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Presentation Title: Chronic Tumor Necrosis Factor-Alpha Induces Oxidative Stress in the Paraventricular Nucleus of the Hypothalamus: Blockade with Pentoxifylline

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Abstract Body: Immune-mediated mechanisms have been shown to play an important role in cardiovascular regulation. Recent studies suggest that cytokines induce oxidative stress in the vascular tissues. In this study, we demonstrate that chronic TNF- α infusion induces oxidative stress in the PVN and increases gp91 phox and its subunits Nox1 and Nox4 in normal rats. **Methods:** A metabolic study was performed in which groups of rats were treated with TNF- α (30 μ g/kg, subcutaneous), TNF- α and pentoxifylline (PTX, 30 mg/kg, intraperitoneally), or vehicle for 5 days. On day 5 an echocardiogram was performed to measure LV function followed by conscious RSNA. The next day rats were sacrificed and the PVN was removed for capture microscopy and LV tissue removed by dissection. The gene expression for gp91 phox, Nox1 and Nox4 was measured using real-time PCR. **Results:** are tabulated. The real-time PCR values are shown as Δ CT values (Δ CT = CT of gene of interest - CT of GAPDH) and the fold increase compared to control is also shown in parenthesis. **Conclusions:** 1) TNF- α increases RSNA in rats. 2) TNF- α induces gp91 phox, Nox1, and Nox4 in the PVN of rats. 3) Treatment with PTX attenuates the TNF- α evoked increase in RSNA and gp91 phox, Nox1, and Nox4 in rats. 4) TNF- α induces oxidative stress in the PVN and contributes to the exaggerated RSNA leading to a possible role in sympathoexcitation.

<i>Parameters</i>	VEH (n=5)	TNF+VEH (n=6)	TNF+PTX (n=6)
RSNA (mV)	4.8 \pm 0.7	11.7 \pm 0.3*	5.7 \pm 1.4*,#
TNF-α mRNA (PVN)	-9.5 \pm 0.2	-7.4 \pm 0.1(4.7 fold)	-8.9 \pm 0.2*,#(1.5 fold)
gp91phox mRNA(PVN)	-13.5 \pm 0.1	-9.9 \pm 0.3*(8.8 fold)	-13.9 \pm 0.3#(0.5 fold)
Nox1 mRNA (PVN)	-14.8 \pm 0.4	-10.6 \pm 0.2*(18.5 fold)	-15.0 \pm 0.2#(0.8 fold)
Nox4 mRNA (PVN)	-13.9 \pm 0.3	-11.2 \pm 0.2*(6.5 fold)	13.1 \pm 0.1*,#(1.7 fold)
TNF-α mRNA (LV)	-9.3 \pm 0.2	-6.8 \pm 0.2*(5.66 fold)	-8.8 \pm 0.2*#(1.35 fold)
gp91phox mRNA(LV)	-8.37 \pm 0.1	-7.0 \pm 0.1*(2.56 fold)	-8.6 \pm 0.1#(0.87 fold)
Nox1 mRNA (LV)	-15.8 \pm 0.5	-13.4 \pm 0.2*(5.58 fold)	-15.6 \pm .4#(0.74 fold)
Nox4 mRNA (LV)	-8.7 \pm 0.1	-6.54 \pm 0.2*(4.46 fold)	-8.55 \pm 0.2#(0.6 fold)