manner; its effects were inhibited by NOS inhibitors (e.g. L-NAME).

Conclusion and implication The tissue-protective properties of EPO-related cytokines are likely to be mediated by NO in pathophysiological settings associated with poor oxygenation. Further work should be directed towards an understanding of the cellular redox status and some of the signalling events down-stream of the emerging EPO/EPOR/NO axis that underpin its beneficial biological effects. These findings may be particularly relevant to atherogenesis and post-angioplasty restenosis.

193 LACK OF FIBROBLAST GROWTH FACTOR-23 (FGF23) PRESERVES CARDIAC FUNCTION IN A MURINE MODEL OF ACUTE MYOCARDIAL INFARCTION

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Myocardial infarction (MI) is a major cause of death worldwide. We recently showed that intact circulating fibroblast growth factor-23 (FGF23) is profoundly up-regulated after experimental MI in mice and rats. FGF23 is a bone-derived hormone involved in systemic phosphate homeostasis and vitamin D metabolism. Although the pathophysiological mechanisms remain to be identified, clinical studies have shown a strong association between FGF23 and left ventricular hypertrophy, atrial fibrillation and cardiac systolic dysfunction. Here, we explored the hypothesis that FGF23 may be causally linked to progression of cardiac dysfunction post-MI, using a mouse model lacking both *Fgf23* and a functioning vitamin D receptor (VDR). Surgery was performed on 3-month-old, male, wild-type (WT), VDR and *Fgf23*$^{-/-}$/VDR$^{\hat{I}"/\hat{I}"}$(Fgf23/VDR) compound mutant mice on a C57BL/6 background. To normalise mineral homeostasis in VDR-ablated mice, all mice were kept lifelong on a rescue diet enriched with calcium, phosphorous and lactose. MI was induced by permanent ligation of the left descending coronary artery. Sham-operated (Sham) mice served as a control. One week after MI, cardiac function was assessed by echocardiography and electrocardiography (ECG). Intracardial pressure monitoring was performed by catheterization as a terminal procedure, 2 weeks post-MI. Echocardiography confirmed left ventricular infarction, and ECG recordings revealed comparable ST depression in MI mice of all genotypes. However, Fgf23/VDR compound mutant MI mice showed improved fractional shortening, relative to WT and VDR MI controls. In addition, Fgf23/VDR compound mutant MImice were more resistant against the impairment of ventricular contraction and relaxation observed in WT and VDR MI mice, as measured by left ventricular dP/dt_{max}, dP/dt_{min}, and relaxation time tau, 2 weeks post-MI surgery. Our data indicate that lack of Fgf23 improves cardiac contractile function following experimental MI. This finding underscores the potential importance of the heart-bone-axis and of the new field of cardio-osteology because the levels of circulating intact FGF23 may influence cardiac recovery after MI.

194 FERRITIN OXIDISES LOW DENSITY LIPOPROTEIN AT LYSOSOMAL PH

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Background Many lines of evidence support the role of oxidised low density lipoprotein (LDL) as the main culprit in atherogenesis. Our laboratory has previously shown that iron is involved in the oxidation of LDL in lysosomes, a possible mechanism for the progression of atherosclerosis. Ferritin is an iron-storage protein which might enter lysosomes by autophagy and be involved in lysosomal LDL oxidation. The aim of this study was to test the hypothesis that ferritin can catalyse the oxidation of LDL at lysosomal pH and that antioxidants protect against this oxidation.

Method LDL (50 ug protein/ml) was oxidised by ferritin (0.05–0.2 uM) at 37°C and pH 4.5, the formation of conjugated dienes was monitored spectrophotometrically at 234 nm up to 1200 min. The effect of pH on LDL oxidation was tested by comparing the oxidation of LDL by ferritin (0.1 and 0.2 uM) at pH 4.5 or pH 7.4. The iron released from ferritin was monitored spectrophotometrically using the ferrous iron chelator bathophenanthroline. Ferritin (0.1 uM) was incubated at 37°C at pH 4.5 and pH 7.4. Bathophenanthroline (30 uM) was added at different time intervals up to 24 h and the amount of ferrous complex was measured at 535 nm. Iron release was also measured by ultrafiltration followed by atomic absorption spectrophotometry.

Results LDL was oxidised effectively by ferritin (0.05–0.2 uM). The oxidation was much faster at lysosomal pH 4.5 than at pH 7.4, which could be attributed to our finding that more iron was released from ferritin at pH 4.5. EDTA and diethylenetriamine pentaacetate inhibited the oxidation, but did not inhibit it entirely. The water-soluble lysosomotropic drug cysteamine (5 uM-10 mM) inhibited the initial oxidation of LDL in a concentration-dependent manner, although the lower concentrations exhibited a delayed prooxidant effect which was less marked with the higher concentrations. Concentrations above 1 mM had no prooxidant effect. Cysteamine was shown, using the ferrous iron chelator bathophenanthroline, to release iron from ferritin and this might explain the prooxidant effect. The lipid-soluble antioxidant N, N′-diphenyl-p-phenylenediamine (5 and 10 uM) inhibited the oxidation of LDL by ferritin without any prooxidant effect.

Conclusion These findings support the possible involvement of ferritin in lysosomal LDL oxidation and the use of appropriate antioxidants to prevent this oxidation in atherosclerosis.

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