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Actions of medroxyprogesterone acetate on 17α oestradiol-induced vascular muscle relaxation

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Objectives Several epidemiological studies suggested that oestrogens in hormone replacement therapy (HRT) can protect women from coronary heart disease. The vascular relaxant effects of oestrogens may contribute to these beneficial effects of HRT, reducing cardiovascular risk in postmenopausal women. However, the Womens Health Initiative (WHI) study in the USA, in which the HRT consisted of conjugated oestrogens plus medroxyprogesterone acetate, was terminated prematurely, partly due to an increased incidence of cardiovascular disease in year one. Possibly progestins used in HRT modulate the beneficial relaxant effects of oestrogens by a direct or indirect action on vascular muscle. Previous studies showed potentiation, by progesterone, of oestrogen effects on endothelium-dependent production of the vascular relaxant, nitric oxide (Simoncini et al 2004), whereas Cox et al (2005) recently reported that progesterone decreased nitric oxide synthase in vascular endothelium, and detrimental effects on vasorelaxation. We previously showed that natural progesterone did not reduce oestradiol-induced relaxation of either vascular or intestinal smooth muscle (McCurrie et al 2005). Our present objective was to study direct effects of medroxyprogesterone acetate on oestrogen-induced vascular muscle relaxation in the absence of endothelium-derived factors, using rat portal vein.

Methods Longitudinal muscle in portal veins derived from male Hooded-Lister rats (250–350 g) was studied in Krebs' solution (37 °C, 95% O_2, 5% CO_2) containing 10 μM indometacin under 0.5 g tension. Control concentration–response curves were constructed to KCl (10–100 mM) and repeated in the presence of one of the following: 17α oestradiol (EST, 4 or 8 μM), medroxyprogesterone acetate (MED, 4 or 8 mM) or a combination of either: EST (4 μM) plus MED (4 μM) or EST (8 μM) plus MED (8 μM). Steroids were incubated with tissues for 20 min prior to construction of the second concentration–response curve. No vehicle (EST: 60% alcohol, 40% distilled water, MED: 100% alcohol) or time-dependent effects were observed, N = 4–5.

Results KCl-induced contraction was superimposed on spontaneous activity in the portal vein. Oestradiol (4–8 μM) caused rightward shifts in the KCl concentration–response curve and concentration-dependent reduction in Emax: Emax was reduced to 56.7 ± 4.9% by EST (4 μM) and 36.2 ± 2.4% by EST (8 μM) ($P < 0.01$). Medroxyprogesterone acetate (MED 4 and 8 μM) produced a very small concentration-dependent reduction in Emax to 91.8 ± 10.8% and 82.6 ± 11.2%, respectively ($P < 0.05$, compared to control). A combination of EST (4 μM) and MED (4 μM) also displaced KCl concentration–response curves to the right and reduced Emax to 64.3 ± 11.3%, which was a smaller reduction than that observed with EST (8 μM) alone ($P < 0.05$, Student's two tailed paired *t*-test). The combination of EST and MED (8 μM) reduced Emax to 46.8 ± 8.5%, a smaller decrease in contraction than observed with oestradiol (8 μM) alone.

Conclusions These results show that both oestradiol and medroxyprogesterone acetate induce concentration-related inhibition of vascular muscle and that addition of medroxyprogesterone acetate significantly reduces oestrogen-induced relaxation in rat portal vein. We conclude that, unlike the action of natural progesterone, the medroxyprogesterone acetate component of HRT in the WHI study could have antagonised beneficial relaxant actions of the oestrogens.

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McCurrie, J. R., et al (2005) *J. Pharm. Pharmacol*. **56** (Suppl.): 233
Simoncini, T., et al (2004) *Endocrinology* **145**: 5745–5756