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Sex Difference In Endothelial Function Of The Porcine Isolated Coronary Artery

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Endothelium-derived vasorelaxant nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarising factor (EDHF) are crucial in the regulation of vascular tone. Studies have reported that the cardiovascular risk in men and postmenopausal women are greater than premenopausal women (Villar *et.al*, 2008 *J Endocrinol* **197**(3)**:** 447-462) and a clear sex differences in the relative contributions of the endothelium-derived relaxing factors have been previously reported (McCulloch et. al., 1998 *Br J Pharmacol* **123**(8)**:** 1700-1706). However, the majority of studies on the endothelium-dependent responses in the commonly used porcine coronary arteries (PCAs) have been conducted on mixed gender populations. Therefore, the effects of sex differences on endothelial function of isolated PCAs were investigated here. Distal PCAs were mounted in a wire myograph, pre-contracted with U46619 (2nM to 50µM), a thromboxane A_2 mimetic and concentration-relaxation curves to bradykinin (0.01nM to 1µM) were constructed. NO and prostanoid synthesis were inhibited using L-NAME (300µM) and indomethacin (10µM) respectively. PEG-catalase ($300Uml^{-1}$) was added in some preparations to eliminate intracellular H_2O_2. Carbenoxolone (100µM), a non-selective gap junction inhibitor was used to study the role of gap junctions. Apamin (500nM) and TRAM-34 (10 µM), small (SK_{Ca}) and intermediate (IK_{Ca}) - calcium activated potassium channel blockers respectively were used to study the role of K^+ channels in the bradykinin-induced vasorelaxation. All drugs were added an hour before pre-contraction with U46619. Data were analysed using one-way ANOVA, followed by Bonferroni's *post hoc* test. In male (maximum relaxation of (R_{max}) of 91.9 ± 3.4%,pEC_{50} =8.38±0.08,n=12) and female (R_{max}=91.4±3.4%, pEC_{50}=8.50 ±0.08,n=8) PCAs, bradykinin caused comparable concentration-dependant relaxation and in the presence of L-NAME and indomethacin the maximum relaxation were significantly reduced in both genders ($P<0.05$). Interestingly, the reduction in relaxation to bradykinin was greater in male (R_{max}=45.0±7.9%,pEC_{50}=7.33±0.27,n=11) compared to female (R_{max}=66.8±6.2%, pEC_{50}=7.65±0.16,n=8) PCAs. In female PCAs, PEG-catalase significantly reduced the relaxation in the absence (R_{max}=70.8±4.7%,pEC_{50}=8.23±0.13,n=9) ($P<0.05$) but not in the presence of L-NAME and indomethacin (R_{max}=54.7±5.8%,pEC_{50}=7.92±0.2,n=9). PEG-catalase had no effect in male PCAs under either condition (n=10-14). Carbenoxolone caused a further reduction in relaxation in the presence of L-NAME and indomethacin in female (R_{max}=31.1±4.1%,pEC_{50}=7.62 ±0.23,n=7) ($P<0.05$) but not in male (R_{max}=44.2±3.1%,pEC_{50}=7.54±0.11,n=6) PCAs. In female PCAs, addition of apamin (R_{max}=72.2±10.5%,pEC_{50}=7.6±0.2,n=5) or TRAM-34 (R_{max}=58.4±7.9%,pEC_{50}=7.5±0.2, n=5) alone in the presence of L-NAME and indomethacin (R_{max}=87.5±2.7%, pEC_{50} =7.6±0.05,n=5) significantly reduced the relaxation to bradykinin ($P<0.05$). Blockade of both SK_{Ca} and IK_{Ca} channels together in the presence of L-NAME and indomethacin (R_{max}=26.6±3.7%, pEC_{50}=7.2±0.2,n=6) further inhibited the relaxation. Whereas in male PCAs, addition of TRAM-34 in the presence of L-NAME and indomethacin (R_{max}=61.3±10.0%,pEC_{50}=7.4±0.3,n=9) had no effect (R_{max}=52.2±6.7%, pEC_{50}=7.5±0.2,n=9).In conclusion, a clear sex differences in the endothelial function have been demonstrated here where the EDHF plays a greater role in female compared to male PCAs and only in female PCAs that H_2O_2 plays a role in the bradykinin-induced relaxation. Similarly in the EDHF-mediated pathway, only in female PCAs that gap junctional communication and IK_{Ca} channels are more important compared to male PCAs.