Journal of Thrombosis and Circulation Open Access

Menezes-Rodrigues et al., J Thrombo Cir 2017, 3:1
DOI: 10.4172/2572-9462.1000e106

Editorial Open Access

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

Francisco Sandro Menezes-Rodrigues[1], José Gustavo Padrão Tavares[1], Paolo Ruggero Errante[1], Ênio Rodrigues Vasques[2], Maria do Carmo Maia Reis[3], Bráulio Luna-Filho[3], Fulvio Alexandre Scorza[4], Afonso Caricati-Neto[1], Leandro Bueno Bergantin[1*]

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

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

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

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

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

Received date: Feb 27, 2017, **Accepted date**: Mar 3, 2017, **Published date**: Mar 6, 2017

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 ($[Ca^{2+}]i$) 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 Ca^{2+} channels (LTCCs) are highly expressed, and are in close proximity to cardiac ryanodine receptors (RyR2), which are responsible to release Ca^{2+} from SR [5]. This LTCC-RyR2 implies that Ca^{2+} ions, which enter via LTCC, cause high increase of $[Ca^{2+}]$ due to Ca^{2+} release from SR by opening RyR2 during excitation-contraction coupling. This event is called Ca^{2+}-induced Ca^{2+}-release, which causes Ca^{2+} efflux from the SR during cardiac contraction (systole) [5].

In addition, Ca^{2+} 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 Ca^{2+} overload, has been implicated as a major cause of severe, and lethal, cardiac arrhythmias due to ICD, such as AMI. Indeed, the cytosolic Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} is lowered, such as by the LTCC blockade with Ca^{2+} 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 Ca^{2+}, 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 Ca^{2+}/cAMP-adenosine signaling pathways may be used to produce cardioprotective effects in patients with ICD, such as AMI.

Acknowledgments

Research supported by CNPq, FAPESP and CAPES.

References

1. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. (2016) Heart disease and stroke statistics-2016 update: a report from the american heart association. Circulation 133: e38-360.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. (2015) Heart disease and stroke statistics--2015 update: a report from the american heart association. Circulation 131: e29-322.
3. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ (2006) Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 48: 1527-1537.
4. Verma S, Fedak PW, Weisel RD, Butany J, Rao V, et al. (2002) Fundamentals of reperfusion injury for the clinical cardiologist. Circulation 105: 2332-2336.
5. Bers DM (2008) Calcium cycling and signaling in cardiac myocytes. Annu Rev Physiol 70: 23-49.
6. Wagner S, Maier LS, Bers DM (2015) Role of sodium and calcium dysregulation in tachyarrhythmias in sudden cardiac death. Circ Res 116: 1956-1970.
7. Mishra S, Sabbah HN, Rastogi S, Imai M, Gupta RC (2005) Reduced sarcoplasmic reticulum Ca2+ uptake and increased Na+Ca2+ exchanger expression in left ventricle myocardium of dogs with progression of heart failure. Heart Vessels 20: 23-32.

8. Xie LH, Weiss JN (2009) Arrhythmogenic consequences of intracellular calcium waves. Am J Physiol Heart Circ Physiol 297: H997-H1002.
9. Yu HJ, Ma H, Green RD (1993) Calcium entry via L-type calcium channels acts as a negative regulator of adenylyl cyclase activity and cyclic AMP levels in cardiac myocytes. Mol Pharmacol 44: 689-693.
10. Bergantin LB, Souza CF, Ferreira RM, Smaili SS, Jurkiewicz NH, et al. (2013) Novel model for "calcium paradox" in sympathetic transmission of smooth muscles: role of cyclic AMP pathway. Cell Calcium 54: 202-212.
11. Caricati-Neto A, García AG, Bergantin LB (2015) Pharmacological implications of the Ca2+/cAMP signalling interaction: from risk for antihypertensive therapy to potential beneficial for neurological and psychiatric disorders. Pharmacol Res Perspect 3: e00181.
12. Bergantin LB, Jurkiewicz A, García AG, Caricati-Neto A (2015) A calcium paradox in the context of neurotransmission. Journal of Pharmacy and Pharmacology 3: 253-261.
13. Bergantin LB, Caricati-Neto A (2016) Challenges for the pharmacological treatment of neurological and psychiatric disorders: Implications of the Ca2+/cAMP intracellular signalling interaction. Eur J Pharmacol 788: 255-260.
14. Menezes-Rodrigues FS, Pires-Oliveira M, Duarte T, Paredes-Gamero EJ, Chiavegatti T, et al. (2013) Calcium influx through L-type channels attenuates skeletal muscle contraction via inhibition of adenylyl cyclases. Eur J Pharmacol 720: 326-334.
15. Sellers ZM, Naren AP, Xiang Y, Best PM (2012) MRP4 and CFTR in the regulation of cAMP and β-adrenergic contraction in cardiac myocytes. Eur J Pharmacol 681: 80-87.
16. Chiavegatti T, Costa VL Jr, Araújo MS, Godinho RO (2008) Skeletal muscle expresses the extracellular cyclic AMP-adenosine pathway. Br J Pharmacol 153: 1331-1340.
17. Duarte T, Menezes-Rodrigues FS, Godinho RO (2012) Contribution of the extracellular cAMP-adenosine pathway to dual coupling of β2-adrenoceptors to Gs and Gi proteins in mouse skeletal muscle. J Pharmacol Exp Ther 341: 820-828.