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EDITORIAL

Mitochondrial Function and Blood Pressure Regulation: From Bioenergetics to Pathophysiology

Ighodaro Igbe* and Osaze Edosuyi

The mitochondrion is the powerhouse of all living cells as it provides the energy needed to maintain obligatory regulatory functions.[1] The generation of adenosine triphosphate (ATP) via oxidative phosphorylation underlies the principal role of the mitochondrion in cell survival. Aside this basic contribution to energy generation, the mitochondria has been established to regulate cell death (apoptosis), redox and ion signaling.[2] The crosstalk between redox signaling and a myriad of pathological disorders created a nexus between the mitochondrion and the cardiorenal system.[3,4] Similarly, the high distribution of mitochondria in organs of the cardiorenal system, meant that these organs such as the kidney, are subject to the effect of mitochondria-induced alterations in redox signaling.[5] For instance, mitochondrial dysfunction has been linked to the pathophysiology of kidney disorders.[6] Considering the intricate link between the kidneys and blood pressure regulation, mitochondrial dysfunction was suggested to contribute significantly to distortions in renal control of blood pressure.

Recently, it was reported that the tricarboxylic acid (TCA) cycle plays a role in the etiology of genetic hypertension.[7] This novel discovery linked the activity of the TCA cycle enzyme, fumarase to a reduction in nitric oxide production and an upregulation in redox signaling in the renal medulla of salt-sensitive rats.[7,8] In these animals, an innate mutation in the fumarase enzyme, reduced its activity and increased cellular levels of its substrate, fumarate. Hence, the role of these TCA cycle intermediaries was shifted from being 'mere' participants in the generation of energy to endogenous ligands with biochemical targets that alter renal function and by extension, blood pressure. Furthermore, fumarate was shown to reduce blood pressure and modulate the expression of genes that ameliorated hypertension-induced renal damage in deoxycorticosterone acetate (DOCA) hypertension, a non-genetic form of hypertension.[9] Subsequently, succinate, the upstream product of fumarate was reported to directly stimulate GPR91 receptors to increase blood pressure.[10] These actions of fumarate and its intermediaries, exceed the renal system as reports have shown a cardioprotective role via upregulation of nuclear erythroid factor-2 (Nrf2).[11] Fumarate is now known to regulate the expression of genes such as hypoxia inducible factor (HIF-1), transforming growth factor (TGF-β), kidney injury molecule (KIM-1) amongst others. What is evident from the foregoing is that the mitochondrion is no longer just an idle energy-generating center. It is now listed as a probable etiology in hypertension, and this has opened new vistas of possibilities as it relates to the pathophysiology of hypertension.[8] Is it possible that these intermediaries are involved in the physiological control of blood pressure? Could they also be exerting direct vasoactive effects? Is it likely that they may be modulating the expression of genes that underlie vascular/organ remodeling? And finally, is it possible that mitochondrial dysfunction could partly explain the etiology of idiopathic hypertension? As, far-reaching as these insights may be, it is not completely out of place to be optimistic as the foray into these previously uncharted areas of mitochondrial metabolism progress. What is very clear is that there is now a paradigm shift in the function of the mitochondria in blood pressure regulation from that of a bioenergetic center to pathophysiological axis which contributes significantly to the etiology of hypertension.[12]

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Ighodaro Igbe
*Corresponding author. e-mail: igbe.ighodaro@uniben.edu

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Osaze Edosuyi

Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria

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