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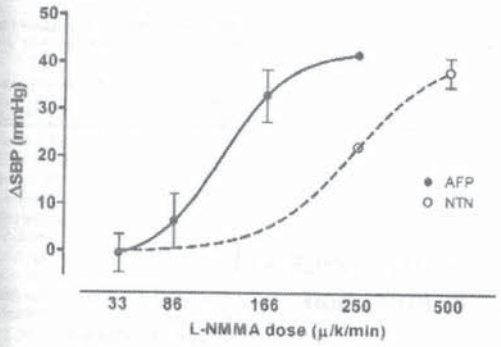
of membranous RhoA and phosphorylated ERM in brainstem were greater both in angiotensin II-treated rats and SHR than in WKY. Valsartan reduced the expression levels of membranous RhoA in angiotensin II-treated rats and SHR. In addition, Y-27632 or valsartan reduced the expression levels of phosphorylated ERM in both groups. Subcutaneous infusion of phenylephirine increased SBP to the same level of angiotensin II infusion in WKY. However, it did not alter the expression levels of membranous RhoA and phosphorylated ERM. Conclusions: These results suggest that 1) the pressor response induced by central infusion of angiotensin II is substantially mediated by activation of Rho/Rho-kinase pathway in brainstem via AT1 receptors, 2) this pathway may also be involved in hypertensive mechanism in SHR.

1412

Endothelial Nitric Oxide and Hypertension in Autonomic Failure

Alfredo Gamboa, Cyndya Shibao, Andre Diedrich, Bonnie K Black, Ginnie Farley, Satish R Raj, David Robertson, Italo Biaggioni; Vanderbilt Univ, Nashville, TN

More than half of patients with autonomic failure (AF) have severe supine hypertension despite low or unresponsive norepinephrine levels and often undetectable plasma renin activity. Supine hypertension is related to increased vascular resistance but the mechanism is not known. To test the hypothesis that nitric oxide deficiency contributes to supine hypertension we blocked endogenous nitric oxide synthase with L-NMMA in 5 AF patients and 7 normal controls (supine SBP 173±6 and 107±5 mmHg, respectively). Systolic blood pressure (SBP) was normalized to 110 mmHg in AF with graded head-up tilt, and baroreflexes were eliminated with trimethaphan in normal controls to mimic autonomic failure. The pressor response to graded doses of L-NMMA was shifted to the left in AF (Figure); The dose necessary to increase SBP by 30 mmHg was 3.4-fold lower in AF compared to controls (136±24 and 465±103 μg/k/min respectively, $p<0.02$). In conclusion, contrary to our original hypothesis, our results suggest an increased tonic release of nitric oxide in AF. Thus, NO deficiency does not contribute to supine hypertension in autonomic failure. On the contrary, this enhanced tonic NO may contribute to orthostatic hypotension in these patients.



1413

Oral Administration of a Mineralocorticoid Receptor Antagonist Reduces Brain, Heart, and Blood-borne Proinflammatory Cytokines in Heart Failure

Yu-Ming Kang, Carver College of Med, Univ of Iowa, Iowa City, IA; Ralph F Johnson, Univ of Iowa, Iowa City, IA; Zhi-Hua Zhang, Carver College of Med, Univ of Iowa, Iowa City, IA; Robert M Weiss, Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA; Alan K Johnson, Univ of Iowa, Iowa City, IA; Robert B Felder; Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA

Introduction: Brain and blood-borne cytokines may contribute to neurohumoral excitation in heart failure (HF). We previously reported that blockade of mineralocorticoid receptors (MR) in the central nervous system with spironolactone (SL) reduces circulating tumor necrosis factor (TNF)-α in HF rats. The effect of SL on proinflammatory cytokines (PIC) in the brain and on other important circulating PIC - interleukin (IL)-1β and IL-6 - was not determined. **Hypothesis:** Chronic treatment with oral SL will reduce brain and blood-borne PIC in rats with HF following MI. **Methods and Results:** Rats underwent coronary artery ligation to induce MI (48.2±2.0% of left ventricle, with ejection fraction of 35.5±4.1% by echocardiography), or sham surgery (SHAM). Six weeks later, immunohistochemistry of the paraventricular nucleus (PVN) of hypothalamus, a region critical to cardiovascular regulation, revealed more PVN neurons (MI vs SHAM, **$P<0.01$) positive for TNF-α (59.5±3.3** vs 10.8±0.9) and IL-1β (70.7±3.9** vs 13.8±1.2) in MI (n=6) than in SHAM (n=6) rats. Double staining demonstrated that these neurons were distributed among PVN neurons expressing Fra-like immunoreactivity, indicating chronic neuronal activation. MI rats (n=6) treated with SL (1 mg/kg/day orally for 6 weeks) had fewer (MI+SL vs MI, #$P<0.01$) Fra-like positive PVN neurons (85.5±5.4# vs 183.8±5.0), and fewer PVN neurons positive for TNF-α (22.4±1.8%# vs 32.4±1.7%) and IL-1β (19.1±1.3%# vs 38.4±2.1%). Levels of TNF-α, IL-1β and IL-6 in brain and heart tissues and in plasma were also lower in MI rats treated with SL (see table). **Conclusion:** In rats with ischemia-induced heart failure, orally administered SL has a global inhibitory influence on the appearance of proinflammatory cytokines in brain, heart and plasma. The beneficial influence of MR antagonism in patients with HF may result at least in part from blocking aldosterone-induced cytokine synthesis. (Table: *$P<0.05$ MI+SL vs MI+VEH)

Group	plasma IL-1β (pg/ml)	plasma IL-6 (pg/ml)	heart IL-1β (pg/mg protein)	hypothalamus IL-1β (pg/mg protein)	hypothalamus TNF-α (pg/mg protein)	brainstem TNF-α (pg/mg protein)	brainstem IL-6 (pg/mg protein)	cortex IL-1β (pg/mg protein)	heart/BW Ratio (mg/g)	lung/BW Ratio (mg/g)
MI+VEH (n=7)	131.1±10.9	119.5±9.7	53.4±6.5	47.1±7.9	6.8±0.7	6.1±0.9	57.1±10.1	26.4±4.1	7.2±0.2	13.5±0.6
MI+SL (n=7)	97.5±3.1*	53.3±6.6*	32.8±5.9*	29.4±5.1*	3.8±0.8*	2.8±0.5*	38.4±5.5*	25.8±5.2	6.4±0.3*	12.1±0.6*
SHAM+SL (n=6)	48.2±3.6	33.7±2.8	23.7±6.5	17.4±4.9	2.8±0.7	2.1±0.6	25.3±4.8	24.3±4.9	3.3±0.1	5.2±0.3
SHAM+VEH (n=6)	53.9±2.4	36.1±2.8	27.8±5.4	18.8±4.0	3.2±0.9	2.4±0.8	26.0±8.7	23.6±6.5	3.4±0.1	5.1±0.3

Pulmonary Arterial Hypertension: New Therapies

Subspecialty: Integrative Biology
Wednesday
Ernest N Morial Convention Center, Hall I2
Abstracts 1414–1418

1414

Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension

Robert Voswinckel, Beate Enke, Andre Kreckel, Frank Reichenberger, Stefanie Krick, Henning Gall, Tobias Gessler, Thomas Schmehl, Markus G Kohstall, Friedrich Grimminger, Hossein A Ghofrani, Werner Seeger, Horst Olschewski; Univ Hosp Giessen, Giessen, Germany

Objective: To evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess safety, tolerability and clinical efficacy in patients with severe PH. **Background:** TRE is a stable prostacyclin analogue that has been approved for treatment of pulmonary arterial hypertension as a continuous subcutaneous infusion. Iloprost, another prostacyclin analogue, has been shown to be efficacious in a randomised controlled study as repetitive inhalation. **Methods:** In an open-label study a preservative free solution of inhaled TRE was applied to 17 patients with severe pulmonary hypertension during Swan-Ganz catheter investigation. Patients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 μg/ml). Hemodynamics were observed for 2 hours. Two patients with idiopathic PAH received compassionate treatment with 4 inhalations of TRE per day after the acute test. **Results**: Patients (male/female= 4/13) suffered from iPAH (n=5), PAH other (n=8) and CTEPH (n=4); PVR 948 ± 112 dyn*s*cm^{-5}, PAP 48.3 ± 2.7 mmHg, PAWP 8.9 ± 0.5 mmHg, CVP 10.8 ± 1.6 mmHg, CO 3.8 ± 0.3 l/min, SvO2 61.8 ± 1.8 %. TRE inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes. Maximum PVR decrease was -31.2 ± 4.5 % after 30 min. PVR and SVR at 120 minutes after inhalation were 89.2 ± 4.2 % and 101.0 ± 4.0 % of the baseline values, respectively. The AUC for the observation period (120min) was -22.9 ± 3.8 % for PVR and -4.9 ± 3.2% for SVR. The compassionate use patients have been treated for more than 3 months. In both patients NYHA class improved (from IV to III and from III to II), and six minute walk increased (from 0 m (bedridden) to 143 m, and from 310 m to 486 m, respectively). No side effects have been observed by the patients during long-term treatment. **Conclusion:** Inhaled TRE shows strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing. Tolerability is excellent even at high drug concentrations and short inhalation times (3 breaths). Long-term treatment effects are very promising. The current results warrant controlled studies investigating this approach in a larger series of patients. Supported by Lung RX

1415

Rho-kinase in Pulmonary Hypertension

Ken Ishikura, Norikazu Yamada, Akihiro Tsuji, Satoshi Ota, Mashio Nakamura, Masaaki Ito, Naoki Isaka, Takeshi Nakano; Mie Univ Sch of Med, Tsu, Japan

Objectives: Pulmonary hypertension (PH) is a poor prognostic disease with limited treatment. Rho-kinase is involved in the pathophysiology of several diseases underlying smooth muscle hypercontraction. But the role of is unknown. The purpose of this preliminary report was to indicate the efficacy of fasudil, a Rho-kinase inhibitor in patients with pulmonary hypertension using interventional hemodynamic assessment. Methods: Fasudil was intravenously injected in 10 patients (9 female, mean ± SD, 46 ± 15 years, NYHA II n=2, III n=7, IV n=1) with primary (n=5) and secondary (n=5) PH who were not received any vasodilator. Fasudil was administrated 30mg with 1mg/min. Hemodynamic data were measured using Swan-Ganz catheter until 60 minutes after starting administration of fasudil. Hemodynamic and arterial blood gas data of baseline and the lowest total pulmonary resistance (TPR) time were compared. Results: The lowest TPR time was within 30 to 60 minutes after administration. Administration of fasudil significantly decreased TPR from 13.6 ± 6.8 U to 10.3 ± 4.9 U (-23.2 ± 9.2 %, $p < 0.001$) and mean pulmonary arterial pressure (mPAP) from 43.6 ± 14.5 mmHg to 38.8 ± 13.9 mmHg (-11.6 ± 10.4 %, $p < 0.02$). Cardiac index (CI) was significantly increased from 2.39 ± 0.66 L/min/m^2 to 2.74 ± 0.73 L/min/m^2 (+16.5 ± 15.1 %, $p < 0.01$). Although TPR was equally decreased in both primary and secondary PH, the changes in the parameters that prescribed TPR, namely CI and mPAP, were different between the two groups subjects. Increased CI was a major factor into reducing TPR in primary PH, while reduced mPAP