Journal of Pediatric Neurological Disorders
ISSN: 2572-5203

Leandro and Afonso, J Pediatr Neurol Disord 2017, 3:1
DOI: 10.4172/2572-5203.1000112

Mini Review Open Access

Novel Concepts for Neurology and Medicine from the Interaction between Signalling Pathways Mediated by Ca^{2+} and cAMP: An Intriguing History

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Received date: April 12, 2017; **Accepted date**: April 24, 2017; **Published date**: May 04, 2017

Abstract

It is now well-established that the signalling pathways mediated by Ca^{2+} and cAMP can interact (Ca^{2+}/cAMP signalling interaction), thus playing a vital role in cellular processes of mammalians. In the neurology and medicine, it has opened novel opportunities for the development of pharmaceuticals more efficient, and safer, for treating neurodegenerative diseases. The solution for the so-called “calcium paradox” has been revealed 4 years ago, when we demonstrated the involvement of the Ca^{2+}/cAMP signalling interaction in this enigma. The “calcium paradox” emerged 4 decades ago, when numerous clinical studies have concluded that prescription of L-type Ca^{2+} channel blockers (CCBs) for hypertensive patients decreased arterial pressure, but produced stimulation of sympathetic hyperactivity. Indeed, initially these adverse effects of CCBs have been attributed to adjust reflex of arterial pressure, but this conclusion remained not completely satisfactory. The year of 2013 would change this history forever! Through an original experiment, we revealed that the "calcium paradox" phenomenon came from increased transmitter release from sympathetic neurons stimulated by CCBs due to its handling on the Ca^{2+}/cAMP signalling interaction. Then, the manipulation of Ca^{2+}/cAMP signalling interaction could improve therapeutic strategies for stimulating synaptic transmission compromised by transmitter release deficit, and attenuating death of neurons.

Keywords: Ca^{2+}/cAMP signalling interaction; Paradoxical efects produced by CCBs; Neurology

Introduction

From the past years, it has been shown that the signalling pathways mediated by Ca^{2+} and cAMP can interact (Ca^{2+}/cAMP signalling interaction), thus playing a vital role in cellular processes of mammalians. In the neurology and medicine, it could improve therapeutic strategies for stimulating synaptic transmission compromised by transmitter release defcit, and attenuating death of neurons.

It has been almost 4 years since we revealed the involvement of the Ca^{2+}/cAMP signalling interaction in the enigma of the so-called “calcium paradox”. For understanding the “calcium paradox”, we should return to the past. Indeed, the concept of stimulus-secretion to elucidate neurotransmitters release has been achieved from creative experiments made by Douglas, et al. [1]. By their concepts, in 1970´s Baker and Knight [2] showed that an increase in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]c$) is a fundamental requirement to start transmitter release. In addition, the unquestionable result showing a correlation between neurotransmitter release and elevation in $[Ca^{2+}]c$ came from the interesting experiments made by the Nobel laureate Erwin Neher [3]. Tus, by reducing extracellular Ca^{2+} through blocking Ca^{2+} channels, we should have a reducing in the neurotransmitter release. Nonetheless, many reports have demonstrated that L-type Ca^{2+} channel blockers (CCBs), in concentrations below 1 µmol/L, could induce neurotransmitter release, a “paradox” [4-6]. In addition, many reports have demonstrated that cAMP enhances neurotransmitter release at several synapses in autonomic nervous system of mammalians [7]. Recently, we demonstrated that Ca^{2+}/cAMP signalling interaction is implicated in the modulation of transmitters release from sympathetic neurons, and adrenal chroma f n cells [8-11].

T e interaction between Ca^{2+} and cAMP signalling pathways as a classical concept: an intriguing history

It is well established that the interaction between Ca^{2+} and cAMP signalling pathways is as a vital cellular process in mammalians [8-11]. T is classical concept assumes that these signalling pathways virtually exist in all mammalian cells, modulated by adenylyl cyclases (ACs) and phosphodiesterases (PDEs) [8-11]. In addition, endoplasmic reticulum (ER) Ca^{2+} channels have particularly been a forefront for the interaction between Ca^{2+} and cAMP signalling pathways feld, such as Ca^{2+} channels modulated by ryanodine receptors (RyR) [8-11]. We reinforced the idea that the interaction between Ca^{2+} and cAMP signalling pathways plays a fundamental participation in the modulation of neurotransmitter release from neurons and neuroendocrine cells [8-11]. T en, the interaction of Ca^{2+} and cAMP signalling pathways could be a new therapeutic goal for pharmaceuticals.

T e interaction between Ca^{2+} and cAMP signalling pathways and neurology

T e prescription of L-type CCBs in hypertensive patients has been reported to decrease arterial pressure, but also produces sympathetic hyperactivity [12]. Initially, these adverse efects of CCBs have been attributed to adjust refex of arterial pressure, but this conclusion remained not completely satisfactory. T e year of 2013 would change

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