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EDITORIAL

# Antenatal Glucocorticoid Therapy for Fetal Heart Development

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Mitochondria occupy approximately 30% cell volume of cardiac myocytes. They are key organelles that orchestrate cardiac function under physiological and pathological conditions. Their principal function is ATP production via their electron transport system. However, recent studies indicate that mitochondria have additional roles in oxidative stress production,[1] intracellular $Ca^{2+}$ handling,[2] and apoptosis induction,[3] all of which interplay to create the single functional machinery of the mitochondria. For example, intracellular $Ca^{2+}$ concentration is a trigger that activates pyruvate dehydrogenase, isocitrate dehydrogenase, $\alpha$-ketoglutarate dehydrogenase and ATP synthase, enzymes of ATP production. Intracellular $Ca^{2+}$ concentration is controlled by the sarcoplasmic reticulum $Ca^{2+}$-ATPase (SERCA2) protein, whose function depends on the amount of ATP supplied by the mitochondria. In the failing heart, impaired SERCA2 function decreases intracellular $Ca^{2+}$, which leads to further decreases in ATP production, resulting in a vicious cycle of impaired ATP production and $Ca^{2+}$ cycling.[4]

Article p171

Recent models using genetically engineered mice have clarified the importance of the mitochondria in securing proper cardiac function. Mitochondria possess their own DNA that encodes 13 key proteins in their electron transport system. mRNA for these proteins are transcribed by the mitochondrial DNA-specific transcription factor, Tfam, a regulator of mitochondrial DNA replication. Heart-specific Tfam knockout mice develop hearts with a dilated left ventricular chamber, low ejection fraction and atrioventricular conduction delay, resembling dilated cardiomyopathy,[5] and have a lifespan that is significantly shorter than that of wild-type mice. In contrast, Tfam transgenic mice develop hearts that cannot undergo cardiac remodeling after myocardial infarction and show better survival than wild type mice.[6]

In this issue of the *Circulation Journal*, Mizuno et al[7] provide experimental evidence that antenatal administration of dexamethasone enhances ATP production after birth by activating the mRNA expression of creatine kinases (CKs), key enzymes for energy transfer from sites of ATP production to those of consumption.[8] Antenatal corticosteroid hormone treatment is recommended by the National Institutes of Health for maturation of the fetal lungs in the case of premature delivery.[9] The serum cortisol concentration is lower in preterm infants than in mature infants, and cortisol accelerates the maturation of the lung, liver, gut and kidney.[10] However, the effect of glucocorticoid on heart development, especially on the ATP production and transfer system, has not been fully elucidated. Cardiac myocytes express 3 different isoforms of CK: myofibrillar M-type CK (M-CK), myofibrillar B-type CK and mitochondrial CK (miCK). miCK transforms ATP produced in mitochondria into phosphocreatine (PCr), an energy "currency" in the cell, and then PCr is re-converted into ATP by myofibrillar CK located in the vicinity of ATP-consuming sites such as myofibrils and the sarcoplasmic reticulum. Models using genetically engineered mice reveal that two-thirds of the energy needed for ATPases is provided by PCr, while the remaining energy comes from ATP itself.[11]

This study demonstrates quite low mRNA expression and M-CK concentration during the fetal stage, but which gradually increase after birth. Thus, babies are not born with a fully functional heart. Furthermore, induction of miCK mRNA expression is relatively late compared with that of M-CK, which confirms a previous report on the time difference in the development of M-CK and miCK function.[12] Because of the low $PO_2$ environment in the fetus, the fetal heart does not produce energy by $\beta$-oxidation of fatty acids in the mitochondria, which requires large amounts of oxygen, but by glycolysis in the cytosol, where M-CK is expressed. High concentration of oxygen after birth may thus activate both M-CK and miCK function and mRNA expression.

This study also found that antenatal glucocorticoid administration significantly increased mRNA and protein levels of M-CK and miCK, even in the late fetal, anaerobic stage. Because M-CK and miCK mRNA failed to be induced by glucocorticoid in the presence of a glucocorticoid receptor antagonist, CKs are most likely induced by signaling through such glucocorticoid receptors. The glucocorticoid receptor is a nuclear receptor that complexes with glucocorticoids to initiate transcription of many genes by binding with the glucocorticoid responsive element (GRE) of target genes.[13] Unlike genes that have GRE, such as insulin-like growth factor II, angiotensinogen and erythropoietin, the CK genes appear to lack apparent GRE in their regulatory region. The precise mechanism for post-transcriptional control of CKs requires further investigation.

Antenatal glucocorticoid administration was also demonstrated to increase ATP levels after birth. The principal function of the CK system is energy transport from the mitochon-


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dria to ATPase, known as CK shuttling.[8] However, the CK system is capable of increasing ATP production by enhancing the conversion of PCr to ATP when mitochondrial function is impaired[11] or visa versa when CK function is impaired. Thus, the CK system works with the mitochondria in both a competitive and compensatory manner. Notably, ATP production can be enhanced by manipulating the CK system by antenatal glucocorticoid administration.

Glucocorticoid induces myocyte differentiation rather than myocyte proliferation. Cardiac myocytes are able to proliferate through cell division, even after birth. Therefore, antenatal glucocorticoid therapy may decrease the number of cardiac myocytes and induce cell hypertrophy. In fact, a decrease in cell number has been reported after glucocorticoid administration.[14] It is unknown whether glucocorticoid-treated cardiac myocytes have the potential to divide after birth. In this case, antenatal glucocorticoid therapy may be able to improve heart development temporarily but not to a level sufficient for adulthood. Further investigation and thorough follow-up of currently treated babies[15] are required to establish this treatment as a standard therapy.

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