Evidence for altered communication between the L-type Ca^{2+} channel and mitochondria in a model of cardiomyopathy

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The progression of cardiac hypertrophy to failure and development of many cardiomyopathies involves myocyte remodelling, disorganisation of cytoskeletal proteins and reduced energy metabolism. The mechanisms by which cytoskeletal disruption leads to mitochondrial dysfunction and compromised cardiac function responsible for the development of the myopathy are poorly understood. Calcium influx through the L-type Ca^{2+} channel is a requirement for contraction in the heart. The L-type Ca^{2+} channel can also regulate mitochondrial function. Activation of the channel can influence mitochondrial superoxide production, NADH production and metabolic activity in a calcium-dependent manner. Activation of the channel can also increase mitochondrial membrane potential in a calcium-independent manner. This response is dependent upon an intact cytoskeleton. We hypothesized that the absence of a cytoskeletal protein and disruption of the normal architecture will result in altered communication between the L-type Ca^{2+} channel and mitochondria. We investigated this hypothesis in a murine model of Duchenne Muscular Dystrophy (mdx) that lacks dystrophin. Cardiac myocytes were isolated from C57BL/10ScSn-Dmdmdx/Arc (mdx) and C57BL/10ScSnArc (control) mice that were anaesthetized with pentobarbitone sodium (160mg/kg) by intraperitoneal injection according to the National Health and Medical Research Council Australian code of practice for the care and use of animals for scientific purposes 7th Edition, 2004. In myocytes from 8 week old mdx mice that exhibit disorganised cytoskeletal protein networks but not yet overt cardiomyopathy, calcium influx through the channel was significantly greater due to the delayed inactivation rate of the channel. However activation of the L-type Ca^{2+} channel did not increase mitochondrial membrane potential or increase metabolic activity (measured as formation of formazan from tetrazolium salt) in myocytes isolated from mdx hearts. Application of 4,4′-diisothiocyano-2,2′-stilbenedisulfonic acid, that blocks anion transport mimicked the response of BayK(−) in control myocytes and “restored” the increase in mitochondrial membrane potential in mdx myocytes. The activities of the mitochondrial respiratory complexes were normal in mitochondria isolated from 8 week old mdx hearts and in mitochondria isolated from 40 week old mdx hearts that had developed cardiomyopathy. We conclude that the communication between the L-type Ca^{2+} channel and the mitochondria is altered in the dystrophin-deficient cardiomyocyte. This appears to involve an alteration in the association between the channel protein, cytoskeletal proteins and mitochondrial anion transport and precedes the development of cardiomyopathy