Signe H. Østoft,[1,2,3] Jonatan I. Bagger,[1,2,3] Torben Hansen,[3,4] Oluf Pedersen,[3] Jens J. Holst,[2,3] Filip K. Knop,[1,2,3] and Tina Vilsbøll[1]

Incretin Effect and Glucagon Responses to Oral and Intravenous Glucose in Patients With Maturity-Onset Diabetes of the Young—Type 2 and Type 3

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PATHOPHYSIOLOGY

Maturity-onset diabetes of the young (MODY) is a clinically and genetically heterogeneous subgroup of nonautoimmune diabetes, constituting 1–2% of all diabetes. Because little is known about incretin function in patients with MODY, we studied the incretin effect and hormone responses to oral and intravenous glucose loads in patients with glucokinase (GCK)-diabetes (MODY2) and hepatocyte nuclear factor 1α (HNF1A)-diabetes (MODY3), respectively, and in matched healthy control subjects. Both MODY groups exhibited glucose intolerance after oral glucose (most pronounced in patients with HNF1A-diabetes), but only patients with HNF1A-diabetes had impaired incretin effect and inappropriate glucagon responses to OGTT. Both groups of patients with diabetes showed normal suppression of glucagon in response to intravenous glucose. Thus, HNF1A-diabetes, similar to type 2 diabetes, is characterized by an impaired incretin effect and inappropriate glucagon responses, whereas incretin effect and glucagon response to oral glucose remain unaffected in GCK-diabetes, reflecting important pathogenetic differences between the two MODY forms.

Maturity-onset diabetes of the young (MODY) represents monogenic forms of nonautoimmune diabetes characterized by autosomal dominant inheritance, non–insulin-dependent diabetes at onset, and diagnosis often before 25 years of age (1). MODY is a clinically and genetically heterogeneous form of diabetes, with mutations in at least eight different genes, leading to specific forms of MODY (2,3). The two most common forms result from mutations in the genes encoding glucokinase (GCK) (GCK-diabetes: MODY2; 10–20% of all MODY patients [4,5]) and hepatocyte nuclear factor 1α (HNF1A) (HNF1A-diabetes: MODY3; 36–60% of all MODY patients [4,5]). More than 50% of carriers of HNF1A mutations develop diabetes before the age of 25 years, with a lifetime risk >95%. Typically, the disease shows a rapid progression from impaired glucose tolerance to overt diabetes owing to continued deterioration of β-cell function (6). Less than half of the carriers of GCK mutations are diagnosed with diabetes. The mutation results in a "glucose sensing" defect with an increased plasma glucose (PG) threshold (by 1–2 mmol/L) for secretion of insulin, resulting in higher PG levels in GCK-diabetes patients compared with healthy individuals (7).

The incretin effect describes the amplification of insulin response after oral glucose compared with glucose administered intravenously (8) and is a major contributor to normal glucose tolerance. Normal regulation of glucagon secretion is also essential, but little is known about incretin and glucagon physiology in patients with MODY.

[1]Diabetes Research Division, Department of Medicine, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark
[2]Department of Biomedical Sciences, Panum Institute, University of Copenhagen, Copenhagen, Denmark
[3]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark
[4]Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
Corresponding author: Signe H. Østoft, s.ostoft@dadlnet.dk.

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Here, we report incretin effect and glucagon and incretin hormone responses in patients with HNF1A-diabetes and GCK-diabetes, respectively, and in a group of healthy control individuals (CTRLs).

RESEARCH DESIGN AND METHODS

Subjects

Anthropometric data are listed in Table 1. Ten patients with HNF1A-diabetes and 9 patients with GCK-diabetes were included. Specific mutations are provided in Supplementary Data. Three GCK-diabetes patients were related: two siblings and their mother. Six patients with HNF1A-diabetes were treated with oral blood glucose–lowering drugs. The remaining MODY patients (n = 13) were treated with diet only. No patients had complications of diabetes. CTRLs (n = 9) were without family history of diabetes and had normal glucose tolerance. No patients used drugs suspected to influence glucose tolerance or hormone responses, apart from blood glucose–lowering drugs. Participation was agreed to after oral and written information was provided.

Design

The protocol was approved by the Scientific-Ethical Committee of the County of Copenhagen, Denmark (registration no. 1H-2010-130). The trial was conducted according to the principles of the Helsinki Declaration II.

Participants were studied on two separate experimental days: *1*) a 4-h 50-g oral glucose tolerance test (OGTT) and *2*) a 4-h isoglycemic intravenous glucose infusion (IIGI). The two days were separated by at least 48 h, and each day was preceded by 1-week washout of blood glucose–lowering drugs and an overnight 10-h fast. Acetaminophen (1.5 g) (Panodil; GlaxoSmithKline A/S, Copenhagen, Denmark) was added the OGTT to estimate gastric emptying. The IIGI was performed with sterile 20% w/v glucose infusion adjusted to duplicate the PG profile of the OGTT.

Blood Samples

Blood samples were drawn at predefined time points before, during, and after glucose administration. Blood was distributed into relevant tubes for centrifugation and storage.

Analytical Procedures

PG concentrations were measured by the glucose oxidase method (YSI Model 2300 STAT Plus analyzer; YSI, Inc., Yellow Springs, OH). Serum insulin and C-peptide concentrations were measured using two-sided electrochemiluminescence immunoassay (Siemens Healthcare, Ballerup, Denmark). Plasma concentrations of glucagon, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) were measured by radioimmunoassay. Plasma acetaminophen was measured by the VITROS ACET slide method (Johnson & Johnson, Birkerød, Denmark).

Statistical Analysis and Calculations

Baseline, peak, area under the curve (AUC), and incretin effect values are expressed as mean ± SEM. Differences resulting in P values <0.05 were considered significant. Linear mixed-effect modeling was used for analysis of longitudinal and repeated measures using statistical software R (R Foundation for Statistical Computing, Wirtschaftsuniversität, Vienna, Austria). Data were transformed according to distribution patterns, including family identity as a random variable (9). The experimental days were compared using a paired two-sample t test (two-tailed). Insulin secretion rate (ISR) values were calculated by deconvolution of measured C-peptide concentrations and application of population-based variables for C-peptide kinetics. Insulinogenic index was used to assess β-cell secretory function and was calculated based on plasma insulin (PI) as $(PI_{30\ min} - PI_{baseline})/(PG_{30\ min} - PG_{baseline})$. Incretin effect values were calculated by relating the difference in integrated β-cell secretory responses between stimulation with OGTT and IIGI to the response after OGTT: 100% [incretin effect (%) = $100\% \times (AUC_{OGTT} - AUC_{IIGI}) / AUC_{OGTT}$].

RESULTS

Glucose

Time courses for PG are illustrated in Fig. 1; baseline, peak, and AUC values are given in Table 1. Fasting PG was higher in patients with GCK-diabetes and HNF1A-diabetes compared with CTRLs. AUC for PG during OGTT was higher in both patients with GCK-diabetes and with HNF1A-diabetes compared with CTRLs. Isoglycemia was obtained in all groups (P = 0.991 [CTRL], P = 0.931 [GCK-diabetes], and P = 0.885 [HNF1A-diabetes]) (Fig. 1). The amount of glucose needed to obtain isoglycemia during IIGI was higher in patients with HNF1A-diabetes (37 ± 4 g) compared with CTRLs (24 ± 2 g; P = 0.017) but not compared with patients with GCK-diabetes (30 ± 3 g; P = 0.316). No difference between GCK patients and CTRLs was seen (P = 0.607).

Insulin, C-Peptide, ISR, and Incretin Effect

Time courses for insulin, C-peptide, and ISR are illustrated in Fig. 1, and baseline, peak, and AUC values are given in Table 1. Similar fasting values of insulin and C-peptide, respectively, were observed on the two experimental days in each group. Patients with HNF1A-diabetes exhibited lower insulin and C-peptide responses and peak values during both OGTT and IIGI compared with CTRLs and patients with GCK-diabetes. No differences were seen between patients with GCK-diabetes and CTRLs. No differences in fasting ISR between the groups were found. Patients with HNF1A-diabetes had lower peak ISR compared with GCK-diabetes and CTRLs and exhibited lower ISR responses during OGTT compared with CTRLs and GCK-diabetes patients, while the difference was only significant between patients with HNF1A-diabetes and GCK-diabetes during IIGI. In all groups, ISR responses were higher during OGTT compared with IIGI. The incretin effect, calculated from insulin release, was similar in CTRLs and patients with GCK-diabetes (CTRL 48 ± 5%, GCK-diabetes 44 ± 3%; P = 0.587), whereas patients with HNF1A-diabetes exhibited a lower incretin effect (HNF1A-diabetes 19 ± 8%) compared with the other groups (vs. CTRL, P = 0.008; vs. GCK-diabetes, P = 0.011).

Table 1—Anthropometric data and responses of glucose, insulin, and C-peptide

	CTRL (n = 9)	GCK-diabetes (n = 9)	HNF1A-diabetes (n = 10)	P_{ANOVA}
N (females)	9 (5)	9 (7)	10 (5)	0.432†
Age (years)	41 ± 5	43 ± 5	31 ± 3	0.119
BMI (kg/m^2)	24 ± 1	24 ± 2	24 ± 1	0.934
HbA_{1c} (%)	5.3 ± 0.1‡§	6.7 ± 0.2*	7.0 ± 0.3*	<0.001
HbA_{1c} (mmol/mol)	34 ± 1‡§	50 ± 2*	53 ± 3*	<0.001
$II_{0–30\ min}$	119 ± 17§	95 ± 24§	19 ± 5*‡	0.001
HOMA-IR	1.8 ± 0.1	3.6 ± 1.0	1.9 ± 0.2	0.066
Matsuda index	17 ± 2	11 ± 2§	21 ± 2‡	0.003
Fasting PG (mmol/L)	5.1 ± 0.2‡§	7.3 ± 0.3*§	8.4 ± 0.8*‡	<0.001
Peak PG (mmol/L)				
OGTT	8.6 ± 0.4‡§	13.4 ± 0.6*	17.0 ± 1.5*	<0.001
IIGI	8.7 ± 0.4‡§	13.9 ± 0.6*§	17.8 ± 1.7*‡	<0.001
$P_{t\ test}$	0.410	0.008	0.059	
Glucose, tAUC (min · mmol/L)				
OGTT	1,351 ± 21‡§	2,139 ± 59*§	3,042 ± 302*‡	<0.001
IIGI	1,376 ± 26‡§	2,204 ± 65*§	3,154 ± 311*‡	<0.001
$P_{t\ test}$	0.762	0.701	0.651	
Insulin, baseline (pmol/L)				
OGTT	55 ± 3§	75 ± 17§	37 ± 5*‡	0.016
IIGI	55 ± 7§	68 ± 15§	36 ± 6*‡	0.060
$P_{t\ test}$	0.983	0.149	0.928	
Insulin, peak values (pmol/L)				
OGTT	417 ± 52§	557 ± 100§	137 ± 20*‡	<0.001
IIGI	187 ± 20§	192 ± 29§	69 ± 9*‡	<0.001
$P_{t\ test}$	<0.001	0.001	0.005	
Insulin, tAUC (min · nmol/L)				
OGTT	38 ± 5§	50 ± 10§	14 ± 1*‡	<0.001
IIGI	19 ± 3§	29 ± 6§	11 ± 1*‡	0.033
$P_{t\ test}$	0.002	0.003	0.040	
C-peptide, baseline (pmol/L)				
OGTT	437 ± 31	474 ± 88	349 ± 18	0.342
IIGI	410 ± 34	458 ± 74	336 ± 24	0.339
$P_{t\ test}$	0.292	0.511	0.558	
C-peptide, peak values (pmol/L)				
OGTT	1,805 ± 148§	1,976 ± 255§	865 ± 94*‡	<0.001
IIGI	1,003 ± 91§	1,214 ± 110§	586 ± 59*‡	0.008
$P_{t\ test}$	<0.001	<0.001	0.013	
C-peptide, tAUC (min · nmol/L)				
OGTT	239 ± 21§	276 ± 36§	142 ± 11*‡	0.005
IIGI	152 ± 16§	202 ± 25§	114 ± 9*‡	0.016
$P_{t\ test}$	<0.001	0.001	0.016	
ISR, baseline (pmol/L)				
OGTT	1 ± 0	2 ± 0	1 ± 0	0.373
IIGI	1 ± 0	2 ± 0	1 ± 0	0.300
$P_{t\ test}$	0.321	0.638	0.511	
ISR, peak values (pmol/L)				
OGTT	11 ± 1§	11 ± 1§	4 ± 1*‡	<0.001
IIGI	5 ± 1§	6 ± 1§	3 ± 0*‡	<0.001
$P_{t\ test}$	<0.001	<0.001	0.025	
ISR, tAUC (min · nmol/L)				
OGTT	797 ± 83§	958 ± 105§	501 ± 48*‡	0.001
IIGI	496 ± 55	684 ± 71§	397 ± 28‡	0.006
$P_{t\ test}$	<0.001	<0.001	0.028	

Data are means ± SEM unless otherwise indicated. $II_{0–30\ min}$, insulinogenic index$_{0–30\ min}$; tAUC, total area under the curve. *P* values are derived from two-tailed *t* tests for variation within the group and repeated-measurement ANOVA for variations between the groups. †*P* value is derived from a χ^2 test for sex difference. *Significant difference ($P < 0.05$) from the CTRL group in the observations between the groups (post hoc analysis). ‡Significant difference ($P < 0.05$) from the GCK-diabetes group in the observations between the groups (post hoc analysis). §Significant difference ($P < 0.05$) from the HNF1A-diabetes group in the observations between the groups (post hoc analysis).

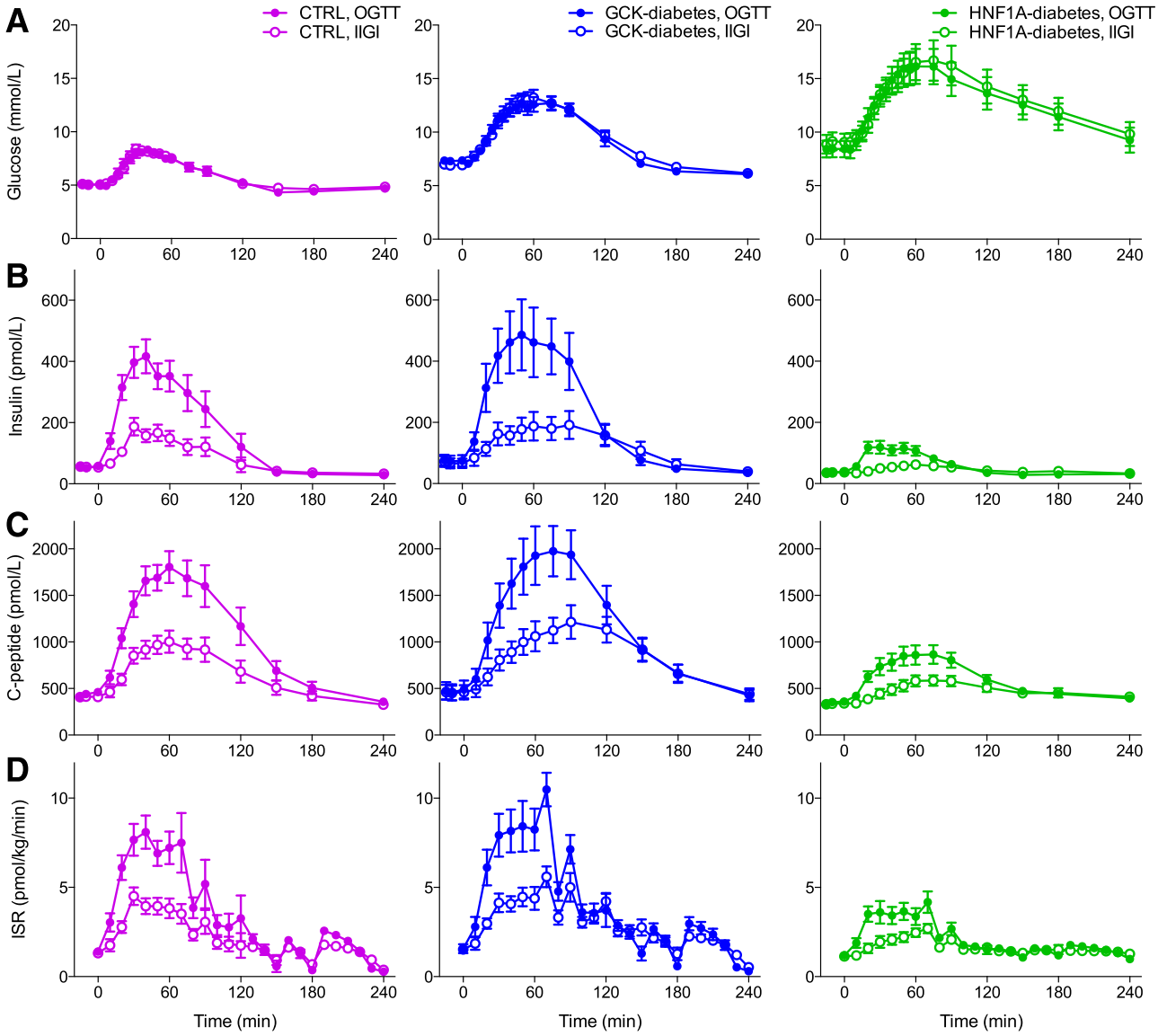

Figure 1—Glucose, insulin, C-peptide, and ISR. PG (*A*), plasma insulin (*B*), plasma C-peptide concentrations (*C*), and ISR (*D*) (means ± SEM) during 50-g oral OGTT and IIGI in CTRLs and in patients with GCK-diabetes and HNF1A-diabetes.

When the incretin effect from C-peptide and ISR was calculated, patients with HNF1A-diabetes exhibited lower incretin effect (C-peptide, HNF1A-diabetes 17 ± 5%, GCK-diabetes 26 ± 3%, and CTRL 37 ± 4%) compared with CTRLs (C-peptide, $P = 0.018$; ISR, $P = 0.031$) but not with patients with GCK-diabetes (C-peptide, $P = 0.216$; ISR, $P = 0.602$). The differences between patients with GCK-diabetes and CTRLs were not significant (C-peptide, $P = 0.145$; ISR, $P = 0.499$). Additionally, patients with HNF1A-diabetes had lower β-cell secretory capacity according to insulinogenic index than CTRLs and patients with GCK-diabetes (Table 1).

Insulin Sensitivity

According to homeostasis model assessment of insulin resistance (HOMA-IR) and Matsuda index (Table 1), patients with GCK-diabetes tended to be more insulin resistant than CTRLs and patients with HNF1A-diabetes.

Glucagon

Similar fasting values were observed on the two days in each group (Table 2). As illustrated in Fig. 2, plasma glucagon dropped abruptly in the CTRLs and in the patients with GCK-diabetes after both oral and intravenous administration of glucose and continued to decrease for 60 min with equal suppression after OGTT and IIGI. In contrast, in patients with HNF1A-diabetes, glucagon secretion initially increased after OGTT and later decreased to values that were lower than those observed after IIGI, which resulted in immediate suppression of glucagon levels (Fig. 2 and Table 2).

GIP and GLP-1

Plasma GIP and GLP-1 levels increased during the OGTT but remained unchanged after the IIGI. Responses were similar in the three groups (Fig. 2 and Table 2).

Table 2—Responses of glucagon, GIP, GLP-1, and acetaminophen

	CTRL (n = 9)	GCK-diabetes (n = 9)	HNF1A-diabetes (n = 10)	P_{ANOVA}
Glucagon, baseline (pmol/L)				
OGTT	8 ± 1	8 ± 1	7 ± 2	0.784
IIGI	8 ± 2	7 ± 1	7 ± 1	0.735
$P_{t\ test}$	0.842	0.563	0.545	
Glucagon, $\Delta AUC_{0–240\ min}$ (min · nmol/L)				
OGTT	−517 ± 193	−750 ± 133	−781 ± 257	0.759
IIGI	−850 ± 280	−662 ± 152	−475 ± 122	0.397
$P_{t\ test}$	0.333	0.640	0.961	
Glucagon, $\Delta AUC_{0–60\ min}$ (min · nmol/L)				
OGTT	−121 ± 46	−142 ± 36	46 ± 33*	0.009
IIGI	−190 ± 55	−132 ± 34	−83 ± 20	0.150
$P_{t\ test}$	0.344	0.856	0.005	
GIP, baseline (pmol/L)				
OGTT	11.1 ± 2.4	8.8 ± 2.6	8.9 ± 1.5	0.215
IIGI	9.1 ± 1.7	7.2 ± 1.5	7.5 ± 0.9	0.316
$P_{t\ test}$	0.516	0.390	0.102	
GIP, peak values (pmol/L)				
OGTT	48.8 ± 6.3	59.1 ± 8.8	50.2 ± 5.5	0.984
IIGI	15.7 ± 2.1	8.6 ± 1.6	7.7 ± 0.9	0.176
$P_{t\ test}$	<0.001	<0.001	<0.001	
GIP, tAUC (min · nmol/L)				
OGTT	5.8 ± 0.6	6.7 ± 1.0	5.0 ± 0.4	0.366
IIGI	2.0 ± 0.4	1.7 ± 0.3	1.8 ± 0.2	0.670
$P_{t\ test}$	<0.001	<0.001	<0.001	
GLP-1, baseline (pmol/L)				
OGTT	9.4 ± 0.4	7.4 ± 1.1	9.9 ± 1.6	0.410
IIGI	9.1 ± 0.9	9.4 ± 0.9	8.6 ± 0.9	0.804
$P_{t\ test}$	0.778	0.070	0.424	
GLP-1, peak values (pmol/L)				
OGTT	24.0 ± 2.4	24.6 ± 3.1	27.3 ± 4.7	0.849
IIGI	11.4 ± 1.4	12.8 ± 4.4	9.5 ± 1.3	0.513
$P_{t\ test}$	<0.001	0.060	0.003	
GLP-1, tAUC (min · nmol/L)				
OGTT	3.3 ± 0.3	3.1 ± 0.4	3.1 ± 0.4	0.947
IIGI	2.1 ± 0.2	2.4 ± 0.4	1.9 ± 0.1	0.423
$P_{t\ test}$	0.002	0.042	0.005	
Acetaminophen, OGTT				
Peak values (mmol/L)	0.122 ± 0.011	0.148 ± 0.005	0.138 ± 0.006	0.102
Time to peak values (min)	82 ± 9	83 ± 6	67 ± 8	0.184
iAUC (min · mmol/L)	18 ± 2	21 ± 1	19 ± 1	0.109

Data are means ± SEM. P values are derived from two-tailed t tests for variation within the group and repeated-measurement ANOVA for variations between the groups. Plasma glucagon responses are calculated as baseline-subtracted area under the curve (ΔAUC). iAUC, incremental area under the curve; tAUC, total area under the curve. *Significant differences ($P < 0.05$) from the CTRL and GCK-diabetes groups in the observations between the groups (post hoc analysis).

Gastric Emptying (Acetaminophen)

Similar gastric emptying, assessed by the acetaminophen absorption test, was seen in all groups (Table 2).

DISCUSSION

The primary findings in our study are *1*) a normal incretin effect and glucagon response in patients with GCK-diabetes, *2*) a reduced incretin effect and inappropriate suppression of glucagon during OGTT (but not during IIGI) in patients with HNF1A-diabetes, and *3*) normal responses of the gut incretin hormones GIP and GLP-1 to oral glucose in patients with GCK-diabetes and HNF1A-diabetes.

The effects of GCK and HNF1A mutations for the incretin effect and glucagon responses to glucose were unclear until now. It has been shown that mutations in GCK, the rate-determining enzyme converting glucose to glucose-6-phosphate in the β-cells, may result in an increased glucose threshold for insulin secretion (3,5,7). Our findings demonstrate that patients with GCK-diabetes have intact insulin responses to both oral and intravenous glucose administration, supporting the view that patients with GCK-diabetes primarily have a "glucose-sensing defect" in their β-cells. In spite of their impaired glucose tolerance, they also had a normal incretin effect consistent

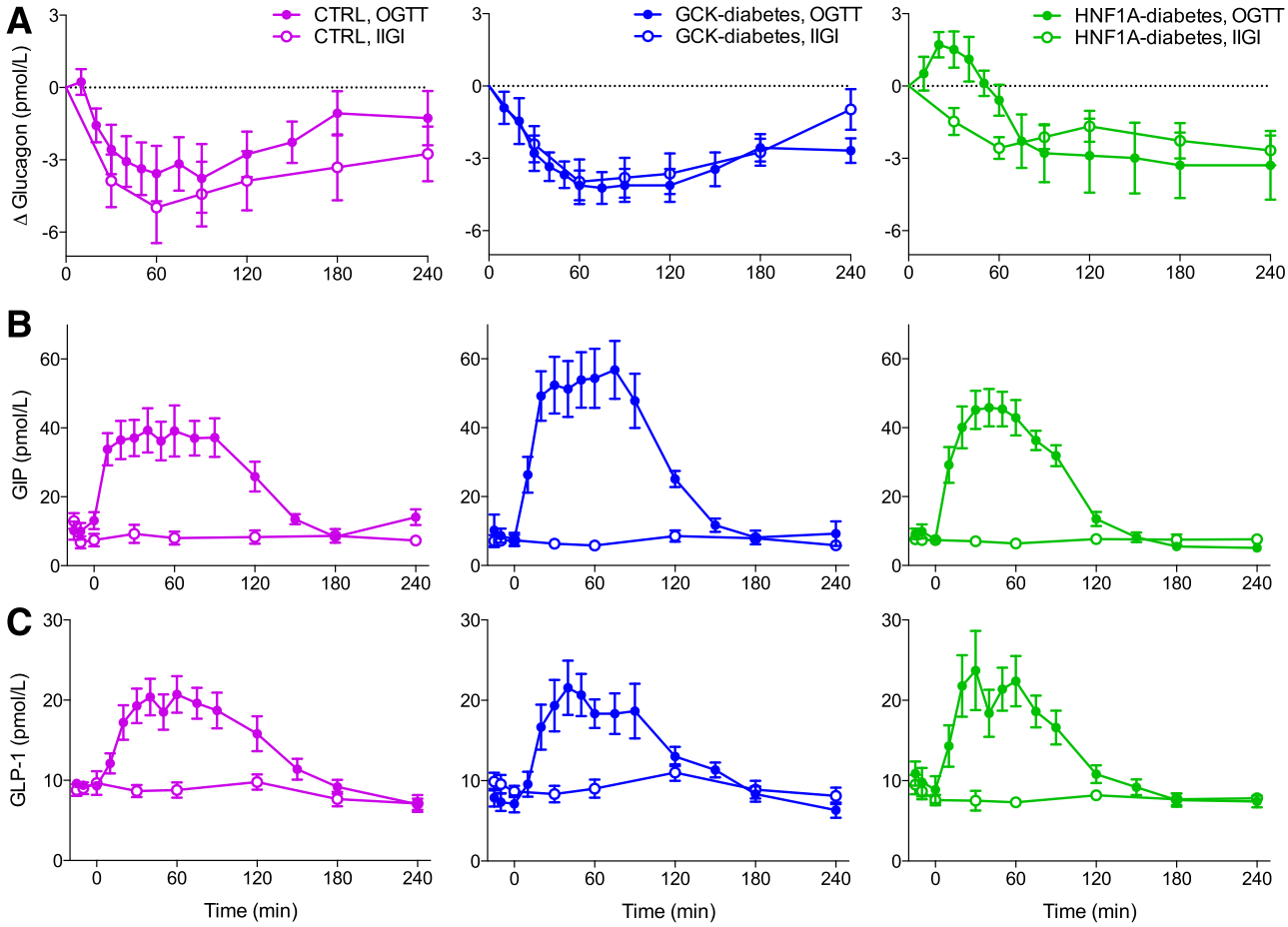

Figure 2—Glucagon, GIP, and GLP-1. Plasma glucagon (*A*), GIP (*B*), and GLP-1 concentrations (*C*) (means ± SEM) during 50-g OGTT and IIGI in CTRLs and in patients with GCK-diabetes and HNF1A-diabetes. Glucagon data are baseline subtracted.

with the interpretation that have not "true" diabetes but, rather, "benign familial hyperglycemia," not requiring blood glucose–lowering drugs (3). We also found completely normal suppression of glucagon in response to both intravenous and oral glucose stimulation in patients with GCK-diabetes, supporting this concept. It has previously been shown that insulin resistance may develop in patients with GCK-diabetes (10). However, the slightly elevated HOMA-IR and lowered Matsuda index in our patients may merely reflect a higher "set point" for glucose uptake in the hepatocytes, which also depend on GCK for normal glucose phosphorylation.

In contrast, mutations in HNF1A result in progressive β-cell dysfunction, involving impaired expression of the genes encoding insulin and GLUT2 as well as reduced pyruvate kinase activity resulting in reduced formation of ATP (3,11–13), eventually leading to decreased insulin secretion and thereby glucose intolerance. Since the incretin hormones act to enhance glucose-induced insulin secretion, a diminished incretin effect might be expected in patients with HNF1A-diabetes, consistent with the findings in our study. Insulin sensitivity was normal in our patients with HNF1A-diabetes, as also found previously (10,14) but in contrast to a tendency of reduced insulin sensitivity found in another study (15). Thus, insulin resistance does not seem to be involved in their reduced incretin effect, and neither do changes in the release of incretin hormones, which was normal both in this and in two previous studies (OGTT [16] and mixed meal [17]). We previously found an impaired insulinotropic action of GIP particularly in patients with HNF1A-diabetes during hyperglycemic (15 mmol/L) clamps (18) suggesting that a reduced sensitivity to the incretin hormones may explain the impaired incretin effect. A reduced action of the incretin hormones in HNF1A-diabetes may be due to the reduced formation of ATP, since the incretin hormones may act to sensitize the ATP-sensitive K channels to ATP via formation of cAMP and activation of protein kinase A (19–21). In addition to impaired β-cell function, it is possible that defective HNF1A may influence other cell types, i.e., α-cells and hepatocytes, although this remains to be elucidated. Also, defective GIP and/or GLP-1 receptor signaling caused by the HNF1A mutation could be involved.

Normal glucose tolerance depends on normal regulation of glucagon secretion. In a previous study, patients with HNF1A-diabetes suppressed glucagon normally during

a hyperglycemic clamp (18), similar to our finding of normal glucagon suppression after intravenous glucose administration, but we also found delayed suppression after OGTT similar to that in patients with type 2 diabetes (22). The role of HNF1A in the α-cell is not known. The normal suppression during IIGI seems to exclude the possibility that a defective β-cell function is responsible.

Treatment of patients with MODY using an incretin-based strategy has been described in a few cases (23,24). Our study demonstrates that HNF1A-diabetes shares incretin-related pathophysiology with type 2 diabetes, i.e., reduced incretin effect, which was one of the incentives for incretin-based treatment for type 2 diabetes. Therefore, incretin-based therapy to patients with HNF1A-diabetes seems relevant, and randomized, and perhaps controlled clinical trials might be considered.

In conclusion, patients with GCK-diabetes exhibit preserved incretin physiology, while patients with HNF1A-diabetes are characterized by a reduced incretin effect, marked β-cell dysfunction, and an inappropriate glucagon response to OGTT but have normal insulin sensitivity.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.H.Ø. contributed to the study design, executed all experiments, researched data, and wrote the manuscript. J.I.B. contributed to the statistical analyses and reviewed and edited the manuscript. T.H. contributed to the study design and contributed to recruitment of MODY patients and to reviewing and editing the manuscript. O.P. contributed to recruitment of MODY patients and to reviewing and editing the manuscript. J.J.H. analyzed plasma for incretin hormones and glucagon and reviewed and edited the manuscript. F.K.K. contributed to the study design and reviewed and edited the manuscript. T.V. designed the study and reviewed and edited the manuscript. S.H.Ø. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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