



## Lessons from the Discovery of the “Calcium Paradox” due to Ca<sup>2+</sup>/cAMP Interaction

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### Abstract

What have we learned from the discovery of the “calcium paradox” due to Ca<sup>2+</sup>/cAMP interaction? Our discovery of the involvement of interaction between the intracellular signalling pathways mediated by Ca<sup>2+</sup> and cAMP (Ca<sup>2+</sup>/cAMP interaction) in the neuronal protection has produced new paths for the understanding of the cellular and molecular mechanisms involved in the pathogenesis of neurodegenerative diseases, such as Alzheimer’s and Parkinson’s diseases. Interestingly, tachycardia and increment of catecholamine plasma levels (sympathetic hyperactivity) have been reported by hypertensive patients that use L-type Ca<sup>2+</sup> channel blockers (CCBs) since seventies. Despite these adverse effects of CCBs have been initially attributed to adjust reflex of arterial pressure, during almost four decades this enigmatic phenomenon named “calcium paradox” remained unclear. We revealed that this phenomenon was resulting of increase of transmitter release from sympathetic neurons stimulated by CCBs due to its interference on the Ca<sup>2+</sup>/cAMP interaction. In this way, novel journeys for the development of new pharmacological strategies more effective for the treatment of neurodegenerative diseases may be started.

### Keywords

Ca<sup>2+</sup>/cAMP interaction, Calcium paradox, Neurodegenerative diseases

### Introduction

The notion of stimulus-secretion initially resulted from the experiments performed by Douglas and Rubin in the sixties [1]. Using adrenal chromaffin cells, Baker and Knight revealed in seventies that a rise in the cytosolic Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>c</sub>), is an elementary requirement to trigger transmitter release [2]. The demonstration of direct relationship between rapid neurotransmitter release and rise in [Ca<sup>2+</sup>]<sub>c</sub> derived from the experiments using photo released caged Ca<sup>2+</sup> in adrenal chromaffin cells performed Neher and Zucker in nineties [3]. 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 and molecular mechanisms involved in these synergistic effects of cAMP on the release of neurotransmitter and hormones are indistinct, the evidences suggest that this important intracellular messenger modulates intracellular signalling mediated by Ca<sup>2+</sup> involved in the regulation of neurotransmitter, and hormones release.

### Lessons from the Discovery of the Ca<sup>2+</sup>/cAMP Interaction

In fact, the hypothesis for a suitable interaction between the intracellular signalling pathways mediated by Ca<sup>2+</sup> and cAMP, named Ca<sup>2+</sup>/cAMP interaction, has been widely studied in different cell types and tissues. In general, this interaction results in synergistic actions of these intracellular messengers on cell functions regulated by adenylyl cyclases (ACs), or phosphodiesterases

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**Received:** January 10, 2017; **Accepted:** March 10, 2017; **Published online:** March 13, 2017

**Citation:** Bergantin LB, Caricati-Neto A (2017) Lessons from the Discovery of the “Calcium Paradox” due to Ca<sup>2+</sup>/cAMP Interaction. J Neurodegener Disord 1(1):1-4

(PDEs) [5-8]. The Ca<sup>2+</sup>/cAMP interaction has particularly been extensively studied at the endoplasmic reticulum (ER) Ca<sup>2+</sup> channels, such as Ca<sup>2+</sup> channels regulated by ryanodine receptors (RyR) [5-8]. Indeed, Ca<sup>2+</sup>/cAMP interaction plays a role in neurotransmitter release from neurons and neuroendocrine cells [5-8]. In addition, this interaction has been described in the smooth muscle [6], cardiac [9] and skeletal muscles [10]. Then, novel therapeutic goals for medicines could be developed by the manipulation of the Ca<sup>2+</sup>/cAMP interaction.

### Lessons from the Discovery of the “Calcium Paradox” due to Ca<sup>2+</sup>/cAMP Interaction: Consequences in Neuronal Protection

Sympathetic hyperactivity such as tachycardia, and increment of catecholamine plasma levels have been evidenced by several medical studies dealing with CCBs [11]. 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 unclear.

In 2013, we discovered that “calcium paradox” phenomenon resulted from the increment of transmitter release from sympathetic neurons, and adrenal chromaffin cells, stimulated by CCBs due to its interference on the Ca<sup>2+</sup>/cAMP interaction. 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 μmol/L), but unpredictably and paradoxically, potentiated in concentrations below 1 μmol/L, characterized by sympathetic hyperactivity induced by CCBs [12-14]. Indeed, this paradoxical sympathetic hyperactivity is caused by increment of neurotransmitter release from sympathetic neurons due to its interference on the Ca<sup>2+</sup>/cAMP interaction. In fact, CCBs reduce the influx of extracellular Ca<sup>2+</sup>, thus promoting des inhibition of ACs activities (notable AC<sub>5</sub> and AC<sub>6</sub> isoforms), finally increasing cAMP levels [5-8] (Figure 1).

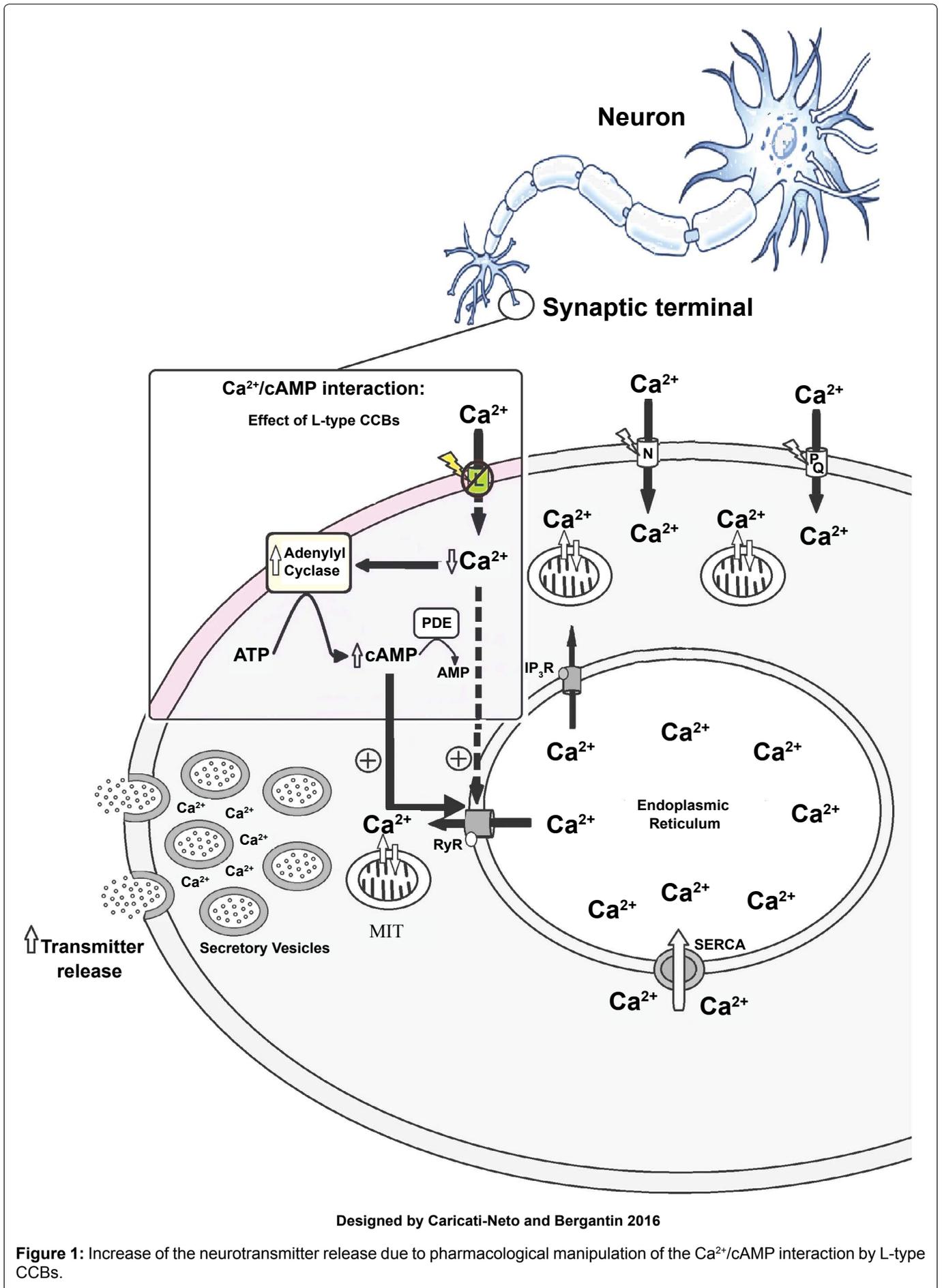
**Schematic representation of the model:** Ca<sup>2+</sup> entry through L-type voltage-activated Ca<sup>2+</sup> channels inhibits Ca<sup>2+</sup>-sensitive adenylyl cyclase, inhibiting cAMP signaling pathway-Ca<sup>2+</sup> release from the endoplasmic reticulum. Typically, by reducing Ca<sup>2+</sup> influx, and consequently [Ca<sup>2+</sup>]<sub>c</sub>, L-type CCBs may reduce transmitter release. However, CCBs may also activate Ca<sup>2+</sup>-sensitive adenylyl cyclase, activating cAMP signalling pathway-Ca<sup>2+</sup> release from the endoplasmic reticulum. Ca<sup>2+</sup> channel blockers (CCBs); Ryanodine Receptors (RyR); mitochondria (MIT); phosphodiesterase (PDE); adenosine triphos-

phate (ATP); cyclic adenosine monophosphate (cAMP); adenosine monophosphate (AMP); endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA).

Undeniably, several studies showed that neuroprotective response can be achieved by increase of cytosolic cAMP concentration ([cAMP]<sub>c</sub>) stimulation [15,16]. In this way, we could propose that a rise of [cAMP]<sub>c</sub> by interfering in the Ca<sup>2+</sup>/cAMP interaction could attenuate neuronal death triggered by cytosolic Ca<sup>2+</sup> overload [5-8,17-22]. Then, the pharmacological handling of the Ca<sup>2+</sup>/cAMP interaction produced by combination of the L-type CCBs used in the antihypertensive therapy, and [cAMP]<sub>c</sub> 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 from neurotransmitter release deficit, and/or neuronal death [5-8,17-22]. Indeed, it was showed that the treatment with L-type CCBs reduces motor symptoms, and attenuates progressive neuronal death in animal model of degenerative disease, suggesting that L-type CCBs are potentially viable neuroprotective agents [23]. In addition, a 10-year follow-up study (2000 to 2010), involving 82,107 hypertensive patients of more than 60 years of age, showed that use of L-type CCBs reduced blood pressure and risk of dementia in hypertensive patients, suggesting that these drugs could be clinically used to treat Alzheimer’s disease [24]. Supportive findings for the neuroprotective effects of CCBs have been demonstrated in 1,241 elderly hypertensive patients with memory impairment [25]. The use of CCBs decreased the risk of cognitive impairment, and Alzheimer’s disease, independently of blood pressure levels, when compared to patients not receiving CCBs [25]. These findings reinforced the idea that attenuation of cytosolic Ca<sup>2+</sup> overload produced by L-type CCBs due to blockade of Ca<sup>2+</sup> influx through L-type voltage-activated Ca<sup>2+</sup> channels could be an excellent pharmacological strategy to attenuate, or prevent, neuronal death in neurodegenerative diseases. These results could open a new path for the drug development more effective and safer for the treatment of neurodegenerative diseases.

### Conclusion

Lessons from the discovery entitled “calcium paradox” due to Ca<sup>2+</sup>/cAMP interaction have been emerging to treat neurodegenerative diseases. Pharmacological handling of this interaction could be a more efficient and safer therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and attenuating neuronal death in the neurodegenerative diseases.



**Figure 1:** Increase of the neurotransmitter release due to pharmacological manipulation of the  $Ca^{2+}$ /cAMP interaction by L-type CCBs.

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