plaquettes. Cependant de fortes doses de DHA peuvent favoriser l'induction de la peroxydation lipidique due au fort degré d'insaturation de cet acide gras et masquer partiellement voire contrebalancer les effets bénéfiques.

Objectifs — Notre objectif a été de déterminer l'effet du DHA sur la fonction plaquettaire et sur le stress oxydant chez des volontaires sains lorsque cet acide gras est ingéré à doses croissantes (200, 400, 800 et 1600 mg par jour sous forme de triglycérides, chaque dose pendant deux semaines).

Méthodes — La composition en acides gras des lipides plasmatiques et plaquettaires avant et après supplémentation en DHA a été déterminée par chromatographie en phase gazeuse. Nous avons évalué l'évolution de la fonction plaquettaire en analysant l'agrégation plaquettaire induite par le collagène et en mesurant par ELISA la concentration basale de thromboxane B2 (TxB2), catabolite stable du thromboxane A2, puissant agent pro-agrégeant. Deux marqueurs du stress oxydant ont été quantifiés : la vitamine E par HPLC couplée à une détection fluorimétrique et la 8-iso-PGF2α par ELISA.

Résultats — Nous avons ainsi montré que dès la plus faible dose, le DHA s'incorpore dans les lipides plasmatiques et les phospholipides plaquettaires, puis ceci de manière dose dépendante. De plus l'activité plaquettaire est significativement réduite dès 400 mg de DHA/jour de supplémentation et la concentration basale de TxB2, diminue après 400 et 1600 mg/jour de supplémentation. Pour les marqueurs du stress oxydant, la concentration en vitamine E plaquettaire augmente uniquement après 200 mg/jour de DHA et les concentrations d'isoprostanes urinaires sont d'une part réduites à la plus faible dose et d'autre part augmentées après la plus forte dose de DHA.

Conclusion — L'ingestion par des volontaires sains de faibles doses de DHA (400 et 800 mg/jour) diminue la fonction plaquettaire et la plus faible dose (200 mg/jour) possède un effet antioxydant tandis que la plus forte induit un effet pro-oxydant.

B005
DIETARY-INDUCED INSULIN RESISTANCE ASSOCIATED WITH DYSLIPIDEMIA INDUCES PROGRESSIVE CARDIAC DYSFUNCTION IN RATS AS EVIDENCED BY ECHOCARDIOGRAPHY

S. GRAUZAM [1], M.-C. TOUFEKTSIAN [1], O. ORMEZZANO [2], M.-G. JOUAN [1], F. BOUCHER [1], T. SULPICE [3]
[1] *Laboratoire TIMC-PRETA, La Tronche, France*
[2] *Centre Hospitalier Universitaire, Grenoble, France*
[3] *Physiogenex SAS, Toulouse, France*

Background — A major complication of diabetes is the development of cardiac dysfunction in absence of vascular disease. Metabolic disorders such as insulin resistance (IR) and dyslipidemia (DL) might contribute to the induction of diabetic cardiomyopathy (DCM). However, few relevant animal models are currently available for studying the time-course of DCM and evaluating experimental therapeutics. We developed a rodent model of dietary-induced IR combined or not with DL in order to investigate the impact of chronic IR and DL on in vivo myocardial function.

Methods & Results — Male Sprague-Dawley rats were fed a western-type diet (65% fat; 15% fructose; WD: n=12). DL was induced by combining the western diet with i.p. injections of a nonionic surface-active agent (P-407; 0.2 mg/kg, 3 times/wk; WD-P407 n=9). A chow diet was used as control (Chow: n=9). At 6, 11 and 14 wks, cardiac function was assessed by echocardiography. After 6 wks, plasma insulin was significantly increased in both WD and WD-P407 groups ($P<0.05$ vs. Chow). Fasting blood glucose increased in WD group while plasma lipids markedly accumulated in WD-P407-treated rats ($P<0.05$ and $P<0.01$ vs. Chow, respectively). Pulse-wave Doppler indicated impaired diastolic function at 14 wks (E/A wave ratio: WD-P407: 1.42±0.06 vs. Chow: 1.65±0.11). M-mode imaging showed no significant differences in cardiac function and geometry under basal conditions. However, fractional shortening (FS) was significantly depressed under dobutamine stress in WD group at 14 wks (FS in% of baseline: 151±9% vs 196±7%; $P<0.05$) whereas systolic dysfunction appeared as early as 11 wks and worsened at 14 wks in WD-P407 animals ($P<0.05$ and $P<0.01$ vs. Chow, respectively). Finally, compared to Chow, myocardial lipid tissue content were significantly higher in WD and WD-P407 groups, the cardiac lipid accumulation being more pronounced in the later.

Conclusions — DL exacerbated cardiac lipotoxicity and functional complications associated with IR. This experimental model of combined IR and DL closely mimics the main clinical manifestations of DCM and might therefore constitute a useful tool for the evaluation of pharmacological treatments.

B006
EFFECTS OF LOSARTAN IN AN EXPERIMENTAL MODEL OF METABOLIC SYNDROME

L. FELLMANN [1], P. BOUSQUET [1]
[1] *Laboratoire de Neurobiologie et Pharmacologie Cardiovasculaire, Inserm U715, Strasbourg, France*

Introduction — A large body of experimental and clinical evidence indicates that some AT1 receptor antagonists may have beneficial metabolic effects in addition to their well-known cardiovascular actions. Whether or not these metabolic effects are related to additional PPARγ agonist activity of some AT1 antagonists is still under debate. Therefore, the aim of the present study was to check the cardiovascular and metabolic effects of losartan lacking any PPAR agonist activity in a suitable experimental model of metabolic syndrome, namely SHHF rats (Spontaneously Hypertensive, Heart Failure). These rats exhibit obesity, hypertension, dyslipidemia and glucose intolerance. They lack leptin receptors. WKY and SH rats were considered as control of SHHF rats.

Methods — Losartan was delivered in the drinking water (10 mg/kg/day during 3 months) to 12-week-old male rats. Cardiovascular and metabolic parameters were measured at the end of the treatment and compared to those of untreated SHHF rats at the same age. Intravenous glucose tolerance tests (IVGTT) were also performed. Total cholesterol, LDL, HDL, triglycerides and glucose were measured on plasma samples (0,5 ml) taken from caudal veins. Blood pressure was measured (right femoral artery) under pentobarbital anaesthesia (60 mg/kg, ip).

	Untreated SHHF (n=10)	Losartan treated SHHF (n=10)
Mean blood pressure (mmHg)	176 ± 6	102 ± 4.3 *
Body weight (g)	587.3 ± 8.9	584 ± 10.9
Glucose (mmol/l)	8.04 ± 0.4	10.35 ± 0.74 *
Cholesterol (mmol/l)	3.844 ± 0.2	3.96 ± 0.16
HDL (mmol/l)	2.335 ± 0.12	2.38 ± 0.13
LDL (mmol/l)	0.629 ± 0.024	0.59 ± 0.044
Triglycerides (mmol/l)	5.589 ± 0.2	6.74 ± 0.37 *
Free fatty acids (mmol/l)	0.942 ± 0.03	1.5 ± 0.075 *