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From a “Eureka Insight” to Novel Concepts in Pharmaceutical Sciences: Role of Ca²⁺/cAMP Intracellular Signalling Interaction

Leandro Bueno Bergantin and Afonso Caricati-Neto

Laboratory of Autonomic and Cardiovascular Pharmacology, Department of Pharmacology, Paulista School of Medicine, Federal University of São Paulo, São Paulo, Brazil

Corresponding author: Leandro Bueno Bergantin, Laboratory of Autonomic and Cardiovascular Pharmacology, Department of Pharmacology, Paulista School of Medicine, Federal University of São Paulo (UNIFESP), Rua Pedro de Toledo, 669-Vila Clementino, São Paulo, Brazil, Tel: 551155764973; E-mail: leanbio39@yahoo.com.br

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Abstract

It has been almost 4 years since we revealed the explanation for the enigma of the so-called “calcium paradox”. Our discovery of the involvement of Ca²⁺/cAMP signaling interaction in the regulation of neurotransmitter release, and neuroprotection, was clearly a serendipitous discovery. It has produced new avenues in the understanding of the cellular and molecular mechanisms involved in the pathogenesis of neurological and psychiatric disorders, such as Alzheimer’s disease. Interestingly, this discovery initiated decades ago when numerous clinical studies have reported that use of L-type Ca²⁺ channel blockers (CCBs) by hypertensive patients decreased arterial pressure, but produced typical symptoms of sympathetic hyperactivity, such as tachycardia and increment of catecholamine plasma levels. Despite these adverse effects of CCBs have been initially attributed to adjust reflex of arterial pressure, during almost four decades this enigmatic phenomenon (the so-called “calcium paradox”) remained unclear. In 2013, through an ingenious experiment, we discovered that this phenomenon was resulting of increment of transmitter release from sympathetic neurons, and adrenal chromaffin cells, stimulated by CCBs due to its interference on the Ca²⁺/cAMP signaling interaction. In this way, our discovery of the role of Ca²⁺/cAMP intracellular signaling interaction in the neurotransmitter release, and neuronal death triggered by cytosolic Ca²⁺ overload, opened novel adventures for the development of new pharmacological strategies more effective for the treatment of neurological and psychiatric disorders resulting of neurotransmitter release deficit, and neuronal death. These novel concepts have been extensively documented in several cited international papers of our own authorship (Bergantin and Caricati-Neto), and in an international book.

Keywords: Ca²⁺/cAMP signaling interaction; Calcium paradox; Neurological/psychiatric disorders

Introduction

The notion of stimulus-secretion coupling to explain neurotransmitters and hormones release has been resulted from ingenious experiments performed by Douglas and Rubin [1]. Complementing their concepts, Baker and Knight revealed in 1970’s that a rise in the cytosolic Ca²⁺ concentration ([Ca²⁺]_c) is an elementary requirement to trigger transmitter release [2]. Indeed, the definite demonstration of a direct relationship between neurotransmitter release and increase in [Ca²⁺]_c derived from the fundamental experiments performed by the Nobel laureate Erwin Neher [3]. More recently, many results have shown that cAMP increases neurotransmitter release at many synapses in autonomic nervous system of vertebrate, including sympathetic neurons [4]. Although the cellular mechanisms involved in these enhancer effects of cAMP on the release of neurotransmitters and hormones are under debate, the evidences indicate that this important intracellular messenger modulates signalling pathways mediated by Ca²⁺ involved in the regulation of neurotransmitter, and hormones release.

The Ca²⁺/cAMP signalling interaction as a universally-operated concept

The interaction between the intracellular signalling pathways mediated by Ca²⁺ and cAMP, named Ca²⁺/cAMP signalling interaction, has been widely studied in different cell types and tissues. This now a days accepted concept assumes that this interaction results in synergistic actions of these intracellular messengers on cell functions regulated by adenylyl cyclases (ACs), and phosphodiesterases (PDEs) [5-8]. The Ca²⁺/cAMP signalling interaction has particularly been extensively studied at the endoplasmic reticulum (ER) Ca²⁺ channels, such as Ca²⁺ channels regulated by ryanodine receptors (RyR) [5-8]. Our own experiments established that Ca²⁺/cAMP signalling interaction plays a key role in the regulation of neurotransmitter release from neurons and neuroendocrine cells [5-8]. Then, dysfunctions of cellular homeostasis of Ca²⁺ and/or cAMP in these cells could result in the dysregulation of Ca²⁺/cAMP signalling interaction, and could be a novel therapeutic goal for medicines.

From a "eureka insight" to novel concepts in pharmaceutical sciences

Indeed, several medical studies have been evidencing that acute and chronic use of L-type Ca^{2+} channel blockers (CCBs) in the antihypertensive therapy, such as nifedipine and verapamil, decreased peripheral vascular resistance and arterial pressure arterial, but produced typical symptoms of sympathetic hyperactivity such as tachycardia, and increment of catecholamine plasma levels [9]. Despite these adverse effects of CCBs have been initially attributed to adjust reflex of arterial pressure, during almost four decades the cellular and molecular mechanisms involved this enigmatic phenomenon named "calcium paradox" remained without additional explanation.

In 2013, through an ingenious experiment, we discovered that the "calcium paradox" phenomenon was resulting of increment of transmitter release from sympathetic neurons, and adrenal chromaffin cells, stimulated by CCBs due to its interference on the Ca^{2+} /cAMP signalling interaction [6]. Using isolated tissues richly innervated by sympathetic nerves (rat vas deferens) to exclude the influence of adjusting reflex, we showed that neurogenic responses of the vas deferens were completely inhibited by L-type CCBs in high concentrations ($>1 \mu\text{mol/L}$), but unpredictably, and paradoxically, potentiated in concentrations below $1 \mu\text{mol/L}$, characterized by sympathetic hyperactivity induced by CCBs [10-12]. Our studies showed that this paradoxical sympathetic hyperactivity is caused by increment of neurotransmitter release from sympathetic neurons produced by L-type CCBs due to its interference on the Ca^{2+} /cAMP signalling interaction [5-8] (**Figure 1**).

In addition, several studies have showed that increase of cytosolic cAMP concentration ($[\text{cAMP}]_c$) stimulates neuroprotective response [13,14]. In this way, increase of $[\text{cAMP}]_c$ by interfering in the Ca^{2+} /cAMP signalling interaction could attenuate neuronal death triggered by cytosolic Ca^{2+} overload [5-8]. Then, the pharmacological handling of the Ca^{2+} /cAMP signalling interaction produced by combination of the L-type CCBs used in the antihypertensive therapy, and $[\text{cAMP}]_c$ enhancer compounds used in the anti-depressive therapy such as rolipram, could be a new pharmacological strategy for enhancing neurotransmission in neurological and psychiatric disorders resulting of neurotransmitter release deficit, and/or neuronal death [5-8]. These findings could open a new avenue for the drug development more effective and safer for the treatment of Alzheimer's diseases [15-21].

Conclusion

From a "eureka insight" to novel concepts in pharmaceutical sciences. Pharmacological handling of the Ca^{2+} /cAMP signalling interaction could be a more efficient and safer therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and attenuating neuronal death.

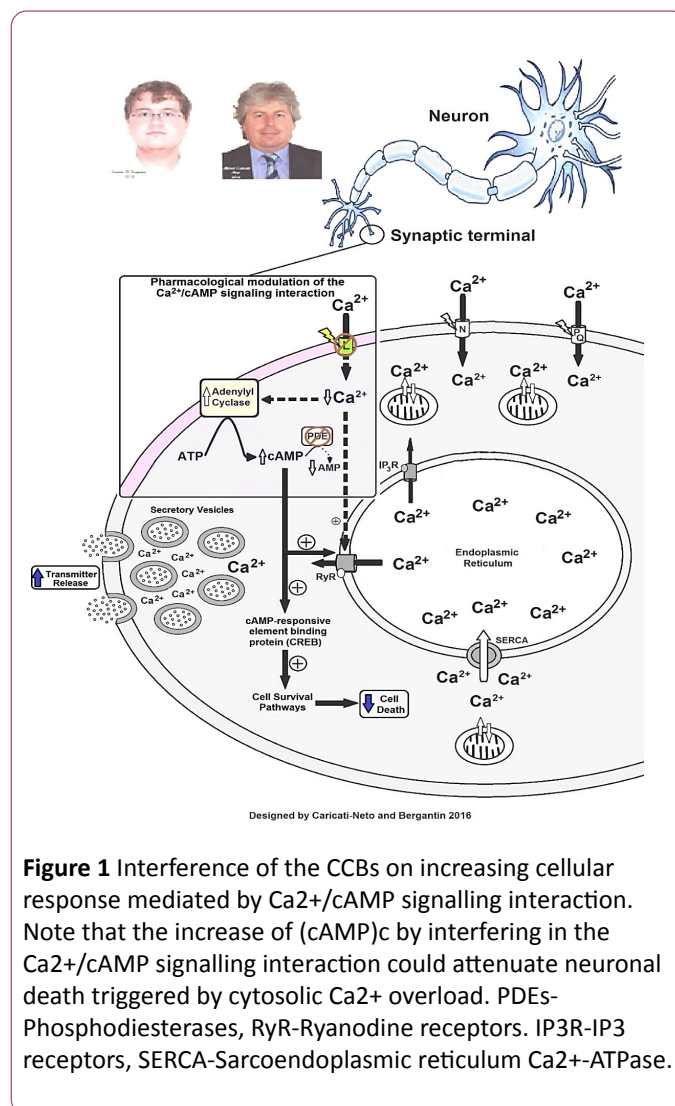


Figure 1 Interference of the CCBs on increasing cellular response mediated by Ca^{2+} /cAMP signalling interaction. Note that the increase of $[\text{cAMP}]_c$ by interfering in the Ca^{2+} /cAMP signalling interaction could attenuate neuronal death triggered by cytosolic Ca^{2+} overload. PDEs- Phosphodiesterases, RyR-Ryanodine receptors. IP3R-IP3 receptors, SERCA-Sarcoendoplasmic reticulum Ca^{2+} -ATPase.

Disclosure Statement

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