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INFLUENCE OF INSULIN RESISTANCE ON HYPERTENSION IN DIABETICS

Laure d'Estève-Bonetti, Jacques Amar, Hélène Hanaire-Broutin, Thierry Brillac, Catherine Calazel-Fournier, Gisèle Hernandez, Michel Salvador, Bernard Chamontin. [1]Internal Medicine, Hôpital Purpan, Toulouse, Hte Garonne, France, [2]Diabetology, Hôpital Rangueil, Toulouse, Hte Garonne, France

Multiple lines of evidence link high blood pressure and insulin resistance. However the influence of insulin resistance on hypertension in type 2 diabetics remains to be assessed to compare insulin resistance in hypertensive and normotensive patients with type 2 diabetes

The study group concerned 41 patients recruited in an outpatient clinic. 23 patients with BP>130/85 mmHg were identified as mild hypertensive (20 from 23 under treatment). Insulin sensitivity was assessed with the use of the euglycemic insulin-clamp technique and biologic parameters such as lipids, PAI-1, insulin and proinsulin. An ambulatory blood pressure monitoring was performed in all patients.

No significant difference was observed in age, body mass index, waist circumference, and insulin sensitivity.

	hypertensives	normotensives	p
Age	53,91 ± 1,43	52,33 ± 1,55	NS
BMI (kg/m2)	30.57 ± 1,03	28,69 ± 1,07	NS
waist circumference	106.22 ± 2,57	101,82 ± 2,53	NS
24h SBP (mmHg)	129,1 ± 2,96	121,86 ± 2,8	0.099
24h DBP (mmHg)	80,56 ± 1,55	76,64 ± 1,61	0.098
Triglycerides (g/l)	1,62 ± 0,14	1,63 ± 0,21	NS
PAI-1 (UI/ml)	26,27 ± 1,97	28,5 ± 2,4	NS
insulin (mUI/l)	25,62 ± 18.83	22,63 ± 14,66	NS
proinsulin (pmol/l)	29,62 ± 26,61	32,69 ± 18,5	NS
Clamp Rc (mg/kg/mn)	5,43 ± 0,78	6,32 ± 0,5	NS

In this selected population of type 2 diabetics, insulin resistance was not significantly different between hypertensives and normotensives ; it is suggested that normotensive and mild hypertensive type 2 diabetics may present a similar degree of insulin resistance.

Key Words: Insulin resistance, Type 2 diabetes, Hypertension

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OBESITY REGULATES RENAL ENDOTHELIN AND ENDOTHELIN ET_A RECEPTOR EXPRESSION IN VIVO. DIFFERENTIAL EFFECTS OF CHRONIC ET_A RECEPTOR BLOCKADE

Jian Zhang, Livius V. d'Uscio, Sidney Shaw, Klaus Münter, Michael Klainguti, Matthias Barton. [1]Department of Medicine, University Hospital Zurich, Zurich, Switzerland, [2]Anaesthesia Research, Mayo Clinic, Rochester, MI, United States, [3]Clinical Research, University of Berne, Berne, Switzerland, [4]Cardiovascular Research, Knoll AG, Ludwigshafen, Germany

ET_A receptors have been implicated in obesity-associated hypertension (*Hypertension* 1999; 33: 1169). We characterized the renal endothelin system in diet-induced obesity and determined the effects of chronic treatment with the ET_A antagonist darusentan. C57BL/6J mice were fed a standard diet (control) or a high-fat diet (Harlan TD88137) with or without darusentan (50 mg/kg/d, 30 wk). Total RNA was extracted from whole kidneys and mRNA expression of preproendothelin-1 (ppET-1), ET_A receptors, and β-actin were determined by RT-PCR using mouse-specific primers. PCR-products were normalized vs. β-actin or 18S rRNA. Renal ET-1 protein was measured by RIA/HPLC. High fat diet increased body weight by 257% compared to 54% (control diet). Darusentan had no effect on body weight in obese mice (263%) and treatments had no effect on systolic blood pressure. Obesity was associated with upregulation of renal ET_A receptors (144±5% vs 100±7%, $p<0.05$ vs. control) and to a lesser extent, preproendothelin-1 (113±5% vs.100±2%, $p<0.05$ vs. control). In obese mice chronic darusentan treatment in part prevented the ET_A receptor upregulation (126% vs. 144±5%, $p<0.05$) but had no significant effect on ppET-1 mRNA expression (101±9 vs. 100±2%, n.s.). Renal ET-1 protein increased in obese animals (from 190±18 to 267±19 pg/g tissue, $p<0.05$ vs. control). This increase was not affected by concomitant darusentan treatment (n.s.).

These data for the first time demonstrate that obesity in normotensive rats is associated with upregulation of renal ET_A receptor expression suggesting that body weight *per se* affects ET receptor expression in the kidney. Our data further indicate that in this model ET_A receptors control expression of the ET_A receptor but not the ppET-1 gene, suggesting autocrine regulation *in vivo*. These mechanisms might contribute to the pathogenesis of obesity-associated diseases affecting the kidney and/or blood pressure.

Key Words: obesity, hypertension, kidney

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EFFECT OF ORLISTAT IN PATIENTS WITH HYPERTENSION AND EITHER HIGH OR NORMAL FASTING INSULIN LEVELS

Gerald M. Reaven, Karen R. Segal, Jonathan Hauptman, Mark N. Boldrin, Charles P. Lucas. [1]Medical Department, Roche Laboratories, Nutley, NJ, United States

All 214 subjects with elevated blood pressure (BP)(≥140/≥90 mmHg) were selected from the total pool of overweight or obese individuals who completed one year of treatment consisting of diet + placebo (P) or diet + orlistat (O). Compared to subjects with normal fasting insulin levels (<90 pm/L), hypertensive subjects with high fasting insulin levels (≥90 pm/L) had significantly higher ($p<0.05$) initial values for body weight, fasting glucose, LDL-cholesterol (LDL-C), LDL/HDL-C, triglycerides and systolic BP plus lower levels of HDL-C.

After 1 year, no significant differences were observed between O and P in normal insulin subjects for changes in blood pressure, glucose, insulin or lipids despite greater weight loss with O vs P (-10.3±1.0% vs -6.4 ± 0.9%, $p=0.0028$). In high insulin subjects, the following changes were significantly greater for O than P: body weight (-9.3 ± 0.7% vs -5.2 ± 0.6%, $p=0.0001$), systolic BP (-17.6 ± 1.7 vs -12.6 ± 1.8 mmHg, $p=0.035$), diastolic BP (-10.6 ± 1.1 vs -8.5 ± 1.2 mmHg, $p=0.022$), insulin (-39 ± 5.8 vs -25 ± 7.5 pm/L, $p=0.013$), LDL-C (-0.49 ± 0.09 vs -0.18 ± 0.08 mm/L, $p=0.035$), or LDL/HDL-C (-0.44 ± 0.09 vs -0.09 ± 0.09, $p=0.044$).

In conclusion, CV risk factors are more likely to be abnormal in high insulin hypertension, and orlistat was more effective than placebo in improving these risk factors.

Consultant: Roche Labs

Key Words: Insulin, Obesity, Cholesterol

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CARDIOVASCULAR EVENTS AND ABNORMALITIES OF GLUCOSE METABOLISM IN PATIENTS WITH HYPERTENSIVE NEPHROSCLEROSIS AND REDUCED CREATININE CLEARANCE

Laura Zingaro, Cristiana Catena, Daniele Casaccio, Sergio De Marchi, Leonardo A. Sechi. [1]Internal Medicine, DPMSC, University of Udine, Udine, Italy

Abnormalities of glucose metabolism and hyperinsulinemia have been demonstrated in patients with end-stage renal disease and may contribute to the development of atherosclerotic complications in these patients. This study was performed in hypertensive patients with mild to moderate impairment of renal function to investigate at what stage of renal failure abnormalities of glucose metabolism develop and whether these abnormalities are associated with increased prevalence of cardiovascular events. In 321 untreated essential hypertensive patients recruited at a hypertension clinic and 92 matched normotensive controls we assessed the renal function by measurement of 24-hour creatinine clearance, urinary protein excretion,