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Adiponectin negatively correlated with carotid arterial structure in the leptin-resistant Zucker diabetic fatty rat

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Zucker diabetic fatty rats

Abstract *Background:* Despite adipocytokines are implicated in arterial hemodynamic and stiffness, their effects on arterial histomorphometry remain poorly explored. The aim of the present study was to evaluate, in Zucker Diabetic Fatty (ZDF) rats, a model of type 2 diabetes with leptin resistance, carotid arterial structural changes and their determinants, with special focus on adiponectin and leptin.
Methods: Proximal aortic blood pressure (BP) was measured in conscious ZDF rats ($n = 6–8$) and their Lean controls ($n = 6–8$) at 6, 12 and 24 weeks. The contralateral carotid was harvested and fixed at the mean BP for histomorphometric quantification.
Results: Mean BP was similar in both strains and increased with age ($p < 0.001$). Medial thickness, luminal cross-sectional area (LCSA), medial cross-sectional area (MCSA) and wall stress (WS) increased with age ($p < 0.001$). LCSA and WS were higher in Lean than in ZDF rats ($p < 0.001$ for both). Leptin levels were higher in ZDF than in Lean rats ($p < 0.001$) but remained unchanged during development in ZDF rats. Adiponectin levels decreased with age in ZDF rats ($p < 0.001$) but remained unchanged in Lean rats. In all rats, adiponectin negatively correlated with medial thickness ($r = -0.50$, $p < 0.01$), LCSA ($r = -0.64$, $p < 0.001$), MCSA ($r = -0.59$, $p < 0.001$) and WS ($r = -0.43$, $p < 0.05$). These correlations were significant ($p < 0.001$) in ZDF rats considered separately ($r = -0.73$, $r = -0.87$, $r = -0.83$ and $r = -0.79$, respectively) but not in Lean rats; independently of mean BP and age after stepwise regression analyses.

Abbreviations: BP, blood pressure; Di, mean internal diameter; EP, external perimeter; h, medial thickness; IMT, intima-media thickness; IP, internal perimeter; LCSA, luminal cross-sectional area; MBP, mean BP; MCSA, medial cross sectional area; R/h, radius/medial thickness ratio; WS, wall stress; ZDF, Zucker Diabetic Fatty.

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Conclusion: These associations suggest a protective role for adiponectin against arterial wall thickening and wall stress. However for causal relation, further investigation is needed.

Introduction

Type 2 diabetes is associated with a high cardiovascular morbidity and mortality related to accelerated atherosclerosis. Several factors contribute to the increase of cardiovascular events, including long-term hyperglycemia, insulin resistance, dyslipidemia, hypertension, changes in clotting factors, vago-sympathetic imbalance and arterial wall structure.[1–3]

The role of adipocytokines has been extensively highlighted in the recent years.[4–7] In particular, leptin level is increased in type 2 diabetic patients, with a relative leptin resistance in this population.[4] Inversely, decreased levels of adiponectin have been shown in insulin resistance states.[2,5] Both leptin and adiponectin are likely to play a role in arterial hemodynamics.[2,4,8] Arterial stiffness and high leptin levels predict cardiovascular events.[4,7,9–12]

However the relationships between arterial structure and adipocytokines are poorly known. Matsuda *et al*. have demonstrated that adiponectin-deficient mice showed severe neointimal thickening in mechanically injured arteries, whereas adenovirus-mediated supplement of adiponectin attenuated neointimal proliferation.[13] In humans, adiponectin but not leptin levels have been shown to be negatively associated with intima-media thickness (IMT) in middle-aged healthy white subjects, in type 2 diabetes and in 64 year-old women whatever their glycemic status.[14–16] In another report, the negative association between IMT and adiponectin observed in men disappeared after adjustment for HbA1c and insulin resistance index.[17] Störk *et al*. have recently shown in post-menopausal non-diabetic women that low levels of adiponectin were associated with adverse changes in morphology and function of central arteries over a 12-month period, independently of other cardiovascular risk factors[18] No association was observed for leptin,[18] and some authors suggest to consider leptin/adiponectin ratio as a better atherosclerotic marker.[19] Furthermore, low adiponectin levels have been associated with increased plaque volume, lipid-rich plaque and pathological intimal thickening.[20,21]

To our knowledge the putative association between adipocytokines and arterial wall structure has never been studied in animals. Zucker Diabetic Fatty (ZDF) rats develop with time obesity, insulin resistance, diabetes and dyslipidemia, with controversial data regarding arterial blood pressure (BP).[22] In addition, ZDF rats are leptin-resistant because of homozygous mutation of the leptin receptor and are therefore of interest to explore the role of adipocytokines, especially adiponectin, in arterial structural changes.

The aim of the present study was then to evaluate, during development in ZDF rats, carotid wall structural changes, and to explore their determinants, with a special focus on adiponectin and leptin.

Methods

Animals

Male ZDF rats (Gmi-*fa*/*fa*, $n = 22$) and their age-matched male controls (Lean (*?/fa)*; $n = 20$) were obtained from Charles River France (L'Arbresle, France) at 5 or 6 weeks of age and were acclimatized for at least one week before the experiments. The animals were maintained at 22–24 °C with light on from 0600 to 1800. They were fed A04 (UAR) with tap water *ad libitum*. The study was performed at the 6th, 12th, and 24th week of age, after an overnight fasting. The protocol was approved by the Animal Ethic Committee of Institut National de la Santé et de la Recherche Médicale, Paris, France. The investigation conforms with *the Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996).

Blood pressure recording

The technique for BP measurement in rats has been recently described in details.[23] Briefly, the rats were anaesthetized with pentobarbital sodium (60 mg/kg, ip). A polyethylene catheter, filled with heparinised 0.9% NaCl (50 U/ml), was inserted into the descending aorta, through the right common carotid artery, to measure proximal (central) aortic BP. The catheter was tunneled subcutaneously under the skin of the back to exit between the scapulae and was plugged with a short piece of stainless steel wire. The rats were allowed to recover during 24 h in individual cages. Then, in unanesthetised unrestrained rats, the catheter was connected to a signal processor (MacLab 8, AD Instruments, Oxfordshire, UK) via a pressure transducer (BP-T, EMKA Technologies, Paris, France). Aortic BP signals were recorded during at least 1 h on-line at a sampling rate of 1000 points/sec (Chart version 5.2, AD Instruments) and stored on a microcomputer (PowerMac 4400/200, Apple). Further, a stationary 60 s recording, selected at the end of the recording was analyzed beat-to-beat by means of Chart version 5.2 software. This software automatically detected the minimal value of proximal BP (diastolic BP), maximal value of proximal BP (systolic BP) and calculated mean BP (MBP) and heart rate (HR).

Biochemical assays

Blood samples were taken just after BP recording and before the rats were euthanized. Plasma glucose was analyzed using the Infinity glucose test (Thermotrace, Melbourne, Australia). Plasma insulin concentration was assayed with an ELISA kit (ELIT) obtained from Eurobio (Les Ulis, France). Serum triglycerides and total cholesterol