

037P SELECTIVE INHIBITION OF CYPTOCHROME P450 EPOXIDATION MODULATES ENDOTHELIAL DEPENDENT VASODILATION

Louise S. Harrington, John R. Falck* and Jane A. Mitchell

Cardiothoracic Pharmacology, Unit of Critical Care Medicine, The National Heart and Lung Institute, Imperial College, Dovehouse Street, London, SW3 6LY, UK.

* Dept. of Biochemistry, UT Southwestern medical centre, Texas 75390-9038, USA

It is increasingly recognised that cytochrome P-450 (CYP) epoxidase metabolites including the Epoxyeicosatrienoic acids (EETs) are likely candidates for endothelial derived hyperpolarising factor (EDHF). A novel inhibitor, N-Methylsulfonyl-6-(2-proparygoxyphenyl) hexanamide (MS-PPOH) has been described that selectively inhibits the epoxidation of arachidonic acid (Wang *et al*, 1998), and thus inhibits vasodilation by the release of EETs. ATP is an important vasoactive mediator, which, at high concentrations, induces vasodilation predominantly via the release of EDHF (Stanford *et al*, 2001; Harrington and Mitchell, 2003). Here we have investigated the effects of MS-PPOH on ATP induced vasodilation in murine mesenteric arteries.

Male Black 6 mice ($25 \pm 1.9\text{g}$) were killed by lethal exposure to CO_2 . First order arteries were isolated and mounted in wire myographs immersed in physiological salt solution (PSS). Arteries were equilibrated (30mins) and tensions normalised as described previously (Mulvany and Halpern, 1977). Arteries were incubated for 30 minutes with or without MS-PPOH (10^{-5}M) before contraction with U46619 (10^{-8}M) and dilation with either a acetylcholine (3×10^{-8} – $3 \times 10^{-5}\text{M}$) or ATP ($3 \times 10^{-5}\text{M}$). Inhibition of EET release by incubation with MS-PPOH significantly inhibited vasodilation by acetylcholine (figure 1) or by ATP (figure 2) in U46619 pre-contracted arteries.

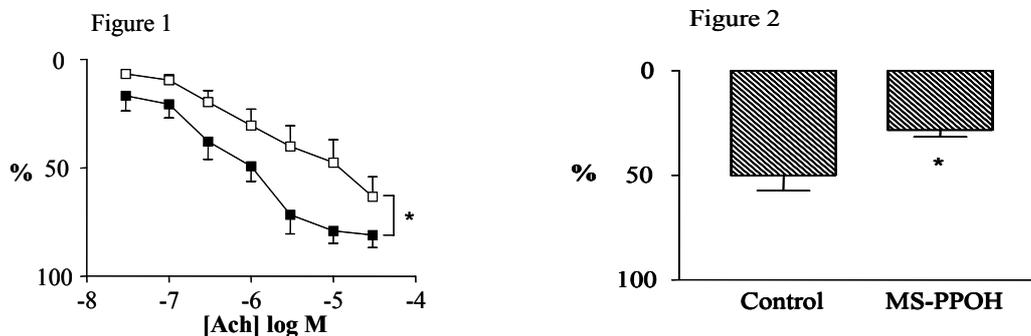


Figure 1: Concentration response curve to acetylcholine in the presence (□) or absence (■) of MS-PPOH. Figure 2: Vasodilation in response to a single addition of ATP ($3 \times 10^{-5}\text{M}$) in the absence (control) or presence (MS-PPOH) of MS-PPOH (10^{-5}M). Data is shown as a % of U46619 induced tone, \pm SEM for $n=3$ experiments.

These results indicate that vasodilation induced by either ATP or acetylcholine in the murine mesenteric artery is mediated in part by CYP P-450 epoxidase metabolites. This data supports the hypothesis that EETs are important EDHFs in resistance arteries.

Harrington and Mitchell (2003). pA₂ online Vol.1 Issue 2 abstract 008P

Mulvany and Halpern (1977). Circ.Res. 41:19-26

Stanford *et al* (2001). BJP Jul 133(6): 825-32

Wang *et al* (1998). J. of Pharm. And Exp. Therapeutics. Vol 284(3): 966-973

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