Actions Of Calcium-sensing Receptor Ligands In Mesenteric, Femoral and Pulmonary Arteries From The Rat

Paul Gyimah, Vanessa Ho. St George's University of London, London, UK

The cell surface, extracellular calcium-sensing receptor (CaR), which is activated by Ca^{2+} ions, has been reported in the endothelium, smooth muscle and perivascular sensory nerves, and thus could contribute to vascular control. Increasing $[Ca^{2+}]_o$ (from 1 to 5mM) was shown to relax rat mesenteric, basilar and renal arteries, thought to be mediated by CaR in perivascular sensory nerves expressing Transient Receptor Potential Vanilloid type1 receptors (TRPV1; Wang & Bukoski, 1988). Our recent study (Thakore & Ho, 2011) confirmed that mesenteric relaxation to Ca^{2+} is sensitive to the negative allosteric modulator of CaR, calhex231 and functional desensitization of sensory nerves by capsaicin (a potent TRPV1 agonist). However, we also reported that relaxation elicited by Ca^{2+} and positive allosteric modulators of CaR (calcimimetics) could differ in their mechanisms of action, including the involvement of CaR (Thakore & Ho, 2011). Here, we further investigated the relaxant effects of $[Ca^{2+}]_o$ and the two calcimimetics, calindol and cinacalcet in different vascular regions. Small mesenteric, intrapulmonary and femoral arteries from male Wistar rats (250-350g; Charles river) were mounted in a wire-myograph for tension recording. Data are expressed as mean±s.e.m.($n \geq 4$) and analysed by two-way analysis of variance of the whole data set. $P<0.05$ was considered statistically significant. All vessels were precontracted with 10µM methoxamine. In mesenteric arteries bathed in physiological solution containing 1mM Ca^{2+}, incremental additions of $CaCl_2$ (1.5-5mM) induced relaxation that was inhibited by 3µM calhex231 (control, EC_{50}=2.3±0.2mM, R_{max}=69±9%; +calhex231, EC_{50}=3.8±0.2mM, R_{max}=38±18%; $P<0.01$), confirming our previous data. Treatment with ruthenium red (10µM), which is a non-selective TRPV blocker, also reduced the maximal relaxation to Ca^{2+} (EC_{50}=2.6±0.3mM, R_{max}=30±18%, $P<0.01$). By comparison, smaller Ca^{2+}-induced relaxations and a smaller calhex231-sensitive component were seen in femoral arteries (control, EC_{50}=2.7±0.3mM, R_{max}=42±5%; +calhex231, EC_{50}=2.9±0.2mM, R_{max}=37±4%; $P<0.05$). Interestingly, femoral relaxation to Ca^{2+} was attenuated by ruthenium red but potentiated by capsaicin (control, EC_{50}=2.5±0.3mM, R_{max}=40±6%; +10uM ruthenium red, EC_{50}=2.8±0.6mM, R_{max}=29±10%, $P<0.01$; +10uM capsaicin, EC_{50}=2.3±0.1mM, R_{max}=58±6%, $P<0.01$). On the other hand, in intrapulmonary artery, increasing $[Ca^{2+}]_o$ predominantly resulted in small contraction, which was enhanced by calhex231 (at 3mM, control, -15±10%; +calhex231, -49±5%; $P<0.01$), perhaps due to an underlying, CaR-mediated relaxation. However, capsaicin treatment had no significant effect (+capsaicin, at 3mM, -5±11%). On the other hand, the relaxant effects of Ca^{2+} were mirrored by those of calcimimetics in the different vascular regions; with rank order of potency and efficacy, mesenteric>femoral>>pulmonary artery (data not shown). In fact, in intrapulmonary artery, calindol caused contraction (-36±6%), followed by relaxation at higher contractions (31±12%). To conclude, the vascular action of Ca^{2+} and calcimimetics differ greatly depending on the vascular regions. Our data also question the role of CaR and capsaicin-sensitive nerves in Ca^{2+}-induced relaxation in regions beyond the mesenteric circulation.

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Thakore P & Ho WS (2011). *Br J Pharmacol* **162**: 749