Modulatory effects of progestins on long-term estrogen treatment in coronary arteries from hyperlipidemic rabbits

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Summary

In contrast to epidemiological and experimental studies, randomized clinical trials have refuted a beneficial cardiovascular effect of long-term combined hormone replacement treatment (HRT) in post-menopausal women. It has been proposed that the progestin component in HRT may oppose the potentially beneficial effects of estrogen on vascular function.

This study elucidates possible mechanisms of actions of long-term 17β-estradiol (E_2) treatment alone or in combination with two commonly applied progestins i.e. medroxyprogesterone acetate (MPA) and norethisterone acetate (NETA) in an animal model of human menopause. It is hypothesized that the progestin component modulates the effect of estrogen and that different progestins exert differential effects on coronary vascular function. The effect of long-term E_2 treatment alone and in combination with either MPA or NETA on the endothelin-1 (ET-1) system and on nitric oxide, K^+ and Ca^{2+}-mediated mechanisms was investigated.

Watanabe Heritable Hyperlipidemic rabbits were treated orally with either E_2 (4mg/day), MPA (10mg/day), NETA (2mg/day), E_2 + MPA, E_2 + NETA, or placebo for 16 weeks (n=10 in each group). Intramural distal coronary arteries were used for mRNA and myograph analyses.

The study demonstrated a reduction in the vasoconstrictor response to ET-1 with E_2 treatment. This reduction was sustained with ET_B but not ET_A receptor stimulation and ET_B mRNA was increased

with E_2 treatment, which suggests that the vascular response was mediated through regulation of the ET_B receptor. The alteration in coronary responsiveness and gene expression was opposed by the addition of MPA and NETA. Furthermore, E_2 decreased the production of ET-1 and this was not opposed by the two progestins. ET_A receptor and endothelin-converting-enzyme mRNA was unaffected by treatment.

Also, E_2 treatment increased vasodilatation induced by sodium nitroprusside and decreased vasocontraction induced by potassium. The first but not the latter response was opposed by MPA. The combination of MPA and E_2, but neither compound alone enhanced nimodipine induced vasodilatation and increased the expression of voltage-gated Ca^{2+} channel mRNA. NETA had no opposing effects. Hormone treatment did not affect large-conductance Ca^{2+} -activated K^+-channel, ATP-sensitive K^+-channels or cGMP-dependent protein kinase mRNA expression.

In conclusion, long-term E_2 treatment exerted beneficial vascular effects in coronary arteries from hyperlipidemic rabbits, and the progestin component modulated the effects of estrogen. A differential effect of MPA and NETA was observed when evaluating calcium-mediated mechanisms but not the ET-1 system. The results may contribute some understanding to the effects of combined HRT on coronary vascular function.