β-Cell-Targeted Expression of a Dominant-Negative Hepatocyte Nuclear Factor-1α Induces a Maturity-Onset Diabetes of the Young (MODY)3-Like Phenotype in Transgenic Mice

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Mutations in the transcription factor hepatocyte nuclear factor-1α (HNF-1α) cause maturity-onset diabetes of the young 3, a severe form of diabetes characterized by pancreatic β-cell dysfunction. We have used targeted expression of a dominant-negative mutant of HNF-1α to specifically suppress HNF-1α function in β-cells of transgenic mice. We show that males expressing the mutant protein became overtly diabetic within 6 wk of age, whereas females displayed glucose intolerance. Transgenic males exhibited impaired glucose-stimulated insulin secretion, detected both in vivo and in the perfused pancreas. Pancreatic insulin content was markedly decreased in diabetic animals, whereas the glucagon content was increased. Postnatal islet development was altered, with an increased α-cell to β-cell ratio. β-Cell ultrastructure showed signs of severe β-cell damage, including mitochondrial swelling. This animal model of maturity-onset diabetes of the young 3 should be useful for the further elucidation of the mechanism by which HNF-1α deficiency causes β-cell dysfunction in this disease. (Endocrinology 142: 5311–5320, 2001)

MATURITY-ONSET DIABETES of the young (MODY) is a monogenic form of type 2 diabetes characterized by early age of onset (<25 yr) and autosomal dominant transmission. A number of genetically distinct forms of MODY, which together represent 2–5% of type 2 diabetes, have been identified. MODY3, accounting for 65% of MODY cases in the United Kingdom, is the most common, and also the most severe form of MODY. MODY3 patients progressively develop a severe hyperglycemia, which can lead to the typical complications of blindness, gangrene, and renal failure, and require treatment with either oral hypoglycemic agents or insulin (1). Clinical studies have shown that the chronic hyperglycemia observed in MODY3 patients is primarily due to a defect in the insulin-secreting pancreatic β-cells, rather than in insulin action on target tissues (2–4).

Mutations in the gene coding for the transcription factor hepatocyte nuclear factor-1α (HNF-1α) cause MODY3. The HNF-1α protein is composed of three functional domains: a short myosin-like amino-terminal dimerization domain, an atypical homeobox DNA-binding domain, and a carboxyl-terminal transactivation domain. Dimerization of HNF-1α is essential for DNA binding. Patient mutations in any of these domains could lead to diminished amounts of functional HNF-1α by either a haploinsufficiency or a dominant-negative mechanism.

HNF-1α was originally characterized as a transcription factor involved in the control of expression of a wide variety of liver-specific genes (5), and has more recently been shown to be an essential transcriptional regulator of bile acid and high density lipoprotein cholesterol metabolism (6). However, HNF-1α is also expressed in the kidney, intestine, spleen, and the exocrine and endocrine pancreas (7). Notably, HNF-1α has been shown to regulate genes expressed in the pancreatic β-cell, such as glucose transporter 2 (Glut-2) and α-type pyruvate kinase (7–11). HNF-1α has also been proposed to transactivate the rat insulin I gene (8, 9, 12). Targeted disruption of the hnf-1α gene in mice indeed results in elevated plasma glucose levels, in addition to hepatomegaly and renal dysfunction (13, 14). However, the pleiotropic effects of the HNF-1α-knockout complicate the analysis of the precise role of HNF-1α in determining normal pancreatic β-cell function. The specific mechanisms by which mutations in HNF-1α cause MODY3 thus remain unclear.

In this study, we specifically suppressed HNF-1α function in the β-cells of transgenic mice. This was achieved by β-cell-targeted overexpression of a dominant-negative mutant of rat HNF-1α (DNHNF1α). We have previously shown that DNHNF-1α, which lacks DNA binding activity, exerts its dominant-negative effect by heterodimerizing with endogenous HNF-1α, thus preventing it from binding to DNA (8). Controlled overexpression of DNHNF-1α in rat insulinoma cells affects insulin gene transcription and metabolite secretion coupling (8). Here we show that transgenic mice expressing DNHNF-1α in pancreatic β-cells develop either glucose intolerance or overt diabetes.

**Materials and Methods**

**Transgenic mice**

The rat insulin promoter (RIP)-DNHNF1α transgene was constructed by inserting the DNHNF-1α cDNA (8) into a plasmid under the control of the RIP (15), between the rabbit β-globin intron and polyadenylation
FIG. 1. Overexpression of DNHNF-1α in β-cells of transgenic mice induces diabetes in males and glucose intolerance in females. A, Evolution of fasting (6 h) blood glucose levels in control (Ctr) and RIP-DNHNF-1α (Trg) males. RIP-DNHNF-1α males become overtly diabetic around the age of 6 wk, with a mean fasting glycemia of 18.1 ± 2.01 mM vs. 9.58 ± 1.03 mM in controls. B, Thirteen-week-old females were subjected to an ip (IP) glucose tolerance test after an overnight (15 h) fast (see Materials and Methods). At all time points measured, blood glucose values were significantly higher in RIP-DNHNF-1α (Trg) than in control (Ctr) females. C, Nonfasting blood glucose levels in 3-wk-old control (Ctr, black bars) and transgenic (Trg, hatched bars) male and female mice. There is a similar increase in nonfasting glycemia in transgenic animals, whether males (10.47 ± 0.56 mM vs. 7.61 ± 0.25 mM in controls) or females (10.13 ± 0.48 mM vs. 7.58 ± 0.35 mM in controls). *, P < 0.05; **,
Results

\( \beta \)-specific expression of DNHNF-1α induces diabetes or glucose intolerance

To express DNHNF-1α in pancreatic \( \beta \)-cells, we placed the DNHNF-1α transgene under the transcriptional control of the RIP II (RIP-DNHNF-1α mice). Six RIP-DNHNF-1α founder mice were obtained. One female founder became severely diabetic and had no offspring, whereas the transgenic offspring of two other founders died around 3–4 d after birth of severe hyperglycemia. Hence, 3 RIP-DNHNF-1α transgenic families could be established, 2 of which exhibited no detectable phenotype. Monitoring of fasting blood glucose in the third family, however, showed that transgenic males became markedly diabetic around 6 wk of age (Fig. 1A). Although transgenic females remained normoglycemic (at least up to the age of 15 months), an ip glucose tolerance test on 3-month-old females showed that they were glucose intolerant (Fig. 1B). Females also exhibited elevated nonfasting blood glucose values at weaning (134% of controls, \( P < 0.001 \)) similar to males (138% of controls, \( P < 0.001 \) (Fig. 1C)).

Immunostaining of pancreas sections with an antibody against the N terminus of HNF-1α indicated clear overexpression of DNHNF-1α in the \( \beta \)-cell nuclei of 6-wk-old transgenic males (Fig. 1D, panel b). It is noteworthy that a similar overexpression was seen in the \( \beta \)-cells of the normoglycemic RIP-DNHNF-1α females (Fig. 1D, panel c). In each case, consecutive sections were stained with an antibody against insulin (not shown). RT-PCR on total newborn pancreas RNA also confirmed that the DNHNF-1α message was expressed in the transgenic animals (not shown). Thus, suppression of HNF-1α function in the \( \beta \)-cell induces diabetes in male and glucose intolerance in female mice.

DNHNF-1α expression affects pancreatic insulin and glucagon contents

We next determined by immunohistochemistry whether DNHNF-1α expression affects islet structure. Staining of pancreas sections from RIP-DNHNF-1α mice with an antibody against insulin showed that, at birth, there was no apparent difference in the number and the organization of \( \beta \)-cells between transgenic and control mice (Fig. 2, A and B). However, at 3 wk (the age of weaning), the islets of the

\( P < 0.01; *** P < 0.001, \) as determined using an unpaired two-tailed \( t \) test comparing transgenic vs. control animals. Values are presented as mean ± SEM. Numbers in parentheses denote the number of animals analyzed. D, Section 80-μm diameter ink cryostat sections of pancreas from 6-wk-old mice were stained with an antibody against the amino terminus of HNF-1α, as described in Materials and Methods. Endogenous levels of HNF-1α were barely detectable in the islets of control mice (a), whereas overexpression of DNHNF-1α was detected both in the islets of RIP-DNHNF-1α males (b) and females (c). Note that the islet shown in panel a is much larger than those shown in panels b and c. Calibration bar, 50 μm.
transgenic mice started to become disorganized, with fewer β-cells and heterogeneous insulin immunostaining. This was seen in males (Fig. 2, C and D) as well as in females (Fig. 2, E and F), and was consistent with the elevated nonfasting blood glucose observed in these animals (cf. Fig. 1C). At 10 wk of age, the islets of transgenic RIP-DNHNF-1α males had a clearly reduced number of β-cells compared with wild-type littermates (Fig. 2, G and H). The islets of the transgenic males
were moreover disorganized, with an apparently higher number of β-cells scattered throughout the islet instead of their normal peripheral localization (Fig. 2, I and J).

To confirm the immunohistochemical results, we measured total pancreatic insulin and glucagon content at 3, 6, and 10 wk of age in RIP-DNHNF-1α males and females. The results presented in Table 1 show that at 3 wk, pancreatic insulin content in transgenic males and females was 42.9 and 35.5% of control, respectively. Subsequently, whereas insulin content in females increased (54.4 and 59.3% of control at 6 and 10 wk, respectively), the insulin content in males continued to decline (31.1% of control at 6 wk) until reaching a mere 21.1% of control at 10 wk. This decrease in insulin content contrasted with the 2.2-fold increase in pancreatic glucagon content observed in 10-wk-old RIP-DNHNF-1α males compared with controls (Table 1).

Together, these results thus suggest that the loss of HNF-1α function in β-cells leads to a decrease of both pancreatic insulin content and β-cell number.

**DNHNF-1α expression inhibits insulin secretion**

To see whether expression of DNHNF-1α in β-cells leads to a specific insulin secretion defect, we perfused the pancreas of 5-wk-old RIP-DNHNF-1α males (before the onset of diabetes). The insulin secretion profiles of transgenic and control mice are shown in Fig. 3A. The perfusion protocol included a 15-min stimulation with 16.7 mM glucose, directly followed by a 16.7 mM glucose plus 20 mM arginine challenge. To calculate the insulin secreted (the area under the curve), we further subdivided the secretory responses into a glucose “first phase,” a glucose “second phase,” and an “arginine response” (Fig. 3A). The results show that the first phase of glucose-stimulated insulin secretion was diminished in transgenic RIP-DNHNF-1α males (51.3% of control), whereas the second phase was less affected (69.4% of control). The insulin secretory response to arginine in the presence of high glucose was even more reduced (26.9% of control [Fig. 3B]).

We also assessed insulin secretion in vivo using an ip glucose challenge. As shown in the left panel of Fig. 3C, 5-wk-old RIP-DNHNF-1α males exhibited a marked inhibition of insulin secretion (1.8-fold induction at 15 min vs. 2.6-fold in controls), similar to what was observed in the perfused pancreas. When the experiment was performed at 6 wk, *i.e.* the age of onset of hyperglycemia, the ability of RIP-DNHNF-1α males to secrete insulin in response to glucose was completely abolished (Fig. 3C, right panel). Measuring plasma insulin 30 min after the glucose challenge probably contributed to exaggerate the complete blunting of the secretory response. The latter still contrasted with the 2.1-fold increase in secretion seen in control animals.

From these data, we conclude that glucose-induced insulin secretion is impaired in RIP-DNHNF-1α males. This secretory defect is detectable already before the onset of hyperglycemia and worsens with time.

**Effects of DNHNF-1α on Glut-2 expression and β-cell ultrastructure**

Glut-2 is one of the target genes of HNF-1α in β-cells (8–11). We therefore performed immunostaining with an antibody against Glut-2 and found that the sugar carrier was severely down-regulated in the islets of 6-wk-old RIP-DNHNF-1α males (Fig. 4, A–C). The down-regulation of Glut-2 cannot be secondary to a prolonged exposure to hyperglycemia, because at 6 wk, the mice just start to become diabetic.

To better understand the mechanism underlying the insulin secretory defect and the islet disorganization observed in RIP-DNHNF-1α males, we then examined the ultrastructure of islet cells by electron microscopy (Fig. 5). Already at low magnification, it was evident that most β-cells of 6-wk-old transgenic males exhibited marked vacuolization (compare Fig. 5, B with A). β-Cells of RIP-DNHNF-1α males were also shown to contain less mature secretory granules (compare Fig. 5, D–F, with C). Moreover, they displayed specific ultrastructural lesions: β-cell mitochondria were swollen, as shown in Fig. 5, D and F, contrasting with the intact organelles seen in a neighboring α-cell (Fig. 5F) or in control β-cells (Fig. 5C). In addition, most transgenic β-cells appeared highly disorganized, with dilated rough endoplasmic reticulum cisternae (Fig. 5E). Together, these alterations suggest that β-cell death is increased in the islets of transgenic mice. This process is not a typical apoptosis, because no apoptotic bodies nor chromatin condensation were ever observed.

### TABLE 1. Pancreatic insulin and glucagon contents in control and transgenic mice

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<td>Males</td>
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<td>Females</td>
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<td>Males</td>
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<td>Females</td>
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<td>Males</td>
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Ctr, Control; Trg, transgenic. Values are expressed as mean ± SEM. *, P < 0.05; **, P < 0.01; ***, P < 0.001, as determined using an unpaired two-tailed *t* test.
**Fig. 3.** Impaired insulin secretion in RIP-DNHNF-1α males. A, Insulin release from the perfused pancreas of control (Ctr, n = 5) and transgenic (Trg, n = 6) 5-wk-old males. The perfusion protocol is shown in boxes on top (arginine was added at a concentration of 20 mM). The areas chosen to calculate the insulin released under the first and second phases of the glucose (Glc) response, as well as under the arginine (arg) response, are delimited by vertical lines. Values are presented as mean ± SEM for each time point. Note that there is a significant difference in the glucose peak value between control and transgenic mice (6.3 ± 1.64 ng/ml and 2.3 ± 0.51 ng/ml, respectively; *, P < 0.05, as determined by an unpaired two-tailed t test). B, The insulin released during the first and second phases of the glucose response, or during the arginine response (arg), was determined by calculating the areas under the curve as shown in A, after subtraction of basal secretion. Ctr, Control (black bars); Trg, transgenic (shaded bars). *, P < 0.05, using an unpaired one-tailed t test. ns, Not significant. Note the logarithmic scale of the y-axis. C, Five-week-old (left panel) and 6-wk-old (right panel) control (Ctr) and transgenic (Trg) RIP-DNHNF-1α males were subjected to an ip glucose challenge after an overnight (15 h) fast. Plasma insulin levels were measured just before (0'), and 15 or 30 min (15/30') after glucose injection. *, P < 0.05; **, P < 0.01; ***, P < 0.001, as determined using a paired (comparing the same animals before and after glucose injection) or an unpaired (comparing Ctr and Trg animals) two-tailed t test. ns, Not significant. Bars represent the means. Numbers in parentheses denote the number of animals in each group.
some is severely down-regulated in the islets of transgenic males, although the pleiotropic impact of the disruption of the HNF-1α gene complicates their use for the study of glucose homeostasis.

The transgenic mice with β-cell-specific suppression of HNF-1α function described in this study phenotypically resemble MODY3 diabetics and carriers. Indeed, expression of DNHNF-1α in the β-cells of RIP-DNHNF-1α males results in overt diabetes, whereas it only causes impaired glucose tolerance in transgenic females. The severity of the syndrome was paralleled by changes in islet morphology and hormone content. RIP-DNHNF-1α females exhibited a much milder phenotype than the males, although they showed the same hyperglycemia and reduction in pancreatic insulin content at weaning. The subsequent partial recovery of pancreatic insulin content occurred despite similar DNHNF-1α expression levels in both sexes. The hormonal profile of the females probably explains this protection from diabetes, as reported in other studies (24, 25). This also indicates that the phenotype of the RIP-DNHNF-1α males cannot be explained by a nonspecific effect of DNHNF-1α overexpression.

HNF-1α has been shown to control insulin gene transcription in rat insulinoma cell lines (8, 9). In RIP-DNHNF-1α males, there was a gradual decrease in pancreatic insulin content, also seen by immunohistochemistry as an apparent decrease in the number of β-cells and heterogeneous insulin staining. Ultrastructural analysis confirmed the immunohistochemical observations, showing that most β-cells in RIP-DNHNF-1α males exhibited a decrease in the number of mature secretory granules. Reduced expression of other HNF-1α target genes, including Glut-2, probably contributes to the decreased number of insulin-positive cells seen at 10 wk. The Glut-2-knockout mouse indeed displays a decrease in β-cell mass (26). In RIP-DNHNF-1α males, there was also a progressive disorganization of the islets, with an augmented ratio of α-cells to β-cells. This islet disorganization could be due, at least in part, to the down-regulation of the cell adhesion molecule E-cadherin observed in a similar mouse model (27). The increased α-cell to β-cell ratio was paralleled by an enhanced pancreatic glucagon content, which could contribute to aggravate the diabetic phenotype. It is of interest in this context that the normal suppression of glucagon secretion during a hyperglycemic clamp is impaired in MODY3 patients (3).

Glucose-stimulated insulin secretion was impaired in RIP-DNHNF-1α males both in vivo and ex vivo. Pancreas perfusions revealed that, as in MODY3 patients (2, 3), the first phase of the secretory response to glucose was attenuated. The response to the combination of arginine and glucose was also markedly inhibited. These results are similar to published data on diabetic HNF-1α-knockout mice, which exhibit a pronounced suppression of glucose- and arginine-evoked insulin secretion (22). It is of interest that Glut-2-knockout mice, like RIP-DNHNF-1α males, display a specific loss of the first phase of glucose-induced insulin secretion (26). However, down-regulation of Glut-2 in the β-cells of RIP-DNHNF-1α males is apparently not sufficient to explain the secretory defect because the glyceraldehyde-evoked response is preserved in Glut-2- but not in HNF-1α-knockout mice. The secretory

**Discussion**

MODY3 is one of the most frequent monogenic subforms of type 2 diabetes. β-Cell dysfunction has been suggested as the primary cause of the disease, which is severe, often requiring insulin therapy (1, 18, 19). Diabetic MODY3 patients display severely impaired glucose-stimulated insulin secretion, with the first phase being particularly affected. Interestingly, nondiabetic carriers of the MODY3 mutation display an intermediary phenotype, with subnormal insulin secretion and decreased glucose tolerance (2, 4). Unlike most type 2 diabetics, MODY3 patients are not insulin resistant (2, 3, 20). Although liver and kidney express high levels of HNF-1α, the patients do not show signs of altered function of these organs that could explain the etiology of the disease (21). In contrast, HNF-1α-knockout mice, while being diabetic, suffer from multiple organ manifestations such as renal dysfunction with massive glucosuria, pathological liver tests,
defect observed in RIP-DNHNF-1α males can already be detected in prediabetic animals, whether assessed *in vivo* or *ex vivo*. At the age of onset of diabetes, the *in vivo* insulin secretory response is completely abolished. Interestingly, this inhibition is more drastic than could be expected from the 70% decrease in pancreatic insulin content observed in these animals. As it is generally assumed that 10% of residual pancreatic insulin content/β cell mass is enough to maintain euglycemia (28), these results suggest that additional mechanisms could account for the impaired glucose-induced insulin secretion in RIP-DNHNF-1α males.
Electron microscopy studies indeed revealed ultrastructural lesions in most β-cells of RIP-DNHF-1α males. Variable degrees of cell damage could be observed, such as prominent disorganization of the rough endoplasmic reticulum appearing as dilated cisternae, mitochondrial swelling, and reduced numbers of fully mature secretory granules. Some cells were clearly dying, exhibiting general vacuolization, but neither apoptotic bodies nor chromatin condensation were ever observed in the damaged β-cells of RIP-DNHF-1α males. Interestingly, it has been reported before that β-cell death can occur without characteristic features of apoptosis (29). Moreover, it has been shown that cellular ATP is needed for a cell to undergo classical apoptosis, with chromatin condensation and fragmentation (30–32). It is of interest in this context that overexpression of DNHF-1α in a rat insulinoma cell line leads to impaired mitochondrial glucose oxidation and ATP production (8). Similarly, glucose-induced mitochondrial hyperpolarization, an essential step in β-cell activation, is diminished in a cell line expressing a human HNF-1α mutant (9). The ultrastructural lesions and the inhibition of insulin secretion observed in RIP-DNHF-1α males are thus compatible with deficient ATP generation by the mitochondria. The resulting increased β-cell death could also explain the disorganization of the islets in transgenic mice.

In conclusion, the results presented here suggest that suppression of HNF-1α function affects β-cell metabolism downstream of glucose transport. Our transgenic mouse model with β-cell-specific suppression of HNF-1α function clearly demonstrates that β-cell dysfunction must be the primary cause of MODY3. Studies on these animals should help to further clarify the role of HNF-1α in β-cell pathophysiology, to definitively identify this gene in different tissue and cell types. This work was supported by Swiss National Science Foundation Grants Nos. 32–49755.96 (to C.B.W.) and 31–53027.97 (to P.L.H.). It was also supported by the Juvenile Diabetes Research Foundation (C.B.W. and P.L.H.), the Bonizzoni-Thaler Stiftung, Zürich (C.B.W.), and the Novartis Foundation, Basel (C.B.W.).

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Erratum

In the article by C. M. Komar et al. (Endocrinology 142:4831–4838, 2001), part of the first sentence in the legend to Fig. 3 appeared incorrectly. PPARγ should have been PPARα. Additionally, Fig. 8 appeared incorrectly. The correct figure and its legend appear below. The printer regrets the errors.

![Graph A](https://example.com/graphA.png)

**A**

Concentrations of progesterone (ng/ml) in conditioned media from rat granulosa cells cultured for 48 h as described in Materials and Methods (n = 5 independent experiments). Cntrl, Control, PGJ10, PGJ25, Cig25, Cig50.

![Graph B](https://example.com/graphB.png)

**B**

Concentrations of E2 (pg/ml) in conditioned media from rat granulosa cells cultured for 48 h as described in Materials and Methods (n = 5 independent experiments). Cntrl, Control, PGJ10, PGJ25, Cig25, Cig50.

*Significantly different from control (P < 0.05).