with DPN and PPT. DPN treatment improved LVDP from 94.68 ± 5.14 in HF to 119.3 ± 5.5 and RPP from 39749.9 ± 4527.03 in HF to 62794.04 ± 5534.62. PPT treatment had no effect on LV mechanical performance as both LVDP and RPP were not significantly different from their corresponding values in HF. The relaxation and contraction defects of HF mice (dP/dtmax and dP/dtmin) were also partially restored by DPN but not by PPT. Our data strongly support the view that ERb is the main player in rescuing advanced HF by E2.

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Phosphorylation of GSK-3b is Required for Intralipid to Protect the Heart Against Ischemia/Reperfusion Injury

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Recently we found that administration of Intralipid (ILP) during reperfusion significantly improves post-ischemic cardiac function and reduces the myocardial infarct size by ~70% , both in the isolated mouse heart and in-vivo rat heart. Here we investigated whether ILP-induced cardioprotection is mediated through the inhibition of GSK-3b. Wild type (WT) C57BL/6 male mice and GSK-3b Knockin (KI) were used. The isolated hearts were subjected to 20 min of global normothermic ischemia followed by reperfusion with 1% ILP (40 min for heart function and infarct size and 10 min for calcium retention capacity (CRC) experiments). The left ventricular (LV) systolic pressure, LV end-diastolic pressure (LVDP), heart rate, maximum velocity of contraction (dP/dt max) and maximum velocity of relaxation (dP/dt min) were recorded. Myocardial necrosis was assessed using TTC staining. Mitochondria were isolated to measure CRC by calculating the number of pulses required to trigger the opening of the mitochondrial transition permeability pore as a result of calcium overload. Before ischemia, the baseline RPP, LVDP, dP/dtmax and dP/dtmin in GSK-3b KI mice were similar to WT. However, the functional recovery during reperfusion was very poor in GSK-3b KI mice. At the end of 40 min of reperfusion, the RPP was 1990 ± 499 in GSK-3b KI mice vs. 15405 ± 1011mmHg*beats/min in WT, the LV dP/dtmax was 239.7 ± 17.8 in GSK-3b KI vs. 2703 ± 145 mmHg/s in WT and the LV dP/dtmin was 219 ± 14 in GSK-3b KI vs. 1683 ± 66 mmHg/s in WT. The infarct size was significantly larger compared to WT (45.3 ± 10.3 vs. 16.7 ± 2.33% in WT, $P<0.001$). Postischemic administration of ILP in GSK-3b KI mice demonstrated lower CRC than WT (1.3 ± 0.1 vs. 2.7 ± 0.06 μM/mg-mitochondrial protein in WT). In conclusions, these data demonstrate that phosphoryltaion of GSK-3b is required for the cardioprotective action of ILP.

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CVT Inhibits the Intralipid Rescue of Bupivacaine-Induced Cardiotoxicity in a Dose-Dependant Manner

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Intralipid (ILP) is effective in resuscitating Bupivacaine-induced cardiac arrest, but it's mechanism of action is not clear. Here we investigated whether protective action of ILP is mediated through fatty acid oxidation pathway using CVT-4325, a fatty acid oxidation inhibitor. Male Sprague-Dawley rats (300-350 g) were anesthetized (ketamine (80mg/kg) and xylazine (8mg/kg, i.p.)) and then ventilated. In control (CTRL, n=8), asystole was achieved with a single dose of Bupivacaine (10mg/kg over 20 seconds, i.v.) and then resuscitation was started immediately using ILP (5ml/kg bolus, and 0.5ml/kg/min maintenance) together with cardiac massage. In CVT group (n=12), the protocol was identical to CTRL, except that rats were pre-treated with different doses of CVT (0.5, 0.25, 0.125 and 0.0625mg/kg bolus i.v.) for 5 min. The heart rate (HR), ejection fraction (EF) and fractional shortening (FS) were measured by echocardiography. As expected, in CTRL group, administration of Bupivacaine resulted in asystole and ILP improved HR and cardiac function gradually within 10 min; HR increased from 73 ± 3beats/min at 1 min to 180 ± 23beats/min at 5min, and further to 243 ± 20beats/min at 10min. The left ventricular systolic function fully recovered in all rats within 5min of ILP treatment (EF=70 ± 3%, FS=40 ± 3%). In CVT pretreated group, however, there was no recovery of cardiac function with ILP at CVT doses of 0.5, 0.25 and 0.125mg/kg within 10min of ILP therapy. ILP was only able to rescue Bupivacaine-induced cardiotoxicity at lowest dose of 0.0625 mg/kg CVT as cardiac function improved gradually within 10min (HR from 65 at 1min to ~170min at 10 min; EF=~55%, FS=~29% at 10min and QRS from 33 ms at 1 min to 27 ms at 10 min). In conclusion CVT-4325 prevents intralipid rescue of Bupivacaine-induced cardiotoxicity in a dose dependant manner.

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Elasticity of Developing Cardiac Tissue and Influence on Early Cardiomyocyte Beating

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Recent studies have demonstrated the effects of cardiomyocyte mechanosensitivity to ECM elasticity on beating physiology of 10 day chick embryo cardiomyocytes[1] and also of neonatal rat cardiomyocytes[2], developmental stages for which the heart mechanics are established and the Young's modulus is E~10-20 kPa. Here we study the evolution of embryonic cardiac tissue mechanics in parallel with the effects of microenvironment mechanics on individual cardiomyocyte function throughout early development. To measure the changing mechanical properties of cardiac tissue, we used micropipette aspiration to measure local and average bulk elastic moduli of embryonic avian heart tissue. We observe stiffening of the looping heart tube (days 2-4) from 1 kPa average elasticity to 2 kPa. We measure a greater local elastic modulus in the inner curvature of the looping heart tube than the outer curvature. Treating heart tubes with blebbistatin led to a uniform 30% decrease in elasticity, indicating that the local elasticity is not solely due to actomyosin contractility. We performed a proteomic analysis of various anatomical positions along the 2-4 day heart tubes by mass spectrometry, to measure the relative spaciotemporal changes in protein expression. To explore the effects of the immediate microenvironment mechanics on early cardiomyocyte function, heart cells were isolated from 2-4 day chicken embryos, cultured on collagen-coated polyacrylamide gels of varying stiffness, and observed for effects of substrate elasticity on spontaneous beating and morphology. After 24 hours in culture, cardiomyocyte beating magnitude was larger on softer 1 kPa gels than on stiffer 5-34 kPa gels, with no measurable difference in behavior with developmental stage.

[1] A. Engler et al. Journal of Cell Science 121: 3794-3802 (2008).
[2] J. Jacot, et al. Biophysical Journal 95(7): 3479-3487 (2008).

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Mechanisms of Prevention of Pulmonary Hypertension-Induced Right-Ventricular Failure by Intralipid

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Intralipid (ILP) has been used for treatment of local anesthetic-induced cardiac-arrest and as source of parenteral nutrition. Some of its constituents are precursors of pulmonary vasodilator prostaglandins. Pulmonary hypertension (PH) is associated with pulmonary vascular remodeling leading to right-ventricular (RV) hypertrophy and failure. Recently we found that ILP prevents PH in rats. Here we investigated the mechanisms involved in this prevention. Rats were treated with monocrotaline(60 mg/kg) to induce PH, and then either received daily ILP (1 mL of 20% ILP/day) for 30days or left untreated to develop RV failure (RVF). Saline treated rats served as control. Serial echocardiography was performed to monitor cardiopulmonary hemodynamics., RV pressure (RVP) was recorded by direct cardiac catheterization right before sacrifice. Immunohistochemistry, confocal-microscopy, Western Blot analysis and RT-PCR were performed. RVF group developed PH that led to RVF later with significantly increased RVP (70 ± 5mmHg,n=10) and depressed RV ejection fraction (RVEF=34 ± 2%). Severe structural changes in RV and lung were observed in RVF group including RV-hypertrophy, increased lung weight, pulmonary medial hypertrophy, fibrosis, apoptosis (upregulation of Caspase-3 (~10fold)), inflammation (increased expression of IL-6) and suppression of angiogenesis (decreased VEGF and capillary-density). Furthermore, RVF was associated with downregulation of phospho-eNOS(~4fold), Caveolin-1 (~6fold) adenosine-A2B receptor and estrogen receptor-β in lungs. In the RV, adenosine-A2A receptor and estrogen receptor-b were downregulated in RVF. ILP therapy prevented PH-induced RVF by restoring RVP (30 ± 2mmHg,n=8) and RVEF(63 ± 1.5%) and attenuating RV hypertrophy and lung remodeling. ILP suppressed inflammation and fibrosis along-with improving angiogenesis and restoring phospho-eNOS, Caveolin-1 in lungs and Caspase-3, adenosine-A2 and estrogen receptor-β expression in lungs and RV. In conclusion ILP prevented PH and RV-failure by preserving cardiopulmonary structure and function and enhancing perfusion via adenosine receptor, estrogen receptor-b and eNOS-mediated mechanisms.

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Sex Differences in the Mechanical Properties of Rat Myocardium After Exposure to Simulated Microgravity

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Female astronauts are more likely than male astronauts to develop presyncope and orthostatic intolerance when they return to normal gravity after spaceflights. The underlying mechanisms for this are unclear but could include myocardial adaptations to micro-gravity conditions. This study was designed to test whether there are sex-specific changes in the mechanical properties of myocardial tissue in rats subjected to a period of simulated microgravity. Multicellular myocardial preparations were isolated from control male and female Sprague-Dawley rats and corresponding experimental animals that were hindlimb unloaded (HLU) for 14 days. Preparations were subjected to standard mechanical tests imposed under muscle length control in solutions with pCa