Letter to the Editor

Mitochondria in β-adrenergic signaling: emerging therapeutic perspectives in heart failure and ventricular arrhythmias

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We read with great interest the editorial article "*Electrical storm: mechanistic and therapeutic considerations to avoid death in the survivors*" by Tsuji and Dobrev which brings into spotlight mitochondria as an emerging and significant determinant of heart failure (HF) outcome. Despite the fact that current treatments for HF as well as electrical storm treatment do not directly target mitochondria, it would be interesting to approach their effects on them, with focus on β-adrenergic signaling.

Mitochondria are key-organelles that modulate cell viability through energy production and induction of apoptosis. Interestingly, adrenergic signaling has been shown to affect both functions in cardiomyocytes either through the adenyl-cyclase, mostly through protein kinase A (PKA) activation or PI3K/Akt pathway. Binding of agonists to β-receptors (βR) triggers calcium influx. In this context, mitochondrial calcium uniporter, a crucial protein for calcium re-uptake in mitochondria, regulates adaptation on adrenergic activity (1). Sequentially, a cytochrome C leak from mitochondria is noted and the intrinsic apoptotic pathway is triggered leading to cardiomyocyte cell death.

Recent studies indicated that β signaling-mediated calcium loading results in opening of mitochondrial permeability transition pore (MPTP) and increased reactive oxygen species (ROS) production that triggers apoptosis. ROS production in response to adrenergic stimulation is divided into an acute and a delayed phase that are both dependent on PKA and independent of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which constitutes the other important producer of ROS in the cell. Increased apoptosis was shown to be PKA dependent, which recruits neurofibromin 2 and thus, upregulates Bad and Bax pro-apoptotic proteins (2). PKA's inhibition abolished the observed increase in pro-apoptotic proteins after challenge of cardiomyocytes with dobutamine (3). In regards to cell metabolism, a gain of function mutation in β1R resulted in increased cell respiration and fatty acid oxidation (4). Increased cell respiration after βR activation results in augmented production of ROS, which were shown to induce phosphorylation of ryanodine receptors and thus, a sarcoplasmic reticulum Ca^{+2} leak that can induce arrhythmias (5). Especially under hypoxic conditioning, β-signaling is detrimental for cardiomyocyte viability and leads to mitochondrial depolarization and membrane damage (6).

Given the central role of mitochondria in transducing adrenergic signaling, pre-clinical research soughs to also assess cardiac mitochondrial response to treatment with β-blockers. As early as in 1980 Bhayana *et al.* were the first to notice that treating rats with propranolol resulted in a decrease in respiratory control index (RCI) of cardiac

mitochondria (7). Metoprolol was later shown to inhibit β oxidation by downregulating carnitine palmitoyl-transferase I (8). Along this line, treatment of cardiomyocytes with carvedilol inhibited MPTP opening and ROS induced cell injury. Importantly carvedilol, apart from cell injury protection, conferred an increase in mitochondria biogenesis as well as in expression of cytochrome C and cytochrome oxidase, complex IV of oxidative phosphorylation (9). Finally, rats treated with atenolol demonstrated significant reduction in both mitochondria oxygen consumption and ROS production, however, these adaptations were not associated with a survival benefit (10).

Despite accumulating evidence on the relationship between adrenergic stimulation and mitochondrial activity, data from human studies are not available. As a consequence, dose response curves to evaluate the impact of current therapeutic regimens on mitochondrial function cannot be derived. In fact, two large randomized clinical trials that compared β-blockers to placebo in HF patients provided contradictory results with one study demonstrating a significant decrease in peak oxygen consumption in treated patients (11), while the other did not (12).

In our study, we have found that treating electrical storm with the combination of propranolol (a non-selective β-blocker) leads to marked improvement of outcomes compared to β2 selective metoprolol (13). Could adrenergic effects on mitochondria account for that difference? There has been evidence for a differential effect of β2 and β1 signaling on cardiomyocytes, as myocardial apoptosis was shown to be β1 dependent with limited contributing effect of β2 activation (14). However, holding this difference responsible for the advantage shown in treating electrical storm with propranolol in our study is largely hypothetical, as there are many other factors that forge the pathophysiological background for the observed difference (15). Hence, we will fervently await the result of further animal and clinical studies which will prove whether targeting mitochondria can really switch gears in the treatment of HF.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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