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, intracellular Ca\(^{2+}\) handling, and apoptosis induction, 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.

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, and have a lifespan that is significantly shorter than that of wild type mice. In contrast, Tfam transgenic mice develop hearts with a dilated left ventricle and show better survival than wild type mice.

In this issue of the Circulation Journal, Mizuno et al. 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. Antenatal corticosteroid hormone treatment is recommended by the National Institutes of Health to those of consumption.

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dra to ATPase, known as CK shuttling. 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.

References

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