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17β-ESTRODIAL INCREASES ABCA1 EXPRESSION AND CHOLESTEROL EFFLUX TO APOA I IN VIVO AND IN VITRO

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Objectives Evidence from clinical trials and animal experiments has shown that oestrogen has anti-atherosclerotic effects that are independent of its cholesterol-lowering activity; these activities include reducing the proliferation of smooth muscle cells and leukocyte adhesion and increasing the synthesis of nitric oxide. However, whether oestrogen can regulate foam cell formation remains unknown. Here, we investigated the effects of 17β-oestradiol (E2) on cholesterol efflux in vivo and in vitro.

Methods ApoE-null mice (B6.129P2-ApoEtm1Unc) underwent an ovariectomy (OVX) or Sham operation at 5 weeks of age and then were treated with E2 or vehicle for the following 8 weeks. After above treatment, serum and aorta of mice were harvested and then lipid level, plaque size and composition were detected. RAW267.4 cells were pretreated with or without interferon-gamma (IFN-gamma) for 12 h then treated with E2 for additional 12 h, then ATP-binding cassette transporter A1 (ABCA1), ATP-binding cassette transporter G1 (ABCG1) and CD36 expression and cholesterol efflux rate to apoA I and HDL were detected.

Results Compared with the vehicle-treated mice, the serum total cholesterol level were decreased by 27.72% in the Sham group and 35.32% in the OVX+E2 group $p<0.01$ for both), and the serum triglyceride level was decreased by 22.64% in the Sham group and 23.84% in the OVX+E2 group $p<0.05$ and $p < 0.01$, respectively). Compared with the OVX group, the size of the plaque area was significantly reduced by 22.03% in the Sham group and by 21.84% in the OVX+E2 group $p<0.01$ for both). Oil Red O staining showed that the lipid deposits in the plaques decreased by 20.57% and 30.36%, respectively $p<0.01$ for both). The immunohistochemical staining showed the percentage of ABCA1-positive areas in the plaque were 1.61 and 1.57 times higher $p<0.01$ for both) in the Sham and OVX+E2 groups, respectively, than in the OVX group. According to above results, compared with the OVX group, the mRNA expression of ABCA1 in the aorta also increased by 2.09 and 2.43 times, respectively $p<0.01$ for both). In vitro, E2 treatment alone did not influence ABCA1 expression, but reversed the IFN-gamma inhibited ABCA1 expression of RAW 264.7 cells. Compared with the untreated cells, ABCA1 mRNA levels decreased by 35.29% in the presence of IFN-gamma and were reversed to 87.25% $p<0.01$, for both) by the E2 treatment, no change was found in ABCG1 or CD36 expression. Finally, we also found that E2 enhanced the cholesterol efflux to apoA I (28.66±1.76% for E2 vs 15.80±3.77% for control, $p<0.01$) in RAW264.7 cells, but not to HDL.

Conclusions In summary, E2 increased ABCA1 expression and cholesterol efflux, both in vivo and in vitro. Thus, E2 delayed the

atherosclerotic plaque progression in ApoE-null mice. These results provide new insight into the athero-protective effects of oestrogen.