Enhanced T-type calcium channel function, but not L-type or TRPC3 channels, augments uteroplacental arterial vascular tone in late pregnancy

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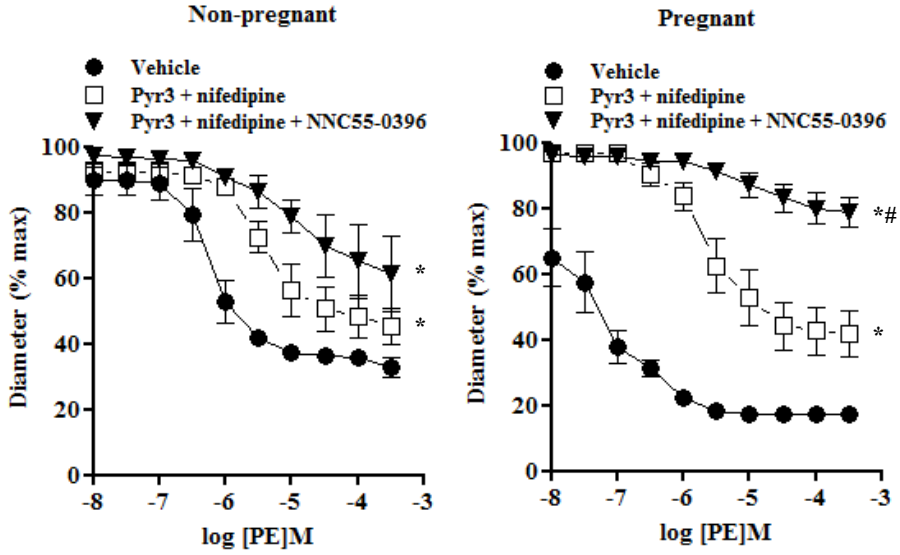
Introduction. Control of vascular tone is altered in pregnancy, with the underlying mechanisms remaining largely unknown. Modulation of intracellular calcium is important for control of tone, with voltage-dependent calcium and transient receptor potential (TRP) channels being critical. This study determined whether TRP canonical type-3 (TRPC3) and L- and T-type voltage-dependent calcium channels contribute to augmented tone in pregnancy.

Methods. Age matched non-pregnant (NP) and late pregnant (LP; day 20) Sprague-Dawley rats were anesthetized (pentothal, 100mg/kg, i.p.) and uterine radial arteries isolated. TRPC3 expression and localization were determined using Western blotting and immunofluorescence, respectively. TRPC3, L- and T-type channel contribution to tone was determined using pressure myography (60mmHg) with pharmacological intervention.

Results. TRPC3 was expressed in the smooth muscle, at similar levels in NP and LP rats. Maximal passive diameters were 90±8 and 188±6µm, in NP and LP rats, respectively. Phenylephrine (PE) was a more potent constrictor of arteries from LP rats compared to NP. Pyr3 (0.001-3µM) inhibition of TRPC3 caused vasodilation in PE pre-constricted arteries (~80%; 1µM in NP; 0.3µM in LP), with no difference in dilation in NP (pEC50, 5.9±0.7µM) and LP (pEC50, 6.5±0.8µM) rat vessels. Alone, Pyr3 (1µM) nor nifedipine (1µM; L-type inhibitor) had an effect on PE-induced constriction. However, combined Pyr3 and nifedipine inhibited PE-induced constriction compared to vehicle in NP (Emax, 46±5 cf/. 37±2, vehicle; *P*>0.05; Figure) and LP rat vessels (Emax, 40±7 cf/. 18±2, vehicle; *P*>0.05; Figure). Subsequent T-channel inhibition with NNC 55-0396 (3µM) differentially inhibited PE-induced constriction compared to vehicle in NP (Emax, 59±10 cf/. 37±2, vehicle; *P*>0.05; Figure) and LP (Emax, 78±5 cf/. 18±2, vehicle; *P*>0.05; Figure), with greater inhibition in LP rat vessels.



***Emax relative to vehicle. # Emax relative to Pyr3 + nifedipine.**

Conclusion. Medial radial artery TRPC3 may serve to facilitate L- and T-type channel activity, with T-channel function having a greater role in the regulation of tone in LP rats.