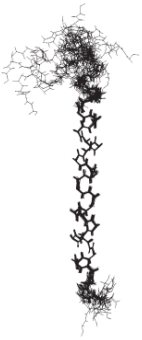
# The influence of (type and degree of) food processing on metabolic responses

By **Gábor Erdősi**

MSc, industrial starch processing expert

Presented at Food News 2018, Prague, 19th May

# Primary concepts

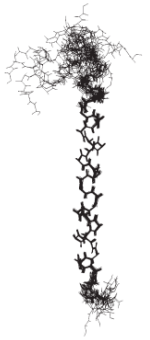


Speed and small intestinal location of food absorption largely determine metabolic outcomes. The presentation is arranged based on this principle.

When talking about food processing, an argument against its role is that ’processing’ cannot be properly defined. Another one that often comes up is that humans have been processing their food for hundreds of thousands years. Some of the main questions raised by this presentation therefore will be:

- Are all kinds of processing created equal?
- What has changed about processing over the last few hundred years or so, and do these changes have to do anything with the epidemic of metabolic diseases humanity is experiencing right now?

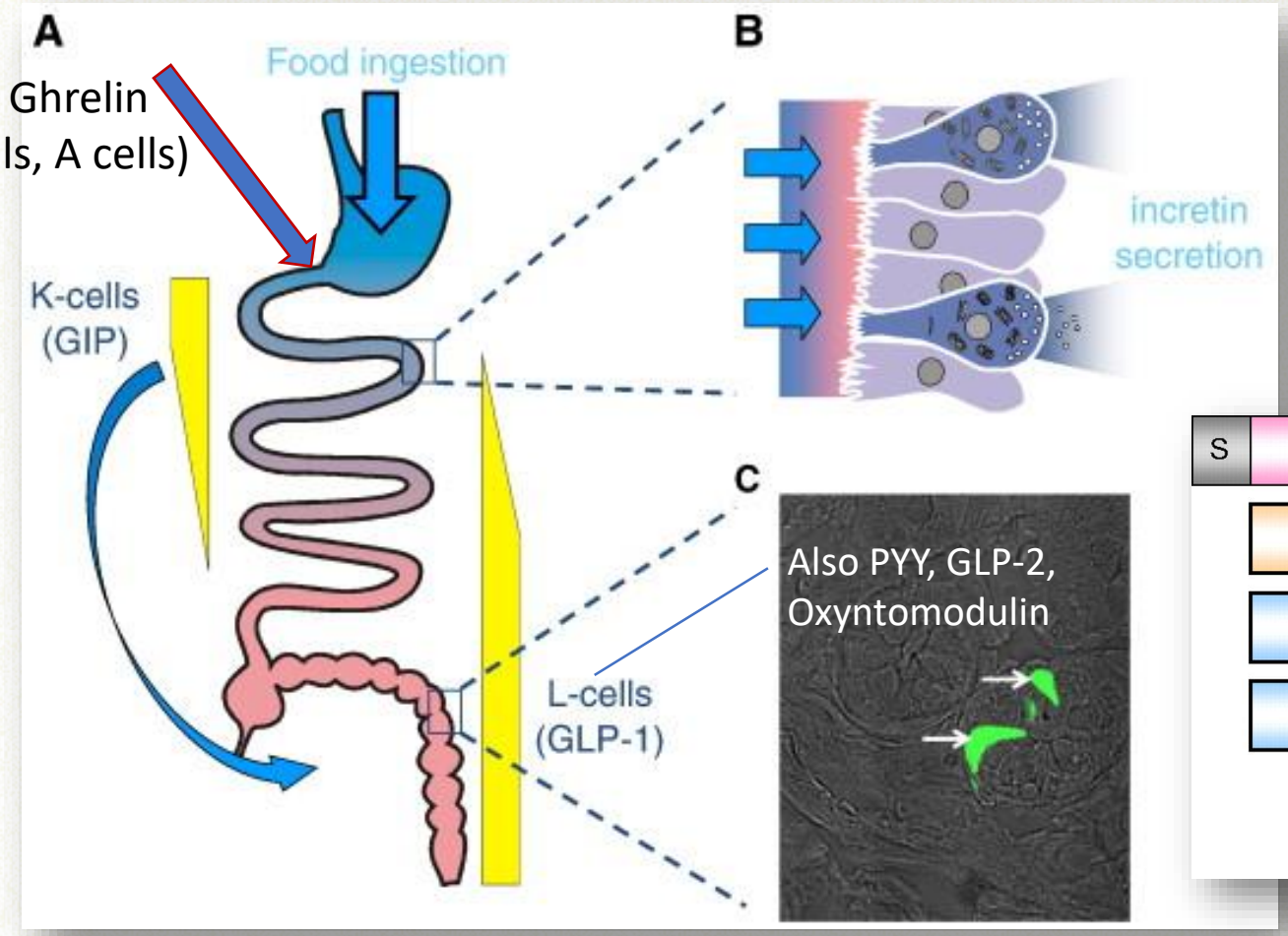
# Presentation outline



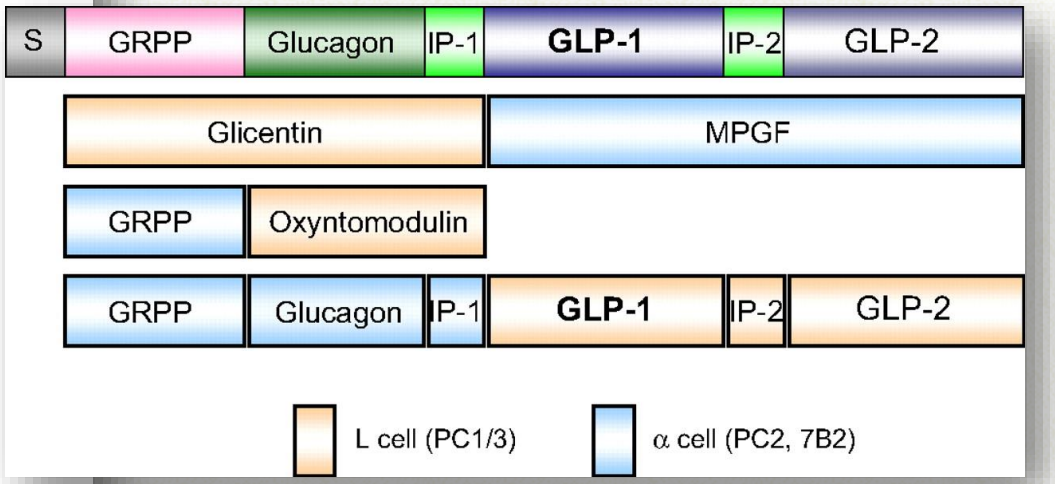
Within the boundaries of this presentations an attempt is made to

- Get a quick glimpse into recent advances in gastrointestinal physiology.
- Understand nutrient sensing, the incretin effect/actions, and hunger-satiety signaling in the gut.
- Briefly examine how processing of protein and fat rich foods  influences hormonal responses.
- Peak into ancient plant processing techniques, such as cooking and grinding.
- Synthesize above to understand how carbohydrate processing alters hormonal responses.
- Look at what influence the addition of fats and proteins makes.
- Investigate how fiber content or addition influences metabolic outcomes.
- Elaborate on downstream effects of intestinal hormonal imbalances.
- Highlight a potential connection with how bariatric surgery dramatically improves diabetes symptoms in a matter of days.
- Draw conclusions integrating the roles of processing, speed and place of absorption and subsequent hormone secretions.
- Give some practical advices based on the implication of all the above points.

# Endocrine anatomy of the GI system




**Proglucagon splicing**



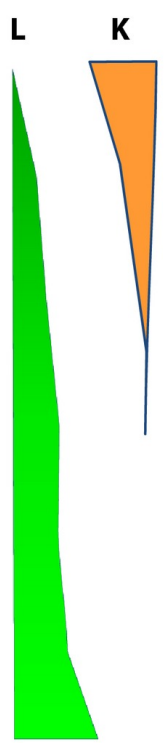
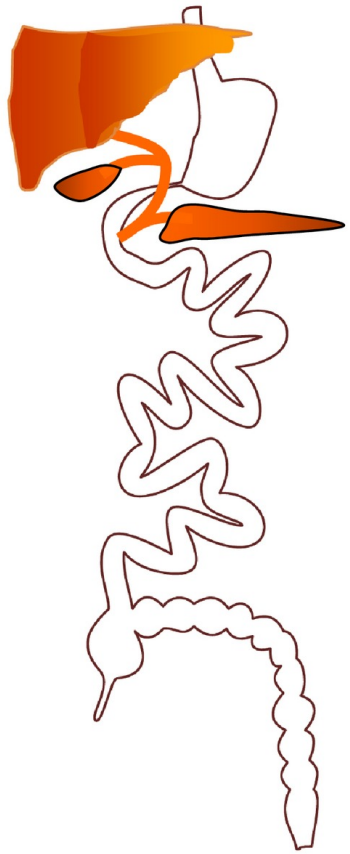
JDI Journal of Diabetes Investigation
Official Journal of the Asian Association for the Study of Diabetes

Mini Review | Open Access

# Mechanisms underlying glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 secretion

Frank Reimann, Fiona M Gribble

First published: 14 March 2016 | https://doi.org/10.1111/jdi.12478 | Cited by: 10

| K/L cell distribution | | | Enteroendocrine stimulus | EEC Transporter/ ion channel | EEC Receptor |
|---|---|---|---|---|---|
|   |  | Small intestine | Monosaccharide | SLC5A1 (SGLT1) | Tas1R2/3 (?) |
| | | | Long chain fatty acid | | FFAR1, FFAR4 |
| | | | Mono-acyl glycerol, acyl-ethanolamide | | GPR119, CB1 |
| | | | Amino acid | B0AT1 (SLC6A19) ATA2 (SLC38A2) | CASR, GPRC6A |
| | | | Di/tripeptide | SLC15A1 (PEPT1) | CASR |
| | | | Bile acid | | GPBAR1 |
| | | | | | |
| | | Colon | Short chain fatty acid | | FFAR2, FFAR3 |
| | | | Bile acid | | GPBAR1 |
| | | | Indole | Kv channels | |

# Nutrient sensing in the GI system

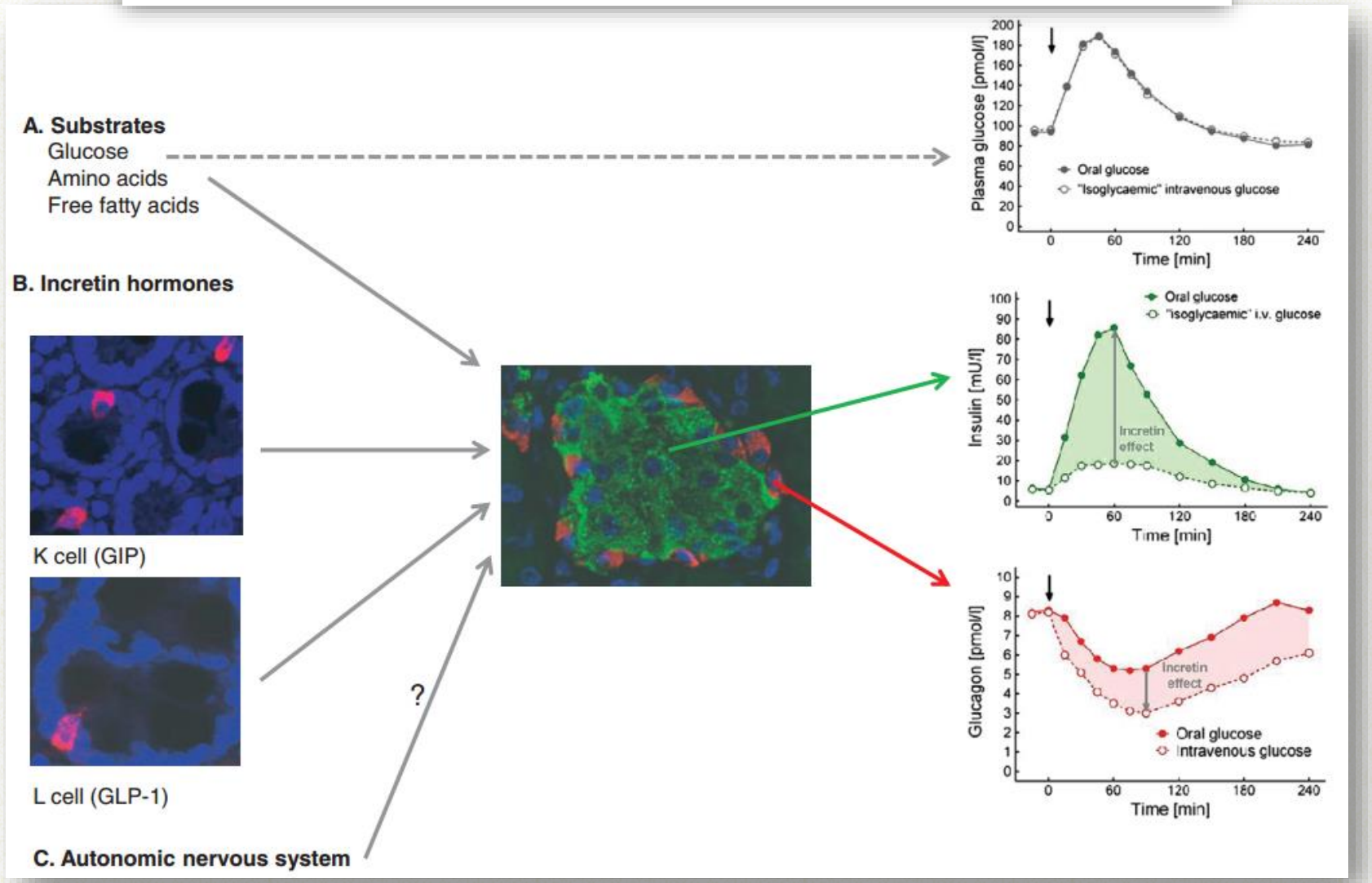
DOI: 10.1111/dom.13129

WILEY

REVIEW ARTICLE

# Incretin hormones: Their role in health and disease

Michael A. Nauck MD | Juris J. Meier MD



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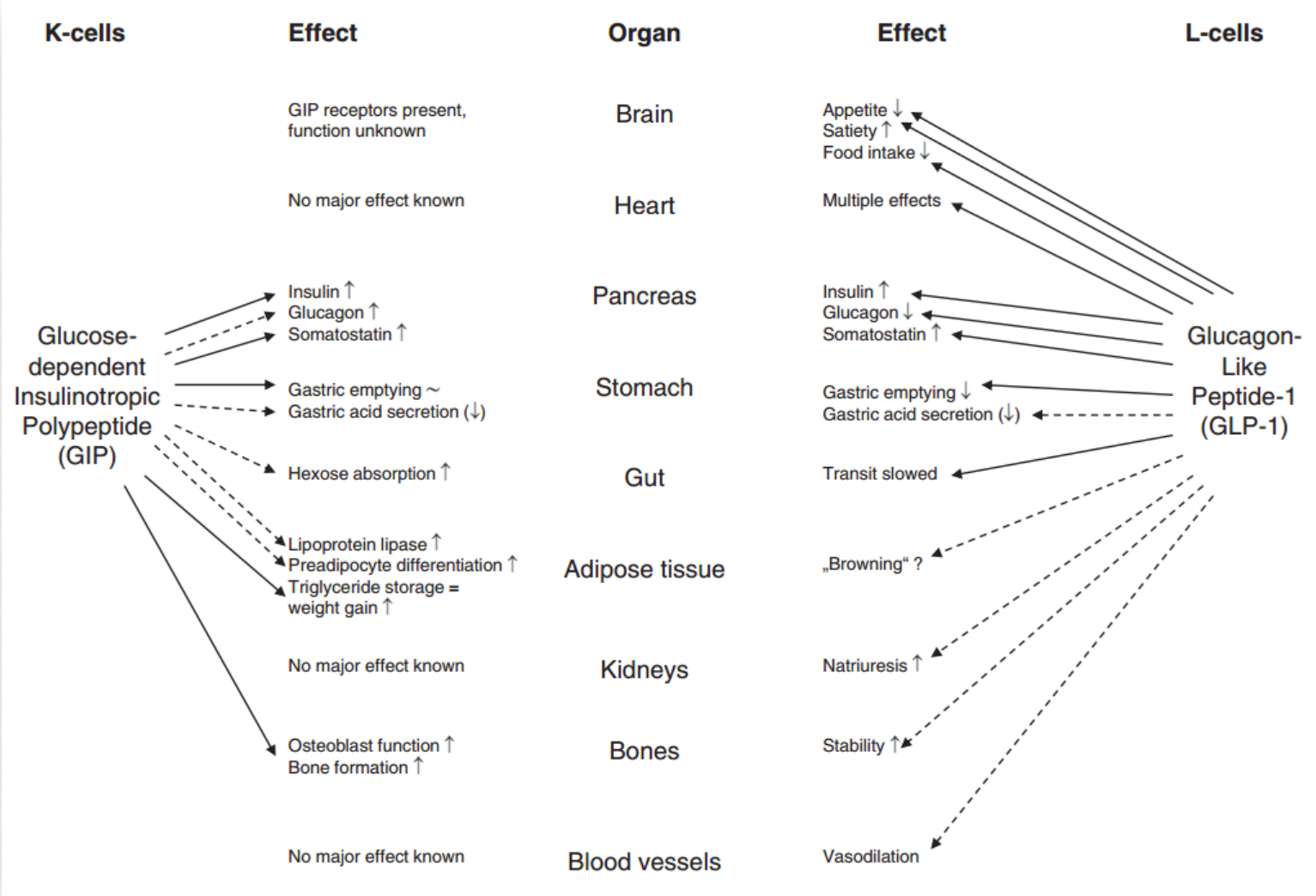
REVIEW ARTICLE

# Incretin hormones: Their role in health and disease

Michael A. Nauck MD | Juris J. Meier MD



# Effects of intestinal hormones on hunger-satiety signaling

| *Gut hormone* | *Site of synthesis* | *Food intake-regulating receptor* | *Peripheral effect on food intake* |
|---|---|---|---|
| CCK | Intestinal L-cells | $CCK_A$ | Decrease |
| Ghrelin | Stomach | GHS | Increase |
| PP | Pancreas/colon | Y4R | Decrease |
| PYY | Intestinal L-cells | Y2R | Decrease |
| GLP-1 | Intestinal L-cells | GLP1R | Decrease |
| OXM | Intestinal L-cells | GLP1R? | Decrease |

Abbreviations: CCK, cholecystokinin; $CCK_A$, cholecystokinin receptor subtype A; GHS, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide-1; GLP1R, GLP-1 receptor; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide YY; Y2R, PYY Y2 receptor; Y4R, PP Y4 receptor.

# The Effect of Cooking vs. Raw Food on Weight



**Table 2**
Body Mass Index by diet type[a].

| % raw food | Sex | Diet type | Mean or median age (y) | *n* | BMI | Reference |
|---|---|---|---|---|---|---|
| Cooked | F | "Typical American diet" | 53 | 7 | 25.4 | Fontana et al., 2005 |
| Mostly cooked | F | Mixed diet (not vegetarian) | 45 | 23,147 | 24.2 | Rosell et al., 2005 |
| Mostly cooked | F | Vegetarian since birth | 43 | 257 | 23.7 | Rosell et al., 2005 |
| Mostly cooked | F | Vegetarian starting between 1 and 9 years old | 33 | 257 | 23.9 | Rosell et al., 2005 |
| Mostly cooked | F | Vegetarian starting between 10 and 14 years old | 25 | 1042 | 23.8 | Rosell et al., 2005 |
| Mostly cooked | F | Vegetarian starting between 15 and 19 years old | 27 | 2226 | 23.6 | Rosell et al., 2005 |
| Mostly cooked | F | Vegetarian starting after 19 years old | 39 | 7880 | 23.5 | Rosell et al., 2005 |
| Mostly raw | F | Vegan; includes cooked vegetables | 53 | 87 | 21.5 | Donaldson, 2001 |
| All raw | F | Vegetarian and raw for mean of 3.6 years | 56 | 7 | 20.1 | Fontana et al., 2005 |
| All raw | F | Vegetarian | | | 20 | Hobbs, 2005 |
| Cooked | M | "Typical American diet" | 52 | 11 | 25.5 | Fontana et al., 2005 |
| Mostly cooked | M | Mixed diet (not vegetarian) | 48 | 6103 | 25.2 | Rosell et al., 2005 |
| Mostly cooked | M | Vegetarian since birth | 47 | 122 | 24.2 | Rosell et al., 2005 |
| Mostly cooked | M | Vegetarian starting between 1 and 9 years old | 42 | 71 | 25.4 | Rosell et al., 2005 |
| Mostly cooked | M | Vegetarian starting between 10 and 14 years old | 30 | 118 | 24.4 | Rosell et al., 2005 |
| Mostly cooked | M | Vegetarian starting between 15 and 19 years old | 30 | 538 | 24.2 | Rosell et al., 2005 |
| Mostly cooked | M | Vegetarian starting after 19 years old | 41 | 3011 | 24.3 | Rosell et al., 2005 |
| Mostly raw | M | Vegan, includes cooked vegetables | 57 | 54 | 22.9 | Donaldson, 2001 |
| All raw | M | Vegetarian and raw for mean of 3.6 years | 53 | 11 | 20.7 | Fontana et al., 2005 |
| All raw | M | Vegetarian | | | 21.0 | Hobbs, 2005 |
| 70–79% raw | F + M | Overall sample: 44.2% meat-eaters, 32.2% vegetarian, 23.6% vegan | Adult | 66 | 21.1 | Koebnick et al., 1999 |
| 80–89% raw | F + M | " | Adult | 103 | 21.0 | Koebnick et al., 1999 |
| 90–99% raw | F + M | " | Adult | 248 | 20.2 | Koebnick et al., 1999 |
| 100% raw | F + M | " | Adult | 96 | 19.3 | Koebnick et al., 1999 |

[a] In studies by Rosell et al. (2005), ages are medians. Body Mass Indices (BMI) for studies by Koebnick et al. (1999) were read off a graph. For all raw-foodists in the Koebnick et al. (1999) study, the mean percentage of raw food eaten was 91% (obtained by self-report), age-adjusted BMI was 20.1 (female) and 20.7 (male).

# Cooking Carbohydrate Rich Foods

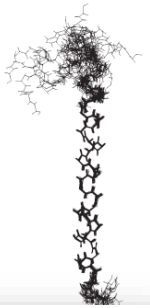




**Table 3**
Ileal digestibility of starch (%) in relation to processing[a].

| Starch type | Starch source | *In vivo* | | *In vitro* | | Change in digestibility from raw to cooked | Reference |
|---|---|---|---|---|---|---|---|
| | | Raw | Cooked | Raw | Cooked | | |
| A | Wheat | 71.2 | 96.0 | | | +34% | Muir et al., 1995 |
| A | Oats | | | 74.5 | 95.7 | +28% | Muir and O'Dea, 1992 |
| A | Barley | 93 | 99 | | | +6% | Sun et al., 2006 (pigs) |
| B | Green banana | 47.3 | 98.8 | 45.8 | | +109% | Langkilde et al., 2002 |
| B | Green banana | 49.4 | 96.9 | | | +96% | Muir et al., 1995 |
| B | Plantain | | | 53.6 | 100 | +87% | Englyst and Cummings, 1986 |
| B | Potato | | 96.7 | 50.7 | | (+91%) | Englyst and Cummings, 1987 |
| B | Potato | 32–47 | 98 | | | +108–206% | Sun et al., 2006 (pigs) |
| C | Pea | 80 | 91 | | | +14% | Sun et al., 2006 (pigs) |

[a] Data are for humans unless otherwise stated. Studies *in vivo* used collections of ileal fluids in ileostomy patients or cannulated pigs. Studies *in vitro* measure resistant starch (RS) as starch that is not hydrolysed following six hours of enzymatic hydrolysis. Silvester et al. (1995) showed that 97% of RS assayed in foods was recovered in ileal fluids.

# Cooking lipid and protein rich foods

## Cooking Increases Net Energy Gain From a Lipid-Rich Food

Emily E. Groopman,[1,2*] Rachel N. Carmody,[1,3] and Richard W. V

[1]*Department of Human Evolutionary Biology, Peabody Museum, Harvar*
[2]*Columbia College of Physicians and Surgeons, New York, NY 10032*
[3]*FAS Center for Systems Biology, Harvard University, Cambridge, MA 0*

*KEY WORDS* dietary fat; nuts; oil bodies; food processin

*ABSTRACT* Starch, protein, and lipid are three major sources of calories in the human diet. The unique and universal human practice of cooking has been demonstrated to increase the energy gained from foods rich in starch or protein. Yet no studies have tested whether cooking has equivalent effects on the energy gained from lipid-rich foods. Using mice as a model, we addressed this question by examining the impact of cooking on the energy gained from peanuts, a lipid-rich oilseed, and compared this impact against that of nonthermal processing (blending). We found that cooking consistently increased the energy gained per calorie, whereas blending had no fecal fat exc when peant microstructu integrity of that otherw effects were observed wi tance of coo humans, bo 000:000–000

**Evenepoel, Pieter, Dirk Claus, Benny Geypens, Martin Hiele, Karen Geboes, Paul Rutgeerts, and Yvo Ghoos.** Amount and fate of egg protein escaping assimilation in the small intestine of humans. *Am. J. Physiol.* 277 (*Gastrointest. Liver Physiol.* 40): G935–G943, 1999.—Studies attempting to evaluate protein assimilation in humans have hitherto relied on either ileostomy subjects or intubation techniques. The availability of stable isotope-labeled protein allowed us to determine the amount and fate of dietary protein escaping digestion and absorption in the small intestine of healthy volunteers using noninvasive tracer techniques. Ten healthy volunteers were studied once after ingestion of a cooked test meal, consisting of 25 g of $^{13}C$-, $^{15}N$-, and $^{2}H$-labeled egg protein, and once after ingestion of the same but raw meal. Amounts of 5.73% and 35.10% ($P < 0.005$) of cooked and raw test meal, respectively, escaped digestion and absorption in the small intestine. A significantly higher percentage of the malabsorbed raw egg protein was recovered in urine as fermentation metabolites. These results *1*) confirm that substantial amounts of even easily digestible proteins may escape assimilation in healthy volunteers and *2*) further support the hypothesis that the metabolic fate of protein in the colon is affected by the amount of protein made available.

# Energetic consequences of thermal and nonthermal food processing

Rachel N. Carmody[a,1], Gil S. Weintraub[a], and Richard W. Wrangham[a,b]

[a]Department of Human Evolutionary Biology, Peabody Museum, Harvard University, Cambridge, MA 02138; and [b]Stellenbosch Institute for Advanced Study (STIAS), Wallenberg Research Centre at Stellenbosch University, Stellenbosch 7600, South Africa

Edited by James O'Connell, University of Utah, Salt Lake City, UT, and approved October 6, 2011 (received for review July 26, 2011)

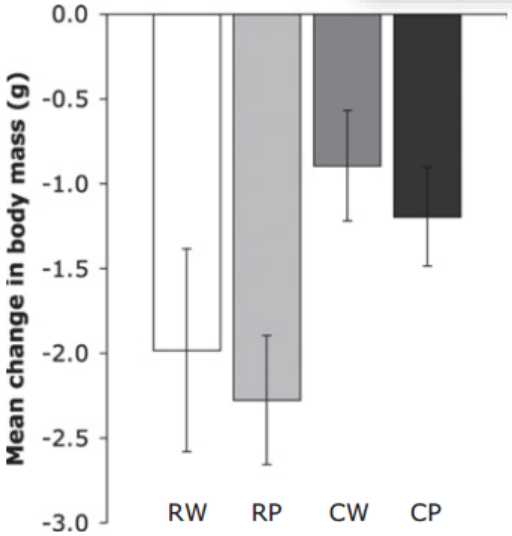



**Fig. 3.** Changes in body mass on meat diets. Mean cumulative change in body mass (±95% CI) over 4 d in mice ($n$ = 16) fed standardized ad libitum diets of organic beef (*B. taurus*) eye round served raw and whole (RW), raw and pounded (RP), cooked and whole (CW), and cooked and pounded (CP). Diets were administered based on a counterbalanced within-subjects study design.

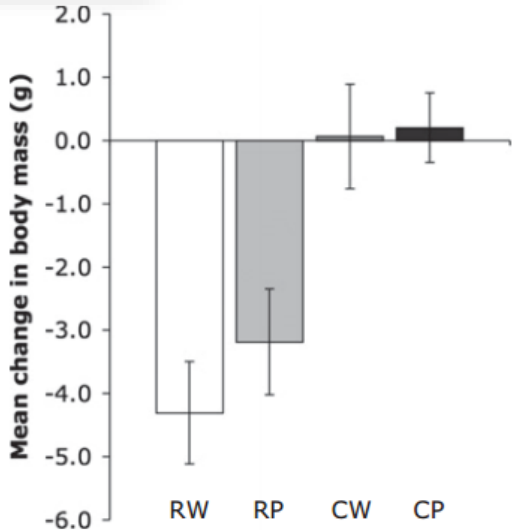



**Fig. 1.** Changes in body mass on tuber diets. Mean cumulative change in body mass [±95% confidence interval (CI)] over 4 d in mice ($n$ = 17) fed standardized ad libitum diets of organic sweet potato (*I. batatas*) served raw and whole (RW), raw and pounded (RP), cooked and whole (CW), and cooked and pounded (CP). Diets were administered based on a counter-balanced within-subjects study design.

**„our results indicate that human dieters who count calories and eat similar mixed diets but cook them to different extents would experience different weight gain outcomes at comparable levels of physical activity. This prediction is consistent with recent long-term data indicating that preparation-specific factors affect the relationship between caloric consumption and weight gain in humans."**

# Hydrolyzing protein

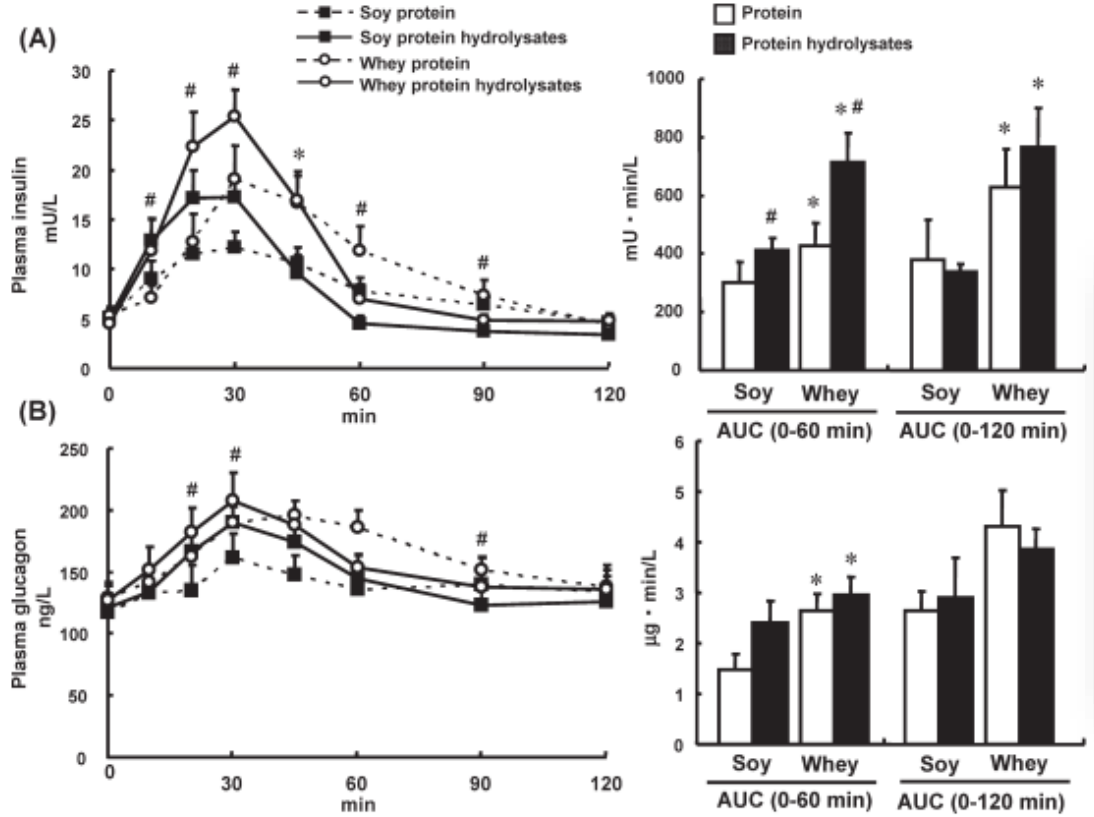



**Figure 5.** Plasma (**A**) insulin and (**B**) glucagon concentrations. The left-hand graphs show the plasma concentration of insulin over the 120 min study period. The right-hand graphs show the area under the curve (AUC) for the 0−60 and 0−120 min periods. Values are expressed as means ± SEM, $n$ = 5/group. #, $P < 0.05$ significant difference between nonhydrolyzed protein and protein hydrolysates; ∗, $P < 0.05$ significant difference between dietary protein source.

**Comparison of Different Sources and Degrees of Hydrolysis of Dietary Protein: Effect on Plasma Amino Acids, Dipeptides, and Insulin Responses in Human Subjects**

Masashi Morifuji*†§, Mihoko Ishizaka†, Seigo Baba†, Kumiko Fukuda†, Hitoshi Matsumoto†, Jinichiro Koga†, Minoru Kanegae† and Mitsuru Higuchi#

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*J. Agric. Food Chem.*, **2010**, *58* (15), pp 8788–8797
**DOI:** 10.1021/jf101912n
Publication Date (Web): July 8, 2010

**Cite this:** *J. Agric. Food Chem.* 58, 15, 8788-8797
RIS Citation GO

# Pureeing and juicing apples

The rebound fall in plasma-glucose which occurred during the second and third hours after juice, and to a lesser extent after purée, was in striking contrast to the practically steady level after apples. This finding indicates that dietary fibre plays a role in glucose homœostasis and that, after fibre-depleted food these homœostatic mechanisms may be disturbed. The purée data indicate that, surprisingly, this may also apply to foods in which fibre has merely been physically disrupted.

THE LANCET, OCTOBER 1, 1977

## DEPLETION AND DISRUPTION OF DIETARY FIBRE

### EFFECTS ON SATIETY, PLASMA-GLUCOSE, AND SERUM-INSULIN

G. B. HABER* K. W. HEATON
D. MURPHY

*University Departments of Medicine and Chemical Pathology, Royal Infirmary, Bristol*

L. F. BURROUGHS

*Long Ashton Research Station, Bristol*

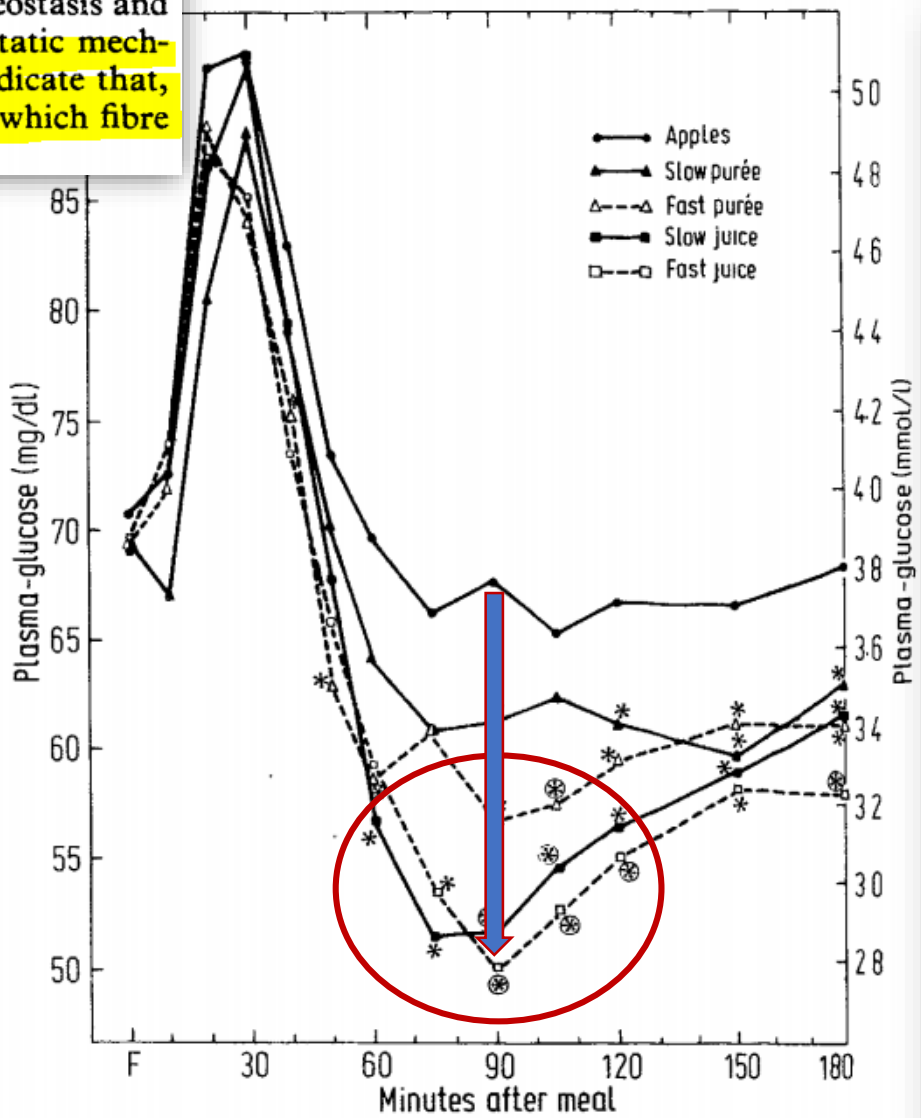



**Fig. 3—Mean plasma-glucose levels in nine normal subjects after ingesting 60 g carbohydrate as whole apples, apple purée, and apple juice.**

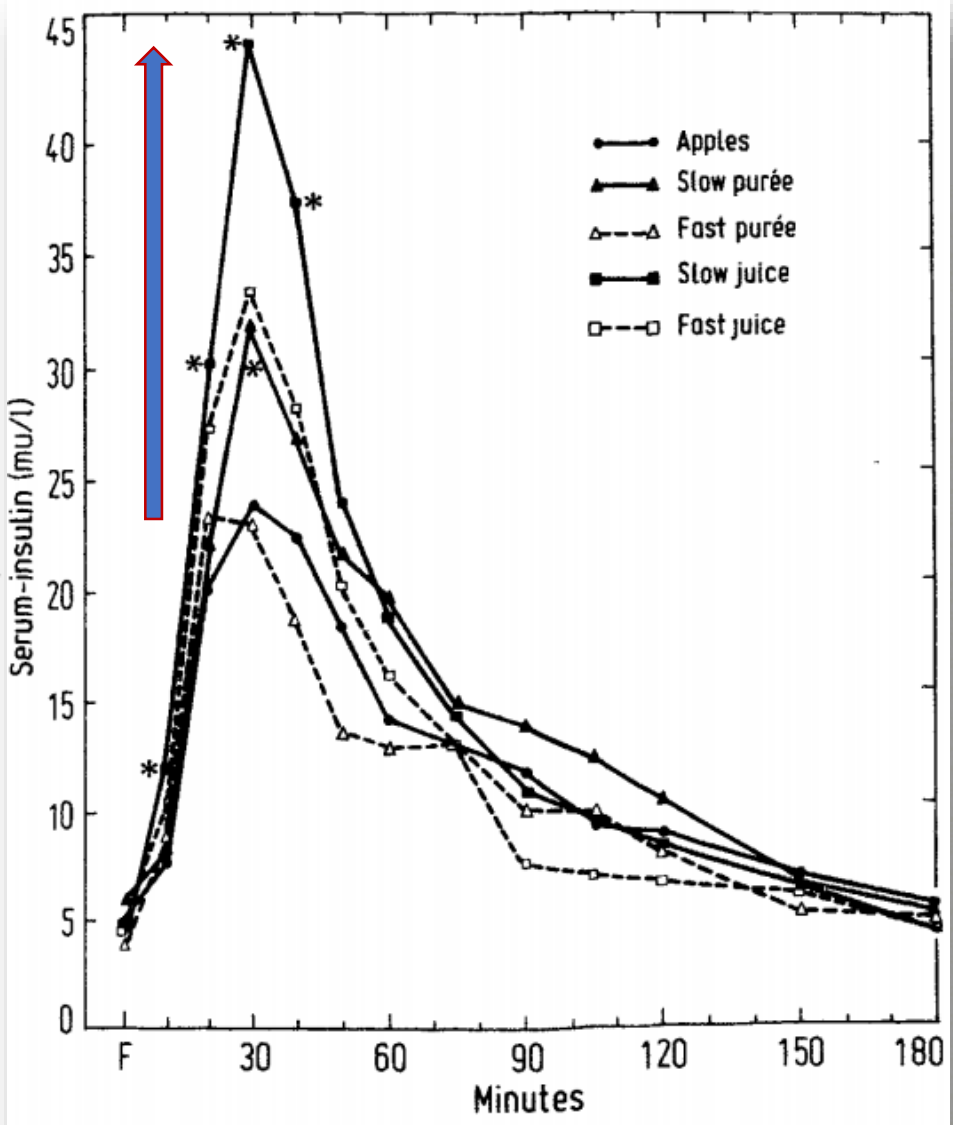



**Fig. 4—Mean serum-insulin levels in nine normal subjects after ingesting 60 g carbohydrate as whole apples, purée (fast and slow), and juice (fast and slow) (see legend to fig. 3).**

# Grinding grains: 1) Wheat

## Particle size of wheat, maize, and oat test meals: effects on plasma glucose and insulin responses and on the rate of starch digestion in vitro[1–3]

*Kenneth W Heaton, MD; Samuel N Marcus, MD; Pauline M Emmett, BSc; and Colin H Bolton, PhD*

**ABSTRACT** When normal volunteers ate isocaloric wheat-based meals, their plasma insulin responses (peak concentration and area under curve) increased stepwise: whole grains < cracked grains < coarse flour < fine flour. Insulin responses were also greater with fine maizemeal than with whole or cracked maize grains but were similar with whole groats, rolled oats, and fine oatmeal. The peak-to-nadir swing of plasma glucose was greater with wheat flour than with cracked or whole grains. In vitro starch hydrolysis by pancreatic amylase was faster with decreasing particle size with all three cereals. Correlation with the in vivo data was imperfect. Oat-based meals evoked smaller glucose and insulin responses than wheat- or maize-based meals. Particle size influences the digestion rate and consequent metabolic effects of wheat and maize but not oats. The increased insulin response to finely ground flour may be relevant to the etiology of diseases associated with hyperinsulinemia and to the management of diabetes. *Am J Clin Nutr* 1988;47:675–82.

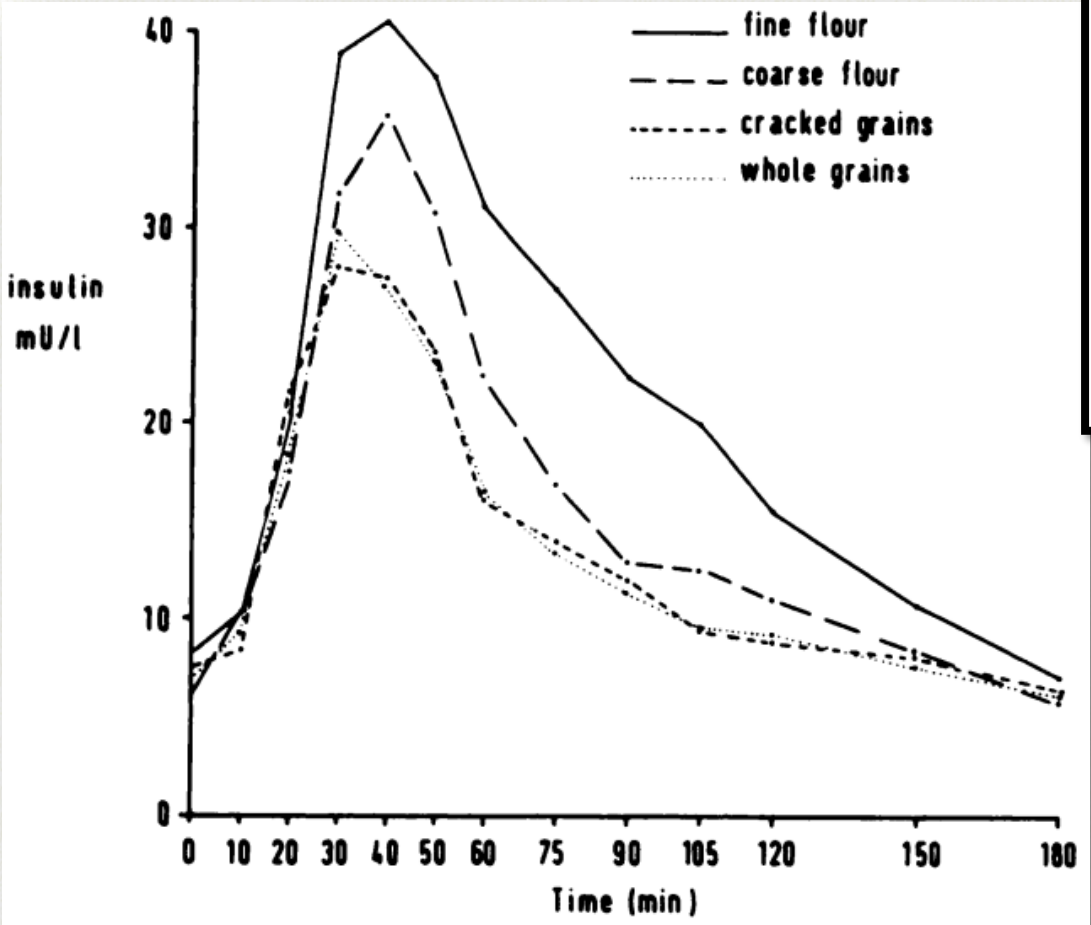



FIG 2. Mean plasma insulin concentration in 10 normal subjects after four isocaloric whole-wheat meals of different particle size. (1 mU/L = 7.175 pmol/L.)

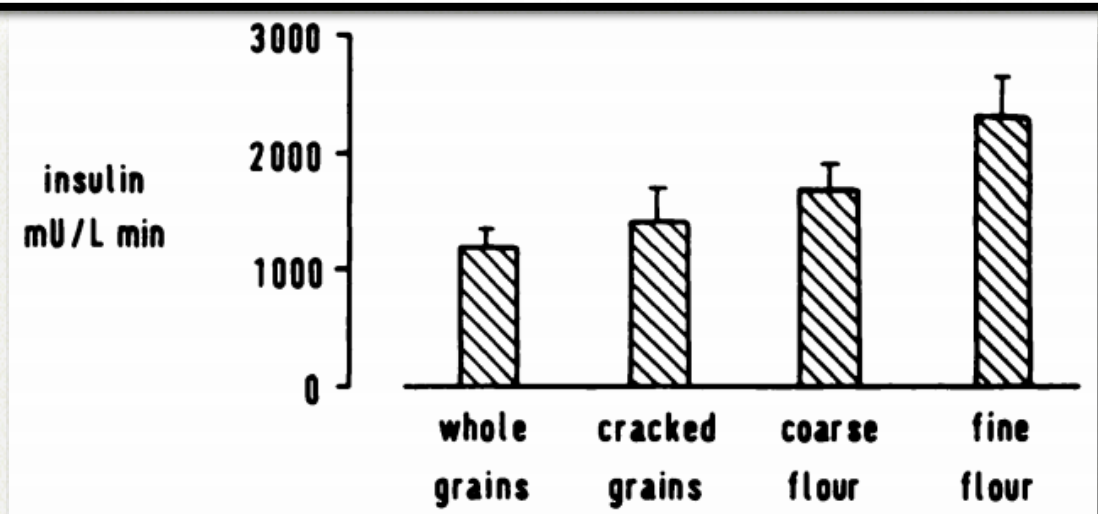



FIG 3. Area under plasma insulin concentration curve (mean ± SEM) after four isocaloric whole-wheat meals. Significant differences as follows: fine flour > all others, coarse flour > whole grains.

# Grinding grains: 2) Rice

## Physical factors influencing postprandial glucose and insulin responses to starch[1]

*Kerin O'Dea,[3] Ph.D., Paul J. Nestel, M.D., F.R.A.C.P., and Lynne Antonoff*

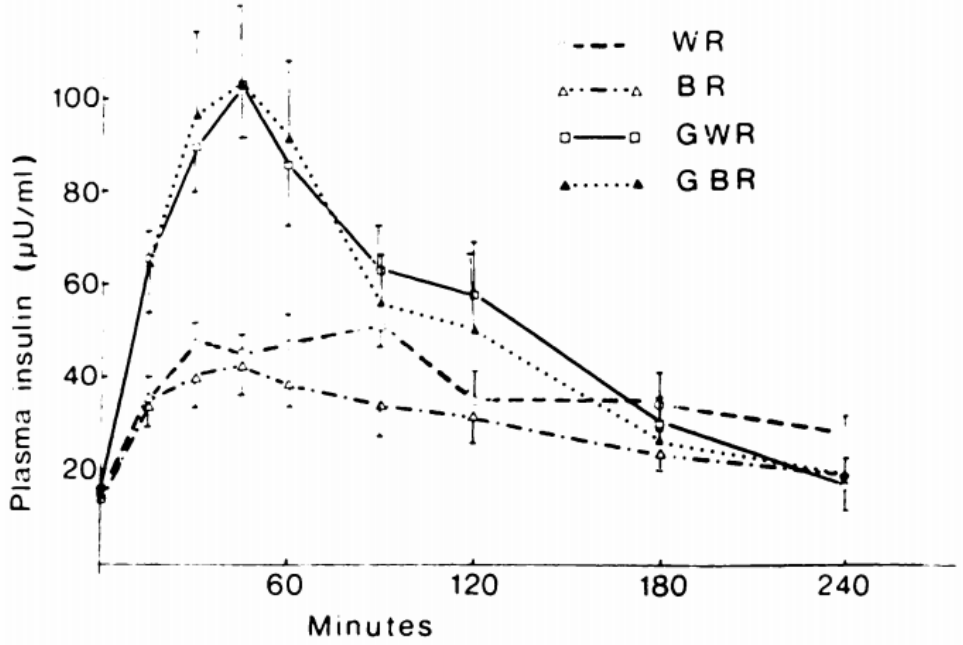
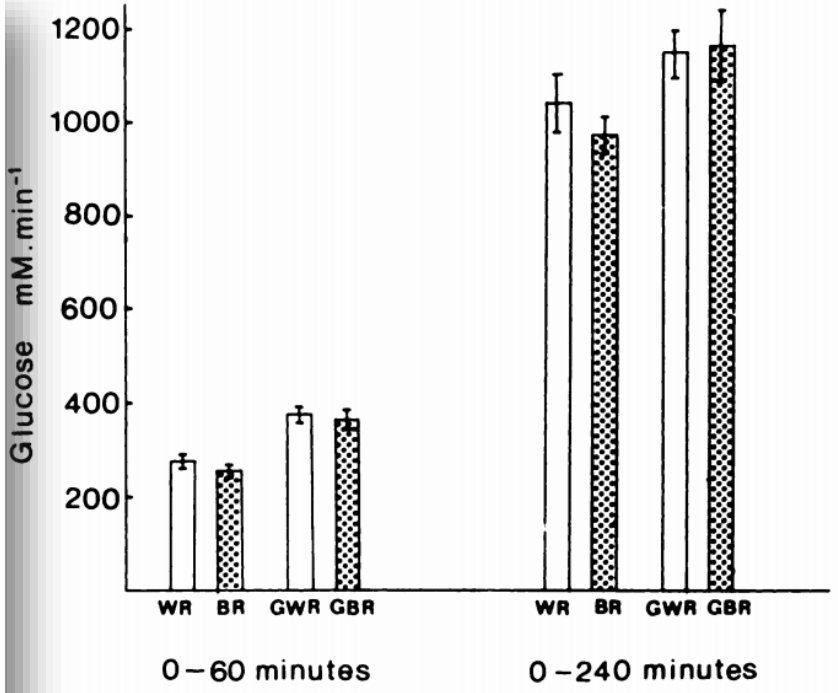



FIG. 2. Plasma insulin responses to white rice (WR), brown rice (BR), ground white rice (GWR), and ground brown rice (GBR). Mean ± SEM (n = 6). Statistics: GWR > WR: 15 min ($P < 0.005$), 30 min ($P < 0.005$), 45 min ($P < 0.001$), and 60 min ($P < 0.005$); GBR > BR: 15 min ($P < 0.025$), 30 min ($P < 0.005$), 45 min ($P < 0.005$), 60 min ($P < 0.005$), and 90 min ($P < 0.025$).




der the blood glucose *curves* during the first 60 min (0 to 60) and for the entire test period (0 t
ce (WR), brown rice (BR), ground white rice (GWR), and ground brown rice (GBR). Mean
cs: 0 to 60 min: GWR > WR, $P < 0.01$, GBR > BR, $P < 0.001$.

# Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects

FREE

Katri S Juntunen ✉, Leo K Niskanen, Kirsi H Liukkonen, Kaisa S Poutanen, Jens J Holst, Hannu M Mykkänen

*The American Journal of Clinical Nutrition*, Volume 75, Issue 2, 1 February 2002, Pages 254–262, https://doi.org/10.1093/ajcn/75.2.254

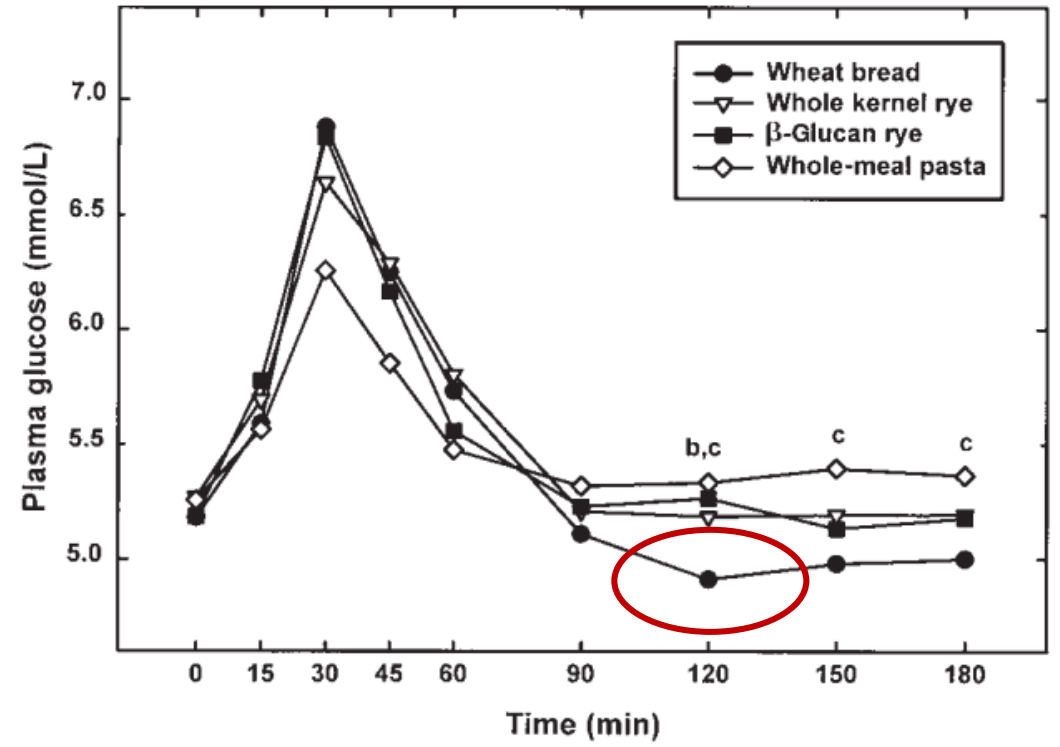



**FIGURE 2.** Mean fasting and postprandial glucose responses to rye and wheat products over 180 min ($n$ = 20). Postprandial glucose responses to β-glucan rye bread (b) and pasta (c) were significantly different from those to wheat bread, $P < 0.05$. The pooled SEM was 0.9 for the whole-kernel rye bread, 0.9 for the β-glucan rye bread, 0.6 for the pasta, and 0.8 for the white wheat bread.

**„The results indicate that the lower insulinemic response to the rye breads and pasta than to the wheat bread is not explained by the fiber content, type of cereal, or rate of gastric emptying, but by the structural properties of the food."**

**„Our findings agree with those of Järvi et al, who compared diets with identical nutrient compositions and type and amount of fiber and produced differences in the glycemic index mainly by altering the structure of the starchy foods. They found that consumption of a diet with a low glycemic index and a preserved food structure improved glucose and insulin responses."**

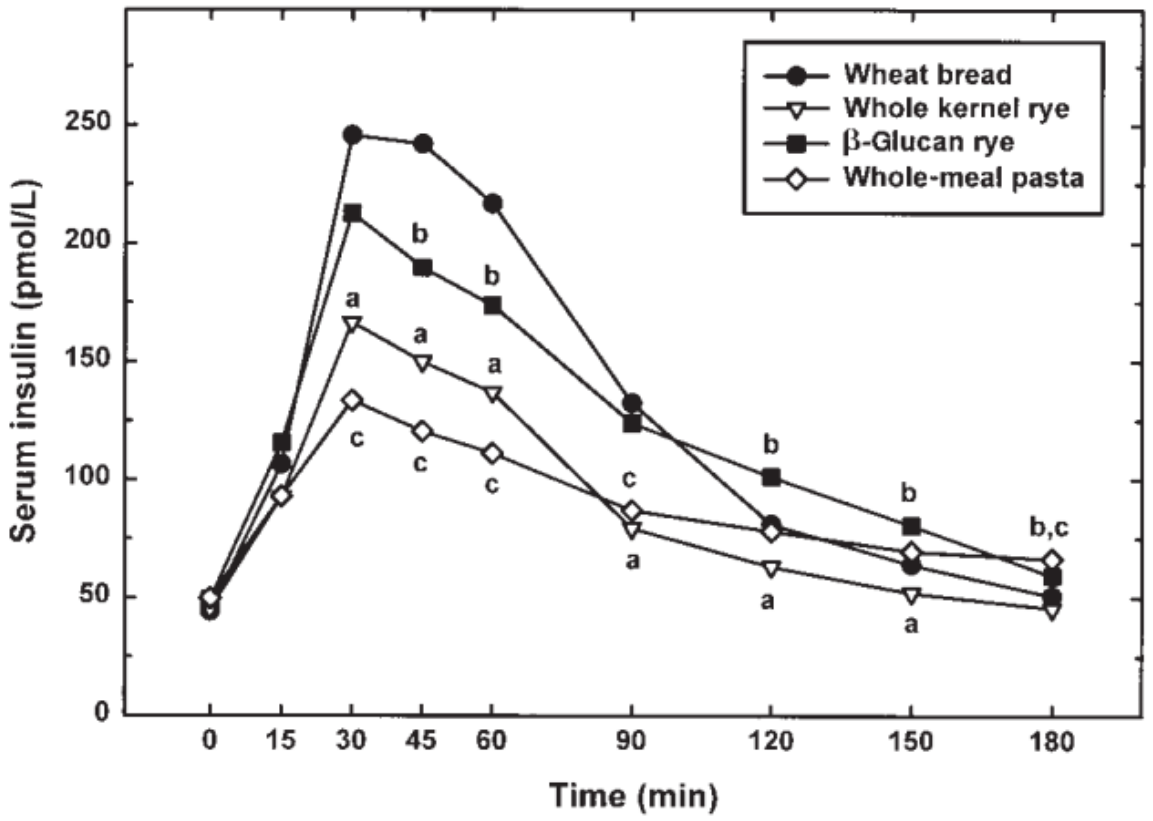



**FIGURE 3.** Mean fasting and postprandial insulin responses to rye and wheat products over 180 min ($n$ = 20). Postprandial insulin responses to whole-kernel rye bread (a), β-glucan rye bread (b), and pasta (c) were significantly different from those to white wheat bread, $P < 0.05$. The pooled SEM was 40.5 for the whole-kernel rye bread, 56.3 for the β-glucan rye bread, 36.3 for the pasta, and 73.8 for the white wheat bread.

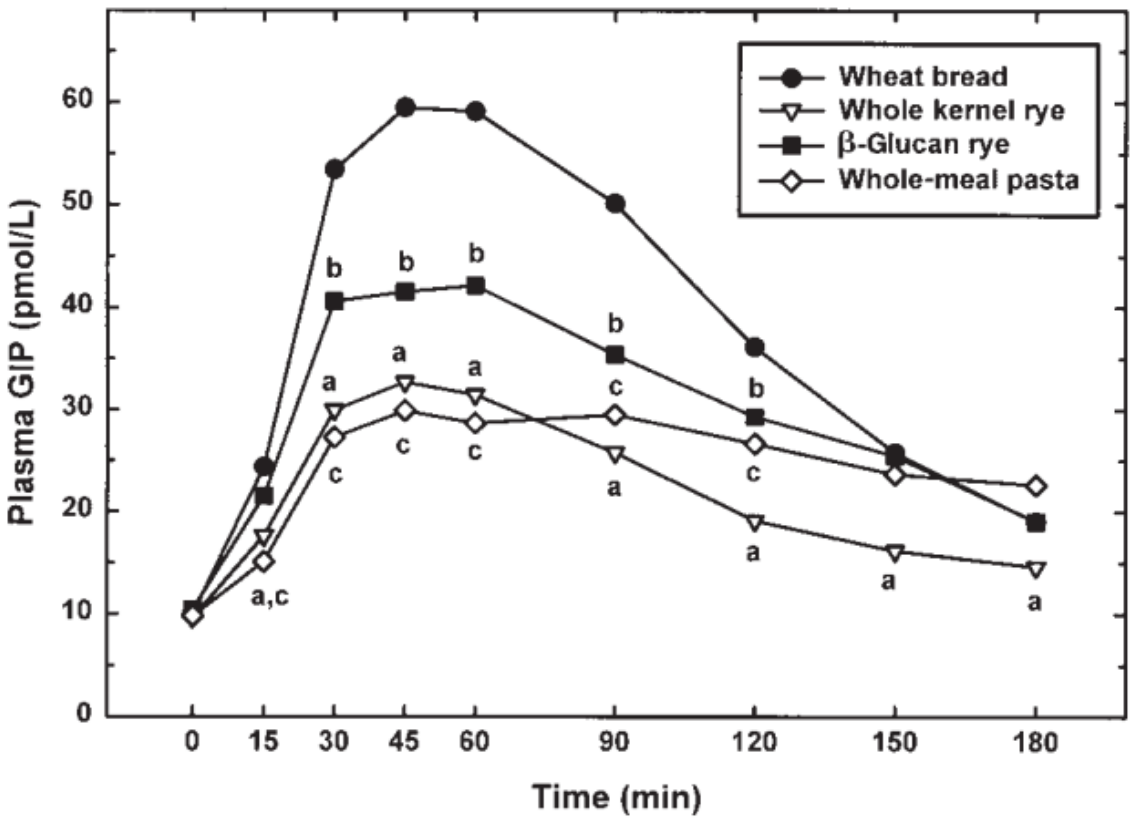



**FIGURE 4.** Mean fasting and postprandial glucose-dependent insulinotropic polypeptide (GIP) responses to rye and wheat products over 180 min ($n$ = 20). Postprandial GIP responses to whole-kernel rye bread (a), β-glucan rye bread (b), and pasta (c) were significantly different from those to white wheat bread, $P < 0.05$. The pooled SEM was 7.6 for the whole-kernel rye bread, 11.1 for the β-glucan rye bread, 8.9 for the pasta, and 12.1 for the white wheat bread.

# Structural differences between rye and wheat breads but not total fiber content may explain the lower postprandial insulin response to rye bread

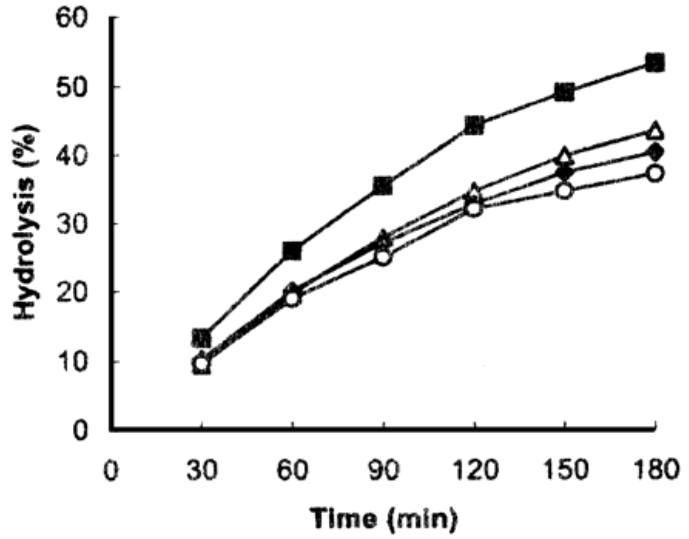
Katri S Juntunen ✉, David E Laaksonen, Karin Autio, Leo K Niskanen, Jens J Holst, Kari E Savolainen, Kirsi-Helena Liukkonen, Kaisa S Poutanen, Hannu M Mykkänen

*The American Journal of Clinical Nutrition*, Volume 78, Issue 5, 1 November 2003, Pages 957–964, https://doi.org/10.1093/ajcn/78.5.957

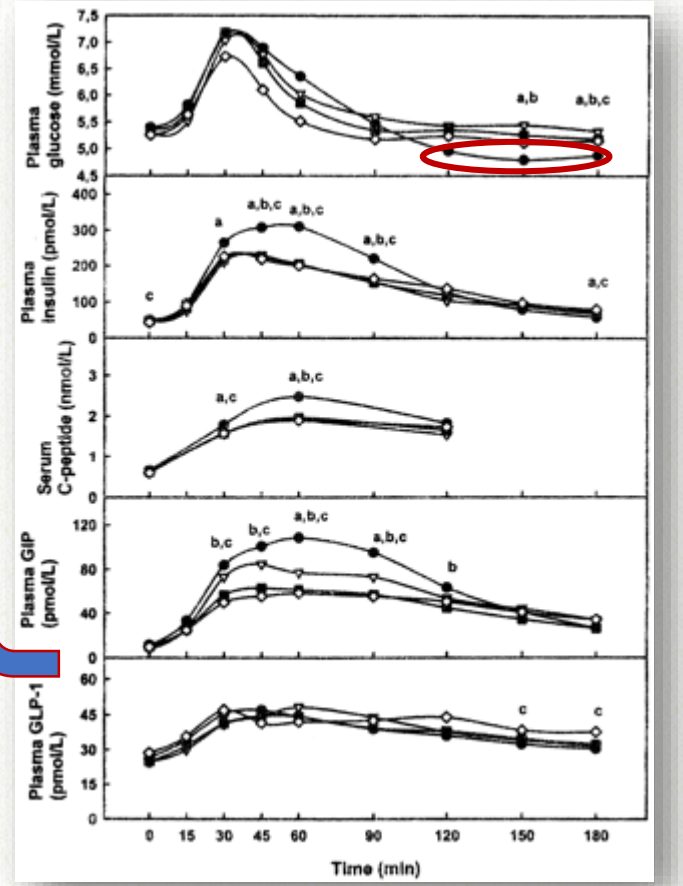
## In vitro starch hydrolysis

In vitro starch hydrolysis differed among the test breads ($P = 0.029$; Figure 2). Hydrolysis indexes of 82 ± 3, 76 ± 2, and 71 ± 4 were obtained for the endosperm, traditional, and high-fiber rye breads, respectively.

FIGURE 2




| AUC | | | | |
|---|---|---|---|---|
| Hormones \ Breads | Refined wheat | Endosperm rye | Traditional rye | High fiber rye |
| GIP (pmol · min/L) | 10496 | 8347 | 6357 | 6506 |
| GLP-1 (pmol · min/L) | 2089 | 2557 | 2309 | 2141 |
| GIP/GLP-1 | 5.02 | 3.26 | 2.75 | 3.04 |



# Insulin and glycemic responses in healthy humans to native starches processed in different ways: correlation with in vitro alpha-amylase hydrolysis

F R Bornet, A M Fontvieille, S Rizkalla, P Colonna, A Blayo, C Mercier, G Slama

*The American Journal of Clinical Nutrition*, Volume 50, Issue 2, 1 August 1989, Pages 315–323, https://doi.org/10.1093/ajcn/50.2.315

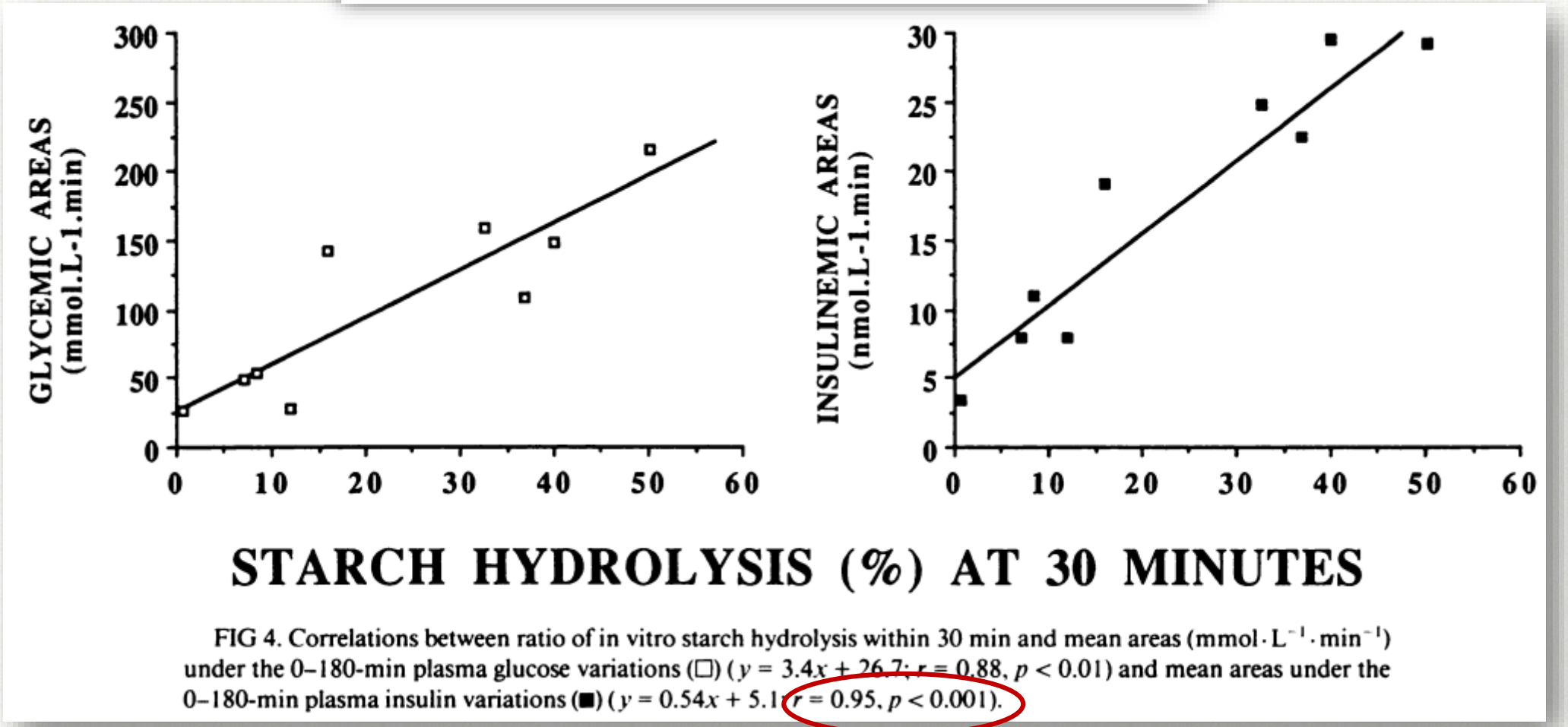



FIG 4. Correlations between ratio of in vitro starch hydrolysis within 30 min and mean areas ($mmol \cdot L^{-1} \cdot min^{-1}$) under the 0–180-min plasma glucose variations (□) ($y = 3.4x + 26.7$; $r = 0.88$, $p < 0.01$) and mean areas under the 0–180-min plasma insulin variations (■) ($y = 0.54x + 5.1$; $r = 0.95$, $p < 0.001$).

# Contributions of fat and protein to the incretin effect of a mixed meal

*Guillaume Carrel, Léonie Egli, Christel Tran, Philippe Schneiter, Vittorio Giusti, David D'Alessio, and Luc Tappy*

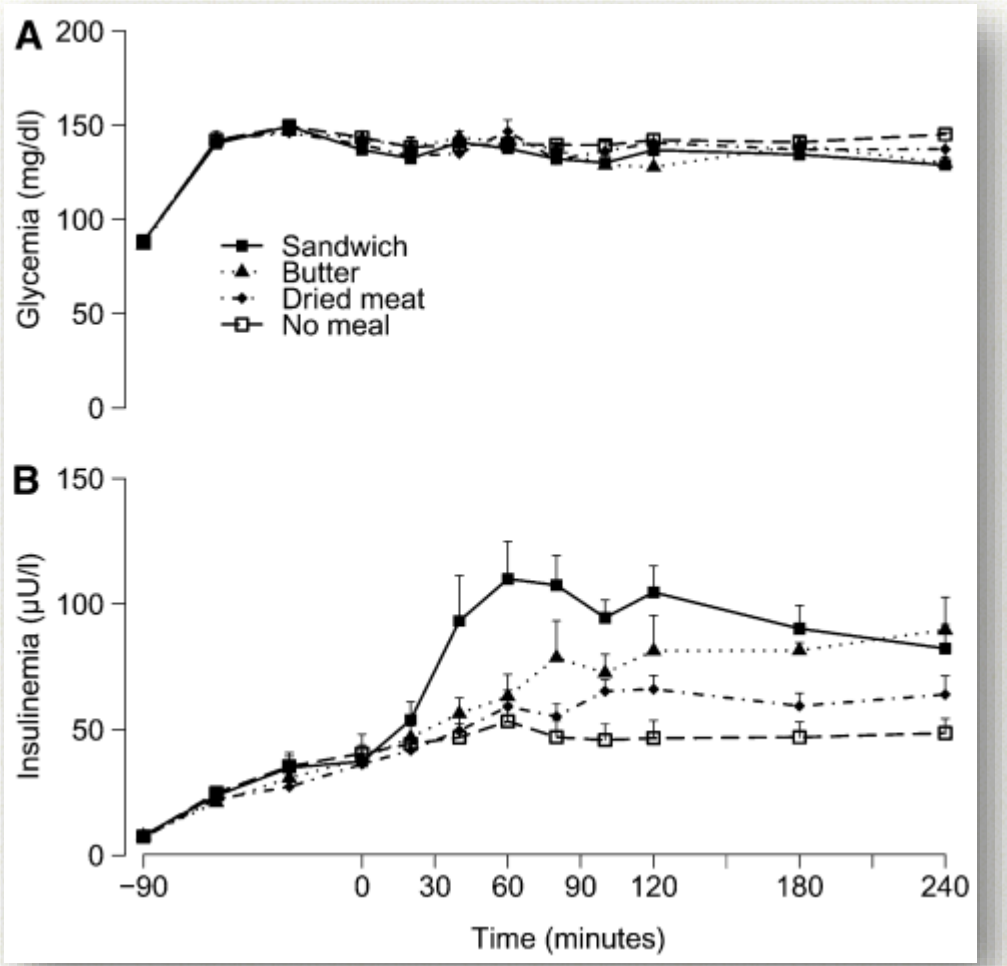
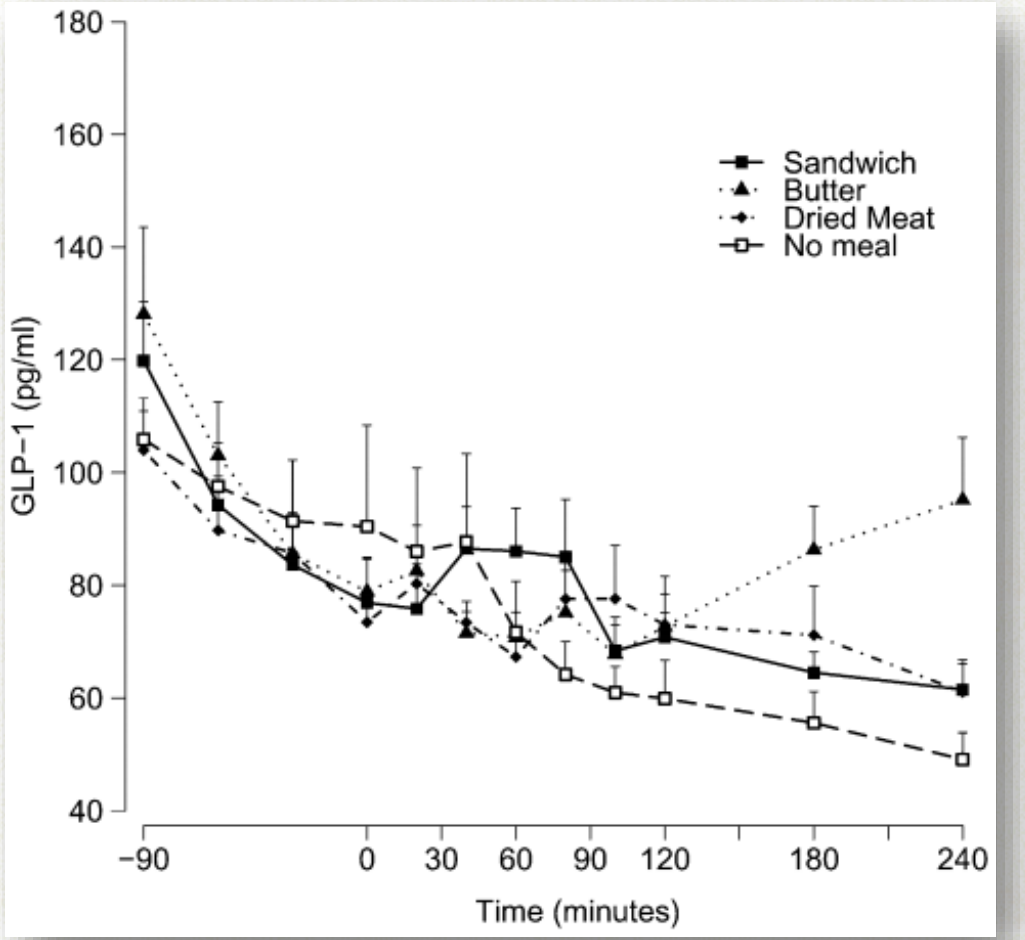


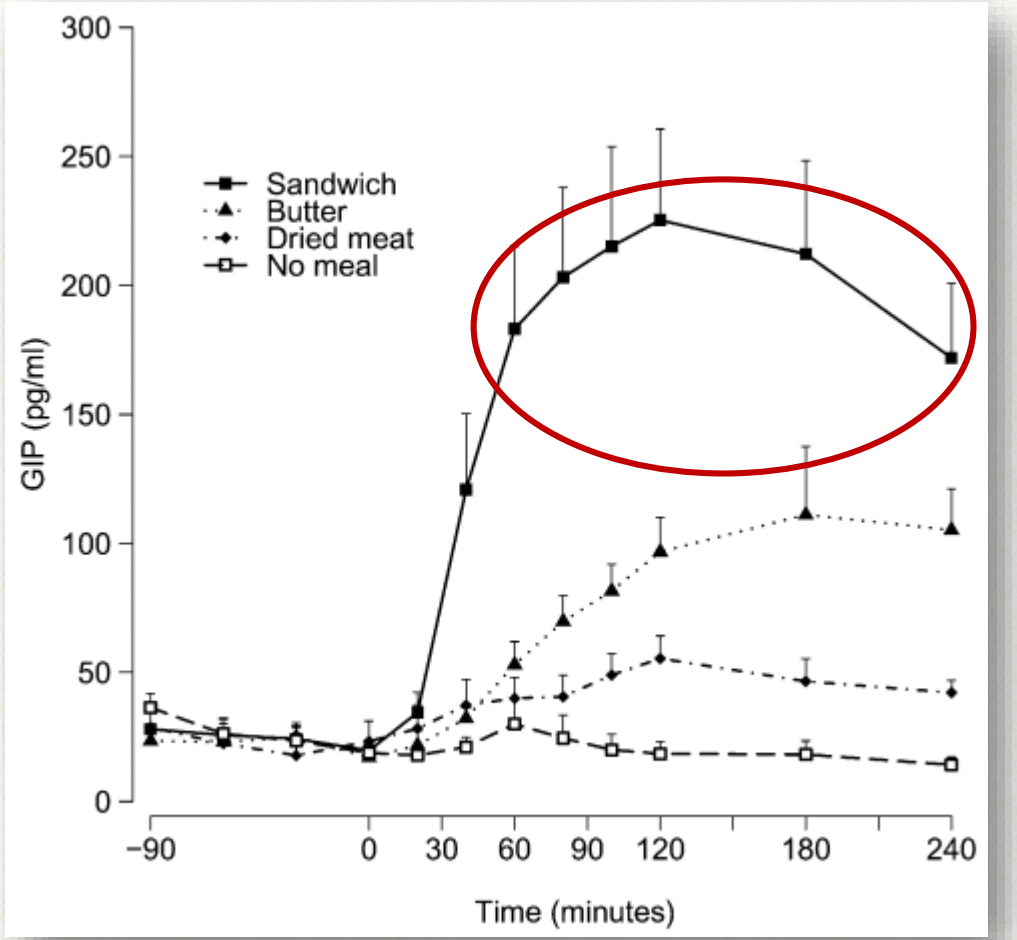

**TABLE 1**
Composition of the different test meals

| Meal content | Proteins | Lipids | Carbohydrates |
|---|---|---|---|
| | *g* | *g* | *g* |
| Sandwich | | | |
| 120 g White bread | 10.9 | 1.1 | 63.2 |
| 20 g Butter | 0.1 | 16.4 | 0.1 |
| 10 g Dried meat | 3.9 | 0.5 | 0.1 |
| Total | 14.9 | 18.0 | 63.4 |
| Dried meat alone | | | |
| 40 g Dried meat | 15.4 | 2.0 | 0.2 |
| Butter alone | | | |
| 20 g Butter | 0.1 | 16.4 | 0.1 |

# Contributions of fat and protein to the incretin effect of a mixed meal

*Guillaume Carrel, Léonie Egli, Christel Tran, Philippe Schneiter, Vittorio Giusti, David D'Alessio, and Luc Tappy*



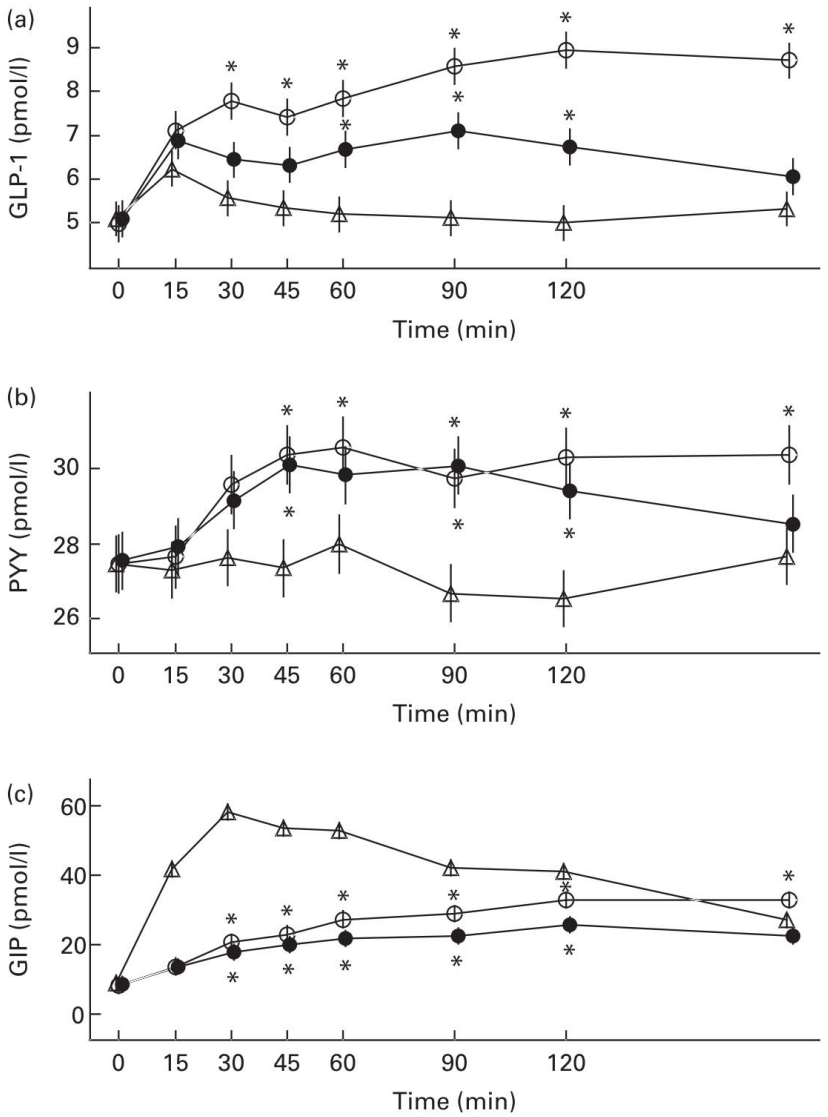



**Fig. 2.** Postprandial plasma glucagon-like peptide 1 (GLP-1) (a) peptide YY (PYY) (b) and glucose-dependent insulinotropic peptide (GIP) (c) responses after consumption of Palaeolithically inspired PAL1 (○) and PAL2 (●), and a reference meal (REF). Values are means, with standard errors represented by vertical bars. * Mean value was significantly different from that of the reference meal ($P<0{\cdot}05$). A Bonferroni adjustment was used to preserve the 0·05 error rate within each time point. The mean AUC for 180 min for GLP-1 were 1494 (SE 66·1) min × pmol/l for PAL1, 1180 (SE 64·4) min × pmol/l for PAL2 and 980 (SE 63·3) min × pmol/l for the REF (PAL1 *v.* REF $P<0{\cdot}001$; PAL2 *v.* REF $P=0{\cdot}003$).

# Plant-rich mixed meals based on Palaeolithic diet principles have a dramatic impact on incretin, peptide YY and satiety response, but show little effect on glucose and insulin homeostasis: an acute-effects randomised study

H. Frances J. Bligh [a1], Ian F. Godsland [a2], Gary Frost [a3], Karl J. Hunter [a1] ...

https://doi.org/10.1017/S0007114514004012 Published online: 09 February 2015

**Table 1.** Macronutrients and ingredients for the three test meals*

| | Reference | PAL1 | PAL2 |
|---|---|---|---|
| Available carbohydrate, desired target (g) | 50 | 50 | 50 |
| Available carbohydrate, analysed (g) | 46·1 | 43·3 | 44·2 |
| Fibre, calculated (g) | 3 | 12 | 10 |
| Total carbohydrates, calculated target† (g) | 53 | 66 | 65 |
| Energy, calculated (kJ) | 1602 | 2326 | 1606 |
| Total carbohydrates, calculated (g (% of energy)) | 57 (60) | 65 (43) | 66 (60) |
| Fat, calculated (g (% of energy)) | 11 (25) | 18 (28) | 11 (25) |
| Protein, calculated (g (% of energy)) | 13 (15) | 41 (29) | 16 (15) |
| Total phenolics (mg GAE per meal) | 4·47 | 57·2 | 86·1 |
| Rice, white, long-grain, regular, cooked‡§ (g) | 90 | | |
| Strawberries, raw (g) | | 100 | 120 |
| Apples, raw, with skin (g) | | 110 | 110 |
| Peppers, sweet, yellow, raw (g) | | 100 | 100 |
| Fish, haddock, cooked, dry heat‡ (g) | | 90 | |
| Onions, sweet, raw (g) | | 60 | 60 |
| Mango, frozen (g) | 65 | | |
| Carrots, cooked, boiled, drained, without salt‡ (g) | 50 | | |
| Eggplant, raw (g) | | 50 | 50 |
| Mushrooms, white, raw (g) | | 50 | 50 |
| Fish, salmon, Atlantic, farmed, cooked, dry heat‡ (g) | 39 | 39 | 39 |
| Raisins, seedless (g) | | 25 | 25 |
| Nuts, almonds, blanched (g) | | 14 | |
| Oil, olive, salad or cooking (g) | 4 | | |
| Courgettes (g) | | 150 | 150 |
| Cinnamon (g) | | 5 | 5 |
| Capers (g) | | 5 | 5 |
| Flax seed oil (g) | | 4 | 4 |
| Total meal weight, uncooked (g) | 248 | 802 | 718 |

PAL1, Palaeolithic meal 1; PAL2, Palaeolithic meal 2; GAE, equivalents of gallic acid.

# Disrupting food texture vs. 'high-fat diet'. Fat is dispensable?

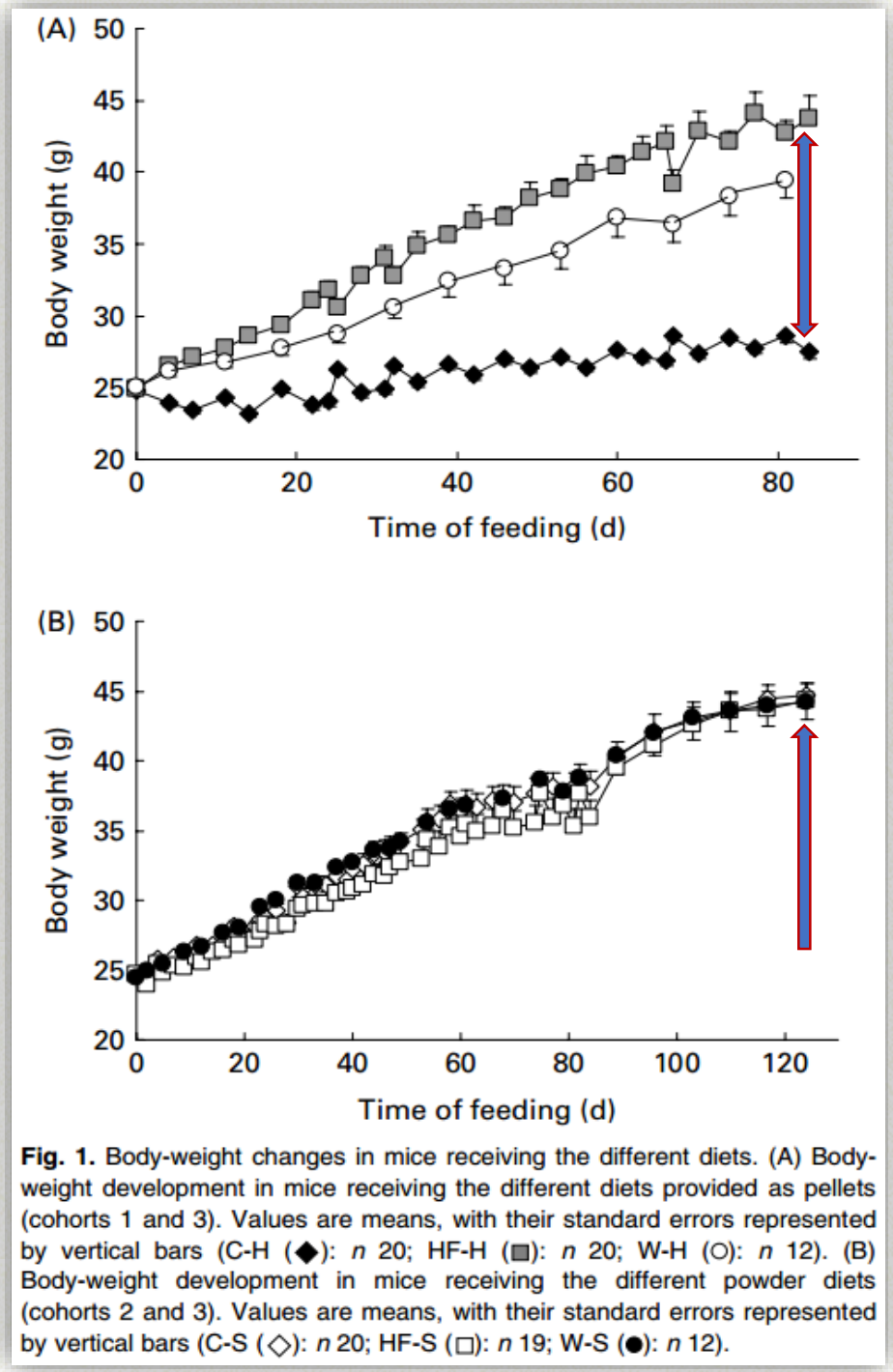



**Fig. 1.** Body-weight changes in mice receiving the different diets. (A) Body-weight development in mice receiving the different diets provided as pellets (cohorts 1 and 3). Values are means, with their standard errors represented by vertical bars (C-H (◆): *n* 20; HF-H (■): *n* 20; W-H (○): *n* 12). (B) Body-weight development in mice receiving the different powder diets (cohorts 2 and 3). Values are means, with their standard errors represented by vertical bars (C-S (◇): *n* 20; HF-S (□): *n* 19; W-S (●): *n* 12).

Volume 109, Issue 8 28 April 2013 , pp. 1518-1527

Cited by 15

Access

**Diet-induced obesity in *ad libitum*-fed mice: food texture overrides the effect of macronutrient composition**

Charles Desmarchelier [a1], Tobias Ludwig [a2], Ronny Scheundel [a1], Nadine Rink [a3] ...

https://doi.org/10.1017/S0007114512003340 Published online: 06 August 2012

„Here, we show for the first time that a pellet-based high carbohydrate/starch diet fails to trigger obesity, whereas the same diet given in powder form produces an obese phenotype similar to a HF or W diet. While all mice receiving the high-carbohydrate C diets ingested very similar amounts of food and lost similar quantities of energy through faeces, they displayed quite different body-weight gains. The most striking difference, however, was that feed efficiency was 4-fold higher in the powder diet compared with the pellet variant."

# Meal size and meal frequency

**Incretin Secretion in Relation to Meal Size and Body Weight in Healthy Subjects and People with Type 1 and Type 2 Diabetes Mellitus** FREE

T. Vilsbøll ✉, T. Krarup, J. Sonne, S. Madsbad, A. Vølund, A. G. Juul, J. J. Holst

*The Journal of Clinical Endocrinology & Metabolism*, Volume 88, Issue 6, 1 June 2003, Pages 2706–2713, https://doi.org/10.1210/jc.2002-021873

**„it is possible to modulate the β-cell sensitivity to glucose in obese healthy subjects, and possibly also in type 2 diabetic patients, by giving them a large meal, compared with a small meal."**

**Incretin and Islet Hormone Responses to Meals of Increasing Size in Healthy Subjects** FREE

Wathik Alsalim, Bilal Omar, Giovanni Pacini, Roberto Bizzotto, Andrea Mari, Bo Ahrén ✉

*The Journal of Clinical Endocrinology & Metabolism*, Volume 100, Issue 2, 1 February 2015, Pages 561–568, https://doi.org/10.1210/jc.2014-2865

**„Glucose profiles were similar after the two larger meals, whereas after the smaller meal, there was a postpeak reduction below baseline to a nadir of 3.8 ± 0.1mmol/L after 75 minutes ($P < .001$). The AUC for GLP-1, GIP, insulin, and C-peptide were significantly higher by increasing the caloric load as was β-cell sensitivity to glucose. …**
**The adaptation at larger meals results in identical glucose excursions, whereas after a lower caloric lunch, the insulin response is [disproportionately] high, resulting in a postpeak suppression of glucose below baseline."**

**Hypercaloric diets with increased meal frequency, but not meal size, increase intrahepatic triglycerides: A randomized controlled trial**

Karin E. Koopman, Matthan W.A. Caan, Aart J. Nederveen, Anouk Pels, Mariette T. Ackermans, Eric Fliers, Susanne E. la Fleur, Mireille J. Serlie ✉

First published: 26 March 2014 | https://doi.org/10.1002/hep.27149 | Cited by: 29

# Meal size and meal frequency 2.

**A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults** FREE

Kim S Stote, David J Baer ✉, Karen Spears, David R Paul, G Keith Harris, William V Rumpler, Pilar Strycula, Samer S Najjar, Luigi Ferrucci, Donald K Ingram ...
Show more

*The American Journal of Clinical Nutrition*, Volume 85, Issue 4, 1 April 2007, Pages 981–988, https://doi.org/10.1093/ajcn/85.4.981

**„when consuming 1 meal/d, subjects had a significant increase in hunger; a significant modification of body composition, including reductions in fat mass; significant increases in blood pressure and in total, LDL-, and HDL-cholesterol concentrations; and a significant decrease in concentrations of cortisol."**
**(„without a reduction in overall calorie intake")**

**Downregulation of Adipose Tissue Fatty Acid Trafficking in Obesity**

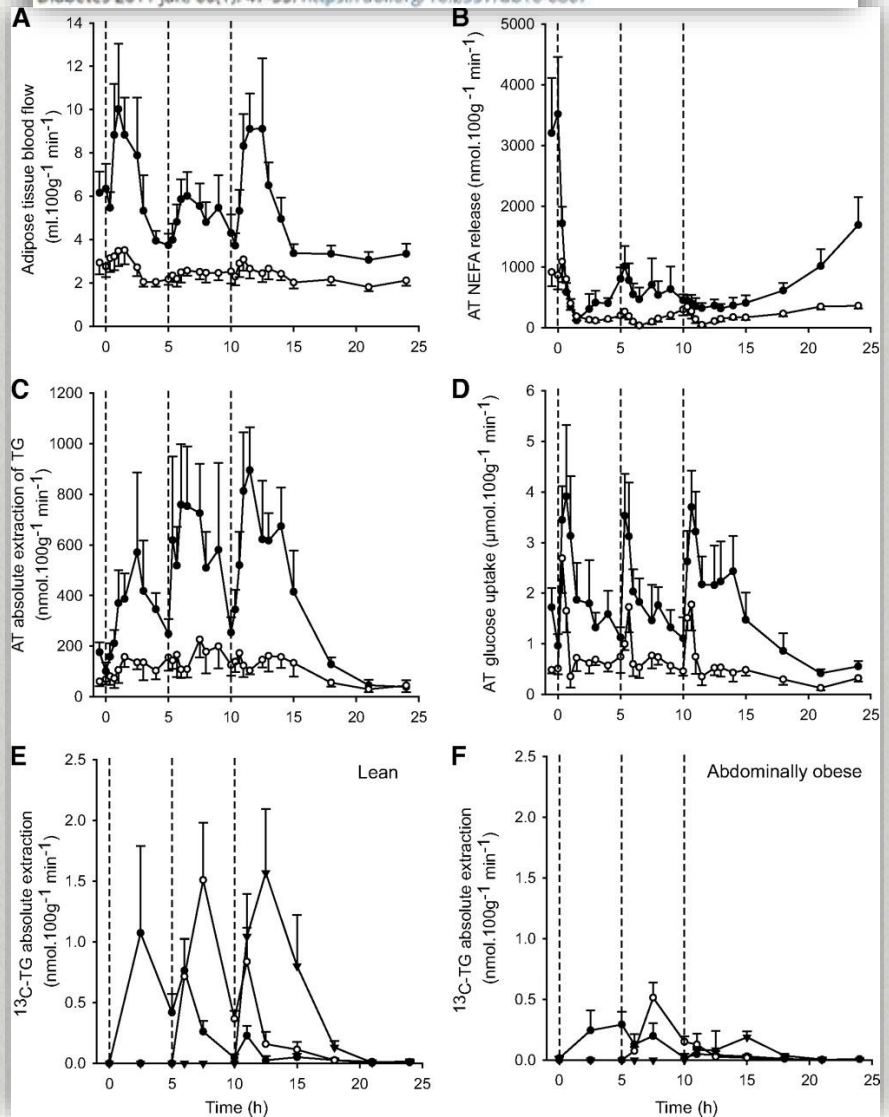
**A Driver for Ectopic Fat Deposition?**

Siobhán E. McQuaid[1], Leanne Hodson[1], Matthew J. Neville[1], A. Louise Dennis[1], Jane Cheeseman[1,2], Sandy M. Humphreys[1], Toralph Ruge[1], Marjorie Gilbert[1], Barbara A. Fielding[1], Keith N. Frayn[1] and Fredrik Karpe[1,2]

Author Affiliations

Corresponding author: Fredrik Karpe, fredrik.karpe@ocdem.ox.ac.uk.

Diabetes 2011 Jan; 60(1): 47-55. https://doi.org/10.2337/db10-0867



# Eating slowly

**Eating Slowly Increases the Postprandial Response of the Anorexigenic Gut Hormones, Peptide YY and Glucagon-Like Peptide-1** FREE

Alexander Kokkinos ✉, Carel W. le Roux, Kleopatra Alexiadou, Nicholas Tentolouris, Royce P. Vincent, Despoina Kyriaki, Despoina Perrea, Mohammad A. Ghatei, Stephen R. Bloom, Nicholas Katsilambros

*The Journal of Clinical Endocrinology & Metabolism*, Volume 95, Issue 1, 1 January 2010, Pages 333–337, https://doi.org/10.1210/jc.2009-1018

**Anorexigenic postprandial responses of PYY and GLP1 to slow ice cream consumption: preservation in obese adolescents, but not in obese adults**

A E Rigamonti[1], F Agosti[2], E Compri[2], M Giunta[1,2], N Marazzi[2], E E Muller[1],

This Article

Published online before print December 12, 2012, doi: 10.1530/EJE-12-0867

Eur J Endocrinol March 1, 2013 168 429-436

**„Peptide YY area under the curve (AUC) was higher after the 30-min meal than after the 5-min meal (mean ± SEM AUC 5 min meal: 4133 ± 324, AUC 30 min meal: 5250 ± 330 pmol/liter · min, *P* = 0.004), as was glucagon-like peptide-1 AUC (mean ± SEM AUC 5 min meal: 6219 ± 256, AUC 30 min meal: 8794 ± 656 pmol/liter · min, *P* = 0.001).”**

**„Eating at a physiologically moderate pace leads to a more pronounced anorexigenic gut peptide response than eating very fast.”**

**Eating rate is a heritable phenotype related to weight in children** FREE

Clare H Llewellyn, Cornelia HM van Jaarsveld, David Boniface, Susan Carnell, Jane Wardle ✉

*The American Journal of Clinical Nutrition*, Volume 88, Issue 6, 1 December 2008, 1560–1566, https://doi.org/10.3945/ajcn.2008.26175

# Proxies for carbohydrate processing: Glycemic load

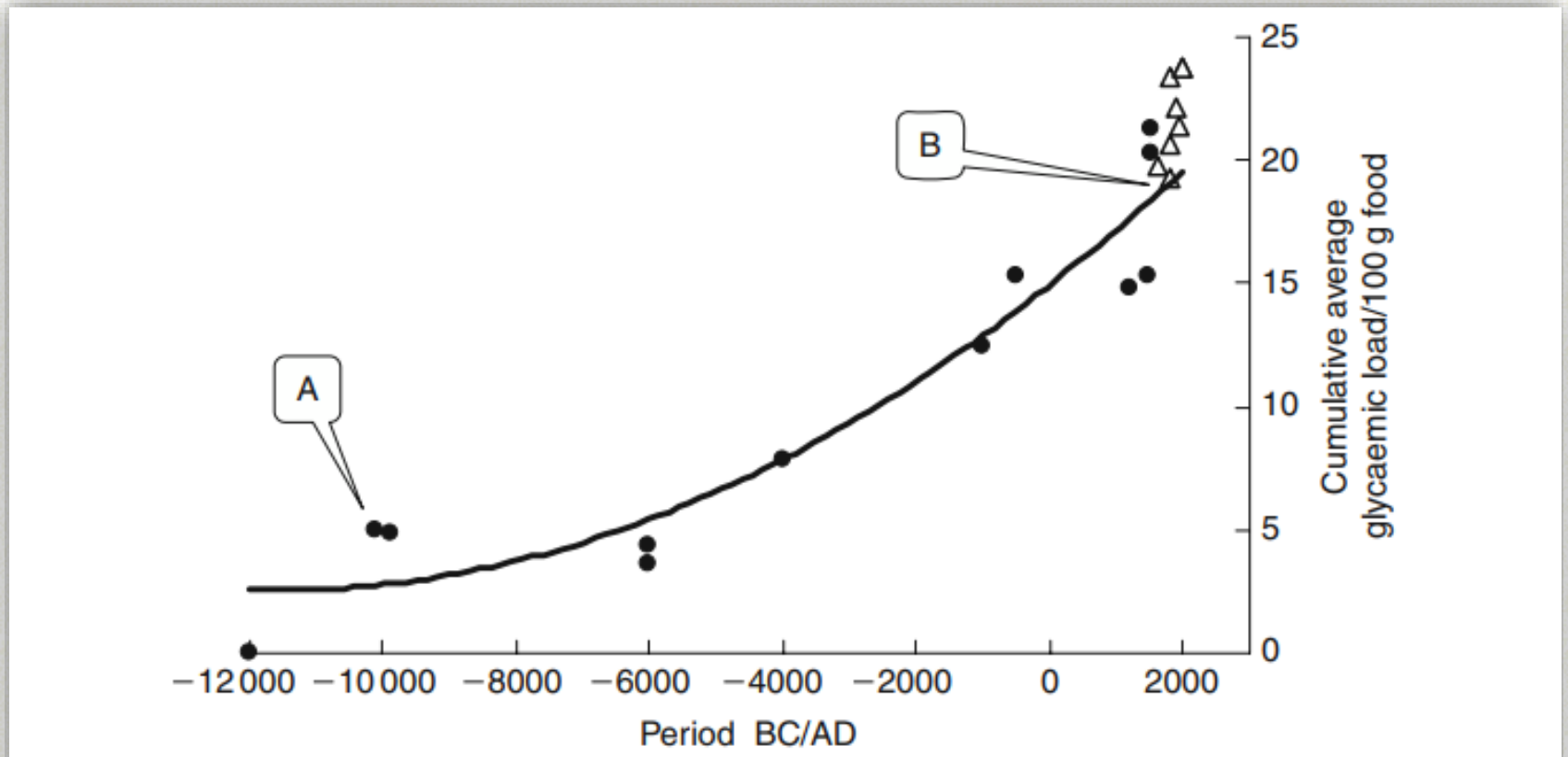



**Fig. 1.1** Evolutionary adaptation to ancient diets of low glycaemic load may have left mankind genetically predisposed to non-communicable diseases provoked by today's high-glycaemic diets. Based on the history of foods in Europe,[32] with calculations by this author (A, agricultural revolution; B, industrial revolution). Open symbols show values post the industrial revolution.

## Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment

Lee S Gross ✉, Li Li, Earl S Ford, Simin Liu

*The American Journal of Clinical Nutrition*, Volume 79, Issue 5, 1 May 2004, Pages 774–779,
https://doi.org/10.1093/ajcn/79.5.774

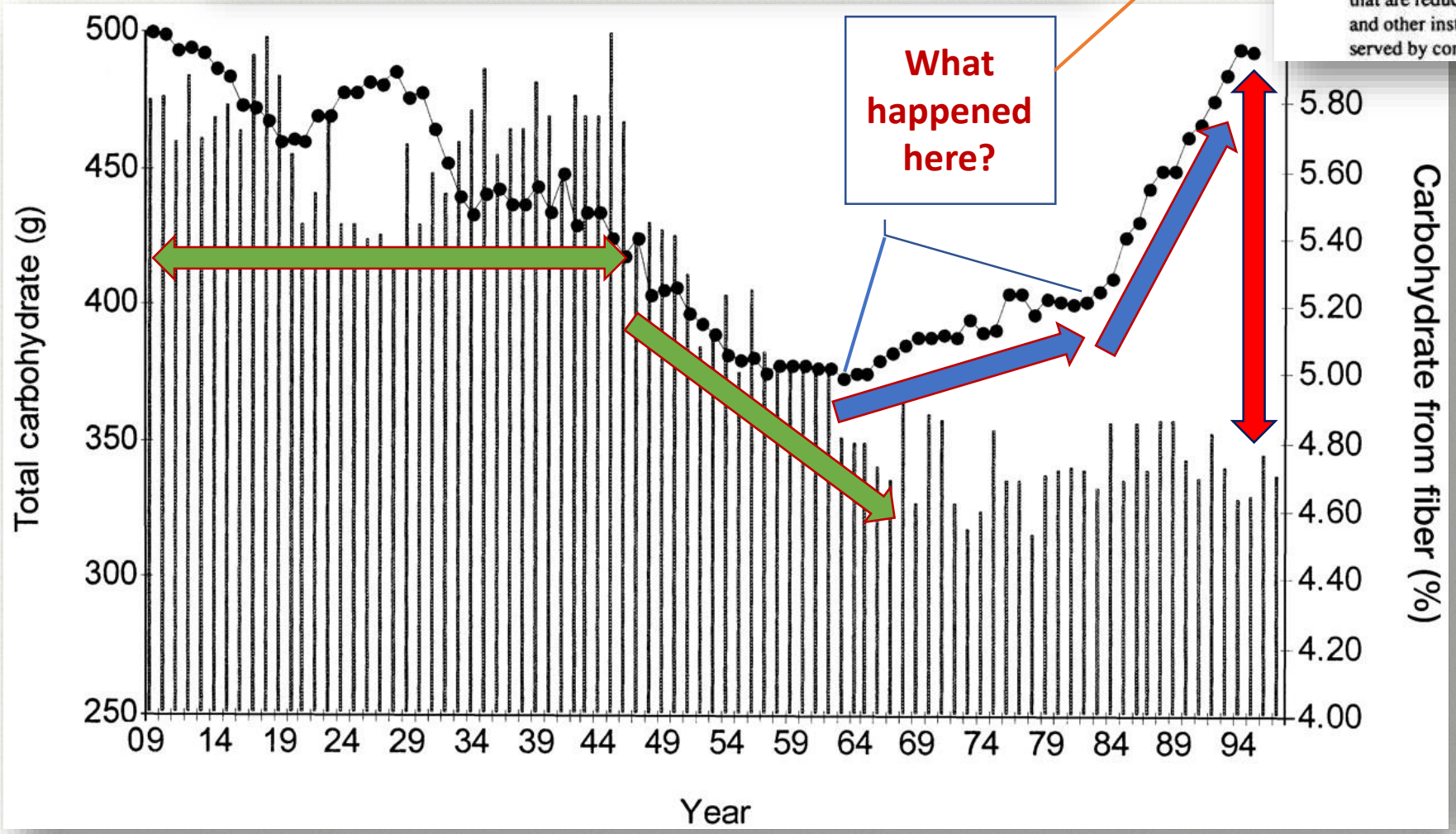
???

**2.15** **Increase to at least 5,000 brand items the availability of processed food products that are reduced in fat and saturated fat. (Baseline: 2,500 items reduced in fat in 1986)**

*Note: A brand item is defined as a particular flavor and/or size of a specific brand and is typically the consumer unit of purchase.*

**Baseline data source:** Nielsen Company National Scantrack.

If Americans are to meet the objective for reduction of dietary fat and saturated fat in their diets by the year 2000 (see Objective 2.5), sufficient food choices must be available. Considerable progress has already been achieved in increasing the availability of processed food products with lowered sodium. It is equally important that a wide selection of lower fat and saturated fat foods be offered to the public. Processed food products that are reduced in fat and saturated fat should also be made more available to schools and other institutions, low-income families, and American Indians living on reservations served by commodity food programs.




# Proxies for carbohydrate processing: Fiber

# Structure and speed of absorption

## Accelerated Intestinal Glucose Absorption in Morbidly Obese Humans: Relationship to Glucose Transporters, Incretin Hormones, and Glycemia

Nam Q. Nguyen, Tamara L. Debreceni, Jenna E. Bambrick, Bridgette Chia, Judith Wishart, Adam M. Deane, Chris K. Rayner, Michael Horowitz, Richard L. Young

*The Journal of Clinical Endocrinology & Metabolism*, Volume 100, Issue 3, 1 March 2015, Pages 968–976, https://doi.org/10.1210/jc.2014-3144

**Results:**

The increase in plasma 3-OMG ($P < .001$) and blood glucose ($P < .0001$) were greater in obese than lean subjects. Plasma 3-OMG correlated directly with blood glucose ($r = 0.78$, $P < .01$). In response to intraduodenal glucose, plasma GIP ($P < .001$), glucagon ($P < .001$), and insulin ($P < .001$) were higher, but GLP-1 ($P < .001$) was less in the obese compared with lean. Expression of SGLT-1 ($P = .035$), but not GLUT2 or T1R2, was higher in the obese, and related to peak plasma 3-OMG ($r = 0.60$, $P = .01$), GIP ($r = 0.67$, $P = .003$), and insulin ($r = 0.58$, $P = .02$).

**Conclusions:**

In morbid obesity, proximal intestine glucose absorption is accelerated and related to increased SGLT-1 expression, leading to an incretin-glucagon profile promoting hyperinsulinemia and hyperglycemia. These findings are consistent with the concept that accelerated glucose absorption in the proximal gut underlies the foregut theory of obesity and type 2 diabetes.

## The effect of dietary fibre on reducing the glycaemic index of bread

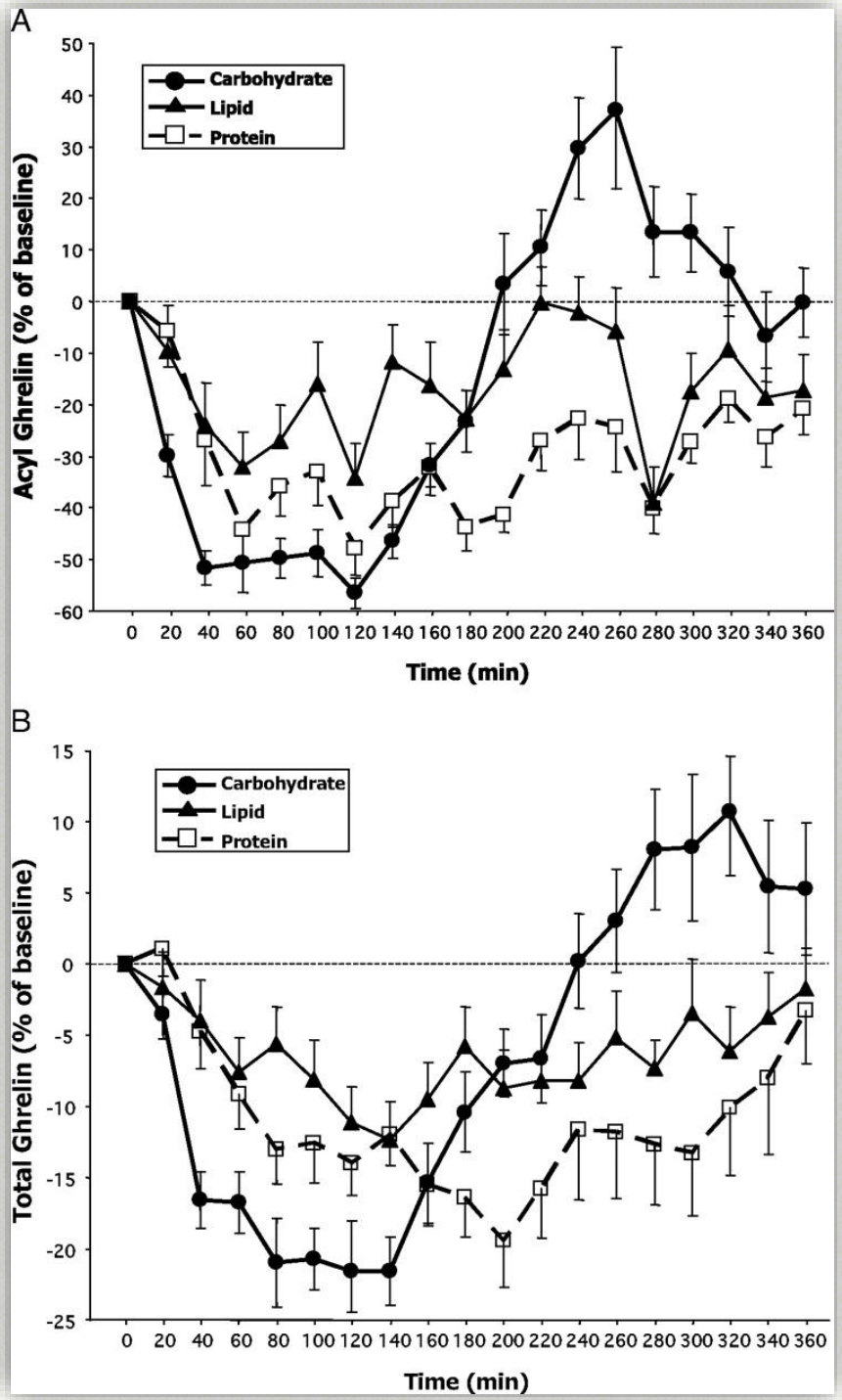
Francesca Scazzina [a1], Susanne Siebenhandl-Ehn [a2] and Nicoletta Pellegrini [a1]

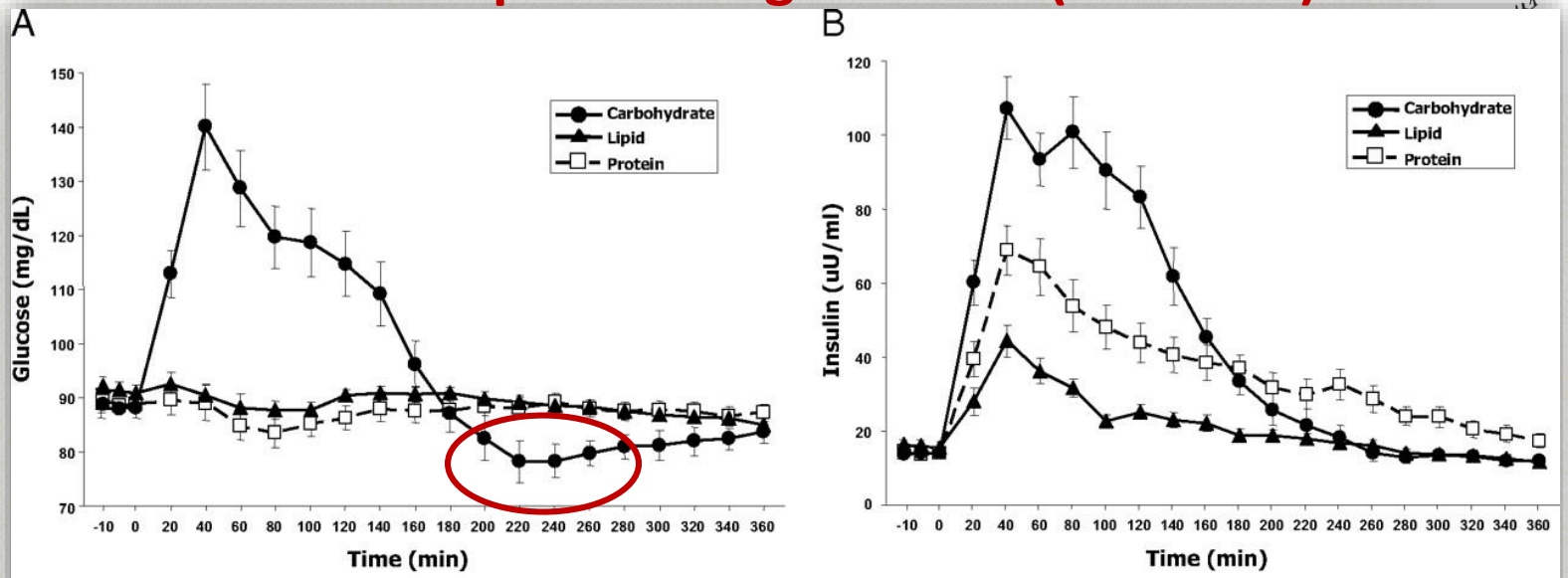
https://doi.org/10.1017/S0007114513000032 Published online: 18 February 2013

**„The reviewed literature suggests that the presence of intact structures not accessible to human amylases, as well as a reduced pH that may delay gastric emptying or create a barrier to starch digestion, seems to be more effective than dietary fibre *per se* in improving glucose metabolism, irrespective of the type of cereal."**

„All test beverages were equivalent in terms of their volume, total caloric content, and energy density."

**100 % purified ingredients! (80-10-10)**




## Acyl and Total Ghrelin Are Suppressed Strongly by Ingested Proteins, Weakly by Lipids, and Biphasically by Carbohydrates

FREE

Karen E. Foster-Schubert ✉, Joost Overduin, Catherine E. Prudom, Jianhua Liu, Holly S. Callahan, Bruce D. Gaylinn, Michael O. Thorner, David E. Cummings

*The Journal of Clinical Endocrinology & Metabolism*, Volume 93, Issue 5, 1 May 2008, Pages 1971–1979, https://doi.org/10.1210/jc.2007-2289

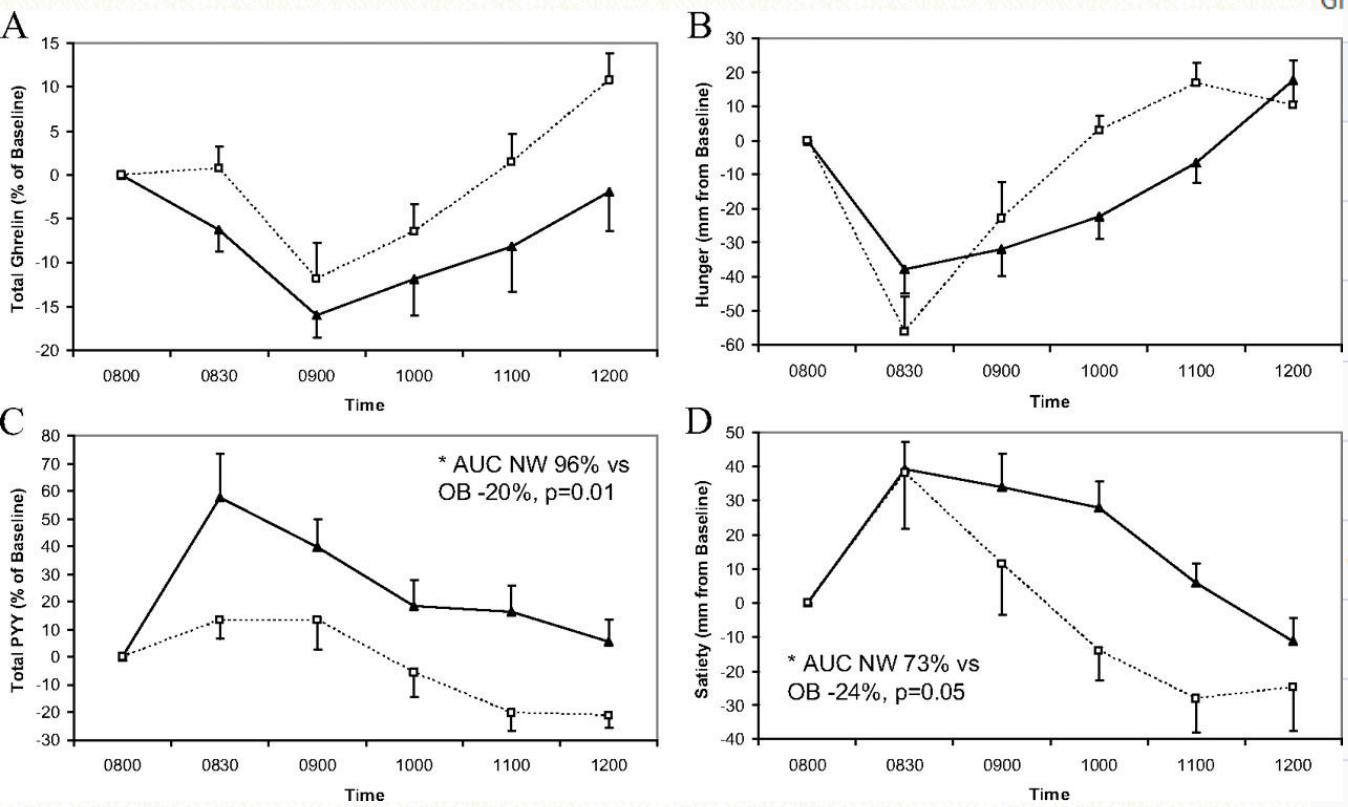



**Table 2**

Ghrelin, hunger, PYY, and satiety AUC comparisons within NW and OB groups to the three test meals

| | | Carbohydrate | Protein | Fat | *P* value |
|---|---|---|---|---|---|
| | | | 36-44-20 | | |
| NW | | 88-2-10 | | 17-2-81 | |
| | Ghrelin (%) | −36 ± 13 | −61 ± 10 | −42 ± 8 | F (2, 27) = 1.5; *P* = 0.24 |
| | Hunger (mm) | −63 ± 17 [a] | −137 ± 27 | −71 ± 27 [b] | F (2, 27) = 2.8; *P* = 0.08 |
| | PYY (%) | 96 ± 30 | 130 ± 35 | 163 ± 36 | F (2, 27) = 1.0; *P* = 0.39 |
| | Satiety (mm) | 73 ± 23 | 122 ± 26 | 97 ± 31 | F (2, 27) = 0.8; *P* = 0.44 |
| OB | | | | | |
| | Ghrelin (%) | −8 ± 10 | −28 ± 7 | −8 ± 10 | F (2, 26) = 1.6; *P* = 0.22 |
| | Hunger (mm) | −22 ± 22 [c] | −158 ± 42 | −63 ± 30 [d] | F (2, 26) = 4.7; *P* = 0.02 |
| | PYY (%) | −20 ± 27 [e] | 181 ± 34 | 53 ± 31 [f] | F (2, 26) = 11.3; *P* = 0.0003 |
| | Satiety (mm) | −24 ± 41 [g] | 170 ± 44 | 65 ± 36 [h] | F (2, 26) = 5.8; *P* = 0.008 |

Data are expressed as mean ± SE from baseline.

[a] *P* = 0.04 *vs.* protein;
[b] *P* = 0.06 *vs.* protein;
[c] *P* = 0.006 *vs.* protein;
[d] *P* = 0.05 *vs.* protein;
[e] *P* < 0.0001 *vs.* protein
[f] *P* = 0.007 *vs.* protein;
[g] *P* = 0.002 *vs.* protein;
[h] *P* = 0.08 *vs.* protein.

„The high-carbohydrate meal consisted of one Fruit Roll-up, one low-fat Pop-tart, one package of Sunkist fruit chews, and one juice box (430 kcal, 88% carbohydrate, 2% protein, 10% fat).”

„In conclusion, our data show that the macronutrient content of foods has differential effects on ghrelin and PYY secretion and appetite ratings in prepubertal children and are consistent with the observed effectiveness of high-protein/low-carbohydrate diets.”

## Effects of Meals High in Carbohydrate, Protein, and Fat on Ghrelin and Peptide YY Secretion in Prepubertal Children FREE

Jefferson P. Lomenick ✉, Maria S. Melguizo, Sabrina L. Mitchell, Marshall L. Summar, James W. Anderson

*The Journal of Clinical Endocrinology & Metabolism*, Volume 94, Issue 11, 1 November 2009, Pages 4463–4471, https://doi.org/10.1210/jc.2009-0949

RESEARCH ARTICLE

# A high carbohydrate, but not fat or protein meal attenuates postprandial ghrelin, PYY and GLP-1 responses in Chinese men

**Ehsan Parvaresh Rizi[1,2], Tze Ping Loh[3], Sonia Baig[1], Vanna Chhay[1], Shiqi Huang[4], Jonathan Caleb Quek[1], E. Shyong Tai[1,2,5], Sue-Anne Toh[1,2,5,6], Chin Meng Khoo[1,2]***

**1** Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, **2** Department of Medicine, National University Health System, Singapore, **3** Department of Laboratory Medicine, National University Health System, Singapore, **4** Food Science and Technology Program, Department of Chemistry, Faculty of Science, National University of Singapore, Singapore, **5** Duke-National University of Singapore Medical School, Singapore, **6** Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America

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## Abstract

It is known that the macronutrient content of a meal has different impacts on the postprandial satiety and appetite hormonal responses. Whether obesity interacts with such nutrient-dependent responses is not well characterized. We examined the postprandial appetite and satiety hormonal responses after a high-protein (HP), high-carbohydrate (HC), or high-fat (HF) mixed meal. This was a randomized cross-over study of 9 lean insulin-sensitive (mean ±SEM HOMA-IR 0.83±0.10) and 9 obese insulin-resistant (HOMA-IR 4.34±0.41) young (age 21–40 years), normoglycaemic Chinese men. We measured fasting and postprandial plasma concentration of glucose, insulin, active glucagon-like peptide-1 (GLP-1), total peptide-YY (PYY), and acyl-ghrelin in response to HP, HF, or HC meals. Overall postprandial plasma insulin response was more robust in the lean compared to obese subjects. The postprandial GLP-1 response after HF or HP meal was higher than HC meal in both lean and obese subjects. In obese subjects, HF meal induced higher response in postprandial PYY compared to HC meal. HP and HF meals also suppressed ghrelin greater compared to HC meal in the obese than lean subjects. In conclusion, a high-protein or high-fat meal induces a more favorable postprandial satiety and appetite hormonal response than a high-carbohydrate meal in obese insulin-resistant subjects.

# Satiety signaling based on macronutrients

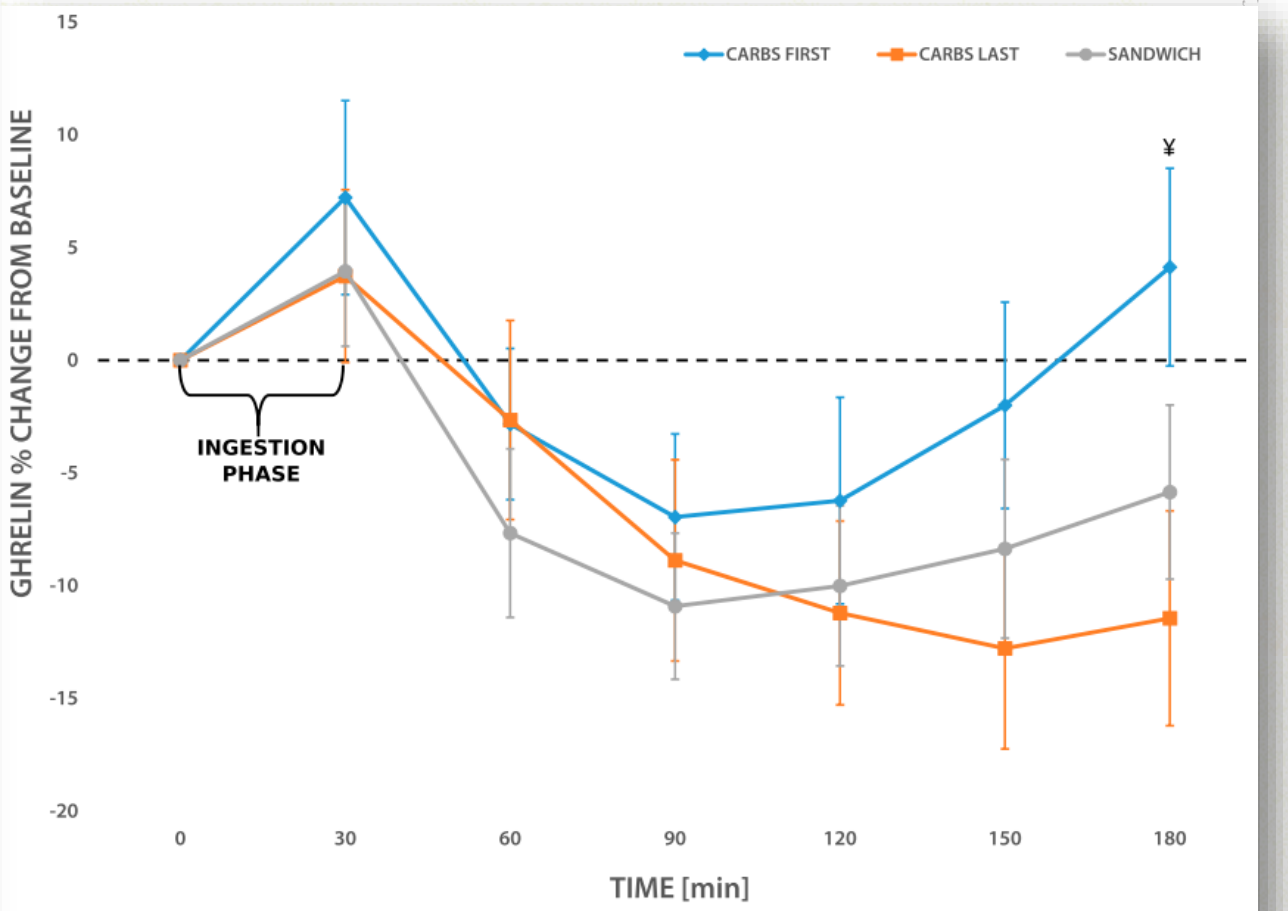



**Figure 1**—Ghrelin percent change from baseline following carbohydrate-first (carbs first), carbohydrate-last (carbs last), and sandwich meal orders. Values are mean ± SEM, $n = 16$. ¥Statistically significant difference ($P = 0.003$, linear mixed-effects model) between carbs first and carbs last at 180 min.

# Placement of carbohydrates

## High orange juice consumption with or in-between three meals a day differently affects energy balance in healthy subjects

Franziska A Hägele, Franziska Büsing, Alessa Nas, Julian Aschoff, Lena Gnädinger, Ralf Schweiggert, Reinhold Carle & Anja Bosy-Westphal

*Nutrition & Diabetes* **8**, Article number: 19 (2018)
doi:10.1038/s41387-018-0031-3
Download Citation

Received: 07 September 2017
Revised: 21 December 2017
Accepted: 07 February 2018
Published: 25 April 2018

After BM-intervention, fat mass increased (+1.0 ± 1.8 kg; $p < 0.05$) and postprandial insulin sensitivity tended to decrease (ΔMatsuda$_{ISI}$: −0.89 ± 2.3; $p = 0.06$). By contrast, after WM-intervention fat mass and gamma-glutamyl transferase (GGT) decreased (−0.30 ± 0.65 kg; −2.50 ± 3.94; both $p < 0.05$), whereas glucose variability was higher (ΔMAGE: +0.45 ± 0.59, $p < 0.05$). Daylong glycaemia, insulin secretion, changes in basal insulin sensitivity, and triglycerides did not differ between WM- and BM-interventions (all $p > 0.05$). In young healthy adults, a conventional 3-meal structure with orange juice consumed together with meals had a favorable impact on energy balance, whereas juice consumption in-between meals may contribute to a gain in body fat and adverse metabolic effects.

# Basic setup of the entero-insular axis

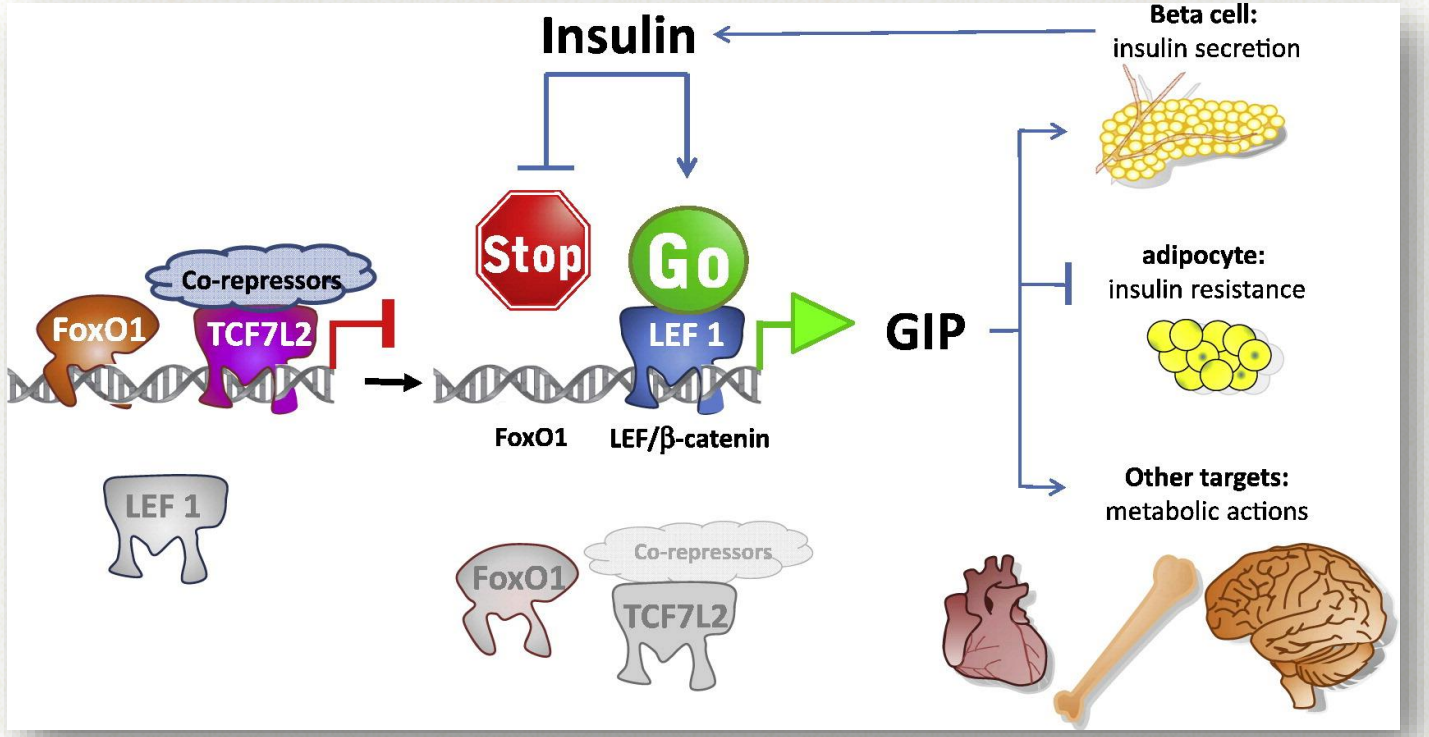
Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms

ELSEVIER

Volume 1839, Issue 11, November 2014, Pages 1141-1150

Insulin drives glucose-dependent insulinotropic peptide expression via glucose-dependent regulation of FoxO1 and LEF1/β-catenin

Jose Manuel García-Martínez [a, 1, 2], Ana Chocarro-Calvo [a, 1, 2, 3], Antonio De la Vieja [b], Custodia García-Jiménez



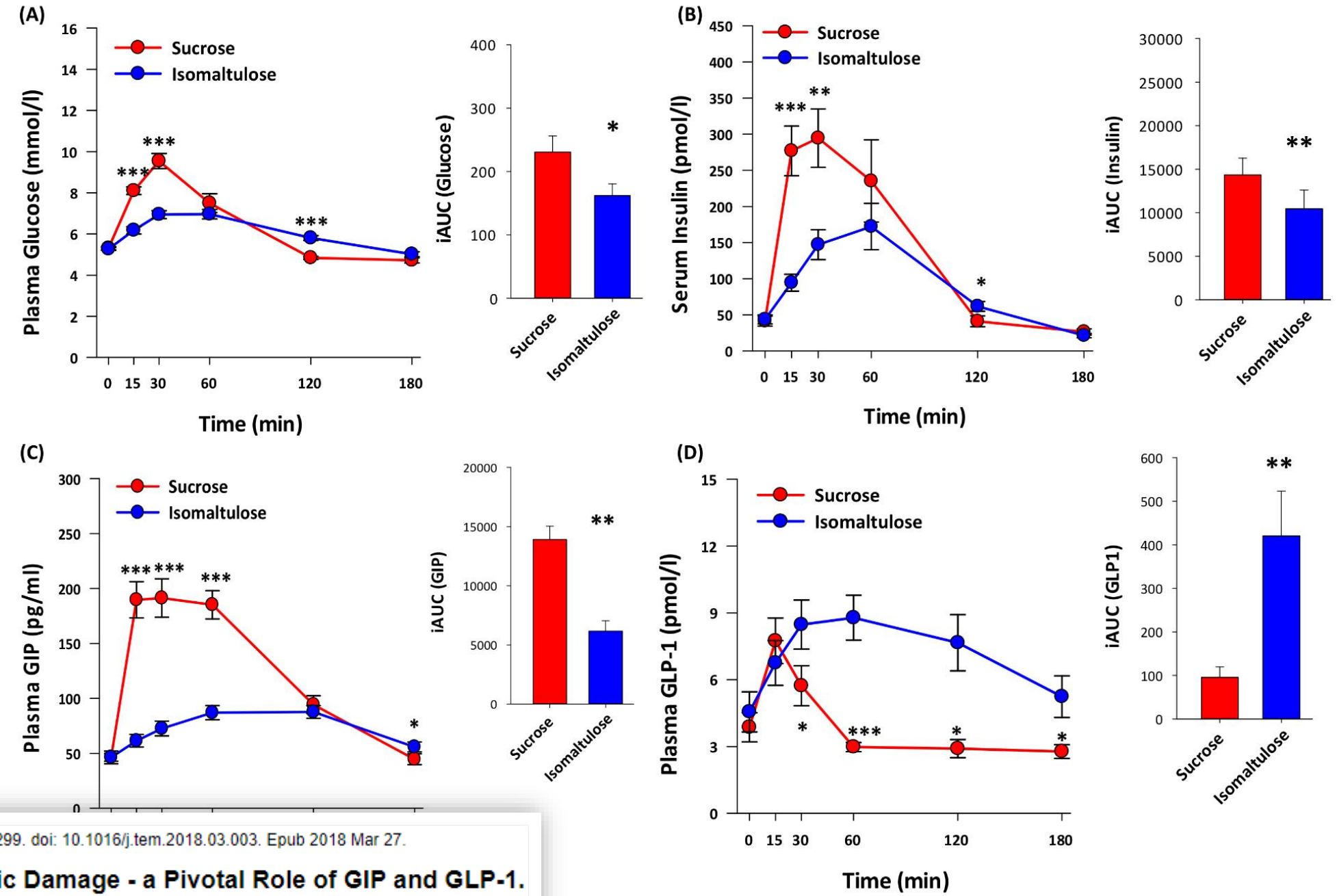

„…insulin stimulates the expression of the major human incretin, glucose-dependent insulinotropic peptide (GIP) in enteroendocrine cells but requires glucose to do it.

…

Our results reveal a glucose-regulated feedback loop at the entero-insular axis, where glucose levels determine basal and insulin-induced *Gip* expression;”

A nice model of the incretin imbalance: Sucrose vs. Isomaltulose <u>in healthy humans</u>

Pure forms not only have a huge effect on incretins, but also on plasma glucose and insulin.

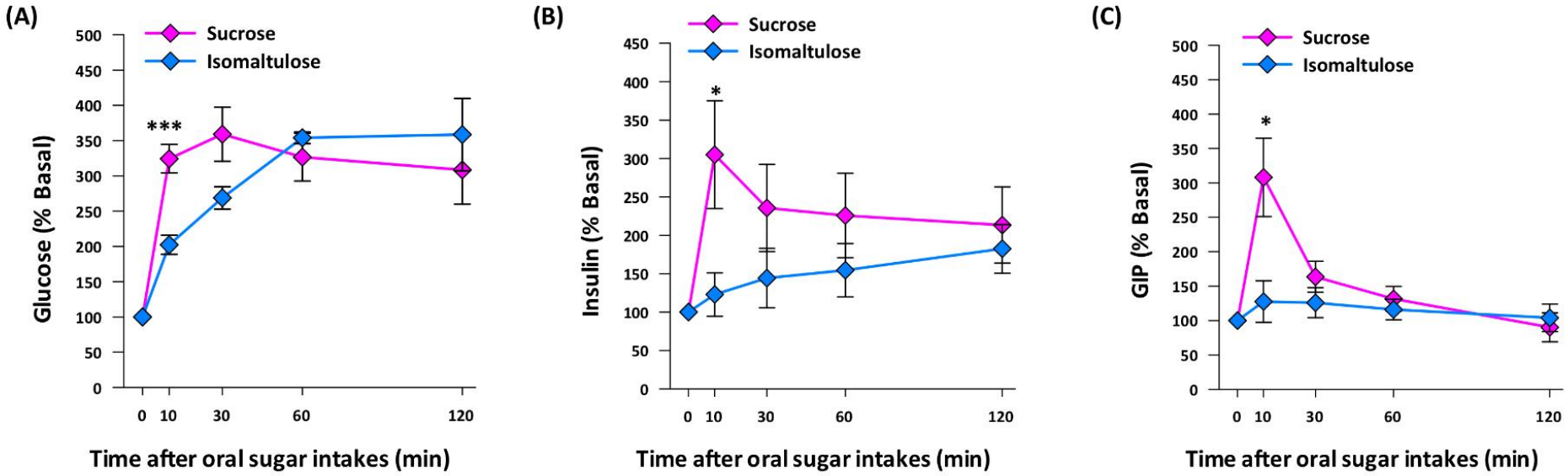



Trends Endocrinol Metab. 2018 May;29(5):289-299. doi: 10.1016/j.tem.2018.03.003. Epub 2018 Mar 27.

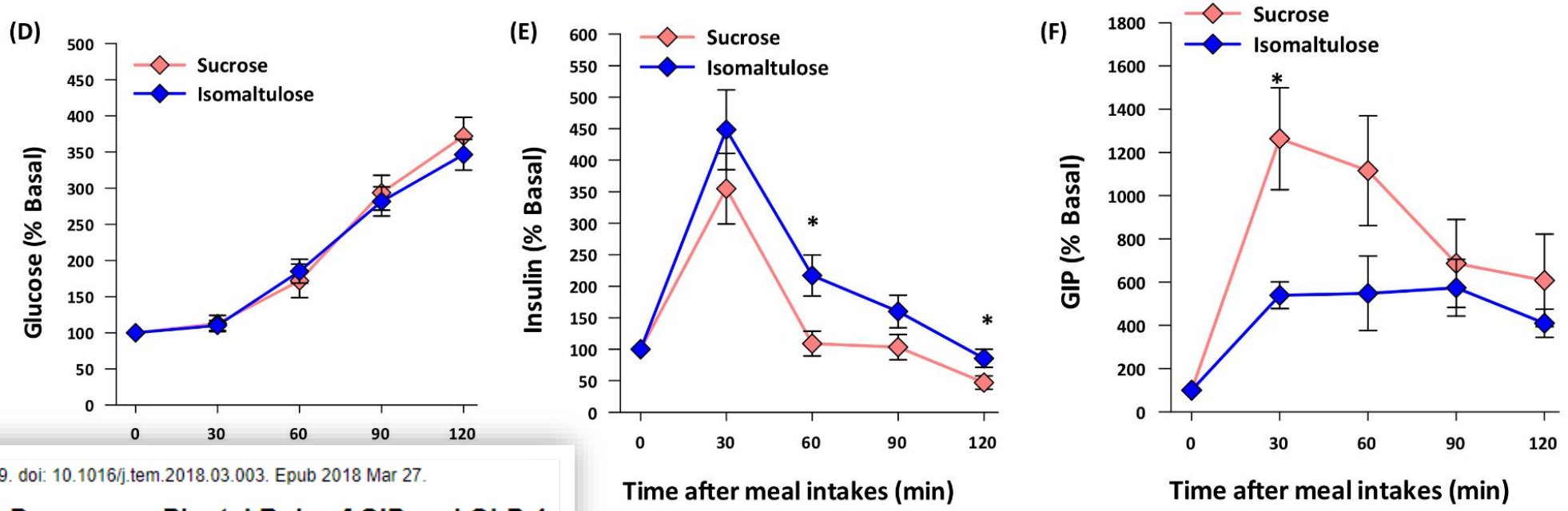
**High Glycemic Index Metabolic Damage - a Pivotal Role of GIP and GLP-1.**

Pfeiffer AFH[1], Keyhani-Nejad F[2].

Pure forms show the same response in mice. Sustained feeding with sucrose induces insulin resistance and fatty liver.




Mixed meal intake supplemented with these two sugars removes the effect on blood glucose and insulin, but it is even more pronounced on GIP. Fatty liver persists in the sucrose group.




Trends in Endocrinology & Metabolism

Trends Endocrinol Metab. 2018 May;29(5):289-299. doi: 10.1016/j.tem.2018.03.003. Epub 2018 Mar 27.

**High Glycemic Index Metabolic Damage - a Pivotal Role of GIP and GLP-1.**

Pfeiffer AFH[1], Keyhani-Nejad F[2].

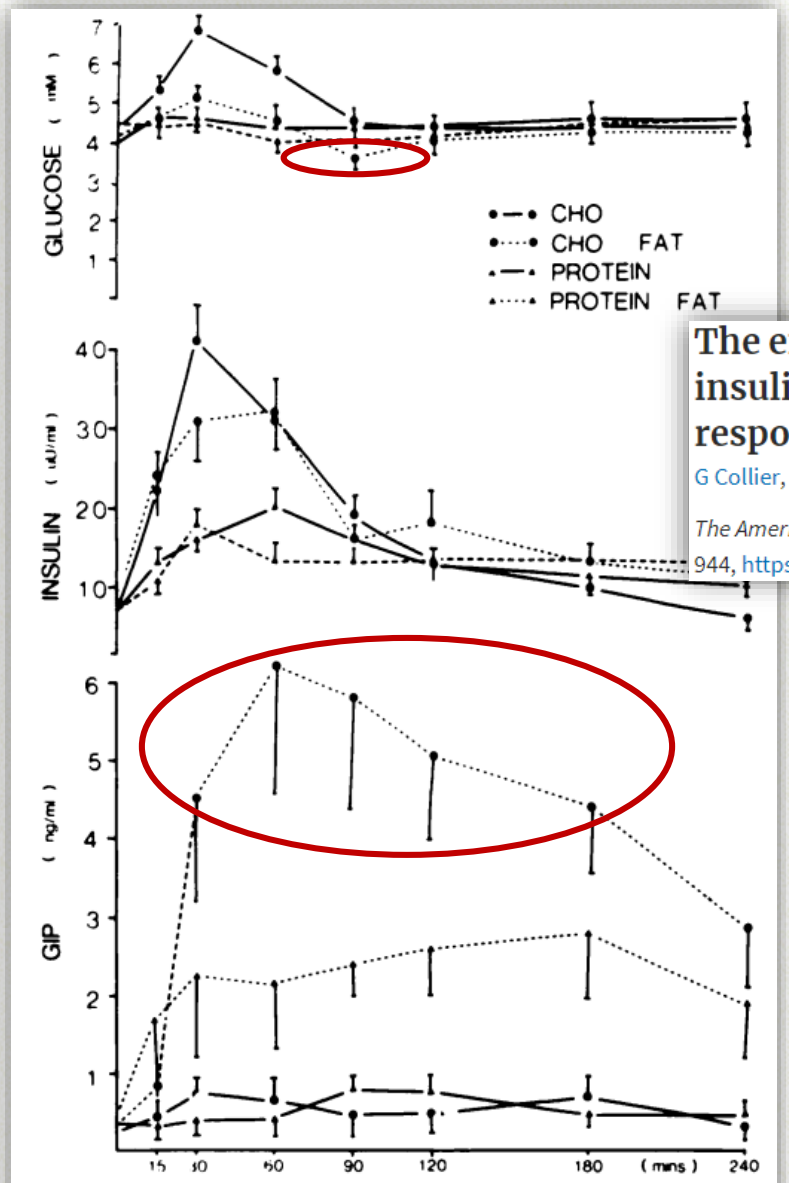



FIG 1. Plasma glucose, insulin, and GIP responses to 50 g carbohydrate ± 50 g fat and 50 g protein ± 50 g fat. Mean ± SEM (n = 8).

**Boiled potato, low-fat veal and butter (50 g from CHO, protein and fat)**

The effect of coingestion of fat on the glucose, insulin, and gastric inhibitory polypeptide responses to carbohydrate and protein

G Collier, K O'Dea

*The American Journal of Clinical Nutrition*, Volume 37, Issue 6, 1 June 1983, Pages 941-944, https://doi.org/10.1093/ajcn/37.6.941

**Perhaps it shouldn't be surprising that the only outlier is the combination that doesn't occur in nature? => Pre-digested carbohydrate with substantial amount of fat added on top.**

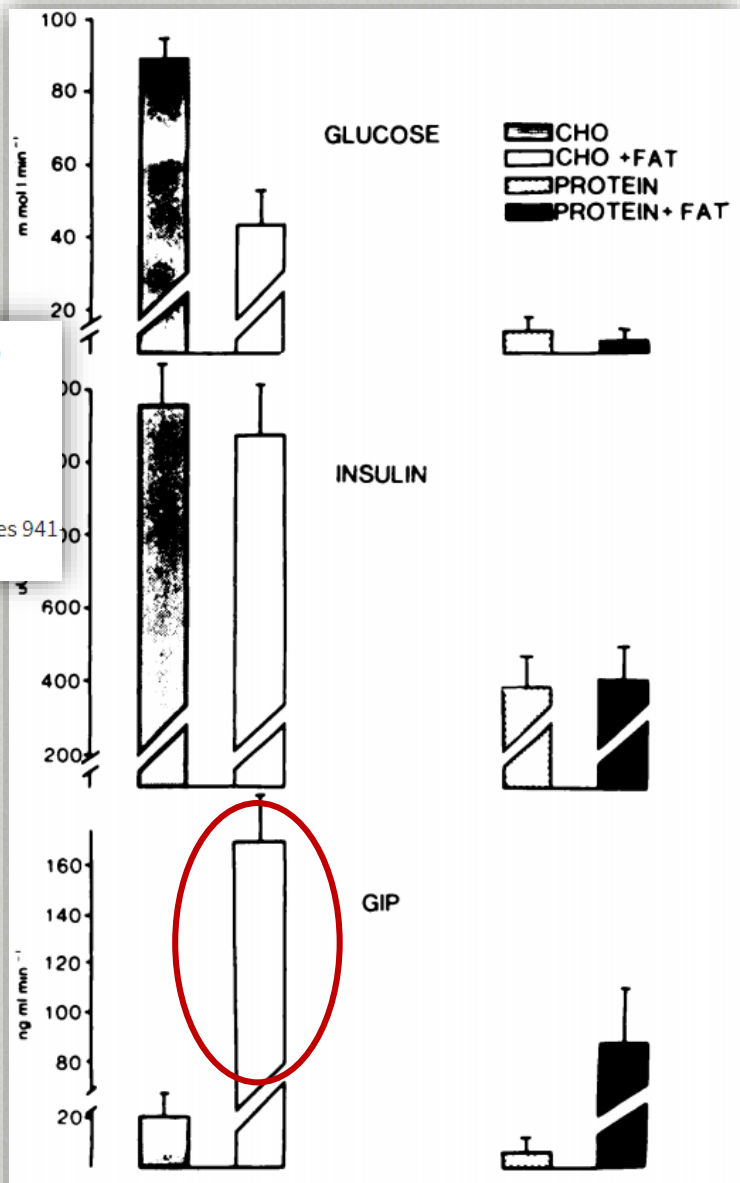



FIG 2. Areas under the incremental curves for glucose, insulin, and GIP for the 1st h after ingestion of 50 g carbohydrate ± 50 g fat and 50 g protein ± 50 g fat. Mean ± SEM (n = 8).

Trends Endocrinol Metab. 2018 May;29(5):289-299. doi: 10.1016/j.tem.2018.03.003. Epub 2018 Mar 27.

**High Glycemic Index Metabolic Damage - a Pivotal Role of GIP and GLP-1.**

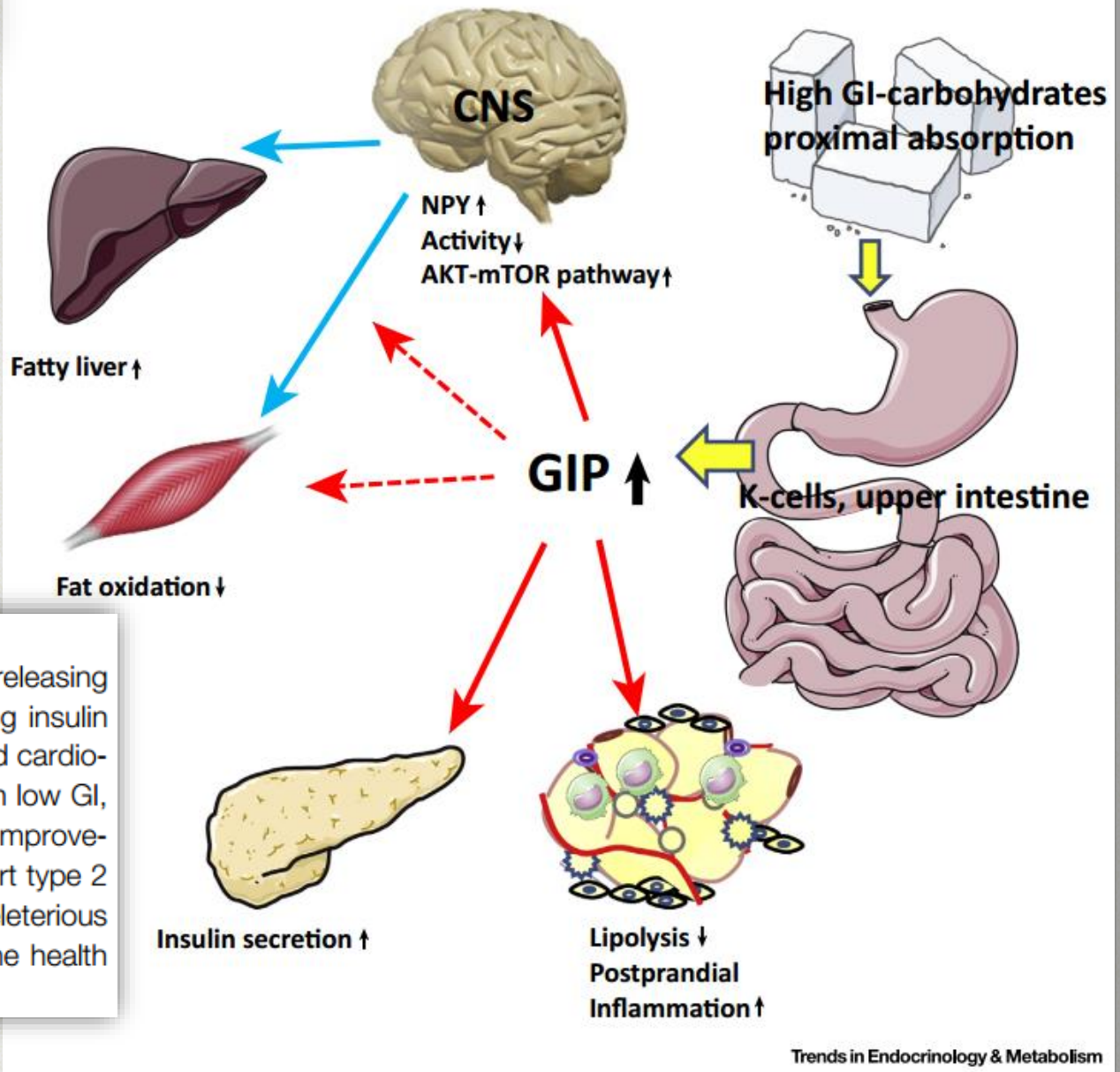
Pfeiffer AFH[1], Keyhani-Nejad F[2].

GIP is not inherently bad, nor GLP-1 is inherently good. Interestingly, GLP1R KO mice are also protected against metabolic damage caused by HFD. It's a system that plays a major role in conveying environmental (food) signals to the organismal metabolism. The tilting balance may be an important signal between storage and usage.

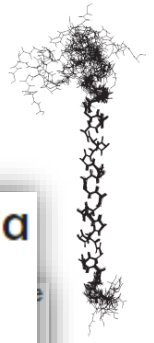
## Concluding Remarks

In summary, high-GI carbohydrates differ from low-GI carbohydrates, specifically by releasing GIP. There is ample evidence for metabolically unfavorable effects of GIP regarding insulin sensitivity, fatty liver disease, subclinical inflammation, and promotion of diabetes and cardiovascular disease (Figure 4). The hormonal responses of the intestine to a sugar with low GI, which induces little release of GIP but greater amounts of GLP-1, result in metabolic improvements in healthy individuals and in people with impaired glucose metabolism or overt type 2 diabetes, providing strong evidence that GIP plays a central role in mediating the deleterious effects of high-GI foods, while reducing the release of GIP may explain much of the health benefits of low GI foods.

Summary of GIP Actions Regulating Metabolism in Response to High-GI Food Intake



# Detrimental effects of the incretin imbalance



Disruption of GIP/GIPR Axis in Human Adipose Tissue Is Linked to Ob… Insu…

Victòria…

Chronic Reducti…

GIP Contributes to Islet Trihormonal Abr… in Type 2 Diabetes FREE

Chee W. Chia ✉, Juliana O. Odetunde, Wook Kim, Olga D. Carlson, Lui…, Josephine M. Egan

*The Journal of Clinical Endocrinology & Metabolism*, Volume 99, Issue 7, 1 July 2014, Pages 2477–2485, https://doi.org/10.1210/jc.2013-3994

Increased GIP signaling induces adipose inflammation via a HIF-1α-dependent pathway and impairs insulin sensitivity in mice

Shu Chen, Fumiaki Okahara, Noriko Osaki, and Akira Shimotoyodome ✉

1 MAR 2015 // https://doi.org/10.1152/ajpendo.00418.2014

Targ… Insul… Tran…

Resistance Induced by a High Fat Diet

Matthew C. Althage‡, Eric L. Ford‡, Songyan Wang‡, Patrick Tso§, Kenneth S. Polonsky‡ and Burton M. Wice‡,1

This Article

First Published on April 17, 2008

doi: 10.1074/jbc.M710466200

…tab.kuhp.kyoto-u.ac.jp.

…0.2337/db13-1563

…vents obesity

…a, Katsushi Tsukiyama, Heying Zhou, …i, Hiroshi Hiai, Wataru Mizunoya, Tohru …

…ens Juul Holst, Mitsuhiro Makino, Akira Tashita, Yukari Kobara, Yoshiharu Tsubamoto, …i Jinnouchi, Takahito Jomori & Yutaka Seino ✉

1 JAN 2013 // https://doi.org/10.1152/ajpendo.00100.2012

*Medicine* **8**, 738–742 (2002)

doi:10.1038/nm727

Received: 01 March 2002

Accepted: 24 May 2002

Glucose-dependent insulinotropic peptide i… insulin signaling *via* inducing adipocyte inflammation in glucose-dependent insulin… peptide receptor-overexpr…

Yaohui Nie, Ronald C. Ma, Juliana C. N. Chan, Haiyan …

**Published Online:** 24 Feb 2012 | https://doi.org/10.…

Elevated plasma glucose-dependent insulinotropic polypeptide associates with hyperinsulinemia in metabolic syndrome

Salvatore Calanna, Francesca Urbano, Salvatore Piro, Rose Maria Zagami, …varova, Michael Kruse, Anne-Cathrin Seltmann, …. Pfeiffer

This Article

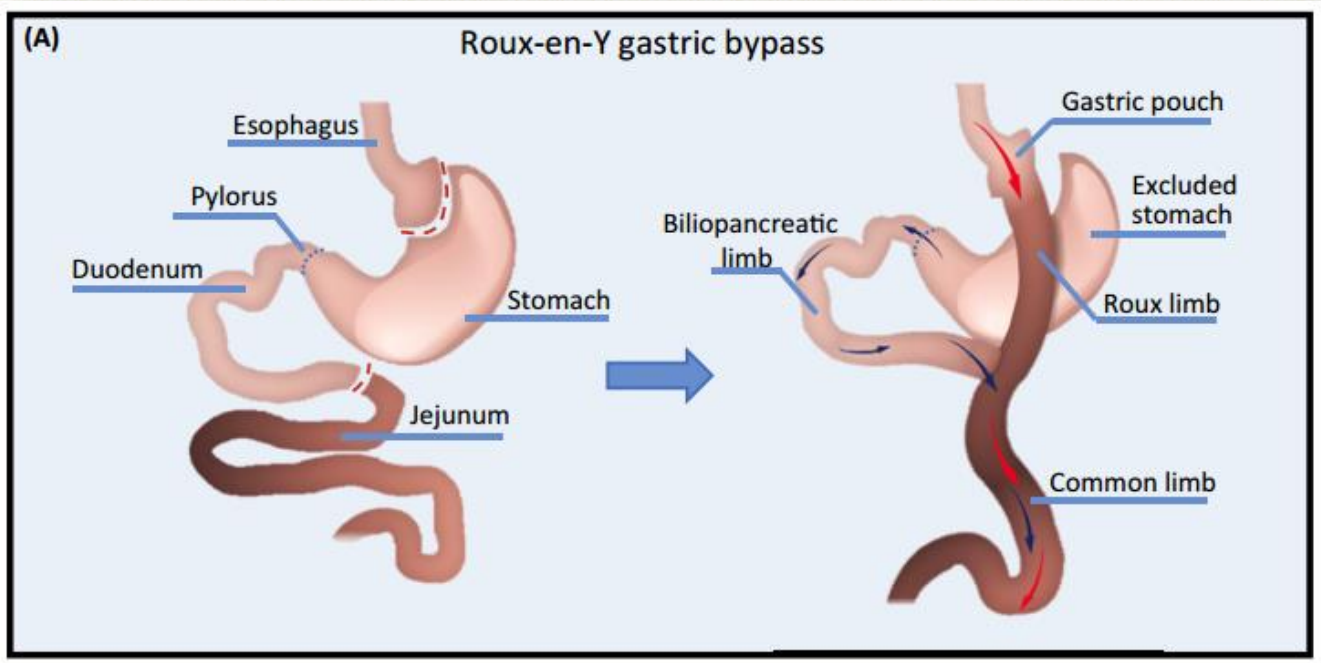
Published online before print March 5, 2012, doi: 10.1530/EJE-11-0765

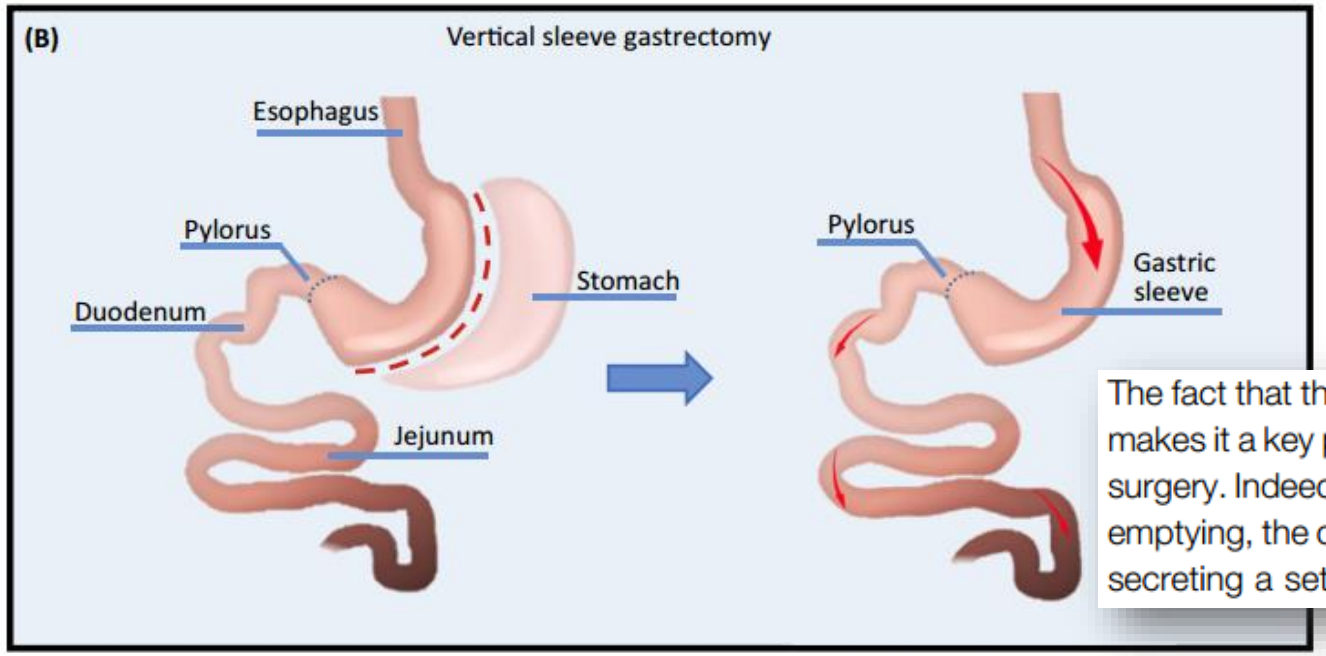
Eur J Endocrinol May 1, 2012 166 917-922

Gastric inhibitory p… attenuates development of obesity in mice

Michael O. Boylan, Patricia A. Glazebrook, Milos Tatalovic, and M. Michael Wolfe ✉

15 DEC 2015 // https://doi.org/10.1152/ajpendo.00345.2015




Trends in Endocrinology & Metabolism

**Trends in Endocrinology & Metabolism**
Volume 28, Issue 5, May 2017, Pages 354-364
CellPress

Review

## Intestinal Adaptations after Bariatric Surgery: Consequences on Glucose Homeostasis

Jean-Baptiste Cavin [1], André Bado [1], Maude Le Gall [1]

# Diabetes: How bariatric (bypass) surgery works

The fact that the gastrointestinal (GI) tract is the direct target of bariatric procedures potentially makes it a key player, although so far underestimated, in the metabolic changes observed after surgery. Indeed, the GI tract can play a direct role in glucose homeostasis by modulating gastric emptying, the digestion of carbohydrates, and absorption of glucose during meals, and also by secreting a set of hormones, including incretins that regulate the release of insulin [6].

Gastroenterology Research and Practice
Volume 2015, Article ID 625196, 4 pages
http://dx.doi.org/10.1155/2015/625196

**Research Article**

# Effect of Modified Roux-en-Y Gastric Bypass Surgery on GLP-1, GIP in Patients with Type 2 Diabetes Mellitus

Shao-Wei Xiong,[1] Jing Cao,[1] Xian-Ming Liu,[1] Xing-Ming Deng,[1] Zeng Liu,[1] and Fang-Ting Zhang[2]

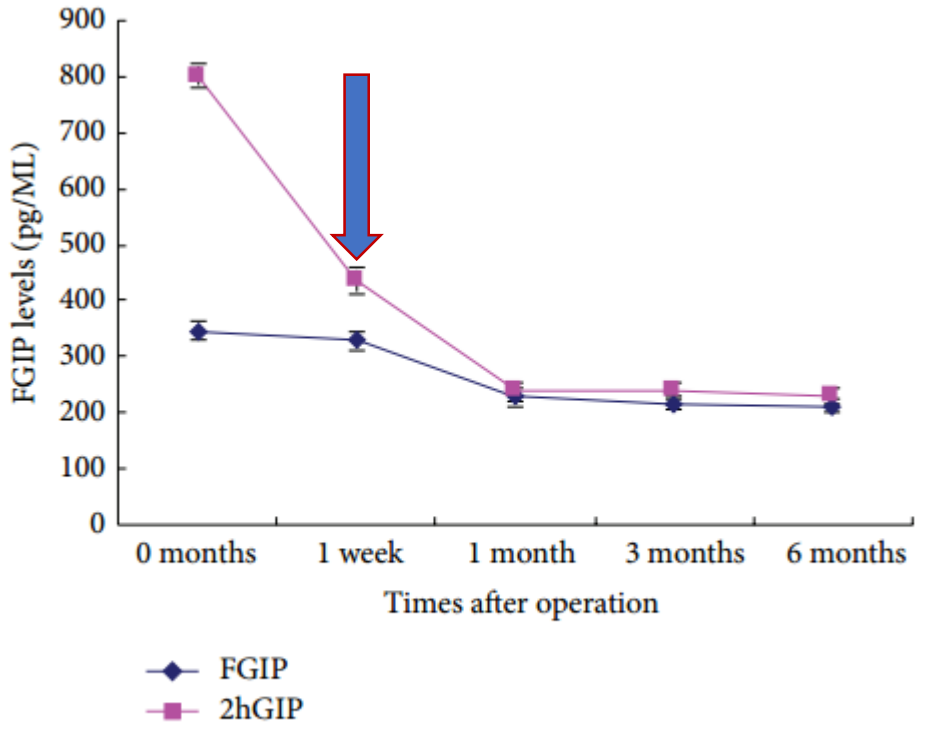



FIGURE 2: FGIP levels before and after the surgery.

TABLE 2: Comparison of GLP-1 and GIP levels before and after the surgery.

| | $n$ | FGLP-1 | 2hGLP-1 | FGIP | 2hGIP |
|---|---|---|---|---|---|
| 0 mo | 50 | 6.5 ± 1.3 | 11.9 ± 1.6$^{*}$ | 347 ± 16 | 801 ± 21$^{*}$ |
| 1 wk | 50 | 9.3 ± 1.1$^{*}$ | 19.7 ± 2.0$^{▲\#}$ | 328 ± 15 | 436 ± 25$^{▲}$ |
| 1 mo | 50 | 11.6 ± 1.7$^{▲}$ | 23.7 ± 1.9$^{▲\#}$ | 229 ± 16$^{*}$ | 238 ± 17$^{▲}$ |
| 3 mo | 50 | 17.9 ± 1.9$^{▲}$ | 28.9 ± 2.1$^{▲\#}$ | 217 ± 12$^{*}$ | 241 ± 15$^{▲}$ |
| 6 mo | 50 | 18.1 ± 1.8$^{▲}$ | 29.2 ± 2.2$^{▲\#}$ | 213 ± 14$^{*}$ | 230 ± 13$^{▲}$ |

Data are shown as mean ± SD, FGLP-1 and 2hFGLP-1 (pmol/L), FGIP, and 2hFGIP (pg/ML).
Compared with the before surgery (0 months) group $^{*}P < 0.05$, $^{▲}P < 0.01$.
Comparison of the same point in time $^{\#}P < 0.01$.

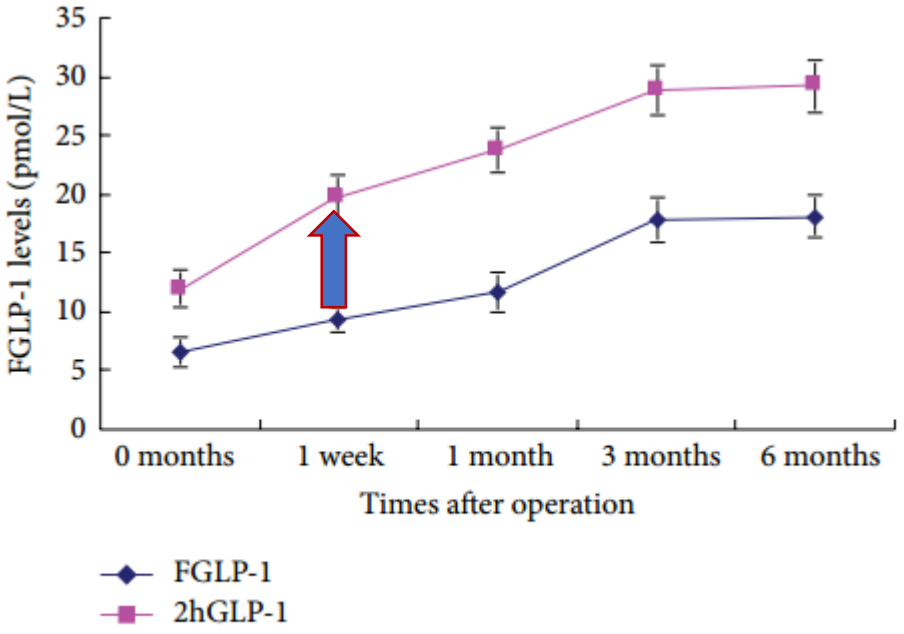
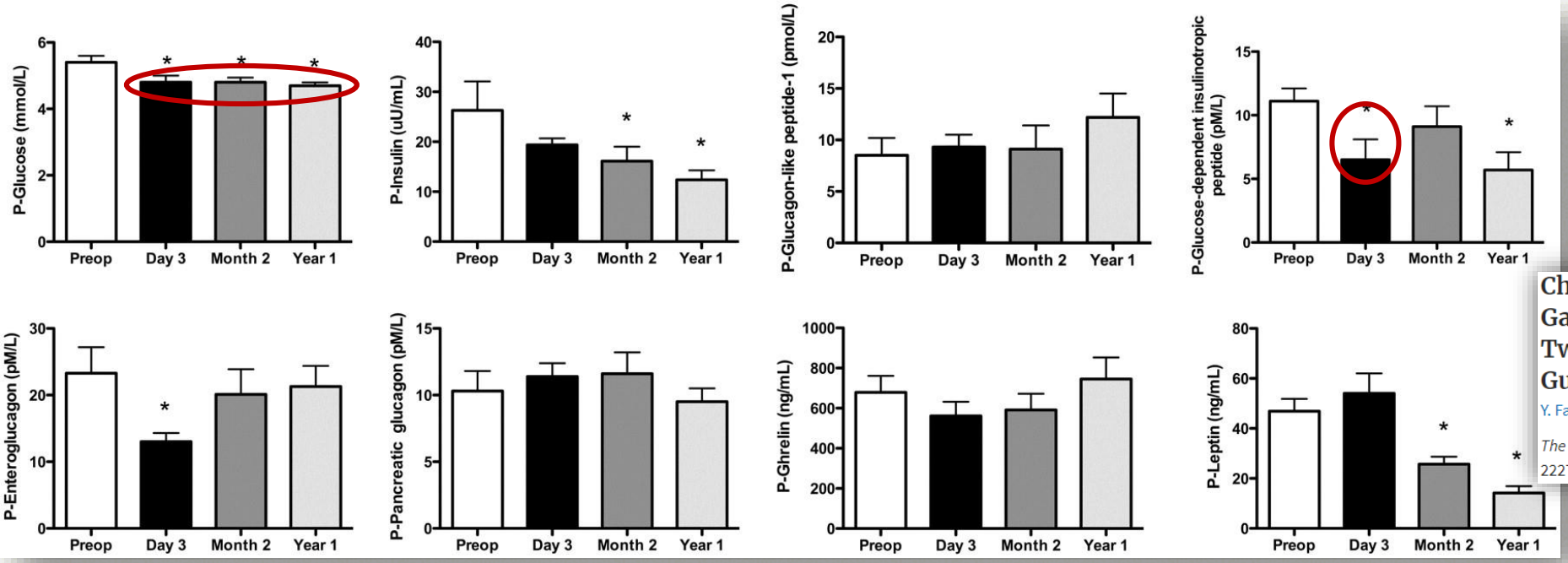



FIGURE 1: FGLP-1 levels before and after the surgery.

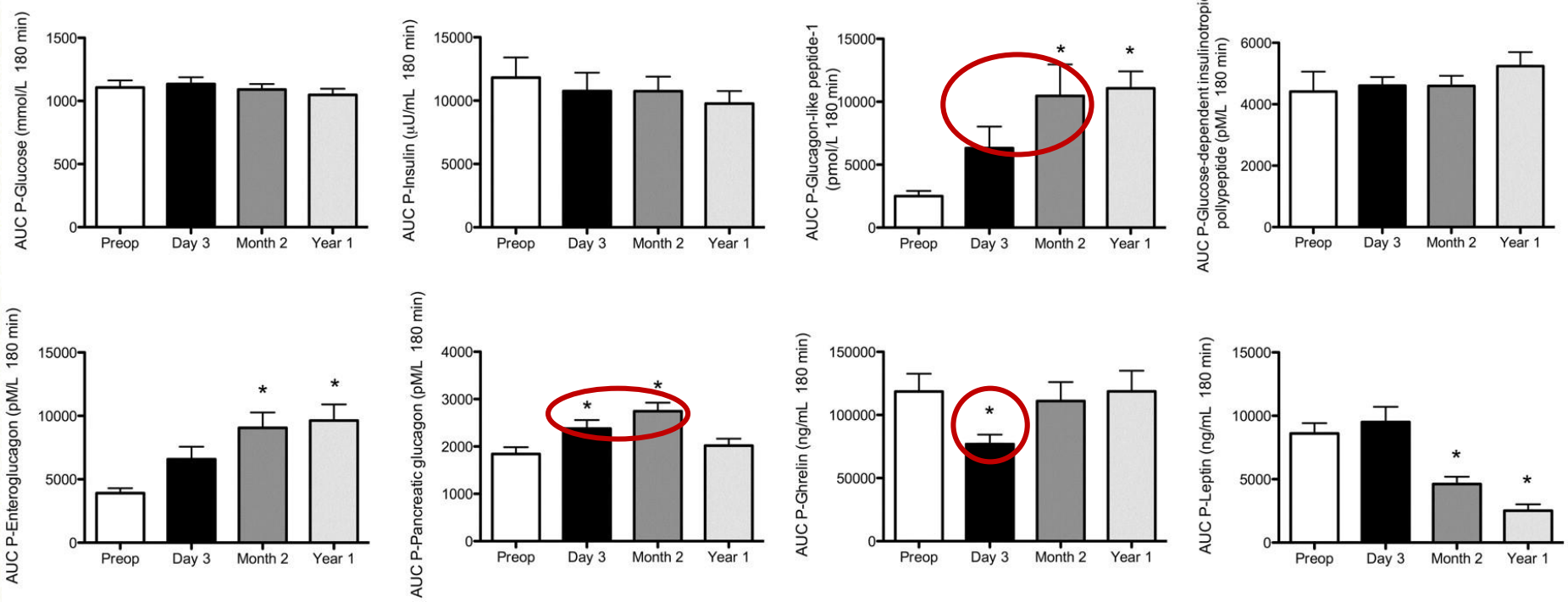



Changes in Glucose Homeostasis after Roux-en-Y Gastric Bypass Surgery for Obesity at Day Three, Two Months, and One Year after Surgery: Role of Gut Peptides FREE

Y. Falkén ✉, P. M. Hellström, J. J. Holst, E. Näslund

*The Journal of Clinical Endocrinology & Metabolism*, Volume 96, Issue 7, 1 July 2011, Pages 2227–2235, https://doi.org/10.1210/jc.2010-2876

# RYGB effects on non-diabetics



# Effect of the Duodenal-Jejunal Bypass Liner on Glycemic Control in Patients With Type 2 Diabetes With Obesity: A Meta-analysis With Secondary Analysis on Weight Loss and Hormonal Changes

Pichamol Jirapinyo[1,2], Andrea V. Haas[2,3] and Christopher C. Thompson[1,2]⇑

Author Affiliations

Corresponding author: Christopher C. Thompson, cthompson@hms.harvard.edu.

Diabetes Care 2018 May; 41(5): 1106-1115. https://doi.org/10.2337/dc17-1985

**RESULTS**

**Primary outcomes were change in $HbA_{1c}$ and HOMA of insulin resistance (HOMA-IR). Secondary outcomes were change in weight and gut hormones glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and ghrelin. Seventeen studies were included. At explant, $HbA_{1c}$ decreased by 1.3% [95% CI 1.0, 1.6] and HOMA-IR decreased by 4.6 [2.9, 6.3]. Compared with control subjects, DJBL subjects had greater $HbA_{1c}$ reduction by 0.9% [0.5, 1.3]. Six months after explant, $HbA_{1c}$ remained lower than baseline by 0.9% [0.6, 1.2]. At explant, patients lost 11.3 kg [10.3, 12.2], corresponding to a BMI reduction of 4.1 kg/$m^2$ [3.4, 4.9], total weight loss of 18.9% [7.2, 30.6], and excess weight loss of 36.9% [29.2, 44.6]. The amount of weight loss remained significant at 1 year postexplantation. After DJBL, GIP decreased, whereas GLP-1, PYY, and ghrelin increased.**

**CONCLUSIONS**

**DJBL improves glycemic control and insulin resistance in T2D patients with obesity. DJBL also appears to induce significant weight loss in this population. Additionally, changes in gut hormones suggest mechanisms similar to RYGB. Study limitations included heterogeneity among studies.**

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

# Comparisons of the effects of 12-week administration of miglitol and voglibose on the responses of plasma incretins after a mixed meal in Japanese type 2 diabetic patients

T. Narita, H. Yokoyama, R. Yamashita, T. Sato, M. Hosoba, T. Morii, H. Fujita, K. Tsukiyama, Y. Yamada

First published: 03 November 2011 | https://doi.org/10.1111/j.1463-1326.2011.01526.x | Cited by: 38

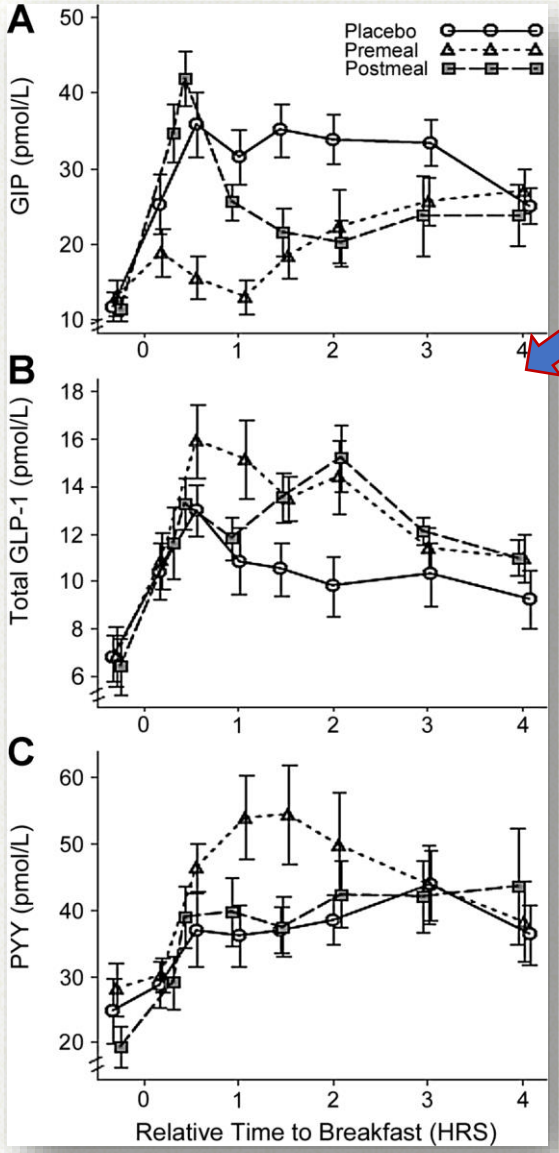
To compare the effects of miglitol [an alpha-glucosidase inhibitor (AGI) absorbed in the intestine] and voglibose (an AGI not absorbed) on plasma glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) levels, 26 and 24 Japanese type 2 diabetic patients were randomly assigned to receive miglitol or voglibose, respectively. After 12-week administration of both drugs, during 2-h meal tolerance test, plasma glucose, serum insulin and total GIP were significantly decreased and active GLP-1 was significantly increased. Miglitol group showed a significantly lower total GIP level than voglibose group. Miglitol, but not voglibose, significantly reduced body weight (BW). In all participants, the relative change in BW was positively correlated with that of insulin significantly and of GIP with a weak tendency, but not of GLP-1. In conclusion, both drugs can enhance postprandial GLP-1 responses and reduce GIP responses. The significant BW reduction by miglitol might be attributable to its strong GIP-reducing efficacy.

*Am J Physiol Gastrointest Liver Physiol* 308: G946–G954, 2015.
First published March 12, 2015; doi:10.1152/ajpgi.00286.2014.

# Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release

Robert L. Dobbins,[1] Frank L. Greenway,[2] Lihong Chen,[1] Yaping Liu,[1] Sharon L. Breed,[1] Susan M. Andrews,[1] Jeffrey A. Wald,[1] Ann Walker,[1] and Chari D. Smith[1]

## Gastric bypass surgery in a pill!

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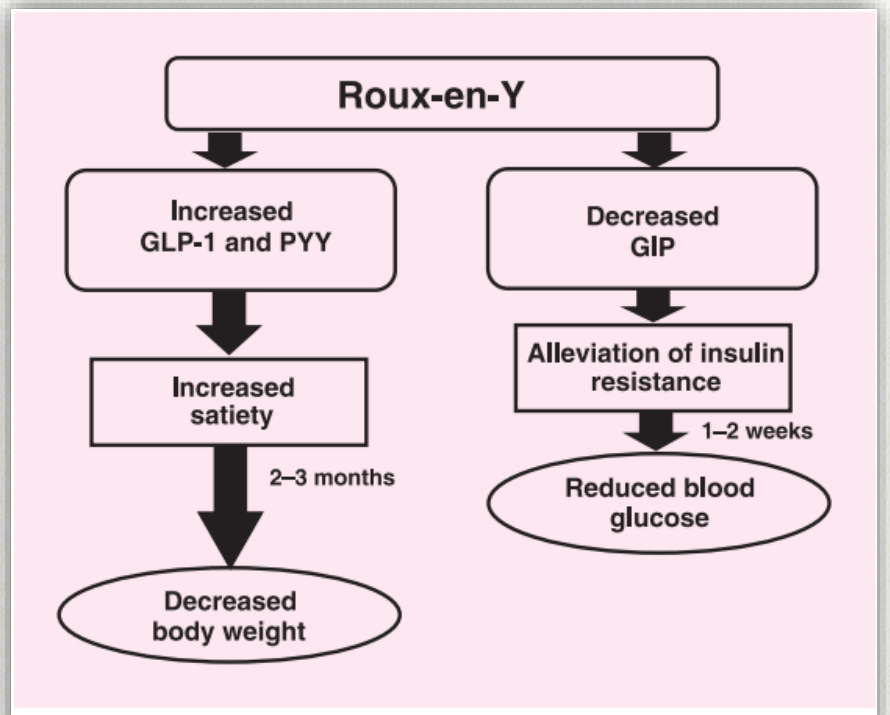


**FIGURE 3** Role of endocrine changes in alleviation of insulin resistance, glucose intolerance, satiety and weight loss following Roux-en-Y bypass surgery. GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; PYY, peptide YY.

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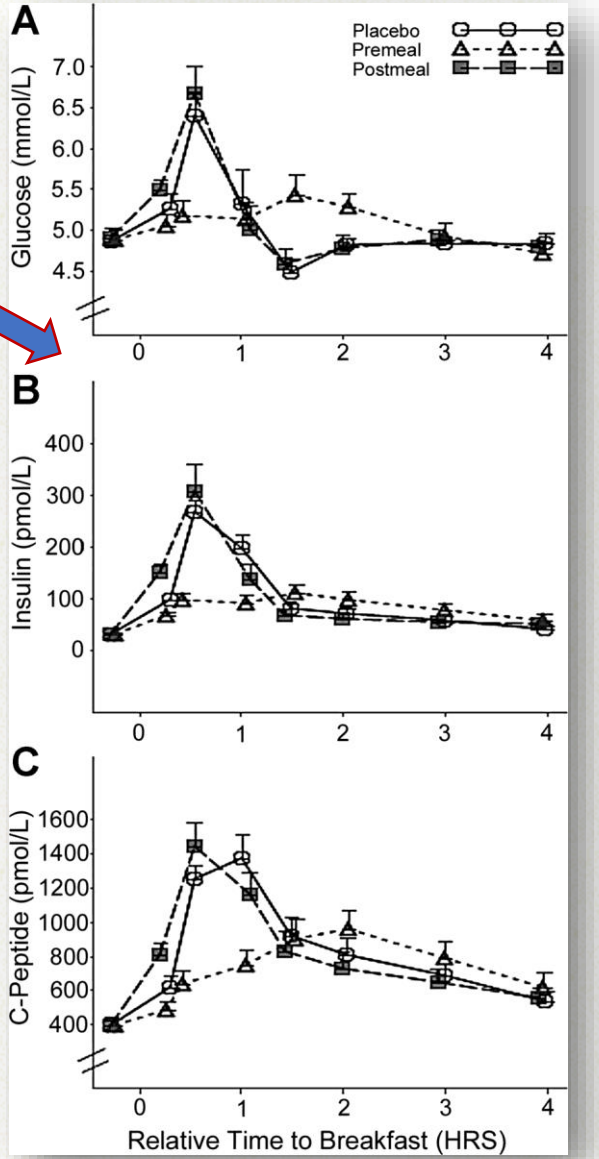


JAMA | Original Investigation

# Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

## A Systematic Review and Meta-analysis

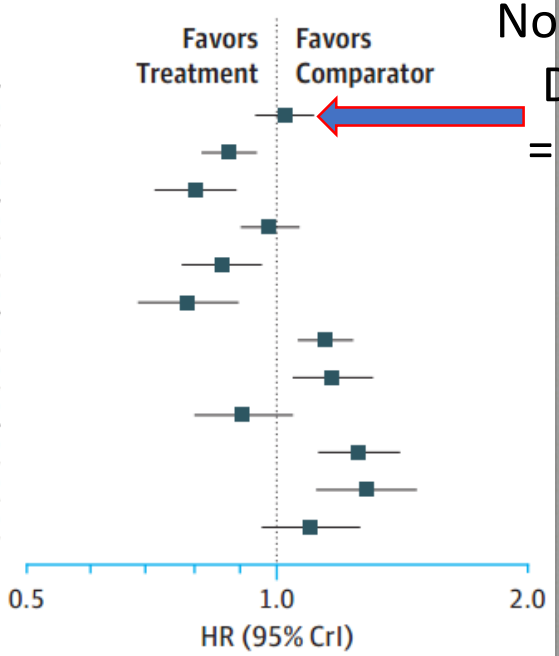
Sean L. Zheng, BM BCh, MA, MRCP; Alistair J. Roddick, BSc; Rochan Aghar-Jaffar, BMedSci, BMBS, MRCP; Matthew J. Shun-Shin, BM BCh, MRCP; Darrel Francis, MB BChir, FRCP, MD; Nick Oliver, MBBS, FRCP; Karim Meeran, MBBS, MD, FRCP, FRCPath

**Figure 3. Forest Plots for All-Cause Mortality, Cardiovascular Mortality, and Heart Failure**

A Primary outcome: all-cause mortality, 97 trials; $I^2 = 12\%$

| Treatment | Comparator | Absolute RD (95% CrI), % | HR (95% CrI) |
|---|---|---|---|
| DPP-4 inhibitor | vs Control | 0.1 (-0.3 to 0.6) | 1.02 (0.94 to 1.11) |
| GLP-1 agonist | | -0.6 (-1.0 to -0.3) | 0.88 (0.81 to 0.94) |
| SGLT-2 inhibitor | | -1.0 (-1.5 to -0.6) | 0.80 (0.71 to 0.89) |
| Control | vs DPP-4 inhibitor | -0.1 (-0.4 to 0.2 ) | 0.98 (0.90 to 1.06) |
| GLP-1 agonist | | -0.5 (-0.9 to -0.2) | 0.86 (0.77 to 0.96) |
| SGLT-2 inhibitor | | -0.9 (-1.2 to -0.4) | 0.78 (0.68 to 0.90) |
| Control | vs GLP-1 agonist | 0.6 (0.3 to 1.0) | 1.14 (1.06 to 1.23) |
| DPP-4 inhibitor | | 0.7 ( 0.2 to 1.3 ) | 1.17 (1.04 to 1.30) |
| SGLT-2 inhibitor | | -0.4 (-0.9 to 0.2 ) | 0.91 (0.79 to 1.04) |
| Control | vs SGLT-2 inhibitor | 0.9 (0.4 to 1.5) | 1.25 (1.12 to 1.40) |
| DPP-4 inhibitor | | 1.0 (0.4 to 1.7) | 1.28 (1.11 to 1.47) |
| GLP-1 agonist | | 0.4 (-0.1 to 0.9 ) | 1.10 (0.96 to 1.26) |

| Treatment | No. of Trials | No. With Events (%) | Total No. of Patients |
|---|---|---|---|
| Control | 88 | 2955 (5.2) | 57022 |
| DPP-4 inhibitor | 49 | 1171 (3.9) | 30178 |
| GLP-1 agonist | 32 | 1195 (4.4) | 27373 |
| SGLT-2 inhibitor | 29 | 714 (3.6) | 19587 |



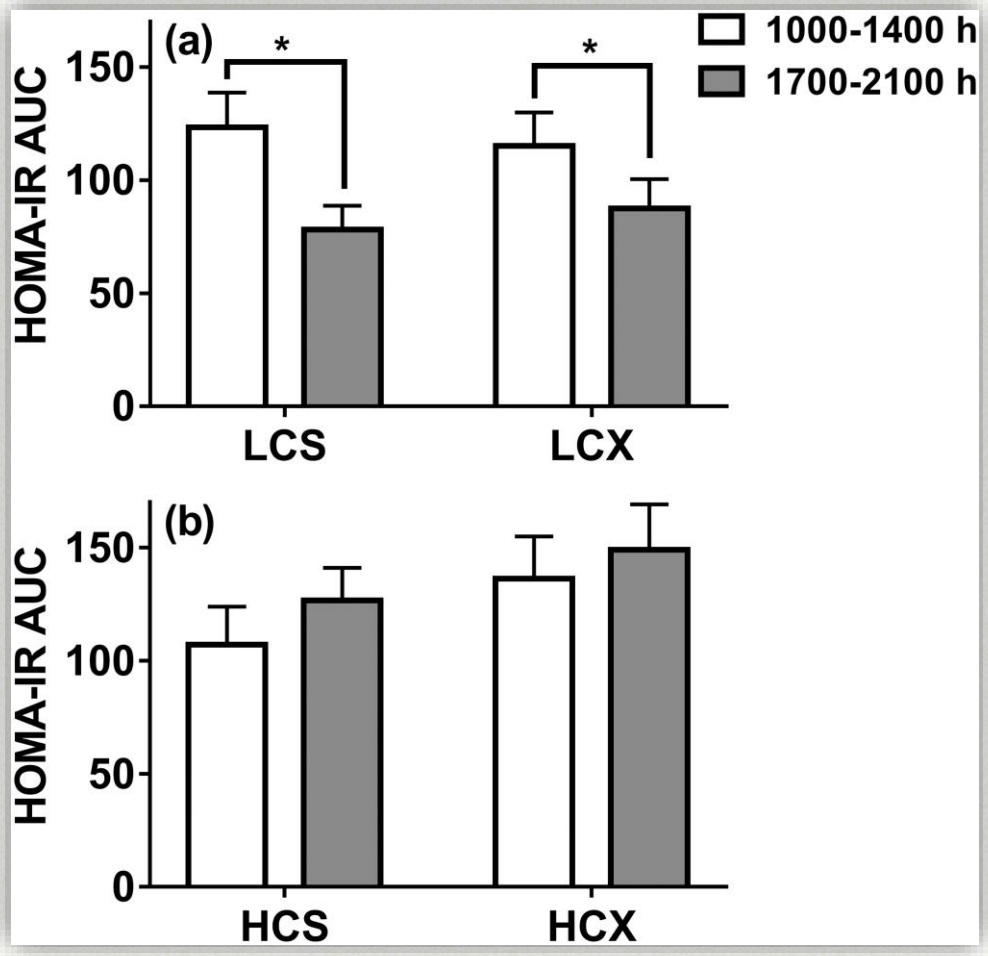

Not saving lives with DPP4 inhibition!
= maintaining the imbalance?

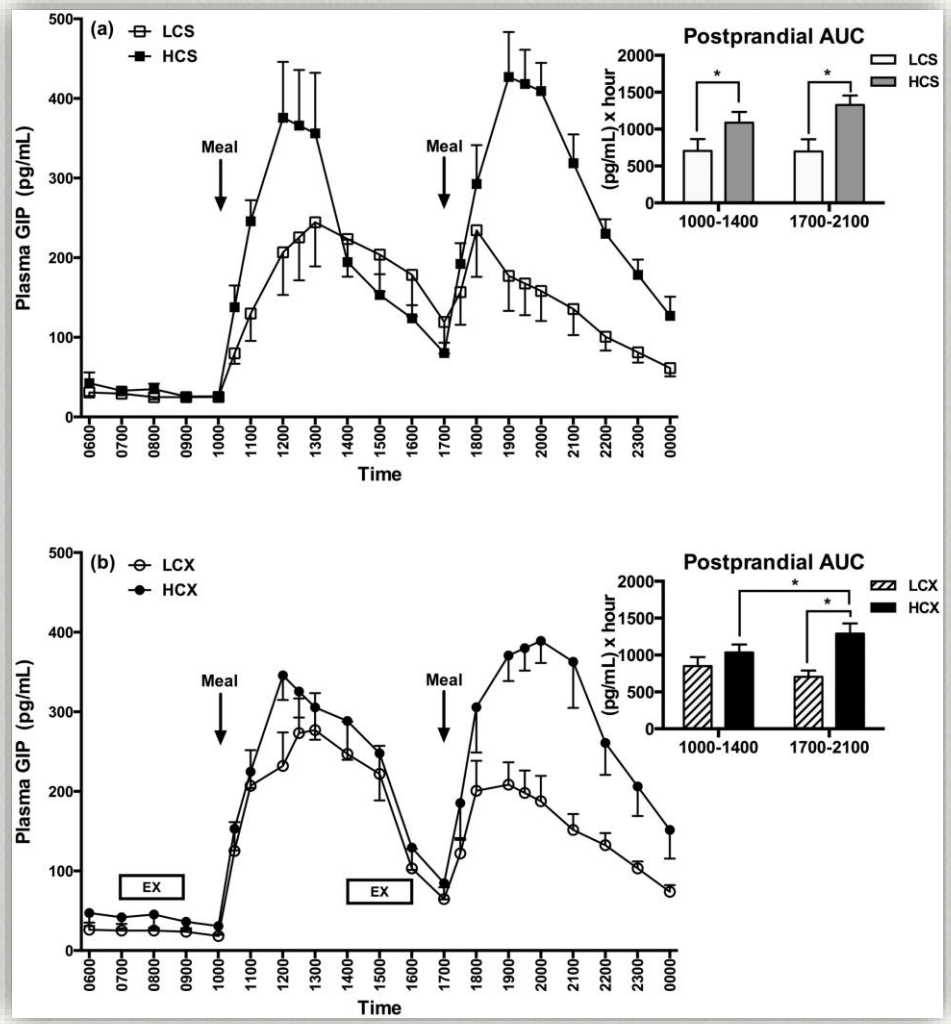
# Low carbohydrate diets remove 'bad carbs', too.

Third Exposure to a Reduced Carbohydrate Meal Lowers Evening Postprandial Insulin and GIP Responses and HOMA-IR Estimate of Insulin Resistance

Po-Ju Lin, Katarina T. Borer

Published: October 31, 2016 • https://doi.org/10.1371/journal.pone.0165378

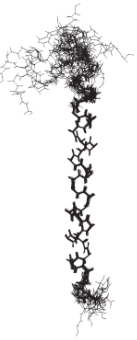


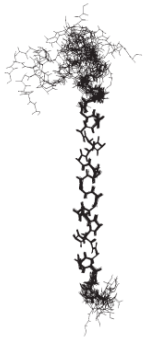
# Scientific conclusions

- Speed and location of intestinal nutrient absorption is crucial in determining metabolic response to food.
- The greatest effect is seen with carbohydrate rich plant processing, thus retaining plant structure is critical.
- Diets high in ultra-refined, quick-absorbing food items plausibly result inan altered intestinal hormonal profile, hunger/satiety signaling, and consequently higher food intake and increased meal frequency.
- This effect is exaggerated when ultra-processed carbohydrates are consumed in combination with significant amounts of fat. The doughnut effect.
- GIP may be part of a „thrifty machinery” in mammals.
  - Easily digestible, high energy density foods overstimulate it.
  - There is a negative feedback from acute elevations in insulin, but positive by chronic hyperinsulinemia, promoting further quick weight gain and IR.

# Practical conclusions, takeaways



- Processing of food items high in protein and fat is mostly harmless, at least as far as short term metabolic responses are concerned. Prioritize food items high in these macronutrients.
- Plant foods (carbohydrates) should be carefully selected on the basis of their (dense) structure. Processing, especially industrial refining disrupts structure and accelerates absorption, resulting in reduced satiation. Excluding most carbohydrate sources also solves this problem…
- Consume carbohydrate rich foods at the end of the meal (dessert).
- Have fewer, larger meals vs. frequent small ones. Snacking is a bad idea.
- Eat your meal slowly to maximize satiation via the increased release of lower intestinal hormones.



# Thank you for your attention!

- Link to compiled reference list:
- I am grateful for the good discussions in the Lower Insulin Facebook group. Thanks to all the online friends that helped form my opinion. Visit the group: https://www.facebook.com/groups/1989810138513366/