Endothelin-1 (ET-1), known as a potent vasoconstrictor, has been implicated in pathogenesis of osteoarthritis (OA). ET-1 could induce matrix metalloproteinase 13 (MMP13) expressions by chondrocytes in vitro. Use of Endothelin 1 receptor A antagonist, might rescue OA in mice. Yet, the direct evidence remains lacking whether overexpressed ET-1 will lead to development of OA. Therefore, we aim to characterize the phenotypes of the articular cartilage and subchondral bone in a transgenic endothelial cell-specific (Tie-1 promoter) overexpressed endothelin-1 (TET-1) mice. Male heterozygous TET-1 mice were generated by microinjection of the ET-1 construct, which contained the mouse ET-1 cDNA with SV40 polyA driven by the Tie-1 promoter. TET-1 mice developed systemic hypertension with altered vascular reactivity since 8 weeks after birth. Tibiae of male, heterozygous TET-1 mice (n = 4) and their non-transgenic littermates (n = 4) of 35-weeks-old were obtained. PCR were used to confirm their genotypes. Micro-CT scan on tibiae were performed before tissue processed to wax blocks. Tibiae in wax blocks were sectioned and histology was studied on 5 μm-thick wax sections. Micro-CT data showed a decrease of bone volume/tissue volume (BV/TV, 10.9 ± 0.4%) in TET-1 mice primary spongiosa when compared to the age- and gender-matched littermates (12.8 ± 0.5%, p < 0.05). In contrast, there was no significant difference in the density of subchondral trabecular bone (secondary spongiosa) between TET-1 mice (23.5 ± 3.6%) and their littermates (25.7 ± 1.4%, p > 0.05). It was revealed histologically that articular chondrocytes underwent hypertrophic changes together with thickening of calcified cartilage in TET-1 mice as compared to their littermates. In summary, TET-1 mice present OA-like changes and overexpression of ET-1 contributes to hypertrophic changes of articular chondrocytes.


Characterisation of the “Endothelin-Like Domain Peptide” (ELDP) co-synthesised with Endothelin-1 from the EDN1 gene

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Background: Endothelin-1 (ET-1) is strongly implicated in cardiac and renal pathologies both as a potent vasoconstrictor and as an inducer of tissue remodelling and fibrosis. However, ET antagonists demonstrated limited efficacy in clinical trials of heart failure and hypertension. Thus, alternative preproendothelin-1 (ppET-1) derived peptides may contribute/interact with vasoconstrictor responses. Our aim was to characterise ppET-1 biosynthesis and to evaluate potential interactions with ET-1 responses. Methods and results: A combination of specific immunoassays and HPLC were used to characterise ppET-1 processing in conditioned media samples from human endothelial (EA.hy 926) and epithelial (A549) cells. Endothelin-like Domain Peptide (ELDP, ppET-1 [93–166]) was identified by immunoassay with LTQ-Orbitrap mass spectrometer confirmation. Specific ELISA for ELDP showed its release from primary cultures of human aortic endothelial cells, which correlated with ET-1. Blood pressure responses were investigated in anaesthetised rats. Although synthetic ELDP alone (3 nmol/kg) had no effect, it significantly increased the duration of the pressor response to ET-1 (0.3 nmol/kg, p < 0.02). On rat mesenteric resistance arteries (rMRA), ELDP alone had no significant vasoconstricter effect up to 10 nM, but after pre-treatment with ET-1 (1–3 nM) produced a concentration-dependent vasoconstriction. Pre-incubation of rMRA with 10 nM ELDP increased the response of 1 nM ET-1 by ~5-fold (p < 0.002). Plasma levels of ELDP, measured by sandwich immunoassay, showed a significant difference between untreated subjects with pre-hypertension/mild hypertension (n = 24) compared to patients with chronic heart failure (n = 24) (6.45 ± 0.19 and 7.80 ± 0.25 fmol/ml; p < 0.001, respectively). Conclusions: ELDP is co-secreted with ET-1 and modulates its vasoconstrictor responses. ELDP may be a useful biomarker for EDN1-linked pathologies.

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