3.2: THE ENDOGENOUS NA,K-ATPASE LIGAND, MARINOBUFAGENIN, INDUCES VASCULAR FIBROSIS VIA A PRESSURE-INDEPENDENT MECHANISM IN NACL-LOADED DIABETIC RATS

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3.1 THE EFFECTS OF ANTICONTRACTILE PROPERTY OF PERIVASCULAR ADIPOSE TISSUE IN OBESE MICE

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It’s known that perivascular adipose tissue (PVAT) has an anticontractile effect maybe mediated by adiponectin, a physiological modulator of local vascular tone with mechanism still unknown. The PVAT function is lost in obese patients with the development of adipocyte hyper trophy, hypoxia, inflammation and oxidative stress (Circulation 2009; 119(12):1661-1670). The aim of the study was to investigate functional responses of small mesenteric arteries in a animal model of genetic obesity.

Materials and Methods: we investigated 8 obese mice (B6.V-Lep ob/OlaHsd, ob/ob) and 8 control lean mice (CLM). Mesenteric small resistance arteries (in- ternal diameter about 200 μm) were dissected and mounted on a wire myograph. A concentration-response curve to norepinephrine (NE, from 10^-9 to 10^-3 M) was evaluated in vessels with intact perivascular fat tissue (WF) and in vessels in which perivascular fat tissue was removed (NoF) in basal conditions and during vascular hypoxia (30%, 95%N2/5%CO2). Concentration response to NE was repeated in the presence of iberiotoxin (100 nm/L for 30'), a selective blocker of calcium-dependent potassium channels (BKCA), that have been previously suggested to be involved in vascular tone regulation.

Results: are summarized in the figure (active media stress: kPa). The presence of PVAT reduced the contractile response to NE in both ob/ob (ANOVA p = 0.002 vs. NoF) and CLM (ANOVA p = 0.001 vs. NoF); however, the effect was reduced in ob/ob compared with CLM. The anticontractile effect of PVAT completely disappeared with iberiotoxin preincubation/Maximum contraction to NE, ob/ob: WF: 176 ± 47, 68, NoF: 218 ± 66, *2*, WF + iberiotoxin: 289 ± 98, 06; CLM: WF: F: 118 ± 53, 92, NoF: 245 ± 51, 8, WF + iberiotoxin: 211 ± 31; *p<0.05 at least vs. WF). In conclusion, the anticontractile effect of perivascular fat tissue is partially maintained in an animal model of genetic obesity. This effect may be related to the activity of BKCa channels, since it is blocked by iberiotoxin, a scorpion toxin that inhibits calcium-dependent potassium channels.

3.2 THE ENDOGENOUS NA,K-ATPASE LIGAND, MARINOBUFAGENIN, INDUCES VASCULAR FIBROSIS VIA A PRESSURE-INDEPENDENT MECHANISM IN NACL-LOADED DIABETIC RATS

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An endogenous steroid marinoobufagenin (MBG) induces fibrosis via inhibition of FII1, a nuclear transcription factor and a negative regulator of collagen synthesis. Because immunization against MBG reduced cardiac fibrosis but minimally affected blood pressure (BP) in uremic rats (Hypertension, 2007;49:215-24), we hypothesized that MBG induces cardiovascular fibrosis via BP-independent mechanism.

We measured BP, urinary MBG, aortic collagen-1, and vascular function in NaCl-loaded male Wistar rats with type 2 diabetes mellitus (DM-NaCl) and in non-diabetic control rats (Ctrl). DM was induced by administration of 65 mg/kg streptozotocin to neonatal animals. At three months, 24 diabetic rats were dietary supplemented with 1.8% NaCl added to the drinking water for four weeks following which rats were twice administered monoclonal anti-MBG antibody (mAb) (n = 12), or vehicle (n = 12). Isolated rings of thoracic aorta were tested for their responsiveness to endothelin-1 and to sodium nitroprusside (SNP) following endothelin-1-induced constriction.

DM-NaCl rats exhibited a 3.5-fold increase in MBG excretion (25.4 ± 4.5 vs. 7.7 ± 1.5 nmol/mmol in Ctrl; P = 0.001) and 2.5-fold increase in collagen-1 in thoracic aorta in the absence of changes of BP or renal function. Compared to Ctrl, in aortic rings from DM-NaCl the responsiveness to endothelin-1 was unaltered (EC50 = 2.2 and 3.2 nmol/L, respectively), but the response to the relaxant effect of SNP was impaired (EC50 = 29 vs. EC50 = 7 nmol/L P < 0.001). In vivo administration of mAb to DM-NaCl rats did not affect BP, but reduced aortic collagen-1, and restored sensitivity of aortic rings to SNP (EC50 = 9 nmol/L). Thus, MBG induces vascular fibrosis and increases vascular stiffness without affecting BP.

3.3 PRESSURE-INDEPENDENT AORTIC STIFFENING EVALUATION IN VARIOUS HYPERTENSIVE RAT MODELS IN VIVO, VIA PULSATILE DIAMETER RECORDING

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We have shown that in addition to compliance and diastolicility, the analysis of the arterial distension (pulsatile diameter) via echotracking (ArtLab) provides information to discriminate the pressure-dependent and independent arterial stiffening. In the present study we evaluated these parameters in different hypertensive rat models. Mean, systolic, diastolic and pulse arterial pressure (AP) and the aortic diameter were recorded in 6 groups of pentobarbital anesthetized rats: 20 week old spontaneously hypertensive rat (SHR), SHR treated with the NOS inhibitor L-NAME 6 mg/kg/day in drinking water (SHRLN), 50-60 week old SHR, DOCA-salt (un-in- nephrectomized, deoxycorticosterone treated rats) and VDN (VitaminD- Nicotine treated rats); all were compared to their respective controls: Wistar-Kyoto (WKY) and Wistar normotensive rats. The diameter was comparable in all groups. Except in the DOCA-salt, increased stiffness index and decreased compliance, diastility and distension were observed, indicating an aortic stiffening. When in each rat AP was decreased acutely by clonidine i.v., reaching the control rat values of AP, stiffness index, compliance and diastility were more or less restored in SHR. In SHR-VDN, the diameter distension wave (area under the curve adjusted to heart rate) was restored in SHR, partially in old SHR, but not in SHR-LN and VDN (table). These data show, via the analysis of the aortic pulse diameter distension, that in SHR and VDN the increase in aortic stiffness is in part pressure-independent and due to arterial wall remodeling. The results are in line with previous structural vascular wall studies.