



CCBs and Neuroprotection: A Genuine Benefit



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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”. Interestingly, this discovery initiated decades ago when numerous clinical studies have reported that use of L-type Ca^{2+} 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 Ca^{2+} /cAMP signalling interaction. In this way, our discovery of the role of Ca^{2+} /cAMP intracellular signalling interaction in the neurotransmitter release, and neuronal death triggered by cytosolic Ca^{2+} 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 (Bergantini and Caricati-Neto), and in an international book.

Keywords: Ca^{2+} /cAMP Signalling Interaction; Calcium Paradox; Neurological/Psychiatric Disorders

Abbreviations: CCBs: Ca^{2+} channel blockers; ACs: *Adenylyl Cyclases*; PDEs: *Phosphodiesterases*; ER: Endoplasmic Reticulum

Introduction

The notion of stimulus-secretion coupling to explain neurotransmitters and hormones release has been resulted from ingenious experiments performed by Douglas and Rubin in the 1960s [1]. Complementing their concepts, Baker and Knight revealed in 1970's that a rise in the cytosolic Ca^{2+} concentration ($[\text{Ca}^{2+}]_c$) is an elementary requirement to trigger transmitter release [2]. Indeed, the definite demonstration of a direct relationship between neurotransmitter release and increase in $[\text{Ca}^{2+}]_c$ 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 Ca^{2+} involved in the regulation of neurotransmitter, and hormones release.

The Ca^{2+} /cAMP signalling interaction as a universally-operated concept

The interaction between the intracellular signalling pathways mediated by Ca^{2+} and cAMP, named Ca^{2+} /cAMP signalling interaction, has been widely studied in different cell types and tissues. This nowadays 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 Ca^{2+} /cAMP signalling interaction has particularly been extensively studied at the endoplasmic reticulum (ER) Ca^{2+} channels, such as Ca^{2+} channels regulated by ryanodine receptors (RyR) [5-8]. Our own experiments established that Ca^{2+} /cAMP signalling interaction play a key role in the regulation of neurotransmitter release from neurons and neuroendocrine cells [5-8]. Then, dysfunctions of cellular homeostasis of Ca^{2+} and/or cAMP in these cells could result in the dysregulation of Ca^{2+} /cAMP signalling interaction, and could be a novel therapeutic goal for medicines.

CCBs and neuroprotection: a genuine benefit

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].

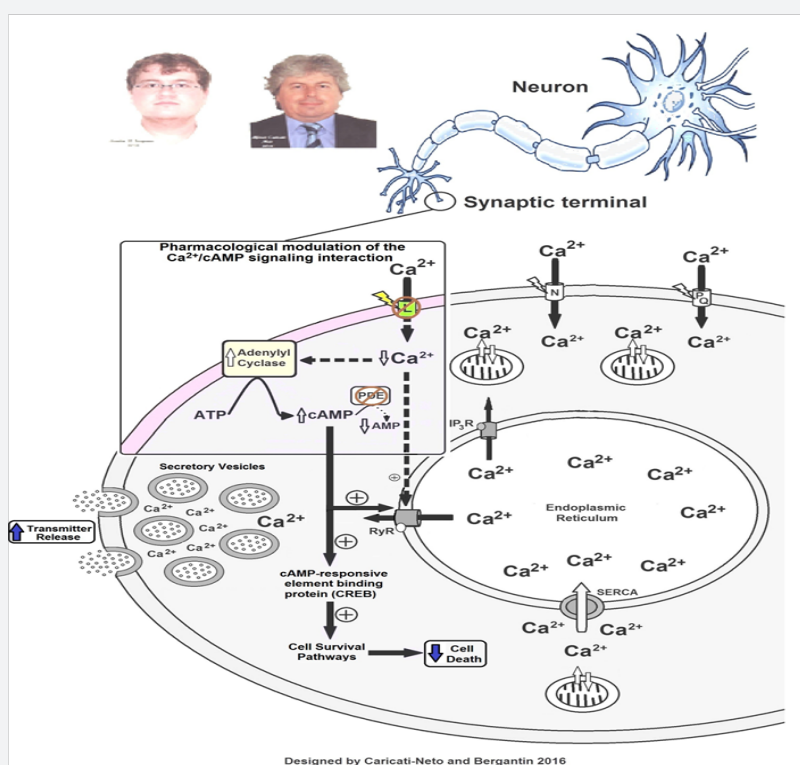


Figure 1: Interference of the CCBs on increasing cellular response mediated by Ca^{2+} /cAMP signalling interaction. Note that the increase of [cAMP]c by interfering in the Ca^{2+} /cAMP signalling interaction could attenuate neuronal death triggered by cytosolic Ca^{2+} overload. PDEs - Phosphodiesterases, RyR - Ryanodine receptors, IP_3R - IP_3 receptors, SERCA - Sarcoendoplasmic reticulum Ca^{2+} -ATPase.

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 ([cAMP]c) stimulates neuroprotective response [13,14]. In this way, increase of [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 [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]. 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 [15].

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 [16].

Supportive findings for the neuroprotective effects of CCBs have been demonstrated in 1,241 elderly hypertensive patients with memory impairment [17]. 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 [17]. These findings reinforced the idea that attenuation of cytosolic Ca²⁺ overload produced by L-type CCBs due to blockade of Ca²⁺ influx through L-type VACC could be an excellent pharmacological strategy to attenuate, or prevent, neuronal death in neurodegenerative diseases. These findings could open a new avenue for the drug development more effective and safer for the treatment of Alzheimer's diseases [18-24].

Conclusion

CCBs and neuroprotection: a genuine benefit. Pharmacological handling of the Ca²⁺/cAMP signalling interaction could be a more efficient and safer therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and attenuating neuronal death.

Disclosure Statement

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