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Perinatal endoplasmic reticulum stress potentiates cardiomyocyte apoptosis

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Keywords

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Abstract

One-third of cardiomyocyte are lost just before birth. We studied the role of endoplasmic reticulum (ER) stress response in cardiomyocyte apoptosis in perinatal sheep hearts. Snap-frozen left ventricular (LV) samples and cultured cardiomyocytes from normally growing lambs at 135 days of gestational age (dGA; term=147 dGA), 143 dGA, 1 day postnatal age (dPN) and 5 dPN, and tissue from ~1 year old adults were used for this study. The ER stress marker protein GRP78 expression is higher in the heart at 143 dGA and decreased after birth. In addition, the ER stress response phosphorylation of eIF2a is transiently suppressed at 1 dPN before returning to 143 dGA-high levels at 5 dPN. Expression of the apoptosis genes caspases -3, -7, and -9 were all lowest at 135 dGA. In primary cardiomyocyte cell cultures treated with the ER stress inducer thapsigargin, cell viability (MTT) assay showed sensitivity was lowest at 135 dGA. TUNEL assays showed significantly greater apoptosis in response to thapsigargin at 143 dGA and 1 dPN compared to 135 dGA and 5 dPN. In addition, six and twelve hours of thapsigargin treatment upregulates ER stress response phosphorylation of EIF2a and caspase 3 and -9 in 143 dGA and 1 dPN. We interpret these data to indicate that levels of ER stress, and sensitivity to ER stress, changes in perinatal cardiomyocytes. The ER stress response can induce cell survival, but it appears to contribute to apoptosis immediately before and after birth.