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Estrogens are needed for the improvement in endothelium-mediated dilation induced by a chronic increase in blood flow in rat mesenteric arteries

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ABSTRACT

Resistance arteries play a key role in the control of local blood flow. They undergo outward remodeling in response to a chronic increase in blood flow as seen in collateral artery growth in ischemic disorders. We have previously shown that mesenteric artery outward remodeling depends on the endothelial estrogen receptor alpha. As outward arterial remodeling is associated with improved endothelium-dependent dilation, we hypothesized that estrogens might also play a role in flow-mediated improvement of endothelium-dependent dilation.

Local increase in blood flow in first order mesenteric arteries was obtained after ligation of adjacent arteries in three-month old ovariectomized female rats treated with 17-beta-estradiol (OVX + E2) or vehicle (OVX).

After 2 weeks, diameter was equivalent in high flow (HF) than in normal flow (NF) arteries with a greater wall to lumen ratio in HF vessels in OVX rats. Acetylcholine-mediated relaxation was lower in HF than in NF vessels. eNOS and caveolin-1 expression level was equivalent in HF and NF arteries.

By contrast, arterial diameter was 30% greater in HF than in NF arteries and the wall to lumen ratio was not changed in OVX + E2 rats. Acetylcholine-mediated relaxation was higher in HF than in NF arteries. The expression level of eNOS was higher and that of caveolin-1 was lower in HF than in NF arteries.

Acetylcholine (NO-dependent)-mediated relaxation was partly inhibited by the NO-synthesis blocker L-NAME in OVX rats whereas L-NAME blocked totally the relaxation in OVX + E2 rats. Endothelium-independent relaxation (sodium nitroprusside) was equivalent in OXV and OVX + E2 rats. Similarly, serotonin- and phenylephrine-mediated contractions were higher in HF than in NF arteries in both OVX and OVX + E2 rats in association with high ratio of phosphorylated ERK1/2 to ERK1/2.

Thus, we demonstrated the essential role of endogenous E2 in flow-mediated improvement of endothelium (NO)-mediated dilatation in rat mesenteric arteries.

1. Introduction

The arterial tree has an important plasticity, which allows adapting to continuous changing conditions, even in the adult. Structural remodeling involves the rearrangement of the components of the vascular wall [1] associated with functional changes in the relative importance of constrictor or dilator pathways as observed in pregnancy, exercise, aging or in pathological conditions such as hypertension and diabetes mellitus [2].

Resistance arteries control local blood flow to organs. They are sensitive to chronic changes in the hemodynamic environment and undergo rapid remodeling. Chronic increases in blood flow (shear stress) induce outward hypertrophic remodeling in mesenteric arteries [3–6] associated with functional changes mainly characterized by improvement of endothelium (NO)-dependent dilation [5,7–10]. Chronic increases in blood flow occur in physiological situations such as growth, pregnancy or regular exercising. In pathological conditions, a chronic increase in blood flow is expected in resistance arteries feeding ischemic tissues. Indeed, high-flow-mediated remodeling has a key role in

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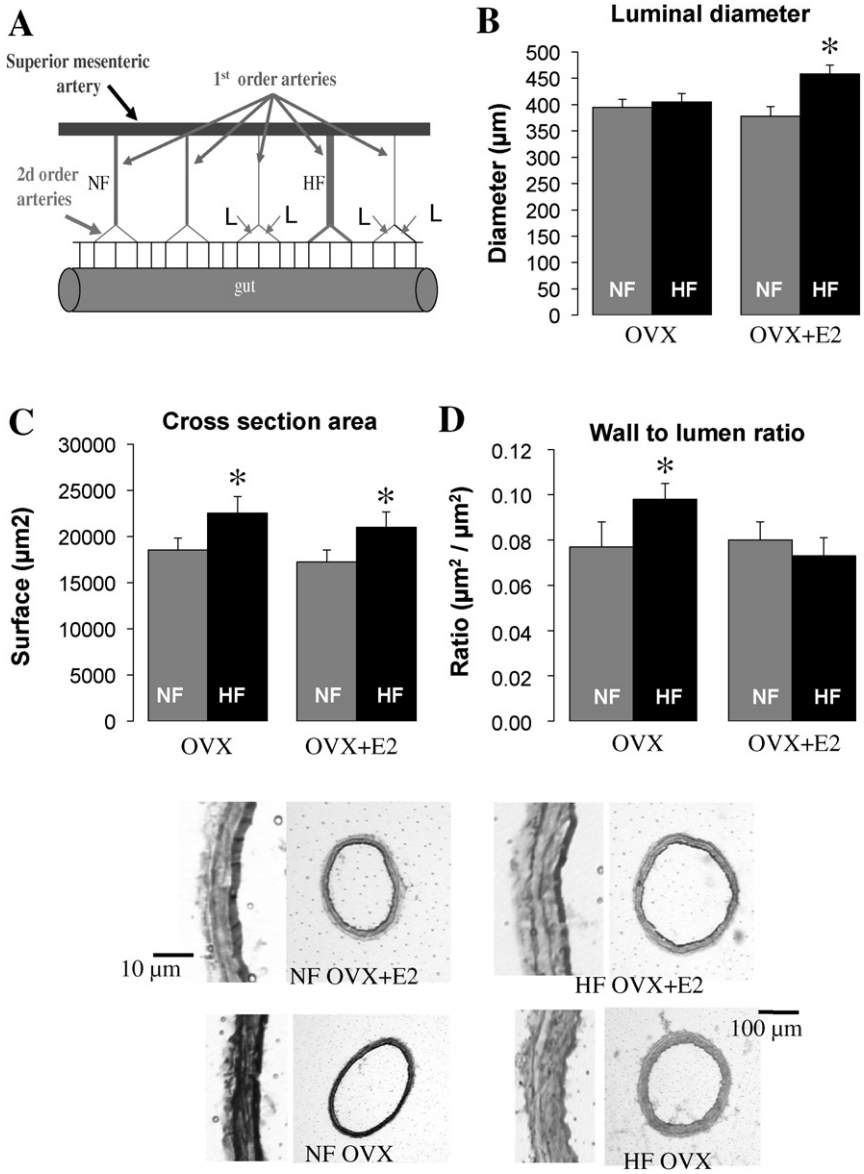

Fig. 1. Arterial structure following a chronic increase in blood flow in vivo: Panel A shows the scheme depicting the surgical procedure applied to the mesenteric arteries in order to increase locally blood flow in one artery (high flow: HF) after ligature of second order mesenteric arteries as shown by the arrows (L). Arteries located at distance were used as control (normal flow: NF) arteries. Luminal diameter (B), cross-section area (C) and wall to lumen ratio (D) measured in mesenteric arteries submitted chronically to a chronic increase in blood flow (HF) and in control arteries submitted to normal flow (NF). Arteries were isolated from ovariectomized (OVX, n = 8 rats) rats and ovariectomized rats treated with 17-beta-estradiol (OVX + E2, n = 8 rats). Mean ± SEM is represented. Typical pictures of NF and HF arteries are shown in the bottom panel. *P < 0.05, HF versus NF arteries.

postischemic revascularization besides arteriogenesis and angiogenesis [11,12].

In the uterine circulation [13] and in mesenteric arteries [14–17] the chronic increase in blood flow (shear stress) induces first a limited inflammatory response with macrophage infiltration in the perivascular space followed by the production of reactive oxygen species (ROS) which associate with NO to form peroxinitrite anions [10] to activate MMPs and extracellular matrix digestion and diameter expansion until normalization of shear stress. This inflammatory response is also associated with COX-2 [18] and hemoxygenase-1 [16,19] induction, two enzymes that produce vasodilator agents in addition to NO during outward remodeling [5]. As the diameter expansion increases wall stress, wall thickening occurs through activation of ERK1/2 by angiotensin II type 1 receptor [20]. Consequently, wall mass increases (as seen by an increased cross-sectional area) without change in the wall to lumen area [3]. In the uterine circulation remodeling is also accompanied by changes in elastin and collagen content [21].

Epidemiological studies show that women, before menopause, are better protected than men against cardiovascular diseases [22]. Both animal and human studies have shown that the decline in ovarian function is associated with decreased NO production [23]. Stimulation of the NO-pathway may explain at least in part, the protective effect of estrogens on the vascular wall [24,25]. Recently, we have shown that the increase in diameter induced by a chronic rise in blood flow in vivo in mesenteric arteries was dependent on the estrogen receptor alpha, not the compensatory increase in wall thickness that accompanied the remodeling [17,26]. Indeed, in both ovariectomized female rats and in ERalpha −/− mice the arterial diameter remained unchanged despite the increase in blood flow whereas hypertrophy occurred with an increased wall to lumen ratio [17,27]. Nevertheless, we did not measure the third part of the remodeling in these studies, i.e., the improved endothelium- and NO-dependent dilation which is associated with the outward remodeling. In search for the mechanism of the vasoprotective action of estrogens we hypothesized that estrogens might also play a