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Insuline het anabole hormoon: en zijn fysiologie.

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Senior Scientist Nutrition and Health

Louis Bolk Institute

Kort CV:

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Radboud University Nijmegen

HARVARD MEDICAL SCHOOL

Joslin Diabetes Center

umcg

LUMC Leids Universitair Medisch Centrum

UNIVERSITY OF CAMBRIDGE
Metabolic Research Laboratories

Voeding Leeft

Louis Bolk Instituut

Disclosures:

Voor deze bijeenkomst mogelijk relevante relaties met bedrijven:

- Sponsoring: Nee
- Honorarium: Nee

Andere activiteiten:

- Medeoprichter Voeding Leeft

Voor deze presentatie:

- Ik zal niet alles (kunnen) behandelen wat insuline doet.
- De referenties zijn over het algemeen uit de jaren 60-70-80 van de vorige eeuw ;-)
- Insuline resistentie wordt zijdelings meegenomen.

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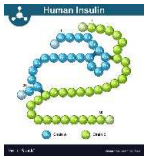

Opbouw:

1) De geschiedenis van Insuline
2) De fysiologie van Insuline
3) De effecten van insuline op verschillende organen
4) Insuline = anabool hormoon

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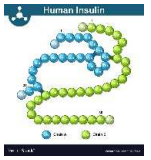
Insuline: Korte geschiedenisles



1921 CE Banting & Best
Canada: Insuline ontdekt!.
Diabetes = Afwezigheid van INSULINE

1500 BC
Egypt/India
Honey Urine

300-500 CE India
Type 1 = Young
Type 2 = Overweight

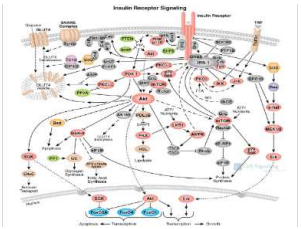
1962-1967 CE
Type 1 = Afwezigheid van Insuline
Type 2 = Ineffectieve insuline

250 BC
"Diabetes"

1675-1776 CE
Dr. Thomas Willis
Dr. John Rollo
"Diabetes Mellitus"

1959 CE
Yalow & Berson
Insulin Assays

1971 tot NU



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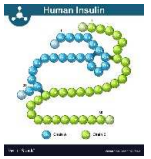

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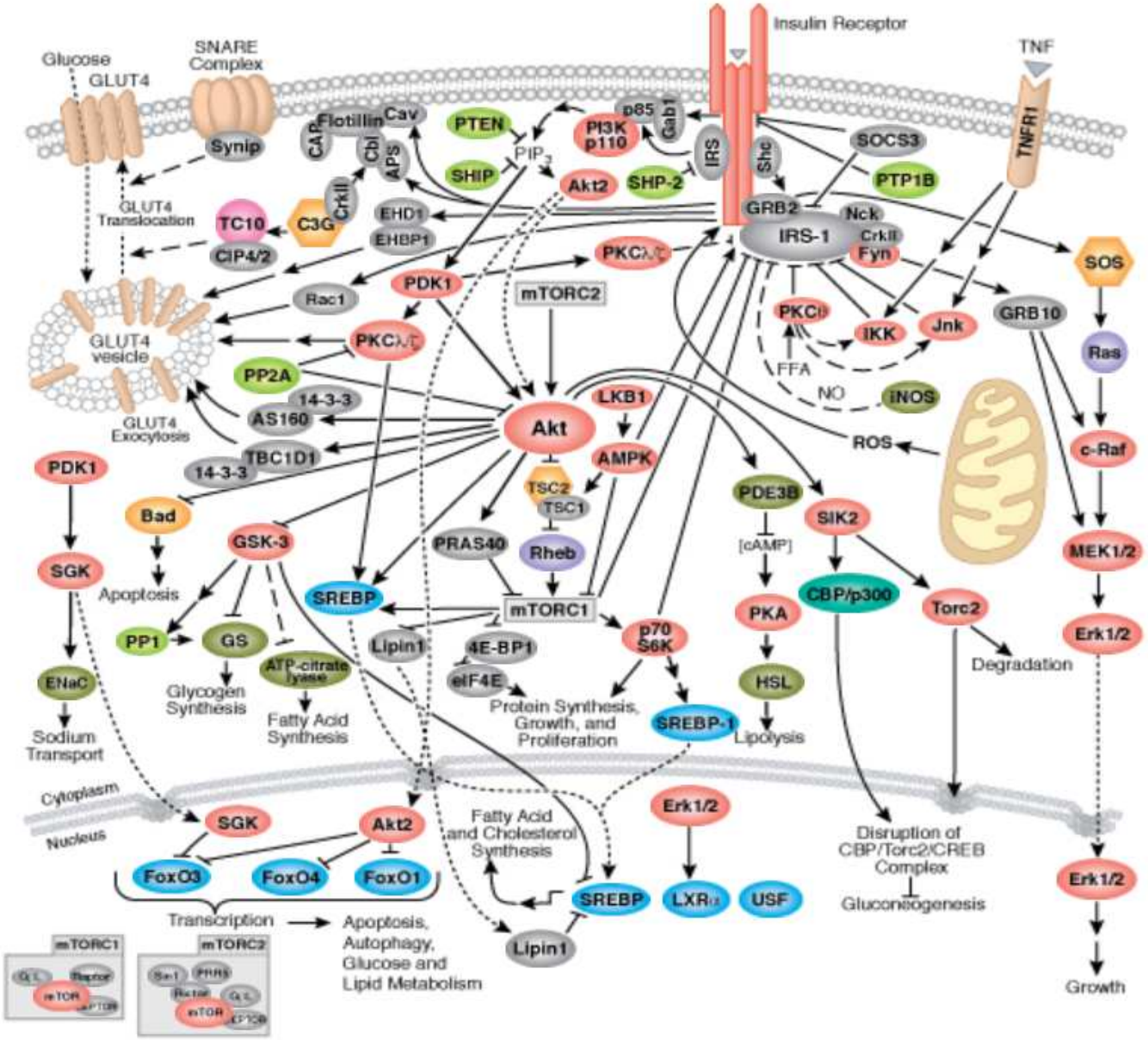

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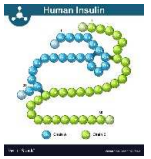

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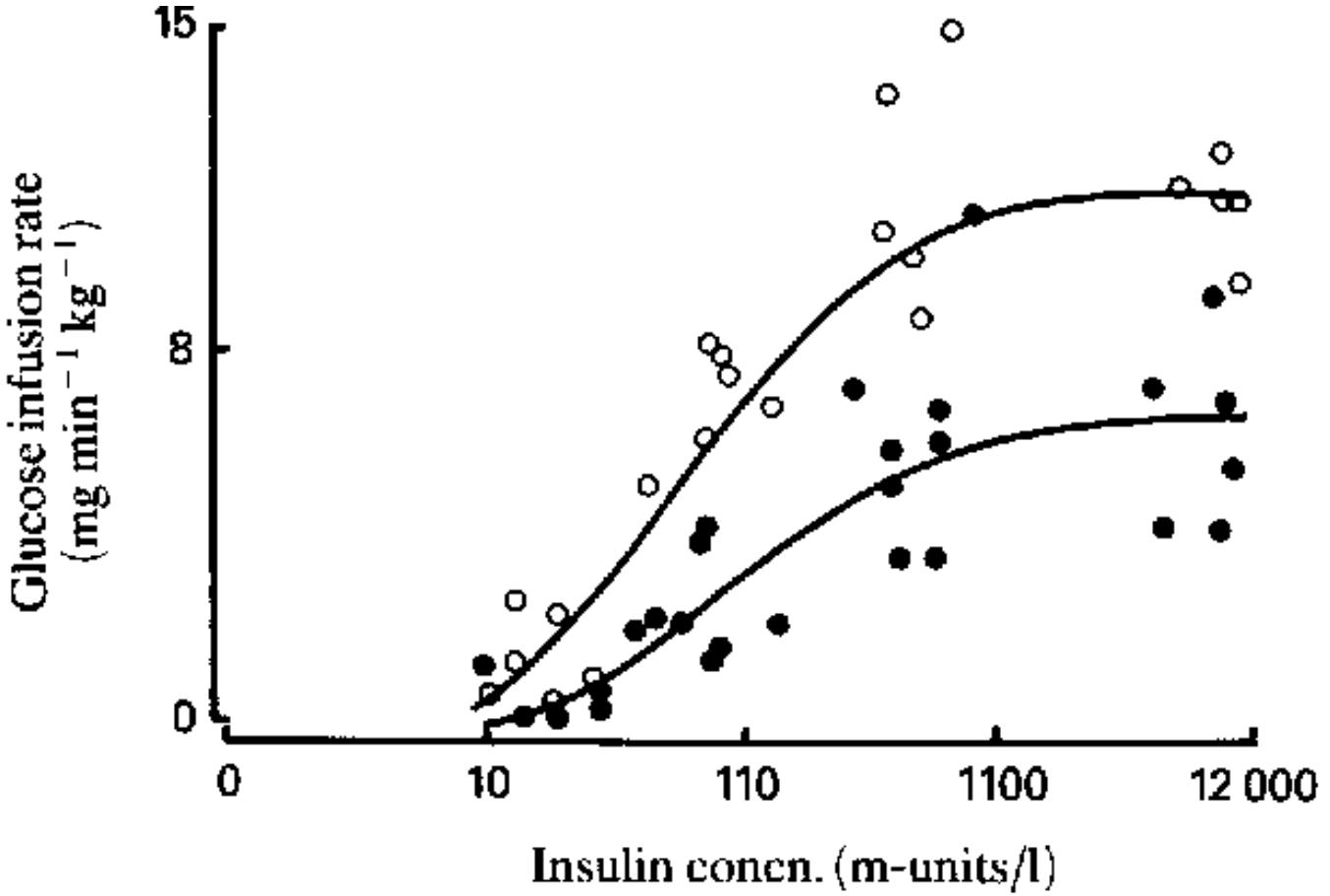

Fig. 1. Dose–response curves for the effect of insulin on

Published in Clinical science 1991

Dose-response relationships for the effects of insulin on glucose and fat metabolism in injured patients and control subjects.

A A Henderson, Keith N. Frayn, Charles S. B. Galasko, R. A. Little

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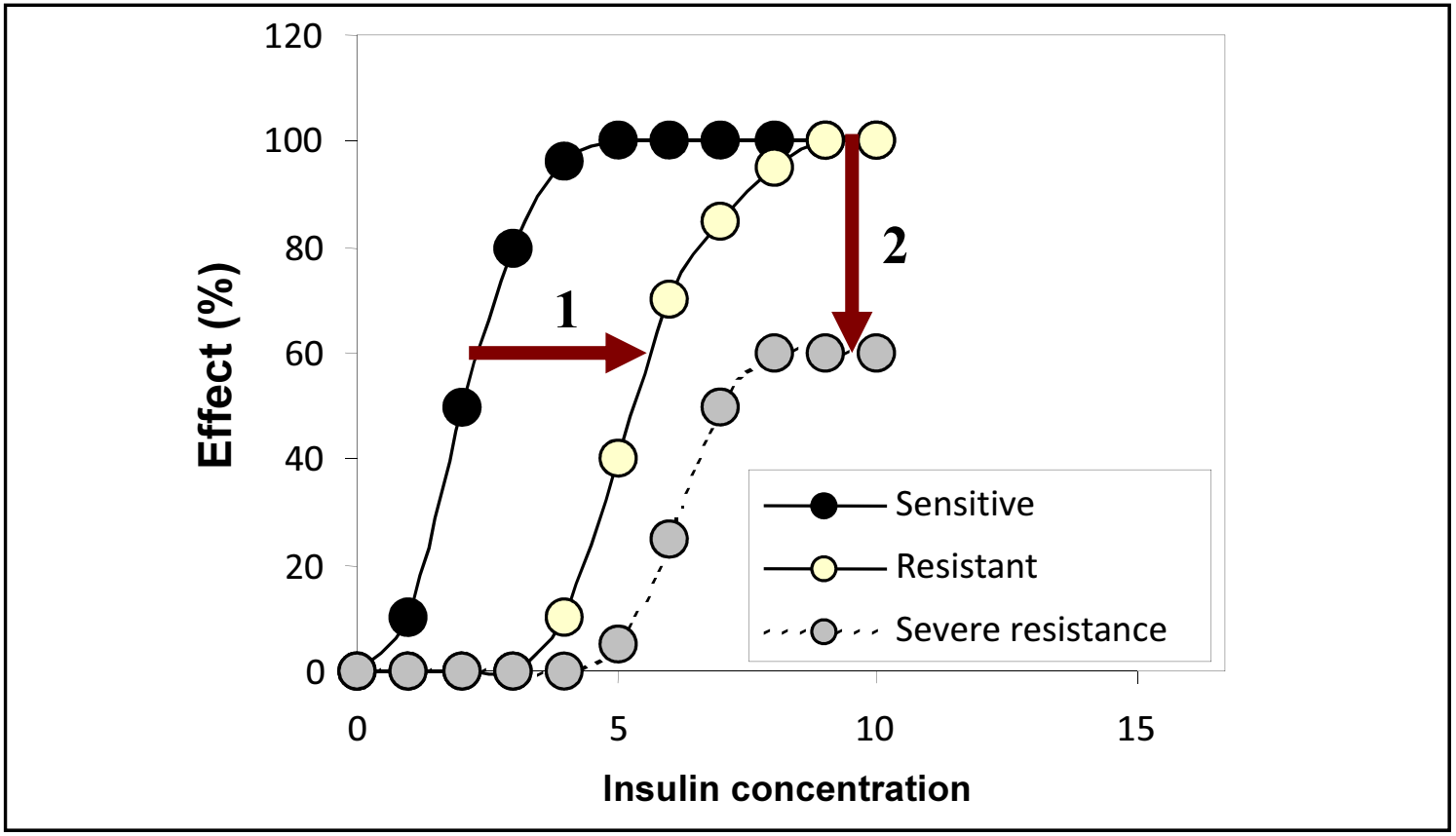
De concentratie-effect relatie van Insuline:
En wat is insulin resistentie?



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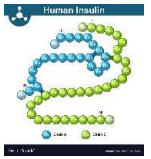

Real human data:

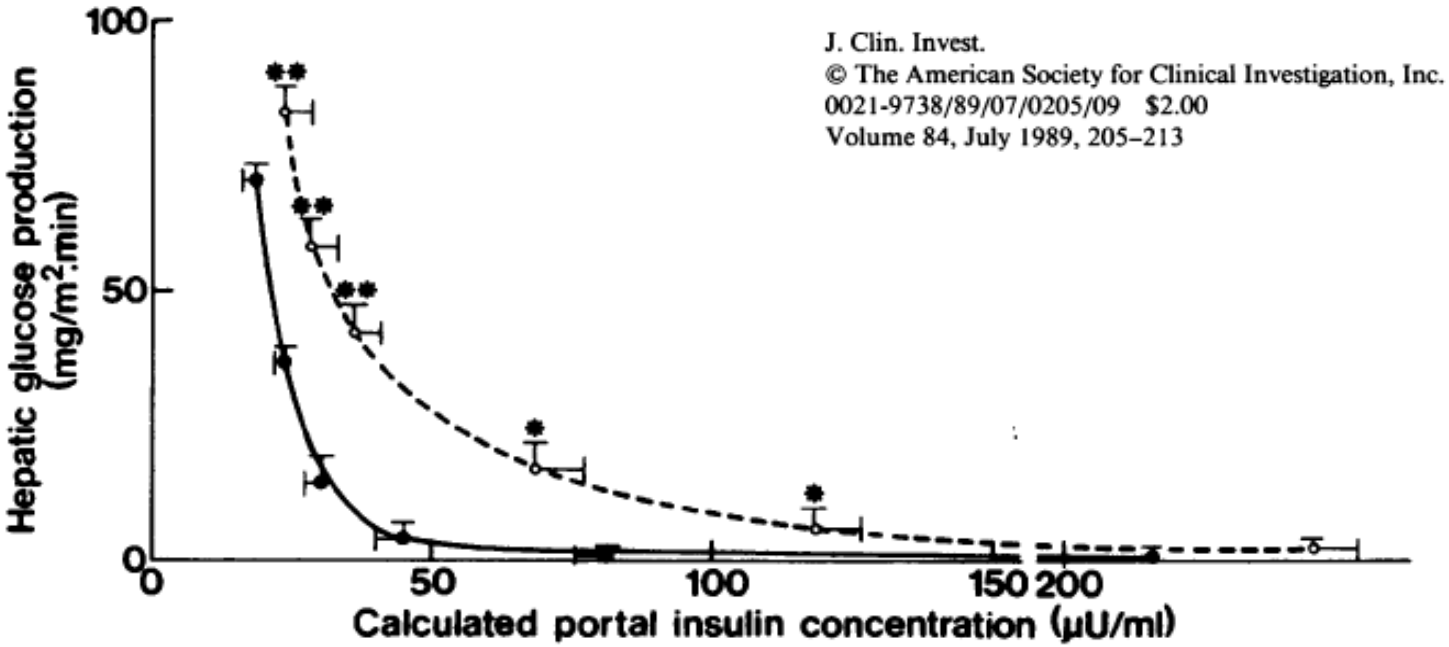

Figure 3. Rate of hepatic glucose production in the basal state and during graded hyperinsulinemia in nonobese NIDD (*broken line*) and in matched control (*solid line*) subjects. The *x*-axis shows the estimated portal insulin concentrations. Values are mean±SEM. **P* < 0.05; ***P* < 0.01 versus control subjects.

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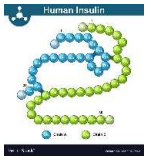

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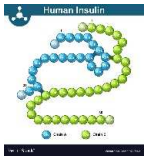
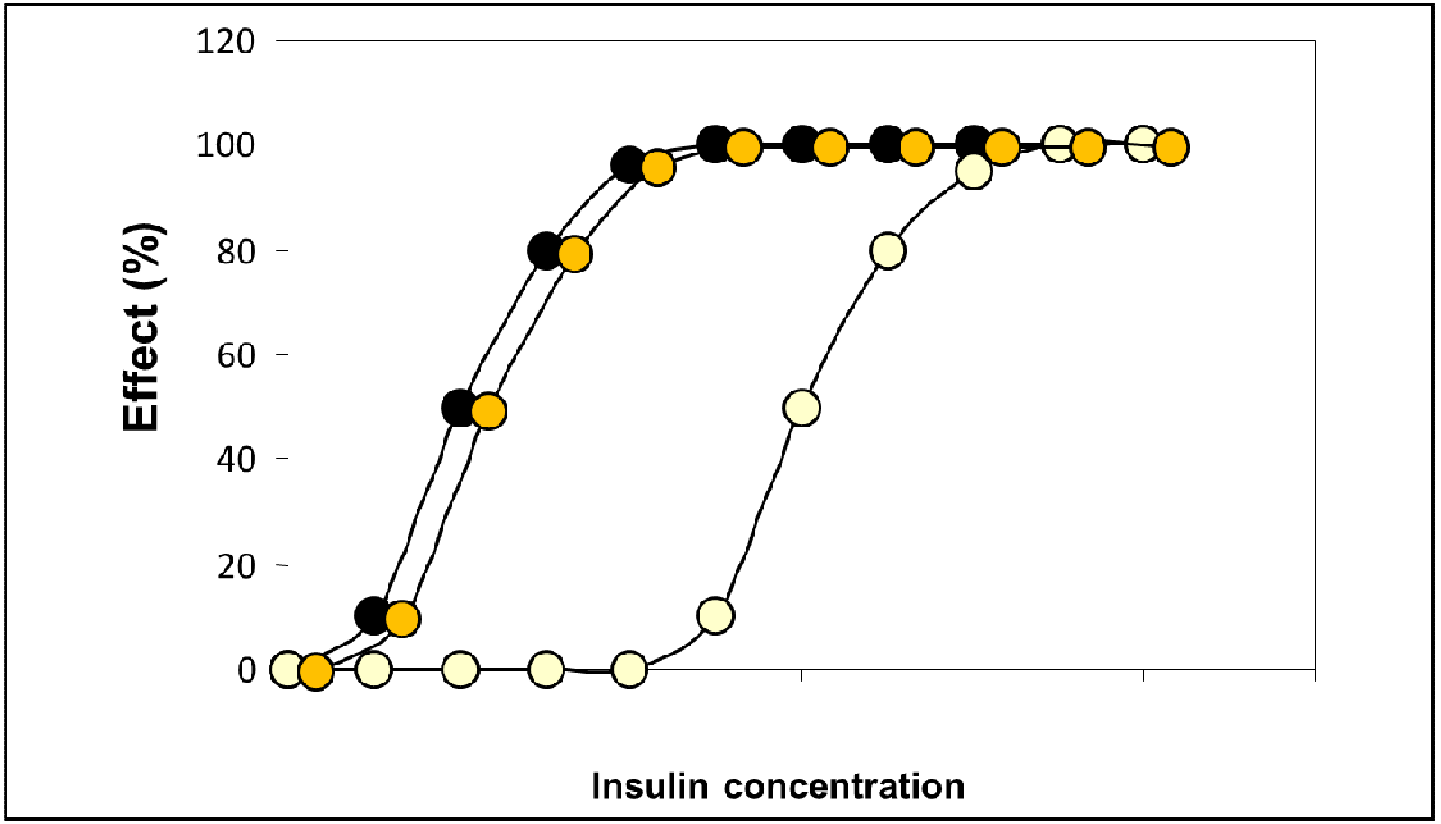


Verschillende organen hebben verschillende insuline gevoeligheden:



Welk orgaan is welke lijn???????

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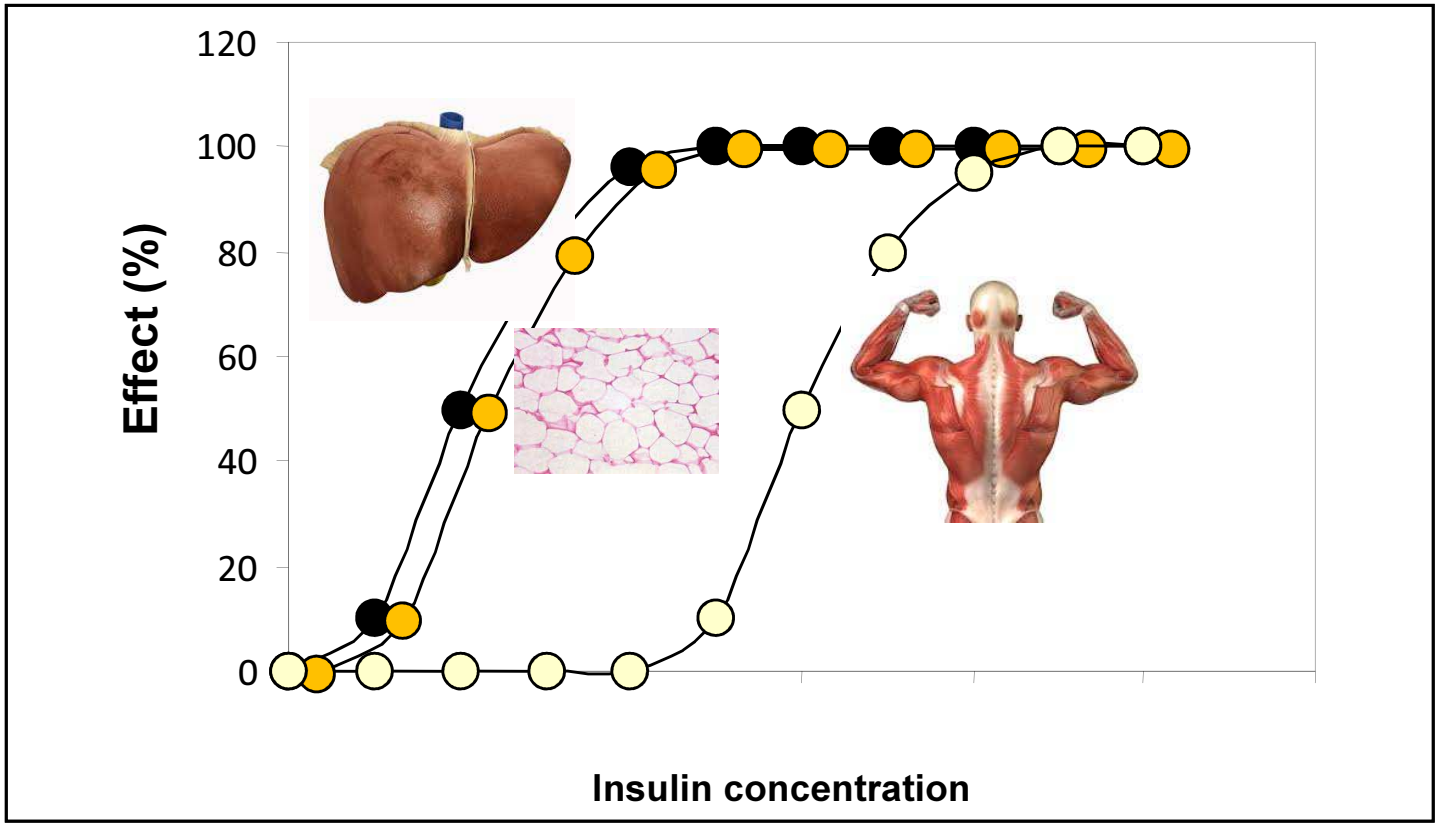

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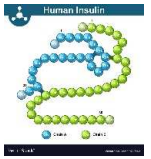

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3) Insuline heeft een circadiaans ritme, secretie en effect op de organen.
4) Insuline het anabole hormoon.

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Glucose dosis en insulin secretie?

THE LANCET, APRIL 14, 1973

DOSE-RESPONSE RELATION BETWEEN PLASMA-INSULIN AND BLOOD-GLUCOSE LEVELS DURING ORAL GLUCOSE LOADS IN PREDIABETIC AND DIABETIC SUBJECTS

EROL CERASI SUAD EFENDIĆ
ROLF LUFT
Department of Endocrinology and Metabolism, Karolinska Hospital, S-104 01 Stockholm 60, Sweden

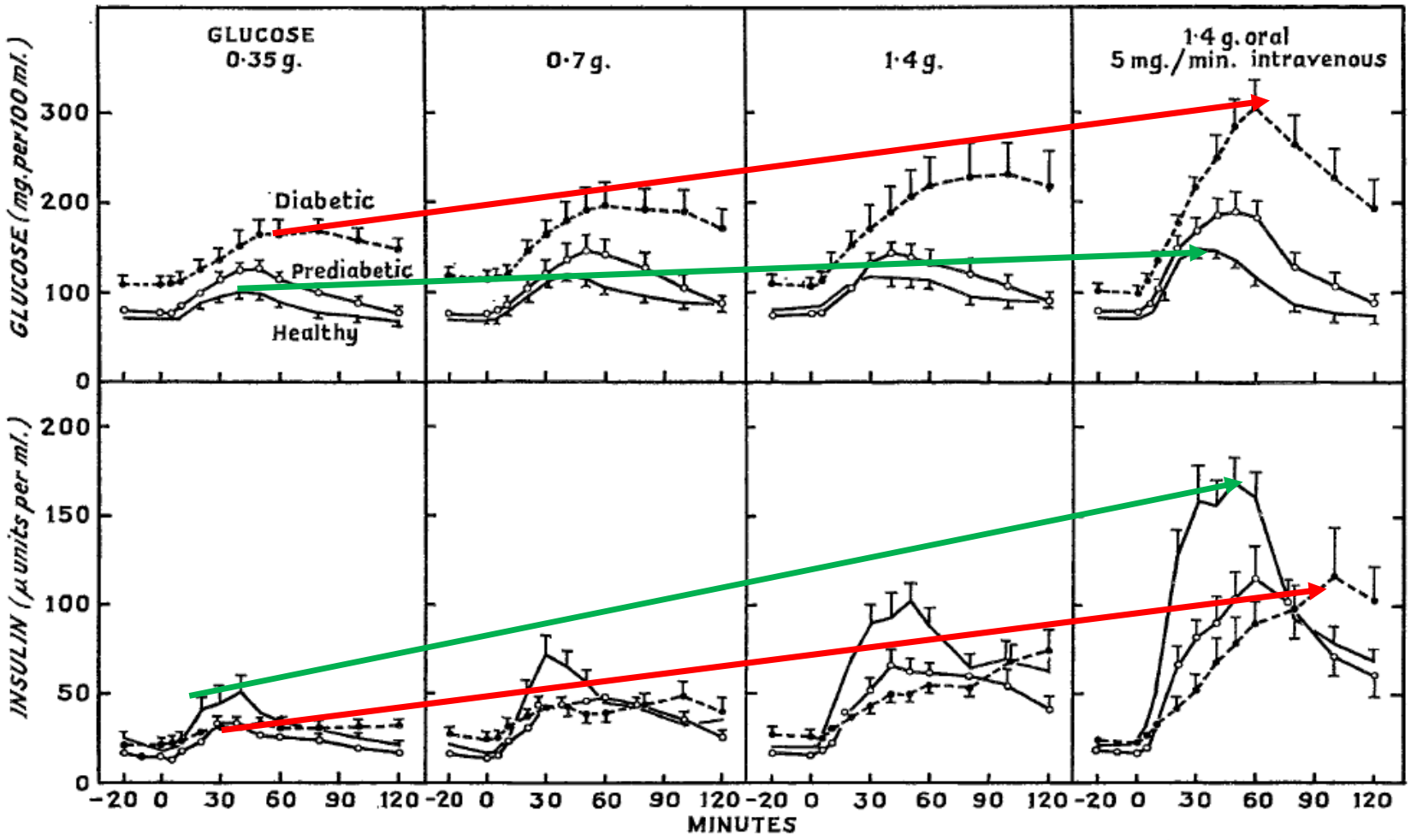

Fig. 1—Plasma-insulin and blood-glucose responses in healthy subjects, prediabetics, and diabetics to varying oral glucose loads per kg. body-weight and to a combination of oral and intravenous glucose loads.

Glucose doses bepaalt insulin response; *niet* bloedglucose response:

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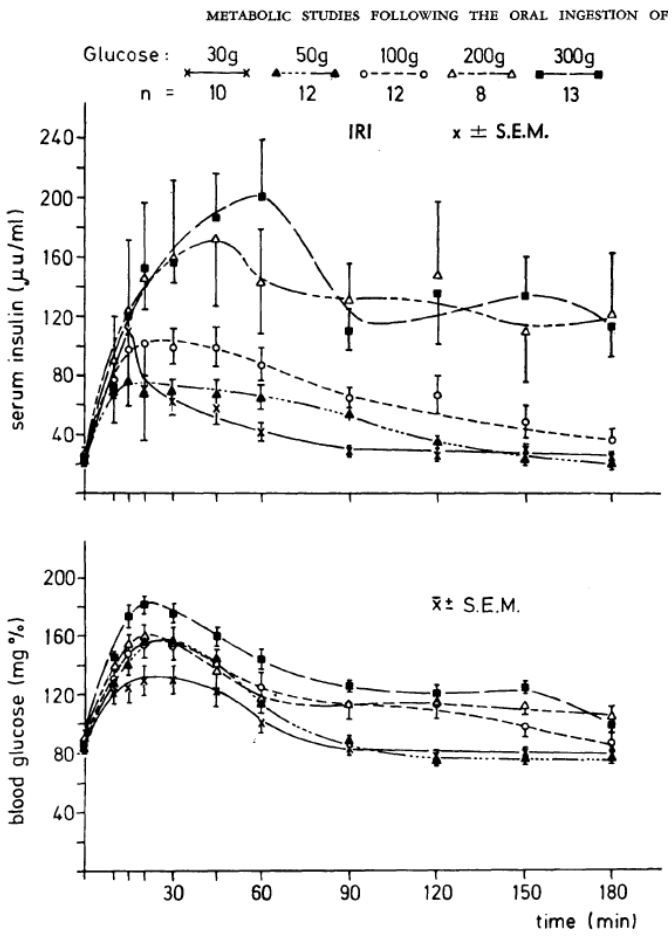

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Hoe je consumeert bepaalt ook je insulin response, en dus de duur van het insulin effect:

VS

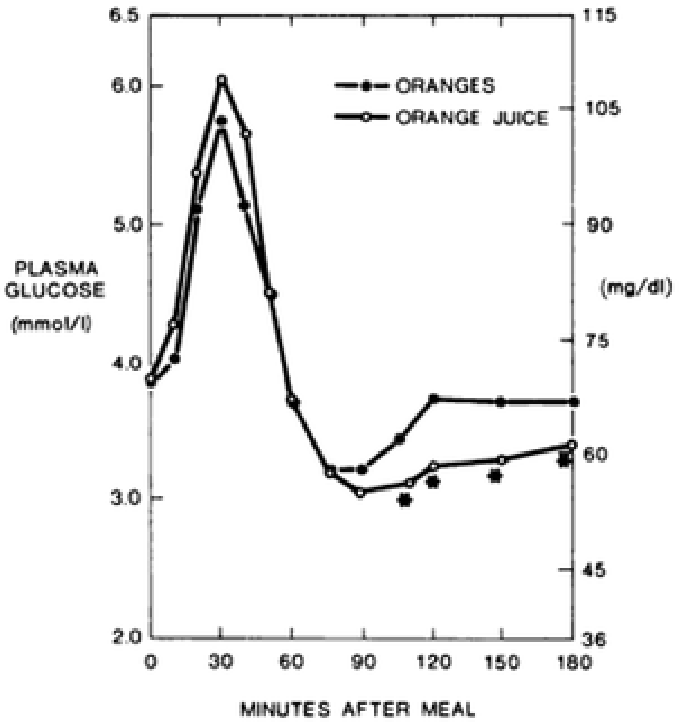

FIG. 1. Mean plasma glucose levels in 10 normal subjects after ingesting 50 g carbohydrate as whole oranges and orange juice. *Asterisks* indicate glucose values significantly lower ($p < 0.05$) after juice than at the corresponding times after fruit.

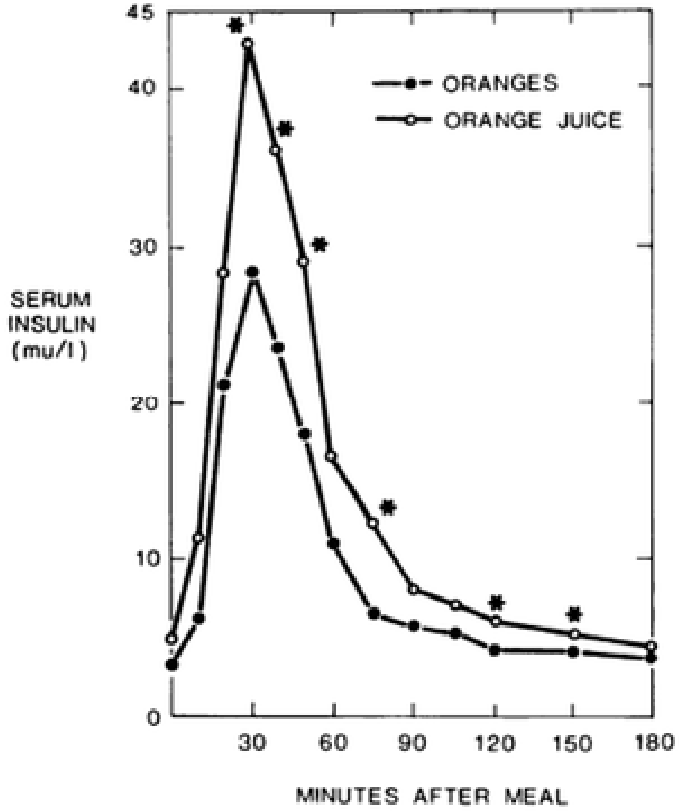

FIG. 3. Mean serum insulin levels in 10 normal subjects after ingesting 50 g carbohydrate as whole oranges and orange juice. *Asterisks* indicate insulin values significantly higher ($p < 0.05$) after juice than at the corresponding times after fruit.

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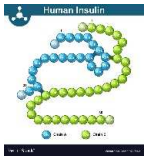
Een kleine maar noodzakelijke uitstap naar glucosemetabolisme



Waarom heeft glucose load per se niet zo een direct effect op bloedglucose curve?

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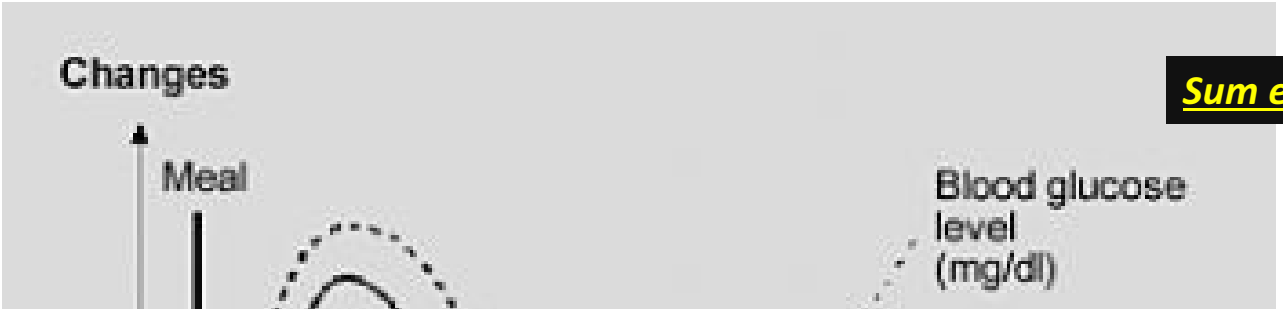
Effect van isuline gedurende een maaltijd: Verschillend effect op verschillende organen



Sum effect

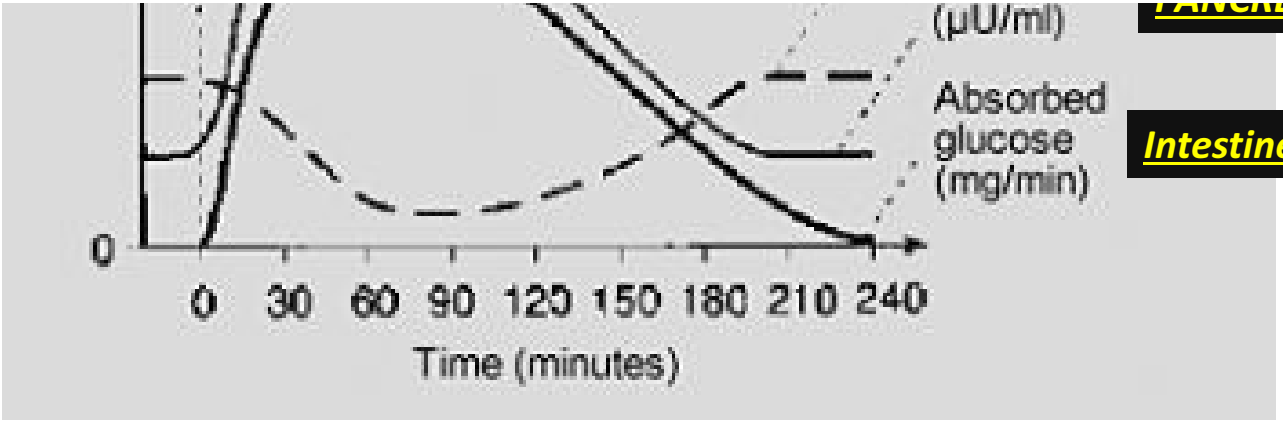
Gastroenterology. 1953 Dec;25(4):548-52.

Oral glucose tolerance as a test of liver function.

RANKIN TJ, JENSON RL, DELP M.

ect

PANCREAS effect



Intestine effect

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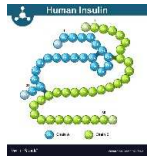
Wat is glucose intolerantie?: verstoord effect van insuline op de lever!



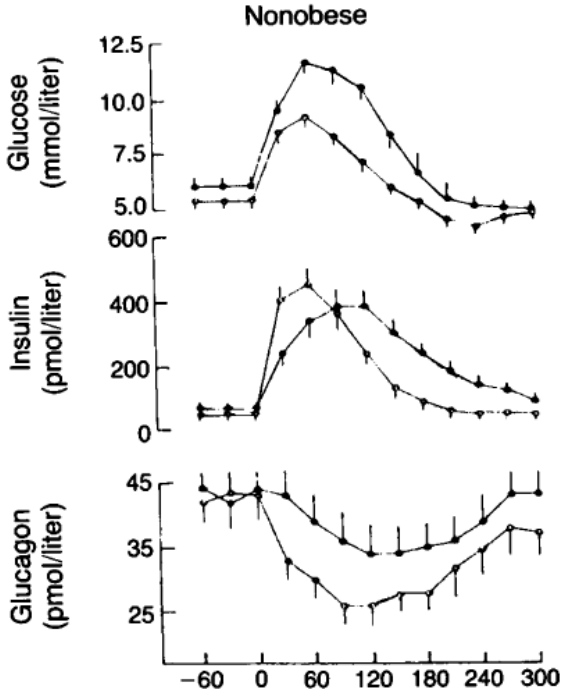


Figure 1. Mean (±SE) Arterial Plasma Glucose, Insulin, and Glucagon Concentrations before and after Glucose Ingestion in 16 Normal Subjects (○) and 15 Subjects with Impaired Glucose Tolerance (●).

22 THE NEW ENGLAND JOURNAL OF MEDICINE Jan. 2, 1992

ROLE OF REDUCED SUPPRESSION OF GLUCOSE PRODUCTION AND DIMINISHED EARLY INSULIN RELEASE IN IMPAIRED GLUCOSE TOLERANCE

Asimina Mitrakou, M.D., David Kelley, M.D., Marian Mokan, M.D., Thiemo Veneman, M.D., Thomas Pangburn, B.A., James Reilly, M.D., and John Gerich, M.D.

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Glucose intolerantie: geen spier problem!

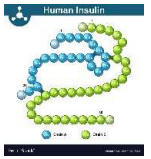

Table 3. Peripheral-Tissue Glucose Metabolism during Assimilation of the Oral Glucose Load.*

GLUCOSE VARIABLE	NONOBESE SUBJECTS		OBESE SUBJECTS	
	NORMAL	IMPAIRED GLUCOSE TOLERANCE	NORMAL	IMPAIRED GLUCOSE TOLERANCE
Total disappearance (mmol/5 hr)	407±10	457±12†	432±10	498±20†
Urinary loss (mmol/5 hr)	0	1.1±0.5	0	0.5±0.5
Total tissue uptake (mmol/5 hr)	406±10	456±2†	432±9	482±21†
Muscle uptake (mmol/5 hr)	207±7	236±20	208±8	198±6

*Plus–minus values are means ±SE. To convert millimoles of glucose to grams, multiply by 0.18.

†$P<0.05$ for the comparison with the subjects with normal glucose tolerance.

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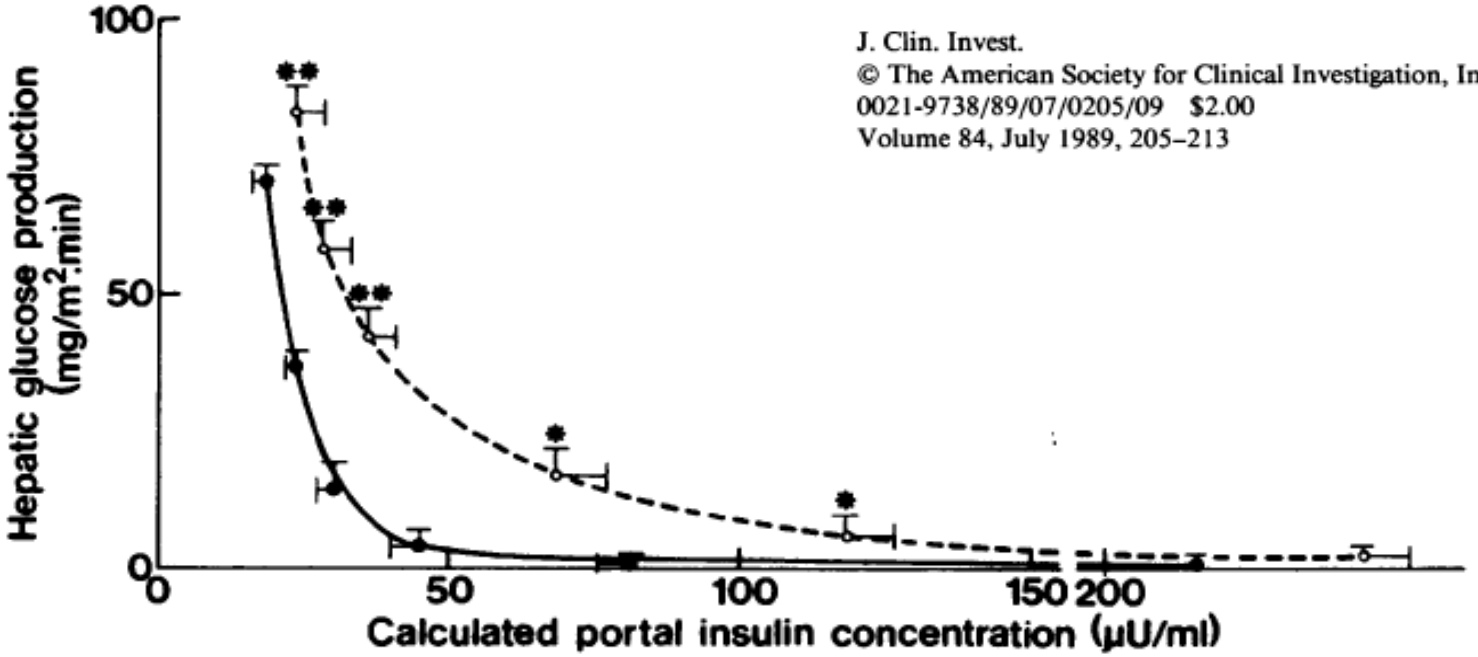
Verstoorde remming glucose productie door de lever bij insulin resistentie



J. Clin. Invest.
© The American Society for Clinical Investigation, Inc.
0021-9738/89/07/0205/09 $2.00
Volume 84, July 1989, 205–213

Figure 3. Rate of hepatic glucose production in the basal state and during graded hyperinsulinemia in nonobese NIDD (*broken line*) and in matched control (*solid line*) subjects. The *x*-axis shows the estimated portal insulin concentrations. Values are mean±SEM. **P* < 0.05; ***P* < 0.01 versus control subjects.

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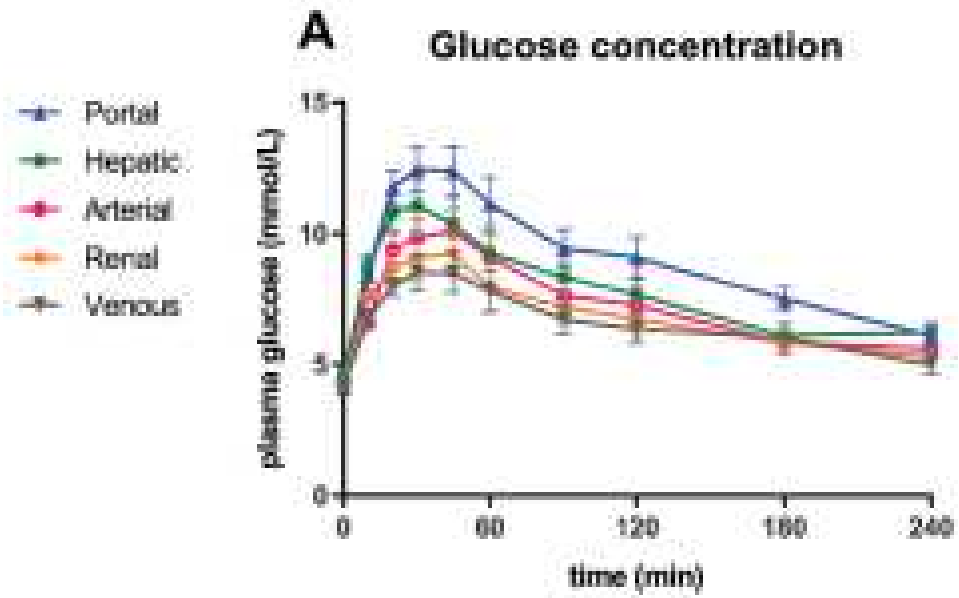
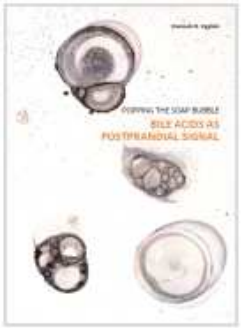
En onthoud AUB dat de lever de meeste insulin ‘ziet’ en dus als eerste reageert!





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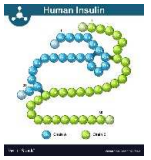

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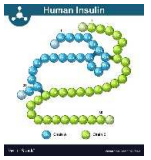

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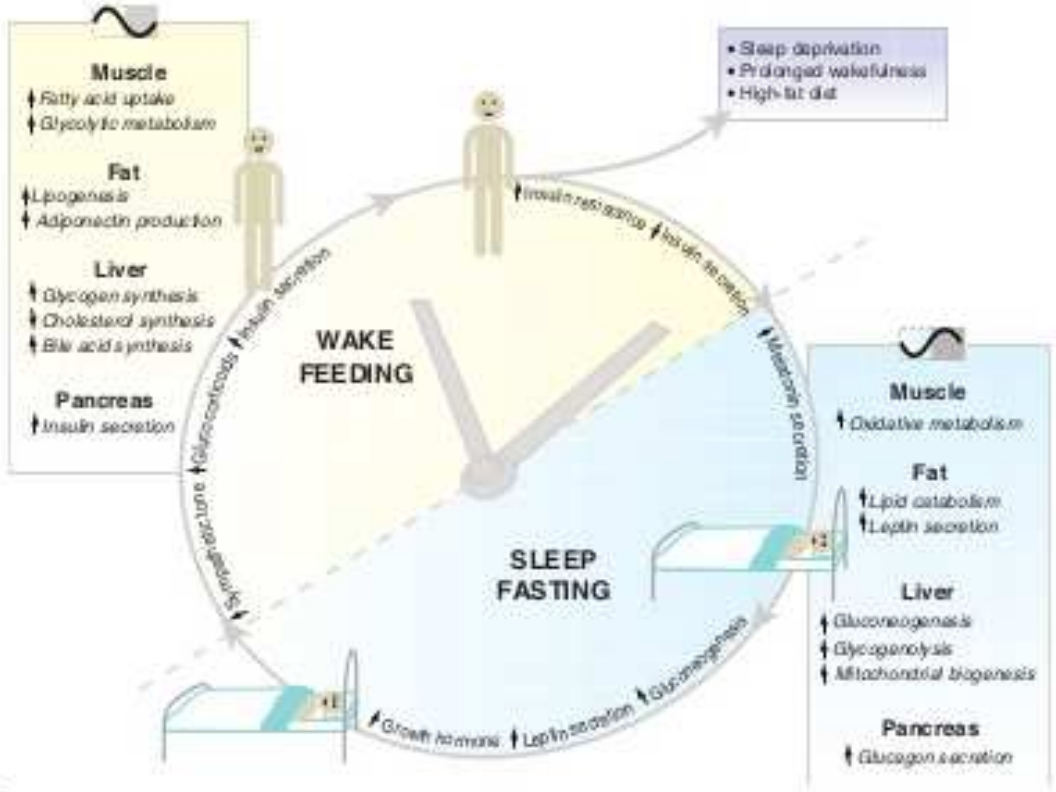
Circadian rhythms

- Affect food metabolism and energy balance



Bass and Takahashi 2010

Circadiaans ritme door clock genen binnen in insulin signalling

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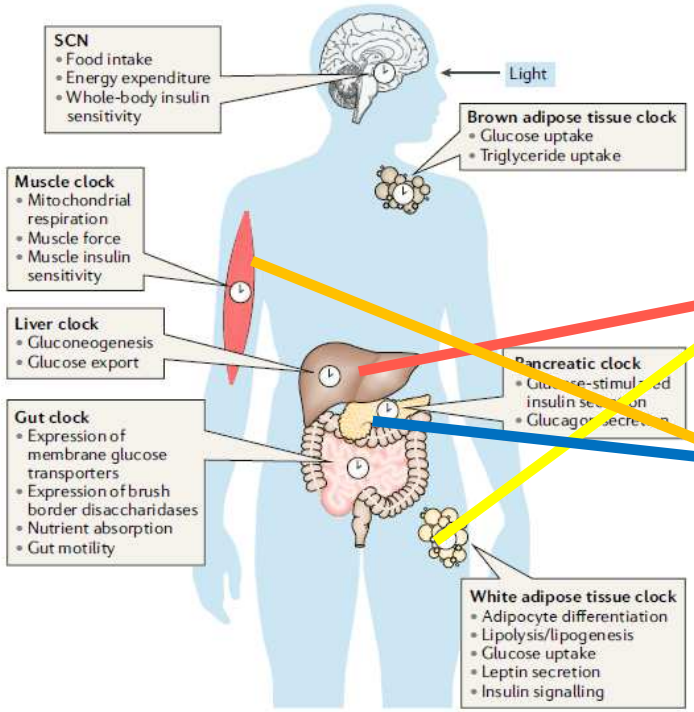

Fig. 2 | **Circadian clocks regulate glucose metabolism, insulin sensitivity and insulin secretion.** The molecular clock consists of a transcriptional translational feedback loop involving the clock proteins CLOCK, ARNTL, PER and CRY and the nuclear receptors NR1D1, NR1D2 and ROR. The central and peripheral clocks are responsible for a variety of functions. SCN, suprachiasmatic nucleus.

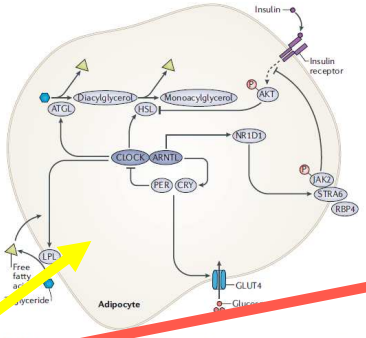

Fig. 6 | **The white adipose tissue clock.** In white adipose tissue, the circadian clock [illegible] regulates the diurnal rhythm in insulin sensitivity via the circadian regulation of the retinol-binding protein receptor stimulated by retinoic acid 6 (STRA6). CLOCK and ARNTL regulate the expression of key enzymes in the regulation of lipolysis. ATGL, adipose triglyceride lipase; GLUT, glucose transporter; HSL, hormone-sensitive lipase; JAK2, Janus kinase 2; LPL, lipoprotein lipase; P, phosphate; RBP4, retinol–binding protein 4.

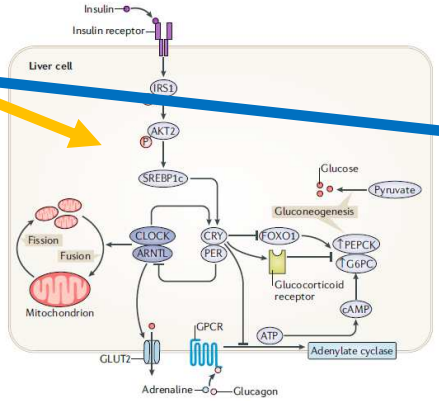

Fig. 7 | **The liver clock.** In the liver, the circadian repression of gluconeogenesis during the habitual feeding period is mediated by the interaction of CRY with the glucocorticoid receptor, G protein-coupled receptor (GPCR) signalling and FOXO1 degradation. The liver clock also regulates the diurnal rhythm in mitochondrial dynamics. FOXO1, forkhead box protein O1; G6PC, glucose 6 phosphatase; GLUT, glucose transporter; IRS1, insulin receptor substrate 1; P, phosphate; SREBP1c, sterol regulatory element-binding protein 1c.

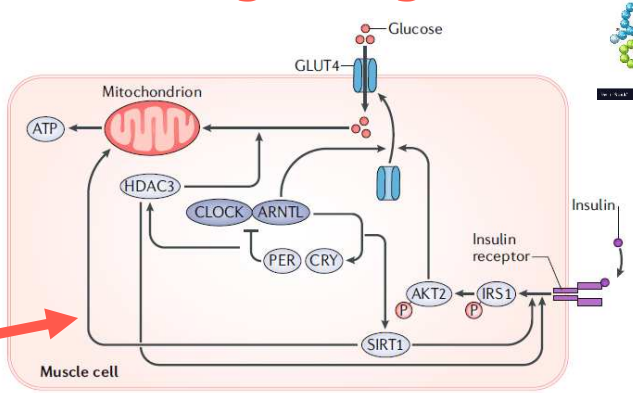

Fig. 5 | **The muscle clock.** In muscle, the muscle clock regulates muscle insulin sensitivity via protein levels and membrane translocation of the insulin-sensitive glucose transporter 4 (GLUT4) and through modulation of the insulin signalling pathway via expression of the deacetylase sirtuin 1 (SIRT1). In addition, the muscle clock regulates muscle insulin sensitivity via histone deacetylation of metabolic genes by histone deacetylase 3 (HDAC3). IRS1, insulin receptor substrate; P, phosphate.

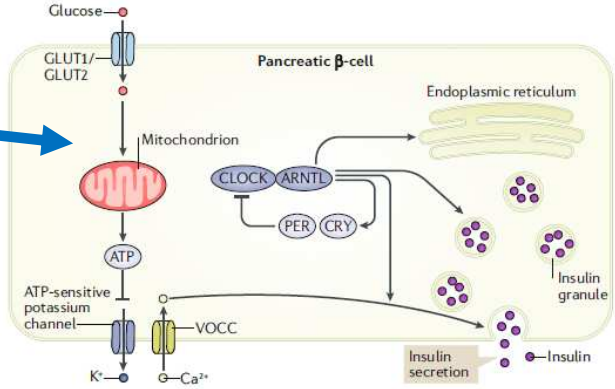

Fig. 8 | **The pancreas clock.** In the pancreas, CLOCK and BMAL1 activate the transcription of genes involved in insulin biosynthesis, insulin transport and glucose-stimulated insulin secretion. All depicted processes show circadian rhythmicity. GLUT, glucose transporter; VOCC, voltage-dependent calcium channel.

REVIEWS

Circadian clocks and insulin resistance

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Circadiaans ritme ook te zien in OGTT: meer glucose intolerant/insuline resistent gedurende de dag.

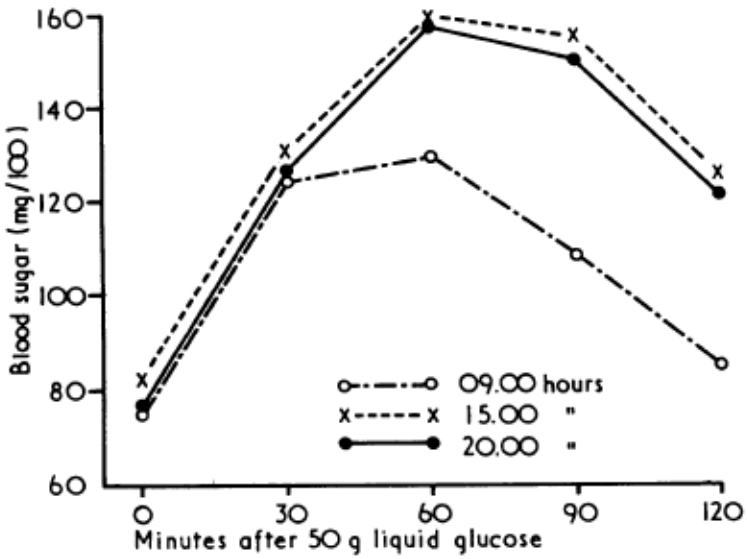

FIG. 1—Mean blood sugar curves in the three glucose tolerance tests.

Diurnal Variation in Oral Glucose Tolerance: Blood Sugar and Plasma Insulin Levels Morning, Afternoon, and Evening

R. J. JARRETT, I. A. BAKER, H. KEEN, N. W. OAKLEY

British Medical Journal, 1972, 1, 199-201

medications, likely to affect glucose tolerance. Details of the participants are given in Table I

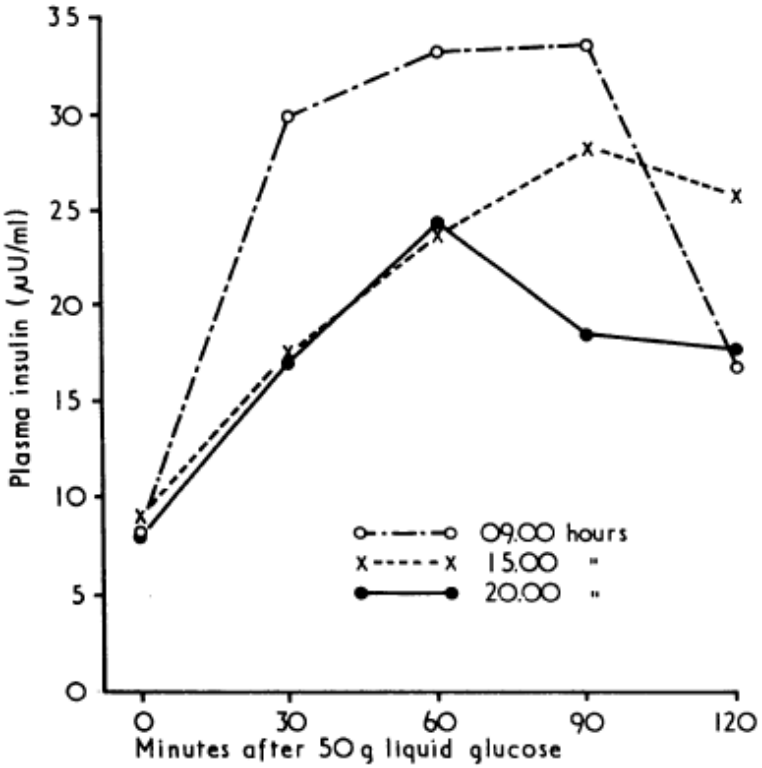

FIG. 2—Mean plasma immunoreactive insulin levels during the three glucose tolerance tests.

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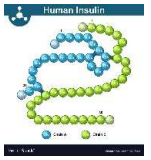

Opbouw:

1) De geschiedenis van Insuline
2) De fysiologie van Insuline
    1) Complexiteit van de signalling.
    2) Geen lineaire relatie dosis insuline en effect.
    3) Elk orgaan reageert op verschillende concentraties insuline.
    4) Glucose load bepaalde insuline secretie (incretin effect)
3) Insuline heeft een circadiaans ritme, secretie en effect op de organen.
4) **Insuline het anabole hormoon.**
    1) **Insuline verlaagd totaal energy expenditure**

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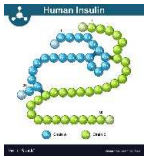

Table 2. Basal energy expenditure before and after insulin treatment, predicted basal energy expenditure, plasma glucose and serum bicarbonate

Patients	Predicted basal energy expenditure (kcal/24 h)	Before insulin treatment				After insulin treatment		
		Observed basal energy expenditure (kcal/24 h)	Plasma glucose (mmol/l)[a]	β-hydroxy-butyrate (mmol/l)[b]	Serum bicarbonate (mmol/l)[c]	Observed[d] basal energy (kcal/24 h)	Plasma[d] glucose (mmol/l)[a]	β-hydroxybutyrate (mmol/l)[b]
Group 1								
1	1620	1732	13.1	–	18.0	1668	6.8	–
2	1825	2165	23.0	1.17	21.0	1862	10.6	0.06
3	2050	1958	23.1	4.5	24.0	1778	5.7	0.67
4	1775	1908	15.6	–	26.0	1740	11.0	–
5	1800	2120	22.4	–	23.0	1732	4.5	–
6	1825	2319	22.3	–	18.0	1796	3.6	–
Group 2								
7	1725	1862	16.2	2.18	28.0	1604	3.7	0.068
8[e]	1460	2256	19.0	4.6	13.0	1763	3.4	0.086
9	1800	2166	19.1	1.8	22.0	1960	3.4	0.064
10[e]	1560	1925	19.1	5.76	16.0	1385	3.4	0.124
Mean ± SEM	1744 ± 52	2042 ± 60	19.3 ± 1.1	3.34 ± 0.76	20.9 ± 1.5	1728 ± 49	5.8 ± 0.8	0.078 ± 0.009

[a] Normal range 3.2–10 mmol/l; [b] normal range 1.7 ± 0.2 (women) 0.9 ± 0.2 mmol (men); [c] normal range 20–30 mmol/l; [d] measured during steady state; [e] female patients

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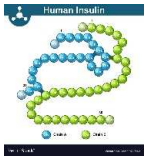

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    2) **De anabole effecten op orgaan niveau.**

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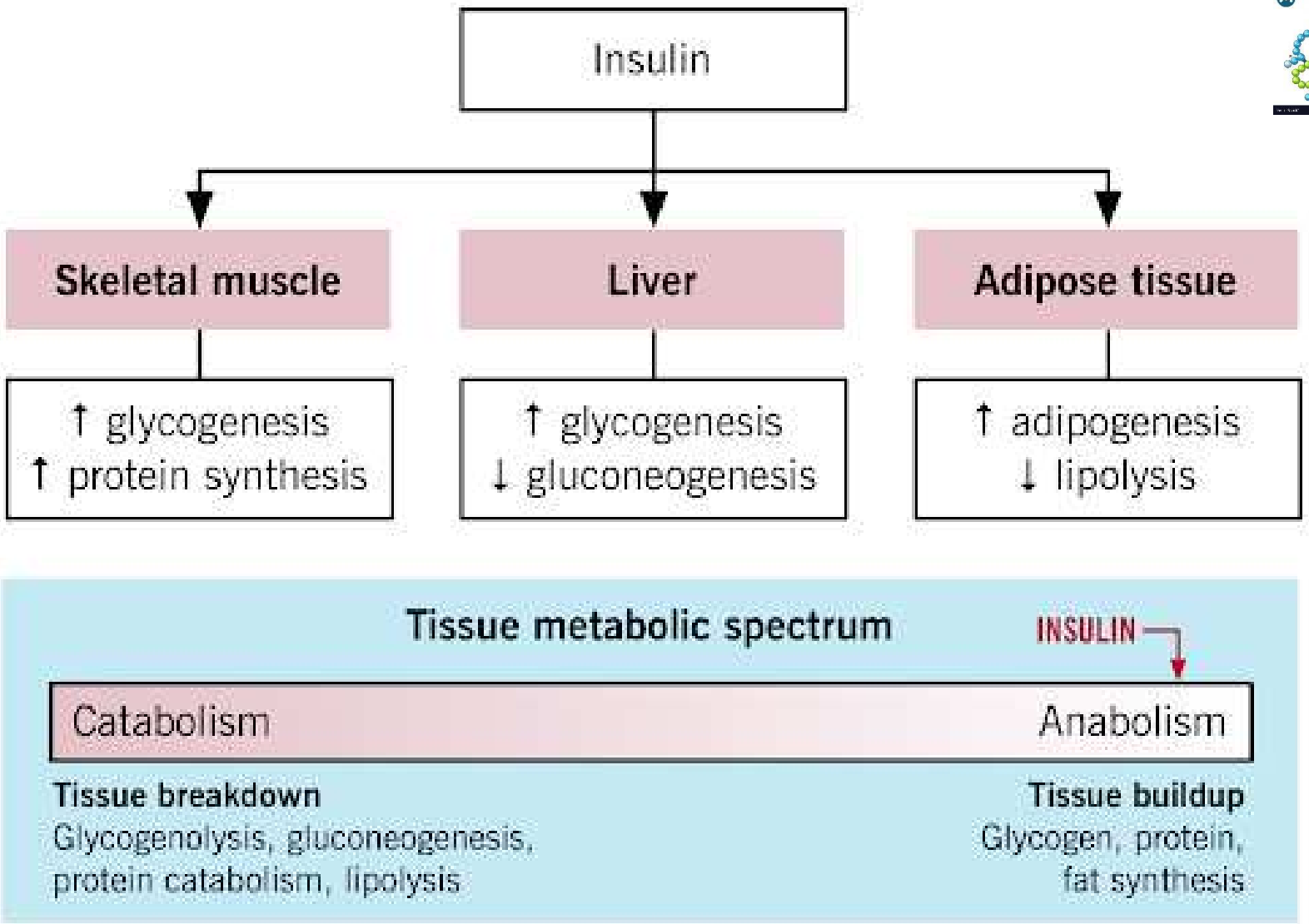

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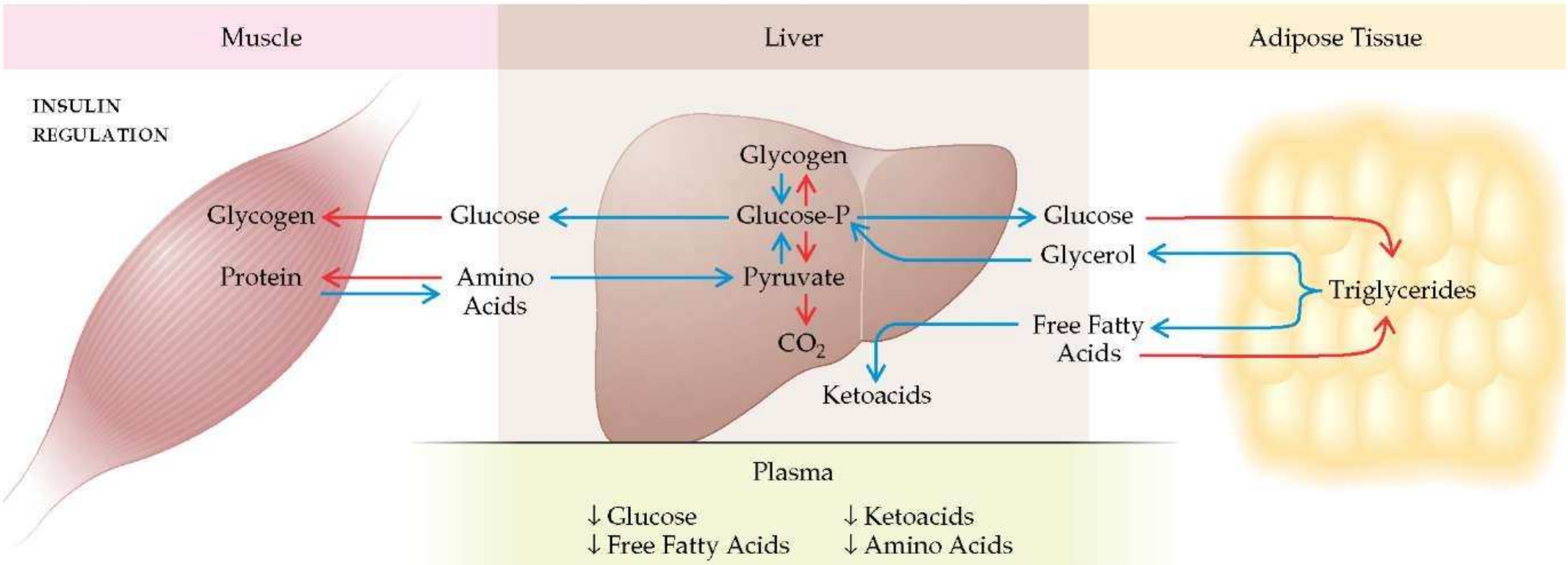

high insulin (postprandial)

low insulin (early morning, fasting, LC etc)

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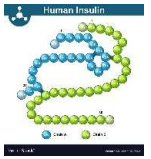

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    3) **Een poging tot totaal plaatje:**

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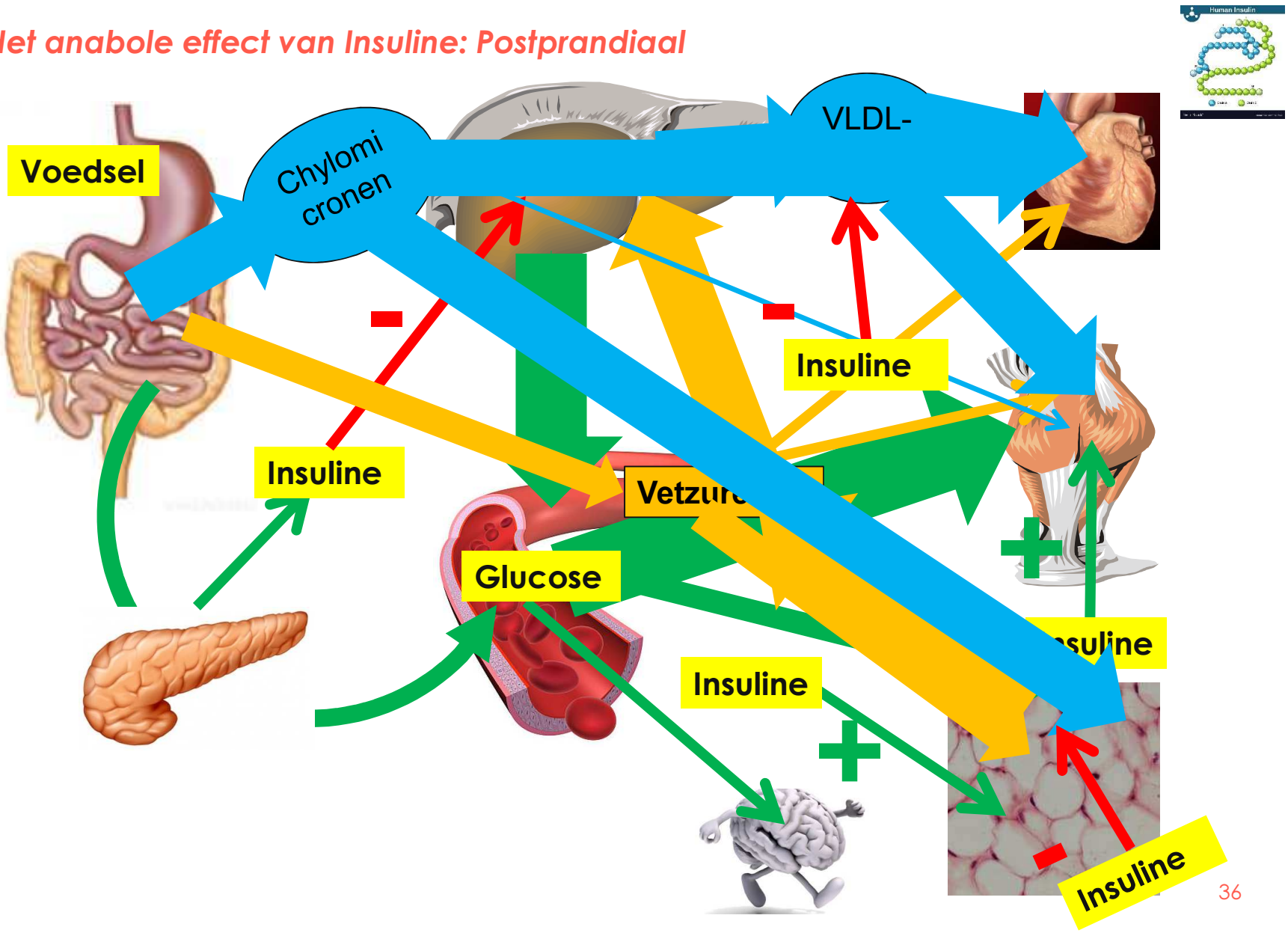
Het anabole effect van Insuline: Postprandiaal



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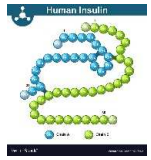
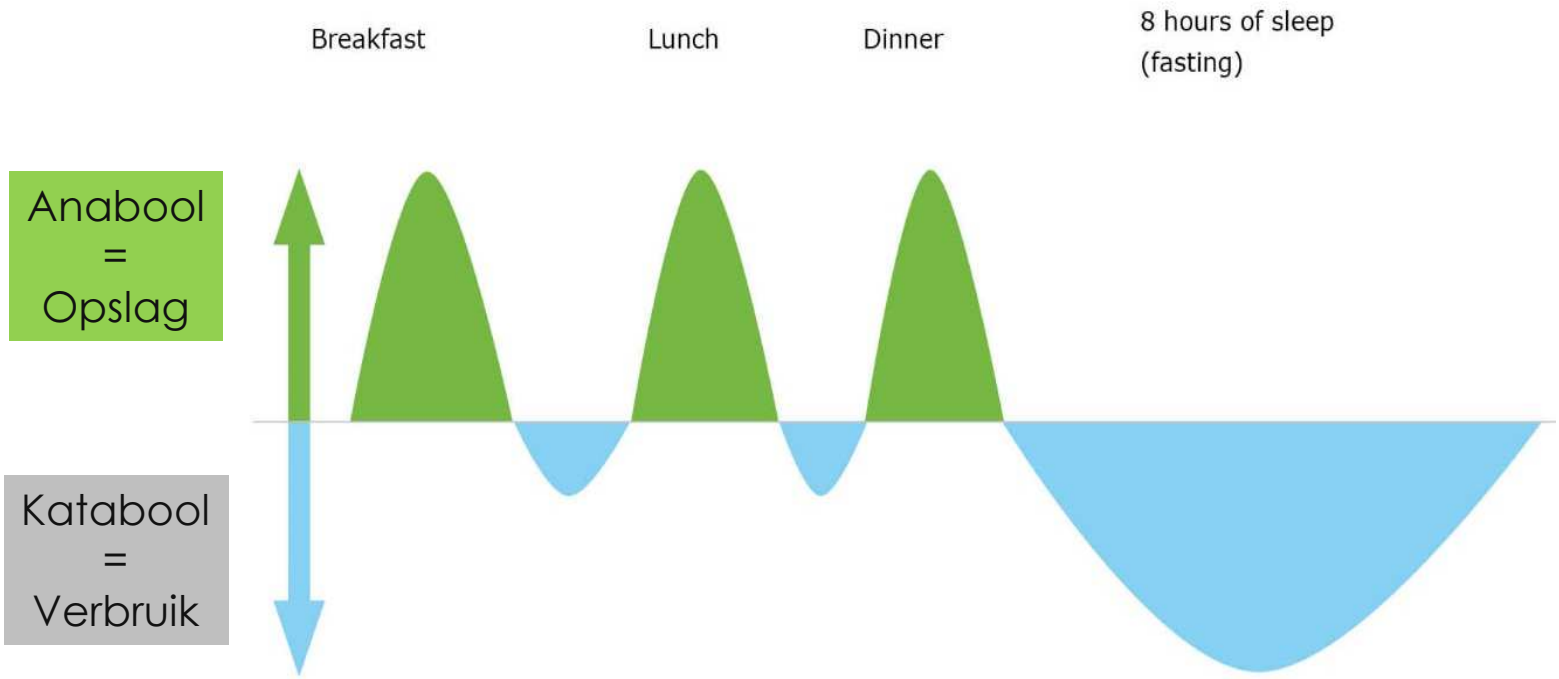
Vrij vertaald:





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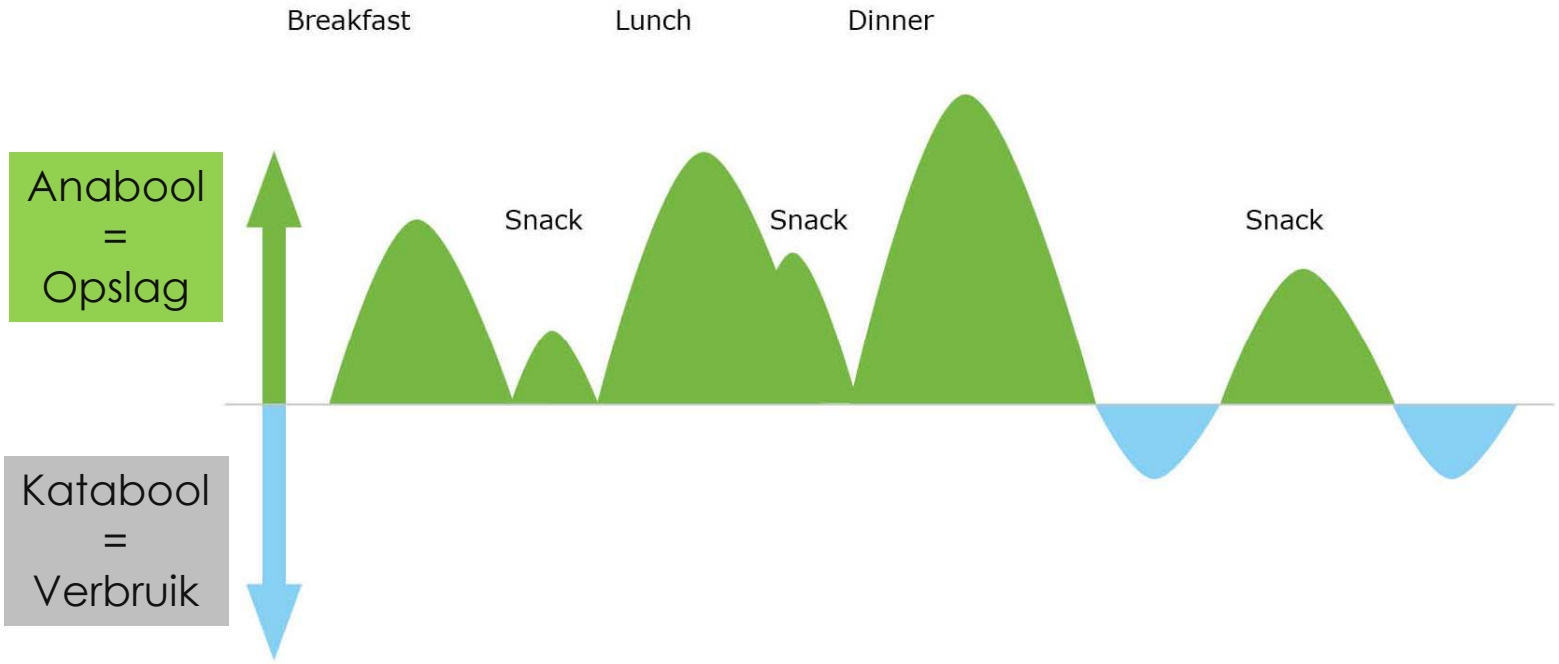
En wat is er eigenlijk aan de hand?



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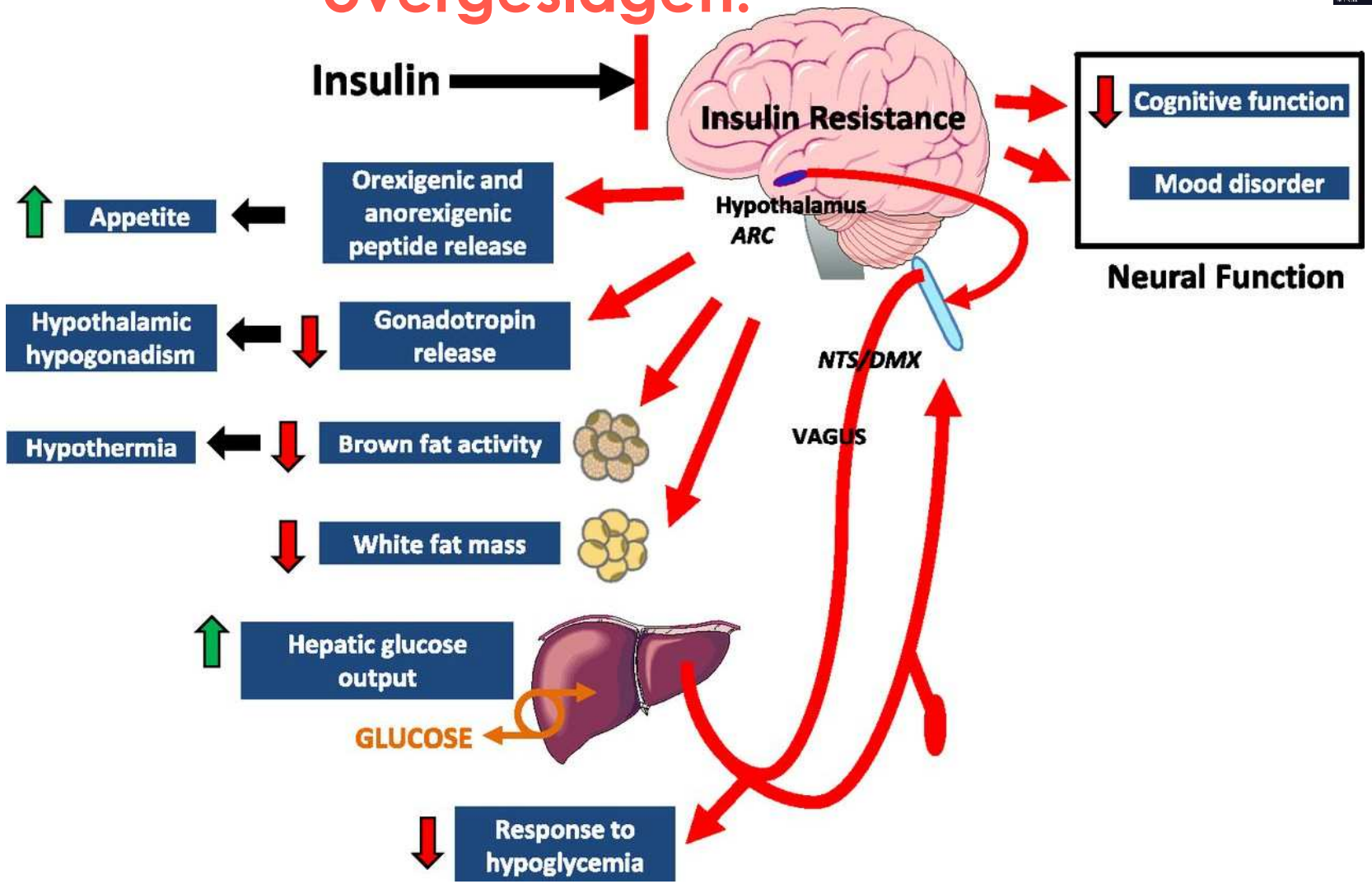
En dan hebben we de hersenen nog overgeslagen:



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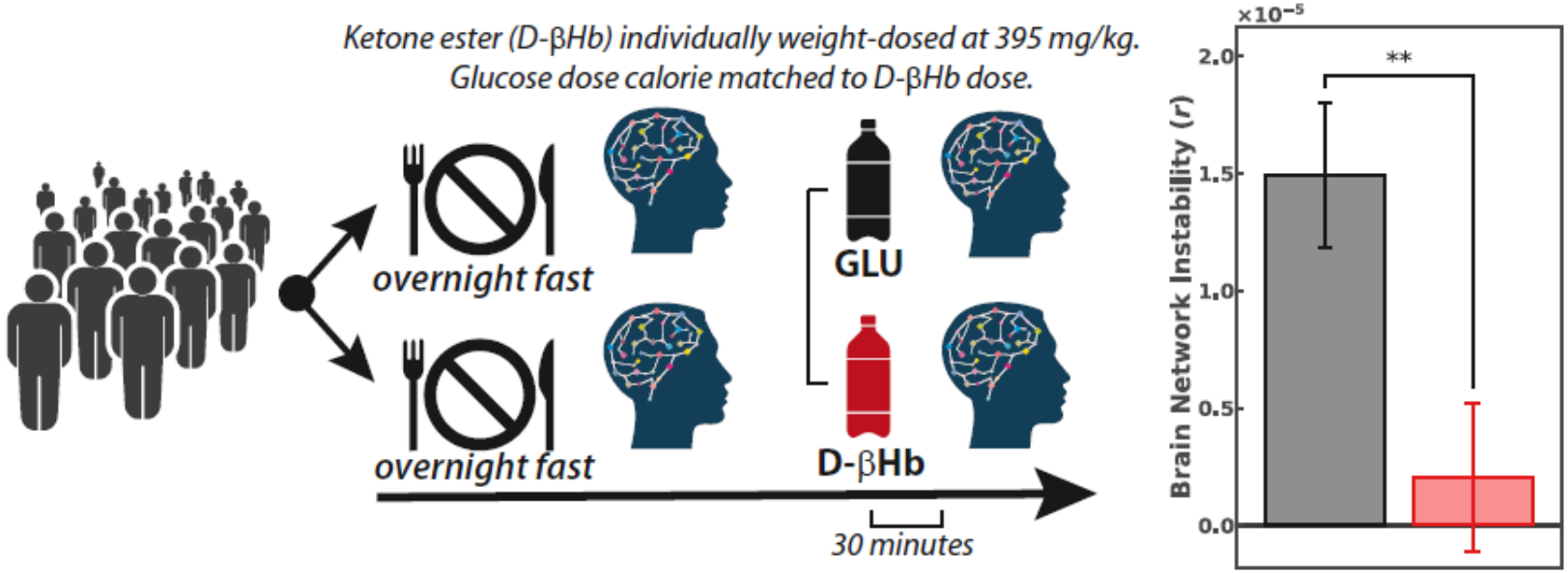
Diet modulates brain network stability, a biomarker for brain aging, in young adults

Lilianne R. Mujica-Parodi[a,b,c,d,1,2], Anar Amgalan[b,c,1], Syed Fahad Sultan[e], Botond Antal[a], Xiaofei Sun[e], Steven Skiena[e], Andrew Lithen[a], Noor Adra[a], Eva-Maria Ratai[d], Corey Weistuch[b,f], Sindhuja Tirumalai Govindarajan[a], Helmut H. Strey[a,b], Ken A. Dill[b,2], Steven M. Stufflebeam[d], Richard L. Veech[g,3], and Kieran Clarke[h]

www.pnas.org/cgi/doi/10.1073/pnas.1913042117



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Dank je wel.

Voeding Leeft

Arts en Voeding

BOLDCOACH ACADEMY