Regulatory Effects of Fenofibrate and Atorvastatin on Lipoprotein A-I and Lipoprotein A-I:A-II Kinetics in the Metabolic Syndrome

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OBJECTIVE — Subjects with the metabolic syndrome have reduced HDL cholesterol concentration and altered metabolism of high-density lipoprotein (Lp)A-I and LpA-I:A-II particles. In the metabolic syndrome, fenofibrate and atorvastatin may have differential effects on HDL particle kinetics.

RESEARCH DESIGN AND METHODS — Eleven men with metabolic syndrome were studied in a randomized, double-blind, crossover trial of 5-week intervention periods with placebo, fenofibrate (200 mg/day), and atorvastatin (40 mg/day). LpA-I and LpA-I:A-II kinetics were examined using stable isotopic techniques and compartmental modeling.

RESULTS — Compared with placebo, fenofibrate significantly increased the production of both LpA-I:A-II (30% increase; $P < 0.001$) and apoA-II (43% increase; $P < 0.001$), accounting for significant increases of their corresponding plasma concentrations (10 and 23% increases, respectively), but it did not alter LpA-I kinetics or concentration. Atorvastatin did not significantly alter HDL concentration or the kinetics of HDL particles.

CONCLUSIONS — In the metabolic syndrome, fenofibrate, but not atorvastatin, influences HDL metabolism by increasing the transport of LpA-I:A-II particles.

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Atherogenic dyslipidemia, reflected by elevated plasma triglyceride and reduced HDL cholesterol concentrations, is a cardinal feature of the metabolic syndrome (1). Recent findings from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrated that metabolic syndrome subjects with atherogenic dyslipidemia had the highest risk of cardiovascular disease (CVD) (2). Disturbed metabolism of high-density lipoprotein (Lp)A-I and LpA-I:A-II particles may partly account for the increased risk of CVD (3).

In a previous study of 11 metabolic syndrome subjects, we reported that fenofibrate, but not atorvastatin, had significant effects on HDL apolipoprotein (apo)A-I kinetics (4). Given the differential role of LpA-I and LpA-I:A-II in reverse cholesterol transport (5), it is important to elucidate the precise effects of these agents on HDL particle kinetics. Using stored samples (4), we extended this study by investigating the effects of these agents on LpA-I and LpA-I:A-II particle kinetics.

RESEARCH DESIGN AND METHODS

— Eleven nondiabetic men with metabolic syndrome entered a randomized, double-blind, placebo-controlled, crossover trial, in which they were randomized to a 5-week treatment period of either fenofibrate (200 mg/day), atorvastatin (40 mg/day), or placebo. A 2-week washout phase was included at the end of each treatment period. All subjects provided written consent as approved by the ethics committee of the South Eastern Sydney Area Health Service. This clinical protocol, including administration of [d_3]-leucine and blood sampling, has previously been described (4).

Measurement of isotopic enrichments and calculation of kinetic parameters

HDL–apoA-I and –apoA-II were isolated by ultracentrifugation and electrophoresis, delipidated, hydrolyzed, and derivatized as previously described (6). Isotopic enrichment was assessed using gas-chromatography mass spectrometry with selected ion monitoring of derivatized samples. The SAAM II program (SAAM Institute, Seattle, WA) was used to fit the model to the observed tracer-to-tracee ratio data. The fractional catabolic rates (FCRs) of apoA-I in LpA-I, LpA-I:A-II, apoA-I, and apoA-II were derived from the model parameters giving the best fit. The corresponding production rates were calculated as the product of FCR and pool size.

Plasma biochemistry

ApoA-I and apoA-II concentrations were determined by immunonephelometry (Dade Behring). ApoA-I concentration in LpA-I particles was measured by differential electroimmuoassay (Sebia, Moulineaux, France). ApoA-I concentration in LpA-I:A-II particles was calculated as total apoA-I − apoA-I in LpA-I. As previously described (4), plasma lipid and glucose

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concentrations were determined by enzymatic methods. Plasma insulin was measured by radioimmunoassay. Insulin resistance was estimated using the homeostasis model assessment score.

Statistical analyses

Data at the end of the three treatment periods were compared using a mixed-effects model (SAS Proc Mixed, SAS Institute). To adjust for multiple comparisons across the three treatment periods, we defined statistical significance at the 1.7% level.

RESULTS — The 11 subjects recruited were middle-aged, centrally obese, normotensive, dyslipidemic, and insulin resistant. Compared with normolipidemic lean subjects, metabolic syndrome subjects exhibited hypercatabolism of both LpA-I and LpA-I:A-II with overproduction of LpA-I (data not shown).

As previously reported (4), fenofibrate significantly decreased plasma concentrations of triglyceride and apoB; it also significantly increased plasma HDL, HDL_2, and HDL_3 cholesterol concentrations. Compared with placebo, atorvastatin significantly decreased total cholesterol, triglyceride, LDL cholesterol, and apoB concentrations. Homeostasis model assessment score did not change significantly on either treatment.

Table 1 gives the kinetic parameters for LpA-I, LpA-I:A-II, apoA-II, and apoA-I after intervention. Compared with placebo, fenofibrate significantly increased the production rates of LpA-I:A-II (by 30%; $P < 0.001$) and apoA-II (by 43%; $P < 0.001$). Furthermore, fenofibrate increased the FCR of LpA-I:A-II (and apoA-II) by 16% ($P = 0.015$) compared with placebo, accounting for the overall 10% ($P = 0.005$) increase in plasma HDL apoA-I FCR. Collectively, these kinetic effects accounted for the significant increase in concentration of LpA-I:A-II (10%), apoA-II (23%), and apoA-I (6%) on fenofibrate treatment. Compared with placebo, atorvastatin did not significantly alter the kinetics or concentrations of LpA-I, LpA-I:A-II, or apoA-II.

CONCLUSIONS — Our new findings show that in subjects with the metabolic syndrome, fenofibrate significantly increased the production of both LpA-I:A-II and apoA-II, accounting for the significant increase in their plasma concentrations. These effects were achieved with no significant alteration in

Table 1—*Kinetic parameters of LpA-I, LpA-I:A-II, apoA-II, and plasma apoA-I after treatment with fenofibrate, atorvastatin, or placebo*

				Group differences (*P*)		
	Fenofibrate	Atorvastatin	Placebo	Fenofibrate vs. placebo	Atorvastatin vs. placebo	Fenofibrate vs. atorvastatin
FCR (pools/day)						
LpA-I	0.54 ± 0.06	0.44 ± 0.07	0.44 ± 0.06	0.10 ± 0.08 (0.186)	0.01 ± 0.06 (0.825)	0.10 ± 0.06 (0.115)
LpA-I:A-II	0.29 ± 0.02	0.26 ± 0.03	0.25 ± 0.01	0.04 ± 0.01 (**0.015**)	0.01 ± 0.02 (0.699)	0.03 ± 0.03 (0.028)
ApoA-II	0.29 ± 0.02	0.26 ± 0.03	0.25 ± 0.01	0.04 ± 0.01 (**0.015**)	0.01 ± 0.02 (0.699)	0.03 ± 0.03 (0.028)
ApoA-I	0.33 ± 0.02	0.29 ± 0.03	0.29 ± 0.01	0.04 ± 0.02 (**0.005**)	0.01 ± 0.02 (0.948)	0.04 ± 0.02 (0.004)
Production rate ($mg \cdot kg^{-1} \cdot day^{-1}$)						
LpA-I	6.41 ± 0.62	5.50 ± 1.08	6.14 ± 1.16	0.27 ± 1.03 (0.725)	−0.64 ± 1.21 (0.589)	0.91 ± 0.83 (0.855)
LpA-I:A-II	11.90 ± 1.10	9.18 ± 0.76	9.18 ± 0.67	2.72 ± 0.63 (**<0.001**)	−0.01 ± 0.44 (0.799)	2.71 ± 0.90 (**<0.001**)
ApoA-II	4.88 ± 0.36	3.37 ± 0.29	3.41 ± 0.24	1.47 ± 0.24 (**<0.001**)	−0.03 ± 0.26 (0.885)	1.50 ± 0.41 (**<0.001**)
ApoA-I	17.88 ± 0.99	14.52 ± 1.08	14.41 ± 0.71	3.47 ± 1.02 (**0.002**)	0.11 ± 0.85 (0.540)	3.36 ± 1.24 (**<0.001**)
Plasma concentration (g/l)						
ApoA-I in LpA-I	0.28 ± 0.03	0.30 ± 0.05	0.30 ± 0.03	−0.01 ± 0.02 (0.584)	0.001 ± 0.03 (0.983)	−0.01 ± 0.03 (0.569)
ApoA-I in LpA-I:A-II	0.92 ± 0.06	0.82 ± 0.05	0.84 ± 0.05	0.08 ± 0.04 (**0.016**)	−0.01 ± 0.04 (0.352)	0.1 ± 0.04 (**0.002**)
ApoA-II	0.38 ± 0.02	0.29 ± 0.01	0.31 ± 0.01	0.07 ± 0.01 (**<0.001**)	−0.01 ± 0.01 (0.156)	0.08 ± 0.01 (**<0.001**)
ApoA-I	1.20 ± 0.06	1.11 ± 0.04	1.13 ± 0.05	0.07 ± 0.03 (**0.010**)	−0.01 ± 0.04 (0.597)	0.09 ± 0.03 (**0.003**)

Data are means ± SEM unless otherwise indicated. ApoA-I and apoA-II kinetics were determined from direct measurements of the corresponding tracer enrichment. The primary enrichment data for apoA-I and apoA-II were used to calculate LpA-I and LpA-I:A-II kinetic parameters. Values in bold are statistically significant.

insulin resistance or body weight. By contrast, atorvastatin had no significant effect on any parameters of HDL metabolism.

The fenofibrate data concur with previous reports showing that this agent increased the production of apoA-I in mixed hyperlipidemia and metabolic syndrome (7). We extend our previous study (4) by showing that the increased apoA-I production is restricted to apoA-I in LpA-I:A-II particles and is closely coupled with the increased production of apoA-II. This is consistent with the notion that the gene expression of both apoA-I and apoA-II is increased with this peroxisome proliferator–activated receptor-α agonist (8).

The lack of significant effect of atorvastatin on HDL apoA-I kinetics concurs with the findings of a previous study (9). We extend these findings to metabolic syndrome subjects and a wider range of HDL kinetic measurements including new data on apoA-II, LpA-I, and LpA-I:A-II. We do not confirm data showing that atorvastatin increases LpA-I and decreases LpA-I:A-II concentrations in patients with coronary heart disease (10). This may be due to metabolic differences in study populations and that the coronary heart disease patients studied were not obese or insulin resistant. It is noteworthy that rosuvastatin, a more potent HDL cholesterol–raising agent than atorvastatin, decreases LpA-I and LpA-I:A-II catabolism in subjects with the metabolic syndrome (11). A recent study by Verges et al. (12) also showed that rosuvastatin reduces HDL apoA-I catabolism in type 2 diabetes. The precise reason for the difference between atorvastatin and rosuvastatin remains unclear.

Our kinetic findings could be clinically important. Decreased plasma LpA-I:A-II concentration is a predictor of coronary events in population studies (3) and, in type 2 diabetes, is independently associated with angiographic coronary disease (13). In the FIELD trial, fenofibrate altered HDL composition and increased the plasma concentration of A-II and LpA-I:A-II (14). Our study suggests that this may be due to increased production of apoA-II and LpA-I:A-II particles. The complementary effects of fenofibrate and atorvastatin on lipoprotein metabolism, including disparate changes in apoB-100 kinetics (4) and, as we show here, in the kinetics of LpA-I and LpA-I:A-II particles, support the use of combination therapy to optimally regulate dyslipidemia in metabolic syndrome.

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