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008P ACTIVATION OF P2X-LIKE RECEPTORS IN RAT ISOLATED 2ND ORDER MESENTERIC ARTERIES INDUCES VASODILATION: ROLE OF EDHF

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ATP is released by a range of vascular cells under inflammatory conditions. ATP induces vasodilation in some vascular beds via the release of nitric oxide (NO) and prostacyclin (PGI_2) from the endothelium, by way of P2Y receptor activation. Recently, we have shown, using rat perfused mesenteric preparations, that high doses of ATP also induce a profound vasodilator response which we characterised as EDHF-like in nature (Stanford and Mitchell, 1998; Stanford *et al*., 2001). Furthermore, and by contrast to the initial transient NO-mediated vasodilatation induced by ATP, the 'EDHF' component does not appear to be mediated by traditional vasodilator P2Y receptors (Gitlin *et al*., 2001a), but may be mediated by either a P2X receptor (Gitlin *et al*., 2002; Ralevic, 2002) or an unidentified purinergic receptor. In order to further understand this phenomenon we have investigated the effects of ATP and the P2X selective ligand α,β methylene ATP on vasomotor tone of isolated 2nd order rat mesenteric arteries.

Male Wistar rats (200 ± 15.4g) were killed by lethal exposure to CO_2 followed by cervical dislocation. The mesenteric bed was removed and 2nd order arteries (240-250μm) isolated and mounted in wire myographs using a dissecting microscope. Tissues were immersed in physiological salt solution (PSS), equilibrated (30 min) and tensions normalised as described previously (Mulvany and Halpern, 1977). Vessels were then contracted with approximately EC_{80} concentration of methoxamine (10^{-5}M). Single concentrations of either ATP, α,β methylene ATP (10^{-4}M each), acetylcholine or sodium nitropruside (10^{-5}M each) were then added to tissues. Dilator responses were calculated as a percentage of tone induced by methoxamine. In some experiments the nitric oxide synthase inhibitor, L-N^G nitro-L-arginine (L-NAME; 10^{-3}M), the cyclo-oxygenase inhibitor indomethacin (10^{-5}M), or apamin ($5x10^{-7}$M) plus charybdotoxin (10^{-7}M), which together inhibit EDHF responses were added.

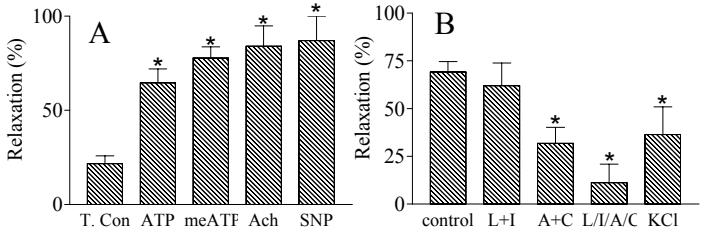

*Figure 1: (A) ATP, α,β methylene ATP, acetylcholine (ACh) or sodium nitroprusside (SNP) induced dilation; time control (T.Con.).(B) Effect of L-NAME plus indomethacin (L+I), apamin plus charybdotoxin (A+C),L+I plus A+C (L/I/A/C) or KCl on the vasodilator actions of ATP. Data is shown as the mean ± s.e.m. for n=3-8 experiments. Significance (one-way ANOVA; p<0.05) between ATP-induced response with or without drugs is denoted by**

Both ATP and α,β methylene ATP induced vasodilation of pre-constricted mesenteric vessels. In both cases vasodilation was insensitive to the combination of L-NAME and indomethacin, but reduced by the combination of apamin plus charybdotoxin or high KCl ($124x10^{-3}$M).

Here we have reproduced a phenomenon previously only noted in intact perfused mesenteric beds where either ATP or a selective P2X ligand induces vasodilation, and is possibly mediated by EDHF. Since P2X receptors have previously been linked to vasoconstrictor responses, these findings prompt us to re-examine the role of P2X receptors in the regulation of vasomotor tone.

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