hypertensive rats and human hypertensives (Lu et al., 2005; 2006). In this study, we investigate whether TRPC3 up-regulation in aorta from SHR is associated with angiotensin II receptor (AT1R) mediated calcium influx. 

**Methods:** Blood pressure was measured using tail-cuff plethysmography and a pressure transducer. Vasoinnervation of aortic rings was measured by organ chamber. Aortic smooth muscle cells (VSMCs) were cultured. Cytosolic calcium concentration was measured by the fluorescence technique. TRPC3 and AT1R expressions were detected by western blotting. **Results:** TRPC3 expression was significantly increased in aorta form SHR compared to WKY (1.48 ± 0.05 vs. 1.00 ± 0.06, p < 0.01). AT1R expression was no significantly different in aorta from SHR compared to WKY (p > 0.05). Administration of Ang II significantly increased TRPC3 expression in VSMCs from SHR compared to SHR control conditions (p < 0.05). Administration of telmisartan, an AT1R blocker, significantly down regulated TRPC3 expression in cultured VSMCs (p < 0.05). Immunofluorescence showed that TRPC3 and AT1R coexisted in cultured VSMC. Ang II significantly increased mean arterial blood pressure in SHR compared to WKY (53 ± 3 vs. 22 ± 4 mmHg, p < 0.01). Ang-II-induced vasoinnervation was significantly higher in aortic rings from SHR compared to WKY (82 ± 3% vs. 54 ± 6%, p < 0.01). After administration of telmisartan (5mg/kg/day) in SHR for 4 weeks systolic blood pressure was significantly reduced from 202 ± 20 mmHg to 124 ± 18 mmHg (n = 6, p < 0.01). Upregulation of TRPC3 by overexpressing TRPC3 gene in the cultured VSMCs significantly increased TRPC3 expression (p < 0.01), and Ang-II-induced calcium influx was significantly increased to 155 ± 12% (n = 6; p < 0.01). After siRNA against TRPC3 significantly reduced TRPC3 expression by 30 ± 5% in the cultured VSMCs and Ang II-induced calcium influx was accompanied reduced (p < 0.05). **Conclusion:** This study for the first time highlights the importance of AT1R mediated calcium influx through TRPC3 channel in genetic hypertension (supported by 973 program 2006CB503804).

**Effects of Recombinant Human Brain Natriuretic Peptide on a Porcine Model of Acute Pulmonary Hypertension**

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**OBJECTIVES:** The effects of brain natriuretic peptide (BNP) on the pulmonary hypertensive remains unknown. The aim of the present study was to evaluate the effects of recombinant human BNP (rHBNP) on pulmonary and systemic haemodynamics in a porcine model of thromboxane A2-induced acute pulmonary hypertension. **METHODS:** Acute pulmonary hypertension was induced with a continuous infusion of the thromboxane analogue, U46619. Fifteen adult swine were randomized into two groups. Group 1 (n = 8) received an intravenous bolus rHBNP at 0.3 mg/kg/min, followed by an infusion at a rate of 0.15 mg/kg/min, and group 2 (n = 7) received a saline solution instead of rHBNP. **RESULTS:** Acute pulmonary hypertension was achieved in all animals. The administration of rHBNP reversed pulmonary hypertension, with a significant decrease in mean pulmonary artery pressure and pulmonary vascular resistance, a moderate decrease in systemic arterial pressure and a concomitant increase in cardiac index, but no marked changes in heart output. **CONCLUSIONS:** The administration of rHBNP is associated with predominant pulmonary vasodilatation with moderate systemic vasodilatation in this porcine model of acute pulmonary hypertension. This study was supported by Natural Science Foundation of China (No. 30602242 and 30670860).

**HMG-CoA Reductase Inhibitor Ameliorates Aortic Stiffness in Spontaneously Hypertensive Rats**

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Systemic hypertension is associated with elevated cardiovascular morbidity and mortality and is at least partly due to large artery stiffening. Cholesterol-lowering therapy has been efficacious in reducing arterial stiffness in patients with hypercholesterolemia, and thus may be beneficial in systemic hypertension. The present study was to examine whether HMG CoA reductase inhibitor plays a role in the regulation of vascular stiffness. Pulse wave velocity (PWV) was determined as the time delay between the foot of pressure waves recorded simultaneously at the aortic arch and abdominal aorta (just above the bifurcation) in anesthetized Spontaneous Hypertensive Rats (SHR). Eight-week-old SHRs were given standard chow or chow containing rosvastatin at a dose of 10 mg/kg for 8 weeks: an untreated control group (CON, n = 12), and an Ang-II reductase inhibitor, rosvastatin (ROS, n = 12). PWV was measured at the same blood pressure (BP) level as in the control group, and the level of collagen content and advanced glycation end products (AGE) was measured in aortic wall. PWV was improved after treatment (CON vs. ROS: 1073.65 ± 251.3 mm/sec vs. 874.24 ± 159.3mm/sec, p < 0.05). Aortic stiffness blood pressure was not changed after rosvastatin treatment (180.17 ± 189.02 mm Hg, p = ns), as were mean (151.3 ± 16 vs. 156.1 ± 24 mm Hg, p = ns), diastolic blood pressures (137.0 ± 16 vs. 139.6 ± 17 mm Hg, p = ns) and pulse pressure (42.9 ± 8 vs. 49.4 ± 13 mm Hg, p = ns). Hydroxyproline content was significantly reduced by treatment (CON vs. ROS: 14.8 ± 5mg/g vs. 10.4 ± 3.2%, p < 0.05), whereas AGE content was not changed (315.89 ± 907.6U/mg vs. 291.20 ± 881.6U/mg). This study demonstrates that rosvastatin reduces collagen content in the aortic wall and is also associated with a concomitant reduction in aortic PWV. This suggests that HMG CoA reductase inhibitor has effect modifying arterial stiffness and improves vascular function in hypertension.

**Arterial and Venous Endothelin-1 Content in Humans: Interactions with Other Predictors of Hypertension**

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**Introduction:** Local production of endothelin-1 (ET-1) by vascular endothelial cells may contribute to hypertension development by causing vascular constriction or hypotropy. Most studies have shown, however, that arterial content of ET-1 is not higher in patients with mild to moderate essential hypertension. Nevertheless, such measures are possibly confounded by concomitant factors of hyperphosphorylation of ET-2 diabetes, and other factors on ET-1 content. In addition, ET-1 is a potent vasoconstrictor, but relatively few studies report venous ET-1 content. **Hypothesis:** We tested the hypothesis that arterial or venous ET-1 content can predict hypertension when adjusted for these confounding variables. **Methods:** We determined ET-1 content in internal mammary artery and saphenous veins of 57 subjects, who underwent coronary artery bypass graft surgery for atherosclerotic disease. A chemiluminescent ELISA was used to measure ET-1 content. Other patient data was obtained from medical records and patient interviews. Univariate comparisons, correlation analyses and logistic regression modeling were used to analyze the data. **Results:** No statistically significant differences in arterial or venous ET-1 content were found when comparing patients according to blood pressure, age, sex, smoking, lipids, fasting glucose levels, or type II diabetes status. Also no differences were found in patients taking statins, ACE inhibitors, or beta-blockers. Arterial ET-1 content did not predict hypertension when added to any logistic regression model; but the data revealed a strong correlation between arterial ET-1 content and plasma triglyceride levels. The only logistic model that strongly predicted (p = 0.0038) hypertension included sex and venous ET-1 content as predictor variables. **Conclusions:** Two important conclusions are drawn from these results. First, in confirmation of earlier work, arterial ET-1 content is not higher in hypertension, but such measures may be confounded by an influence of plasma triglycerides on arterial ET-1. Second, venous ET-1 may have a larger effect on hypertension development than previously appreciated.

**Regulation of Blood Pressure by Prostaglandin F2a Receptor Gene (FP)**

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Aspirin reduces renin and blood pressure in renovascular hypertension and there is a rebound rise in renin after reversible inhibition of cyclooxygenases by salicylates in humans. It has been assumed that these effects reflect modulation of prostanlucylin (PGI2) a potent renin secretagogue. However, recent development of novel methodology indicates that prostaglandin (PG) F2a is a far more abundant prostaglandin in urine of mice and humans and little is known of its cardiovascular function. Intravenous PGF2a results in a dose dependent elevation of blood pressure in wild type mice. This response is lost in mice lacking the F prostastin (FP) receptor, while the hypertensive response to angiotensin II is augmented, consistent with increased expression of AT1a and AT1b receptors in large arteries. Deletion of the FP reduces blood pressure betrays artherosclerosis in hypervascular mice and also reduces blood pressure in normolipidemic mice on either a chow or a high fat diet. Curiously, expression of the FP, while evident in arterioles and the renal collecting ducts, is not detectable in the heart or large arteries. Deletion of the FP decreases neuronal nitric oxide synthase, angiotensin and aldosterone under basal conditions and following salt depletion. These findings demonstrate that PGF2a plays a critical role in maintenance of blood pressure homeostasis by regulating the renin-angiotensin system in the kidney of mice. Antagonism / deletion of the I prostastin receptor (IP) which accelerates atherosclerosis. Pharmacological blockade of the FP may represent a novel therapeutic strategy in syndromes of renin dependent hypertension with a more cardioprotective profile than suppressing synthesis or disrupting activation of the IP by PG2.
In the western society one major risk factor associated with aging are vascular diseases. The risk of heart attack and coronary diseases increases with aging. Therefore, it is important to understand aging on a cellular level. One factor of cell aging is the shortening of telomeres, the oxidative stress induced nuclear export of TERT was completely abolished. Taken in these embryonic fibroblasts deficient in the Src kinase family members Src, Fyn and Yes. In these nuclear TERT protein and activity already under basal conditions. For identification of the protein levels and activity. Nuclear Shp-2 associated with TERT and overexpression of Shp-2 localization of Shp-2 is necessary. Thus, we first demonstrated that endogenous Shp-2 was activity of the Src kinase family. For inhibiting the nuclear export of TERT the nuclear one potential “inhibitor” is the tyrosine phosphatase Shp-2, which can reduce the shortening of H2O2-induced wildtype H2O2-induced nuclear export of TERT. This inhibition was dependent on Src-2phosphatase activity, since a dominant negative Src-2 mutant (Shp-244S) reduced nuclear TERT protein and activity already under basal conditions. For identification of the member of the Src kinase family, which is responsible for the export of TERT, we used mouse embryonic fibroblasts deficient in the Src kinase family members Src, Fyn and Yes. In these cells the oxidative stress-induced nuclear export of TERT was completely abolished. Taken together, these data demonstrate for the first time that a function for nuclear Src-2 exists in inhibiting nuclear export of TERT. Thus, increasing the amount of nuclear Src-2 may a useful therapeutic to delay/inhibit vascular aging processes.

The Role of Nr2 and Unfolded Protein Response in the Induction of Antioxidant Enzymes by Oxidized Phospholipids

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Besides their well-characterized proinflammatory and proatherogenic effects, oxidized phospholipids (oxPLs), such as oxPAPC (oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-phosphocholine) have been shown to have beneficial responses in vascular cells via induction of antioxidant enzymes such as heme oxygenase-1 (HO-1). We therefore hypothesized that oxPAPC could evoke a general cytoprotective response via activation of antioxidative transcription factor Nr2. Here we show that oxPAPC increases nuclear accumulation of Nr2. Using the siRNA approach, we demonstrate that Nr2 is critical in mediating the induction of glutamate-cysteine ligase modifier subunit (GCLM) and NADPH quinone oxidoreductase-1 (NQO1) by oxPAPC in human endothelial cells, whereas the contribution to the induction of HO-1 was less significant. The induction of GCLM and NQO1 was attenuated by reduction of endothelial cells oxidative stress induced Src kinase family-dependent tyrosine phosphorylation of TERT, which resulted in nuclear export of TERT and reduction of nuclear TERT activity. This led to accelerated senescence and enhanced apoptosis sensitivity of endothelial cells. Therefore, the aim of this study was to investigate the mechanism inhibiting nuclear export of TERT. One potential “inhibitor” is the tyrosine phosphatase Src-2, which can reduce the activity of the Src kinase family for inhibiting the nuclear export of TERT the nuclear localization of Src-2 is necessary. Thus, we first demonstrated that endogenous Src-2 was located in the nucleus and in the cytoplasm. Next, we observed that oxidative stress reduced Src-2 protein levels and activity. Nuclear Src-2 associated with TERT and overexpression of Src-2 wildtype inhibited H2O2-induced nuclear export of TERT. This inhibition was dependent on Src-2phosphatase activity, since a dominant negative Src-2 mutant (Shp-244S) reduced nuclear TERT protein and activity already under basal conditions. For identification of the member of the Src kinase family, which is responsible for the export of TERT, we used mouse embryonic fibroblasts deficient in the Src kinase family members Src, Fyn and Yes. In these cells the oxidative stress-induced nuclear export of TERT was completely abolished. Taken together, these data demonstrate for the first time that a function for nuclear Src-2 exists in inhibiting nuclear export of TERT. Thus, increasing the amount of nuclear Src-2 may a useful therapeutic to delay/inhibit vascular aging processes.

Inhibition of PPAR-γ Agonists on TNF-α-Induced Oxidative Stress in Human Aortic Smooth Muscle Cells by PPAR-γ-Derpendent Mechanism

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have shown that PPAR-γ agonists reduce the progression of atherosclerotic lesions by direct anti-atherogenic and anti-inflammatory actions with PPAR-γ dependent or independent mechanisms. Oxidative stress and reactive oxygen species (ROS) are key mediators of cardiovascular diseases including atherosclerosis. NADPH oxidase is a predominant source of ROS and activation of this enzyme leads to intracellular signaling events causing endothelial dysfunction. We aimed to investigate the inhibition of PPAR-γ agonists rosiglitazone (Rz2) and 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2) on TNF-α-induced oxidative stress in human aortic smooth muscle cells (ASMC) by PPAR-γ dependent mechanism. METHODS: ASMC were treated with TNF-α (10ng/ml) for 12h and superoxide production was examined by lucigenin-enhanced chemiluminescence assay. ASMC was pre-treated with Rz2 (5μM) or 15d-PGJ2 (10μM) for 12h prior to treatment of selective PPARγ antagonist GW9662 (10μM) and treated with TNF-α (10ng/ml) for 12h. DMSO (0.1%) was used as vehicle control. Real time RT-PCR analysis was performed to determine the NADPH oxidase subunits Nox4 gene expression level. RESULTS: Superoxide production was detected in ASMC after treatment with TNF-α through upregulation of Nox4 (p<0.05). Both Rz2 and 15d-PGJ2 significantly inhibited TNF-α-induced superoxide production and this effect was reversed by selective PPARγ antagonist GW9662 (n=4, P<0.05). Rz2 significantly inhibited TNF-α-induced Nox4 gene up-regulation by nearly 50% whilst 15d-PGJ2 showed significant inhibition of more than 80%. The inhibitory effect of Rz2 and 15d-PGJ2 was reversed by GW9662. (n=4, P<0.05). CONCLUSIONS: We demonstrated that TNF-α stress elicits elevated ASMC superoxide and that TNF-α induced superoxide production is mediated by Nox4. Our data reveals that, for the first time, both synthetic PPAR-γ agonist Rz2 and endogenous PPAR-γ agonist 15d-PGJ2 inhibit TNF-α induced Nox4 mediated-oxidative stress in ASMC by PPAR-γ dependent mechanism.