Pathways from being small or preterm to a vulnerable heart

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Left ventricular hypertrophy is an indicator of poor cardiovascular outcome. It is possible that slow growth in fetal life upregulates cardiac signalling pathways involved in left ventricular hypertrophy and thus puts the individual at risk of further cardiovascular disease in adult life. We have shown that the IUGR fetus has higher cardiac IGF-2 and IGF-2R gene expression. This may be a response to the chronic hypoxemia that these fetuses are exposed to. If this is the case, it is not clear why this change in cardiac gene expression is maintained into postnatal life in the low birth weight lamb at 21d of age, at a time when oxygen and nutrient supply are normal. *In vitro* rat experiments have shown that IGF-2R activation can induce cardiomyocyte hypertrophy *via* a G protein coupled receptor (Gαq)-dependent manner.

Does the increase in IGF-2R gene expression represent increased clearance of IGF-2 or does IGF-2R activate pathological hypertrophy signalling pathways in the heart of the intrauterine growth restricted (IUGR) fetus and the low birth weight lamb?

Cardiomyocytes from sheep fetuses at 126d gestation were isolated and cultured in the presence of Leu^{27}IGF-2, to selectively activate the IGF-2R signalling pathway, and inhibitors of proteins in that pathway. Leu^{27}IGF-2 increased the area of cultured binucleated, but not mononucleated, cardiomyocytes. Inhibition of PKC with Gö6976 did not prevent the Leu^{27}IGF-2 induced increase in the cell area of binucleated cardiomyocytes; however, inhibition of CaMKII with KN-93 blocked the effect of Leu^{27}IGF-2. These data suggest that activation of IGF-2R increases cardiomyocyte area *via* CaMKII *in vitro.* To confirm these effects in the normally grown fetus in late gestation, we inserted a catheter into the left circumflex coronary artery to infuse Leu^{27}IGF-2 selectively to the left ventricle. Infusion of Leu^{27}IGF-2 did not change fetal weight or heart weight. Importantly, Leu^{27}IGF-2 did not increase blood pressure, the major contributor to hypertrophy of cardiomyocytes. There was no effect cardiomyocyte proliferation or binucleation, but there was an increase in the area of cardiomyocytes. These data show that both *in vitro* and *in vivo*, activation of cardiac IGF-2R signalling pathway in the fetus results in hypertrophic growth of cardiomyocytes. The specific proteins mediating these effects are unclear and require elucidation.