How do flavonols cause relaxation of vascular smooth muscle?

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Flavonols are well known as effective, if not potent, vasorelaxants but their precise mechanism of action remains uncertain. Flavonol-induced relaxation is predominantly endothelium-independent with removal of the endothelium resulting in a small shift to the right of the concentration response curve with no change in the maximum response (Chan *et al.*, 2000). In conductance arteries, such as the rat aorta, 3′,4′-dihydroxyflavonol (DiOHF) caused relaxation that was found to be insensitive to a range of K^+ channel blockers (4-aminopyridine, charybdotoxin, apamin and glibenclamide) and to cause concentration-dependent relaxation in the presence of KCl (50 mM) with the same potency and efficacy observed when contraction was induced by the α-adrenoceptor agonist phenylephrine or U46619, a thromboxane A_2 mimetic (Song *et al.*, 2010). Interestingly, the non-selective K^+ channel blocker tetraethylammonium (TEA, 10 μM) does cause a partial inhibition of DiOHF-induced dilatation of pressurised rat cremaster arterioles suggesting that there may be different mechanisms involved in resistance *versus* conductance vessels. DiOHF causes concentration-dependent inhibition of contraction caused by elevation of extracellular calcium concentration in the presence of a depolarising concentration of KCl (Chan *et al.*, 2000). In addition contractile responses to the release of intracellular calcium stores in response to phenylephrine are impaired. Whilst it has been suggested that flavonols might act as blockers of voltage operated calcium channels (VOCCs) this appears unlikely as relaxation responses to DiOHF are unaffected by the presence of the calcium channel blocker nifedipine. Rather than, or in addition to, reducing free intracellular calcium levels flavonols may decrease calcium sensitivity. DiOHF effectively inhibits fluoride-induced contraction which occurs by the activation of the RhoA-Rhokinase pathway, an effect that is accompanied by a decrease in GTP-RhoA activity (Song *et al.*, 2010). We have recently obtained evidence that flavonols may directly inhibit myosin light chain phosphatase (MLCP) as DiOHF was unable to reverse contraction caused by calyculin A, an inhibitor of serine/threonine phosphatases such as MLCP (Kim *et al.*, 2011). By contrast DiOHF does effectively reverse contraction in response to pervanadate which inhibits tyrosine phosphatases. Thus it is suggested that flavonols, rather than decreasing the availability of intracellular calcium, alter the sensitivity to calcium by decreasing phosphorylation of myosin light chain. There is limited evidence that flavonols have antihypertensive activity, a possibility that is worthy of further investigation.

Chan ECH, Pannangpetch P, Woodman OL. (2000) *Journal of Cardiovascular Pharmacology* **35**, 326-333.

Kim HY, Seok YM, Woodman OL, Williams SJ, Kim IK. (2011) *Naunyn-Schmiedebergs Archives of Pharmacology* (accepted).

Song MJ, Baek I, Seo M, Kim SH, Suk K, Woodman OL, Williams SJ, Kim IK. (2010) *Clinical and Experimental Pharmacology and Physiology* **37**, 803-810.