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Tissue-specific and time-dependent regulation of the endothelin axis by the circadian clock protein Per1

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Renal collecting duct endothelin-1 is a critical regulator of the epithelial sodium channel (ENaC) and blood pressure (BP). Recently, we showed that mice lacking the circadian clock protein Per1 exhibited dramatically lower BP compared to wild type mice. Since ET-1 reduces Na+ retention and Per1 represses expression of ET-1 mRNA in the kidney, we hypothesized that elevated renal ET-1 levels contribute to the lower BP in Per1 KO mice. Examination of ET-1 peptide levels in the inner medulla of Per1 KO and WT mice showed that Per1 KO mice expressed higher levels of ET-1. ET-1 peptide levels varied with a circadian pattern that correlated with dipping of BP in wild type mice. To further investigate a role for Per1 in the regulation of the endothelin axis, ET-1, ETAR and ETBR mRNA expression were measured in lung, heart, liver and the renal inner medulla. Measurements were performed at noon and midnight, representing the peak of murine rest and active phases, respectively. The effect of reduced Per1 expression on levels of the endothelin axis and the circadian pattern of expression appeared to be tissue specific. For example, in the renal inner medulla, ETAR and ETBR exhibited peaks of expression in opposite circadian phases. In contrast, lung expression of ET-1, ETAR and ETBR did not vary with a circadian pattern, but ET-1 expression was dramatically decreased in Per1 heterozygous mice. Heart and liver also showed distinctive circadian expression of ET-1, ETAR and ETBR. These observations may have important implications for our understanding of the best time of day to deliver endothelin receptor antagonists.

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Endothelin signaling in craniofacial and cardiac development

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Since a series of gene knockout studies in 1990s, the endothelin system has emerged as a key determinant in embryonic development. We have shown that the endothelin-1 (ET-1)/endothelin type-A receptor (ETAR) pathway acts as a molecular switch that specifies the ventral identity of the pharyngeal arches to form the lower jaw and related structures. Mice deficient in ET-1/ETAR signaling also showed anomalies in the great arteries. The preotic (cranial) and postotic (cardiac) neural crest cells are responsible for these processes as a target cell population. Recently, we found that the cranial neural crest from the preotic region, rather than post-otic 'cardiac' neural crest cells, migrate into the heart and differentiate into coronary artery smooth muscle cells in the proximal region (Nat. Commun. 3: 1267, 2012). Ablation of the preotic neural crest in chick embryos causes abnormalities in coronary septal branch and orifice formation. Appropriate migration and deployment of neural crest cells and subsequent smooth muscle differentiation require multicellular interactions involving ET-1/ETAR signaling possibly through G12/13-mediated mechanisms, whereas ET-1/ETAR signaling is involved in ventral identification of the pharyngeal arches through Gq/11-mediated, Dlx5/6-dependet mechanisms. These findings indicate that the ET-1/ETAR signaling pathway is involved in craniofacial and cardiac development through different trimeric G-proteins.

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Erythropoietin induced blood pressure rise, vascular inflammation and oxidative stress in mice overexpressing human endothelin-1: Improvement by exercise

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Erythropoietin (EPO) is used to correct anemia in chronic kidney disease (CKD). EPO has been shown to increase blood pressure (BP) in patients and animals with CKD. Plasma endothelin (ET)-1 levels are increased in CKD animals and patients, and enhanced by EPO. EPO-induced BP rise was blunted by ETA receptor blockers. This study was designed to determine whether pre-existing ET-1 overexpression is required for EPO to cause adverse vascular effects, and whether this could be prevented by exercise training. We treated 8–10-week old male mice with endothelial specific ET-1 overexpression (eET-1) with EPO (100 IU/kg, SC, 3 times/week) or not, and subjected or not the mice to swimming exercise training (1 h/d, 6 d/week) for 8 weeks. Wild-type littermate mice were treated or not with EPO as above and maintained sedentary. EPO increased systolic BP by 24 mm Hg ($P < 0.05$) in eET-1 mice, and decreased vasodilatory responses to acetylcholine by 25% ($P < 0.01$). EPO enhanced ET-1-induced increase in resistance artery media/lumen by 31% ($P < 0.05$), aortic NADPH oxidase activity by 50%