

## PPAR $\beta$ ACTIVATION INDUCES VASCULAR HYPOREACTIVITY: COMPARISON WITH OTHER PPAR LIGANDS

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Our understanding of the role of the nuclear receptor peroxisome proliferator-activated receptor beta (PPAR $\beta$ ) is incomplete, although it has been associated with cardiovascular and inflammatory functions (Wahli, 2002). For example, PPAR $\beta$  is expressed in the heart and can modulate inflammation (Lee et al., 2003). However, the effects of activation of PPAR $\beta$  (or other PPAR receptors) in vasomotor responses is not known. Here we have addressed this question using rings of murine aorta in organ cultures.

Male C57BLK6 mice (25-32g) were killed by exposure to CO<sub>2</sub>. Aortic rings were incubated in DMEM in the presence of PPAR ligands or vehicle for 48 h at 37 °C before being mounted in myographs. Vasoconstriction and vasodilatation (% reduction in pre-constricted tone, EC<sub>80</sub> concentration of U46619) were determined as described previously (Harrington and Mitchell, 2004).

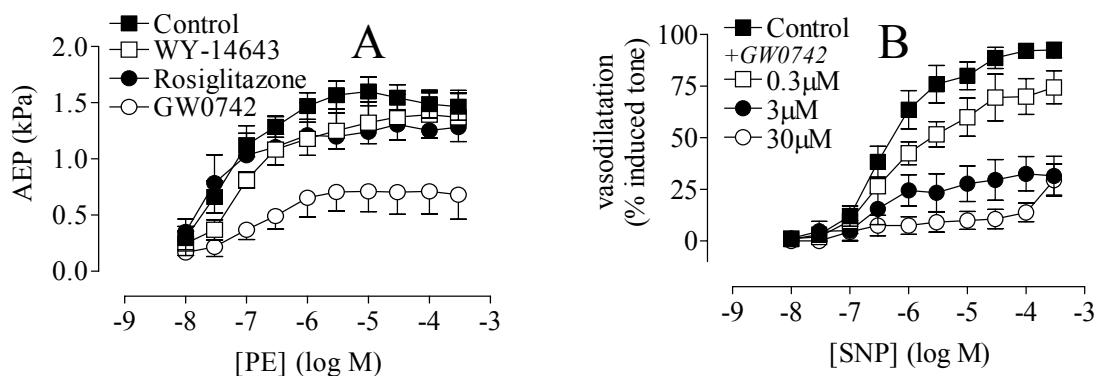


Figure (A) Contractile effects of phenylephrine (PE) in vessels pre-incubated (48 h) with vehicle (control) or with ligands to PPAR $\alpha$  (WY-14643), PPAR $\gamma$  (rosiglitazone) or PPAR $\beta$  (GW0742) (all 30 $\mu$ M). (B) Effect of pre-incubation (48 h) with GW0742 (0.3-30 $\mu$ M) on vasodilator responses to sodium nitroprusside (SNP) in U46619 (EC<sub>80</sub>) contracted vessels. Data is mean  $\pm$  s.e.m. for n=5 determinants.

Incubation with PPAR $\alpha$  or PPAR $\gamma$  ligands did not affect aortic contractility. However, incubation with the PPAR $\beta$  ligand caused aortae to become hyporeactive to the contractile effects of phenylephrine (Figure 1A), although not to the contractile effects of U46619 (e-max; control vessels 1.36 $\pm$ 0.24 kPa: plus GW0742, 1.34 $\pm$ 0.25). GW0742 also greatly inhibited vasodilatations in response to SNP (Figure 1B). These data suggest that PPAR $\beta$ , but not PPAR $\alpha$  or PPAR $\gamma$ , has an important modulatory role in the maintenance of vasomotor tone.

Harrington, L. and Mitchell, J.A. (2004). *Br J Pharmacol* **143**: 611-617.

Lee, C.H. et al. (2003). *Science* **302**: 453-457.

Wahli, W. (2002). *Swiss Med Wkly* **132**: 83-91.

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