J001

VASOPRESSIN MODULATES SYMPATHETIC NERVE ACTIVTIY IN VARIOUS MODELS OF HYPERTENSION. F Muders, D Elsner, U Bahner, K Jandeleit, GAJ Riegger, M Palkovits. Klinik und Poliklinik für Innere Medizin II, University of Regensburg; Germany

Central vasopressin (AVP) plays an important role in the control of blood pressure and heart rate in hypertension. AVP stimulates sympathetic outflow via the locus coeruleus (LC) which receives vasopressinergic innervation and microinjection of AVP in the LC produces an increase in blood pressure and heart rate.

In order to investigate the functional status of AVP in the LC we determined the AVP content in the LC (micropunch technique) in 5 different models of hypertension (SHR, DOCA salt, Angiotensin II infusions using osmotic minipumps, 1C1K, 1C2K) in the rat. Elevated blood pressure levels (tail cuff method) were comparable in all models used (160 ± 13 mmHg). In comparison to controls (53 ± 9 pg/mg protein) AVP was significantly elevated in the LC of rats with genetic hypertension (SHR; +60%; $p<0.05$) and in the 1C2K model (+172%), whereas in AII induced hypertensive- and DOCA- rats AVP was significantly suppressed in the LC (- 39,2 % and -44.8 % vs. CTRL, respectively. In rats with 1C1K induced hypertension the AVP was unchanged.

Conclusion: In the two models (SHR and 1C2K), which are both characterized by elevated sympathetic nerve activity, high endogenous AVP were demonstrated in the LC. In the other models (AII, DOCA, 1C1K) rats showed unaltered or suppressed AVP content in the LC which may reduce sympathetic outflow and counteract to a further increase of blood pressure.

Our results support the hypothesis that central vasopressin modulates sympathetic nerve activity via the locus coeruleus.

Key Words: brain, vasopressin, locus coeruleus, hypertension, rat

J002

ROLE OF THE SYMPATHETIC NERVOUS SYSTEM DURING THE DEVELOPMENT OF OBESITY-INDUCED HYPERTENSION IN RABBITS. **V Antic, F Kiener-Belforti, A Tempini, BN Van Vliet and JP Montani*. Institute of Physiology, University of Fribourg, Switzerland, and Memorial University of Newfoundland, St. John's, Canada.**

We have previously reported that weight gain induced by high fat diet (HFD) leads to an increase in mean arterial pressure (MAP, +14%) and heart rate (HR, +31%) in the adult rabbit. We tested the hypothesis that an increased activity of the sympathetic nervous system is involved in the development of obesity-induced hypertension. A combination of α/β sympathetic blockers (terazosin/propranolol, 15-25 mg/kg/day each, in the drinking water) was chronically administered to rabbits housed in customized metabolic cages for daily measurement of urine output and continuous monitoring of arterial pressure by telemetry, 24 hr a day. The degree of sympathetic blockade was assessed by testing the MAP and HR reactivity to intravenous sympathetic agonists. After the first two weeks of treatment with sympathetic blockers under control diet (Control α/β), animals were switched to HFD for the following six weeks. HFD induced a progressive increase in body weight (BW), but no rise in MAP and only a small increase in HR as shown in the Table (n=5). A slight rise in glomerular filtration rate (GFR) was observed under α/β blockers and was further potentiated under HFD.

Period	MAP (mmHg)	HR (bpm)	BW (kg)	GFR (ml/min)
Before α/β	66.1 ± 2.1	202 ± 4	4.3 ± 0.1	10.2 ± 0.8
Control α/β	63.9 ± 1.9	194 ± 5	4.4 ± 0.1	12.2 ± 1.3
HFD-Wk 1	65.4 ± 2.0	213 ± 4	4.7 ± 0.2	13.2 ± 1.7
HFD-Wk 2	65.2 ± 1.4	213 ± 5	4.9 ± 0.2	13.9 ± 1.0
HFD-Wk 3	65.0 ± 1.0	213 ± 6	5.1 ± 0.2	14.1 ± 0.9
HFD-Wk 4	64.3 ± 1.1	213 ± 6	5.2 ± 0.2	13.5 ± 0.8
HFD-Wk 6	63.8 ± 1.3	222 ± 8	5.4 ± 0.2	14.4 ± 1.1

Time-control animals fed normal diet showed no changes in MAP or HR under long-term treatment with α/β blockers.

Our results indicate that the activation of the sympathetic nervous system may play an important role in the pathogenesis of obesity-induced hypertension.

Key Words: obesity, experimental hypertension, sympathetic nervous system

J003

THE KINETICS OF Na^+-H^+ ANTIPORTER ACTIVITY IN PLATELETS OF DAHL-IWAI SALT SENSITIVE RATS. K Otsuka[1], K Shibagaki[2], Y Ohno[2], M Hayashi[2] and T Saruta*[2]. Tokyo Senbai Hospital[1], Department of Internal Medicine, Keio University[2], Tokyo, Japan.

We have previously shown that altered intracellular Ca^{2+} metabolism is associated with sodium-induced hypertension in Dahl-Iwai salt sensitive (DS) rats(Otsuka K et al. *Am J Hypertens* 1997; 10:1396-1403). Altered intracellular Ca^{2+} metabolism and increased Na^+-H^+ antiporter activity have been demonstrated in the blood cells of hypertensive subjects. However, few reports have investigated the Na^+-H^+ antiporter activity in the blood cells of sodium-induced hypertension. Therefore, we characterized the kinetics of Na^+-H^+ antiporter activity in platelets of DS rats. Intracellular pH (pHi) was determined in platelet suspensions using 2,7-biscarboxyethyl-5(6)-carboxyfluorescein tetraacetoxymethyl ester, a fluorescent pH indicator. The kinetics properties of Na^+-H^+ antiporter activity were determined using platelets acidified with nigericin and challenged with varying extracellular concentrations of Na^+. Initial rate (IR) of pHi change was estimated by the following equation:

$pHi_t = pHi_\infty - [pHi_\infty - pHi_0] \times e^{-kt}$ in which pHi_t is pHi at given time t, pHi_∞ is pHi at new steady state, pHi_0 is the initial pHi at the moment of activation of the Na^+-H^+ antiport, and k is the rate constant. IRs were then used to estimate the kinetic parameters of the Na^+-H^+ antiporter, according to the following model:

$V = V^{max} \times [Na^+]^n / K_{0.5}{}^n + [Na^+]^n$ in which V is the IR of pHi recovery, V^{max} is the maximal IR, $K_{0.5}$ is the $[Na^+]$ corresponding to half-maximal activation, and n is the Hill coefficient. DS rats were fed either a 0.3% NaCl diet (N=6)or an 8% NaCl diet (N=5) from 5 to 9 weeks of age. Although there was not a statistically significant effect of sodium on V^{max} (2.07 ± .27 vs 2.25 ± 27 Δ pH/min, P=.65) and $K_{0.5}$ (56.7 ± 1.9 vs 52.7 ± 2.1mM, P=.20), $K_{0.5}$ was inversely correlated with systolic blood pressure (r=-.133, P=.03). This study demonstrated the kinetics of platelet Na^+-H^+ antiporter activity of DS rats for the first time, and the altered kinetics of Na^+-H^+ antiporter activity was elucidated to be involved in the pathogenesis of the experimental model of sodium-induced hypertension.

Key Words: Na^+-H^+ antiporter, platelet, Dahl rats

J004

ADRENOMEDULLIN REDUCES THE RISK FOR PULMONARY HYPERTENSION IN RATS. P. Vijay, J.W. Brown and T.G. Sharp. Indiana University School of Medicine, Indianapolis, IN 46202

Pulmonary hypertension (PH) is a progressive condition that may result in right ventricle failure and death. Injury to the pulmonary vasculature may lead to an imbalance in the levels of vasoactive mediators such as endothelin-1 (ET-1) and adrenomedullin (ADM), a newly identified 52-amino acid hypotensive peptide.

To evaluate the effects of ADM on the development of PH, we treated 14 Sprague Dawley rats with 60 mg/kg monocrotaline (MC). Control rats received solvent alone (n=10). During a 3-week induction period, group I rats received no treatment, group II rats (n=7) received ADM (30 nmol) on alternate days and group III rats (n=7) received ADM for 3 days prior to testing. Plasma ET-1 and ADM levels were measured as follows:

	ET-1 Levels (ng/ml)			ADM Levels (pg/ml)		
	I	II	III	I	II	III
C	0.4±0.1	0.3±0.1	0.3±0.1	4.4±1.3	2.7±0.1	6.6±0.8
MC	4.3±0.5	2.8±0.3	2.3±0.5	9.8±1.8	4.3±0.2	7.3±0.7

When PH is induced by MC in rats, ET-1 rises significantly ($p<0.05$ in all groups). Elevation of ADM in control animals suggests its role in compensating for vasoconstriction produced by ET-1. ADM treatment reduced ET-1 significantly ($p<0.05$ group I vs either II or III) in the other animals. ADM levels were highest in the control animals ($p< 0.05$ C vs MC). The lower levels of ADM in groups II and III could be the result of increased clearance of ADM, suppression of endogenous release of ADM or a reduction in the extent of MC induced vascular endothelial damage.

We conclude that ADM treatment blunts the rise in ET-1 during the development of PH and may act through different mechanisms depending on the time of administration.

Key Words: Pulmonary hypertension, Adrenomedullin, Rats, Endothelin