammatory cytokines (e.g. TNF-α) release. Even when circulating cytokine levels are low, vagus nerve can detect peripheral inflammation. Inflammatory signals to central nervous

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Original Article

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Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults

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Abstract. Thayer JF, Fischer JE (The Ohio State University, Columbus, OH, USA; and Heidelberg University, Mannheim, Germany). Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults. *J Intern Med* 2009; **265**: 439–447.

Objectives. C-reactive protein (CRP) has been identified as an independent predictor of cardiovascular mortality and morbidity in population-based studies. Recent advances have suggested a prominent role for the autonomic nervous system (ANS) in the regulation of inflammation. However, no *in vivo* human studies have examined indices of sympathetic and parasympathetic nervous system activity simultaneously in relationship to inflammatory markers in apparently healthy adults. Therefore, the objective of this study was to assess the immunomodulatory effects of the ANS.

Methods and results. The study population comprised 611 apparently healthy employees of an airplane manufacturing plant in southern Germany. Urinary NE was positively associated with white blood cell count (WBC) in the total sample. We found an inverse association between indices of vagally mediated heart rate variability and plasma levels of (CRP), which was significantly larger in females than in males after controlling for relevant covariates including NE. Similar results were found using the percentage of interbeat interval differences >50 ms and WBC.

Conclusions. We report here for the first time, in a large sample of healthy human adults, evidence supporting the hypothesis of a clinically relevant cholinergic anti-inflammatory pathway after controlling for sympathetic nervous system activity. This suggests an important role for the vagal control of systemic inflammatory activity in cardiovascular disease.

Keywords: arteriosclerosis, autonomic, heart rate variability, inflammation, nervous system, norepinephrine.

Introduction

Inflammation has been implicated in a wide range of disease processes. One such marker of systemic inflammation, C-reactive protein (CRP), has been identified as an independent predictor of not only cardiovascular disease but all cause mortality and morbidity in population-based studies [1–3]. Recent research has suggested a prominent role for the autonomic nervous system (ANS) in the regulation of inflammation. Whereas the effects of sympathetic nervous system (SNS) activity may have both pro- and anti-inflammatory actions, animal studies and in vitro studies in humans have shown that parasympathetic outflow inhibits macrophage activation and subsequent release of pro-inflammatory cytokines such as IL-6 via a nicotinic alpha-bungarotoxin-sensitive macrophage acetylcholine receptor [4, 5]. In addition, animal studies have reported that electrical stimulation of the vagus nerve inhibits release of pro-inflammatory

Thayer, J. F., & Fischer, J. E. (2009). Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults. Journal of Internal Medicine, 265(4), 439–447. http://doi.org/10.1111/j.1365-2796.2008.02023.x

AP&T Alimentary Pharmacology and Therapeutics

Combat-training increases intestinal permeability, immune activation and gastrointestinal symptoms in soldiers

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SUMMARY

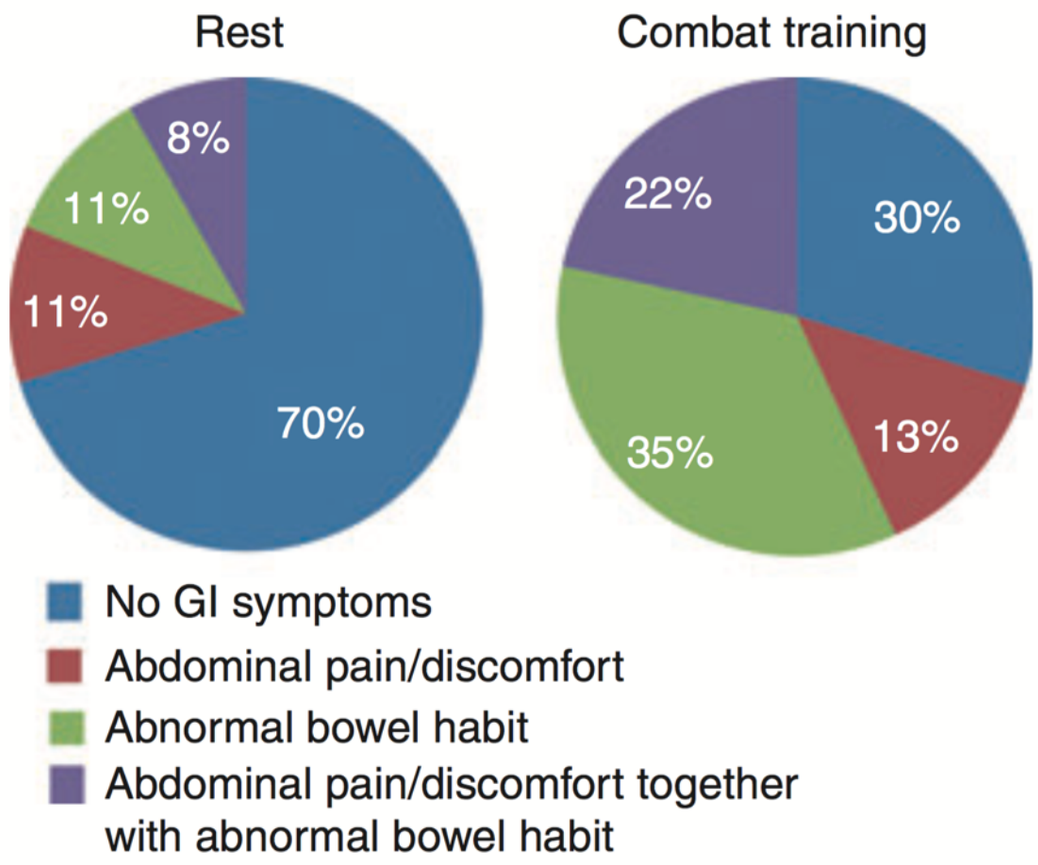
Background
Gastrointestinal (GI) symptoms are common in soldiers in combat or high-pressure operational situations and often lead to compromised performance. Underlying mechanisms are unclear, but neuroendocrine dysregulation, immune activation and increased intestinal permeability may be involved in stress-related GI dysfunction.

Aim
To study the effects of prolonged, intense, mixed psychological and physical stress on intestinal permeability, systemic inflammatory and stress markers in soldiers during high-intensity combat-training.

Methods
In 37 male army medical rapid response troops, GI symptoms, stress markers, segmental intestinal permeability using the 4-sugar test (sucrose, lactulose, mannitol and sucralose) and immune activation were assessed during the 4th week of an intense combat-training and a rest period.

Results
Combat-training elicited higher stress, anxiety and depression scores (all $P < 0.01$) as well as greater incidence and severity of GI symptoms [irritable bowel syndrome symptom severity score (IBS-SSS), $P < 0.05$] compared with rest. The IBS-SSS correlated with depression ($r = 0.41$, $P < 0.01$) and stress ($r = 0.40$, $P < 0.01$) ratings. Serum levels of cortisol, interleukin-6, and tumour necrosis factor-α, and segmental GI permeability increased during combat-training compared with rest (all $P < 0.05$). The lactulose:mannitol ratio was higher in soldiers with GI symptoms (IBS-SSS ≥ 75) during combat-training than those without (IBS-SSS <75) ($P < 0.05$).

Conclusions
Prolonged combat-training not only induces the expected increases in stress, anxiety and depression, but also GI symptoms, pro-inflammatory immune activation and increased intestinal permeability. Identification of subgroups of individuals at high-risk of GI compromise and of long-term deleterious effects of operational stress as well as the development of protective measures will be the focus of future studies.



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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Role of *Helicobacter pylori* infection on nutrition and metabolism

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Abstract

Helicobacter pylori (*H. pylori*) is a gram-negative pathogen that is widespread all over the world, infecting more than 50% of the world's population. It is etiologically associated with non-atrophic and atrophic gastritis, peptic ulcer and shows a deep association with primary gastric B-cell lymphoma and gastric adenocarcinoma. Recently, the medical research focused on the modification of the gastric environment induced by *H. pylori* infection, possibly affecting the absorption of nutrients and drugs as well as the production of hormones strongly implicated in the regulation of appetite and growth. Interestingly, the absorption of iron and vitamin B12 is impaired by *H. pylori* infection, while infected subjects have lower basal and fasting serum levels of ghrelin and higher concentration of leptin compared to controls. Since leptin is an anorexigenic hormone, and ghrelin stimulates powerfully the release of growth hormone in humans, *H. pylori* infection may finally induce growth retardation if acquired very early in the childhood and in malnourished children. This review is focused on the nutritional effects of *H. pylori* infection, such as the reduced bioavailability or the malabsorbption of essential nutrients, and of gastrointestinal hormones, as well as on the relationship between *H. pylori* and the metabolic syndrome.

Key words: *Helicobacter pylori*; Malabsorption; Metabolic syndrome; Gastrointestinal hormones

Core tip: This review analyzes in a very comprehensive way all aspects related to nutrition and metabolism induced by *Helicobacter pylori* (*H. pylori*). Interestingly, this bacterium is able to produce different biological effects on hormones controlling both appetite and growth, mostly depending on the time of acquisition of the infection and of eradication. On the other hand, *H. pylori* is able to induce malabsorption of several nutrients, with a strong effect on nutrition.

Franceschi F, Annalisa T, Teresa DR, Giovanna D, Ianiro G, Franco S, Viviana G, Valentina T, Riccardo LL, Antonio G. Role of *Helicobacter pylori* infection on nutrition and metabolism. *World J Gastroenterol* 2014; 20(36): 12809-12817 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i36/12809.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i36.12809

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Autonomic control of heart period in duodenal ulcer patients insights from spectral analysis of heart rate variability.

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Author information

Abstract

Beyond the fundamental pathogenetic importance of Helicobacter Pylori a possible additional role of vagal innervation in favouring or modulating the clinical history of duodenal ulcer (DU) has been suggested by old studies employing invasive methodologies. Aim of this study was to assess whether vagal prevalence in autonomic modulation was present in healed DU patients (n=20) as compared to controls,(n=50), using a validated non-invasive methodology, based on spectral analysis of cardiovascular variability. This approach provides markers of the sympathetic and vagal modulations of the SA node, respectively by way of the normalized low frequency (LF(RR)) and high frequency (HF(RR)) components of RR interval variability; LF/HF ratio furnishes a marker of sympatho-vagal balance. In addition, sham feeding (SF) provided a means to assess, in DU patients, neurally mediated acid secretion, as the SF acid output (SAO) to basal acid output (BAO) ratio (SAO/BAO). Results showed that LF(RR) was smaller in DU patients than in controls (40.3+/-3.9 vs. 52.3+/-2.3 normalized units, nu; P<0.05). On the contrary, HF(RR) was greater (52.1+/-3.7 vs. 35.7+/-2.3 nu; P<0.05). Conversely the LF component of SAP variability, a marker of sympathetic vasomotor modulations, and the index alpha, a measure of baroreflex control of the SA node, as well as respiratory patterns, were similar in the two groups. SAO/BAO ratio was significantly correlated with markers of autonomic control of the SA node (r = -0.67, P<0.0083 with HF(RR)). In conclusion results suggest an enhanced vagal modulation of heart period in DU patients at rest, that appears linked to indices of neurally mediated gastric acid secretion response.

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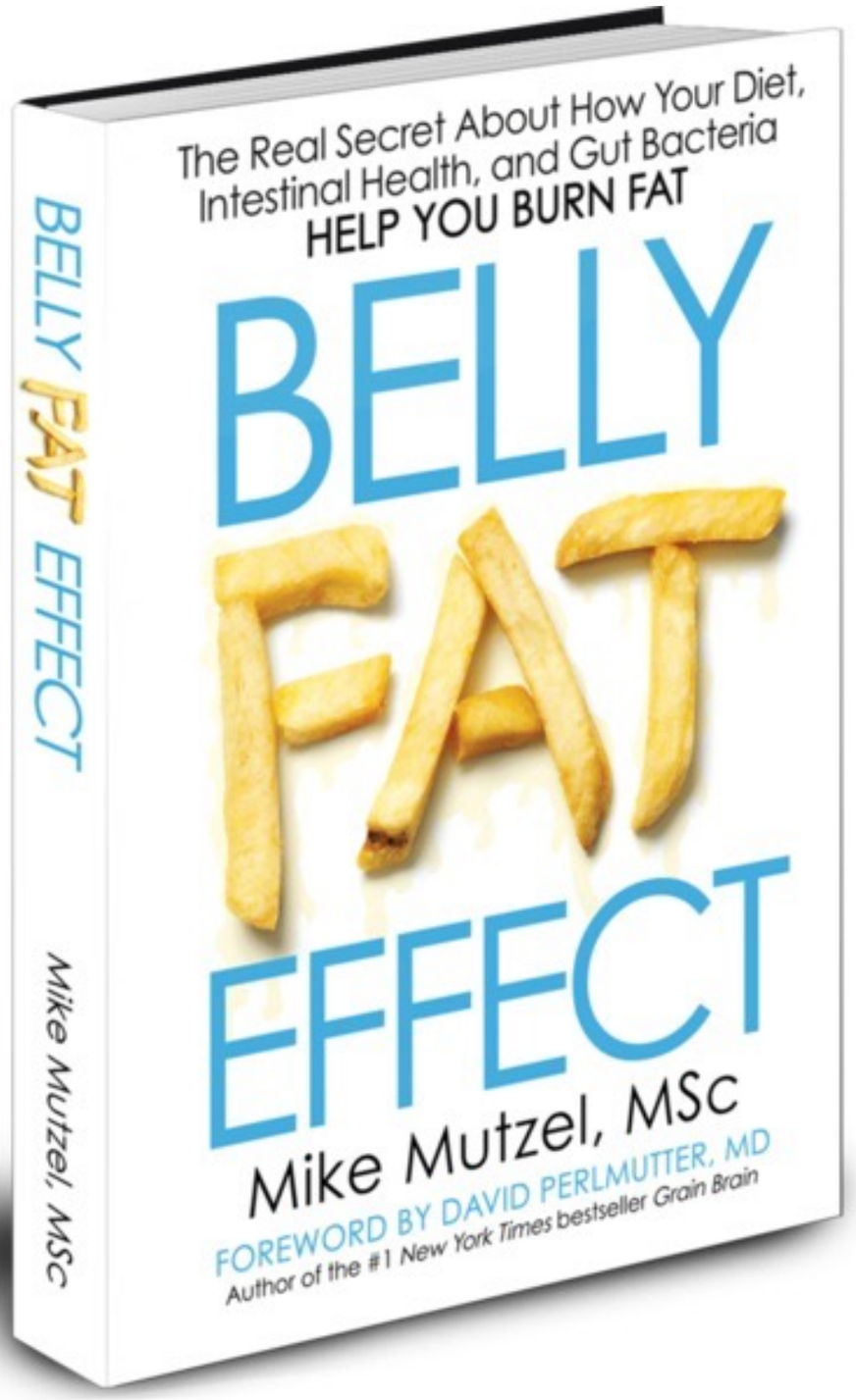

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