The Discovery of the “Calcium Paradox” Due to Ca\textsuperscript{2+}/cAMP Interaction: Novel Adventures for the Pharmacotherapy of Neurological/Psychiatric Disorders

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Abstract

Our discovery of the involvement of the interaction between intracellular signalling pathways mediated by Ca\textsuperscript{2+} and cAMP (Ca\textsuperscript{2+}/cAMP interaction) in the neurotransmission and neuroprotection 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 and Parkinson’s diseases. Interestingly, this discovery initiated decades ago when numerous clinical studies have reported that use of L-type Ca\textsuperscript{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 named “calcium paradox” remained unclear. In 2013, 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\textsuperscript{2+}/cAMP interaction. In this way, our discovery of the role of Ca\textsuperscript{2+}/cAMP interaction in the neurotransmitter release, and neuronal death triggered by cytosolic Ca\textsuperscript{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.

Keywords

Ca\textsuperscript{2+}/cAMP interaction, Calcium paradox, Neurological/Psychiatric disorders

Introduction

Numerous results which have been originated decades ago, using chromaffin cells as secretory model, established the notion of stimulus-secretion coupling to explain neurotransmitter release. This notion was initially resulting from the experiments performed by Douglas and Rubin in the 1960s to study acetylcholine-stimulated secretory response in cat adrenal gland [1]. Using adrenal chromaffin cells, Baker and Knight revealed in 1970’s that a rise in the cytosolic Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]c) is an elementary requirement to trigger transmitter release [2]. The demonstration of direct relationship between rapid neurotransmitter release and rise in [Ca\textsuperscript{2+}]c derived from the experiments using photo released caged Ca\textsuperscript{2+} in adrenal chromaffin cells performed Neher and Zucker in 1990’s [3]. Thus, it has been classically accepted that Ca\textsuperscript{2+} has an important role in several cellular responses, notable by controlling neurotransmitter release and smooth muscle contraction. Putatively, the use of L-type Ca\textsuperscript{2+} channel blockers (CCBs) should reduce these cellular responses. In addition to Ca\textsuperscript{2+}, 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 facilitatory 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\textsuperscript{2+} involved in the regulation of neurotransmitter, and hormones release.

Implications of the Ca\textsuperscript{2+}/cAMP Signalling Interaction in Neuronal Function

In fact, the hypothesis for a suitable interaction between the intracellular signalling pathways mediated by Ca\textsuperscript{2+} and cAMP, named Ca\textsuperscript{2+}/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 (PDEs) [5-8]. The Ca\textsuperscript{2+}/cAMP interaction has particularly been extensively studied at

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the endoplasmic reticulum (ER) Ca\(^{2+}\) channels, such as Ca\(^{2+}\) channels regulated by ryanodine receptors (RyR) [5-8]. Our studies established that Ca\(^{2+}\)/cAMP interaction plays a role in neurotransmitter release regulation in 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 interaction, and could be a novel therapeutic goal for medicines.

Pharmacological Manipulation of the Ca\(^{2+}\)/cAMP Interaction and its Consequences in Neuronal Function and Neuroprotection

Considering that Ca\(^{2+}\) has been classically implicated in several cellular responses, for example by controlling neurotransmitter release and smooth muscle contraction. Then, the use of CCBs should reduce these cellular responses. However, since four decades ago, several medical studies have been evidencing that acute and chronic use of 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 unclear. In addition, besides the role of Ca\(^{2+}\) in controlling neurotransmitter release and smooth muscle contraction, an imbalance of intracellular Ca\(^{2+}\) homeostasis has been implicated in the pathogenesis of aging-related neurodegenerative diseases. Several evidences suggest that aging impairs ability of the brain intracellular Ca\(^{2+}\) degradation, which is likely to induce cellular damage due to cytosolic Ca\(^{2+}\) overload, leading to neural death and resultant cognitive dysfunction, such as Alzheimer’s disease [10]. From this concept in mind, 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 hypertensives, suggesting that these drugs could be clinically used to treat Alzheimer’s disease [11]. Supportive findings for the neuroprotective effects of CCBs have been demonstrated in 1,241 elderly hypertensive patients with memory impairment [12]. 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 [12]. The long-term effects of antihypertensive therapy, initiated with a long-acting dihydropyridine (nitrendipine), have been demonstrated in the double-blind, placebo-controlled Syst-Eur trial in which the incidence of dementia was reduced by 55% [13].

Figure 1: Interference of the CCBs on increasing cellular response mediated by Ca\(^{2+}\)/cAMP 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 [5-8,17,18].

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Returning to the enigma of the "calcium paradox", we discovered about 4 years ago 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 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 \(\mu\)mol/L), but unpredictably, and paradoxically, potentiated in concentrations below 1 \(\mu\)mol/L, characterized by sympathetic hyperactivity induced by CCBs [14-16]. Our study 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 interaction [5-8] (Figure 1).

In addition, several studies showed that increase of cytosolic cAMP concentration ([cAMP]c) stimulates neuroprotective response [17,18]. In this way, increase of [cAMP]c by interfering in the Ca\(^{2+}\)/cAMP interaction could attenuate neuronal death triggered by cytosolic Ca\(^{2+}\) overload [5-8]. Then, the pharmacological handling of the Ca\(^{2+}\)/cAMP 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 and Parkinson’s diseases.

Conclusion

Novel adventures throughout our discovery entitled "calcium paradox" due to Ca\(^{2+}\)/cAMP interaction have been emerging to treat psychiatric and psychiatric disorders. 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 [5-8,19-24].

Disclosure Statement

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