IN VIVO CHRONIC INHIBITION OF NAD(P)H OXIDASE REDUCES CEREBROVASCULAR FIBRONECTIN EXPRESSION IN STROKE-PRONE RENOVASCULAR HYPERTENSIVE RATS
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NAD(P)H oxidase is a major source of vascular superoxide (O$_2^-$) production in hypertension. The present study tested the hypothesis that in vivo chronic inhibition of NAD(P)H oxidase reduces cerebrovascular fibronectin expression in stroke-prone renovascular hypertensive rats (SP-RHR).

mRNA and protein expressions of cerebrovascular NAD(P)H oxidase subunit p22phox were determined by RT-PCR. Western blot and immunohistochemistry in SP-RHR and Sprague Dawley (SD) control rats, respectively. Cerebrovascular fibronectin protein was measured by Western blot.

P22phox immunopositive reactivity was localized in cerebral vasculature of SD and SP-RHR. No significant difference was detected in the expression of mRNA and protein of p22phox between SP-RHR (4 or 8 wks post-operations) and SD rats. However, cerebrovascular fibronectin levels in SP-RHR were significantly higher compared to SD rats 8 wks post-operation (1.29±0.10, n=6, vs. 1.15±0.04 in SD, n=5, p<0.05). Furthermore, chronic treatment of SP-RHR with the selective NAD(P)H oxidase inhibitor apocynin for 4 wks in drinking water (1.5 mmol/L, 5 wks post-operation) resulted in significantly decreased p22phox protein expression (0.85±0.035 vs. 0.93±0.03 in non-treated SP-RHR, n=5, p<0.05) with a concomitant reduction of fibronectin levels in cerebral vasculature (1.31±0.11 vs. 1.56±0.07 in non-treated SP-RHR, n=5, p<0.05).

These findings indicate that chronic inhibition of NAD(P)H oxidase in vivo by apocynin reduces cerebrovascular fibronectin levels and may lessen cerebrovascular fibrosis in SP-RHR.

Key Words: Hypertension, NAD(P)H Oxidase, Stroke

URIC ACID AS A PROGNOSTIC RISK FACTOR IN PATIENTS WITH ACUTE STROKE
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The purpose of this study was to analyze the risk factors for stroke in the Greek population and to estimate the clinical outcome and the fatality rate during hospitalization. All patients admitted in our department between January 2003 and January 2004 with acute stroke were studied. At baseline, the presence of conventional vascular risk factors and concomitant vascular diseases was identified. A total of 142 patients with stroke, aged 76.5±8.4 years, 83 (58.5%) men, were studied. One hundred twenty one (85.2%) of the patients had an ischemic stroke, 11 (7.7%) intracerebral hemorrhage (ICH), and 10 (7%) a transient ischemic attack (TIA). The most prevalent vascular risk factor was hypertension (74.8%), followed by smoking (32.8%). A significant proportion of the study population (46.4%) had experienced another stroke in the past, and 31.4% suffered from ischemic heart disease. Patients with ICH had significantly higher systolic BP at admission compared to both patients with ischemic stroke or TIA (p<0.05 for both comparisons). Patients with TIA had significantly lower total cholesterol compared to patients with ICH (p<0.05). There were no other differences in the prevalence of concomitant vascular diseases, or in clinical and laboratory findings between groups of stroke subtypes. Median duration of hospitalization was 6 days (range 1 to 25 days). Duration of hospitalization was significantly longer for patients with ICH compared to patients with both ischemic stroke and TIA (p<0.01 for both comparisons). Overall fatality rate during hospitalization was 5.6%; case fatality rate for ischemic stroke was 5.8% and for ICH, 9.1%. Death occurred after a median of 7 days (range 2 to 25 days) after admission. Uric acid and creatinine at admission were significantly higher in patients who died (p<0.001 and p=0.01, respectively). No other of the studied parameters was predictive of the occurrence of death. In conclusion, our results foster the concept of stroke as a polyetiologic disease with significant differences between subtypes. Therefore, treatment and secondary prevention should be tailored to stroke etiology and individual risk factors. Serum uric acid emerges as a prognostic risk factor for poor outcome in stroke patients.

Key Words: Hypertension, Stroke, Uric Acid

EXP-2528, A NOVEL ANGIOTENSIN II TYPE 1 RECEPTOR ANTAGONIST, PROTECTS THE BRAIN AFTER TRANSIENT FOCAL ISCHEMIA
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Purpose: There is increasing data showing that angiotensin (Ang) II, the major effector of the renin-angiotensin system may be involve in the initiation and regulation of processes occurring in brain ischemia mainly through stimulation of AT$_1$ receptors. This raises the possibility that selective AT$_1$ antagonists may contribute to prevention and treatment of brain ischemia. The objective of this study is to investigate the protective effect of EXP-2528, A Novel AT$_1$ receptor antagonist, on focal brain ischemia injury in rats.
Methods: Experiment was carried out in the normotensive male Wistar Rats. Focal cerebral ischemia was induced by the middle cerebral artery occlusion of (MCAO) lasting for 2 hours followed by reperfusion. The selective AT1 antagonists losartan (5mg/kg 1-d-1), EXP-2528 (2.5mg/kg 1-d-1 or 5mg/kg 1-d-1), was infused intragastrostically over a 14-day period before the induction of ischemia. 24 hours after reperfusion, We evaluated neurological deficit score, measured the infarct volume by triphenyltetrazolium chloride (TTC) staining, after reperfusion, We evaluated neurological deficit score, measured the infarct volume by triphenyltetrazolium chloride (TTC) staining, determined the plasma Ang II and endothelin-1 concentration by radioimmunoassay.

Results: Treatment of rats with losartan or different doses of EXP-2528 all had a significantly better neurologic score than the control rats 24 hours after ischemia. The improved neurobehavior was related to a reduction in infarct volume. The plasma Ang II and endothelin-1 level increased markedly after focal cerebral ischemia-reperfusion for 24 hours, treatment with losartan or different doses of EXP-2528 decreased the endothelin-1 level, but increased Ang II level compared with normal saline treated group. There were no difference in groups treated with losartan or different doses of EXP-2528.

Conclusions: The present report shows that pretreatment with novel AT1 receptor antagonist EXP-2528, the same as losartan, efficiently reduces brain injury after focal cerebral ischemia followed by reperfusion in rats.

Key Words: Angiotensin II, AT1 Receptor Antagonist, Cerebral Ischemia/Reperfusion Injury

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EXP-2528, A NOVEL ANGIOTENSINII TYPE 1 RECEPTOR ANTAGONIST, PROTECTS CEREBRAL MICROVASCULAR ENDOTHELIAL CELLS AGAINST ANGIOTENSIN II INJURY BY ANTIOXIDANT ROLE
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Purpose: Angiotensin (Ang) II, the main effector of the renin-angiotensin system (RAS) importantly contributes to the pathology of cerebrovascular disease partly by injuring the cerebrovascular endothelial cells. The aim of this study was to investigate the protective effects of EXP-2528, a novel Ang II type 1 receptor (AT1) antagonist, on cultured rat brain derived microvascular endothelial cells (BMECs) injured by AngII and investigate the possible mechanism.

Methods and Results: Ang II increased lactate dehydrogenase leakage and inhibited the viability of BMECs time-dependently. Incubation with Ang II decreased the activity of intracellular glutathione peroxidase and superoxide dismutase, increased the intracellular Malondialdehyde (MDA) content and decreased MDA in the extracellular medium significantly. Pretreatment with the AT1-specific antagonist losartan or EXP-2528 or losartan plus the AT1 receptor antagonist PD123319 prevented alterations in AngII induced BMECs injury. However, pretreatment with PD123319 alone did not inhibit these effects and there were no significant difference in losartan group and losartan plus PD123319 group and EXP-2528 group.

Conclusion: Novel AT1 receptor antagonist, EXP-2528, the same as Losartan could protect against AngII-induced BMECs injury by blocking AT1 receptor at least partly contributing to its antioxidant role.

Key Words: AngiotensinII, Brain Microvascular Endothelial Cell, EXP-2528

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24 HOUR AMBULATORY BLOOD PRESSURE MONITORING DURING AND FOLLOWING STROKE
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Some three-quarters of patients with ischemic stroke have been observed to exhibit elevated blood pressure during the first 24-48 hours of onset, most likely as a physiological response to brain ischemia. In light of the dearth of 24-hour blood pressure monitoring studies during and following such events, we undertook such a study.

Fourteen conscious stroke patients underwent 24 hour ambulatory BP monitoring using the Suntech Accutrack Dx (Suntech Medical Instruments, Raleigh NC, USA) on day 1-2 (period 1) and day 5-6 (period 2) of hospital admission. Data were analyzed by paired T-test and non-parametric sign rank test for assessing differences between baseline and