Calcium/calmodulin-dependent protein kinase II delta – does ageing mirror disease in the cardiovascular system?

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Calcium/calmodulin–dependent protein kinase II delta (CaMKIId) plays a fundamental role in cardiac dysfunction and is known to be overexpressed and hyper-activated in the diseased heart. A role for CaMKIId in compromised cardiovascular function associated with ageing has yet to be established. Here we compare CaMKIId expression and oxidation (a novel route of enzyme activation) in the diseased and in the aged heart and vasculature. Using a minimally invasive transverse aortic banding (MTAB) mouse model of cardiac hypertrophy as our disease model, we investigated whether alterations in CaMKIId and oxidised CaMKII (ox-CaMKII) observed during cardiac disease are also a key feature of ageing, where oxidative stress is apparent. Myocardial function was assessed in vivo by echocardiography and compared with that of sham-operated animals. A significant increase in systolic blood pressure (110±6.3 vs 78±2.6, MTAB vs sham, n=4), mean arterial pressure (75±3.3 vs 60±2.6 (mmHg), MTAB vs sham) and reduction in fractional shortening (39.4±4.4 vs 53.6±3.8 (%FS) MTAB vs sham, n=7, $p<0.05$) was observed in the hearts from hypertrophied animals demonstrating successful surgical intervention. Post-mortem analysis revealed increased heart weight:body weight in MTAB animals (5.48±0.17 vs 4.32±0.01, MTAB vs sham, n=6, $p<0.05$). Quantitative immunoblotting of CaMKIId and ox-CaMKII expression in whole heart homogenates from MTAB animals showed significant up-regulation of both when compared to sham controls (0.68±0.02 vs 0.47±0.01 MTAB v's sham, n=7, $p<0.01$). Interestingly, similar results were obtained in hearts from aged animals. A significant increase in CaMKIId expression was evident in aged hearts (0.81±0.08 vs. 0.46±0.08 aged vs young, p=0.04, n=3) and preliminary data suggests ox-CaMKII levels also show an increase in comparison to young (1.5-fold increase, n=1). Similar experiments were also conducted in young and aged rat aortae to assess CaMKIId involvement in vascular function. Vessels from aged subjects showed a significant increase in wall thickness (16.4±0.9 vs. 28±1.5 (um), young vs. aged, p=0.002, n=3) which may suggest an altered phenotype comparable to that observed during disease. Further quantitative immunoblotting indicated that CaMKIId is highly expressed in the vasculature and initial results suggest some alterations in ox-CaMKII protein levels with ageing, parallel to that observed in the heart. Overall, this work highlights for the first time that ageing alone, produces similar physiological and biochemical alterations in the heart as observed during cardiac disease. In addition to this, preliminary data from the vasculature has revealed a similar trend, suggesting CaMKIId may play an important role in overall deterioration of cardiovascular function with progressive ageing.