

Role of the Extracellular Ca²⁺/cyclic AMP- Adenosine Signaling Pathways in Cardioprotection

Francisco Sandro Menezes-Rodrigues¹, José Gustavo Padrao Tavares¹, Paolo Ruggero Errante¹, Ênio Rodrigues Vasques², Maria do Carmo Maia Reis³, Bráulio Luna-Filho³, Fulvio Alexandre Scorza⁴, Afonso Caricati-Neto¹, Leandro Bueno Bergantim^{*}

¹Department of Pharmacology, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), Brazil.

²Departament of Gastroenterology, LIM 37, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

³Department of Cardiology, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), Brazil.

⁴Department of Neuroscience, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), Brazil.

***Corresponding author:** Dr. Leandro Bueno Bergantim, Department of Pharmacology, Escola Paulista de Medicina-Universidade Federal de São Paulo (UNIFESP), Brazil, Tel: 551155764973, Email: leanbio39@yahoo.com.br

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Editorial

Ischemic cardiac diseases (ICD) produce immense health and economic burdens in the United States, and globally [1,2]. Among the ICD, acute myocardial infarction (AMI) represents the commonest cause of morbidity and mortality worldwide [2,3]. The cardiac muscle can tolerate short periods of severe and total ischemia, which occur in coronary vasospasm (e.g. angina pectoris and acute myocardial infarction). Moreover, it is known that short periods of ischemia are not associated with increased cardiac myocyte death. However, if there is an increasing of duration, and severity of cardiac ischemia, it may be developed great myocardial damage, and susceptibility to further injury during reperfusion (R). Thus, the combined damage of ischemia (I) with clearing of artery (e.g. catheterization) may compromise cardiac structure and function, especially excitation-contraction coupling [2-4].

The excitation-contraction coupling in cardiac myocytes depends on ionic homeostasis, especially by a precise adjustment of the intracellular calcium ([Ca²⁺]_i) which maintains the strength, and frequency, of cardiac function [5]. In cardiac sarcolemmal, the T-tubules presented in myocytes make closely contact with junctional sarcoplasmic reticulum (SR), where the L-type Ca²⁺ channels (LTCCs) are highly expressed, and are in close proximity to cardiac ryanodine receptors (RyR2), which are responsible to release Ca²⁺ from SR [5]. This LTCC-RyR2 implies that Ca²⁺ ions, which enter via LTCC, cause high increase of [Ca²⁺]_i due to Ca²⁺ release from SR by opening RyR2 during excitation-contraction coupling. This event is called Ca²⁺-induced Ca²⁺-release, which causes Ca²⁺ efflux from the SR during cardiac contraction (systole) [5].

In addition, Ca²⁺ acts as an intracellular second messenger that amplifies the cellular response, for example, by interacting with other second messengers, such as cyclic AMP (cAMP). Thus, the ionic imbalance produced by cardiac I/R injury, especially the cytosolic Ca²⁺ overload, has been implicated as a major cause of severe, and lethal, cardiac arrhythmias due to ICD, such as AMI. Indeed, the cytosolic Ca²⁺ and mitochondrial overload, and bioenergetics collapse, compromise the excitation-contraction coupling, favoring the development of cardiac arrhythmias, such as ventricular arrhythmia and atrioventricular blockade, and death [6-8].

Interestingly, the increased entry of Ca²⁺ via LTCC acts as a negative regulator on the effect of β-AR stimulation due to inhibition of adenylyl cyclase (AC) activity. Increases of intracellular cAMP,

produced by β-adrenergic stimulation in the cardiac muscle, are higher when extracellular Ca²⁺ is lowered, such as by the LTCC blockade with Ca²⁺ channel blockers (CCBs) [9]. These CCBs produce increase in the intracellular cAMP of the smooth muscles [10], neuron cell [11-13], skeletal muscle due to reducing the influx of extracellular Ca²⁺, promoting desinhibition of the AC5 and AC6 isoforms activities [14]. In addition, studies demonstrated the existence of the efflux of cAMP mediated by multidrug resistance proteins transporters in cardiac myocytes [15] and skeletal muscle [16]. According to the most experimental evidences, the blockade of adenosine receptors in skeletal muscle reduces the negative inotropic effect promoted by extracellular adenosine due to efflux of intracellular cAMP signaling pathways [17]. Following this line of reasoning, we may propose that pharmacological modulation of the extracellular Ca²⁺/cAMP-adenosine signaling pathways may be used to produce cardioprotective effects in patients with ICD, such as AMI.

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