DOI: 10.36959/734/371 | Volume 1 | Issue 1

Alzheimer's Disease & Dementia

Short Commentary Open Access

From a "Eureka Insight" to a Novel Potential Therapeutic Target to Treat Alzheimer´s Disease

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Abstract

It has been almost 4 years since we revealed the solution for the enigma of the so-called "calcium paradox". Our discovery of the involvement of Ca^{2+}/cAMP signaling interaction in the regulation of neurotransmitter release, and neuro protection, 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 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 signaling interaction. In this way, our discovery of the role of Ca^{2+}/cAMP signaling 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 (Bergantin and Caricati-Neto), and in an international book.

Keywords

Ca^{2+}/cAMP signaling interaction, Calcium paradox, Neurological/psychiatric disorders

Introduction

Classically, 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 ($[Ca^{2+}]_c$) is an elementary requirement to trigger transmitter release [2]. Indeed, the definite demonstration of a direct relationship between neurotransmitter release and rise in $[Ca^{2+}]_c$ 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 signaling pathways mediated by Ca^{2+} involved in the regulation of neurotransmitter, and hormones release.

The Ca^{2+}/Camp Signaling Interaction as a Universally-Operated Concept

The interaction between the intracellular signaling pathways mediated by Ca^{2+} and cAMP, named Ca^{2+}/

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Received: January 28, 2017; **Accepted:** May 08, 2017; **Published online:** May 11, 2017

Citation: Bergantin LB, Caricati-Neto A (2017) From a "Eureka Insight" to a Novel Potential Therapeutic Target to Treat Alzheimer´s Disease. Alzheimers Dis Dement 1(1):34-37

cAMP signaling 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), or phosphodiesterases (PDEs) [5-8]. The Ca^{2+}/cAMP signaling 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 signaling interaction plays 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 signaling interaction, and could be a novel therapeutic goal for medicines.

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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 signaling 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 [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 signaling interaction [5-8] (figure 1).

Neurotransmitter release stimulation, and reduction of neuronal death triggered by cytosolic Ca^{2+} overload, can be achieved due to pharmacological regulation of the Ca^{2+}/cAMP signaling interaction. The reduction of Ca^{2+} influx through L-type voltage-activated Ca^{2+}channels produced by CCBs enhances the adenylyl cyclase activity (and consequently cAMP). These CCBs-effects can be potentiated by cAMP-enhancer compounds (like PDEs inhibitors). PDEs-Phosphodiesterases, RyR-Ryanodine receptors, IP_3R-IP_3 receptors, SERCA-Sarcoendoplasmic reticulum Ca^{2+}-ATPase.

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 signaling interaction could attenuate neuronal death triggered by cytosolic Ca^{2+} overload [5-8]. Then, the pharmacological handling of the Ca^{2+}/cAMP signaling 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]. These findings could open a new avenue for the drug development more effective and safer for the treatment of Alzheimer´s diseases [15-18].

In fact, it was demonstrated that the prescription of L-type CCBs reduces motor symptoms, and reduces progressive neuronal death in animal model of Parkinson´s disease, indicating that L-type CCBs are potentially viable neuroprotective pharmaceuticals [19]. Intriguingly, a 1-decade study involving thousands senile hypertensive patients demonstrated that prescription of L-type CCBs reduced blood pressure, and risk of dementia, in hypertensive patients, indicating that these pharmaceuticals could be clinically used to treat neurodegenerative diseases [20]. These results for the neuroprotective effects of CCBs have been reinvestigated in thousands elderly hypertensive patients with memory dysfunction [21]. These studies concluded that patients who have taken CCBs had their risk of cognitive dysfunction decreased, such as Alzheimer´s disease [21]. These findings reinforce the idea that reduction of cytosolic Ca^{2+} overload produced by L-type CCBs due to blockade of Ca^{2+} influx could be an alternative pharmacological goal to reduce, or prevent, neuronal death in neurodegenerative diseases.

Conclusion

From a "eureka insight" to a novel potential therapeutic target to treat Alzheimer´s disease. Pharmacological handling of the Ca^{2+}/cAMP signaling interaction could be a more efficient and safer therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and attenuating neuronal death.

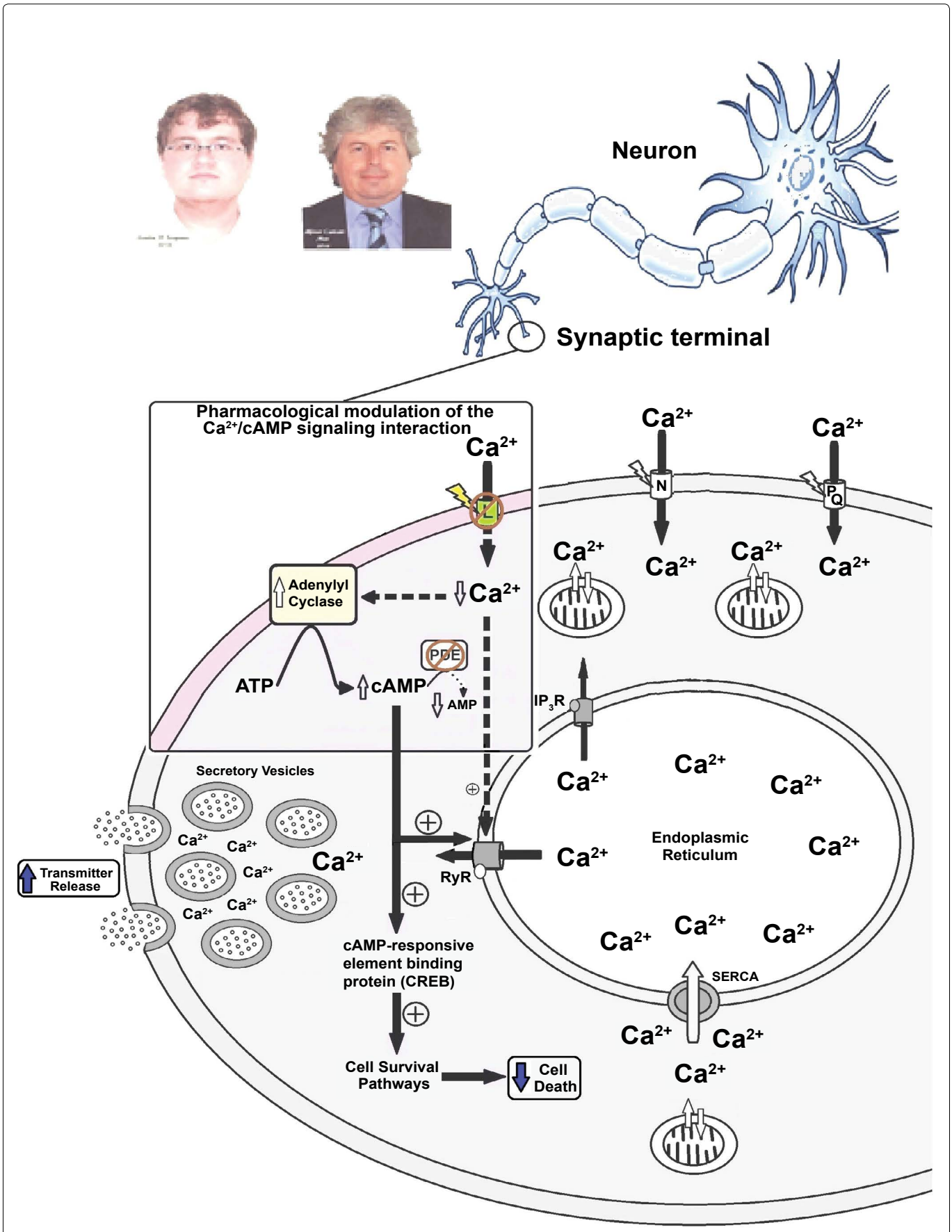

Figure 1: Interference of the CCBs on increasing cellular response mediated by Ca^{2+}/cAMP signaling interaction. Note that the increase of $[cAMP]_c$ by interfering in the Ca^{2+}/cAMP signaling interaction could attenuate neuronal death triggered by cytosolic Ca^{2+} overload.

Disclosure Statement

Caricati-Neto and Bergantin thank the continued financial support from CAPES, CNPq and FAPESP (Bergantin´s Postdoctoral Fellowship FAPESP #2014/10274-3).

The authors also thank Elsevier - "author use": Reuse of portions or extracts from the article in other works : https://www.elsevier.com/__data/assets/pdf_file/0007/55654/AuthorUserRights.pdf.

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