Selective Endothelin A receptor antagonism attenuates neointimal lesion development in the mouse femoral artery

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Although non-selective Endothelin (ET) A/B receptor antagonists inhibit neointimal lesion formation (Reel *et al.*, 2005), studies in transgenic mice suggest that the ETB receptor has a role in attenuating neointimal remodelling (Murakoshi *et al* 2002). This suggests that selective ETA-receptor antagonism may be a better therapeutic option for inhibiting neointimal proliferation. Therefore, this study addressed the hypothesis that the potent, selective ETA receptor antagonist sitaxsentan would inhibit neointimal proliferation in a mouse model of intra-luminal injury.

Methods: The ability of sitaxsentan to selectively block ETA receptors in femoral arteries isolated from adult, male C57Bl6 mice (25-35g) was assessed using isometric wire myography. Femoral arteries were suspended in a myograph chamber (containing physiological salt solution at 37^{o}C) and cumulative concentration-response curves obtained for ET-1 (10^{-11}-10^{-6}M), phenylephrine (PhE; 10^{-9}-10^{-4}M) and acetylcholine (ACh; 10^{-9}-10^{-4}M) after incubation (30min) with antagonist (sitaxsentan; 10^{-9}-10^{-7}M) or vehicle (water; n=6-7). Adult, male C57Bl6 mice (25-35g) underwent femoral artery wire-injury (under anaesthesia by inhalation of isoflurane) and received either ETA antagonist (sitaxsentan; 15mg/kg/day in chow) or vehicle (n=7-8) for 5 weeks (from 1 week before arterial injury). Femoral arteries were harvested 28 days after arterial injury for analysis of lesion size and composition. Data are mean$\pm$s.e.mean, where n indicates the number of different mice, and were analysed using Student's unpaired t-test.

Results: In isolated arteries, sitaxsentan produced a concentration-dependent rightward shift of the ET-1-mediated contraction (pD_2; 7.90$\pm$0.14 Control vs 6.85$\pm$0.15 100nM sitaxsentan; $P<0.0005$) but had no effect on responses to ACh or PhE. Femoral artery injury produced large, concentric fibro-proliferative neointimal lesions. Administration of sitaxsentan reduced lesion (40.2$\pm$3.0% vs 22.7$\pm$4.5%; P=0.007), but not lumen (49.9$\pm$6.3% vs 66.5$\pm$9.1%; P=0.15), size. Sitaxsentan administration also altered lesion composition with collagen content reduced (30.4$\pm$5.3% vs 13.7$\pm$1.5%; P=0.02) but macrophage and α-smooth muscle actin immunoreactivity unchanged.

Conclusions: These results are consistent with selective antagonism of ETA receptors in femoral artery smooth muscle inhibiting neointimal lesion development, although reduced collagen staining suggests lesion vulnerability may be increased.

Murakoshi *et al* (2002) Circulation 106:1991-1998.
Reel,*et al.*, (2005) J Pharm Pharmacol, 57, 1599-1608.