Nicotinic Acid Decreases Apolipoprotein B100-Containing Lipoprotein Levels by Reducing Hepatic Very Low Density Lipoprotein Secretion through a Possible Diacylglycerol Acyltransferase 2 Inhibition in Obese Dogs

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ABSTRACT

Apolipoprotein B100 (apoB100) is an essential component of very low density lipoprotein (VLDL) and low-density lipoprotein (LDL), both independent markers of cardiovascular risk. Nicotinic acid (NA) is an efficacious drug for decreasing VLDL and LDL, but the underlying mechanisms are unclear. For this purpose, six obese insulin-resistant dogs were given 350 mg/day of NA for 1 week and then 500 mg/day for 3 weeks. Turnover of apoB100-containing lipoproteins was investigated using stable isotope-labeled tracers. Multicompartmental modeling was used to derive kinetic parameters before and at the end of NA treatment. Hepatic diacylglycerol acyltransferase 2 (DGAT2), microsomal triglyceride transfer protein (MTP), hepatic lipase (HL), and adipose lipoprotein lipase (LPL) mRNA expression was also determined. NA treatment decreased plasma triglyceride (TG) \( p < 0.001 \), VLDL-TG \( p < 0.05 \), total cholesterol \( p < 0.0001 \), and LDL cholesterol \( p < 0.05 \), whereas plasma nonesterified fatty acids were unchanged. The decrease in VLDL-apoB100 concentration \( p < 0.001 \) was the result of a lower absolute production rate (APR) \( p < 0.001 \), despite a moderate decrease \( p < 0.05 \) in fractional catabolic rate (FCR). LDL-apoB100 concentration was reduced \( p < 0.05 \), an effect related to a decrease in LDL APR \( p < 0.05 \) and no change in FCR. NA treatment reduced DGAT2 expression \( p < 0.05 \), whereas MTP, HL, and LPL expression was unchanged. Our results suggest that NA treatment reduced VLDL and LDL concentration as a consequence of a decrease in VLDL production.

Metabolic syndrome is increasing worldwide (Bruce and Hanson, 2010), and the associated dyslipidemia is by far the strongest cardiovascular risk factor (Tenenbaum et al., 2006). The modified-release preparation of nicotinic acid (NA), which improves safety and reduces side effects compared with the crystalline form, was shown to decrease the progression of atherosclerosis (Taylor et al., 2004), notably by reducing plasma very low density lipoprotein (VLDL) and low-density lipoprotein (LDL) (Goldberg et al., 2000), and could therefore be an appropriate treatment for these metabolic syndrome patients. In humans, it has been reported that acute and chronic NA treatment decreases VLDL-triglyceride (TG) and LDL cholesterol (Kamanna and Kashyap, 2008). Because apolipoprotein B100 (apoB100) reflects directly the metabolism of VLDL and LDL, apoB100 labeling is used to assess the effect of drugs on VLDL and LDL (Duvilleard et al., 2000; Maugeais et al., 2001; Pont et al., 2002; Ouguerram et al., 2003; Lamon-Fava et al., 2008). Using in vivo kinetics methods in subjects with hyperlipidemia [high level of TG and LDL cholesterol, low high-density lipoprotein (HDL) cholesterol concentration], Lamon-Fava et al. (2008) have reported no change in VLDL production. In contrast, two studies in normolipidemic subjects (Wang et al., 2001) and in subjects with steatosis (Fabbri et al., 2010) have...
reported lower VLDL production. These few divergent results were not sufficient to establish a strong conclusion.

The mechanism by which NA lowers VLDL-TG concentrations has not been fully identified. Because NA inhibits the hormone-sensitive lipase (Gille et al., 2008), it was suggested that the reduction of nonesterified fatty acid (NEFA) flux from adipose tissue to liver secondary to this inhibition by NA would decrease hepatic VLDL-TG production. However, a rebound in NEFA plasma concentration 3 to 4 h after NA treatment has been described previously (Wang et al., 2000), and over the long term no change in NEFA plasma level has been shown (Vega et al., 2005), highlighting the existence of another target for NA. Another hypothesis from in vitro experiments has suggested that NA would directly decrease hepatic TG synthesis (Jin et al., 1999) through the inhibition of diacylglycerol acyltransferase 2 (DGAT2), a key enzyme in TG synthesis (Ganjii et al., 2004). Nevertheless, this inhibitory effect on TG synthesis and DGAT2 activity was observed with doses approximately 100-fold higher than plasma concentrations associated with maximal pharmacological effects of NA (Svedmyr et al., 1969).

To determine the effect of NA on the atherogenic apoB100-containing lipoprotein, as well as the underlying in vivo mechanisms, we have measured parameters of turnover of VLDL and LDL apoB100 using stable isotopes in obese and insulin-resistant (IR) dogs. We have also measured mRNA expression of genes implicated in the metabolism of apoB100-containing lipoproteins.

Materials and Methods

Animals and Treatment

Nine male beagle dogs [body weight (BW), 11.1 ± 0.8 kg; mean age, 1.8 ± 0.1 years] were overfed (1.6 times the National Research Council recommendation) during 60 weeks with a high-fat, high (ex­truded) commercial diet (Medium Junior; Royal Canin, Aimargues, France). At the end of the 60 weeks, insulin sensitivity was assessed in obese animals (BW, 16.8 ± 0.7 kg) to ensure that animals were IR (Serisier et al., 2008).

Six obese IR dogs (obese + NA group) were given 375 mg/day of extended-release NA (Niaspan; Abbott Laboratories, Abbott Park, IL) for 1 week (approximately 22.7 mg/kg/day) and then 500 mg/day for 3 weeks (approximately 30.3 mg/kg/day), which corresponds to a standard treatment in humans (approximately 2 g/day). Hepatotoxicity parameters (alanine aminotransferase and aspartate aminotransferase) have been measured and did not change between the beginning and the end of the treatment (data not shown). NA was administered orally each day before the meal. Three obese dogs did not receive NA treatment and served as a control group (obese group) to exclude drug-independent time effect. Experimental protocols adhered to European Union guidelines and were approved by the Animal Use and Care Advisory Committee of the University of Nantes.

Euglycemic Hyperinsulinemic Clamp. A 3-h euglycemic-hyperinsulinemic clamp was conducted in 24-h food-deprived dogs to determine in vivo insulin sensitivity, as described previously (Bailhache et al., 2003b). Only five obese + NA dogs were studied for insulin sensitivity measurement because of technical problems. In brief, human insulin (Actrapid; NovoNordisk, Bagsvaerd, Denmark) was infused (via a catheter placed in a cephalic vein) to induce hyperinsulinemia (4 nU/kg for 1 min and 2 nU/kg/min for the duration of the experiment). Glucose (Glucose 20%; Laboratoire Aguettant, Lyon, France) was clamped at basal levels by adjustment of the glucose infusion rate in the cephalic vein. Blood samples were drawn from a jugular catheter every 5 min from 0 to 60 min and every 10 min from 60 to 180 min. These samples were placed in ice-cold heparinized tubes and centrifuged at 4°C, 2724g for 10 min, and stored at −80°C for further insulin analysis. Insulin sensitivity index ([Ins]) was defined as the mean glucose infusion rate [mg/(kg·min)] divided by the mean plasma insulin concentration (μU/ml) of the last 60 min of the clamp (Radziuk, 2000). Rapid determination of blood glucose during clamping was achieved using the glucose oxidase method (Glucotrend Plus; Roche Diagnostics, Mannheim, Germany). Plasma insulin concentrations were measured using a commercial radioimmunoassay kit (RIA Insik-5; Diasorin, Saluglia, Italy).

Kinetic Studies

Experimental Protocol. Kinetic studies were performed as previously described (Bailhache et al., 2004; Ouguerram et al., 2004) using an 8-h constant infusion of [5,5,5-2H3]leucine, as labeled precursor of apoB100. All the dogs were in fasting state during all the experimental procedures. Approximately 1 h after drug administration, each animal received intravenously a primed constant tracer infusion [10 μmol/(kg·h)] for [5,5,5-2H3]leucine] and then 2 μmol/(kg·h) for 8 h. Venous blood samples were withdrawn in EDTA tubes (Venoject, Paris, France) at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 8.25, 9, 10, 24, and 26 h and were immediately centrifuged (at 4°C, 2124g for 10 min). Sodium azide (inhibitor of bacterial growth) and a protease inhibitor [4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride, Pefabloc; Interchim, Montluçon, France] were added to plasma samples that were stored at −80°C until further analysis.

Isolation of lipoproteins and measurement of leucine enrichment in apoB100 have previously been described (Bailhache et al., 2004). In brief, VLDL was prepared by standard ultracentrifugation methods at 40,000 rpm for 22 h at 4°C. LDL was precipitated from the infranatant by heparin manganese chloride. VLDL and LDL-apoB100 were then isolated by SDS-polyacrylamide gel electrophoresis. ApoB100 bands were dried under a vacuum and then hydrolyzed. The amino acids were purified by cation-exchange chromatography and then esterified and derivatized. Electron-impact gas chromatography/mass spectrometry was performed on a 5891A gas chromatograph connected with a 5971A quadrupole mass spectrometer (Hewlett Packard, Palo Alto, CA). The isotopic ratio was determined by selected ion monitoring at m/z of 282 and 285. Calculations of apoB100 kinetic parameters were based on the tracer/tracee mass ratio (Coelli et al., 1992).

Modeling. Tracer/tracee ratios of apoB100 leucine in VLDL were analyzed by multipartmental modeling. The SAAM II program (version 1.0.1; Resource Facility for Kinetic Analysis, Department of Bioengineering, SAAM Institute, Seattle, WA) was used to fit the model to the observed tracer data by a weighed least-squares approach to find the best fit as previously described (Maugeais et al., 2001; Bailhache et al., 2004) and to determine the parameters of the model. In brief, as described previously (Maugeais et al., 2001; Bailhache et al., 2004), such approach started with the simplest model based on minimal assumptions (i.e., apoB100 enters plasma through secretion of VLDL, which is then converted into LDL by triglyceride lipolysis, which would represent lipoprotein lipid activity). The complexity of the model was then progressively increased by including more known or credible physiological details until the optimal complexity was reached. As in most dogs, experimental data fit satisfactorily using the simplest two-compartment model (Fig. 1); it was not necessary to introduce more complexity as VLDL or LDL heterogeneity. Therefore, the used model, taking into account the absence of intermediate density lipoprotein in dogs (Bailhache et al., 2003a), corresponded to the typically known lipoprotein metabolism scheme, including liver secretion of apoB100 in VLDL followed by direct conversion to LDL, which is then removed from plasma by tissue-specific uptake. To better fit our experimental data, a credible physiological process was introduced corresponding to direct VLDL removal. Testing more complex models did not provide significant improvement in the fitting from F test and Akaike information.
Liver and adipose tissue biopsies were obtained under anesthesia after 24-h food deprivation both before and at the end of the 4-week treatment. Approximately 100 mg of tissue was cleaned in saline.

**Reverse Transcription and Real-Time Polymerase Chain Reaction**

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<tr>
<td>HL</td>
<td>5′-CTTGTGGAGTGGTCTGAGG-3′</td>
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<tr>
<td>LPL</td>
<td>5′-ACGTCAAGCTTGAGAACCAGC-3′</td>
</tr>
<tr>
<td>GAPDH</td>
<td>5′-CCACACATCTACGACGAGG-3′</td>
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TRizol reagent (Invitrogen, Carlsbad, CA) was added, and the tissue was immediately frozen in liquid nitrogen. RNA was extracted from frozen tissue using TRizol reagent according to the manufacturer’s instructions. Total RNA concentration was quantified by spectrophotometric absorbance at 260 nm.

**Statistical Analysis**

Data are expressed as mean ± S.E.M. The statistical analysis was performed by StatView 5.0 software (SAS Institute, Cary, NC) using the Wilcoxon test owing to the small size of our groups, which did not permit assurance of normal distribution of the data. A p value <0.05 was considered significant. The analyses of NEFA kinetics and plasma lipid parameters have been performed by an analysis of variance for repeated measures using a linear mixed-effects model (Splus software version 6.2; TIBCO Software Inc., Somerville, MA).

**Results**

**Insulin Sensitivity.** The overfeeding of the dogs led to an increase in BW (+45%) and to the establishment of IR, highlighted by the decrease in I_{15} (−69%) (data not shown). NA treatment decreased significantly the I_{15} by 36% (p < 0.05) (Table 2). I_{15} was unchanged in the obese group between weeks 0 and 4.

**Lipid Parameters.** Lipid parameter data are summarized in Table 2. Plasma TG was reduced by 31% with NA treatment (0.97 ± 0.02 mM; p < 0.001) as VLDL-TG (from 0.18 ± 0.09 mM; p = 0.02 mM; TC was also reduced by 27% (4.60 ± 0.19 to 3.38 ± 0.15 mM; p < 0.0001) as LDL cholesterol by 43% (0.46 ± 0.06 to 0.26 ± 0.05 mM; p < 0.05).

At basal state, related to fasting, plasma NEFA concentrations were increased slowly during the 26 h of the kinetic study (Fig. 2). In the obese + NA group, we observed a significant decrease in plasma NEFA levels during the 2 h after the drug administration. This decrease was followed by a significant increase (×2) in NEFA concentration between 2 and 3 h. Finally, NEFA concentration decreased slowly to return to a

**TABLE 1**

Sense/antisense primers used for DGAT2, MTP, HL, LPL, and glyceraldehydes 3-phosphate dehydrogenase (GAPDH) relative quantification

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normal level. Statistical analysis showed differences at 1, 2, 3, and 6 h ($p = 0.0004$, $p = 0.017$, $p < 0.0001$, and $p = 0.0098$, respectively). NA treatment had no effect on glycemia or insulinemia. All these parameters did not significantly change in the obese group between weeks 0 and 4.

### ApoB100 Kinetic Studies
ApoB100 concentrations and kinetic parameters are shown in Table 3. NA treatment decreased VLDL-apoB100 concentration ($0.0098 \pm 0.0013$ to $0.0057 \pm 0.0009$ mg/ml; $p < 0.001$) and LDL-apoB100 concentration ($0.080 \pm 0.011$ to $0.038 \pm 0.003$ mg/ml; $p < 0.05$).
VLDDL-apoB100 APR was lower at the end of the NA treatment (from 1.33 ± 0.24 to 0.59 ± 0.16 mg/kg/h; p < 0.001). The conversion rate of VLDDL to LDL, as well as the VLDDL direct removal rate, did not significantly change, but the overall VLDDL-apoB100 FCR significantly decreased (3.01 ± 0.41 to 2.16 ± 0.42/h⁻¹; p < 0.05). Finally, LDL-apoB100 was significantly decreased by NA treatment related to a significant decrease in LDL APR (0.49 ± 0.16 to 0.15 ± 0.03 mg/kg/h; p < 0.05), whereas LDL FCR did not change. All the kinetic parameters did not significantly change in the obese group between weeks 0 and 4.

**Gene Expression.** Compared with baseline, hepatic expression of DGAT2 was decreased approximately by 60 ± 8% (p < 0.05) (Fig. 3). The hepatic mRNA expression of MTP and HL was unchanged by the 4 weeks of NA treatment as LPL expression in adipose tissue. We did not observe any significant change in mRNA expression measurement in the obese group between weeks 0 and 4.

**Discussion**

In this study, NA treatment improves dyslipidemia in obese IR dogs by reducing plasma TG, TC, VLDDL-TG, LDL cholesterol, and apoB100-containing lipoprotein concentrations. These changes were essentially explained by a decrease in VLDDL production. The reduction of DGAT2 expression in liver could suggest a direct effect of NA on TG synthesis.

Dogs are known to show a large variability in plasma cholesterol and TG (Wolfgang et al., 1995; Bailhache et al., 2004). The three dogs enrolled in this study showed different lipid concentrations. Taking into account this small number of dogs, the statistical analysis with an analysis of variance for repeated measures, using a linear mixed-effects model, has shown no significant difference among them, and, moreover, no significant difference in all the studied parameters between the beginning and the end of study.

Kinetic parameters obtained in obese IR dogs before treatment are in the same range compared with that we have previously obtained in similar pathological conditions, taking into account large variability in this species (Briand et al., 2008). Given the animal size, the dog is well adapted to metabolic studies (i.e., kinetic studies and IR assessment). In fact, our previous studies (Bailhache et al., 2003a) have shown that obesity in dog yields IR and dyslipidemia characterized by an increase in plasma TG and VLDDL concentration and by a decrease in HDL cholesterol as in humans. Compared with these previous studies, we observed that NA improved dyslipidemia but was unable to completely normalize all the parameters.

In our study, we have shown a decrease in insulin sensitivity after 4 weeks of NA treatment. Data from several studies suggest that niacin-induced IR (increase in plasma glucose and insulin concentrations) dissipates by 16 weeks of therapy (Wang et al., 2000; Grundy et al., 2002; Vega et al., 2005), and further studies would be needed to confirm whether such inconvenience could be adequately controlled by adjusting the concomitant antidiabetic pharmacotherapy.

NA has been reported as a powerful lipid-lowering agent, which can lower TG, TC, and LDL cholesterol and increase HDL cholesterol in humans (Kabir et al., 2005), leading to a

**Fig. 3.** Relative expression of DGAT2, MTP, and HL mRNA in liver and LPL mRNA in adipose tissue before (week 0, in black) and after the 4 weeks of NA treatment (week 4, in white). Values are presented as the mean ± S.E.M. *p < 0.05 versus baseline.
significant reduction of cardiovascular risk (Taylor et al., 2004; Brown and Zhao, 2008). Doses used in this study are in the same range with those typically used in clinics [30 mg/(kg · day), approximately 2 g/day for a 70-kg human]. The effects of NA on lipid parameters observed were of the same order of magnitude as those previously described in humans (Meyers and Kashyap, 2004). These NA effects have been of the same range with those typically used in clinics [30 mg/kg · day], approximately 2 g/day for a 70-kg human]. The mechanism of NEFA rebound with NA remains unknown. It has been suggested that its magnitude depends on the decrease in NEFA (Blackard and Heidingsfelder, 1969). However, even if an implication of the parasympathetic system has been mentioned, literature did not provide any experimental data to support such hypotheses. Taking together, these observations emphasize that the reduction of the NEFA flux to the liver could not be the main explanation of the effect of NA on plasma TG. Consequently, NA should reduce TG by modulating other molecular target(s). Using pharmacological doses of NA, an inhibition of TG synthesis (Jin et al., 1999) related to an inhibition of DGAT2 activity (Ganji et al., 2004) has previously been shown on cultured cells. Moreover, a reduced VLDL-TG secretion has been recently shown in humans treated with NA (Fabbri et al., 2010). In the present study, we showed for the first time in vivo that, with a dose similar to human treatment, NA lowered the DGAT2 expression with no change in NEFA availability from adipose tissue. This inhibition could lead to a lowered TG synthesis and, therefore, to lower VLDL-apoB100 production as shown in vitro (Jin et al., 1999) and recently in humans (Fabbri et al., 2010). Moreover, the unchanged MTP expression confirmed that NA would directly act on TG synthesis rather than on VLDL assembly. Furthermore, inhibition of DGAT2 with antisense oligonucleotides has been shown to improve some components of metabolic syndrome such as IR, hepatic steatosis, or TG secretion (Choi et al., 2007). Even if we did not measure the protein activity or level, these findings support the interesting potency of DGAT2 inhibition for lowering triglyceridemia, but further studies would be needed to determine the actual implication of DGAT2. Because DGTA1, another isoform, has been shown as an effective target in hypertriglyceridemia (Zammit et al., 2008), we suppose that the synthesis of DGAT2 inhibitors derived from NA could be a useful research area to develop new additional drugs to treat hypertriglyceridemia and potentially other disturbances of metabolic syndrome.

Our kinetic data did not show any modification of the VLDL conversion rate that is in accordance with the expression measurement of LPL and HL. However, our data are inconsistent with those of Lamon-Fava et al. (2008), who showed a trend for an increase in VLDL catabolism without any change in production. The discrepancy with our results could be explained by differences in the characteristics of the studied dyslipidemia. In the study of Lamon-Fava et al. (2008), subjects had combined hyperlipidemia, whereas in our study, dogs were hypertriglyceridemic but normocholesterolemic. Another explanation is that our kinetic study was conducted in fasting state, whereas that of Lamon-Fava et al. (2008) was undertaken in feeding state, leading to higher triglyceridemia in their experiments that could have had an influence on apoB100 production and catabolism. Finally, the treatment drug was not taken at the same time that we administered NA, just before the previous evening in the study of the other study. The study design of Lamon-Fava et al. (2008) and ours was different, and the comparison of the results is questionable.

In the present study, we also observed a decrease in LDL-apoB100 level that was related to a reduced production. Because the VLDL conversion rate did not change significantly, the lower LDL production was explained by the decrease in VLDL concentration and then could be only a consequence of the decrease in VLDL production.

In conclusion, this study reports for the first time both the effect of NA in vivo on apoB100 containing lipoprotein metabolism and key gene expression. We showed that in fasting obese IR dogs, NA decreased plasma TG by reducing VLDL production in accordance with the reduction in DGAT2 expression. In this species, although characterized by a low level of LDL, NA decreases LDL level by reducing LDL production as a consequence of reduced VLDL production. The effect on NA on DGAT2 gene expression and hepatic VLDL production deserves further study.

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References


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