The enteroinsular axis in the pathogenesis of prediabetes and diabetes in humans

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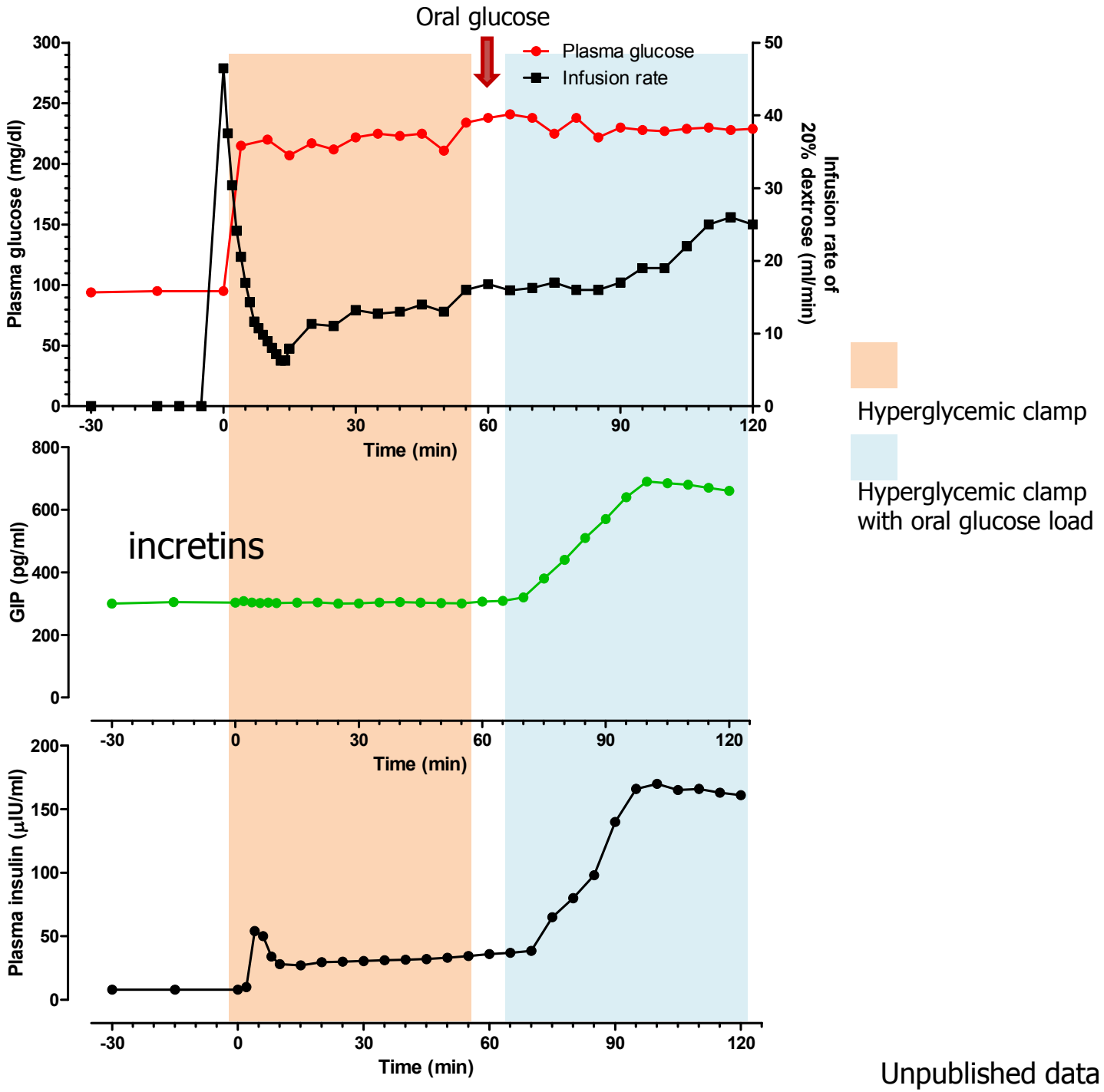
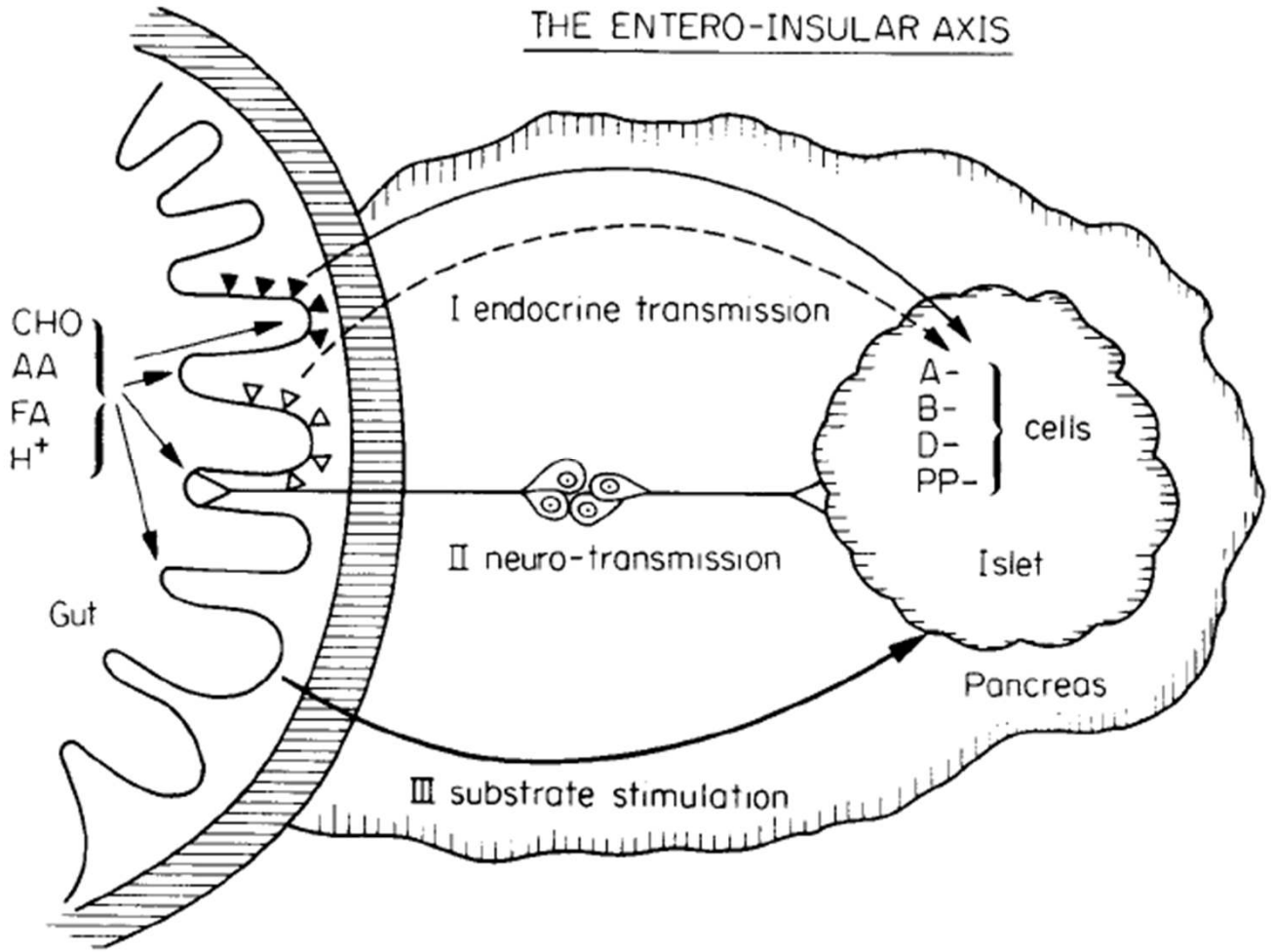


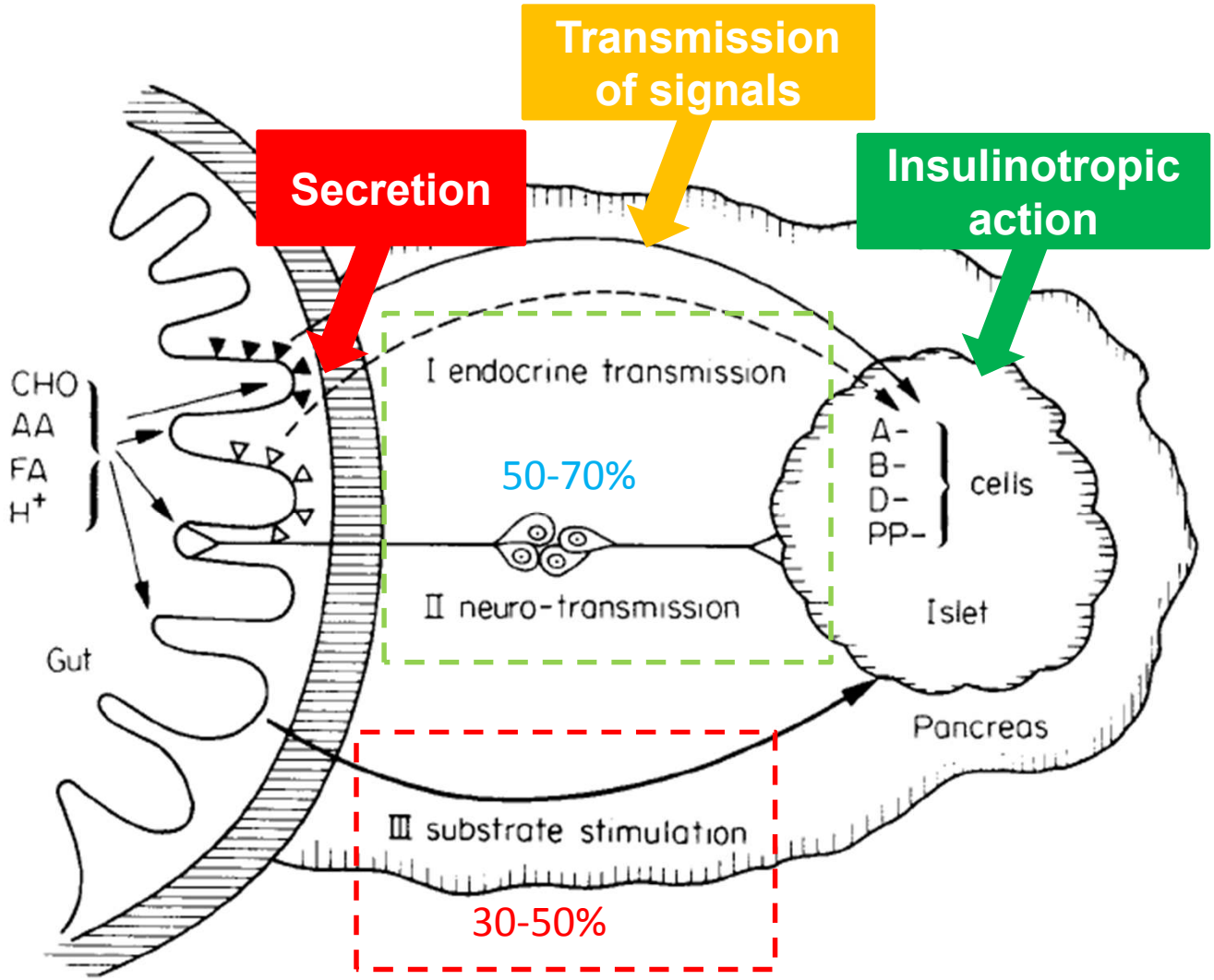
Unpublished data

The enteroinsular axis



W. Creutzfeldt: *Diabetologia* 16:75-85, 1979

Abnormal enteroinsular axis



W. Creutzfeldt: *Diabetologia* 16:75-85, 1979

Abnormal enteroinsular axis in type 2 diabetes
Common belief: fact or myth?

	Secretion	Insulinotropic effect
GLP-1	Decreased	Normal
GIP	Increased or normal	Markedly decreased

Cross sectional study

TABLE 1. Summary of the characteristics of the T2DM, NGT, and IGT groups reported as the mean ± SD (rows 1–6) and SEM (rows 7–13)

	T2DM	NGT	IGT	T2DM *vs.* NGT	ANOVA	ANOVA correcting for covariates
No. (M/F)	54 (44/10)	33 (27/6)	15 (12/3)			
Age (yr)	55.9 ± 8.0	56.2 ± 9.1	55.3 ± 6.8	NS	NS	
BMI (kg/m^2)	30.2 ± 5.3	29.6 ± 6.2	35.0 ± 5.3	NS	0.007[a]	
Treatment (D/SU/B/SU + B)	19/16/12/7					
HbA_{1c} (%)	8.4 ± 1.7	5.9 ± 0.4	6.1 ± 0.6	<0.001	<0.001[b]	<0.000[b]
Fasting PG (mmol/liter)	11.7 ± 4.0	5.9 ± 0.6	6.2 ± 0.6	<0.001	<0.001[b]	<0.000[sex,b]
Fasting plasma insulin (pmol/liter)	48 ± 5.0	40 ± 4.0	78 ± 15.0	NS	0.014[a]	NS[BMI]
Fasting plasma C peptide (pmol/liter)	778 ± 48	667 ± 42	999 ± 134	NS	0.025[c]	NS[BMI]
Fasting plasma glucagon (pmol/liter)	13.0 ± 0.8	8.4 ± 0.9	11.2 ± 1.6	<0.001	<0.001[d]	<0.001[b, BMI, sex]
Fasting plasma PP (pmol/liter)	33 ± 3.9	26 ± 2.9	24 ± 4.0	NS	NS	NS[sex, age]
Fasting NEFA (mmol/liter)	0.78 ± 0.04	0.78 ± 0.04	0.85 ± 0.07	NS	NS	NS
Fasting plasma GIP (pmol/liter)	12.7 ± 1.5	8.6 ± 0.7	9.8 ± 1.2	0.13	NS	NS
Fasting plasma GLP-1 (pmol/liter)	6.6 ± 0.5	4.9 ± 0.4	4.9 ± 0.4	0.037	NS	NS

The significances of differences between the age-, gender-, and BMI-matched T2DM and NGT groups were evaluated by means of Mann-Whitney tests, whereas comparisons involving also the unmatched IGT group were carried out by means of ANOVA (significant or near-significant covariates shown as superscripts).

[a] $P < 0.05$, IGT *vs.* T2DM and NGT.
[b] $P < 0.05$, T2DM *vs.* NGT and IGT.
[c] $P < 0.05$, NGT *vs.* IGT.
[d] $P < 0.05$, T2DM *vs.* NGT.
[e] $P < 0.05$, NGT *vs.* T2DM and IGT.

Toft-Nielsen M et al. J Clin Endocrinol Metab 86: 3717–3723, 2001

GLP-1 secretin is reduced in patients with T2DM

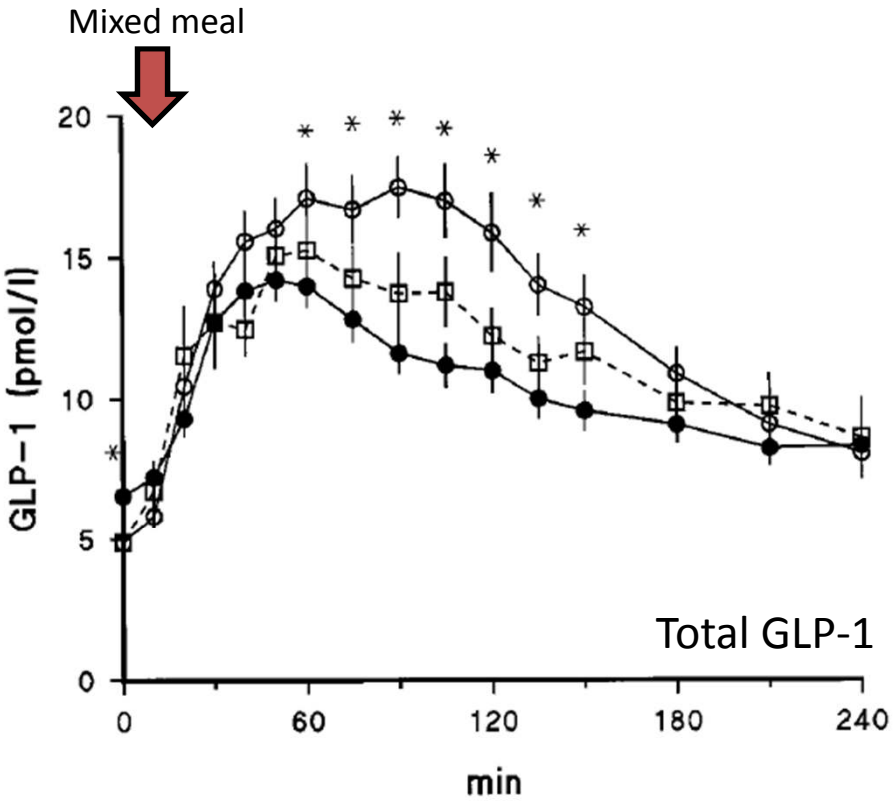
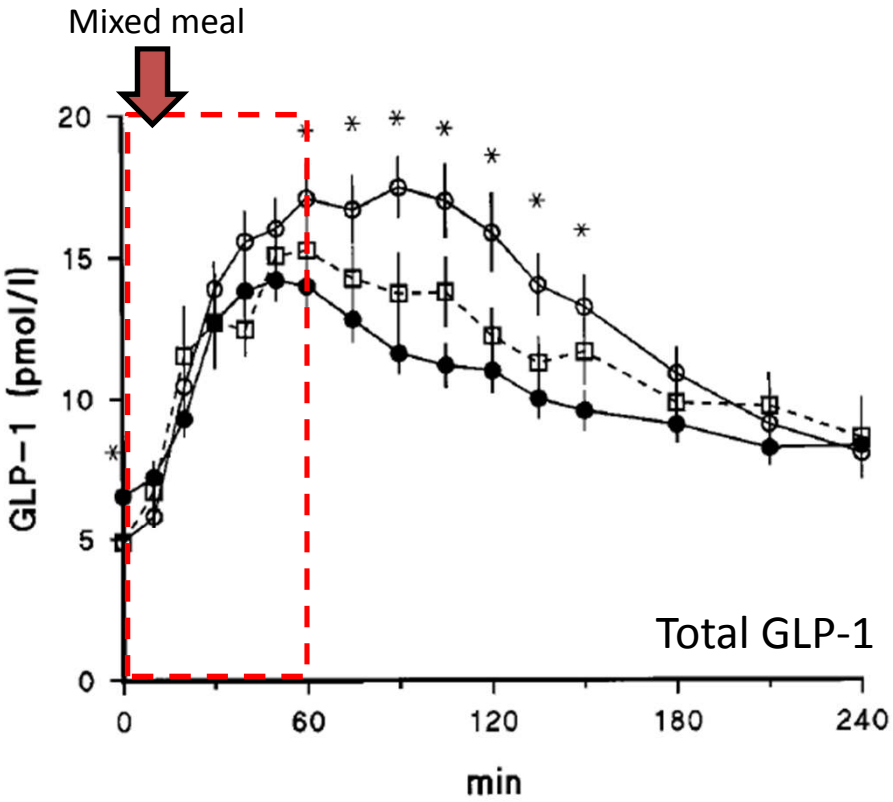


FIG. 3. Plasma GLP-1 concentrations in T2DM patients (●), NGT subjects (○), and IGT subjects (□) during a 240-min meal test. The meal was started at time zero and finished in the 10- to 15-min period. *, $P < 0.05$ between the T2DM and NGT group.

Toft-Nielsen M et al. J Clin Endocrinol Metab 86: 3717–3723, 2001

GLP-1 secretin is reduced in patients with T2DM
only in the late postprandial period



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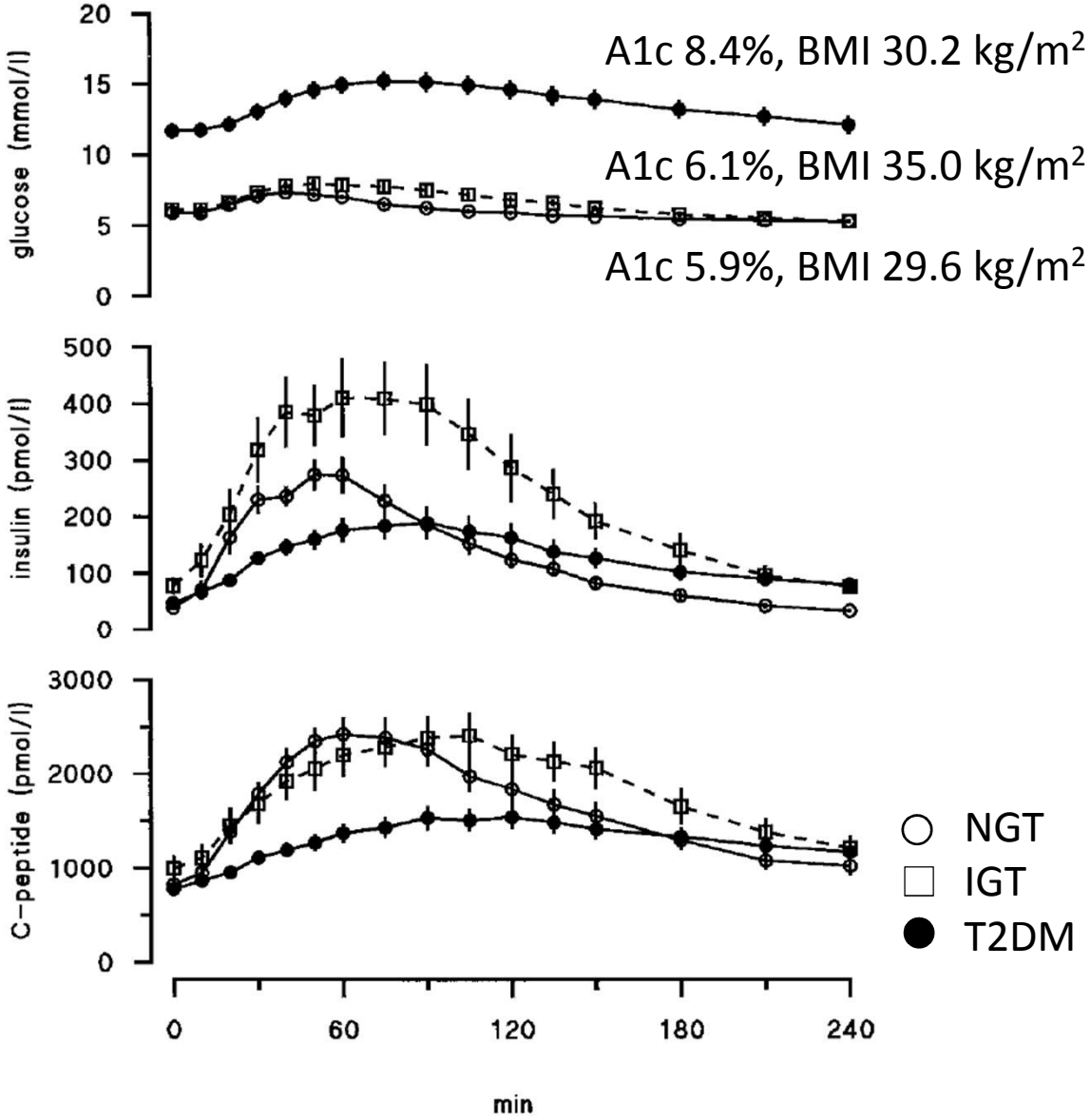
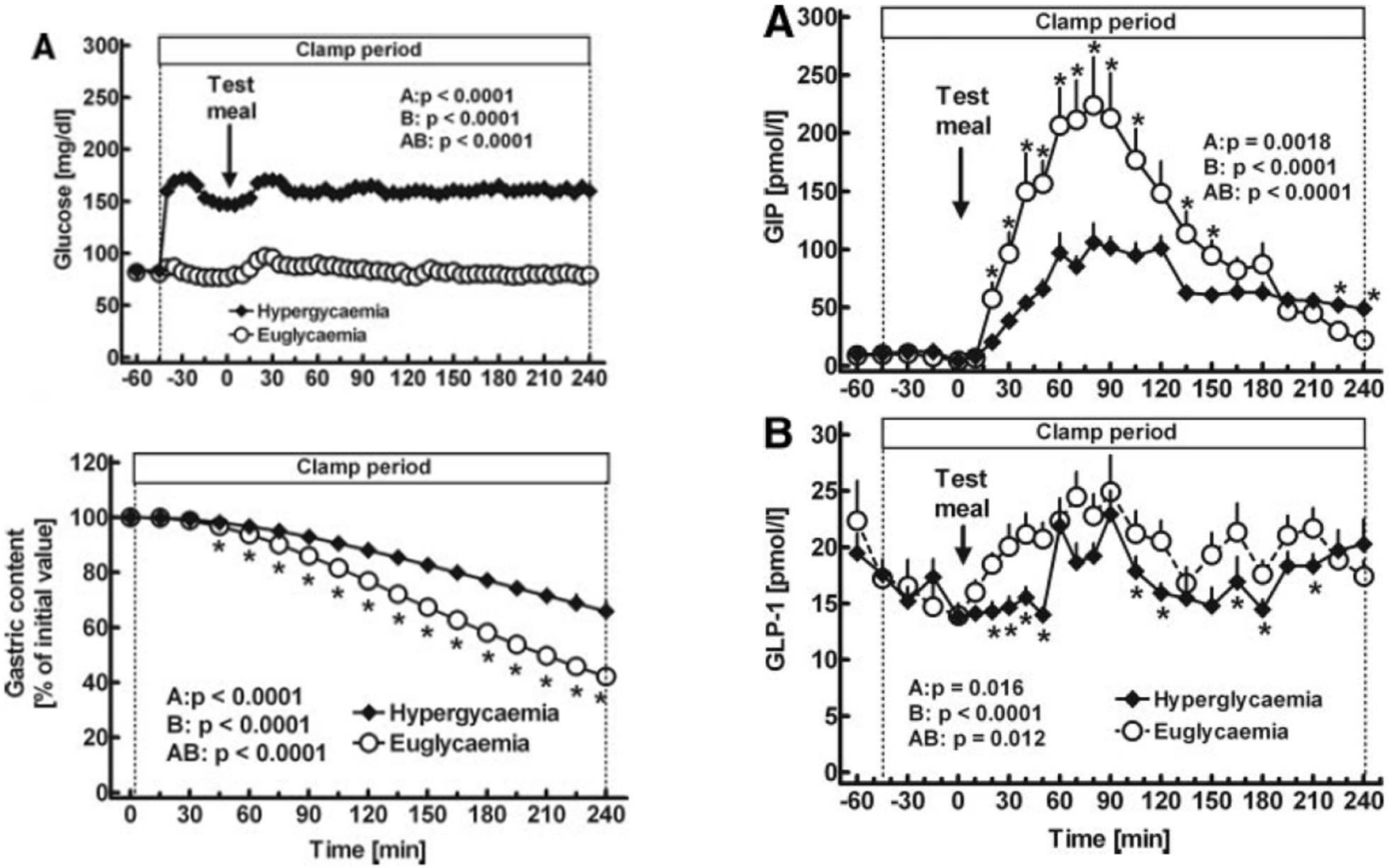


FIG. 1. Plasma glucose (*upper panel*), insulin (*middle panel*), and C peptide (*lower panel*) concentrations in T2DM patients (●), NGT subjects (○), and IGT subjects (□) during a 240-min meal test. The meal was started at time zero and finished in the 10- to 15-min period.

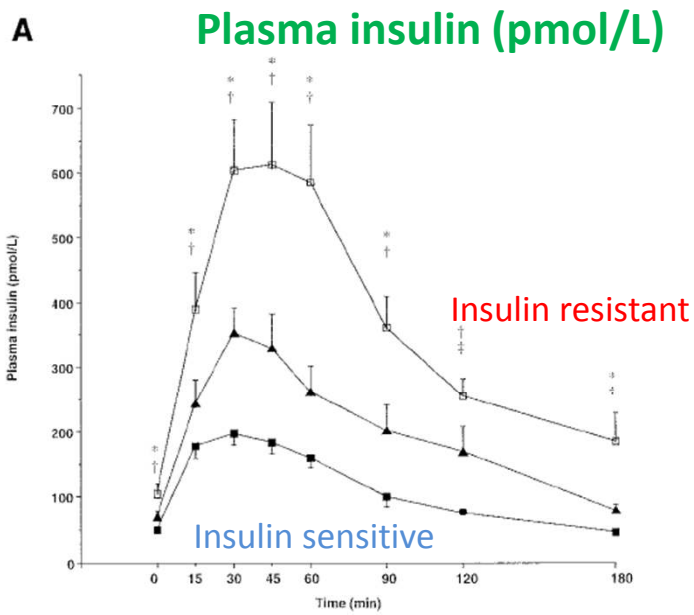
Toft-Nielsen M et al. J Clin Endocrinol Metab 86: 3717–3723, 2001

Effect of acute hyperglycemia



Vollmer K et al. J Clin Endocrinol Metab 94: 1379–1385, 2009

Impaired Incretin Response After a Mixed Meal Is Associated With Insulin Resistance in Nondiabetic Men



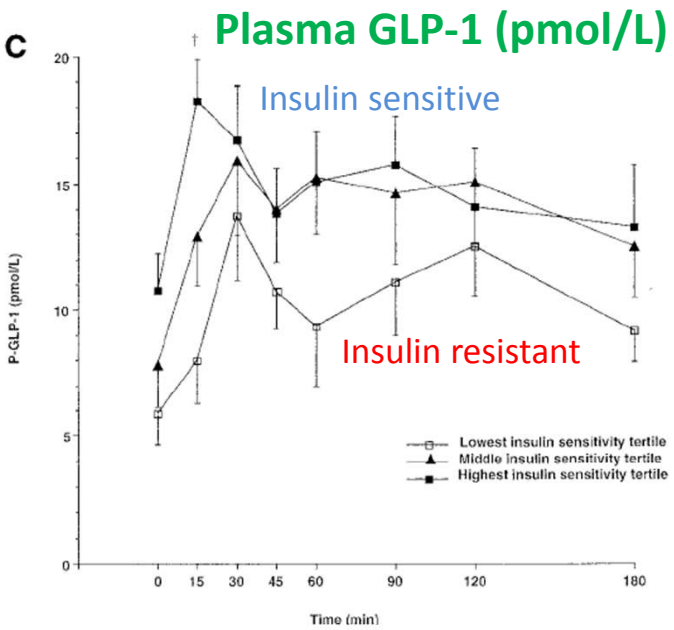


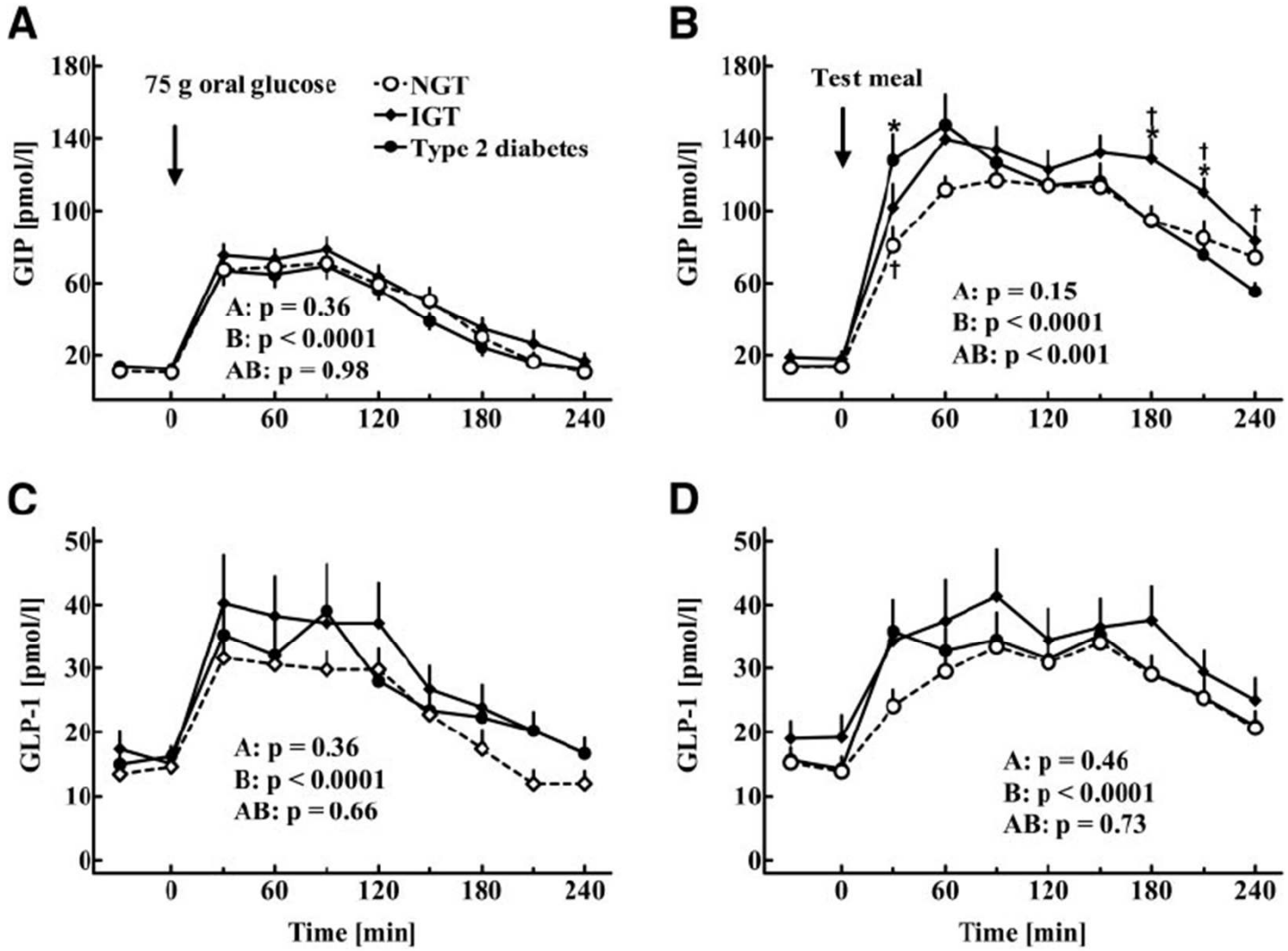
Table 1—*Characteristics of the participants*

	Insulin sensitivity			
	Lowest tertile	Medium tertile	Highest tertile	*F* probability
n	11	11	11	
Age (years)	53.1 ± 11.1	49.1 ± 9.6	47.6 ± 8.6	0.37
BMI (kg/m^2)	30.4 (27.3–32.7)	26.4 (26.3–28.6)	23.9 (22.6–25.6)	<0.001
Fat mass (kg)	28.9 (25.1–45.5)	23.6 (19.1–25.9)	17.1 (13.2–18.7)	<0.001
Waist circumference (cm)	108.0 (103.0–117.4)	98.0 (95.0–103.0)	90.0 (81.0–93.0)	<0.001
Fasting glucose (mmol/l)	4.8 ± 0.4	4.6 ± 0.5	4.7 ± 0.2	0.52
Fasting insulin (pmol/l)	97.0 (66–116)	72.5 (50.5–76.5)	44.0 (40.5–52.5)	<0.01
Insulin sensitivity§	3.1 (2.1–3.2)	7.2 (5.1–7.8)	10.1 (9.4–13.8)	<0.001

(Insulin sensitivity was measured by a hyperinsulinemic euglycemic clamp)

Diabetes Care 24:1640–1645, 2001

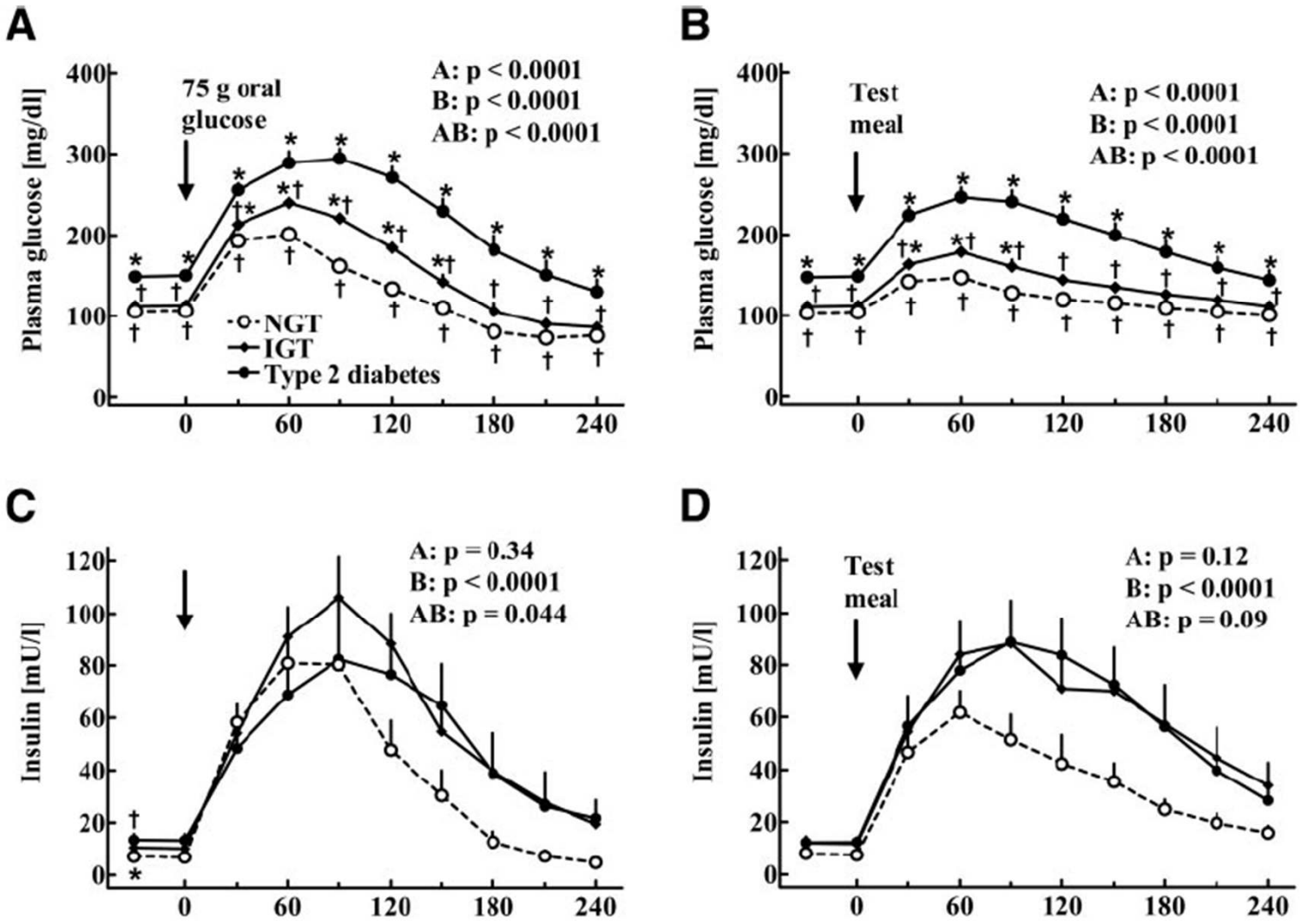
GIP and GLP-1 responses in NGT, IGT, and T2D



Statistics were carried out using repeated-measures ANOVA and denote differences between the experiments (A), differences over time (B), and differences due to the interaction of experiment and time (AB).

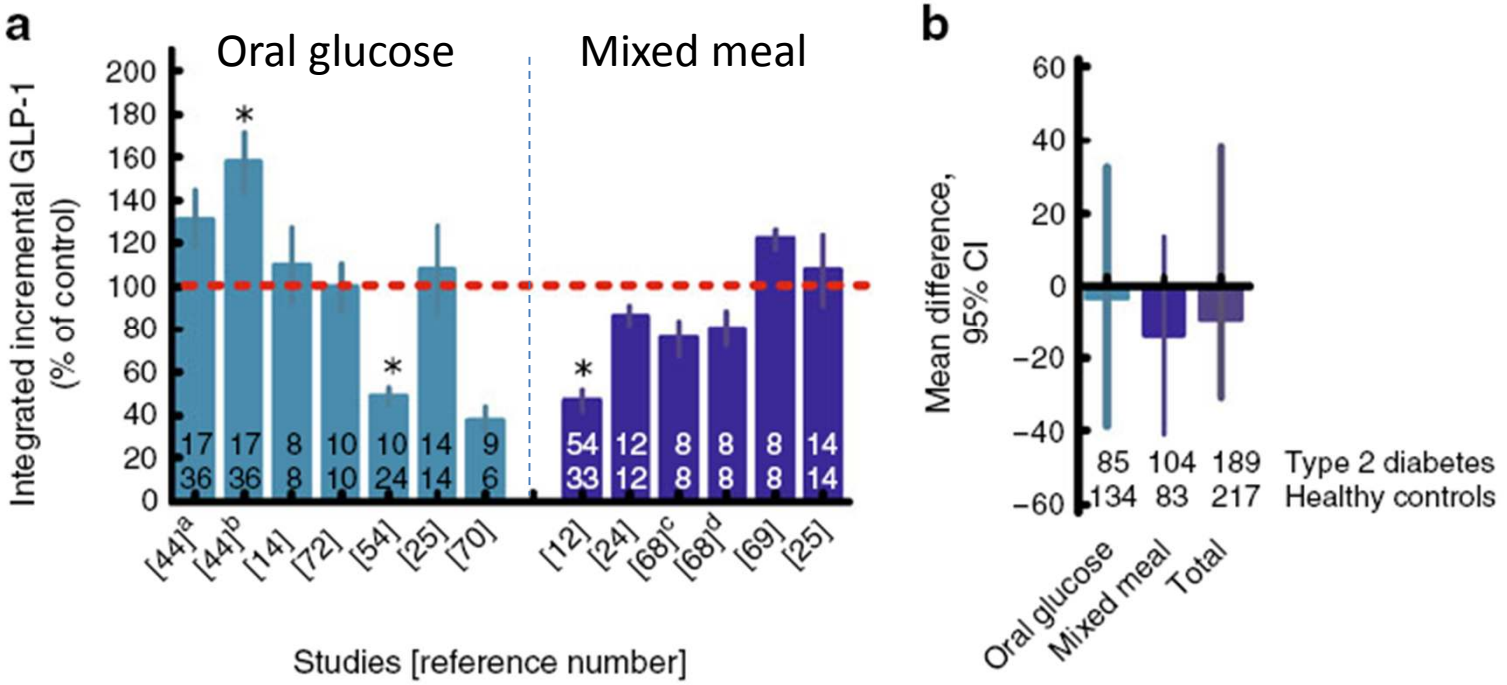
Vollmer K et al., *Diabetes 57:678–687, 2008*

Plasma glucose and insulin levels



T2DM	A1c 6.8%, BMI 32.1 kg/m^2;
IGT	A1c 5.9%, BMI 29.5 kg/m^2;
NGT	A1c 5.8%, BMI 27.5 kg/m^2

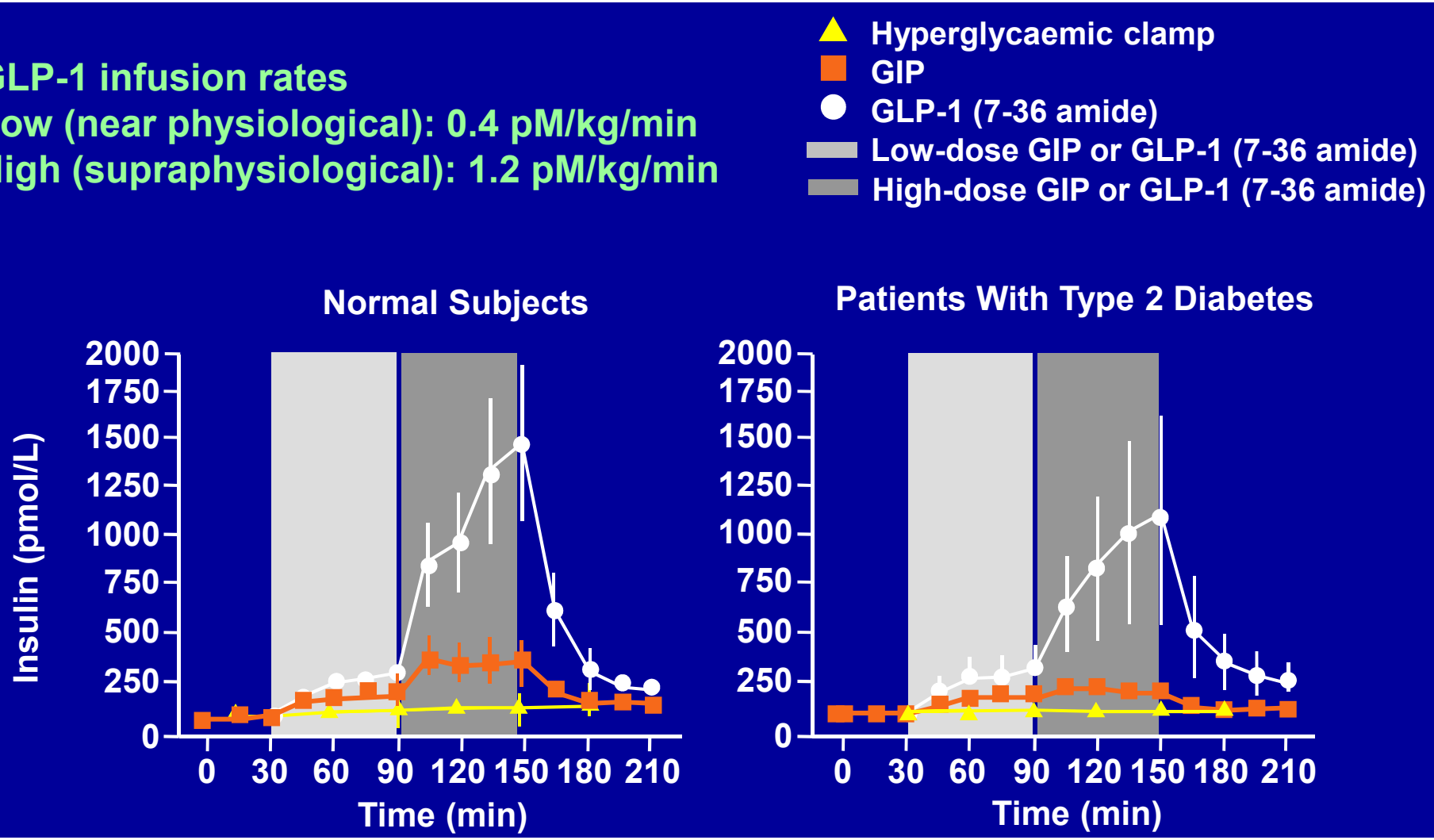
Integrated responses of ‘total’ GLP-1 to oral glucose or mixed meals based on individual studies



Nauck MA et al. Diabetologia (2011) 54:10–18

The insulinotropic action of GLP-1 is also decreased by ~29% compared with normal subjects.

GLP-1 infusion rates
Low (near physiological): 0.4 pM/kg/min
High (supraphysiological): 1.2 pM/kg/min



Mean ± SE; N=18.

Nauck MA, et al. *J Clin Invest.* 1993;91:301-307. Reprinted with permission from The American Society for Clinical Investigation.

Decreased insulinotropic action of GLP-1 in type 2 diabetes

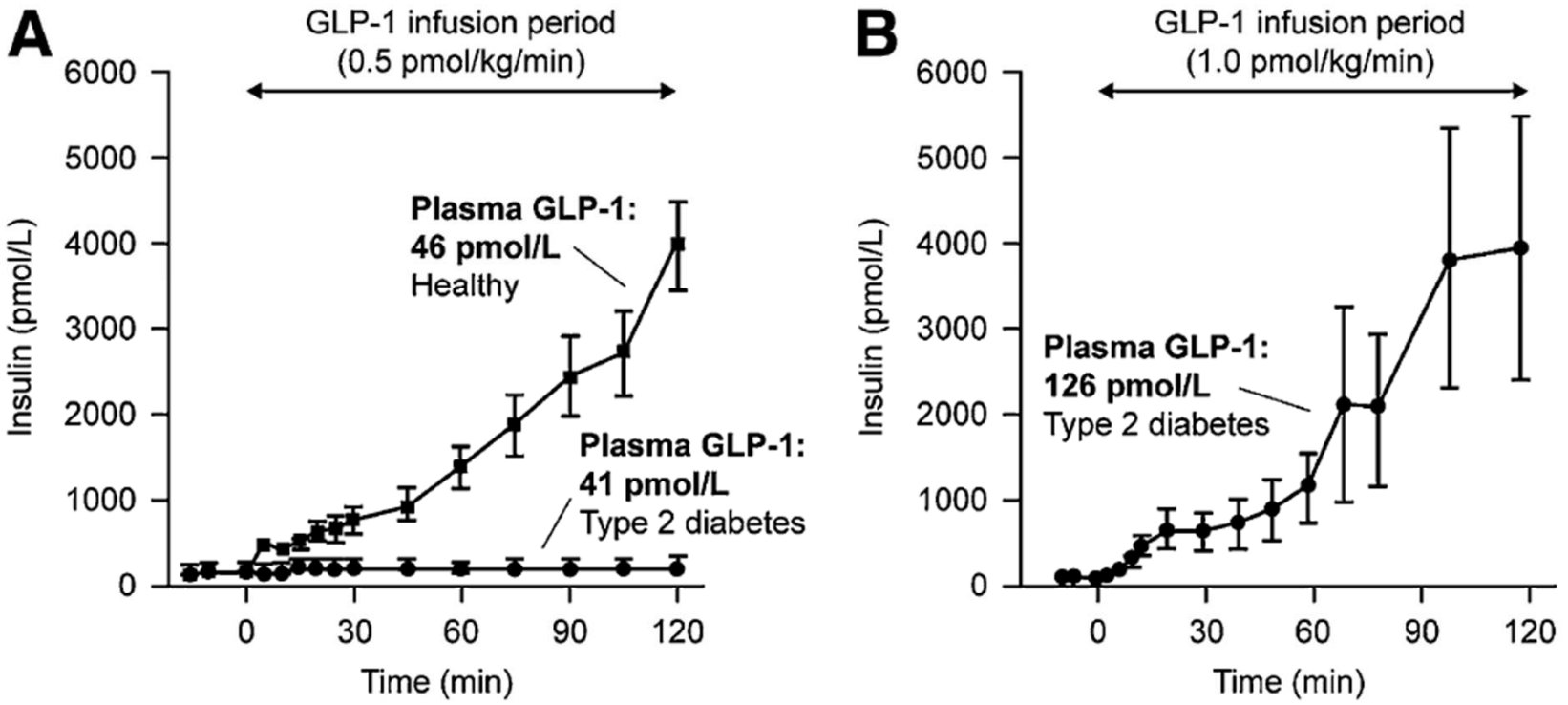


Figure 1—*Pharmacological, but not physiological, levels of GLP-1 enhance insulin secretion in patients with type 2 diabetes. Reproduced with permission from Springer, from Højberg et al. (16) (A), and Vilsbøll et al. (17) (B).*

Garber AJ. Diabetes Care 2011; 34 (suppl.2): S258-63

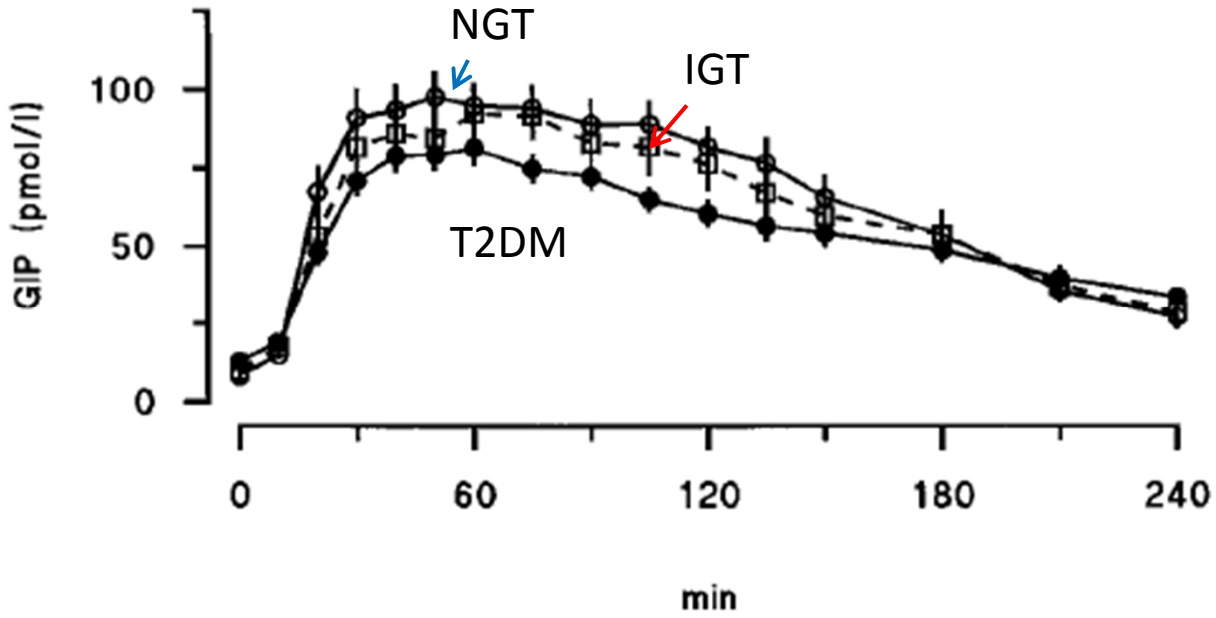
Abnormal enteroinsular axis in type 2 diabetes

	Secretion	Insulinotropic effect
GLP-1	Normal or decreased*	Maintained or slightly decreased**
GIP		

*, in some subjects with marked insulin resistance or severe hyperglycemia

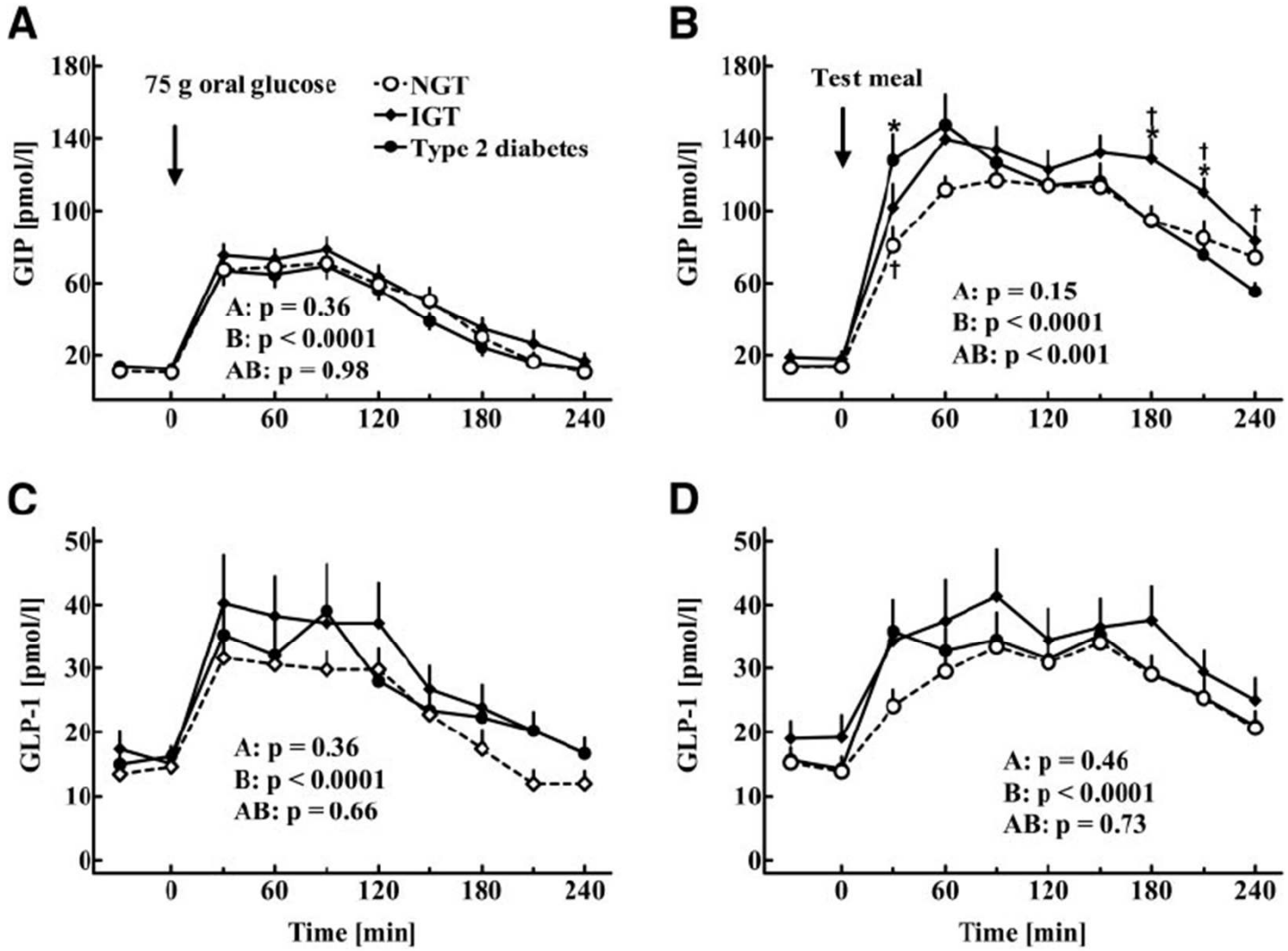
**, correlated with decreased beta-cell functional capacity or mass; decreased response to physiological level of GLP-1

GIP secretion during 4-h mixed meal tests



Toft-Nielsen M et al. J Clin Endocrinol Metab 86: 3717–3723, 2001

GIP and GLP-1 responses in NGT, IGT, and T2D



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Vollmer K et al., *Diabetes 57:678–687, 2008*

Virtually absent insulinotropic effect of GIP in T2D

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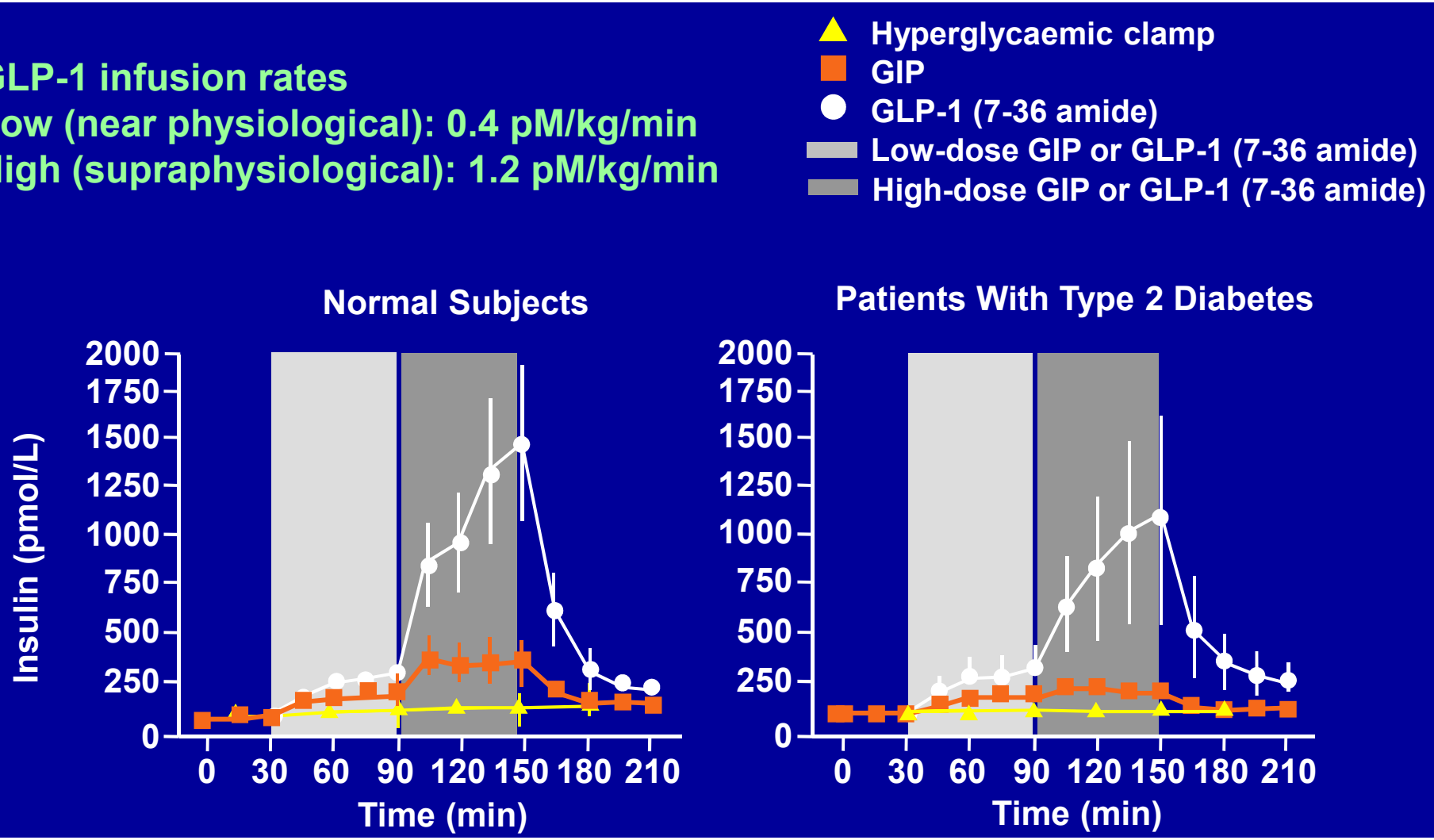
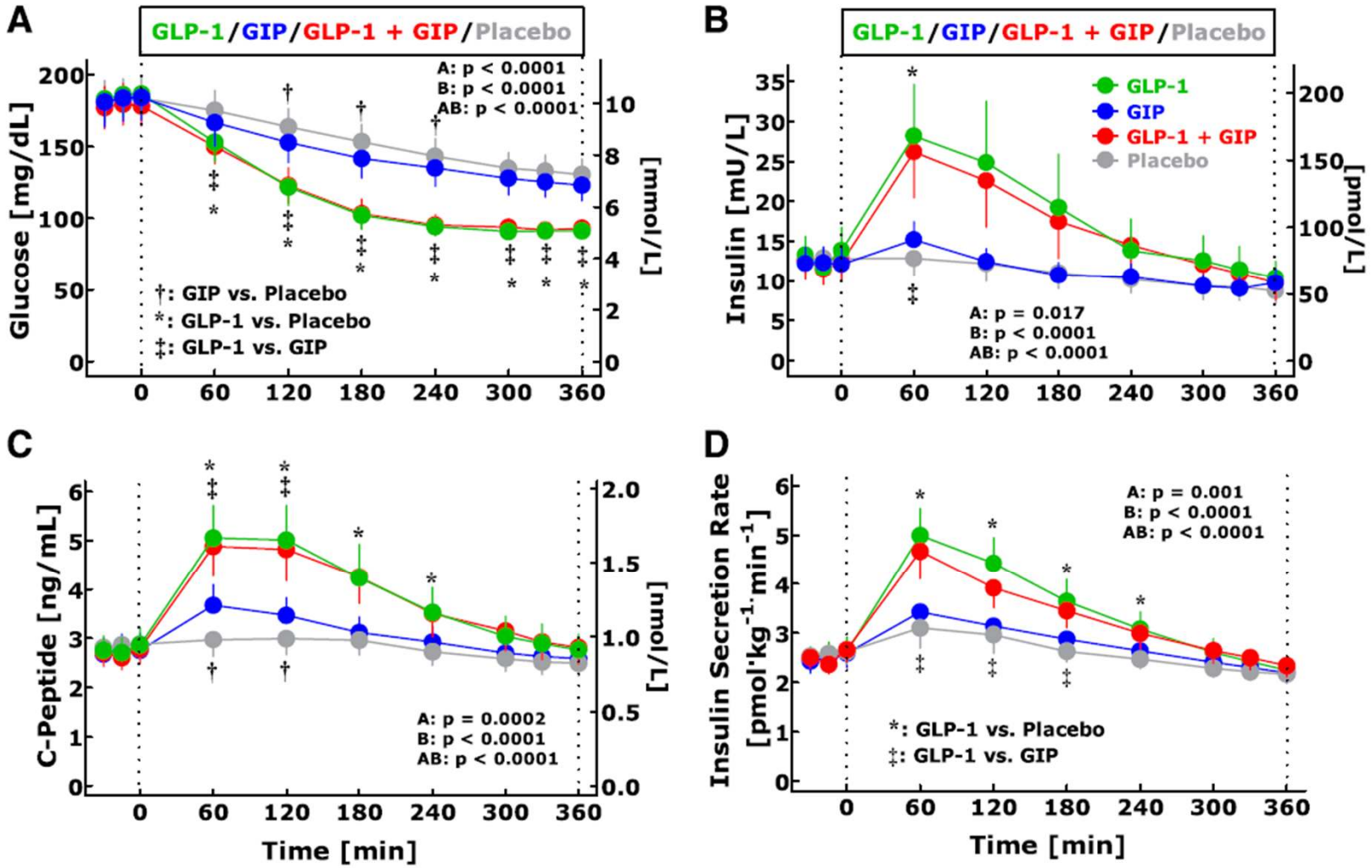


Mean ± SE; N=18.

Nauck MA, et al. *J Clin Invest.* 1993;91:301-307. Reprinted with permission from The American Society for Clinical Investigation.

GIP Does Not Potentiate the Antidiabetic Effects of GLP-1 in Hyperglycemic Patients With Type 2 Diabetes



GLP-1 (1.2 pmol · kg(-1) · min(-1))
GIP (4 pmol · kg(-1) · min(-1))

Mentis N et al. Diabetes 60:1270–1276, 2011

Abnormal enteroinsular axis in type 2 diabetes

	Secretion	Insulinotropic effect
GLP-1	Normal or decreased*	Maintained or slightly decreased**
GIP	Increased or normal or decreased	Markedly decreased†

*, in some subjects with marked insulin resistance or severe hyperglycemia
**, correlated with decreased beta-cell functional capacity or mass
†, marked decrease in GIPR expression was observed in animals.

Cause or result of type 2 diabetes?

	Secretion	Insulinotropic effect
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Cause or result of type 2 diabetes?

- Cohort study (longitudinal)
- Genetic association
- Abnormalities in high risk groups
  - IGT
  - 1st degree relatives
  - Previous GDM
- Abnormalities in other types of diabetes

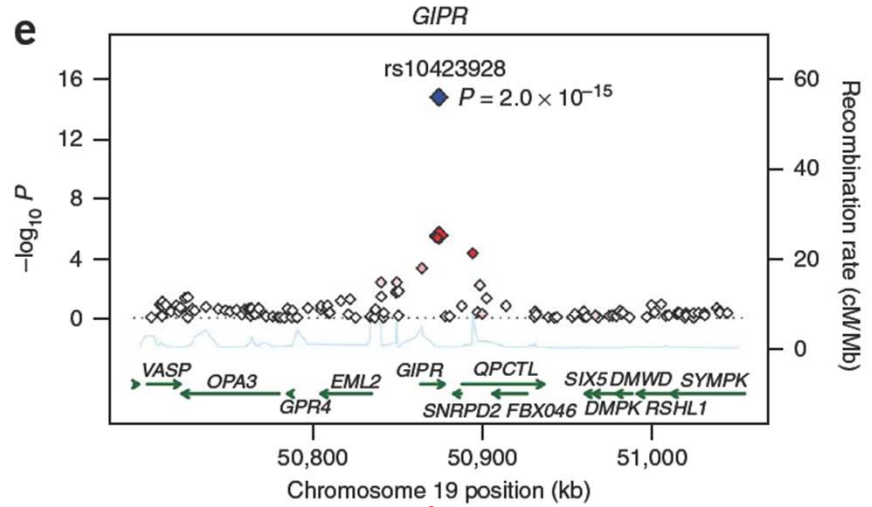
Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge

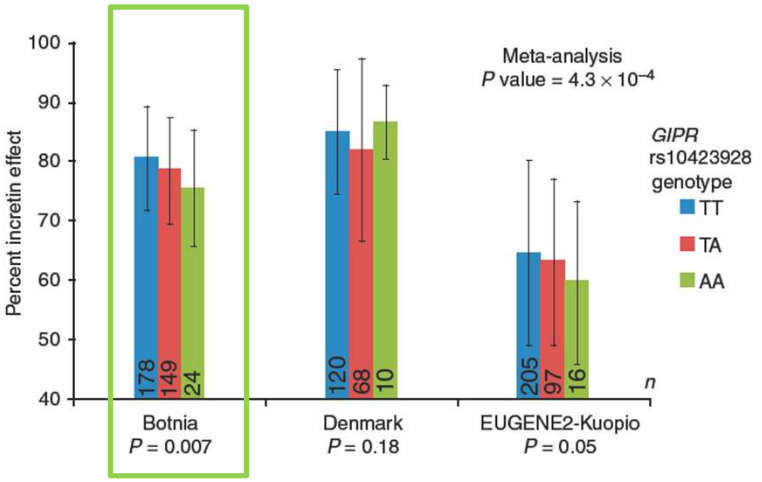
Table 1 Genome-wide significant loci for 2-h glucose during an OGTT from 26 studies in nondiabetic individuals

						Discovery		Replication		Discovery and replication			Discovery and replication (FG adj)		
SNP	Chr	Position (bp)	Nearest gene	Alleles (+/–)	Freq (+)[1]	Effect (s.e.m.) mmol/l	*P* value	Effect (s.e.m.) mmol/l	*P* value	Effect (s.e.m.) mmol/l	*P* value	*P* value (no BMI)	Effect (s.e.m.) mmol/l	*P* value	*P* value (no BMI)
rs1260326	2	27584444	*GCKR*	T/C	0.40	0.09 (0.02)	1.53×10^{-6}	0.06 (0.01)	5.33×10^{-6}	0.07 (0.01)	7.05×10^{-11}	3.00×10^{-10}	0.10 (0.01)	9.23×10^{-21}	2.26×10^{-21}
rs2877716	3	124577141	*ADCY5*	C/T	0.77	0.10 (0.02)	6.26×10^{-6}	0.09 (0.01)	1.21×10^{-11}	0.09 (0.01)	4.19×10^{-16}	7.41×10^{-16}	0.07 (0.01)	1.68×10^{-11}	7.98×10^{-12}
rs12243326	10	114778805	*TCF7L2*	C/T	0.21	0.13 (0.02)	1.20×10^{-9}	0.05 (0.02)	1.27×10^{-3}	0.08 (0.01)	4.23×10^{-10}	1.12×10^{-7}	0.07 (0.01)	9.99×10^{-9}	1.17×10^{-10}
rs17271305	15	60120272	*VPS13C*	G/A	0.42	0.09 (0.02)	1.04×10^{-6}	0.05 (0.02)	1.58×10^{-3}	0.06 (0.01)	4.11×10^{-8}	1.30×10^{-7}	0.07 (0.01)	4.33×10^{-11}	8.41×10^{-11}
rs10423928	19	50874144	*GIPR*	A/T	0.18	0.15 (0.03)	3.33×10^{-6}	0.09 (0.01)	2.30×10^{-11}	0.09 (0.01)	1.98×10^{-15}	3.20×10^{-12}	0.11 (0.01)	2.56×10^{-20}	5.94×10^{-18}
						*n*11,268–15,234		15,103–30,121		30,337–43,104			30,114–42,354		

Results from fixed effects, inverse variance meta-analysis of 9 GWA (ARIC, BLSA, CHSstage1&2, CoLaus, DGI, Fenland, FHS, FUSION, Sorbs) and 17 follow-up studies (Amish, BotniaPPP, CHSstage3, DIAGEN, ELY, FrenchFamilyMembers, FrenchHaguenau, FrenchObeseAdults, FUSIONstage2, Hertfordshire, Inter99, METSIM, NHANES, RISC, Roche, ULSAM, Whitehall II) with adjustment for age, sex and BMI. Position based on hg18, NCBI build36. Combined discovery and replication *P* values for 2-h glucose adjusted for age and sex (no BMI), and further adjusted for fasting glucose are also presented. Replication meta-analysis results and joint discovery and replication meta-analysis results include proxy SNPs with $r^2 > 0.8$ in HapMap CEU.

[1]Allele frequencies based on HapMap phase II CEU sample. FG adj, adjusted for fasting glucose in addition to age, sex, BMI and study-specific covariates (center).





in strong linkage disequilibrium ($r^2 = 0.93$) with a missense mutation in GIPR (Glu354Gln)

Nature Genetics 2010;42:142-148

1st degree relative study

Subject characteristics of first-degree relatives of patients with type 2 diabetes and healthy control subjects participating in oral glucose, "isoglycaemic" intravenous glucose and hyperglycaemic clamp tests with exogenous GIP

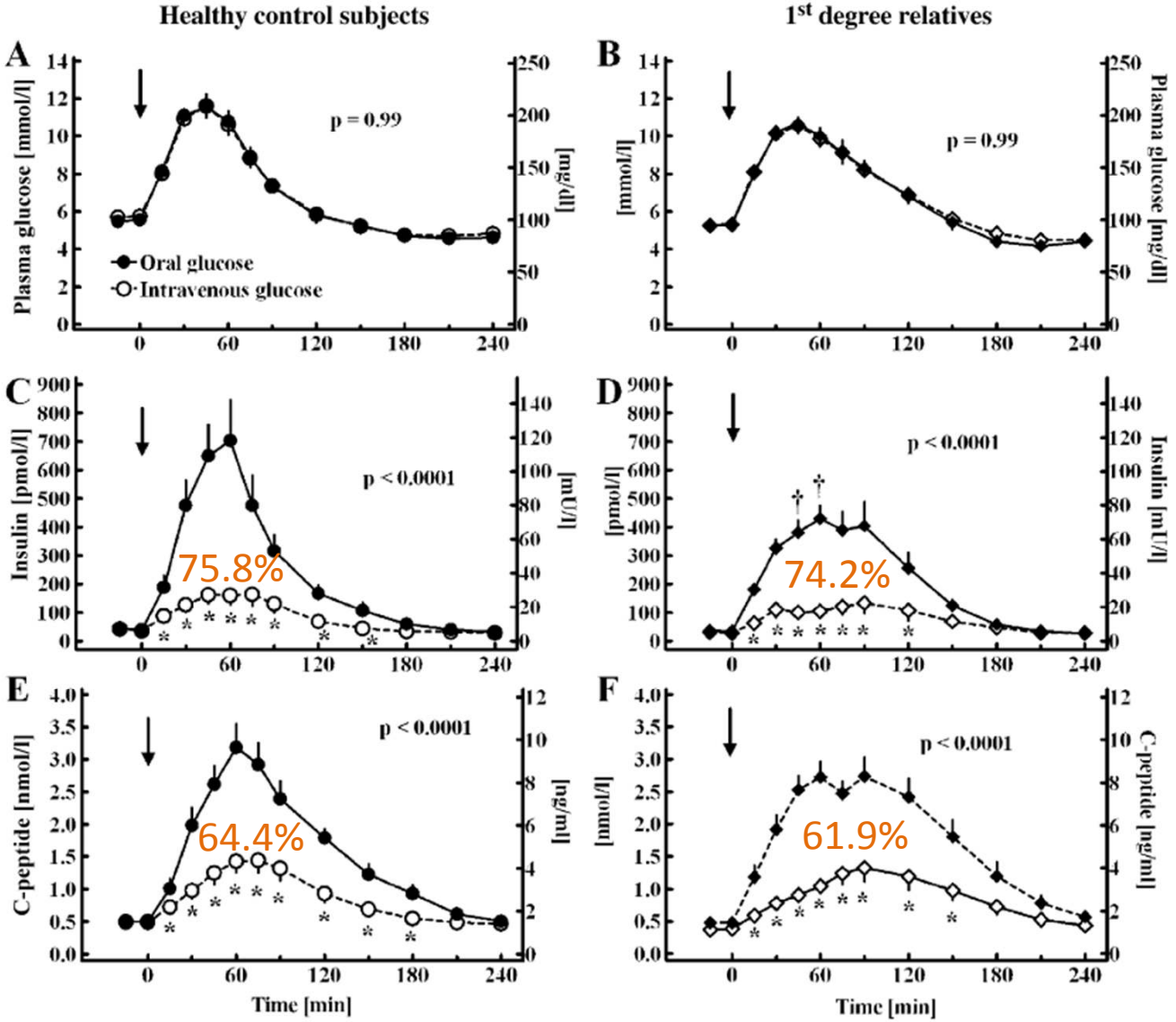
Parameter [unit]	First-degree relatives of type 2-diabetic patients	Healthy control subjects	*p* Value (ANOVA/χ^2 test)
Gender (m/f)	4/12	6/4	0.11
Age [years]	50 ± 12	45 ± 13	0.30
BMI [kg/m^2]	26.1 ± 3.8	26.1 ± 4.2	0.98
WHR [l]	0.83 ± 0.09	0.88 ± 0.09	0.19
RR systolic [mm Hg]	130 ± 17	124 ± 10	0.34
RR diastolic [mm Hg]	80 ± 8	82 ± 6	0.47
HbA_{1c} [%]	5.1 ± 0.3	5.4 ± 0.6	0.08
Glucose			
Fasting [mg/dl]	95 ± 2	99 ± 3	0.33
120 min [mg/dl]	122 ± 7	104 ± 7	0.09
Fasting insulin [mU/l]	6.1 ± 0.8	7.2 ± 1.4	0.48
Fasting C-peptide [nmol/l]	0.48 ± 0.06	0.50 ± 0.06	0.84
HOMA B-cell function [%][a]	69 ± 8	69 ± 11	0.99
HOMA insulin resistance [fold normal][a]	1.47 ± 0.23	1.82 ± 0.40	0.42

Mean ± S.D.

[a] Calculated according to Ref. [45].

Nauck MA et al. Regulatory Peptides 122 (2004) 209– 217

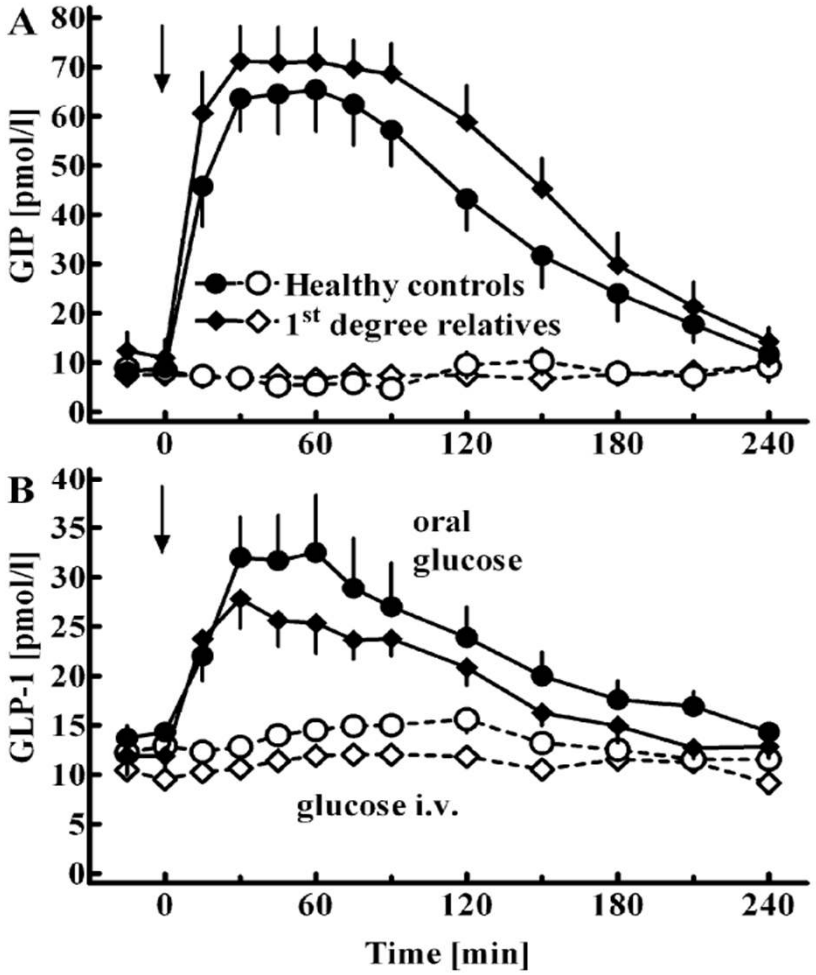
75g OGTT and IIGI



IIGI, isoglycemic intravenous glucose infusion

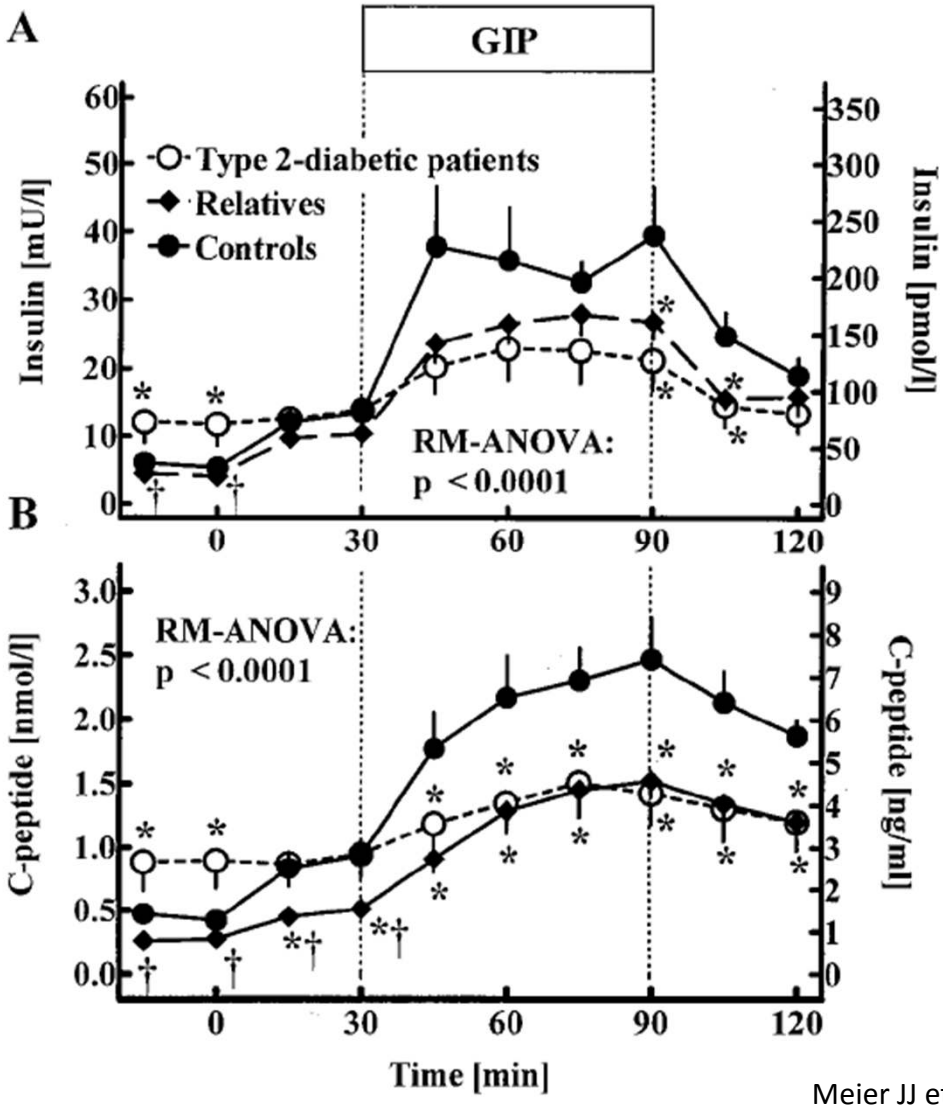
Nauck MA et al. Regulatory Peptides 122 (2004) 209– 217

No differences in GIP & GLP-1 secretion between 1st degree relatives of T2DM patients and matched healthy controls

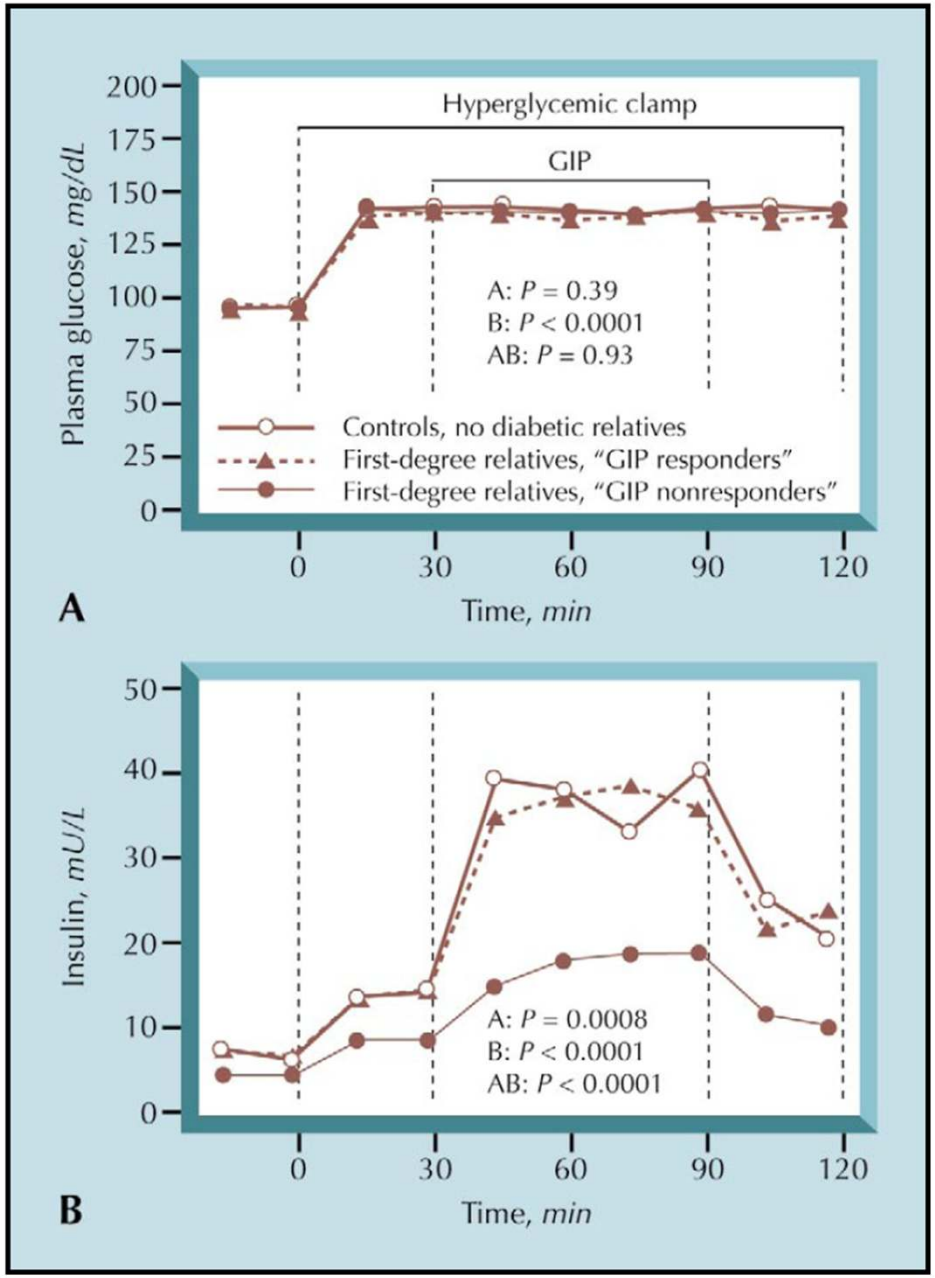


Nauck MA et al. Regulatory Peptides 122 (2004) 209– 217

Reduced insulinotropic effect of GIP in first degree relatives of patients with T2DM



Meier JJ et al. Diabetes 50:2497–2504, 2001



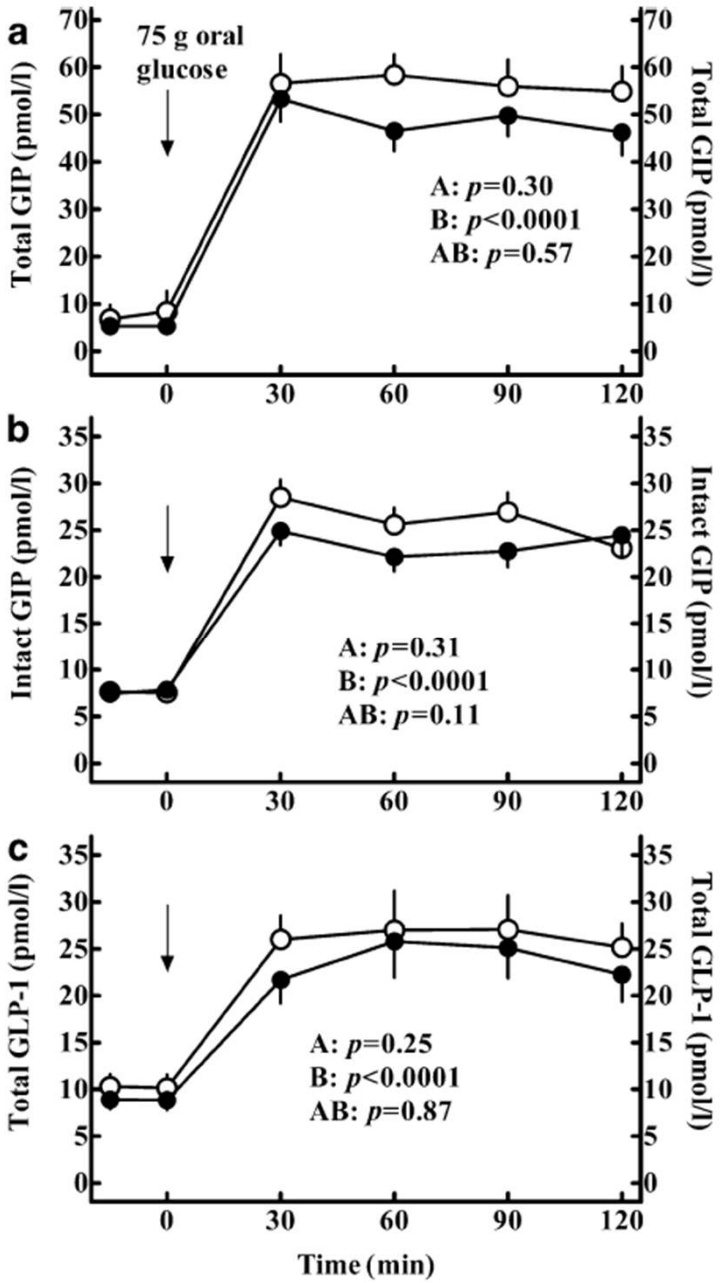
Meier and Nauck: Current Diabetes Reports 2006;6:194-201

A GDM study

Parameter	Women with pGDM	Control women	p value (ANOVA)
Age (years)	36.2±5.1	37.5±7.9	0.57
Weight (kg)	71.8±13.7	63.1±9.7	0.03
Height (cm)	167±6	169±4	0.25
BMI (kg/m^2)	25.9±5.1	22.2±3.2	0.01
WHR	0.82±0.08	0.78±0.07	0.081
Birthweight of infants (g)	3,615±661	3,165±289	0.046
Systolic BP (mmHg)	114±15	110±10	0.40
Diastolic BP (mmHg)	72±12	71±11	0.68
Total cholesterol (mmol/l)	5.02±0.68	5.05±0.80	0.92
HDL-cholesterol (mmol/l)	1.21±0.49	1.53±0.43	0.041
LDL-cholesterol (mmol/l)	3.28±0.97	3.16±0.82	0.69
Triglycerides (mmol/l)	1.29±0.56	0.95±0.57	0.07
HbA_1c (%)	5.5±0.4	5.6±0.6	0.71

pGDM, previous gestational diabetes mellitus

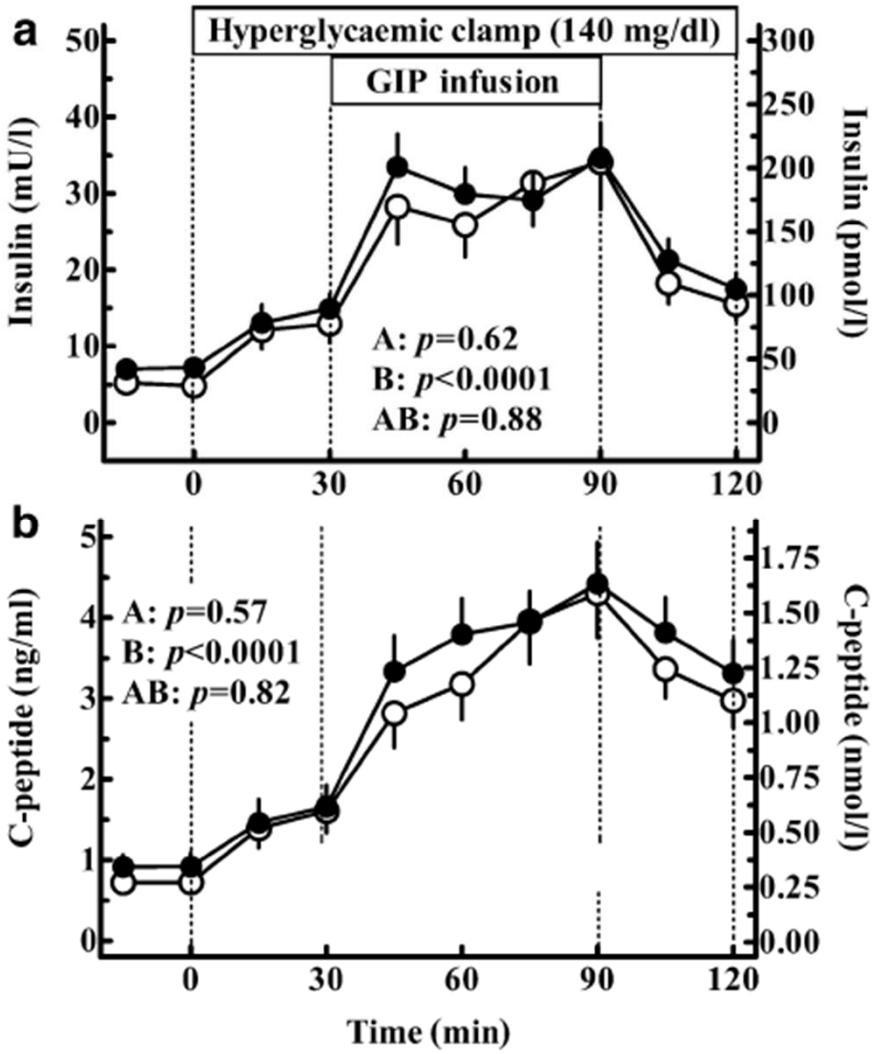
Meier J.J. et al. Diabetologia (2005) 48: 1872–1881



Closed circles, pGDM; open circles, controls

Meier J.J. et al. Diabetologia (2005) 48: 1872–1881

No difference in insulinotropic effect of GIP in subjects with previous GDM



Closed circles, pGDM; open circles, controls

Meier J.J. et al. Diabetologia (2005) 48: 1872–1881

Abnormal enteroinsular axis in subjects with high risk of T2DM

	Secretion	Insulinotropic effect
GLP-1	Normal or decreased*	Maintained (?)
GIP	Normal or decreased*	Decreased in some cases**

*, in some subjects with marked insulin resistance or severe hyperglycemia
**, in some 1st-degree relatives of patients with T2DM
†,correlated with decreased beta-cell functional capacity or mass

Cause or result of type 2 diabetes?

- Cohort study (longitudinal)
  - not available
- Genetic association with GIPR
  - postprandial glucose levels and incretin effects
- Abnormalities in high risk groups
  - No remarkable differences
- Abnormalities in other types of diabetes
  - Decreased incretin effects in patients with chronic pancreatitis and MODY3

β-cell function and incretin effect

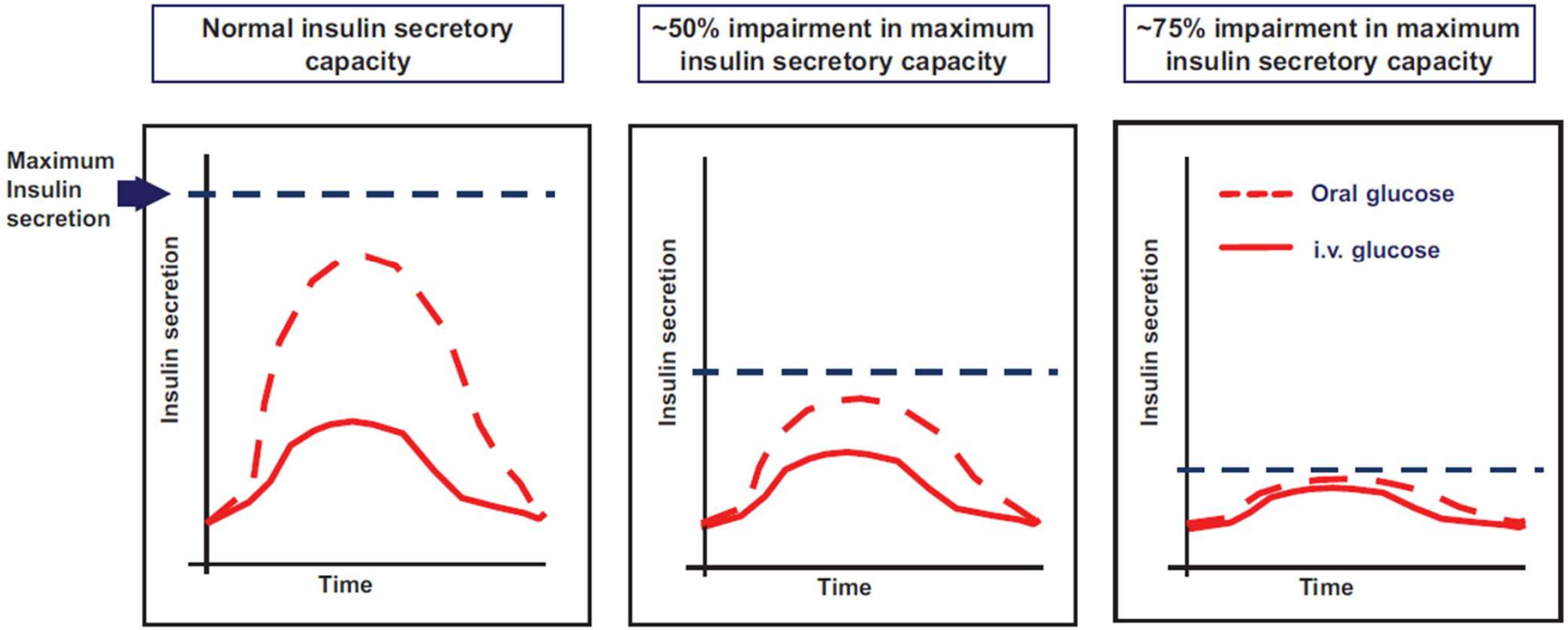


FIG. 2. Hypothetical impact of a general impairment in β-cell function on the incretin effect: In individuals with a normal insulin secretory capacity, an oral glucose load elicits a much greater insulin secretory response than an intravenous (i.v.) glucose load. With a decreasing β-cell secretory capacity, the insulin response to the oral glucose load is relatively more diminished than the insulin response to intravenous glucose infusion. By these means, the incretin effect, i.e., the difference in the insulin responses to oral and intravenous glucose, diminishes with declining β-cell function. For details, see text.

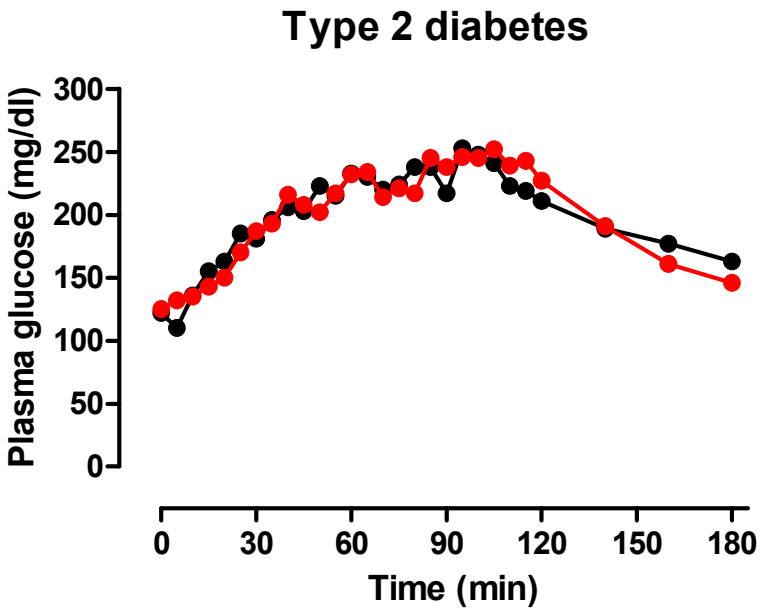
Meier JJ and Nauck MA, Diabetes Care 2010; 59: 1117-1125

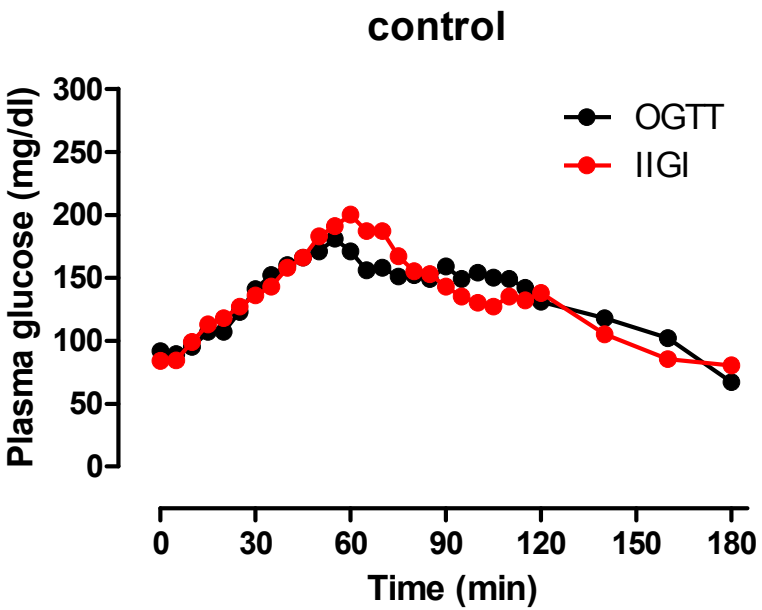
The enteroinsular axis in the pathogenesis of prediabetes and diabetes in humans

Status	Incretin effect	Incretins	Secretion	Insulinotropic effect
High risk of T2DM (IGT, pGDM, and 1st-degree relatives)	Normal	GLP-1	Normal or decreased*	Maintained (?)
		GIP	Normal or decreased*	Decreased in some cases**
T2DM	Decreased†	GLP-1	Normal or decreased*	Maintained or slightly decreased†
		GIP	variable	Markedly decreased††

*, in some subjects with marked insulin resistance or severe hyperglycemia
**, in some 1st-degree relatives of patients with T2DM
†,correlated with decreased beta-cell functional capacity or mass; ; decreased response to physiological level of GLP-1
††, marked decrease in GIPR expression was observed in animals.

In Koreans?


Type 2 diabetes
Plasma glucose (mg/dl)
300
250
200
150
100
50
0
0
30
60
90
120
150
180
Time (min)


control
Plasma glucose (mg/dl)
300
250
200
150
100
50
0
OGTT
IIGI
0
30
60
90
120
150
180
Time (min)

Acknowledgements

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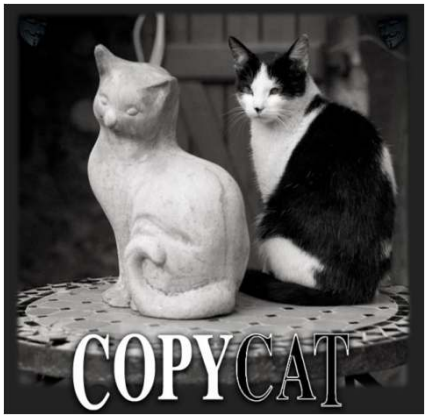
Dr. Tae Jung Oh

Ms. Min Young Kim

Ms. Ji Yeon Shin

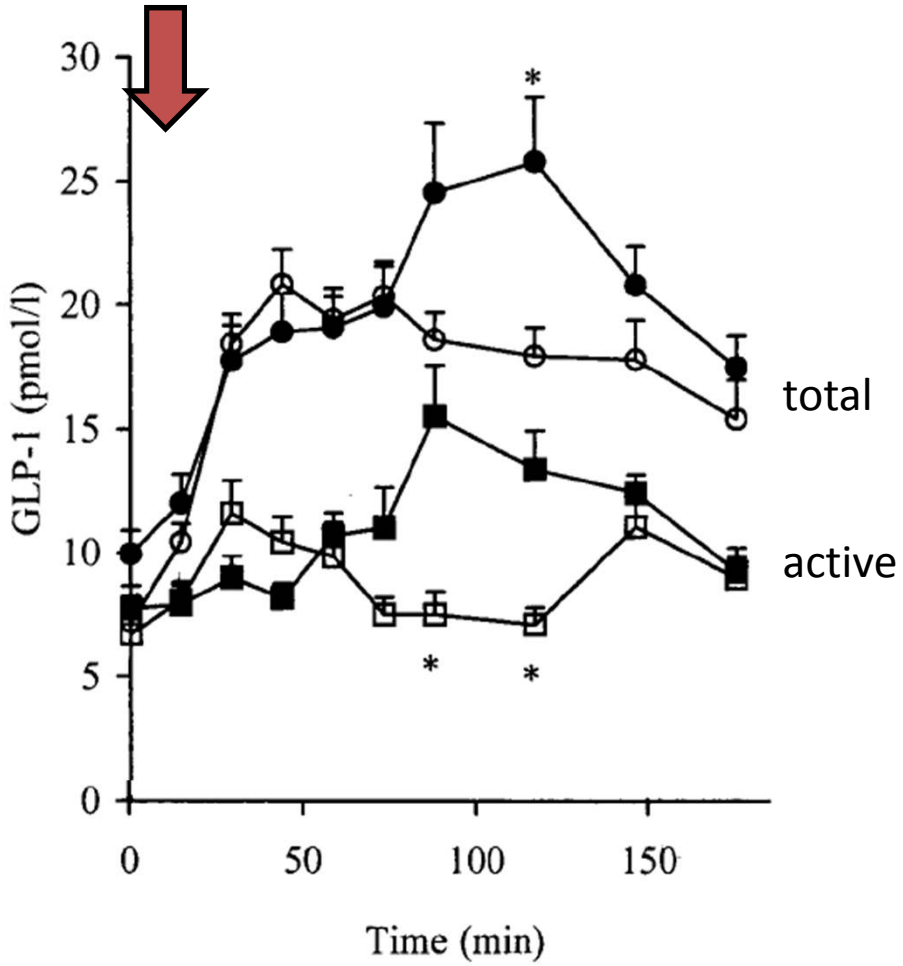
The Copycat Project

Dr. Tae Jung Oh Ms. Min Young Kim



Reduced GLP-1 secretion in the late postprandial period

Mixed breakfast meal (566 kcal)



No difference in AUCs

P for AUC total = 0.2, P for AUC active = 0.07

Vilsbøll T et al. Diabetes 50:609–613, 2001

Plasma glucose levels

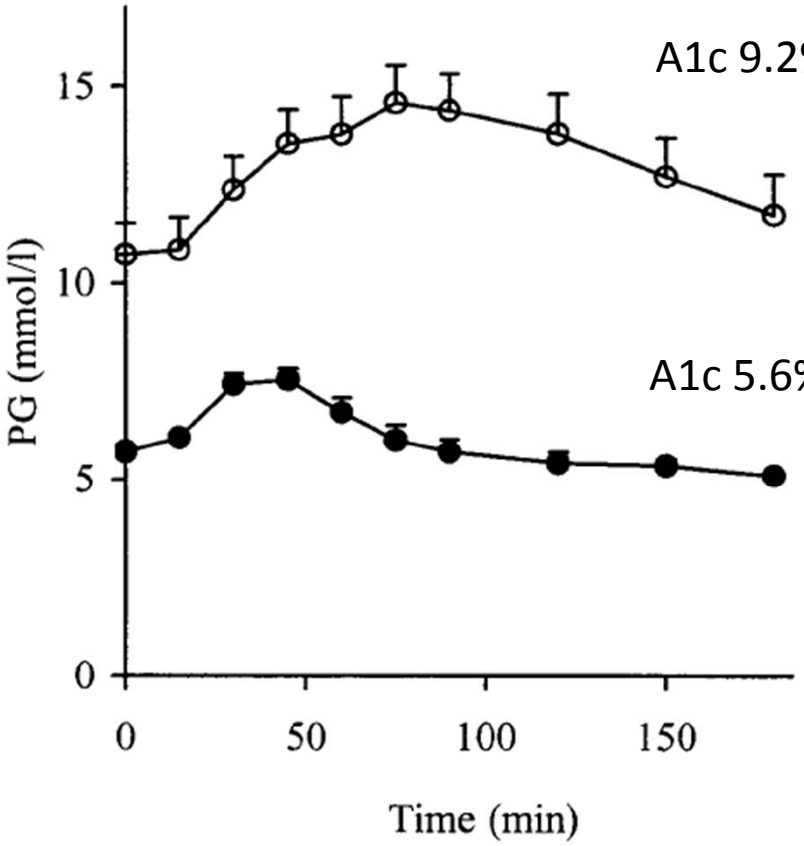
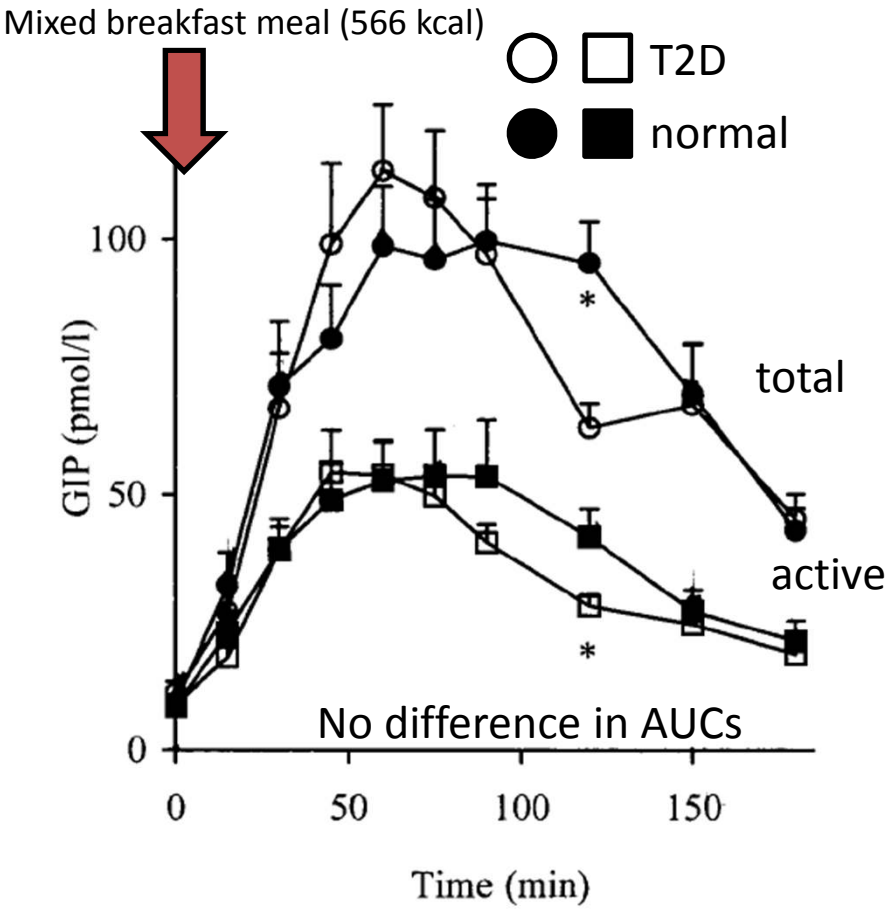


FIG. 1. Plasma glucose concentrations during the 180-min period after meal ingestion for type 2 diabetic patients (○) and healthy subjects (●). Data are means ± SE.

Vilsbøll T et al. Diabetes 50:609–613, 2001

GIP levels and K-cells in type 2 diabetes and obesity

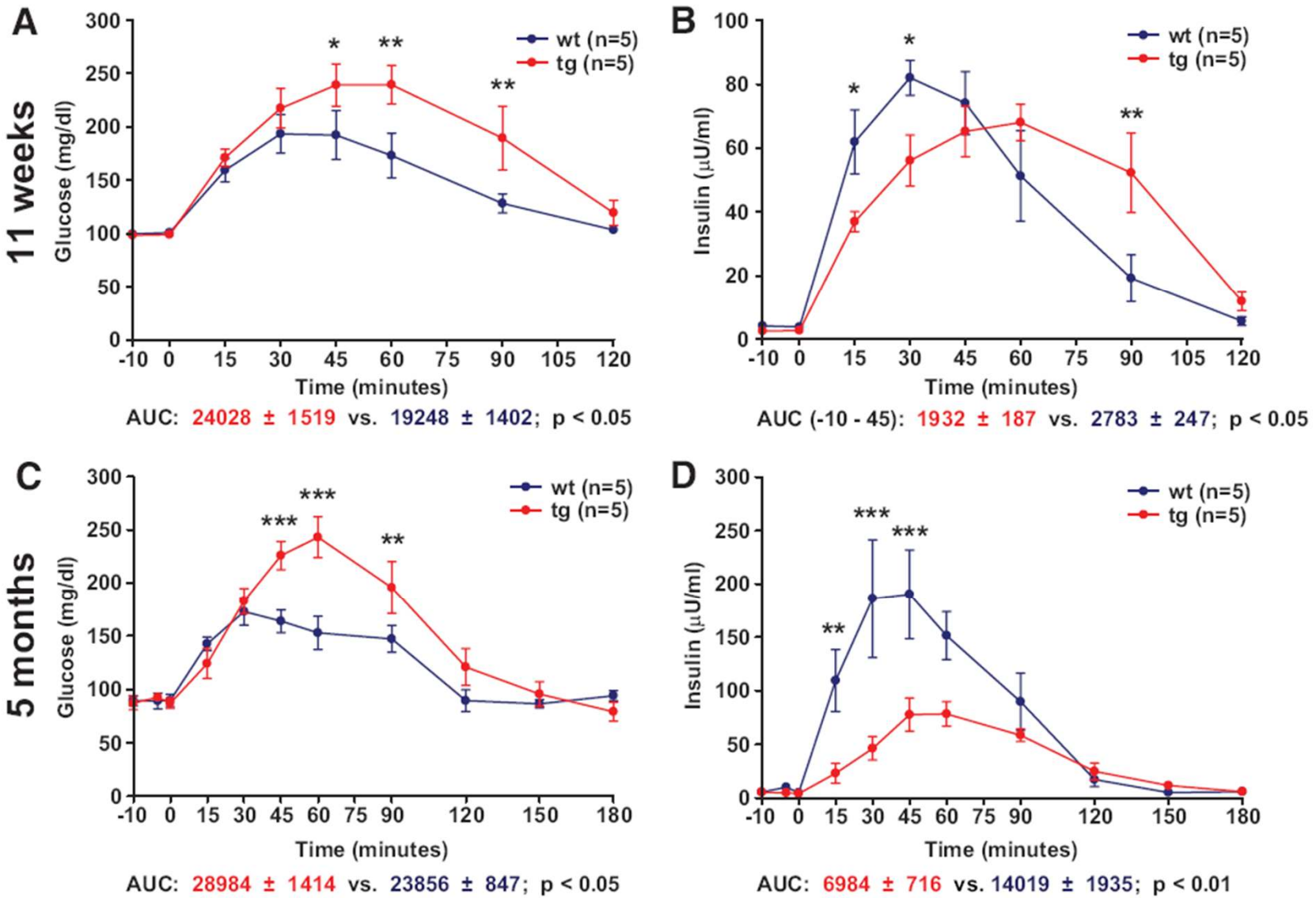
- Elevated or normal or decreased
- ↑ K-cell density in ob/ob mice vs. lean controls.
- Chronic high fat diet increases the density of K-cells in the upper jejunum.



Reviewed in Cho and Kieffer: Vitamins & Hormones 2010

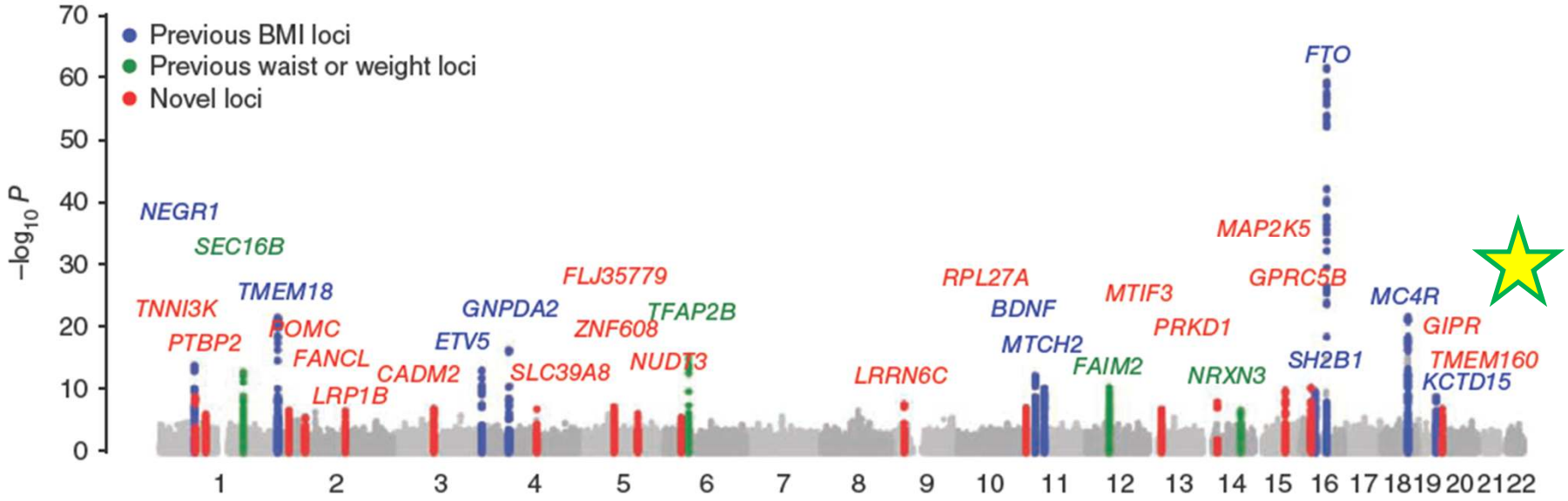
Vilsbøll T et al. Diabetes 50:609–613, 2001

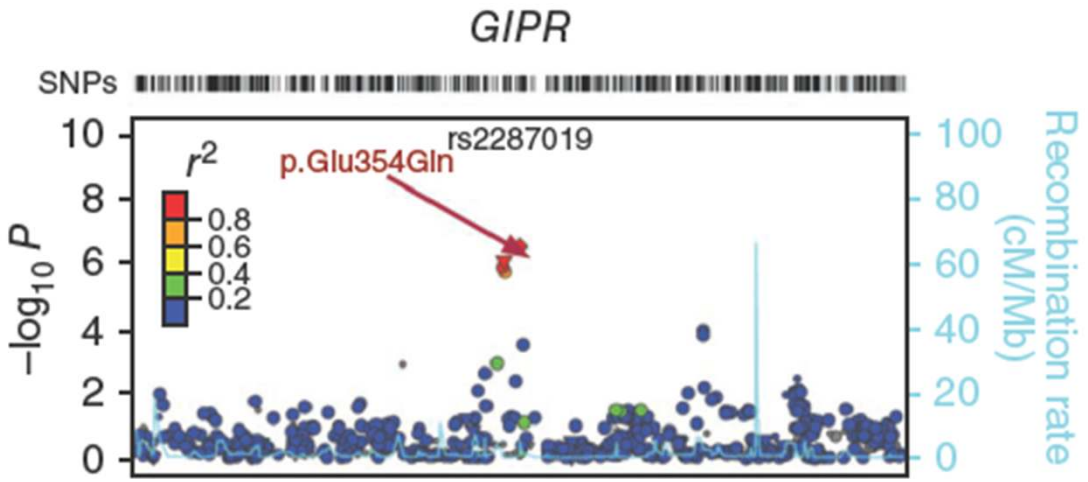
Progressive deterioration of glucose metabolism in GIPR^{dn} transgenic pigs

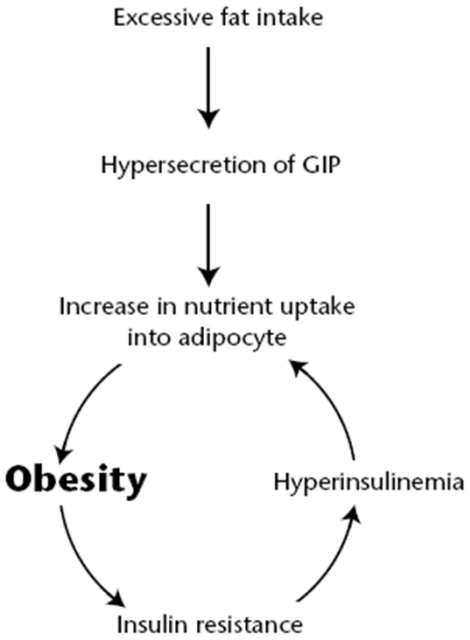


Diabetes. 2010 May;59(5):1228-38.

GIPR polymorphism and obesity

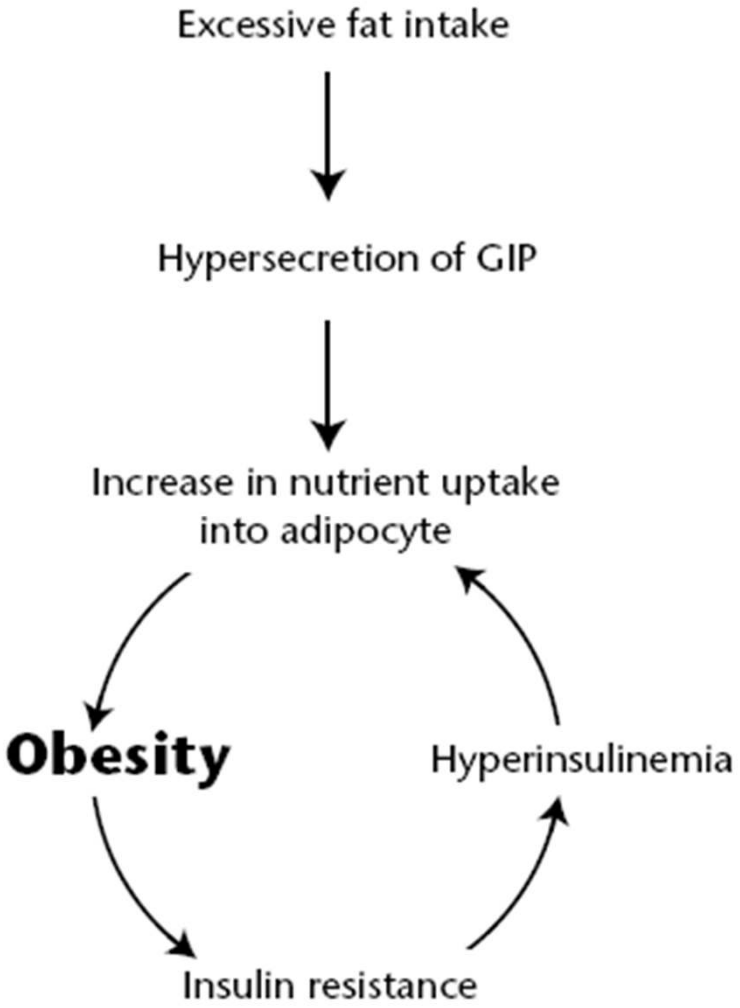






Nat Genet 2010;42:937, Nat Genet 2002;8:738

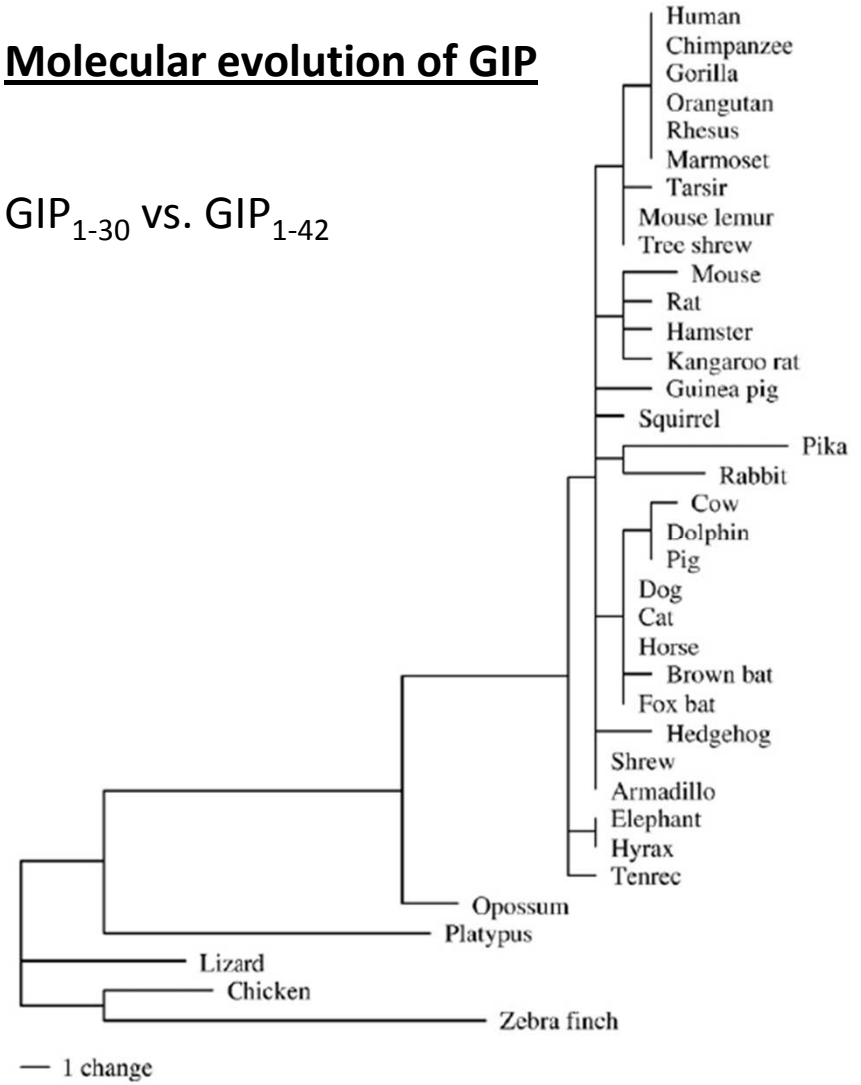
GIP/GIPR: the ultimate thrifty gene!



Nat Genet 2002;8:738

Molecular evolution of GIP

GIP_{1-30} vs. GIP_{1-42}



Regulatory Peptides 2009;155:121

A Korean pGDM study

Table 1. Characteristics of the women with previous gestational diabetes mellitus (pGDM) and of control subjects

Parameter	pGDM	Control	*P* value
No.	34	11	
Age, yr	34.2±3.3	25.7±2.1	0.068
Weight, kg	55.2±6.5	55.8±4.6	0.180
Height, cm	157.3±5.2	159.2±4.9	0.625
BMI, kg/m^2	22.5±2.6	22.0±0.9	0.461
SBP, mm Hg	110.6±11.9	107.7±13.5	0.467
DBP, mm Hg	71.4±7.6	67.3±7.5	0.952
HbA1c, %	5.3±0.2	5.0±0.3	0.020
Total cholesterol, mg/dL	171.5±27.2	186.9±24.4	0.490
Triglyceride, mg/dL	113.3±74.1	75.2±35.4	0.289
HDL-C, mg/dL	46.8±8.9	72.4±10.4	0.289
LDL-C, mg/dL	102.0±26.6	99.5±18.4	0.330
No. of pregnancies	0.47±0.66	0	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Yu SH et al. Diabetes Metab J 2011;35:58-64

A Korean pGDM study

GLP-1 secretion does not differ between pGDM patients and normal women.
GIP was elevated, but that does not seem to induce in increase in insulin secretion.

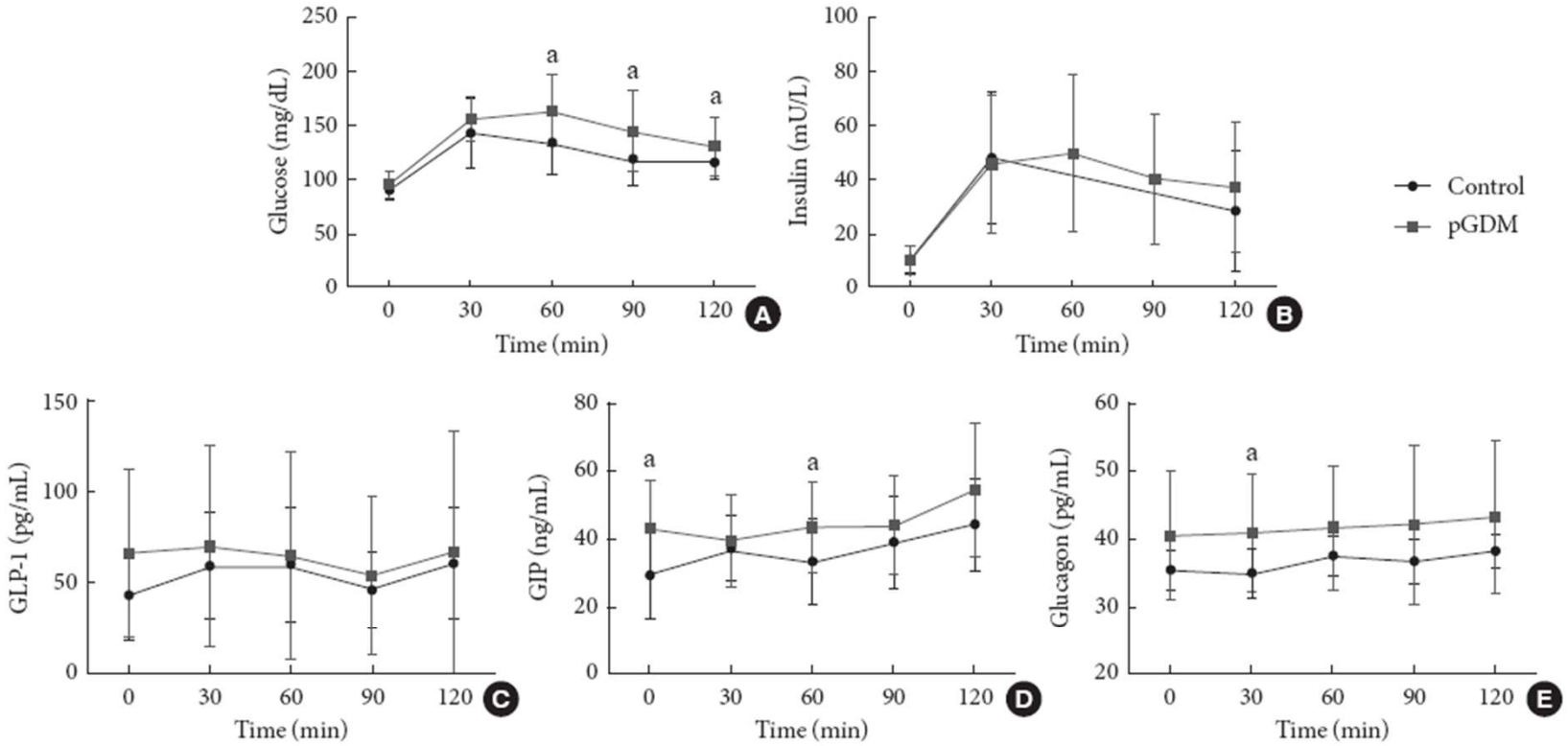


Fig. 1. Plasma concentrations of glucose (A), insulin (B), glucagon like pepide1 (GLP-1) (C), glucose-dependent insulinotropic polypeptide (GIP) (D), and glucagon (E) after the ingestion of 75-g oral glucose in 34 women with a history of previous gestational diabetes mellitus (pGDM) (*square symbols*) and 11 control women (*round symbols*). Data are presented as means±standard deviation; *P* values were calculated using repeated measures ANOVA. [a]Significant differences at individual time points ($P<0.05$ by one-way ANOVA).

Yu SH et al. Diabetes Metab J 2011;35:58-64

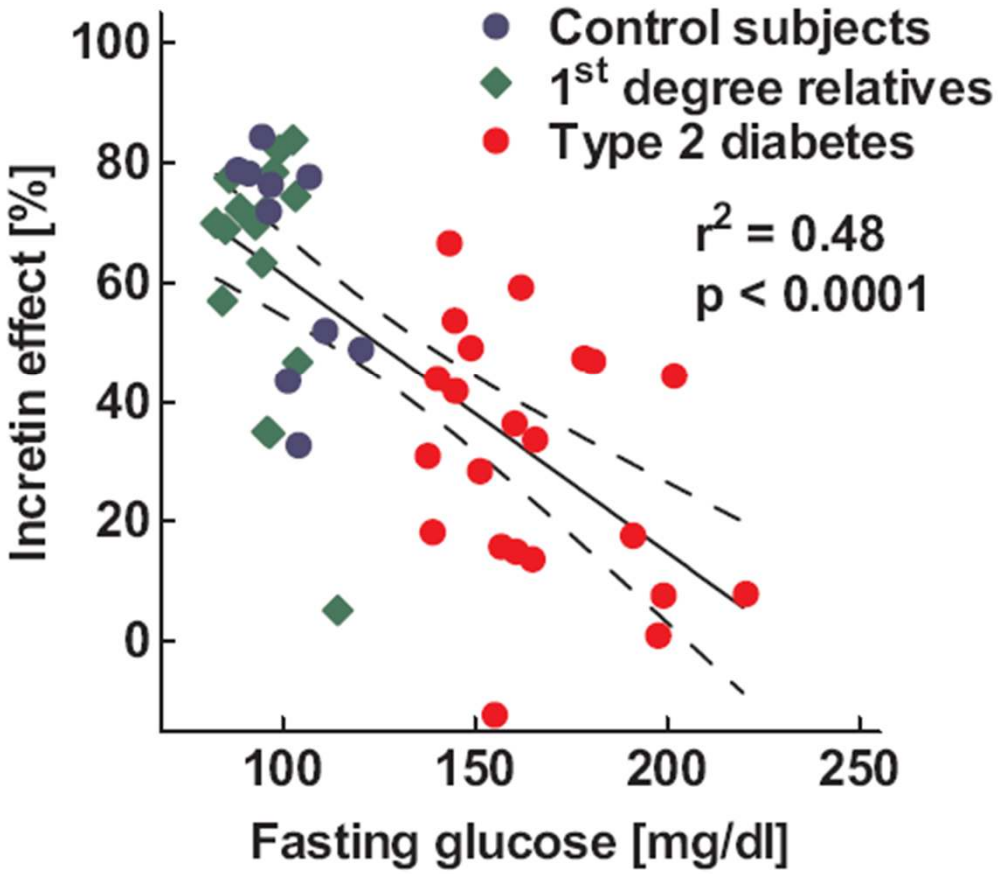


FIG. 3. Relationship between the relative percentage contribution of the incretin effect on the overall insulin responses after oral glucose ingestion and to the respective fasting glucose concentrations in 48 individuals with and without diabetes. Individual data were taken from refs. 35 and 7. The solid line denotes the regression line calculated by regression analyses in relation to the upper and lower 95% CIs.

Meier JJ and Nauck MA, Diabetes Care 2010; 59: 1117-1125

Four weeks of near-normalization of blood glucose improves the insulin response to GLP-1 and GIP in patients with type 2 diabetes

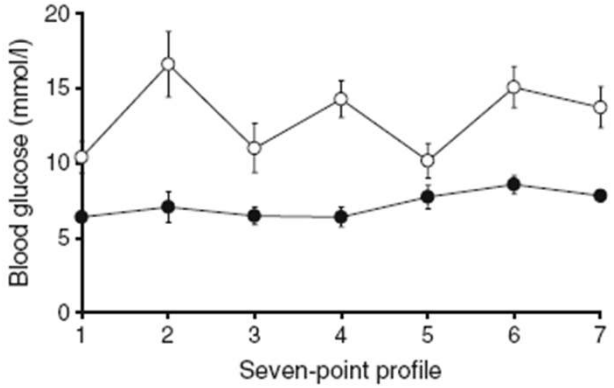
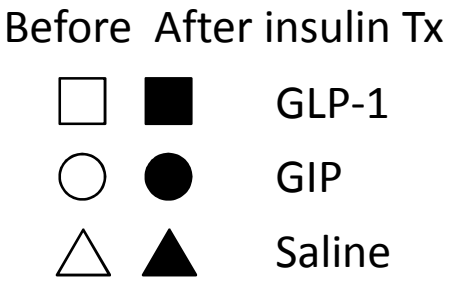
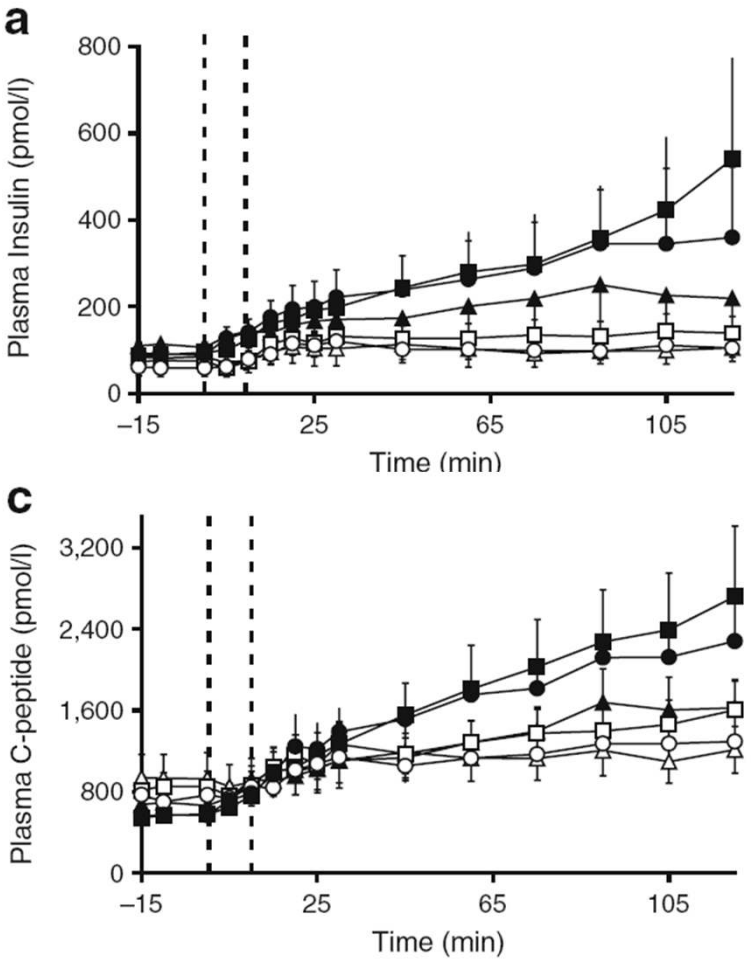


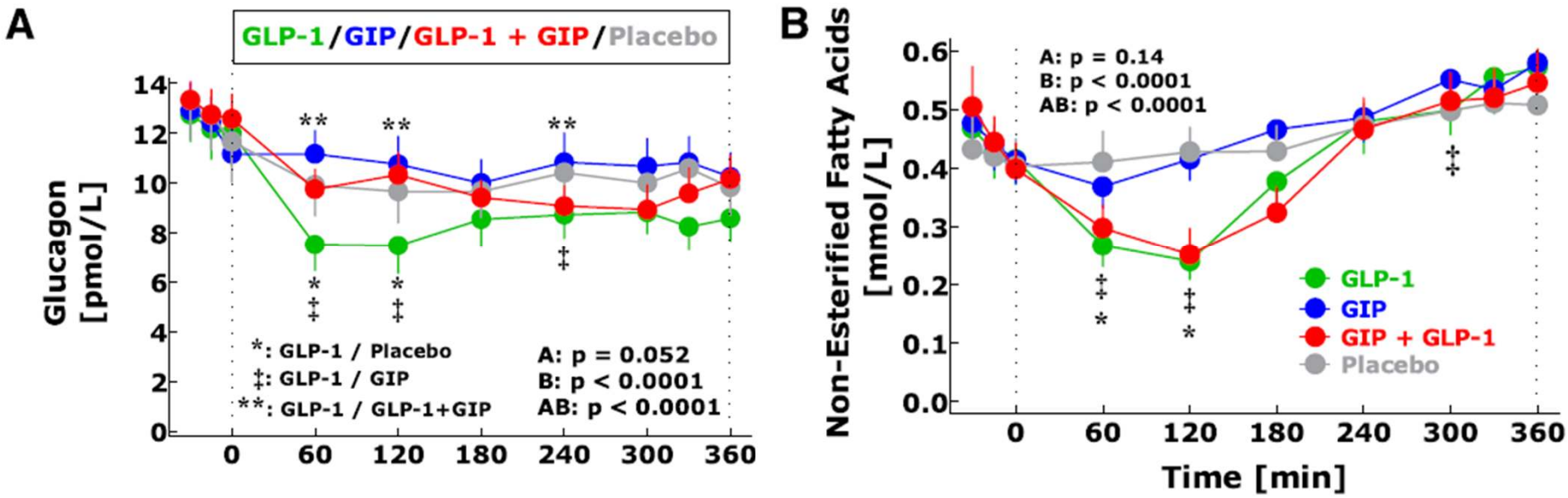
Fig. 1 Mean blood glucose before (white circles) and during (black circles) 4 weeks of insulin treatment. The patients measured blood glucose seven times per day three times per week. Data are mean± SEM





Diabetologia (2009) 52:199–207

Effects on glucagon and NEFA

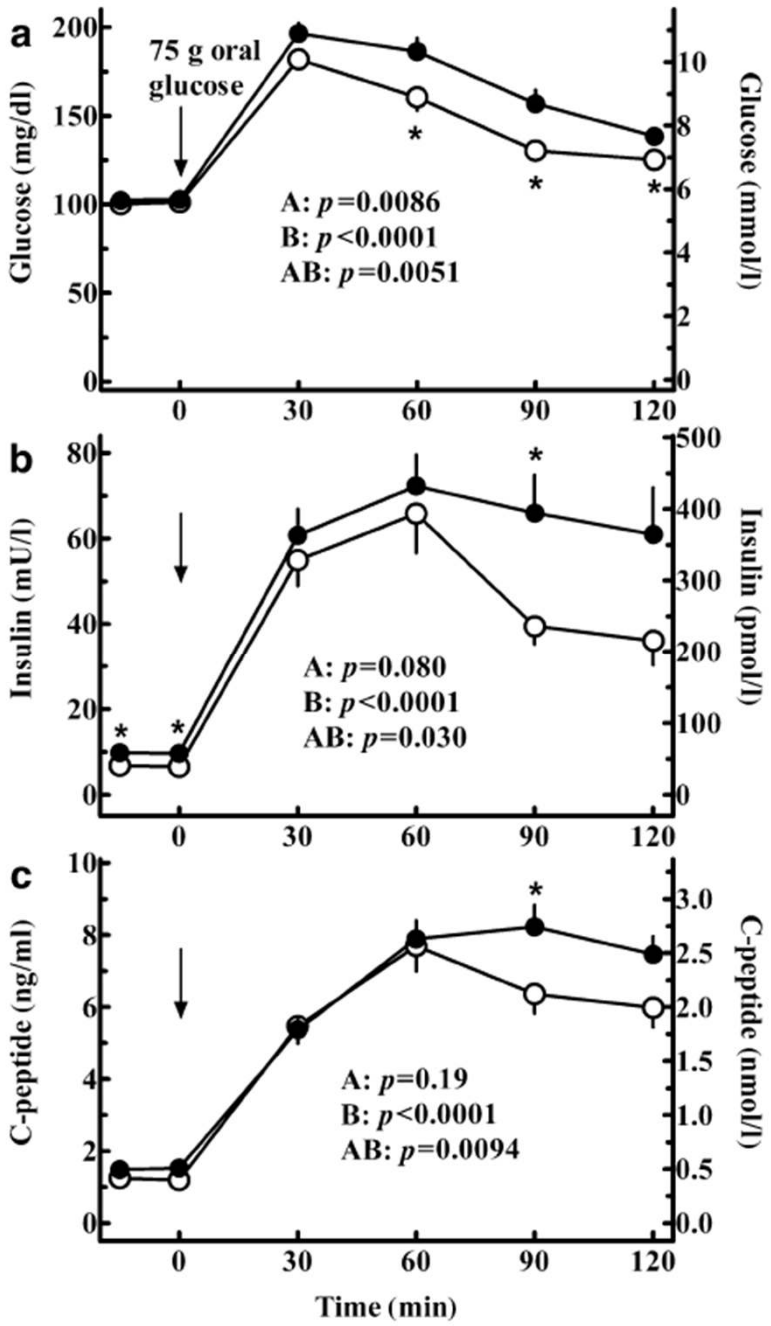


Mentis N et al. Diabetes 60:1270–1276, 2011

Determinants of incretin sensitivity

Factors	Effects on receptor expression in β-cells	Mechanism
TCF7L2 variant*	↓GIPR, ↓GLP-1R	
WFS1 variant**	↓GLP-1R	
KCNQ1	↓ Insulin secretion, ↑ GIP and GLP-1 secretion	
Hyperglycemia	↓GIPR, ↓GLP-1R	PKCα
Metformin	↑GLP-1R	PPARα
Fatty acids†	↑GIPR	PPARα

*, rs7903146; **, rs10010131; †, under euglycemic conditions



Closed circles, pGDM; open circles, controls

Meier J.J. et al. Diabetologia (2005) 48: 1872–1881

Insulin sensitivity and beta-cell function

Index	Women with pGDM	Control women	*p* value (ANOVA)	Reference
Insulin sensitivity/resistance				
HOMA	2.47±0.29	1.67±0.18	0.029	[19]
Matsuda index	3.64±0.29	5.62±0.61	0.0070	[20]
Insulin secretion				
HOMA beta cell function	92.1±12.6	66.1±7.3	0.09	[19]
Insulinogenic index$_{OGTT\ (30')}$	60.1±6.7	65.6±7.5	0.64	[22]
Insulinogenic index$_{clamp\ (15')}$	23.3±4.5	17.6±4.5	0.40	–

GLP-1 secretion and blood glucose

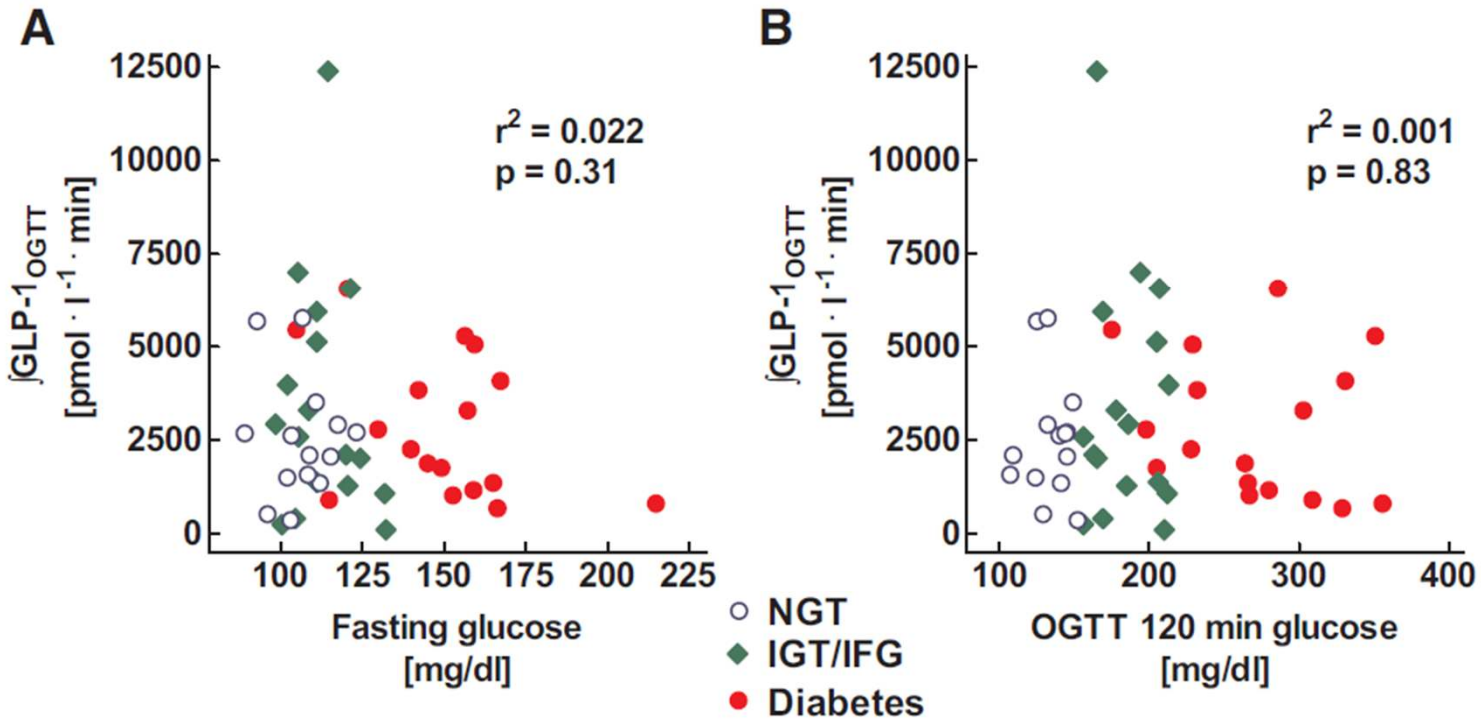


FIG. 1. Relationship between the glucose concentrations at fasting (*A*) and 120 min after the ingestion of 75 g oral glucose (*B*) and the respective integrated GLP-1 levels measured over 240 min after oral glucose ingestion in 14 nondiabetic individuals (blue), 17 people with impaired glucose tolerance or impaired fasting glucose (green), and 17 patients with type 2 diabetes (red). Individual data were taken from ref. 11. r^2 and *P* values were calculated by linear regression analyses. NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

Meier JJ and Nauck MA, Diabetes Care 2010; 59: 1117-1125

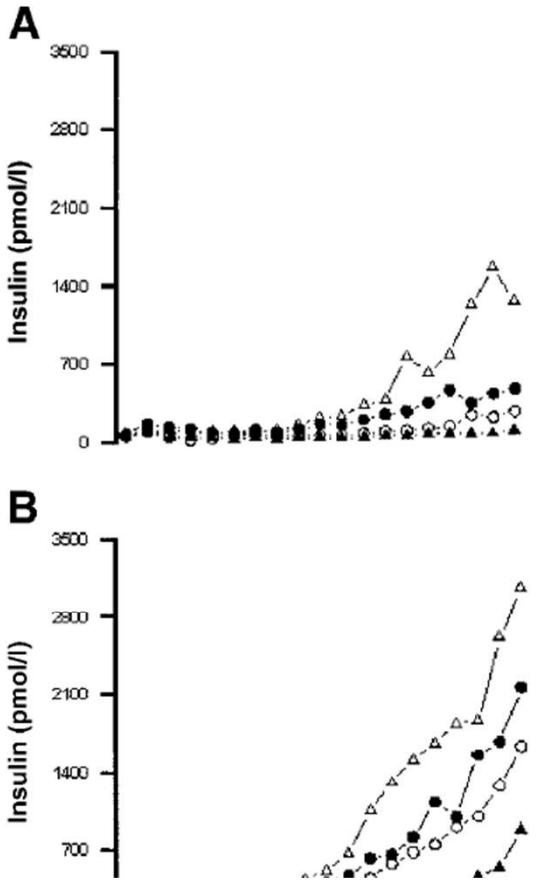


FIG. 3. Plasma insulin concentrations during the graded glucose infusion. From −30 min, saline (▲) or intravenous GLP-1 (7-36 amide) at a dose of 0.5 (○), 1.0 (●) or 2.0 (△) pmol · kg^{-1} · min^{-1} were infused. At t = 0 min, glucose was infused at a rate of 2 mg · kg^{-1} · min^{-1}, followed by 4, 6, 8, and 12 mg · kg^{-1} · min^{-1}. Each infusion rate was maintained for a period of 30 min. Samples were drawn 10, 20, and 30 min into a 30-min period for the measurement of plasma insulin. The type 2 diabetic subjects are depicted in *A*, and the control subjects are depicted in *B*.

Kjems, LL et al Diabetes 52:380–386, 2003

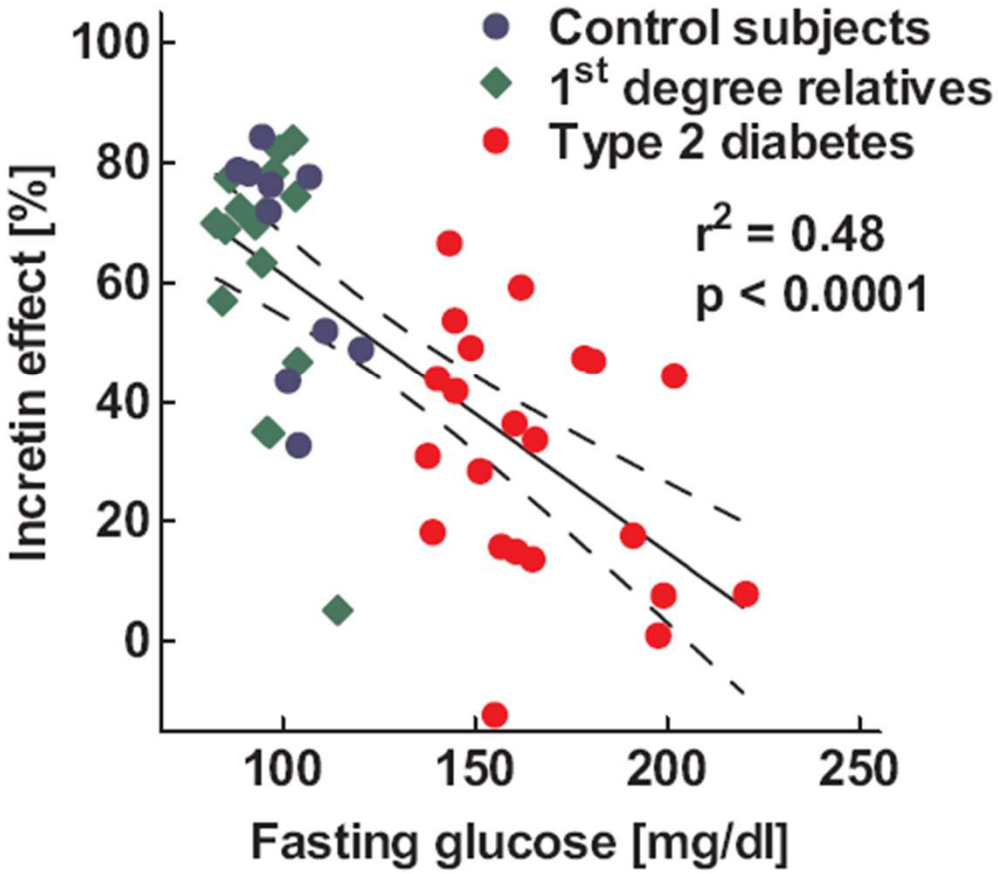
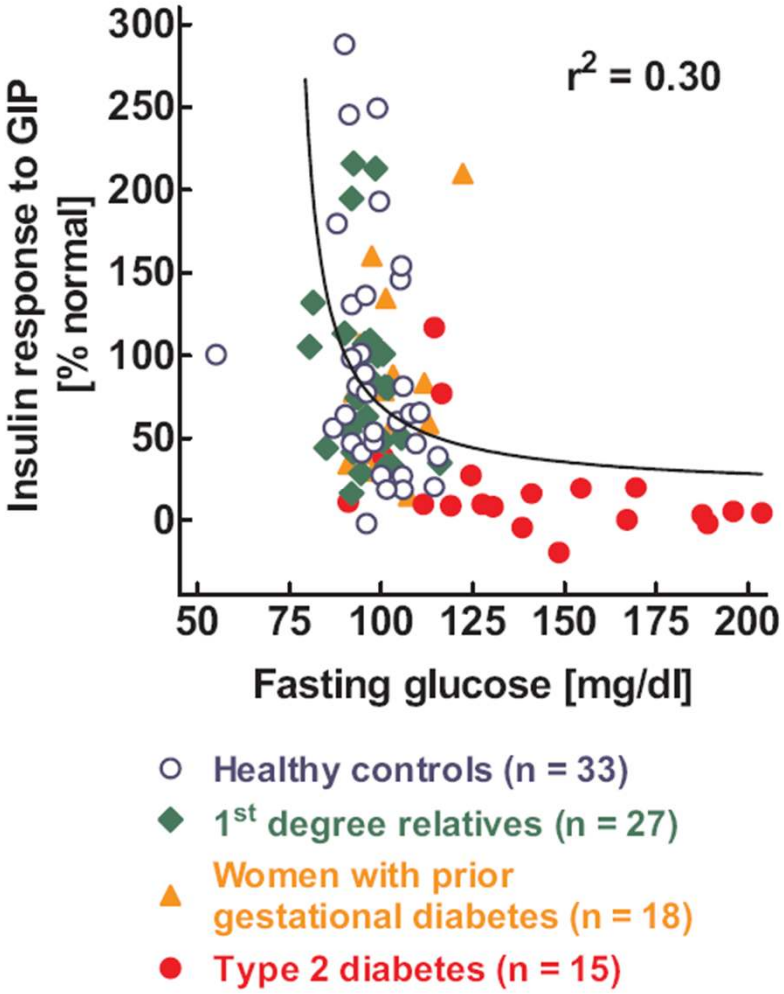


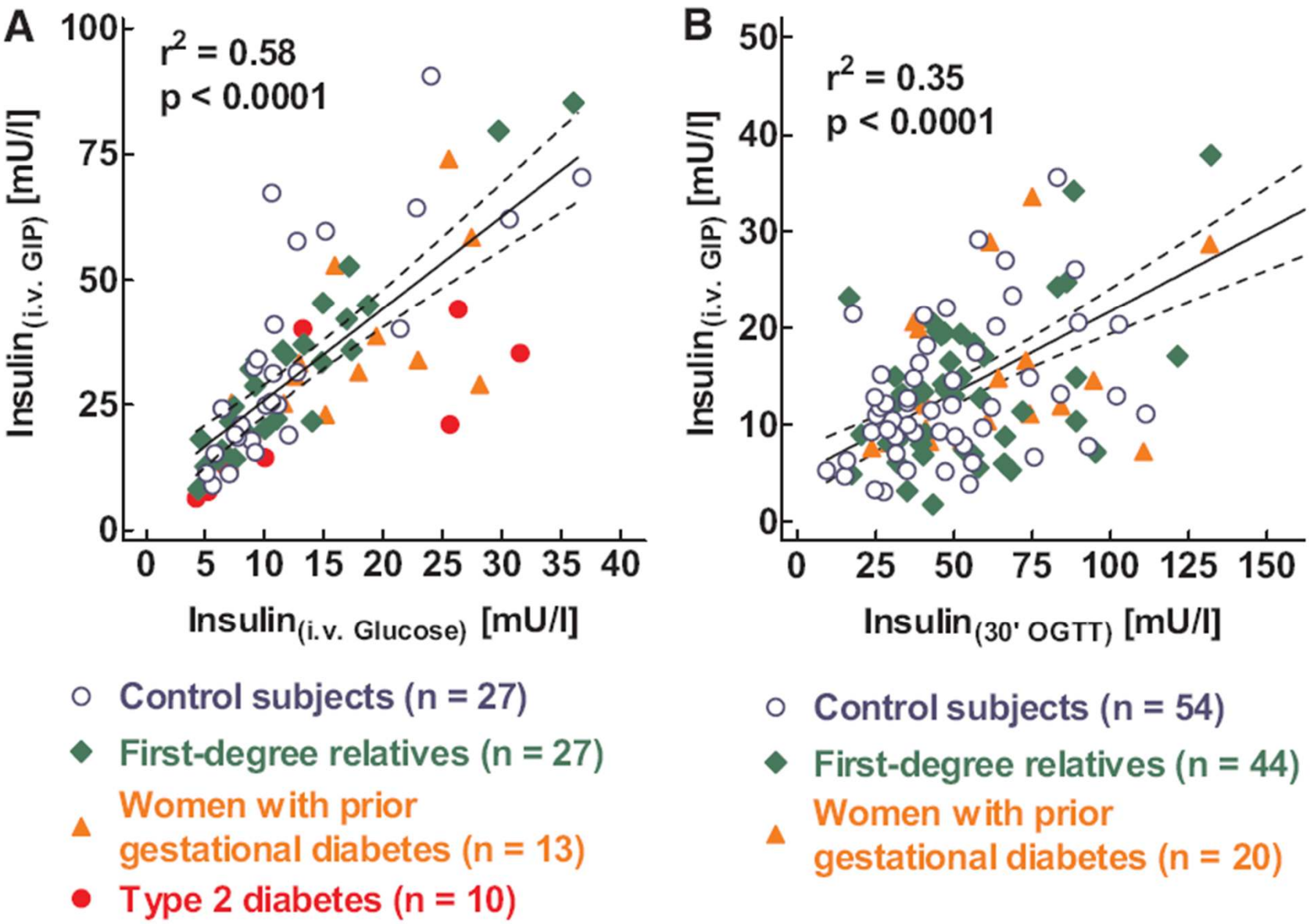
FIG. 3. Relationship between the relative percentage contribution of the incretin effect on the overall insulin responses after oral glucose ingestion and to the respective fasting glucose concentrations in 48 individuals with and without diabetes. Individual data were taken from refs. 35 and 7. The solid line denotes the regression line calculated by regression analyses in relation to the upper and lower 95% CIs.

Meier JJ and Nauck MA, Diabetes Care 2010; 59: 1117-1125

Effect of chronic hyperglycemia

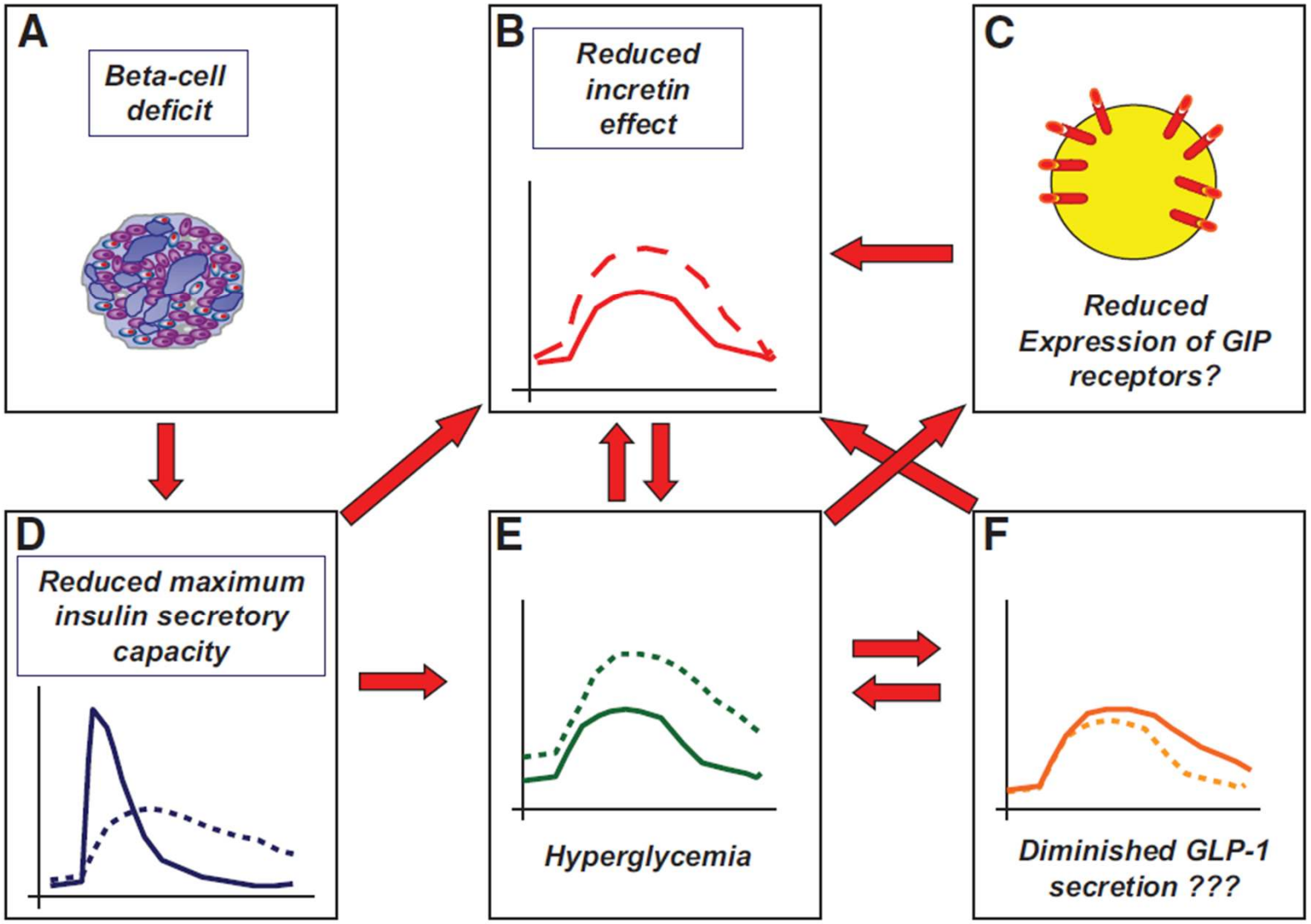


Meier JJ and Nauck MA, Diabetes Care 2010; 59: 1117-1125



Meier JJ and Nauck MA, Diabetes Care 2010; 59: 1117-1125

Proposed mechanisms of the diminished incretin effect in type 2 diabetes



Meier JJ and Nauck MA, Diabetes Care 2010; 59: 1117-1125

Reduced insulinotropic effect of GIP in first degree relatives of patients with T2DM

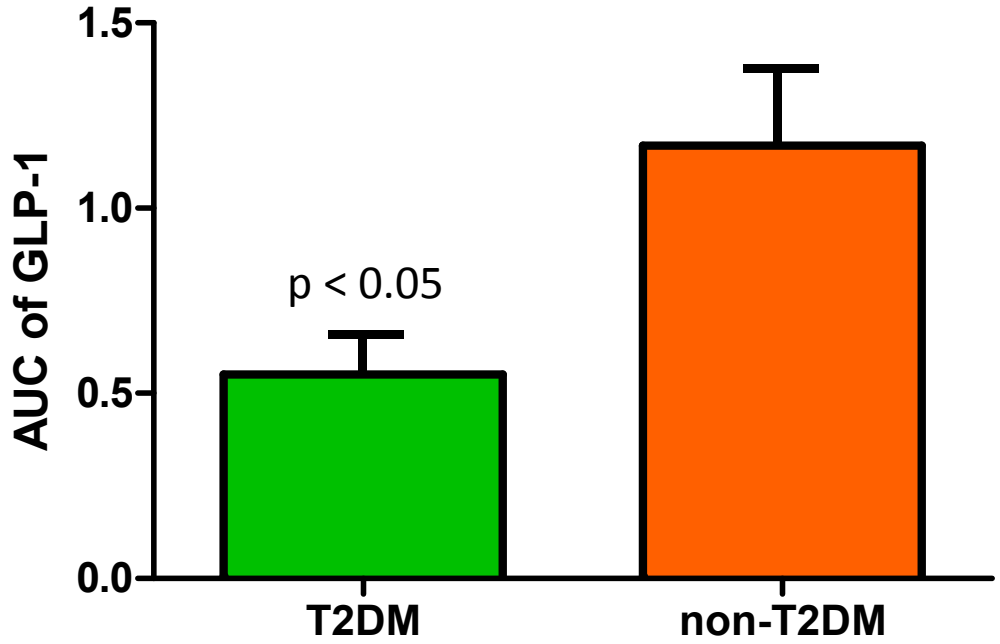
Characteristics of the participants in hyperglycemic clamp experiments with GIP infusion

Parameter	Healthy control subjects	First-degree relatives of type 2 diabetic patients	Type 2 diabetic patients	Significance (P value)*
Sex (female/male)	4/6	15/6	3/7	0.059
Age (years)	49 ± 17	49 ± 12	52 ± 9	0.83
BMI (kg/m^2)	25.7 ± 3.6	26.0 ± 4.2	28.6 ± 5.1	0.23
Waist-to-hip ratio (cm/cm)	0.89 ± 0.1	0.84 ± 0.1§	0.93 ± 0.07	0.028
Participants with first-degree relatives (type 2 diabetes)	0/10§	21/21§	4/10‡	<0.0001
Father	—	8	2	
Mother	—	15	2	
Siblings	—	3	3	
HbA_{1c} (%)†	5.0 ± 0.5§	5.1 ± 0.3§	6.2 ± 0.7‡	<0.0001
Oral glucose tolerance				
Fasting plasma glucose (mg/dl)	94 ± 7§	88 ± 8§	117 ± 15‡	<0.0001
120-min plasma glucose (mg/dl)	101 ± 16	112 ± 15	NE	0.81
Blood pressure				
Systolic (mmHg)	128 ± 9	130 ± 18	131 ± 14	0.93
Diastolic (mmHg)	81 ± 4	80 ± 9	77 ± 5	0.36
Triglycerides (mg/dl)	113 ± 65	117 ± 75	189 ± 107	0.06
HDL cholesterol (mg/dl)	60 ± 26	71 ± 24§	43 ± 19	0.013
LDL cholesterol (mg/dl)	140 ± 30	120 ± 35	146 ± 25	0.70
Creatinine (mg/dl)	1.1 ± 0.1§	1.0 ± 0.1§	1.0 ± 0.1‡	0.017

Data are n and means ± SE. NE, not examined. *ANOVA or χ^2 tests; †normal range, 4.0–6.2%; ‡significant difference ($P < 0.05$) versus healthy control subjects (Duncan's post hoc test); §significant difference ($P < 0.05$) versus patients with type 2 diabetes (Duncan's post hoc test).

Meier JJ et al. Diabetes 50:2497–2504, 2001

GLP-1 in identical twins discordant for T2DM



Eur J Endocrinol. 1996 Oct;135(4):425-32.