

Novel Concepts for Neurology and Medicine from the Interaction between Signalling Pathways Mediated by Ca²⁺ and cAMP: An Intriguing History

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Abstract

It is now well-established that the signalling pathways mediated by Ca²⁺ and cAMP can interact (Ca²⁺/cAMP signalling interaction), thus playing a vital role in cellular processes of mammals. 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 Ca²⁺/cAMP signalling interaction in this enigma. The "calcium paradox" emerged 4 decades ago, when numerous clinical studies have concluded that prescription of L-type Ca²⁺ 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 Ca²⁺/cAMP signalling interaction. Then, the manipulation of Ca²⁺/cAMP signalling interaction could improve therapeutic strategies for stimulating synaptic transmission compromised by transmitter release deficit, and attenuating death of neurons.

Keywords: Ca²⁺/cAMP signalling interaction; Paradoxical effects produced by CCBs; Neurology

Introduction

From the past years, it has been shown that the signalling pathways mediated by Ca²⁺ and cAMP can interact (Ca²⁺/cAMP signalling interaction), thus playing a vital role in cellular processes of mammals. In the neurology and medicine, it could improve therapeutic strategies for stimulating synaptic transmission compromised by transmitter release deficit, and attenuating death of neurons.

It has been almost 4 years since we revealed the involvement of the Ca²⁺/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 Ca²⁺ concentration ([Ca²⁺]_c) is a fundamental requirement to start transmitter release. In addition, the unquestionable result showing a correlation between neurotransmitter release and elevation in [Ca²⁺]_c came from the interesting experiments made by the Nobel laureate Erwin Neher [3]. Thus, by reducing extracellular Ca²⁺ through blocking Ca²⁺ channels, we should have a reducing in the neurotransmitter release. Nonetheless, many reports have demonstrated that L-type Ca²⁺ 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 mammals [7]. Recently, we demonstrated that Ca²⁺/cAMP signalling interaction is implicated in the modulation of transmitters release from sympathetic neurons and adrenal chromaffin cells [8-11].

The interaction between Ca²⁺ and cAMP signalling pathways as a classical concept: an intriguing history

It is well established that the interaction between Ca²⁺ and cAMP signalling pathways is as a vital cellular process in mammals [8-11]. This 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) Ca²⁺ channels have particularly been a forefront for the

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interaction

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