

CLINICAL BREAKTHROUGHS IN METABOLISM AND BODY COMPOSITION

BY MIKE MUTZEL, MS

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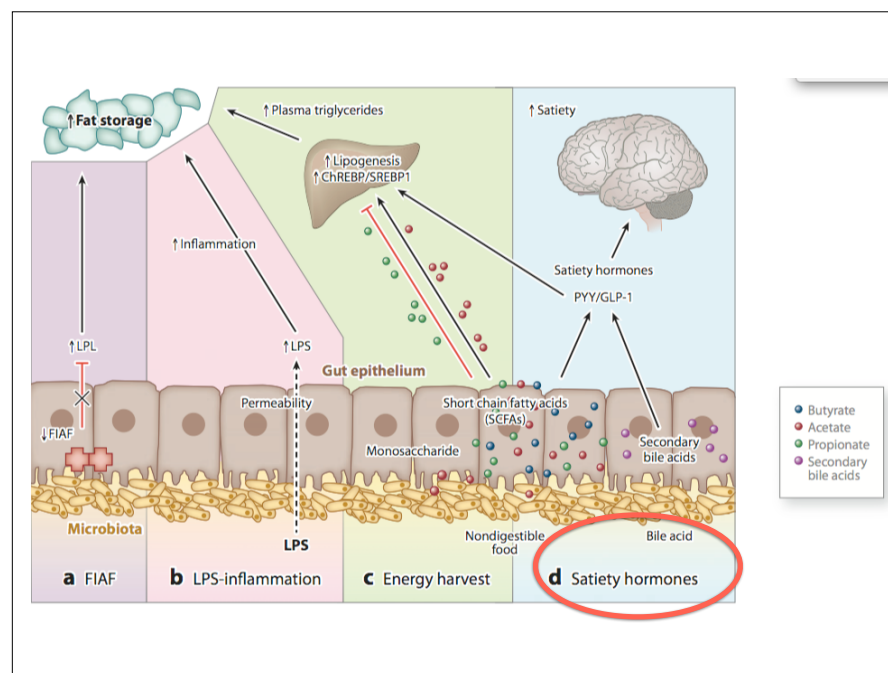
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- I am a consultant for **XYMOGEN**
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THREE BIG IDEAS FROM OUR DISCUSSION

- How gut microbiome metabolites affect your metabolic health
- Bacterial Endotoxin: what is it and why you should care?
- Overview of the metabolic switches of the gastrointestinal tract—that are highly modifiable
- The metabolic potential of muscle
- Ketogenic Diet/Time-Restricted Feeding

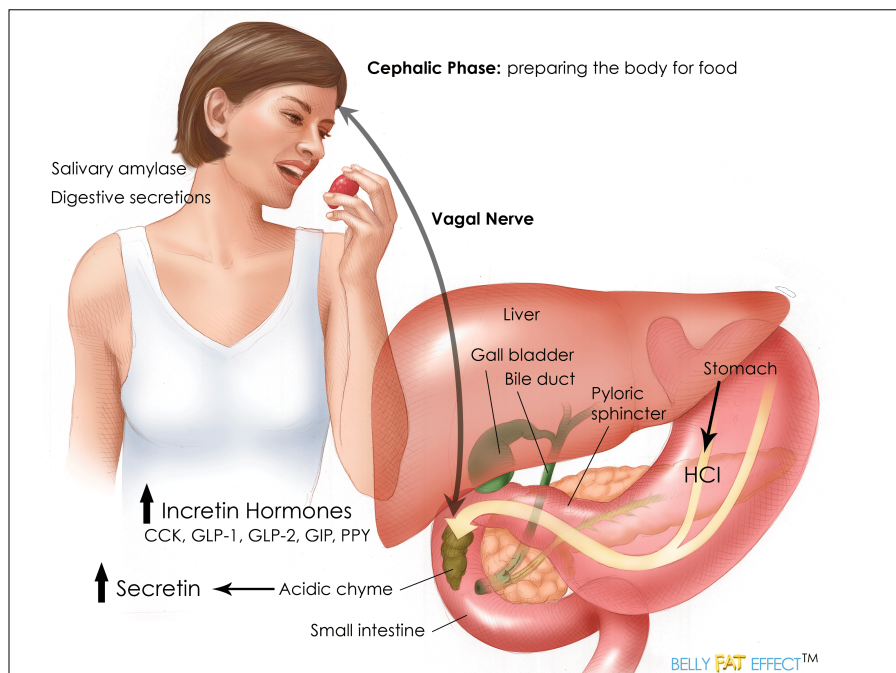


What is the incretin effect?

“....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 McIntyre 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.



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DOI 10.1007/s00125-012-2561-x

THEN AND NOW

The incretin hormones: from scientific discovery to practical therapeutics

S. Mudaliar · R. R. Henry

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Abstract The incretins are gut hormones secreted in response to food intake and are degraded by the ubiquitous protease DPP-4. This has led to

“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.”

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

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

Keywords GIP · GLP-1 · Incretin hormones

Abbreviations

CNS Central nervous system
DPP-4 Dipeptidyl peptidase IV
GIP Glucose-dependent insulinotropic polypeptide
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>

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. Meier¹ · Michael A. Nauck¹

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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

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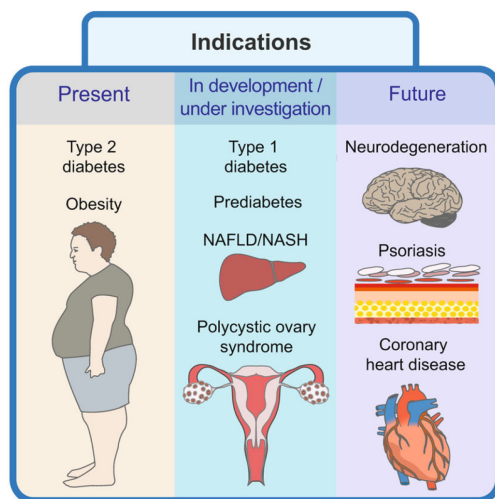
Keywords

GLP-1
DPP-4
GIP
GLP-1
IFG
IGT
Impa
PYY

Where are we

The development of unique 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

incretin hormone (GIP) and glucagon-like peptide-1 (GLP-1) [1]. These peptide hormones were later synthesised and prepared for in-



Changting Xiao,¹ Satya Dash,¹ Cecilia Morganti,² Khosrow Adeli,² and Gary F. Lewis¹

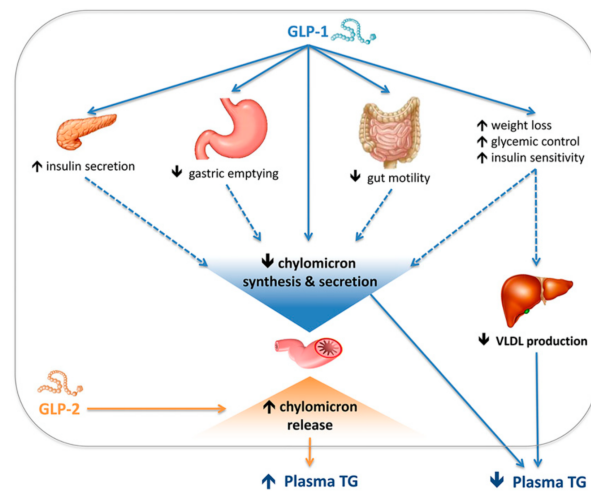


Gut Peptides Are Novel Regulators of Intestinal Lipoprotein Secretion: Experimental and Pharmacological Manipulation of Lipoprotein Metabolism

Diabetologia 2015;64:2310–2318 | DOI: 10.2337/d014-1708

Individuals with metabolic syndrome and type 2 diabetes are at increased risk of atherosclerotic vascular disease, partially due to the presence and lipoprotein abnormalities. In these conditions liver and intestine overproduce lipoprotein exacerbating the hyperlipidaemia of fasting a prandial states. Incretin-based, antidiabetic (i.e., glucagon-like peptide [GLP]-1 receptor and dipeptidyl peptidase-4 inhibitors) have proven efficacy for the treatment of hyperglycaemia. By accumulating that these agents also improve and postprandial lipemia, the latter more significant than the former. In contrast, the gut-derived GLP-2, cosecreted from intestinal L cells, 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 provide opportunities for devising novel strategies to hyperlipidaemia, with the potential for cardiovascular disease reduction.

Individuals with metabolic syndrome and type 2 diabetes (T2D) are at increased risk for cardiovascular disease (CVD) contributed to by the atherogenic dyslipidaemia that frequently accompanies these conditions. The typical lipid abnormalities in these conditions include elevated plasma triglycerides (TG),



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



**GI-side effects, expensive

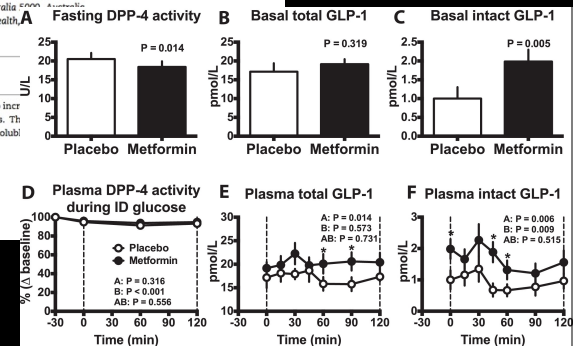
Mechanism of increase in plasma intact GLP-1 by metformin in type 2 diabetes: Stimulation of GLP-1 secretion or reduction in plasma DPP-4 activity?

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,*}

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

ABSTRACT

Metformin was not effective at reducing insulin concentrations in type 2 diabetes. However, it did reduce insulin secretion. A reduced contribution.

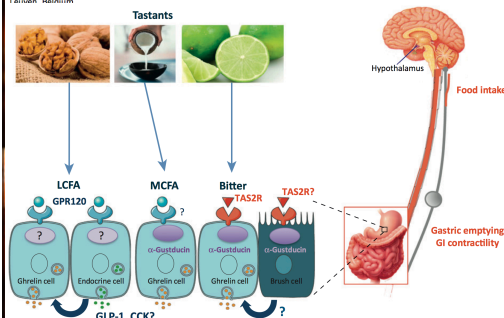


Special Issue: Neuroendocrine control of appetite

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

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

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

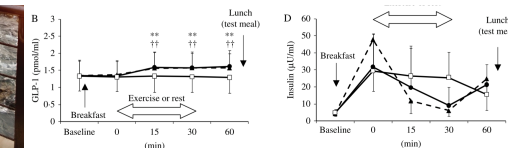
Department of Sports Medicine, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan
(Correspondence should be addressed to T Yoshikawa; Email: tkhr6719@med.osaka-cu.ac.jp)

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 YY₃₋₆ (PYY₃₋₆) 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 $\pm$ S.D., age: 23.4 $\pm$ 4.3 years, body mass index: 22.5 $\pm$ 1.0 kg/m², and maximum oxygen uptake (VO_{2max}): 45.1 $\pm$ 8.5 ml/kg per minute) received a standardized breakfast, followed by a 60-min bout of moderate intensity exercise (50% VO_{2max}, high intensity exercise, 50% VO_{2max} (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 exercise sessions for measurements of glucose, insulin, PYY₃₋₃₆, and GLP-1, which includes GLP-1 (7-36) and insulin (GLP-1 (9-36)amide. Increases in blood PYY₃₋₃₆ were dependent on 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>

ARTICLE INFO

ABSTRACT

The physiological control of appetite regulation involves circulating hormones with orexigenic (appetite-stimulating) and anorexigenic (appetite-inhibiting) properties that induce alterations in energy intake via perceptions of hunger and satiety. As the effectiveness of exercise to induce weight loss is a controversial topic, there is considerable interest in the effect of exercise on the appetite-regulating hormones such as acylated ghrelin, peptide YY (PYY), glucagon-like peptide-1 (GLP-1) and pancreatic polypeptide (PP). Research to date suggests short-term appetite regulation following a single exercise session in PYY, GLP-1, and PP. Further, this effort to guide future research, it is variations of these appetite-regulating hormones, sympathetic nervous system activity, insulin, lactate production, and changes in research suggests blood redistribution, SNS activity, and muscle of PYY and GLP-1. Overall, changes in appetite signals and greater stimulation of exercise-induced responses in appetite. A better understanding of how exercise life stages will be a powerful tool in

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"...changes in appetite-regulating (gut) hormones following acute exercise appear to be **intensity-dependent, with increasing intensity leading to a greater suppression of orexigenic signals** and greater stimulation of anorexigenic signals."

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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

Yong Zhu^{a1}, Walter H. Hsu^{a2} and James H. Hollis^{a1 c1}

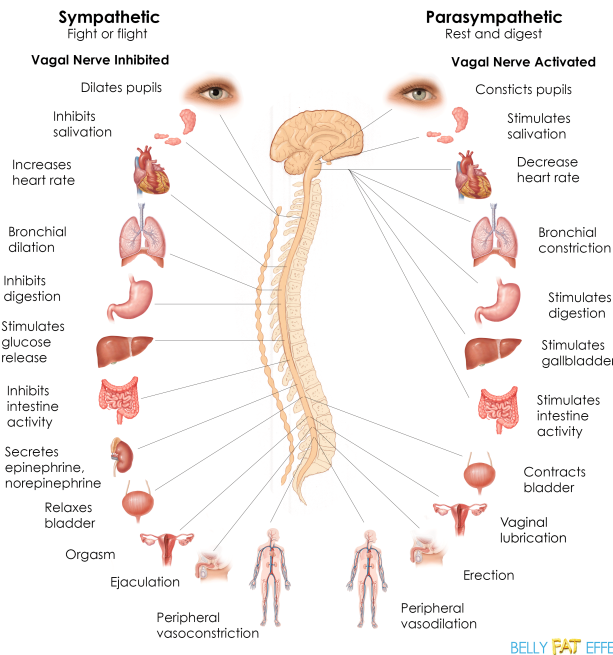
^{a1} Department of Food Science and Human Nutrition, Iowa State University, Ames, IA 50011, USA

^{a2} Department of Biomedical Sciences, Iowa State University, Ames, IA 50011, USA

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



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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

^a Wrigley (Mars Inc.), 1132 West Blackhawk Street, Chicago, IL 60642, USA

^b V&M Nutrition, 1 Rue Claude Daviges, 63100 Clermont-Ferrand, France

^c Nutrition Department, University of California, Davis, 3135 Meyer Hall, One Shields Avenue, Davis, CA 95616-5270, USA

^d School of Psychology, University of Leeds, Leeds LS2 9JT, United Kingdom

Reference	Participants N BMI	Intervention Design	Results 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 ($p=0.055$) 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 <i>ad libitum</i> 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. <https://doi.org/10.1016/j.physbeh.2015.07.017>

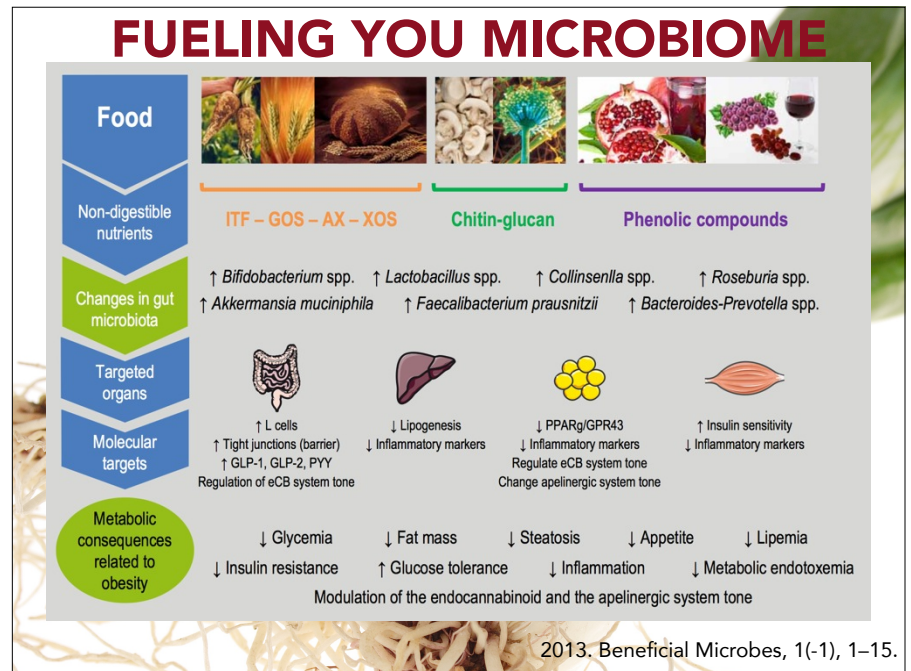
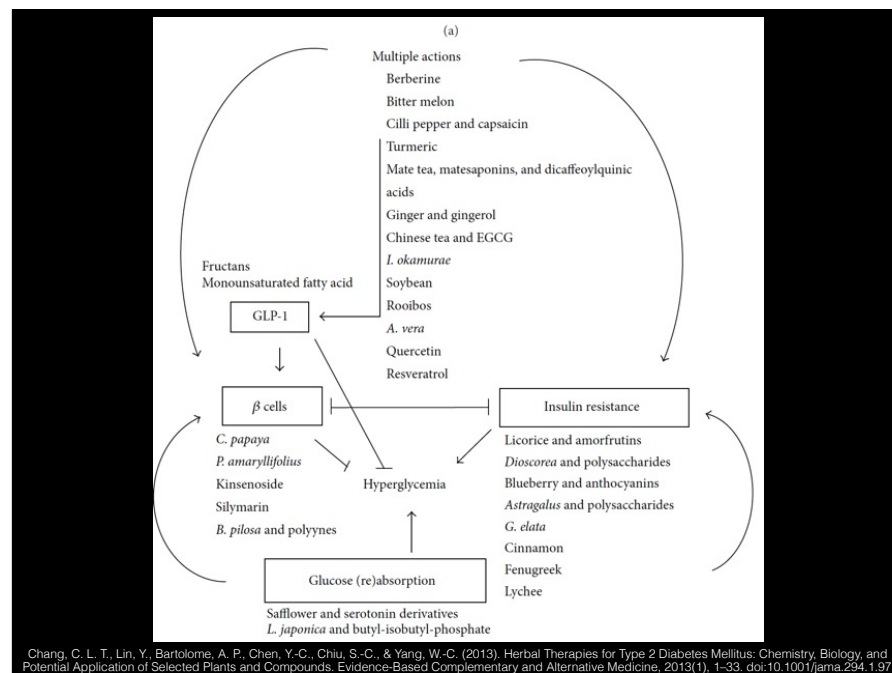


Table 1. Effects of polyphenols on neuropeptides/neurohormones that may have an effect on the central nervous system in obesity			
Polyphenol	Neuropeptide	Observed results	References
Cinnamon polyphenol	Insulin	Improved insulin sensitivity in subjects with type-2 diabetes, metabolic syndrome, and in women with PCOS; anti-oxidant effects in obese subjects; improves insulin sensitivity in an animal model of metabolic syndrome; Increased postprandial serum GLP-1 in healthy subjects (Hsieh et al. 2009)	[6, 124–127]
Curcumin	GLP-1	Increases IGF-1 levels in the rat brain in an animal model of insulin resistance	[128]
Resveratrol	NPY, AgRP	Downregulation of NPY and AgRP activities in N29-4 mouse hypothalamic cells	[129]
	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 lemur without affecting insulin secretion; improved insulin tolerance in KK(Ay) insulin-resistant mice	[131–134]
Grape-seed Extract	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]
	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 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	Attenuated 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 acetylated 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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Resveratrol Increases Glucose Induced GLP-1 Secretion in Mice: A Mechanism which Contributes to the Glycemic Control

Thi-Mai Anh Dao^{1,2,3}, Aurélie Waget^{1,2}, Pascale Klopp^{1,2}, Matteo Serino^{1,2}, Christelle Vachoux^{1,2}, Laurent Pechere⁴, Daniel J. Drucker⁵, Serge Champion³, Sylvain Barthélemy⁶, Yves Barra³, Rémy Burcelin^{1,2*}, Eric Séré^{3*}

1 Institut National de la Santé et de la Recherche Médicale U1048, Institut de recherche sur les Maladies Métaboliques et Cardiovasculaires, I2MC, Toulouse, France, **2** Université de Toulouse, UPS, Institut des Maladies Métaboliques et Cardiovasculaires (I2MC), Hôpital de Rangueil, Toulouse, France, **3** Institut National de la Recherche Agronomique 1260, Faculté de Pharmacie, Marseille, France, **4** ENTERONOVIA SAS, Incubateur Midi-Pyrénées, Toulouse, France, **5** Department of Medicine, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada, **6** VERRY SARL, Marseille, France

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 peptide-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-M, 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 Barthélemy have a duality of interest with ENTERONOVIA and VERRY Cosmetics, because they are employed by the above mentioned companies. Rémy Burcelin and Eric Séré have a duality of interest with ENTERONOVIA as they have a consultancy mission. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

* E-mail: remy.burcelin@inserm.fr (RB); eric.sere@univmed.fr (ES)

Meet Berberine

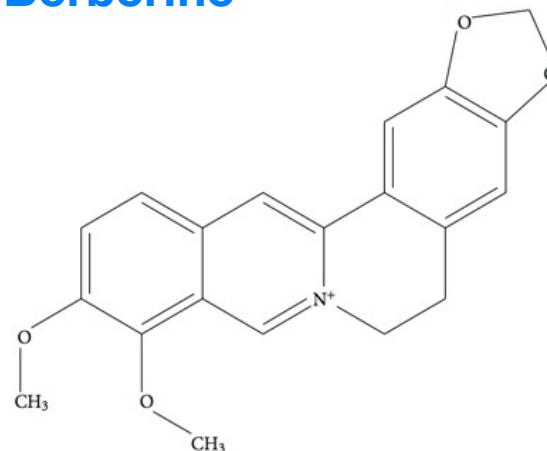


FIGURE 1: Chemical structure of berberine.

Yu, Y., Liu, L., Wang, 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

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

Background: “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 groups before and at 30 min, 60 min and 120 min after oral glucose as like peptide-1 (GLP-1) levels were increased in the berberine-treated group. 2112 genes with significantly changed expression (780 increased, 1332 decreased) that all differentially expressed genes included 9 KEGG pathways. The top pathway and the GnRH signaling pathway, Q-RT-PCR and immunohistochemistry (IHC) showed that the GnRH receptor (GnRH-R) and mitogen activated protein kinase 10 (Mapk10) were significantly up-regulated, in contrast, gonadotropin releasing hormone receptor (GnRH-R) 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

Absorption??



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

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Berberine
Glucagon-like
Prohormone
Proglucagon
Protein kinase

ABSTRACTS

Glucagon-like peptide (GLP)-1 is a potent glucose-dependent insulinotropic gut hormone released from intestinal L cells. Our previous studies showed that berberine increased GLP-1 secretion in streptozotocin-induced diabetic rats. The aim of this study was to investigate whether berberine

“The main finding in the present study was that berberine modulated GLP-1 release and biosynthesis...”

modulated 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 including PKC-dependent pathway were involved in this process. Elucidation of mechanisms controlling berberine-mediated GLP-1 secretion may facilitate the understanding of berberine's antidiabetic effects.

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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 Puer Lu¹

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

Correspondence should be addressed to Hui Dong, tjdonghui@163.com and Puer Lu, felu@tjh.tjmu.edu.cn

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“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

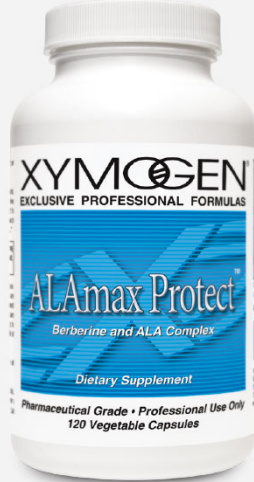
adverse effects limit their widespread use in clinical practice [4].

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 modifications 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].

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		
	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	Transient gastrointestinal adverse effects. No liver or kidney damage	[14]
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		



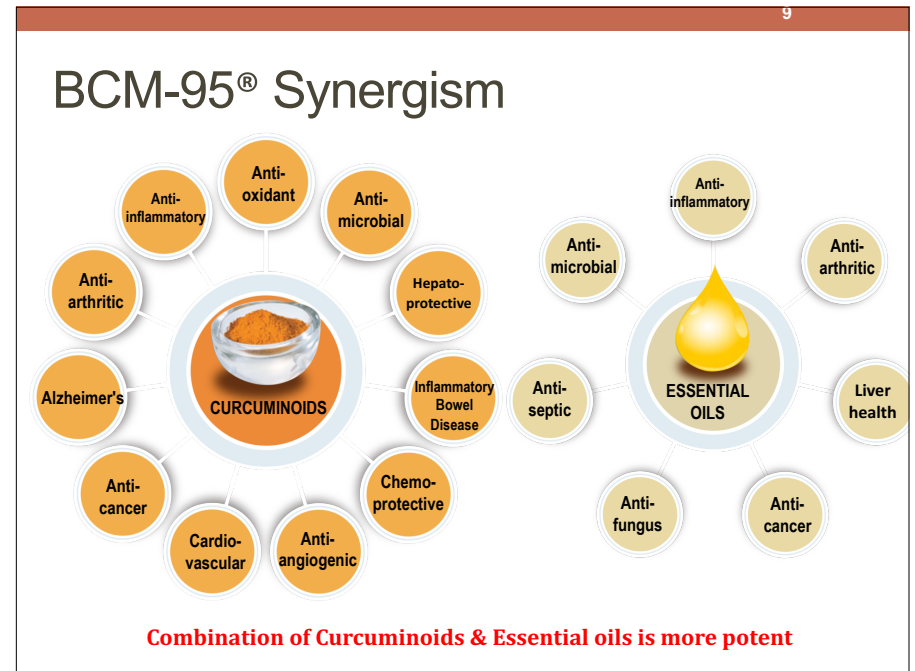


ALAmax™ Protect Supplement Facts
Serving Size: 2 Capsules

	Amount Per Serving	%Daily Value
Berberine HCl	500 mg	**
Alpha-Lipoic Acid	250 mg	**

** Daily Value not established.

Other Ingredients: HPMC (capsule), ascorbyl palmitate, L-leucine, silica, and medium-chain triglyceride oil.



Synergism in study

“

binding activity. These results indicate that both curcuminoids and sesquiterpenoids in turmeric exhibit hypoglycemic effects via PPAR-gamma activation as one of the mechanisms, and suggest that **E-ext including curcuminoids and sesquiterpenoids has the additive or synergistic effects of both components.**

Nishiyama T, et al. J. Agric. Food Chem. 2005.

(DSS)-induced shortening of the large bowel by 52–58%. We also evaluated the chemopreventive effects of oral feeding of TUR, CUR, and their combinations using a model of dimethylhydrazine-initiated and DSS-promoted mouse colon carcinogenesis. At the low dose, TUR markedly suppressed adenoma multiplicity by 73%, while CUR at both doses suppressed adenocarcinoma multiplicity by 63–69%. **Interestingly, the combination of CUR and TUR at both low and high doses abolished tumor formation.** Collectively, our results led to our

Murakami A, et al. Biofactors. 2012

In conclusion, despite the fact that the antileishmanial activity of curcuminoids has been extensively studied by various laboratories worldwide, **the results reported here highlight the positive influence of the volatile constituents (enriched in turmerones) not hitherto associated with antileishmanial activity, reinforcing the scientific evidence of *C. longa* as the botanic species of the century.** In addition, the incorporation of the hexane fractions into liposomes

Amaral AF, et al. BioMed Res Int. 2014

”

Why BCM-95® is more bioavailable

- Turmerones - fragrant constituent of turmeric **usually discarded**
- In BCM-95 as a mixed spectrum – AR (aromatic), α , etc.
- Turmerones increased curcumin absorption in independent study (Yue et al, 2012)
 - Statistically significant increases of curcumin + turmerones inside Caco-2 cells
 - Relative increase in curcumin + turmerones on basolateral surface of Caco-2 cells

Table 3.

Amount of Curcumin Measured Before and After Transport Experiments

Measured curcumin amount (μ g)	Experiment A		Experiment B	
	Curcumin	Curcumin+turmerones	Curcumin	Curcumin+turmerones
Apical (before)	1.90 $\pm$ 0.48	0.67 $\pm$ 0.076	0.60 $\pm$ 0.071	0.60 $\pm$ 0.12
Basolateral (after)	0.028 $\pm$ 0.012	0.030 $\pm$ 0.010 _*	0.025 $\pm$ 0.015	0.035 $\pm$ 0.013 _*
Inside cells (after)	0.032 $\pm$ 0.0052	0.044 $\pm$ 0.0080 _*	0.042 $\pm$ 0.010	0.068 $\pm$ 0.024 _*

- Human PK study finds BCM-95 bioavailable (Antony B, 2008)
 - Found “free” in plasma at 7X the standard unformulated curcumin ($p < 0.05$)
 - Initial peak at 1 hour (vs. 2.5 hours*) and maximum at 4.5 hours
 - Residual curcumin in blood at 8 hours post intake (vs. 4.5 hours*)

Table 5. Human trials reporting pharmacokinetic parameters for curcumin formulations aimed at enhancing curcumin bioavailability

Study population	Dosage form	Product name	No. of subjects	Dose (g)	$T_{max}^{a,b}$ (h)	C_{max} (nmol/L)	AUC (nmol/L $\times$ h)	CUR analysis	Urinary excretion	Ref.
Single oral dose experiments										
Healthy subjects	Capsules of pure curcumin powder combined with 0.02 g of pure piperine powder		10	2	0.75	489 $\pm$ 434	217 $\pm$ 27	Free curcumin ^b	n. d.	[28]
Healthy subjects	Capsules of curcumin with turmeric essential oils	BCM-95™ "BioCurcuma™"	11	2	3	1240	8690	Free curcumin	n. d.	[37]
Healthy subjects	Capsules of solid lipid nanoparticles of which, curcumin		6	0.65	2 $\pm$ 0.4	61 $\pm$ 5	484 $\pm$ 74	Free curcumin	n. d.	[41]
Healthy subjects	Capsules of a phosphatidylcholine complex		9	0.209	4 $\pm$ 0.8	66 $\pm$ 16	740 $\pm$ 186	Total curcumin ^c	n. d.	[38]
Healthy subjects	Submicron (nano) suspension in water		14	0.03	1	80 $\pm$ 35	307 $\pm$ 166	Total curcumin	n. d.	[39]
Healthy subjects	Capsules of a submicron (nano) suspension		6	0.15	4	513 $\pm$ 130	7 $\pm$ 950	Total curcumin	n. d.	[40]
Patients with osteosarcoma	Capsules of solid lipid nanoparticle of which, curcumin >60%		11	2	4 $\pm$ 0.4	98 $\pm$ 11	513 $\pm$ 33	Free curcumin	n. d.	[41]
				3	2 $\pm$ 0.2	85 $\pm$ 16	819 $\pm$ 113			
				4	4 $\pm$ 1.6	111 $\pm$ 24	1017 $\pm$ 74			

a) AUC, area under the blood concentration-time curve; C_{max} , maximum blood concentration; CUR, curcumin; n. d., not detected; T_{max} , time to reach maximum blood concentration.
b) Free curcumin concentrations were quantified by extraction of the analyte without prior enzymatic hydrolysis of conjugates with β -glucuronidase/sulfatase.
c) Total curcumin concentrations were quantified by extraction of the analyte after prior enzymatic hydrolysis of conjugates with β -glucuronidase/sulfatase.



CurcuPlex-95™ Supplement Facts

Serving Size: 1 Capsule

	Amount Per Serving	%DV
BCM-95® Turmeric Extract (<i>Curcuma longa</i>) (rhizome) (95% total curcuminoids complex, including curcumin, curcuminoids, and volatile oils) (86% curcuminoids)(65% curcumin)	500 mg	**

** Daily Value (DV) not established.

Other Ingredients: HPMC (capsule), dicalcium phosphate, ascorbyl palmitate, silica, and carboxymethyl cellulose.
BCM-95® is a registered trademark of DoiCas Biotech, Ltd. Protected under US patents 7,883,728; 7,736,679; and 7,879,373.



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

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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 insulintropic 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 polydiptidases 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.

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.”

BACKGROUND

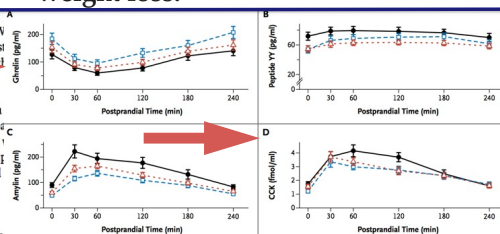
After weight loss, changes in the circulating levels of several hormones involved in the homeostatic regulation of body weight occur. Whether these changes are transient or persist over time may be important for an understanding of the high rate of weight regain after diet-induced weight loss.

METHODS

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

RESULTS

Weight loss (mean $\pm$ SE, 13.5 $\pm$ 0.5 kg) led to significant reductions in levels of 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

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WJG

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

Minoru Ito, Takumi Kawaguchi, Eitaro Taniguchi, Michio Sata

Minoru Ito, Eitaro Taniguchi, Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume 830-0011, Japan
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: Ito 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. takumik@med.kurume-u.ac.jp
Telephone: +81-942-317902 Fax: +81-942-317820
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Published online: April 21, 2013

peptic effects of a DPP-4 inhibitor.

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Key words: Incretin; Viral hepatitis; Insulin resistance; Steatohepatitis; Glipitin; Teneilipitin

Core tip: Dipeptidyl peptidase-4 (DPP-4) is a widely distributed, organ-expressed, pleiotropic enzyme. In this review, we describe the biological effects and the impact of DPP-4 in therapeutic effects.

Binding to ECM
Inhibition or promotion of cell migration and invasion

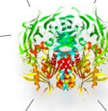
Degradation of ECM
Degradation of type IV collagen
Activation of MMPs

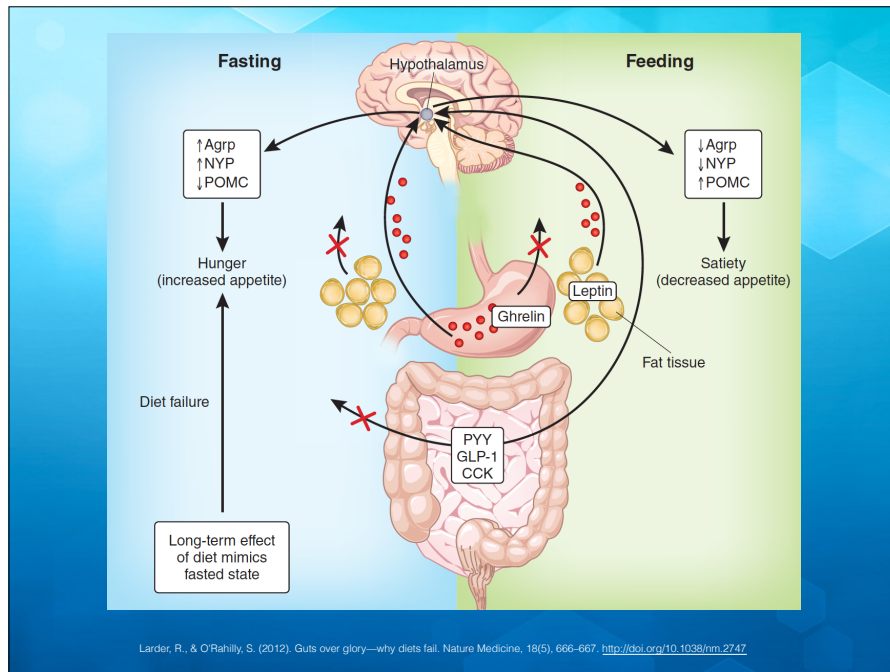
Biological activities of DPP-4

Immune stimulation
T-cell proliferation
Immune globulin production
IL-2 and IFN- γ secretion

Resistant to anti-cancer agents
High topoisomerase II α level

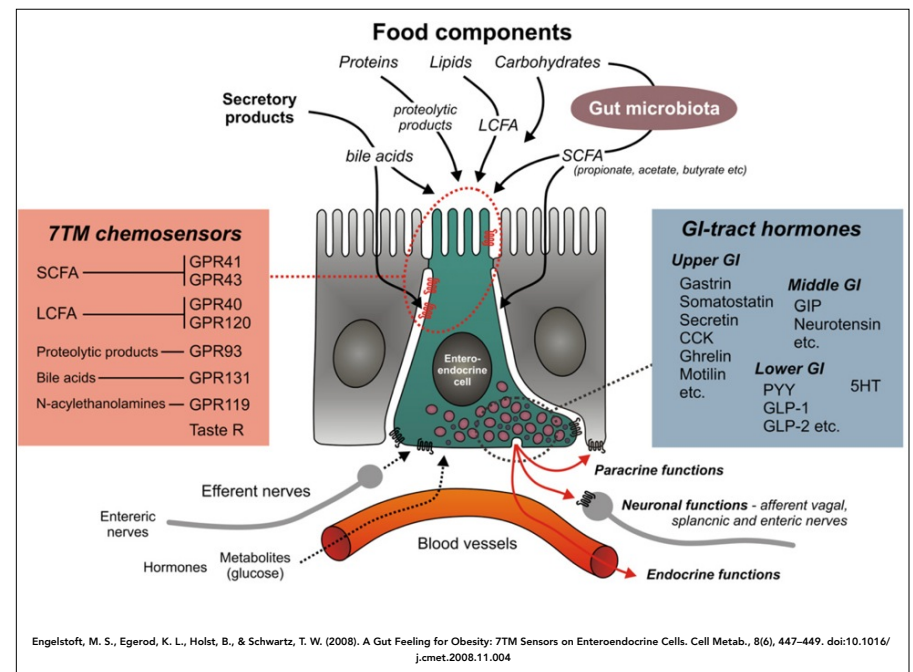
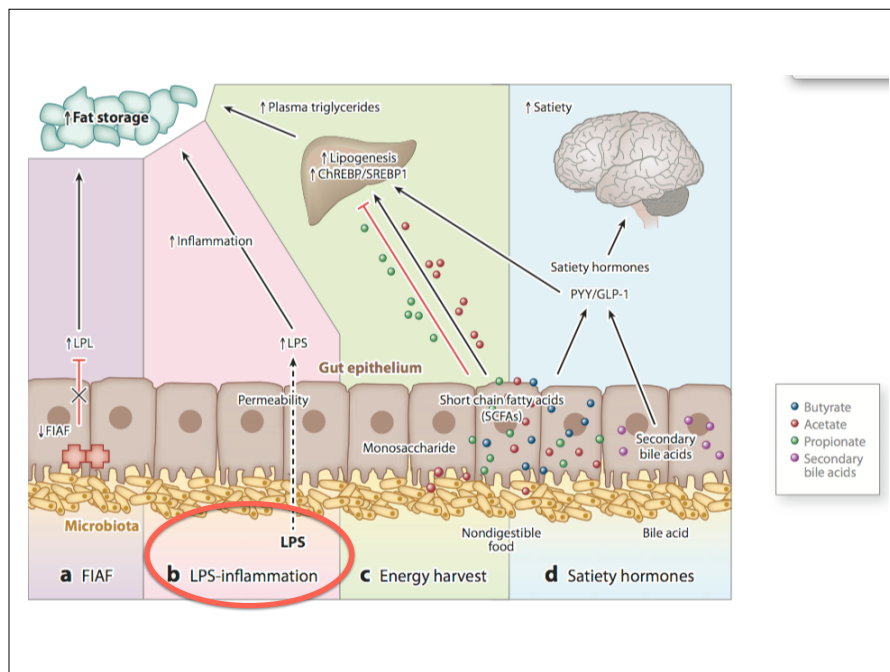
Lipid accumulation
Inactivation of PPAR α
Activation of SREBP-1c

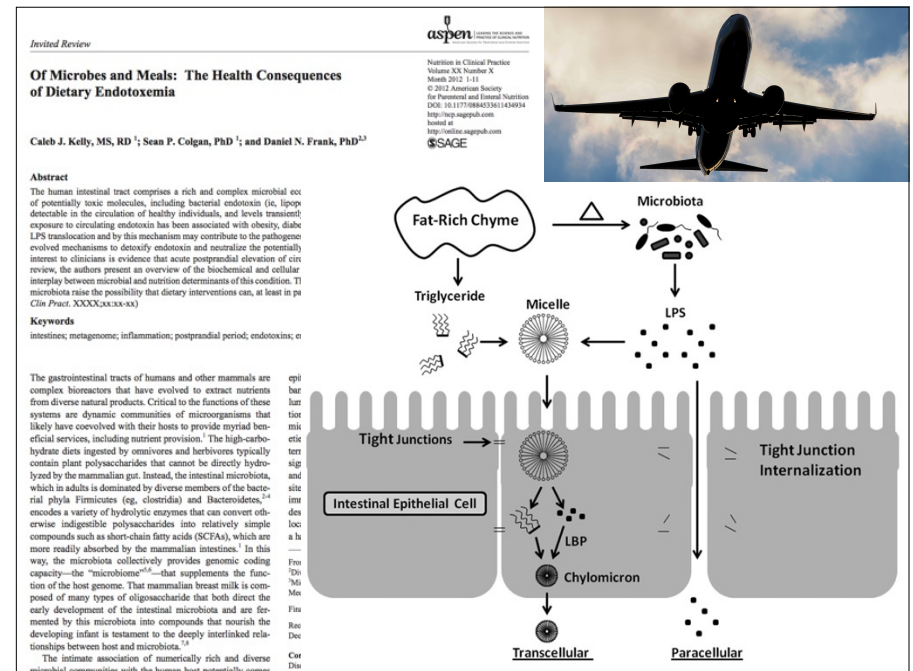
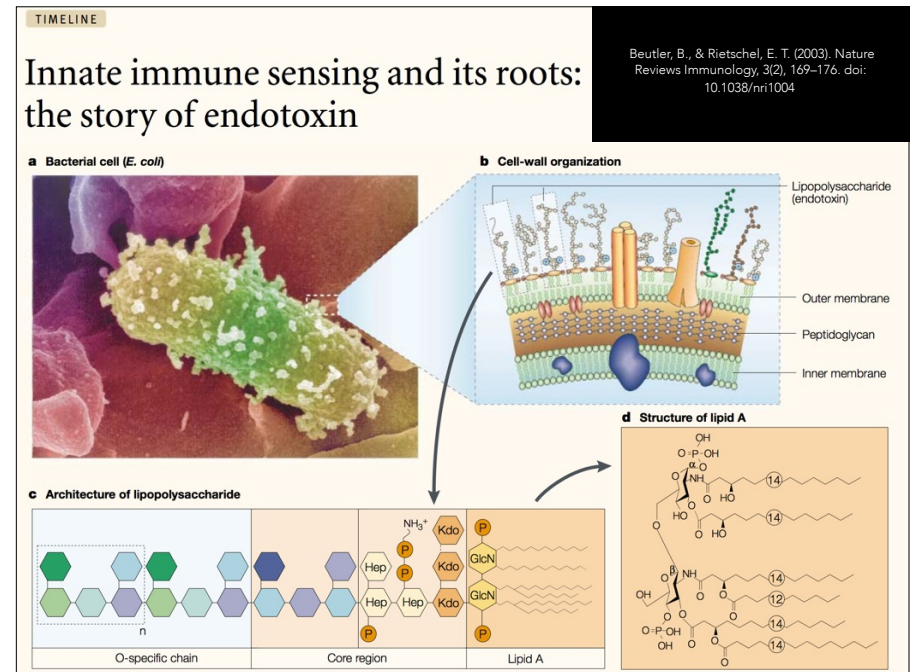
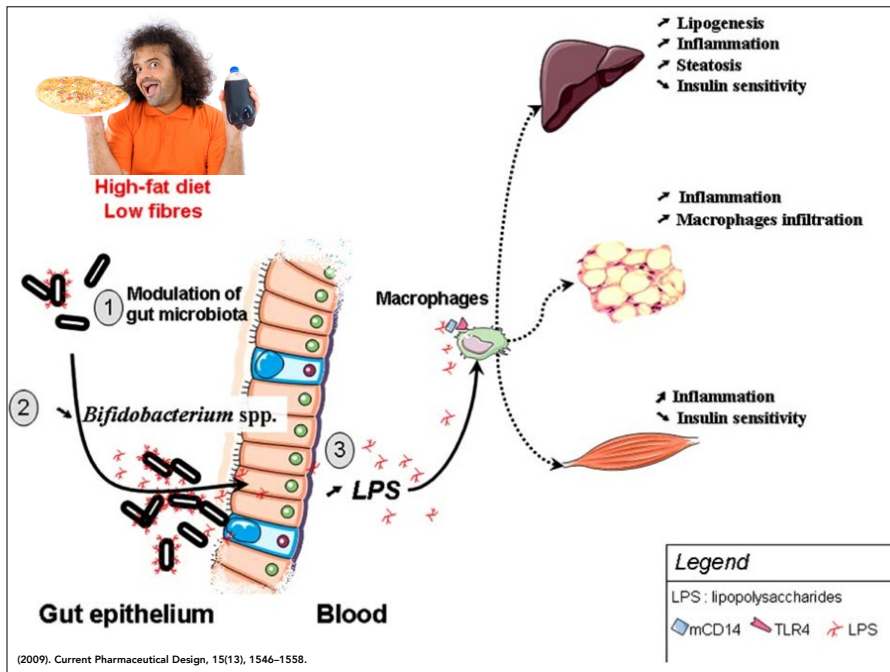




Summary of Gut Hormones

- 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 and Curcumin) increase gut hormone release





SHORT COMMUNICATION

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

Na Fei¹ and Liping Zhao^{1,2}

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

[illegible]

The role of gut microbiota in the pathogenesis of obesity has emerged into an important research area [Blackard et al. 2004]. Gut microbiota and 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].

Epidemiological studies show increased colonization 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 58.6 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

Correspondence: L. Zhao, State Key Laboratory of Systems Biomedicine, Shanghai Centre for Systems Biomedicine, Shanghai Jiao Tong University, Room 3-517, Biology Building, 800 Dongchuan Road, Minhang Campus, Shanghai 200240, China. E-mail: lyzhao3517@gmail.com or lyzhao@sjtu.edu.cn
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endotoxemia in obese and diabetic

R Barclay³, AA Darboe², H Mark², OA Nyan⁴ and AM Prentice^{1,2}

models suggests that translocation of bacterial debris across a leaky gut may trigger insulin resistance. The current study set out to investigate this phenomenon, termed ruitd 93 age-matched middle-aged urban Gambian women into three groups: lean base non-diabetic (BMI: $\leq 30.0 \text{ kg m}^{-2}$) and obese diabetic (BMI: $\geq 30.0 \text{ kg m}^{-2}$ and rum bacterial lipopolysaccharide (LPS) and endotoxin-core IgM and IgG antibodies re and interleukin-6 (IL-6) as a marker of inflammation. nity and positively associated with both obesity and diabetes ($F = 12.7, P < 0.001$). LPS ty compared with the other two groups ($F = 4.4, P < 0.02$). IgM EndoAcAb [but not total base (55% of lean value) and obese diabetic women (30% of lean; $F = 21.7, P < 0.0001$

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
slic endotoxemia; The Gambia

microbiota from obese animals results in adiposity in those who are born germ-free.¹ One suggested mechanism is through a more efficient energy harvest.² An alternative evidence suggests that the gut microbiota of obese animals may be able to degrade separate membrane. Bacterial lipopolysaccharide (LPS), also known as endotoxin, is released from the surface of the bacteria in the gut and under conditions of gut damage can translocate into the circulation (as can whole bacteria where it triggers a systemic inflammatory response).³ In fact, several studies in colleagues have demonstrated that exposure to a high-fat diet induces systemic endotoxin concentration, a phenomenon they termed 'metabolic endotoxemia'.⁴ In fact, endotoxin levels were higher than those observed in septic shock.⁵ In addition, mice infused with similarly low levels of LPS demonstrated raised glucose intolerance and insulin resistance.⁶

Few studies have investigated the association between endotoxemia and obesity in humans. A study in Saudi Arabian adolescents found that endotoxemia was associated with insulin resistance and various components of the metabolic syndrome.⁷ However, another study in healthy French men reported a positive association between endotoxemia and obesity.⁸

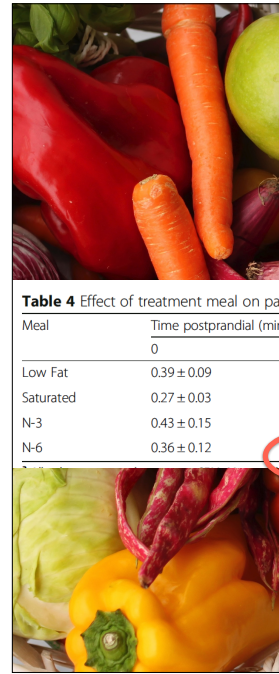
The inner-core of LPS molecules is relatively conserved across species and antibodies to this are therefore cross-reactive.⁹

microbiota from obese animals results in adiposity, those who are born germ-free.¹⁰ One suggested mechanism is through a more efficient energy harvest. Additional evidence suggests that the microbiota influence metabolic disease through a separate mechanism. Bacterial lipopolysaccharide (LPS), also known as endotoxin, is produced by many bacteria that live in the gut and under conditions of gut damage can translocate into the circulation (as can whole bacteria) where it triggers a systemic inflammatory response.¹¹ In a recent study, our colleagues have demonstrated that exposure to a high-fat diet increases systemic endotoxin concentration, a phenomenon they suggest may be a mechanism by which diet-induced obesity is more than observed in leptic shock.¹² In addition, mice infused with similarly low levels of LPS demonstrate raised glucose tolerance and positive energy balance.¹³

Few studies have investigated the association between endotoxaemia and obesity in humans. A study in Saudi Arabian adolescents found that endotoxaemia was associated with several components of the metabolic syndrome,¹⁴ whereas another study in healthy French men reported a positive association between endotoxaemia and visceral adiposity.¹⁵

The inner-core of adipocytes to which is relatively preserved across species and conditions to these tissues.

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



RESEARCH



Postprandial serum endotoxin in healthy humans is modulated by dietary fat in a randomized, controlled, cross-over study

Joshua M. Lyte^{1,2,3*}, Nicholas K. Gabler² and James H. Hollis¹

Abstract

Table 4 Effect of treatment meal on participant postprandial serum endotoxin concentration over time^a

Meal	Time postprandial (minutes)					
	0	60	120	180	240	300
Low Fat	0.39 ± 0.09	0.45 ± 0.14	0.37 ± 0.10	0.28 ± 0.03	0.25 ± 0.02	0.32 ± 0.07
Saturated	0.27 ± 0.03	0.39 ± 0.11	0.51 ± 0.14	0.49 ± 0.11	0.31 ± 0.08	0.38 ± 0.20
N-3	0.43 ± 0.15	0.29 ± 0.07	0.26 ± 0.03	0.24 ± 0.02	0.26 ± 0.02	0.26 ± 0.02
N-6	0.36 ± 0.12	0.59 ± 0.20	0.46 ± 0.16	0.36 ± 0.09	0.24 ± 0.02	0.31 ± 0.09

participants were analyzed using repeated-measures ANCOVA.

Results: Participant serum endotoxin concentration was increased during the postprandial period after the consumption of the saturated fat meal but decreased after the n-3 meal ($p < .005$). The n-6 meal did not effect a different outcome in participant postprandial serum endotoxin concentration from that of the control meal ($p > .05$). There was no treatment meal effect on participant postprandial serum biomarkers of inflammation. Postprandial serum triacylglycerols were significantly elevated following the n-6 meal compared to the n-3 meal. Non-esterified fatty acids were significantly increased after consumption of the saturated fat meal compared to other treatment meals.

Conclusions: Meal fatty acid composition modulates postprandial serum endotoxin concentration in healthy adults. However, postprandial endotoxin was not associated with systemic inflammation *in vivo*.

Trial registration: This study was retrospectively registered at clinicaltrials.gov as NCT02521779 on July 28, 2015.

Keywords: Endotoxin, Lipopolysaccharide, Diet, Lipid, Fat, Oil, Inflammation



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**SHORT COMMUNICATION
INTERGATIVE PHY**

Intestinal Permeability Is Associated With Visceral Adiposity in Healthy Women

Anders Gummesson^{1,2}, Lena M.S. Carlsson¹, Len H. Storlien^{2,3}, Fredrik Bäckhed¹, Pål Lundin², Lars Löfgren², Kaj Stenlöf, Yan Y. Lam², Björn Fagerberg² and Björn Carlsson^{1,2}

Increased visceral fat, as opposed to subcutaneous/gluteal, most strongly relates to key metabolic dysfunction including insulin resistance, hepatic steatosis, and inflammation. Mesenteric fat hypertrophy in patients with Crohn's disease and in experimental rodent models of gut inflammation suggest that impaired gut barrier function may contribute to increased visceral adiposity.

ARTICLE IN PRESS

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ELSEVIER

Original article

Intestinal permeability parameters in obese patients are correlated with metabolic syndrome risk factors^{a,*}

Tatiana E.S. Teixeira^{a,*}, Nílian C.S. Souza^{b,e}, Paula G. Chiarello^{b,f}, Sylva C.C. Franceschini^{a,g}, Josefina Bressan^{a,h}, Célia L.L.F. Ferreira^{c,i}, Maria do Carmo G. Peluzio^{a,j}

^aUniversidade Federal de Viçosa, Departamento de Nutrição e Saúde, Avenida P.H. Rolfs, s/n, Campus Universitário, 35570-000 Viçosa Minas Gerais, Brazil
^bUniversidade de São Paulo, Departamento de Clínica Médica, Faculdade de Medicina de Ribeirão Preto, Av. Bandeirantes, 3900, 14048-900, Ribeirão Preto, São Paulo, Brazil
^cUniversidade Federal de Viçosa, Departamento de Tecnologia de Alimentos, Avenida P.H. Rolfs, s/n, Campus Universitário, 35570-000, Viçosa, Minas Gerais, Brazil

lipid deposition. The aim of this study was to evaluate the association between intestinal permeability and visceral adiposity in healthy humans. A cross-sectional cohort. Intestinal permeability was assessed by mannitol (S/M). In study 1 ($n = 67$), we found no association between S/M and visceral adiposity. In study 2, we found a positive correlation between S/M and visceral adiposity within a time frame of urine collection post-ingestion; $P = 0.022$. These results were confirmed in study 3, where we found a positive correlation between dual energy X-ray absorptiometry to measure visceral adiposity and total body fat of the same women ($r = 0.78$; $P < 0.0001$). There was no association between liver area ($P = 0.0003$) and liver fat content ($P = 0.0003$). Our findings suggest that there is an association between intestinal permeability and visceral adiposity, which may contribute to the development of metabolic syndrome. This relationship suggests that impaired gut barrier function could lead to increased visceral adiposity and subsequent metabolic dysfunction.

ized lipopolysaccharide stimulation induces endoplasmic reticulum stress and immunoglobulin receptor expression in adipocytes. These results suggest that similar interactions between the gastrointestinal tract and adipose tissue exist in humans, and may play a role in the pathogenesis of obesity. If this is confined to pathological conditions, it may have implications for the treatment of obesity. The aim of this study, therefore, was to investigate the relationship between intestinal permeability and visceral adiposity in healthy humans.

Circulating Zonulin, a Marker of Intestinal Permeability, Is Increased in Association with Obesity-Associated Insulin Resistance

José María Moreno-Navarrete, Mónica Sabater, Francisco Ortega, Wifredo Ricart, José Manuel Fernández-Real*

Department of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IDIBGI), CIBERONC (CB06/3-010) and Instituto de Salud Carlos III (ISCIII), Girona, Spain

Abstract

Zonulin is the only physiological mediator known to regulate intestinal permeability reversibly by modulating intercellular tight junctions. To investigate the relationship between intestinal permeability and obesity-associated metabolic disturbances in humans, we aimed to study circulating zonulin according to obesity and insulin resistance. Circulating zonulin (ELISA) was measured in 123 caucasian men in association with inflammatory and metabolic parameters including minimal model-measured insulin sensitivity. Circulating zonulin increased with body mass index (BMI), waist to hip ratio (WHR), fasting insulin, fasting triglycerides, uric acid and IL-6, and negatively correlated with HDL-cholesterol and insulin sensitivity. In multiple regression analysis, insulin sensitivity ($p < 0.002$) contributed independently to circulating zonulin variance, after controlling for the effects of BMI, fasting triglycerides and age. When circulating IL-6 was added to this model, only BMI ($p < 0.01$) contributed independently to circulating zonulin variance. In conclusion, the relationship between insulin sensitivity and circulating zonulin might be mediated through the obesity-related circulating IL-6 increase.

Table 1. Anthropometrical and biochemical parameters from the participants of the study.

	NGT	GI	P
N	82	41	
Age (years)	48.29±11.7	55.9±10.3	0.001
BMI (Kg/m²)	26.6±3.2	28.1±3.8	0.03
WHR	0.929±0.064	0.952±0.069	0.06
Fasting glucose (mg/dl)	92.9±7.3	101.15±10.47	<0.0001
Fasting insulin (mg/dl)	8.1±3.6	11.1±6.5	0.01
HbA1c (%)	4.78±0.32	4.9±0.42	0.1
Log IS (10⁻⁴ min⁻¹ mU per liter)	0.58±0.02	0.43±0.16	<0.0001
HDL-Cholesterol (mg/dl)	52.8±12.9	52.2±10.1	0.8
Fasting triglycerides (mg/dl)	83 (58.5–120.5)	100 (69.5–129)	0.5
Uric acid (mg/dl)	5.6±1.3	6.1±2.14	0.05
Circulating IL-6 (pg/ml)	1.22±1.1	1.37±0.9	0.4
Zonulin (ng/ml)	9.1±4.5	10.9±4.8	0.03

Dysbiosis of the **blood** linked with **heart disease**



LIPOPROTEINS BIND TO ENDOTOXIN

The role of HDL in innate immunity¹

Kenneth R. Feingold² and Carl Grunfeld

Metabolism Section, Department of Veterans Affairs Medical Center, University of California San Francisco, San Francisco, CA 94121

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

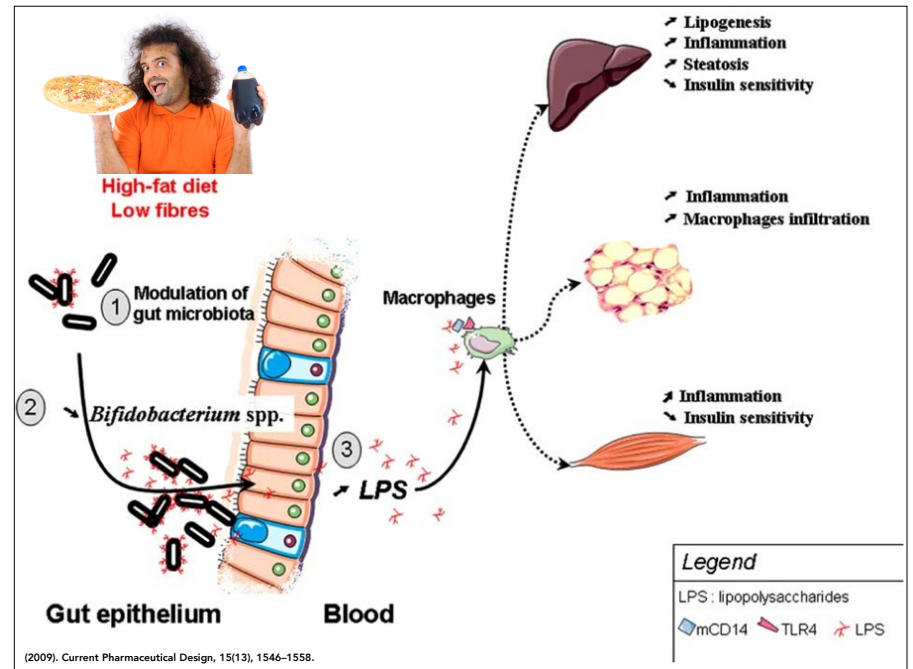
“Numerous studies have shown that **lipoproteins bind** to microorganisms or compounds derived from microbes...the majority of LPS and LTA are bound to HDL...inhibits the ability of LPS and LTA to interact with toll-like receptors (TLR).”

Similarly, several studies have shown that infusion of HDL or apolipoprotein A-I mimetic peptides into animals with experimental sepsis improves survival (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

EAT BETTER MEAT



BIFIDOBACTERIUM BASED PROBIOTICS

"Correlation between **endotoxin level** and **weight reduction** indicates that **probiotics** may play an important role in prevention of **endotoxin production**, which can lead to **gut microbiota dysbiosis** associated with **obesity**."

The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: A randomized double-blind controlled clinical trial. 2014. European Society for Clinical Nutrition and Metabolism

"Enteric coated fish oil
enhances gut barrier
function."

Belluzzi, A.(1996). N Engl J Med, 334(24), 1557-1560.
2013. The Journal of Clinical Endocrinology and Metabolism, 98(6), 2451.



Consumer Report

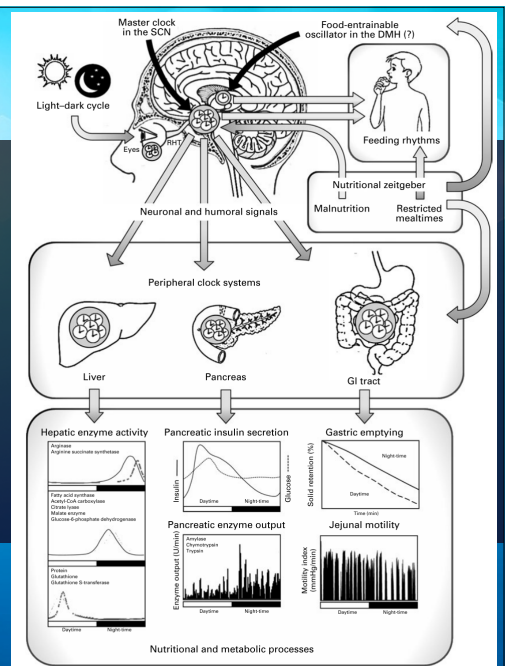
Product Name:	OmegaPure 900 EC™
Product Type:	Ultra Refined
Product Availability:	USA
Product Summary:	Xymogen OmegaPure 900 EC™ is a clean and highly concentrated omega-3 fish oil product. Each capsule contains a minimum 900 mg of omega-3 fatty acids EPA and DHA, as well as natural mixed tocopherols. This product receives a FIVE out of FIVE Star IFOS rating based on the following criteria: ★ Omega-3 Concentration Consistent with Label – YES ★ Passes IFOS Oxidation standards – YES ★ Passes IFOS PCB, PCDD/F standards – YES ★ Passes IFOS Heavy Metal standards – YES ★ Passes all IFOS testing categories – YES
Batch/Lot #:	028/14
Expiry Date:	07/2016
Recommended Daily Allowance:	1 softgel daily
Company Name:	Xymogen
Company Phone:	1-800-647-6100
Company Website:	http://www.xymogen.com

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KEY TAKEAWAYS

- ◆ Pancreatic section diminishes at night
- ◆ GI motility declines at night
- ◆ Fatty acid related enzymes increase at night



Cagampang, F. R., & Bruce, K. D. (2012). The role of the circadian clock system in nutrition and metabolism. British Journal of Nutrition, 108(03), 381-392. doi:10.1017/S0007114512002139

Danica F. Patton and Ralph E. Mistlberger*

Department of Psychology, Simon Fraser University, Burnaby, BC, Canada

Edited by:
Alfonso Abizaid, Carleton University,
Canada

Reviewed by:
Tatsushi Onaka, Jichi Medical
University, Japan
Elliott Albers, Georgia State
University, Georgia

*Correspondence:
Ralph E. Mistlberger, Department of
Psychology, Simon Fraser University,
8888 University Drive, Burnaby BC
V5A 1S6, Canada
e-mail: mistlber@sfu.ca

Circadian rhythms of behavior and physiology are generated by central and peripheral circadian oscillators embedded in periodic environmental or physiological stimuli. A master circadian pacemaker in the hypothalamic suprachiasmatic nucleus (SCN) is directly entrained by light and darkness, and in turn synchronizes peripheral oscillators by direct and indirect neural, hormonal and behavioral outputs. The daily rhythm of food intake provides stimuli that entrain most peripheral and central oscillators, some of which can drive a daily rhythm of food anticipatory activity if food is restricted to one daily meal. The daily rhythms of food intake and food anticipatory activity are driven by the rhythms, and the food-related stimuli that entrain these oscillators, remain to be clarified. Here, we critically examine the role of peripheral metabolic hormones as potential internal entrainment stimuli or outputs for PGCs controlling food anticipatory rhythms in rats and mice. We focus on the hormones leptin, ghrelin, insulin, glucagon-like peptide-1 (GLP-1), glucagon, and glucagon-like peptide-1X. All of these hormones exhibit daily rhythms of synthesis and secretion that are synchronized by meal timing. There is some evidence that ghrelin and leptin modulate the expression of food anticipatory rhythms, but none of the hormones has been shown to modulate the expression of food anticipatory rhythms. Leptin and GLP-1 may modulate food-entrained rhythms by actions in hypothalamic circuits influencing melatonin and orexin signaling, although again food-entrained behavioral rhythms can persist in the absence of these hormones.

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ensuring that biological activities, from gene expression to foraging behavior, occur in the right sequence and at the right time of day. Although daily light-dark (LD) cycles are considered to be the dominant environmental stimulus for synchronizing circadian oscillators to local time, for many circadian processes, it is the timing of food intake that is most important. In this review, we briefly outline the evidence that feeding patterns regulate circadian clocks in mammals. We then critically examine the role of metabolic and stress-related hormones in this process. An important objective for the purposes of this Frontiers Topic (neuroendocrine mechanisms that connect feeding behavior and stress) is to draw attention to chronobiological concepts that provide a framework for understanding how anything that can affect feeding behavior, including acute or chronic stress stimuli

was first revealed by studies of circadian activity rhythms in food-restricted rodents. Acute and chronic food restriction elicit well-known behavioral and physiological responses to maintain metabolic homeostasis. Acute deprivation recruits neural circuits that promote arousal and food seeking behavior. Chronic caloric restriction induces physiological adaptations to facilitate the extraction and storage of energy from ingested nutrients and to reduce energy expenditure. If caloric restriction is chronic and food availability is limited to a particular time of day, further adaptations can occur in the temporal regulation of metabolism and food seeking behavior. These adaptations involve entrainment of circadian clocks in the brain and in peripheral organs and tissues by stimuli associated with food intake.

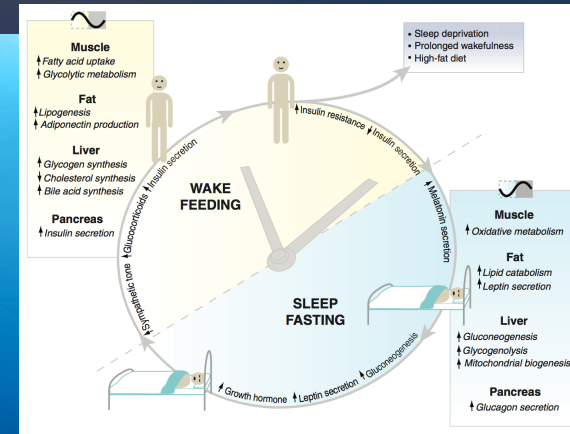
Physiology and behavior are regulated by circadian clocks

BIOLOGICAL TIME KEEPERS

“Circadian time-keeping coordinates cellular and physiological processes internally, and synchronizes these with daily cycles in the environment, ensuring that biological activities, from **gene expression** to foraging behavior, occur in the **right sequence** and at the **right time of day**

Patton, D. F., & Mistlberger, R. E. (2013). Circadian adaptations to meal timing:

CIRCADIAN CLOCK SYSTEM IN THE CONTEXT OF OPTIMAL **METABOLIC HEALTH**



Bass, J., & Takahashi, J. S. (2010). Circadian Integration of Metabolism and Energetics. *Science*, 330(6009), 1349–1354. doi:10.1126/science.1195027

NEUROSCIENCE FOREFRONT REVIEW
CHRONOBIOLOGY AND NUTRITION

Y. TAHARA AND S. SHIBATA*

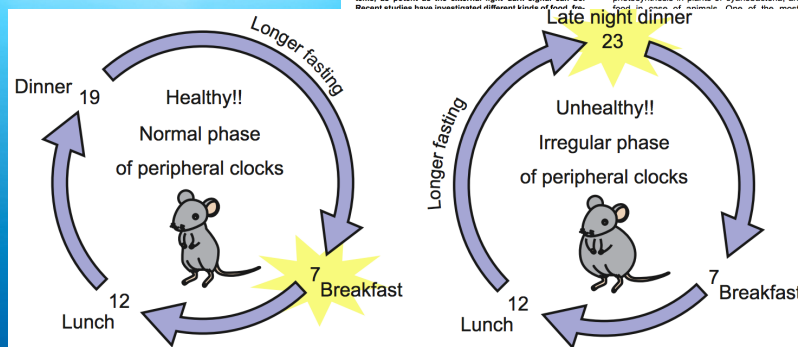
Laboratory of Physiology and Pharmacology, School of Advanced Science and Engineering, Waseda University Tokyo, Japan

Abstract—Numerous long-term studies have investigated the circadian clock system in mammals, which organizes physiological functions, including metabolism, digestion, and absorption of food, and energy expenditure. Food or nutrition can be a synchronizer for the circadian clock systems, as potent as the external light-dark signal can be. Recent studies have investigated different kinds of food, from

CIRCADIAN CLOCK SYSTEM

Circadian clock system in mammals

The circadian clock system has been widely maintained in many species, from prokaryotes to mammals. "Circadian" means "approximately day" in Latin, and therefore, "circadian rhythm" refers to the approximate 24-h cycles. The earth rotates once every 24-h, and our circadian system has been developed to adjust to this 24-h cycle to efficiently utilize sunlight for photosynthesis in plants or cyanobacteria, and to obtain food in cases of animals. One of the most important



Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; DMH, dorsomedial hypothalamus; FAA, food anticipatory activity; FEO, food entrainable oscillator; GluT2, glucose transporter 2; KO, knock-out; LHA, lateral hypothalamus; NAD, nicotinamide adenine dinucleotide; nNOS, neuronal nitric oxide synthase; PARP-1, Poly(ADP-ribose) polymerase 1; SCN, suprachiasmatic nucleus; Sglt1, sodium/glucose cotransporter 1; WT, wild type; ZT, Zeitgeber time.

transcriptional and translational regulations have, in recent years, been reported to serve important roles in maintaining circadian rhythms. Genome-wide RNA-seq and Chip-seq analyses found that only 22% of the rhythmically oscillating messenger RNAs are driven by

Tahara, Y., & Shibata, S. (2013). Chronobiology and nutrition. *Neuroscience*, 253, 78–88. doi:10.1016/j.neuroscience.2013.08.049

Keto + Time-Restricted Feeding Improves Sleep



With time restricted feeding I've experimented

Tahara, Y., & Shibata, S. (2013). Chronobiology and nutrition. *Neuroscience*, 253, 78–88. doi:10.1016/j.neuroscience.2013.08.049

Medical conditions may have been mentioned or implied in our discussion of the circadian clock.

It is important to remember that dietary supplements **CANNOT** mitigate diseases or replace drugs.

However, XYMOGEN products **CAN** give your patients their best chance to stay healthier longer*

* These statements have not been evaluated by the US Food and Drug Administration. These products are not intended to diagnose, treat, cure , or prevent any disease.

Time-Restricted Feeding

16/8 schedule

Benefits the microbiome and gut-hormones (as you're eating within your body's circadian rhythm)

Helps to induce nutritional ketosis

Enhances mitochondrial biogenesis

Time-Restricted Feeding

16/8 schedule

Benefits the microbiome and gut-hormones (as you're eating within your body's circadian rhythm)

Helps to induce nutritional ketosis

Enhances mitochondrial biogenesis

RelaxMax™ Wild Cherry



Supplement Facts

Serving Size: 1 Scoop (3.8 g)
Servings Per Container: 60

	Amount Per Serving	%Daily Value
Magnesium (as DiMagnesium Malate)	75 mg	19%
myo-Inositol	2 g	**
Taurine	500 mg	**
GABA (gamma-aminobutyric acid)	100 mg	**
L-Theanine (Suntheanine®)	50 mg	**

** Daily Value not established.

Other Ingredients: Natural cherry flavor (no MSG), malic acid, natural red beet powder, citric acid, and stevia.

Di-Magnesium Malate covered by Albion Laboratories, Inc. U.S. Patent 6,706,904 and patents pending.

Suntheanine® Suntheanine®: a patented form of L-Theanine, is a trademark of Taiyo International, Inc.

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Melatonin



Supplement Facts

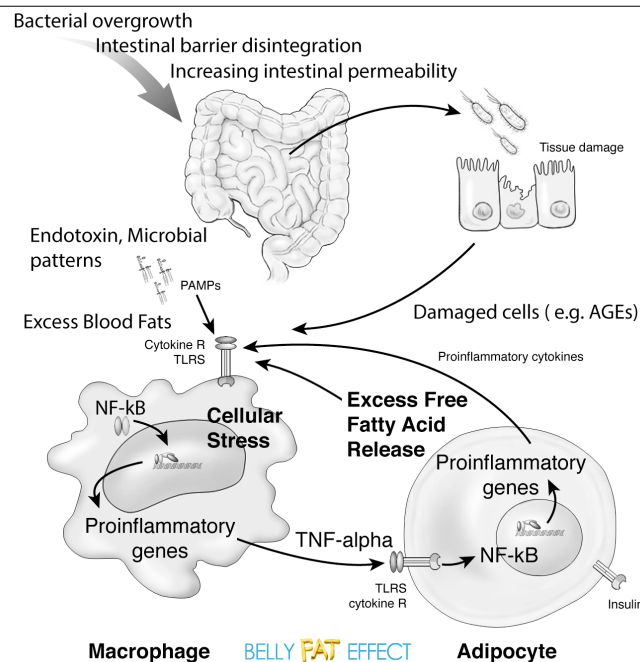
Serving Size: 1 Quick-Dissolve Tablet
Servings Per Container: 60

	Amount Per Serving	%Daily Value
Melatonin	3 mg	**

** Daily Value not established.

Other Ingredients: Xylitol, mannitol, stearic acid, silica, magnesium stearate, and natural peppermint flavor.

* These statements have not been evaluated by the Food and Drug Administration.



Gut microbiota fermentation of prebiotics increases satiety and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal¹⁻³

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

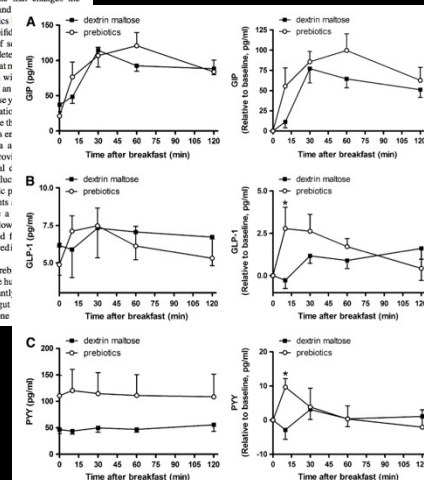
Background: We have previously shown that gut microbial fermentation of prebiotics promotes satiety and lowers hunger and energy intake in humans. In rodents, these effects are associated with an increase in plasma gut peptide concentrations, which are involved in appetite regulation and glucose homeostasis.

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 microdialysis 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 prebiotic or 16 g dextrin maltose 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 area 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 area 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 carbohydrates that changes the composition of gut microbiota and obesity and (4-8). These compounds are called prebiotics; promote the growth of certain bacteria (eg, bifid number correlates with an improvement of a metabolic syndrome (9). In the search to determine prebiotics in the control of body weight and fat in a recent study showed that supplementation with a significant benefit for the maintenance of a mass index and fat mass in primarily obese subjects in addition to its benefit in bone mineralization. Together, these human studies provide evidence that of gut microbiota by using prebiotics affects energy and body weight gain. However, few data on mechanisms involved in these effects are provided. Several results support the relevance of prebiotic in appetite management in healthy and obese subjects, few data are available that concomitantly influence 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 satiety 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