GAVIN PUBLISHERS

Journal of Neurology and Experimental Neural Science

Caricati-Neto A and Bergantin LB, et al. J Neurol Exp Neural Sci 2016: JNENS-111.

DOI: 10.29011/JNNS-111. 100011

Mini Review

Discovery of the Role of Ca^{2+}/Camp Signalling Interaction in the Neurotransmission and Neuroprotection: Contributions for the Pharmacotherapy of Neurological and Psychiatric Disorders

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Citation: Caricati-Neto A and Bergantin LB (2016) Discovery of the Role of Ca^{2+}/Camp Signalling Interaction in the Neurotransmission and Neuroprotection: Contributions for the Pharmacotherapy of Neurological and Psychiatric Disorders. J Neurol Exp Neural Sci 2016: JNENS-111. DOI: 10.29011/JNNS-111. 100011

Received Date: 17 November, 2016; **Accepted Date:** 22 December, 2016; **Published Date:** 29 December, 2016

Abstract

Our discovery of the involvement of the interaction between intracellular signalling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP interaction) in the neurotransmission and neuroprotection has produced important advances 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^{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^{2+}/cAMP interaction. In this way, our discovery of the role of Ca^{2+}/cAMP interaction in the neurotransmitter release, and neuronal death triggered by cytosolic Ca^{2+} overload, opened a large avenue 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^{2+}/cAMP Interaction; Calcium Paradox; Neurological/Psychiatric Disorders

Introduction

Many experiments initiated decades ago, using chromaffin cells as cellular 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 discovered in 1970´s that a rise in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]c$) is an elementary requirement to trigger transmitter release [2]. The demonstration of direct relationship between rapid neurotransmitter release and rise in $[Ca^{2+}]c$ derived from the experiments using photoreleased caged Ca^{2+} in adrenal chromafin cells performed Neher and Zucker in 1990´s [3]. Many studies 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^{2+} involved in the regulation of neurotransmitter, and hormones release.

Importance of the Ca^{2+}/cAMPsignalling interaction in neuronal function

In fact, the hypothesis for a suitable interaction between the intracellular signalling pathways mediated by Ca^{2+} and cAMP, named Ca^{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^{2+}/cAMP 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 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 neurotransmission and neuroprotection

Since four decades ago, 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 unclear.

In 2013, we discovered that "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 µmol/L), but unpredictably, and paradoxically, potentiated in concentrations below 1 µmol/L, characterized by sympathetic hyperactivity induced by CCBs [10-12]. 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 [13,14]. In this way, increase of [cAMP]c interferes in the Ca2+/cAMP interaction, attenuating neuronal death triggered by cytosolic Ca2+ overload [5-8]. Then, the pharmacological handling of the Ca2+/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.

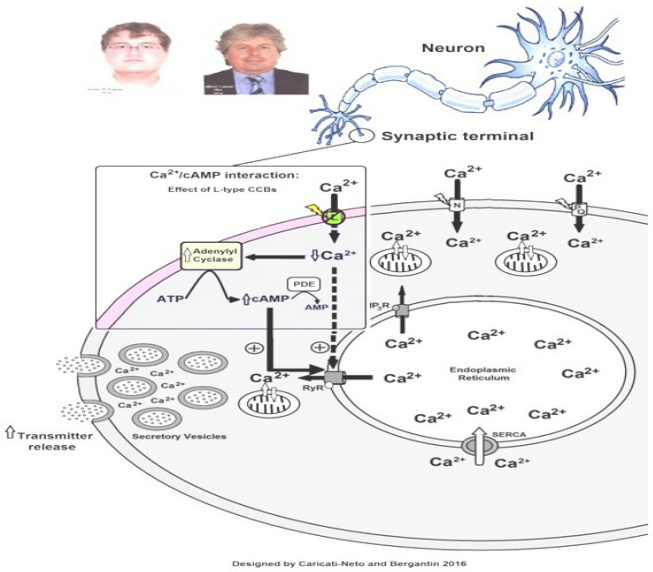

Figure 1: Increment of neurotransmitter release produced by L-type Ca^{2+} channel blockers (CCBs)due to its interference on the Ca^{2+}/cAMP interaction.

Conclusion

Novel therapeutic approaches to treat psychiatric and psychiatric disorders, throughout our recent discovery entitled "calcium paradox" phenomenon due to Ca2+/cAMP interaction. 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.

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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