

AGEs breaking and antioxidant treatment improves endothelium-dependent dilation without effect on flow-mediated remodeling of resistance arteries in old Zucker diabetic rats

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Résumé en
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BACKGROUND: A chronic increase in blood flow in resistance arteries is associated with increased lumen diameter (outward remodeling) and improved endothelium (NO)-mediated relaxation. Flow-mediated remodeling of resistance arteries is essential for revascularization in ischemic diseases. Nevertheless, it is impaired in 12 to 24-month old rats and in young Zucker Diabetic Fatty (ZDF) rats due to advanced glycation end products (AGEs) and oxidative stress. As type 2 diabetes occurs preferentially in older subjects we investigated flow-mediated remodeling and the effect of the AGEs breaker ALT-711 associated or not to the antioxidant TEMPOL in one-year old lean (LZ) and ZDF rats. **METHODS:** Mesenteric resistance arteries were exposed to high (HF) or normal blood flow (NF) in vivo. They were collected after 2 weeks for in vitro analysis. **RESULTS:** In LZ rats, diameter expansion did not occur despite a significant increase in blood flow in HF arteries. Nevertheless, endothelium-mediated relaxation was higher in HF than in NF arteries. ALT-711, alone or in combination with TEMPOL, restored outward remodeling in HF arteries in association with AGEs reduction. TEMPOL alone had no effect. ALT-711, TEMPOL or the combination of the 2 drugs did not significantly affect endothelium-mediated relaxation in HF and NF arteries. In ZDF rats, diameter did not increase despite the increase in blood flow and endothelium-mediated relaxation was further decreased in HF arteries in association with AGEs accumulation and excessive oxidative stress. In both NF and HF arteries, endothelium-mediated relaxation was lower in ZDF than in LZ rats. ALT-711, TEMPOL or their combination did not improve remodeling (diameter equivalent in HF and NF arteries). In parallel, they did not reduce AGEs level and did not improve MMPs activity. Nevertheless, ALT-711 and TEMPOL partly improved endothelium-mediated relaxation through a reduction of oxidative stress and the association of ALT-711 and TEMPOL fully restored relaxation to the level found in LZ rats. **CONCLUSIONS:** ALT-711 did not improve outward remodeling in mature ZDF rats but it reduced oxidative stress and consequently improved endothelium-dependent relaxation. In mature LZ rats, ALT-711 improved outward remodeling and reduced AGEs level. Consequently, AGEs breaking is differently useful in ageing whether it is associated with diabetes or not.

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