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Endothelin in myocardial infarction

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The effects of ET-1 on myocardial necrosis: Myocardial infarction increases plasma ET-1 levels shortly after acute coronary occlusion, causing release from intracellular-storages and de novo production. The effects of ET-1 on the ischaemic and necrotic areas in the absence of reperfusion are debated, but ET-1 may play a role in reperfusion injury. In in vivo rat-models of ischaemia-reperfusion, ETA- or dual-(ETA and ETB) receptor blockade have been shown to decrease myocardial necrosis and improve left ventricular haemodynamics. Importantly, favourable results were demonstrated in a recent small-scale clinical study, in which short-term, selective ETA-receptor blockade prior to percutaneous coronary intervention improved myocardial perfusion, decreased infarct size and improved left ventricular function. ET-1 and sympathetic stimulation: During acute myocardial infarction, ET-1 increases catecholamine-release from the adrenal glands and modulates norepinephrine-release in sympathetic nerve-endings in the ventricular myocardium. These effects result in local norepinephrine-release via ETA-receptor activation, whereas the ETB-receptor appears to exert a protective role by decreasing early sympathetic drive. Arrhythmogenesis: ET-1 exerts significant electrophysiologic effects and contributes to ventricular arrhythmogenesis. ET-1 induces spontaneous calcium-transients, leading into early afterdepolarizations, and inhibits the delayed-rectifier potassium-current. In the in vivo rat-model of myocardial infarction without reperfusion, lower incidence of ventricular tachyarrhythmias and shorter episode duration were reported after selective ETA-receptor blockade, resulting in lower arrhythmic-mortality. In the same animal model, dual (ETA and ETB) receptor blockade decreased arrhythmogenesis, but this effect was evident only during the later-phase of acute infarction. These results point towards an arrhythmogenic effect of ET-1 during acute infarction, mediated mainly by the ETA receptor, consisting of increased sympathetic activation and enhanced repolarization inhomogeneity. The restoration of blood-flow after a prolonged ischaemic period causes marked electrophysiological changes and causes a second wave of myocardial necrosis, associated with arrhythmogenesis. Given the possible role of ET-1 in reperfusion injury, the antiarrhythmic potential of ET-receptor blockade during ischaemia-reperfusion has been subject of research for over a decade. However, hitherto studies have produced conflicting results, possibly due to differences in experimental-protocols, including ex vivo and in vivo models, and the time-window for arrhythmia-recording. Moreover, exogenously administered ET-1 during ischaemia-reperfusion in some studies may even exert antiarrhythmic effects, possibly via a preconditioning effect. Conclusions: The effects of ET-1 during myocardial ischaemia and infarction constitute an intriguing topic with potential clinical ramifications. Further research is required on the arrhythmogenic effects of ET-1 during acute myocardial infarction, placing emphasis on those observed during the pre-hospital phase. Since ventricular tachycardia and ventricular fibrillation shortly after acute coronary occlusion account for the vast majority of sudden cardiac death cases, prompt understanding of the underlying pathophysiology may lead to effective preventive therapeutic strategies.

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Endothelin-1 is a key candidate to exert pathophysiological effects on cardiomyocytes derived from hypertrophic cardiomyopathy-induced pluripotent stem cell

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Background. Despite the accumulating genetic and molecular understandings into hypertrophic cardiomyopathy (HCM), it remains unclear how this condition develops and worsens pathologically and clinically in terms of the genetic-environmental interactions. Thus, establishing human disease models for HCM would help us to evaluate the disease mechanisms and novel therapeutic strategies. Emerging patient-specific induced pluripotent stem cell (iPSC) techniques hold much promise for these tasks. Hypothesis. Interactions between genetic backgrounds and environmental factors are involved in the progression of HCM. Methods. To clarify candidate disease-promoting environmental factors, iPSCs from unrelated three patients with HCM and three healthy-control subjects were generated. The cardiomyocytes differentiated from each iPSC line were stimulated by several cardiomyocyte hypertrophy-promoting factors. The HCM pathological phenotypes were examined based on the morphological properties, such as cell size and intracellular myofilament structures, in randomly chosen cardiac troponin-T-positive singled cardiomyocytes. Next, a high-speed video imaging with motion vector prediction algorithm revealed physiological contractile dynamics in the iPSC-derived singled cardiomyocytes. Results. Control- and HCM-iPSC-derived cardiomyocytes were similar under the basal condition in pathological features and contractile dynamics. However, only the HCM-iPSC-derived cardiomyocytes showed pathological phenotypes, such as cardiomyocyte hypertrophy and facilitated intracellular myofilament disorganization in the presence of endothelin-1 (ET-1) administration with a dose-dependent manner. Moreover, physiological analyses revealed ET-1-induced contractile dispersion in the self-beating HCM-iPSC-derived cardiomyocytes. Finally, these deleterious effects were rescued by blocking the endothelin receptor type-A. Conclusions. Interactions between genetic backgrounds and the environmental factor,

ET-1, promoted the pathophysiological phenotypes of HCM in the iPSC-derived cardiomyocytes.

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Endothelin receptor antagonists exacerbate autoimmune myocarditis in mice

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Background: Experimental autoimmune myocarditis (EAM) is a mouse model of inflammatory cardiomyopathy. The amount of endothelin (ET) increases according to the disease progression; however, the pathological role of ET in myocarditis has not been elucidated. Methods and results: EAM was induced by immunization of cardiac myosin peptide with complete Freund's adjuvant on days 0 and 7 in BALB/c mice. ET-A/-B dual receptor antagonist SB209670 was administered by continuous infusion from a subcutaneous pump for 3 weeks. An increase in heart-to-body weight ratio was observed in SB209670-treated mice compared with vehicle-treated mice. The heart pathology in SB209670-treated mice was remarkable for gross inflammatory infiltration, in contrast to the smaller inflammation in the hearts of vehicle-treated mice. We found that ET blockade decreased the number of Foxp3 + regulatory T cells and inhibited the production of immunoregulatory cytokine IL-10 in the heart. ET blockade also inhibited the expression of suppressor of cytokine signaling 3 (SOCS3) that plays a key role in the negative regulation of both Toll-like receptor (TLR)- and cytokine receptor-mediated signaling. EAM is a CD4 + T cell-mediated disease. CD4 + T cells isolated from SB209670-treated EAM mice produced less IL-10 and more inflammatory cytokines IFN-γ and IL-17 than those isolated from vehicle-treated mice. Conclusions: ET receptor antagonist exacerbated autoimmune myocarditis in mice. ET may play an important role in the regulation of inflammation in myocarditis.

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Imaging of the binding of ET-1 and of linear ET-1 in rat mesenteric resistance arteries

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In engineered cells, endothelin ETA- and ETB-receptors can heterodimerize. We tested whether this is possible in native tissue. Therefore, rat mesenteric resistance arteries were maintained in organ culture for 24 h to upregulate ETB-mediated contractions in addition to their normal ETA-mediated constrictions. Thereafter the vessels were cannulated and maintained at constant distending pressure and 37 °C under a two photon laser scanning microscope. They were then subsequently exposed to first 100 nM linear ET-1 (ETB-agonist) tagged with Oregon Green 488 (OG488) and then to 16 nM intact ET-1 (ETA/ETB-agonist) tagged with the rhodamine dye TAMRA. After incubation with the labeled ligands, the arterial smooth muscle cells in the tunica media were efficiently stained and became visible under the two photon microscope. Wrinkling of the autofluorescent internal and external elastic laminae accompanied agonist-induced constriction. TAMRA-ET-1 bound to all smooth muscle cells with a homogeneous cytoplasmic distribution whereas similar staining was observed for labeled linear ET-1 but only on some group of cells. Fluorescence lifetime measurements were employed to probe the interaction of the two receptor subtypes. Fluorescence lifetime of OG488, which acted as a donor, was reduced in the presence of TAMRA, from 2.8 ps to 2.3 ps, which indicates a fluorescence resonant energy transfer (FRET), a phenomenon which can take place only if the receptors are in close proximity (<10 nm). The methodology that is introduced by these preliminary observations may be useful to asses ET-receptor heterodimerization in biopsies from relevant experimental animal models and human patients.

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Sympathetic endothelin A receptors contribute to the development of heart failure

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In preclinical heart failure (HF) models, endothelin receptor A (ETA) antagonists (ETAi) attenuated the disease progression. However, clinical HF trials failed to demonstrate beneficial effects on cardiac function and prognosis. We hypothesized that established HF drugs such as adrenergic receptor blockers interfere with the mechanism of action of ETAi. Here we report, that mice lacking ETA selectively in sympathetic neurons (SN-KO) showed less adverse structural remodeling and cardiac dysfunction in response to pathological pressure overload induced by transverse aortic constriction (TAC). In contrast, mice lacking ETA selectively in cardiomyocytes (CM-KO) were not protected against HF. TAC led to a disturbed sympathetic nerve function as measured by cardiac norepinephrine (NE) tissue levels and [124I]-MIBG PET, which was prevented in SN-KO. In co-cultures of cardiomyocytes (CMs) and sympathetic neurons (SNs), endothelin-1 (ET1) led to a massive NE release and exaggerated CM hypertrophy as compared to CM mono-cultures. ETA-deficient CMs gained a hypertrophic response through wild type SNs but ETA-deficient SNs failed to mediate exaggerated CM