In Vitro Transcriptional Induction of the Human Apolipoprotein A-II Gene by Glucose

Dominique Sauvaget,1,2 Valérie Chauffeton,2 Sonia Dugé-Pujol,1,2 Athina-Despina Kalopissis,1,2 Isabelle Guillet-Deniau,3 Fabienne Foufelle,7,4 Jean Chambaz,1,2 Armelle Leturque,1,2 Philippe Cardot,1,2 and Agnès Ribeiro1,2

Type 2 diabetic patients present high triglyceride and low HDL levels, significant determinants for the risk of atherosclerosis. Transgenic mice overproducing human apolipoprotein (apo)A-II, one of the two major apos of HDLs, display the same lipid disorders. Here, we investigated the possible regulation of apoA-II gene expression by glucose. In primary rat hepatocytes and in HepG2 cells, the transcription of the human apoA-II gene was upregulated by glucose. This response was mediated by a hormone-responsive element within the enhancer of the apoA-II promoter and was dependent on hepatocyte nuclear factor-4α. Accordingly, in transgenic mice, the human apoA-II gene is stimulated by a high-carbohydrate diet after fasting and at weaning. By contrast, the apoA-II mRNA level is not modified in streptozotocin-induced diabetic rats. In transgenic mice overexpressing the human apoA-II gene, plasma human apoA-II concentration was positively correlated with blood glucose levels. These mice displayed a marked delay in plasma glucose tolerance as compared with control mice. We hypothesize that the following pathogenic pathway might occur in the course of type 2 diabetes: increased apoA-II level causes a rise in plasma triglyceride level and glucose intolerance, resulting in hyperglycemia, which in turn might further increase apoA-II gene transcription. Diabetes 53:672–678, 2004

The leading cause of death for individuals with diabetes is coronary artery disease (CAD). The risk of developing premature arterial atherosclerosis is two to three times higher in patients with type 2 diabetes than in the general population. Type 2 diabetic patients have been shown to display dyslipidemia, including hypertriglyceridemia and low levels of HDL (1).

Epidemiological data have demonstrated that the frequency of CAD is inversely related to plasma HDL level (2). The protective effects of HDLs against CAD have been attributed to their roles in reverse cholesterol transport (RCT)—the process by which excess cholesterol is transferred from extrahepatic tissues to the liver (3)—and in the protection of low density lipoprotein (LDL) against oxidative modifications (4).

Apolipoprotein (apo)A-I and apoA-II are the two major HDL apos. As apoA-I stimulates all of the steps of RCT, the role of HDLs in protecting against atherosclerosis has been attributed to apoA-I. The role of apoA-II remains unclear. In humans, it has been suggested that high plasma apoA-II concentrations are proatherogenic (5). Studies in transgenic mice overproducing apoA-II have not come to clear conclusions concerning the atherogenicity of apoA-II. The results obtained depended on the type of the diet (regular or atherogenic diet), the origin of the apoA-II gene expressed in mice (human or murine), and the genetic background of the mice (6,7). In recent studies of transgenic mice overproducing human apoA-II, we demonstrated that apoA-II acts as a physiological modulator of HDL metabolism. The overproduction of human apoA-II, at three times normal concentrations (transgenic line λ), resulted in a large decrease in HDL levels, associated with very high postprandial levels of very low density lipoproteins (VLDLs). Human apoA-II was found to associate with these VLDLs, impairing their catabolism by lipoprotein lipase (8,9). Further evidence for such a role of apoA-II was provided by a recent clinical study reporting that decreasing plasma apoA-II concentration increases clearance of large-sized postprandial VLDLs (10).

Hyperglycemia may be involved in changes in gene expression observed in type 2 diabetes. Glucose regulates the expression not only of the genes involved in glucose metabolism (11), but also that of genes involved in HDL metabolism, including those encoding apoA-I, human phospholipid transfer protein (PLTP), ATP-binding cassette transporter-A1 (ABC-1), scavenger receptor-B1 (SRB1), and hepatic lipase (12). These effects on gene expression provide a molecular basis for the role of hyperglycemia in the modifications to HDL metabolism observed in diabetes.

In this study, we investigated whether the apoA-II gene was regulated by glucose. We showed that glucose upregulated human apoA-II gene transcription. This regulation was mediated by a hormone responsive element (HRE) within the apoA-II enhancer and a transcriptionally active form of hepatocyte nuclear factor (HNF)-4α. In transgenic

From the 1Institut National de la Santé et de la Recherche Médicale (INSERM) U505, Institut Biomédical des Cordeliers, Paris, France; the 2Institut Fédératif de Recherche 58, Institut Biomédical des Cordeliers, Paris, France; 3INSERM U567, Unité Mixte de Recherche 8104 Centre National de la Recherche Scientifique, Institut Cochin, Paris, France; and 4INSERM U465, Institut Biomédical des Cordeliers, Paris, France.

Address correspondence and reprint requests to Agnès Ribeiro, INSERM U505, 15 rue de l’Ecole de Médecine, 75006 Paris, France. E-mail: agnes. ribeiro-pillet-u505@bhdc.jussieu.fr.

Received for publication 25 June 2003 and accepted in revised form 1 December 2003.

apo, apolipoprotein; CAD, coronary artery disease; CAT, chloramphenicol acetyl transferase; ChoRE, carbohydrate response element; DMEM, Dulbecco’s modified Eagle’s medium; HNF, hepatocyte nuclear factor; HRE, hormone responsive element; INSERM, Institut National de la Santé et de la Recherche Médicale; MODY1, type 1 maturity-onset diabetes of the young; FSK, pBlue-script SK; RCT, reverse cholesterol transport.

© 2004 by the American Diabetes Association.
mice producing various amounts of human apoA-II, we established a strong positive correlation between blood glucose and human apoA-II levels, and we showed a substantial delay in glucose tolerance in mice overproducing human apoA-II.

RESEARCH DESIGN AND METHODS

Transgenic mice. Transgenic mice were producing human apoA-II at physiological plasma concentrations (line β) (9) and at three times higher levels (line λ) (8). Male β-transgenic mice were used for fasting/refeeding studies. The fasted mice (n = 7) were deprived of food for 36 h, and the fasted/refed mice (n = 9) were fasted for 36 h and then re-fed for 18 h with the standard carbohydrate-rich diet (52.2% carbohydrate, 24.9% protein, and 5% lipid by weight). For assessment of the correlation between blood glucose and plasma human apoA-II levels, male and female β- (n = 20) and λ-transgenic (n = 24) mice were fed ad libitum with the diet. Mice were anesthetized by intraperitoneal injection of avertin (0.25 mg/g) and were killed between 9 and 11 A.M. Blood was collected onto EDTA, and plasma was isolated. Blood glucose was determined with the Glucotrend plus test (Roche Diagnostics, Mannheim, Germany). Human apoA-II was assayed in plasma by immunonephelometry, using a specific antibody (Dade Behring), as previously described (13). Livers were removed and immediately frozen in liquid N2 for subsequent RNA analysis. For the glucose tolerance test, male and female β- and λ-transgenic mice and control C57Bl/6j mice (four animals in each group) were fasted overnight and anesthetized by intraperitoneal injection of 0.15 mg/g Imalgene (Merial, Lyon, France). A bolus of glucose (2 mg/g) was injected intraperitoneally and blood glucose measured from the tail vein at the indicated times. Animal care and the experimental procedures used in this study conformed to French guidelines for animal studies.

RT real-time PCR. Human apoA-II transgenic mouse liver RNA and streptozotocin-induced diabetic rat liver RNA (n = 3), kindly given by I. Guillet-Denau (14), were analyzed by RT-real-time PCR (LightCycler System, Roche). Reverse transcription was performed with 1 μg RNA and Moloney murine leukemia virus reverse transcriptase (Gibco BRL). Human and rat apoA-II mRNA levels were determined with the SYBR Green I dye. We carried out 30 cycles of PCR in a SYBER Green buffer containing 3 mmol/l MgCl2, as follows: 10 s of denaturation at 95°C and 10 s of annealing at 55°C for human apoA-II or 65°C for rat apoA-II and 10 s of extension at 72°C. The mouse coding strand primer was 5′GGCACGAACCTGTCATC3′, and the mouse noncoding strand primer was 5′CTCTCCACACATCGCTCTT3′. The rat coding strand primer was 5′TTTACAGCTAGCTGGAATTT3′, and the rat noncoding strand primer was 5′CTTGTTTTCCTCGGGGCCATT3′. As an internal control, we determined levels of 18S RNA with the Ribosomal RNA control kit (18S RNA; Applied Biosystems). Rat hepatocyte primary culture. Hepatocytes were isolated from fed male Wistar rats as previously described (15). Cells were plated at a density of 8 million cells per 100-mm diameter tissue culture plate for RNA analysis and 1 million cells per 60-mm diameter tissue culture plate for transfection experiments and to adhere for 4 h. For RNA analysis, the medium was replaced with M199 medium (5.5 mmol/l glucose) or M199 medium supplemented with 20 mmol/l glucose (25.5 mmol/l total glucose). The cells were incubated for a further 24 h. Total RNA was extracted from hepatocytes in the appropriate amount of RNeasy plus solution (Appligene) according to the manufacturer's instructions. Rat hepatocyte RNA samples (15 μg) were analyzed by northern blotting, as previously described (8), and the membrane was hybridized with a rat apoA-II cDNA probe. An 18S probe was used as an internal standard. Autoradiographs were analyzed by densitometry, with densities expressed in arbitrary units. For transfection experiments, the medium was replaced with M199 medium. Then, 30 μg DOTAP liposomal transfection reagent (Boehringer Mannheim) and 5 μg plasmid DNA in 20 μmol/l Hepes, pH 7.4, were added to the medium for overnight transfection, according to the reagent manufacturer's instructions. After transfection, the medium was removed and replaced with M199 medium or M199 medium supplemented with 20 mmol/l glucose. The cells were then incubated for a further 48 h. Experiments were performed in triplicate and repeated three times.

HepG2 cell culture. Human hepatoma HepG2 cells were plated at a density of 0.4 million cells per well in 6-well tissue culture plate. The medium used was Dulbecco's modified Eagle's medium (DMEM)-glutamax, 1 g/l glucose (5.5 mmol/l) (Gibco) supplemented with 10% FCS and 1% penicillin/streptomycin, and the cells were allowed to adhere overnight. HepG2 cells were transfected by incubation for 24 h with 1 μg of plasmid DNA in opti-MEM medium supplemented with 20 μg of lipofectin reagent (Gibco BRL) according to manufacturer's instructions. After transfection, the medium was replaced with DMEM without sodium pyruvate and glucose, supplemented with glutamine, 1% FCS, 1% penicillin/streptomycin, and the indicated concentration of glucose, and the cells were incubated for a further 24 h. Experiments were performed in triplicate and repeated three to five times.

Chloramphenicol acetyl transferase assay. Transfected rat hepatocytes or HepG2 cells were recovered and chloramphenicol acetyl transferase (CAT) activity (as counts per minute) was measured in a liquid phase assay, as previously described (16). At days 22 and 37, individual liver samples (n = 8) from transgenic mice expressing the CAT gene under the control of the (−911/+29) human apoA-II promoter were homogenized and assayed for CAT activity. The proportion of chloramphenicol converted to acetylated was determined by thin layer chromatography (17).

Vectors and oligonucleotides. The plasmid containing the CAT gene under the control of the −911/+29 human apoA-II promoter (−911) and plasmids containing human apoA-II promoter constructs with deletions (−614, −440, −230, −80, and E-AB) have been described elsewhere (16,18,19). The plasmid encoding the dominant-negative form of IRS-4, CD1b, was kindly provided by Dr. M. Hadzopoulou-Cladaras (Department of Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece) and has been described elsewhere (20). The mutants were constructed by inverse PCR with the Quick Exchange Mutagenesis kit (Stratagene) and sequenced. The M1 mutant was constructed from the −911/+29 plasmid with the coding strand oligonucleotide 5′-GGTT ATCAGATGCACTGTCATC3′ and the complementary noncoding strand oligonucleotide. The M2 mutant was constructed from the LM2 plasmid (19) with the coding strand oligonucleotide 5′-AACATTGACTGATCGTCATCTGTT3′ and the complementary noncoding strand oligonucleotide. The M3 mutant has been described elsewhere (19). The M4 mutant was constructed from the KmLac2 plasmid (19), with the coding strand oligonucleotide 5′-CCA GGTTGTCTACAGACAGGCTGAGATACCTTTCA3′ and the complementary noncoding strand oligonucleotide.

Statistical analysis. Results were expressed as means ± SEM. The statistical significance of differences was determined by unpaired t tests after ANOVA, performed with Excel software. The statistical significance of the correlation between plasma human apoA-II concentration and blood glucose and that of the glucose tolerance test in transgenic mice was calculated by two-way ANOVA, carried out with Graph-Pad Prism software.

RESULTS

We investigated the response of apoA-II gene expression to changes in diet by performing in vivo analysis on transgenic mice expressing human apoA-II at physiological levels (line β) (9). A refeeding with a high-carbohydrate diet induced an increase in hepatic mRNA level and plasma concentration of human apoA-II, 2.5- and 1.5-fold, respectively (Fig. 1A). Hepatic mRNA levels of the endogenous mouse genes Glut-2 and 1-PK, which are known to be induced by carbohydrates, were increased by factors of 8 and 3.6, respectively, following refeeding (data not shown). Previous studies have reported that apoA-II gene expression is induced during weaning (21). Weaning is characterized by a switch from maternal milk to a high-carbohydrate diet. Moreover, in transgenic mice expressing the CAT reporter gene under the control of the human apoA-II (−911/+29) promoter, the CAT activity was stimulated three times at weaning (Fig. 1B). However, in streptozotocin-induced diabetic rats with hyperglycemia (14), rat apoA-II mRNA levels were not modified when compared with control rats (Fig. 1C).

Since in vivo studies do not allow the determination of the respective role of hormones and dietary substrates on apoA-II gene expression, we looked for a direct effect of glucose on apoA-II gene expression in primary rat hepatocytes. Rat apoA-II mRNA levels were twice as high in the presence of 25.5 mmol/l glucose than in the presence of 5.5 mmol/l glucose (Fig. 2A). This effect was not affected by insulin, as a similar doubling was observed in the absence of insulin and at all insulin concentrations tested. We transiently transfected rat hepatocytes with the CAT reporter gene under the control of the human (−911/+29)
apoA-II promoter, which is sufficient to restrict CAT expression to the liver in vivo (17). The CAT reporter gene activity was three times higher in the presence of 25.5 mmol/l glucose than in the presence of 5.5 mmol/l glucose (Fig. 2B). In HepG2 cells, the CAT activity displayed 2-, 1.3-, and 3.7-fold induction by 5 mmol/l glucose with respect to 10 mmol/l lactate/1 mmol/l pyruvate, 1 mmol/l glucose, and no glucose (0 mmol/l), respectively (Fig. 2C). Increasing the concentration of glucose up to 20 mmol/l did not increase the level of induction. As observed with rat hepatocytes, induction of the human apoA-II promoter by glucose in HepG2 cells did not depend on the presence of insulin in the medium (data not shown). Thus, glucose itself stimulates transcription of the apoA-II gene, in vitro, independently of insulin action.

To determine the region(s) of the apoA-II promoter responsible for the response to glucose, we transiently transfected HepG2 cells with the CAT reporter gene under the control of various fragments of the human apoA-II promoter. Deletion of the \((-911/-614)\) apoA-II enhancer abolished the response to glucose of the CAT reporter gene. When the \((-911/-614)\) apoA-II enhancer was fused to the proximal promoter \(-80/+29\) (E-AB), the CAT activity was induced twofold by glucose (Fig. 3B). Thus, the \((-911/-614)\) apoA-II enhancer is required for activation of the CAT reporter gene by glucose.

We then attempted to identify the glucose response element of the apoA-II enhancer. A glucose response element or carbohydrate response element (ChoRE) has been identified in several glucose-regulated genes; the ChoRE consists of two E-boxes (CANNTG) separated by five nucleotides (11). The human apoA-II enhancer contains multiple E-boxes, located between \(-797\) and \(-735\). Upstream stimulatory factor binding was impaired (data not shown), but these mutations did not abolish the induction by glucose of CAT reporter activity in transiently transfected HepG2 cells (Fig. 3C). Therefore, these multiple E-boxes, located between \(-797\) and \(-735\), did not behave as a ChoRE.

Optimization of the response of the L-PK gene to glucose stimulation is based on cooperation between the ChoRE and an HRE (22,23). The human apoA-II enhancer pos-

---

**FIG. 1.** In vivo regulation of apoA-II gene expression. A: Liver mRNA and plasma human apoA-II levels after refeeding with a high-carbohydrate diet in transgenic mice expressing human apoA-II (line \(\beta\)). B: Hepatic CAT activities from suckling (22d) and weaned (37d) transgenic mice expressing the CAT reporter gene under the control of the human \((-911/-29)\) apoA-II promoter. CAT activity was expressed as fold activation, with respect to CAT activity arbitrarily set at 1, at day 22. C: Hepatic rat apoA-II mRNA from streptozotocin (STZ)-induced diabetic rats. ***P < 0.001 and **P < 0.01 with respect to the fasted group in A and to the suckling group (day 22) in B.

**FIG. 2.** ApoA-II gene transcription is stimulated by glucose in vitro. A: ApoA-II mRNA level is induced by glucose in primary rat hepatocytes. The results are expressed as fold activation with respect to the value obtained in the presence of 5 mmol/l glucose arbitrarily set at 1. B and C: Transcription of the human apoA-II gene is induced by glucose. Rat hepatocytes (B) and HepG2 cells (C) were transiently transfected with the CAT reporter gene under the control of the human \((-911/-29)\) apoA-II promoter. CAT activity was expressed as fold activation with respect to CAT activity arbitrarily set at 1 in the presence of 5 mmol/l glucose. ***P < 0.001, **P < 0.01, and *P < 0.05 with respect to the results obtained with 5 mmol/l glucose.
FIG. 3. The HRE in the human apoA-II enhancer is responsible for the stimulation by glucose of apoA-II gene transcription. A: Schematic representation of the −797/−721 sequence of the apoA-II promoter. Mutations in the E-boxes and in the HRE are described. HepG2 cells were transiently transfected with the CAT reporter gene under the control of various deletions (B) or mutations (C) of the human (−911/+29) apoA-II promoter. B: The hatched line indicates that the various regions are fused. C: The mutated nature of the sequences are indicated by dashes. pBluescript SK (PSK) vector (from Stratagene) is an insert-less vector used as a negative external control, and the CAT activity ratio obtained with PSK transfection was arbitrarily set at 1. D: HepG2 cells were transiently transfected with the CAT reporter gene under the control of the human (−911/+29) apoA-II promoter in the presence of various amounts of plasmid encoding a dominant-negative form of HNF-4α, CD1b. Inhibition by CD1b was determined as the ratio of fold stimulation by glucose in the presence of CD1b to fold stimulation in the presence of the same amount of PSK. **P < 0.01 and ***P < 0.001, with respect to PSK in A and C and with respect to the absence of CD1b in D.
Transgenic mice overexpressing human apoA-II (line λ) display high plasma triglyceride and low HDL levels (8), a dyslipidemic profile similar to that observed in type 2 diabetes. However, glycemia had not yet been determined. To evaluate the pathophysiological relevance of our results, we therefore investigated the relationship between apoA-II gene expression and glucose in two lines of transgenic mice, line β, which produced human apoA-II at physiological concentration (9), and line λ, which produced three times the human apoA-II (8). Blood glucose was found to be strongly correlated ($R^2 = 0.588, P < 0.0001$) with the level of human apoA-II in transgenic mice of the β- and λ-lines (Fig. 4A). We investigated whether apoA-II was involved in blood glucose kinetics by carrying out a glucose tolerance test in these transgenic mice (Fig. 4B). Mice overproducing human apoA-II (line λ) displayed a marked delay in blood glucose clearance with respect to control mice (C57Bl/6J) and transgenic mice producing physiological levels of human apoA-II (line β).

**DISCUSSION**

In this study, we investigated the relationship between apoA-II and glucose levels. We found that glucose stimulated (in vitro) the hepatic transcription of the apoA-II gene. We also found that overexpression of the human apoA-II gene in transgenic mice was accompanied by a marked delay in glucose tolerance. These results are consistent with plasma concentrations of human apoA-II being positively correlated with glycemia in transgenic mice.

It has been shown that plasma apoA-II levels are controlled mainly by its rate of synthesis in the liver rather than its catabolism (25,26). Low plasma concentrations of apoA-II have recently been associated with a common polymorphism in the proximal promoter of the human apoA-II gene that leads to a decrease in apoA-II gene transcription (10). In the present study, we showed that the consumption of a high-carbohydrate diet activates the apoA-II gene transcription in vivo. By contrast, in streptozotocin-induced diabetic rats, the apoA-II mRNA levels remained unaffected despite hyperglycemia. This might be due to the effect of counter-regulatory hormones such as corticosteroids, which are elevated in streptozotocin-induced diabetic animals and are known to decrease apoA-II mRNA levels (27). However, in primary rat hepatocytes and HepG2 cells, glucose stimulated the apoA-II transcription independently of insulin action. The response to glucose required both the enhancer (−911−614) and the promoter (−80/29), a region that restricted the human apoA-II gene expression to liver cells (16–19,28). The glucose effect was prevented only when the HRE within the enhancer was mutated and when the active form of HNF-4α is inhibited. HNF-4α has not previously been directly involved in the glucose response but was considered to serve as an accessory factor (22,23). Specific inactivation of HNF-4α gene in the liver abolishes expression of the genes involved in the control of lipid metabolism, such as apoC-III, apoB, and apoA-II, and also inhibits microsomal triglyceride transfer protein (29). Moreover, in humans, mutations in the HNF-4α gene are responsible for type 1 maturity-onset diabetes of the young (MODY1). Significant alterations in triglyceride metabolism have been observed in MODY1 patients and are thought to result from impaired hepatic synthesis of apoA-II, apoB, and apoC-III (30,31). These data indicate that HNF-4α is a major in vivo regulator of genes involved in the control of lipid homeostasis, via the control of apo gene expression.
The modulation of HNF-4α activity by phosphorylation is well documented (32–36). In the fasting state, an increase in serine/threonine phosphorylation of hepatic HNF-4α decreases its DNA binding activity (32). Furthermore, after the consumption of a carbohydrate-rich diet, HNF-4α phosphorylation is decreased and HNF-4α promotes expression of the target genes. The kinases involved in these mechanisms are currently unknown. The AMP-activated protein kinase has been implicated in the inhibition of glucose-dependent gene expression (37) and has been shown to phosphorylate HNF-4 (38,39). Therefore, when glucose is abundant, the increase in binding of HNF-4α to the target gene may be mediated by inactivation of the phosphorylation of HNF-4α.

The overproduction of human apoA-II decreases plasma HDL concentration in a dose-dependent manner (8,40) and induces postprandial hypertriglyceridemia (8,9). This phenotype resembles the dyslipidemia observed in diabetes, suggesting that stimulation of the hepatic synthesis of apoA-II may contribute to the dyslipidemia syndrome that occurs in patients with type 2 diabetes. Several studies in humans have linked the apoA-II gene to type 2 diabetes (41–44). In our transgenic mice, there is a positive correlation between blood glucose and the plasma human apoA-II. A delay in glucose tolerance was impaired in the λ-line overproducing human apoA-II in accordance to the glucose intolerance observed in transgenic mice overproducing murine apoA-II (45). Conversely, apoA-II knockout mice display low plasma levels of free fatty acids, glucose, and insulin, suggesting hypersensitivity to insulin (46). Together with our results, this suggests that the overproduction of apoA-II may contribute to glucose intolerance and that plasma apoA-II levels may be involved in diabetes pathogenesis.

In conclusion, we show that human apoA-II gene transcription is induced by glucose in vitro, and that this regulation requires an HRE that interacts with HNF-4. Our results allow us to hypothesize a possible pathogenic pathway. An increasing apoA-II level causes hypertriglyceridemia and hypoHDLemia. The dyslipidemia results in glucose intolerance; this promotes a rise in blood glucose, which in turn might increase apoA-II gene transcription, thus establishing a vicious circle that may contribute to type 2 diabetes.

ACKNOWLEDGMENTS

This work was supported by INSERM and Pierre & Marie Curie University (PARIS VI, Paris, France). D.S. is supported by a fellowship from the Fondation Pour la Recherche Medicale.

We thank Nathalie Fournier (Service de Biochimie, Faculté de Pharmacie, Chatenay-Malabry, France) for plasma human apoA-II assays and Margarita Hadzopoulou-Cladaras (Department of Biology, Section of Genetics, Development and Molecular Biology, Aristotelian University of Thessaloniki, Thessaloniki, Greece) for providing the CD1b expression vector. We also thank Maryse Seau and Carole Lasne for technical assistance.

REFERENCES


23. Liu Z, Thompson KS, Towle HC: Carbohydrate regulation of the rat L-type
GLUCOSE CONTROLS APOA-II GENE EXPRESSION


30. Shih DQ, Dansky HM, Fleisher M, Assmann G, Fajas SS, Stoffel M: Genotype/phenotype relationships in HNF-4a/Mody1: haploinsufficiency is associated with reduced apolipoprotein (AII), apolipoprotein (CII), lipoprotein(a), and triglyceride levels. Diabetes 49:832–837, 2000


42. Castellani LW, Goto AM, Lusis AJ: Studies with apolipoprotein A-II transgenic mice indicate a role for HDLs in adiposity and insulin resistance. Proc Natl Acad Sci U S A 93:14788–14794, 1996