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Differences in the signalling mechanisms underlying UTP-evoked vasoconstriction of pulmonary and systemic-like arteries

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P2Y receptors are G protein-coupled receptors that are activated by the endogenous nucleotide, UTP. In the vascular system, endothelial P2Y receptors mediate vasodilation, whilst P2Y receptors located on arterial smooth muscle cells mediate vasoconstriction (Chootip *et al.,* 2002). Previously we showed that Ca^{2+} influx via $Ca_v1.2$ ion channels contributes to the UTP-evoked contraction of rat intralobar pulmonary arteries (rIPA) (Mitchell *et al.,* 2012). The aim here was to characterise and compare the contribution of Ca^{2+} release and influx, rho kinase and protein kinase C in rIPA, a low pressure, low resistance vessel, and rat tail artery (rTA), a resistance-like, systemic artery.

5 mm rings of rIPA and rTA were dissected from male Sprague-Dawley rats (200-250g). The endothelium was removed by gentle rubbing of the intima and rings were mounted under isometric conditions in 1ml baths at 37°C and a resting tension of 0.5-0.75g. Tension was recorded by Grass FT03 transducers connected to a Powerlab/4e system (AD Instruments). Contractions were elicited by adding UTP (300 µM-rIPA; 1 mM-rTA) to the bath. Data were analysed using Student's paired and unpaired t tests, as appropriate. Values of $P<0.05$ were considered to be statistically significant.

UTP evoked slowly developing contractions in both tissues, which peaked within 2-3 min. Thapsigargin (1 µM) depressed significantly contractions by 30-40% (rIPA-$P<0.001$, n=8; rTA-$P<0.05$, n=4), but ryanodine was ineffective (n=5). The rho kinase inhibitor, Y27632 (10 µM) significantly reduced the peak amplitude of contractions by about 20% in rIPA ($P<0.01$, n=5) and by more than 80% in rTA ($P<0.01$, n=4) and the inhibition was significantly greater in rTA ($P<0.001$). The protein kinase C inhibitor, GF109203X (10 µM) also significantly reduced the peak amplitude in rIPA by over 20% ($P<0.01$, n=7) and by around 40% in rTA ($P<0.001$, n=5). Inhibition was again significantly greater in rTA ($P<0.05$). In rIPA, adding Y27632 (10 µM), GF109203X (10 µM), thapsigargin (1 µM) and nifedipine (1 µM) together abolished the UTP response (n=4). In rTA nifedipine (1 µM) significantly reduced the amplitude of UTP responses by about 60% ($P<0.01$, n=6). Furthermore, contractions were abolished by Y27632 (10 µM) plus thapsigargin (1 µM, n=5), GF109203X (10 µM, n=4) or nifedipine (1 µM, n=4). Adding thapsigargin (1 µM), GF109203X (10 µM) and nifedipine (1 µM) together abolished UTP-evoked contractions (n=4).

These results indicate that Ca^{2+} release from the sarcoplasmic reticulum and Ca^{2+} influx through $Ca_v1.2$ channels, contribute to UTP-evoked vasoconstriction of rIPA and rTA. Rho kinase and protein kinase C are also involved, but more so in rTA. Thus the relative importance of signalling components differs in pulmonary compared with systemic arteries.

Chootip, K., Ness, K., Wang, J., Gurney, A.M. & Kennedy, C. (2002). *British J. Pharmacol*., **137**, 637-646.

Mitchell, C., Syed, N.H., Gurney, A.M. & Kennedy. C. (2012). *British J. Pharmacol*.,**166**, 1503-1512.