Conclusions: CD163 works as a hemoglobin scavenger and a cytokine-like anti-inflammatory factor. HO1 cleaves heme to biliverdin (subsequently converted to a potent tissue antioxidant, bilirubin), CO and free iron, all of which have complex effects on platelet aggregation, vascular smooth muscle cell relaxation and apoptosis, neutralization of ROS and fatty acid oxidation. Over-expression in the symptomatic CPs and distinct localization to active areas of atherosclerotic process suggest that CD163 and HO1 may have a role in the pro-symptomatic transformation of carotid plaques.

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Aβ-Induced Endonuclease G Translocation and Smac Release via Inhibition of Akt /Bad Activity in Cerebrovascular Endothelial Cells.

Kejie Yin, Jin-Moo Lee, Hong Chen, Jan Xu, Chung Y Hsu; Washington Univ Sch of Med, Saint Louis, MO

Amyloid beta (Aβ) 1–40 or 25–35 has been implicated in vascular degeneration in patients with Alzheimer's disease (AD) and cerebral amyloid angiopathy. Increasing evidence suggests that cerebrovascular endothelial cells (CECs) die by apoptosis after exposure to Aβ; however, little is know about the underlying mechanism. The signaling kinase, Akt/PKB, has been reported to play an important role in cell survival pathways by interfering with several pro-apoptotic signals. In this study, we sought to explore whether Aβ-induced release of apoptotic regulators from the mitochondria was regulated by the Akt pathway, and to examine potential mediators of this activity in CECs. Aβ (25 μM) induced the release of two mitochondrial intermembrane proteins: Endonuclease G (Endo G), an apoptotic effector enzyme responsible for DNA cleavage, and Smac, another pro-apoptotic mediator. Aβ decreased phosphorylation of Akt at Ser 473 and Thr 308 early after exposure, but had no effect on general Akt levels until 24 h later. Aβ also increased levels of mitochondrial Bad, the BH3-only pro-apoptotic BCl-2 family member, while decreasing cellular content of phospho-Bad, suggesting translocation from cytoplasm to mitochondria. In addition, we identified Bcl-xL as a protein that coimmunoprecipitated with Bad, suggesting a physical interaction between these two pro-apoptotic mediators, in the release of mitochondrial intermembranous proteins. Wortmannin, a PI_3/Akt inhibitor, promoted Bad translocation to mitochondria and release of Endo G and Smac after Aβ exposure. Upregulation of Akt, by employing TAT-fusion protein or infecting CECs with a retroviral vector over-expressing Akt, effectively inhibited Bad translocation to mitochondria and the release apoptotic mediators from mitochondria. Furthermore, these manuevers exerted a cytoprotective effect on Aβ-treated CECs. Bad knockdown using an RNA interference strategy suppressed Aβ-induced activation of Bad, and reduced Endo G and Smac release from mitochondria, as well as CEC death. These results suggest that Aβ-induced CEC death may involve the release of pro-apoptotic mediators from the mitochondria via the inhibition of Akt-mediated phosphorylation of Bad and subsequent translocation to the mitochondria.

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Endothelial Progenitor Cells Are Resistant to Cytotoxic Effect of Tumor Necrosis Factor (TNF-α): Role of Manganese Superoxide Dismutase.

Tongrong He, Timothy E Peterson, Mayo Clinic, Rochester, MN; Larry W Oberley, Univ of Iowa, Iowa City, IA; Noel M Caplice, Zvonimir S Katusic; Mayo Clinic, Rochester, MN

Circulating EPCs play an important role in repair of injured vascular endothelium and neovascularization. Oxidative stress is a key mechanism responsible for endothelial dysfunction and progression of vascular disease. We hypothesized that EPCs might be resistant to oxidative stress due to their high antioxidant capacity. Outgrowth colonies of EPCs isolated from human blood were cultured and expanded (passage 4–7 were used). Cobblestone appearance, incorporation of acetylated LDL and isolectin, as well as expression of vWF, Flk-1 and eNOS indicated endothelial phenotype. FACS analysis showed that more than 98% of EPCs were positive for CD31 and CD144. Basal levels of MnSOD protein expression and enzymatic activity were about 3-fold higher in EPCs as compared to (HUVECs; Table). In contrast, no difference was detected in expression and enzymatic activity of CuZnSOD or catalase (n=3). Incubation with increasing concentrations of TNF-α (0.01, 0.1 and 0.5 ng/ml) for 24 h significantly increased expression of MnSOD in EPCs. Induction of MnSOD by TNF-α was significantly higher in EPCs as compared to HUVECs (Table). TNF-α did not affect expression of CuZnSOD or catalase. EPCs were resistant to cytotoxic effect of TNF-α (0.1 ng/ml, for 72 h). Survival rate was 77±0.1% (n=3) for EPCs, but only 43±0.1% (n=3; P<0.05) for HUVECs. These results suggest that increase in MnSOD is an important mechanism underlying resistance of EPCs to oxidative stress, which may contribute to the therapeutic effects of EPCs. Table: Protein levels of MnSOD Data are mean ± SD (n = 3), expressed as ratio to HUVECs control. * P<0.05 vs.

TNF-α (ng/ml)	0	0.01	0.1	0.5
EPCs	3.5 ± 0.2*	4.3 ± 0.2‡	6.0 ± 0.7‡	6.6 ± 1.0‡
HUVECs	1.0 ± 0†	1.3 ± 0.1	2.1 ± 0.8	3.3 ± 1.2

HUVECs control and EPCs with 0.1 ng/ml TNF-α; P<0.001 vs. EPCs with 0.5 ng/ml TNF-α. ‡ P<0.001 vs. HUVECs with the same dose of TNF-α. † P<0.05 vs. HUVECs with 0.5 ng/ml TNF-α.

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Plasma Adrenomedullin Level Is Predicted by Carotid Atherosclerosis in Patients with Chronic Atherothrombotic Ischemic Stroke.

Camelia R Ban, Naohisa Hosomi, Kagawa Med Univ, Kagawa, Japan; Hideo Ohyama, Osaka Neurosurgical Hosp, Kagawa, Japan; Tsutomu Takahashi, Masakazu Kohno; Kagawa Med Univ, Kagawa, Japan

Background and Purpose: Ischemic cerebrovascular disease was described to induce both adrenomedullin mRNA and peptide in ischemic cortical neurons. We hypothesized that plasma adrenomedullin level may show a different pattern in patients with chronic atherothrombotic ischemic stroke when compare to non cerebrovascular patients, and this pattern may be predicted by certain factors. Methods: We studied 61 patients with chronic atherothrombotic ischemic stroke and 50 patients without any cerebrovascular disease. Intima-media thickness and vascular lumen diameters were evaluated by carotid ultrasonography. Plasma mature-adrenomedullin was determined by radioimmunoassay. Results: Plasma mature-adrenomedullin in the patients with chronic atherothrombotic ischemic stroke (2.01 ± 0.58 fmol/ml) was significantly higher than that in the patients without any cerebrovascular disease (1.24 ± 0.18 fmol/ml, p < 0.001). With single regression analysis, plasma mature-adrenomedullin concentration exhibited significant associations with age, systolic blood pressure, pulse pressure, left ventricle ejection fraction and ultrasonographic variables for carotid atherosclerosis. With multiple regression analysis, plasma mature-adrenomedullin was found to be predicted by right and left internal carotid artery-intima-media thickness, left ventricular ejection fraction, and a history of atherothrombotic ischemic stroke ($F_{17,93} = 23.7$, $r = 0.901$, $p < 0.001$, $n = 111$). Controlling for these other variables, the right and left internal carotid artery-intima-media thickness increased plasma mature-adrenomedullin by 0.104 ± 0.039 and 0.094 ± 0.036 fmol/ml/mm, respectively. Plasma mature-adrenomedullin concentration was significantly higher in patients with echolucent intima-media complex (plaque) (n = 16) than that in patients with homogeneous (n = 77) or calcified (n = 18) intima-media complex (plaque) (p < 0.001). Conclusion: Plasma mature-adrenomedullin showed significantly positive associations with carotid atherosclerosis and atherothrombotic ischemic stroke, independent of systolic blood pressure.

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Thomas Willis's Understanding of Cerebrovascular Disorders.

Andrew Williams; Child Development Cntr, Northampton, United Kingdom

Thomas Willis (1621–75) is recognised as the founder of clinical neuroscience. He was an eminent seventeenth century physician, Fellow of the Royal Society and Sedleian Professor of Natural Philosophy at Oxford University. He conceived the word "neurology" and although immortalised by the arterial anastamosis at the base of the brain, his contributions to neuroscience were far wider and equally fundamental. He wrote widely and his published works with their careful observations, clinical history and post mortem findings are increasingly recognised as an invaluable primary source of seventeenth century medicine. Although cerebrovascular disease is not a seventeenth century concept, in his published works Willis gave many descriptions in both adults and childhood. Willis largely placed these in his chapters on Palsy and on Apoplexy and Headache. Willis also supported his clinical studies in this area with elegant dye studies of the carotid circulation, assisted by Sir Christopher Wren amongst others. This paper examines Willis' descriptions and enquiry of cerebrovascular physiology and pathology and are taken from the 1681 reprint of his Cerebri Anatome (1664) and from the posthumous "The London Practice of Physick" published in 1685.

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Cerebral Nitric Oxide—Mediated Vasodilatation Is Impaired in Diabetics.

Fozia Nazir, Manal Alem, Matt Walters, Steven Cleland, Kennedy Lees; Glasgow Univ, Glasgow, United Kingdom

Background Diabetes is a major risk factor for stroke, however the mechanisms which impart the excess risk are unclear. Endothelial dysfunction (ED) is an important early marker of vascular disease which has been demonstrated in the coronary and peripheral vasculature of diabetic patients, however the effect of diabetes on cerebrovascular endothelium has not been examined. We sought to investigate the effect of diabetes on cerebrovascular endothelial function as assessed by vasoconstrictor response to the nitric oxide synthase inhibitor L-NMMA. Methods Fifteen type II diabetics and fifteen age and BMI matched controls were recruited. All participants were taking no vasoactive medication and free from clinical vascular disease. Each received a single 15 minute systemic infusion of L-NMMA (0.8μmol/kg/min). Cerebral blood flow (CBF) was assessed by colour Doppler imaging of the internal carotid artery (ICA) at 5 minute intervals during and for 40 minutes after the infusion. Middle cerebral artery velocity (MCAv) was assessed by transtemporal Doppler ultrasound at the same timepoints. Results There was no significant difference in mean age or BMI between groups. L-NMMA produced a mean reduction in ICA flow AUC in the control group of 13.8% compared with a 2.1% reduction in the diabetic group (p<0.01). There was no significant change in MCAv following L-NMMA in either group. MABP rose 6.4+/- 4.2mmHg in the control group vs. 8.8+/-3.5mmHg in the diabetic group (p=NS). No adverse events or symptoms were reported. Conclusion Basal nitric oxide mediated vasodilatation is impaired in the cerebral circulation of diabetics. This observation is consistent with the elevated cerebrovascular risk reported in this population, and may have implications for risk stratification and primary prevention of stroke.

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Isolated Thrombotic Affections of Cortical Veins and Their Clinical Significance.

Angel Mironov; Dept of Neuroradiology, Kantonsspital Aarau, Aarau, Switzerland

Purpose. Intracranial venous occlusive disease, for the greater part, is equated with occlusion of the dural sinuses. Generally we know very little about the occlusion of deep and cortical veins in the absence of sinus occlusion. The imaging characteristic of non-inflammatory thrombosis limited to cortical or small draining veins and its sequelae is not familiar in practice. We tried to identify the imaging characteristic and its clinical relation in patients with acute stroke as consequence of isolated affections of cortical or small veins in 60 consecutive cases. **Materials & Methods.** From 750 patients undergoing stroke selection 65 cases were considered as non-arterial diseases and prospectively studied: They had experienced sensomotor symptoms from different severity. Each case underwent CT, MRI and catheter angiography studies. The angiographic studies were performed with preferences especially for detailed analyses of the venous angiomorphology, including proper oblique views. **Results**.