A COMPARISON OF ACETYLCHOLINE- AND K^+-INDUCED VASODILATOR RESPONSES IN RAT PRESSURISED MESENTERIC ARTERIES

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Potassium (K^+) has been proposed to be an endothelium-derived hyperpolarising factor (EDHF) in rat small mesenteric arteries (Edwards *et al.,* 1998). The importance of K^+ as an EDHF in these vessels has been questioned however, on the basis of inconsistent relaxant responses evident in the presence of phenylephrine-induced tone (e.g. Lacy *et al*., 2000). This may be explained on the basis that excessive activation of smooth muscle results in the release of a 'K^+ cloud' which increases the background activation of Na^+-K^+-ATPase thus reducing the scope for K^+-mediated smooth muscle hyperpolarisation and vasorelaxation (Richards *et al*, 2001; Dora *et al*., 2002). In the present study we assessed whether the level of smooth muscle activation achieved during the pressure-induced myogenic response impacted upon the response to raised extracellular K^+ or acetylcholine (ACh).

3rd or 4th order mesenteric arteries were dissected from the mesentery obtained from male Wistar rats (150-250g) and placed in physiological salt solution (PSS) at 4°C. Vessels were mounted between two glass cannulae and pressurised to 90mmHg and heated to 36°C. Following the development of myogenic tone and in the presence of indomethacin (1μM) and L-NAME (100μM), changes in vessel diameter in response to ACh (10nM-30μM) or K^+ (6.9-20.9 mM, equimolar exchange with Na^+) were determined. In some experiments, intracellular recordings of membrane potential were made using sharp microelectrodes in vessels pressurised to 30mmHg. Responses were expressed as a % of the difference between the diameter after the development of myogenic tone and that measured in Ca^{2+}-free PSS. Differences between means were compared using a Student's unpaired t-test. Correlations between the level of myogenic tone and vessel responsiveness were assessed by linear regression.

At 90mmHg, small mesenteric arteries spontaneously reduced their diameter by 36.2±2.2% (n=43) (range 9.7-68.7%). Upon this background level of vasoconstriction, ACh produced a near maximal vasodilator response (94.8±1.8%; range 73.4 – 107%) with a log EC_{50} of -6.75±0.06 (n=23). Responses to K^+ were less consistent. Overall, K^+ produced a biphasic response; a vasodilatation at low concentrations and a vasoconstriction at high concentrations. The maximum vasodilator response to K^+ was significantly smaller than that produced by ACh (64.4±6.8%, n=20; $p<0.01$). Furthermore, the variability of the size of the vasodilator response was considerable between arteries (range: 11.8-106%). There was a modest, but significant, inverse correlation between the maximum response to K^+ and the level of myogenic tone ($r^2=0.239$; $p<0.05$; n=20). There was no correlation between the level of myogenic tone and either, the magnitude or, sensitivity of the response to ACh ($r^2= 0.007$ for the maximum response and 0.005 for the EC_{50}; $p>0.05$; n=23). At 30mmHg, ACh (1μM) produced a hyperpolarisation of 18.2±1.7mV (n=6), while K^+ (5mM) was largely without effect 0.8±0.4 mV (n=6).

The present results show a modest correlation between K^+-induced relaxation and the level of pressure-induced myogenic tone, indicating that responses to K^+ are partially dependent upon the prevailing level of smooth muscle activation. The lack of influence of the prevailing level of tone on responses to ACh and, more importantly, the lack of a hyperpolarisation response to raised extracellular K^+ in pressurised small arteries questions the role of K^+ as an EDHF under physiological conditions, in the rat mesentery.

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