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New Concepts for Clinical Pathology From Ca^{2+}/Camp Signalling Interaction

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Abstract

It is now well-accepted that the interaction between intracellular signalling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP signalling interaction) plays as a key role in cellular processes of mammalians. In the clinical pathology field, it has opened a new avenue for the drug development more effective, and safer, for the treatment of neurodegenerative diseases. It has been almost 4 years since we revealed the involvement of the Ca^{2+}/cAMP signalling interaction in the enigma of the so-called "calcium paradox". Interestingly, the "calcium paradox" initiated decades ago, when numerous clinical studies have reported that prescription of L-type Ca^{2+} channel blockers (CCBs) for hypertensive patients decreased arterial pressure, but produced typical symptoms of sympathetic hyperactivity. 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. Thus, 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.

Keywords: Ca^{2+}/cAMP signalling interaction; "Calcium paradox"; Clinical pathology

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Introduction

From the past years, the interaction between intracellular signalling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP signalling interaction) has been well-recognized as a key cellular process in mammalians. In the clinical pathology field, it has opened a new pathway for the drug development more effective, and safer, for treating Alzheimer´s and other neurodegenerative diseases. It has been almost 4 years since we revealed the involvement of the Ca^{2+}/cAMP signalling interaction in the enigma of the so-called "calcium paradox". For understanding the "calcium paradox", we should return to the past. Indeed, the stimulus-secretion concept to describe neurotransmitters, and hormones, release has been resulted from ingenious experiments performed by Douglas and Rubin in the 1960s[1]. From their concepts, in 1970´s Baker and Knight revealed that an increase in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]c$) is a fundamental requirement to start transmitter release[2]. In addition, the irrefutable demonstration of a direct relationship between neurotransmitter release and elevation in $[Ca^{2+}]c$ derived from the fundamental experiments performed by the Nobel laureate Erwin Neher[3]. Thus, by reducing extracellular Ca^{2+} through blocking Ca^{2+} channels, we should have a reducing in the neurotransmitter release. However, many studies have showed that L-type Ca^{2+} channel blockers (CCBs), in concentrations below 1 µ mol/L, could induce neurotransmitter release, a "paradox"[4-6]. In addition, many results have shown that cAMP increases neurotransmitter release at many synapses in autonomic nervous system of vertebrate[7]. Recently, we demonstrated that Ca^{2+}/cAMP signalling interaction is involved in the regulation of transmitters release from sympathetic neurons and adrenal chromaffin cells[8-11].

The Ca^{2+}/cAMP signalling interaction as a classical concept

It is well established that the Ca^{2+}/cAMP signalling interaction is as a key cellular process in mammalians[8-11]. This

nowadays accepted concept assumes that these signalling pathways virtually exist in all mammalian cells, regulated by adenylyl cyclases (ACs) and phosphordiesterases (PDEs)[8-11]. Indeed, endoplasmic reticulum (ER) Ca^{2+} channels have particularly been a forefront for the Ca^{2+}/cAMP signalling interaction field, such as Ca^{2+} channels regulated by ryanodine receptors (RyR) [8-11]. We established that Ca^{2+}/cAMP signalling interaction plays a fundamental participation in the regulation of neurotransmitter release from neurons and neuroendocrine cells[8-11]. Then, Ca^{2+}/cAMP signalling interaction could be a novel therapeutic target for medicines.

The Ca^{2+}/cAMP signalling interaction and the clinical pathology

Several medical studies have been evidencing that prescription of L-type CCBs in the antihypertensive therapy decreased arterial pressure arterial, but produced typical symptoms of sympathetic hyperactivity[12]. 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 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[9]. We showed that neurogenic responses of the vas deferens were completely inhibited by L-type CCBs in high concentrations (> 1 μ mol/L), but unpredictably, and paradoxically, potentiated in concentrations below 1 μ mol/L, characterized by sympathetic hyperactivity induced by CCBs[4-6,9]. 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.

Indeed, many reports have shown that elevation of cytosolic cAMP concentration ([cAMP]c) reduces neuronal death triggered by cytosolic Ca^{2+} overload, stimulating neuroprotective effect[13,14]. As mentioned above, the L-type CCBs increase neurotransmitter release due to its interference on the Ca^{2+}/cAMP signalling interaction. This interference results in the increase of ACs activity and elevation of [cAMP]c that, in turn, stimulates Ca^{2+} release from ER that increases neurotransmitter release[8-11]. In addition, this elevation of [cAMP]c produces neuroprotective effects mediated by Ca^{2+}/cAMP signalling interaction[8-11]. It was proposed that this neuroprotective effect results from activation by cAMP on the cellular survival pathways mediated by PKA/CREB[8-11,13,14]. Then, the pharmacological handling of the Ca^{2+}/cAMP signalling interaction produced by combination of the L-type CCBs prescribed in the antihypertensive therapy, and [cAMP]c-enhancer compounds prescribed 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 neuronal death[8-11]. Figure 1 shows how the pharmacological modulation of the Ca^{2+}/cAMP signalling interaction could produce increase of neurotransmitter release, and attenuation of neuronal death.

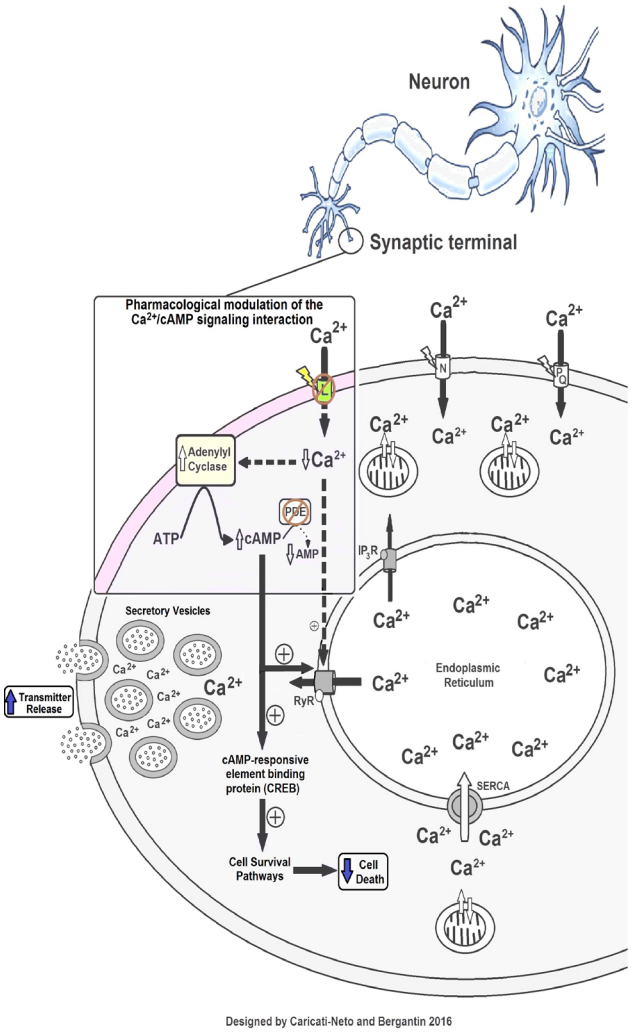

Figure 1: Increase of neurotransmitter release and attenuation of neuronal death triggered by cytosolic Ca^{2+} overload by means pharmacological modulation of the Ca^{2+}/cAMP signalling interaction. In response to the reduction of Ca^{2+} influx through L-type voltage-activated Ca^{2+} channels produced by CCBs, the adenylyl cyclase activity (and consequently cAMP) is increased. These CCBs-effects can be potentiated by cAMP-enhancer compounds (like PDEs inhibitors). PDEs - Phosphodiesterases, RyR - Ryanodine receptors, IP3R - IP3 receptors, SERCA - Sarcoendoplasmic reticulum Ca^{2+}-ATPase.

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[15]. In addition, a 1-decade follow-up study (2000 to 2010), involving 82,107 hypertensive patients of more than 60 years of age, demonstrated that prescription of L-type CCBs reduced blood pressure, and risk of dementia, in hypertensive patients, suggesting that these pharmaceuticals could be clinically used to treat Alzheimer´s disease[16]. These findings for the neuroprotective responses of CCBs have been demonstrated in 1,241 elderly hypertensive patients with memory impairment[17]. The prescription 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 highlight the concept that attenuation of cytosolic Ca^{2+} overload produced by L-type CCBs due to blockade of Ca^{2+} influx could be an excellent pharmacological strategy to reduce, or

prevent, neuronal death in neurodegenerative diseases.

Based in our studies, we have proposed that the pharmacological modulation of the Ca^{2+}/cAMP signalling interaction produced by combination of the L-type CCBs and [cAMP]c-enhancer compounds could be a new therapeutic strategy for enhancing neurotransmission in neurological, and psychiatric disorders, resulting of neurotransmitter release deficit and neuronal death[8-11]. This pharmacological strategy opens a new pathway for the drug development more effective, and safer, for the treatment of Alzheimer´s and other neurodegenerative diseases[18-24].

Conclusion

In conclusion, pharmacological modulation of the Ca^{2+}/cAMP signalling interaction could be a more efficient, and safer, therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and reducing neuronal death.

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