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Pharmaceutical intervention on Ca^{2+}/cAMP signaling interaction: benefits for combating neurodegeneration and diseases related to aging

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Abstract

The pharmaceutical intervention on the interaction between intracellular signaling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP signaling interaction) could bring important benefits for combating neurodegeneration and diseases related to aging. This discovery emerged from classical neurotransmission studies using rodent vas deferens as a model. From classical reports using this model, the concept of Ca^{2+}-dependent processes involved in the neurotransmission (Ca^{2+} influx triggers muscle contraction and neurotransmitter release) is amply accepted. Thus, Ca^{2+} channel blockers (CCB) due to reduction of Ca^{2+} influx through L-type voltage-activated Ca^{2+} channels (VACC) should reduce neurotransmission. Nonetheless, using this model, some studies performed since 1975 reported that reduction of Ca^{2+} influx by low concentrations of CCB (verapamil, diltiazem or nifedipine) produced a paradoxical increase of the contractions mediated by sympathetic nerves, a phenomenon known as "calcium paradox". Recent studies using adrenal chromaffin cells have also demonstrated that CCB caused a paradoxical increase of the catecholamine release. Because these compounds are blocking the L-type VACC, an augmented nerve-mediated response due to increased neurotransmitter release was an unexpected outcome. In 2013, we revealed that the Ca^{2+}/cAMP signaling interaction could properly explain the so-called "calcium paradox". The original paper published by us in Cell Calcium (2013) has appeared four times in ScienceDirect TOP 25 Hottest Articles lists. In conclusion, these findings may significantly impact on neurodegenerative diseases, thus may stimulate the development of new pharmacological strategies to combat the diseases related to aging.

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Introduction

From basic science, we know that in mammals, increases of the concentration of free Ca2+ ions in the cytosol ([Ca2+]c) serve as a messenger signal to couple the stimulus to muscle contraction, or to neurotransmitter release, among other physiological responses [1,2]. A huge number of experiments performed since the discovery of the role of Ca2+ in the control of the heart beat [3] have set the dogma that in excitable cells, the increased Ca2+ influx by voltage-activated Ca2+ channels (VACC) elicited by depolarising stimuli, triggers muscle contraction and the release of neurotransmitters, and hormones. Conversely, the mitigation of Ca2+ influx produced by VACC blockers causes a reduction of those responses [4,5].

The above concepts imply that the enhanced Ca2+ entry during cell depolarisation and/or enhanced Ca2+ release from the sarco-endoplasmic reticulum (ER) augments the [Ca2+]c and the triggering of the contractile, or secretory responses. However, about four decades ago, a study showed that verapamil at low concentrations produced a paradoxical increase of the contractions mediated by sympathetic nerves from vas deferens [6]. On the other hand, nifedipine was recently found to paradoxically augment the exocytosis of catecholamine triggered by double-pulse depolarisations from voltage-clamped bovine adrenal chromaffin cells, another interesting model to study sympathetic neurotransmission [7]. How these two L-type VACC blockers can enhance, instead of reducing, the Ca2+-dependent contractile and secretory responses? We properly gave a response to this "calcium paradox" in 2013 through the Ca2+/cAMP signaling interaction [8].

Pharmaceutical Intervention On Ca2+/Camp Signaling Interaction for Combating Neurodegeneration and Diseases Related to Aging

In the vas deferens, both release and postsynaptic actions of noradrenaline (NA), and other neurotransmitters such as adenosine 5´ triphosphate (ATP), depend on Ca2+ influx by VACC, and the ensuing elevations of [Ca2+]c [9]. Hence, some authors found that verapamil abolished both noradrenergic and purinergic components of the sympathetic neurotransmission in the vas deferens [10,11]. In an old report, however, it was showed that verapamil inhibited the sympathetic contractions of the rat smooth muscles (vas deferens), as predictable; nevertheless, this report also described that the low concentrations of verapamil produced a surprising increase of those neurogenic contractions [6]. This paradoxical effect was corroborated in 1981 by French and Scott [12], also in these contractions. Furthermore, six years later a third study reported that verapamil and diltiazem increased these sympathetic contractions; this result was attributed to an agonist effect of CCB on L-type VACC, thus increasing Ca2+ influx and neurotransmitter release [13]. Another published report (two years later) revealed that both, L- type VACC blockers and activator BAY K 8644, elicited similar increases of the neurogenic contractions of the smooth muscles (vas deferens) mediated by sympathetic nerves; the authors did not provide a reasonable explanation for such paradoxical observation [14].

In a study from our laboratory, we could replicate those previous observations in the sympathetically-mediated contractions of the rat vas deferens: low verapamil concentrations produced a small increase in sympathetic contractions, while high CCB concentrations caused full inhibition of these contractions [8]. Similar to the effects observed with high concentrations of CCB, various cAMP enhancers (e.g., the phosphodiesterase inhibitor rolipram) and adenylyl cyclase (AC) activators (e.g., forskolin) also reduced sympathetic contractions; however, low verapamil concentrations in the presence of cAMP enhancers caused a significant increase of these contractions. The increased neurogenic contraction can in turn be reduced by adding an AC inhibitor, SQ22536, to lower the cytosolic cAMP level. These findings suggest

that interactions in the Ca2+/cAMP signaling pathways could play a key role in explaining the "calcium paradox" as observed in the presence of CCB and cAMP enhancers [8]. Thus, these findings can dramatically impact on the cardiovascular, neurodegenerative disorders, cancer and other diseases related to aging [15-17].

Based on these findings, we have anticipated that the pharmacological modulation of the Ca2+/cAMP signaling interaction by combined use of the L-type CCB and cAMP-enhancer compounds could be a novel therapeutic goal for increasing neurotransmission in neurological, and psychiatric disorders, resulted from neurotransmitter release deficit, and neuronal death [15,16]. This neuroprotector strategy opens a novel pathway for the drug development which is more efficient and safe for the therapy of several neurodegenerative diseases, including Alzheimer´s, Parkinson´s, amyotrophic lateral sclerosis and Huntington´s diseases [15,16]. Briefly, the reduction of Ca2+ influx through L-type VACC produced by CCB enhances the adenylyl cyclase activity (and consequently elevating cAMP levels, please see figure 1). These CCB-effects can be potentiated by cAMP-enhancer compounds (like PDEs inhibitors). In fact, the fundamental mechanisms by which Ca2+/cAMP signaling interaction may increase the transmitter release are due: increasing the content of transmitter in the secretory vesicles (please see figure 1) and enhancing the rate of transmitter release. Thus, by elevating cAMP levels, this second messenger may enhance the release of Ca2+ from ER. Indeed, Ca2+ is crucial for the transmitter release, participating in virtually all the previous mentioned processes: content of transmitter in the secretory vesicles and rate of transmitter release.

In addition, many reports have shown that increase of cytosolic cAMP concentration stimulates neuroprotective effects [18,19]. Thus, elevating cAMP levels by handling Ca2+/cAMP signaling interaction could reduce neuronal death triggered by cytosolic Ca2+ overload [15,16]. Then, the pharmacological handling of the Ca2+/cAMP signalling interaction produced by combination of the L-type CCB prescribed in the antihypertensive therapy, and cAMP-enhancer compounds prescribed in the anti-depressive therapy such as rolipram, could be a novel pharmacological strategy for enhancing neurotransmission in neurological, and psychiatric disorders, resulting of neurotransmitter release deficit, and neuronal death [15,16]. Figure 1 illustrates how the pharmacological modulation of the Ca2+/cAMP signaling interaction could be used in human therapy.

In fact, it was demonstrated that the prescription of L-type CCB reduces motor symptoms, and reduces progressive neuronal death in animal model of Parkinson´s disease, indicating that L-type CCB are potentially viable neuroprotective pharmaceuticals [20]. Intriguingly, a 1-decade study involving thousands senile hypertensive patients demonstrated that prescription of L-type CCB reduced blood pressure, and risk of dementia, in hypertensive patients, indicating that these pharmaceuticals could be clinically used to treat neurodegenerative diseases [21]. These results for the neuroprotective effects of CCB have been reinvestigated in thousands elderly hypertensive patients with memory dysfunction [22]. These studies concluded that patients who have taken CCB had their risk of cognitive dysfunction decreased, such as Alzheimer´s disease [22]. These findings reinforce the idea that reduction of cytosolic Ca2+ overload produced by L-type CCB due to blockade of Ca2+ influx could be an alternative pharmacological goal to reduce, or prevent, neuronal death in neurodegenerative diseases.

Due to involvement of the Ca2+ and cAMP signaling pathways in the regulation of the cellular differentiation process, it is possible that the pharmacological modulation of the Ca2+/cAMP signaling interaction could stimulate the cellular differentiation in stem cells [15,16]. In this case, this pharmacological

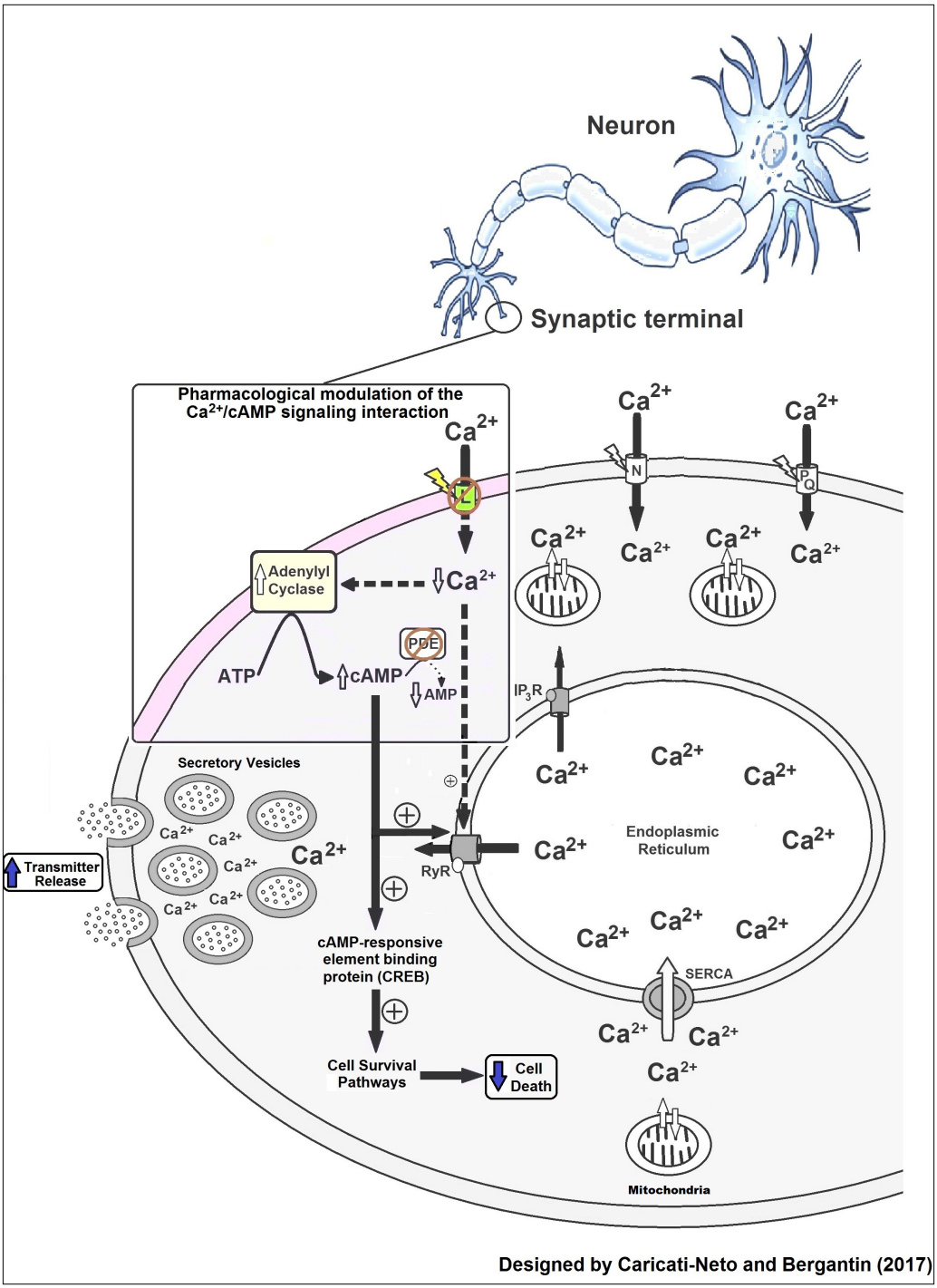

Figure 1. Pharmacological modulation of the Ca^{2+}/cAMP signaling interaction proposed by Caricati-Neto and Bergantin [15,16]. The Ca^{2+}/cAMP signaling interaction can be pharmacologically modulated by combined use of drugs that reduce $[Ca^{2+}]c$ such as CCB, and cAMP-enhancer compounds such as PDE inhibitors and AC activators. This pharmacological modulation could be a new strategy to attenuate neuronal death caused by cytosolic Ca^{2+} overload and to increase neurotransmitter release. L, N, PQ: Ca^{2+} channel types; PDE: phosphodiesterase; RyR: ryanodine receptors; IP_3R: IP_3 receptors; SERCA: sarcoendoplasmic reticulum Ca^{2+}-ATPase; (+): stimulation; dotted arrow: weak effect; solid arrow: strong effect.

strategy could be used in the cell therapy for the treatment of neurodegenerative diseases.

In conclusion, the Ca2+/cAMP signaling interaction may dramatically impact on medical research and therapeutics, stimulating the development of new pharmacological strategies for the therapy of human diseases, including: neurodegenerative diseases, and yet cellular therapy using stem cells for combating diseases related to aging.

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References

1. Berridge MJ. Dysregulation of neural calcium signaling in Alzheimer disease, bipolar disorder and schizophrenia. Prion. 2013;7(1):2-13.
2. Berridge MJ. Calcium regulation of neural rhythms, memory and Alzheimer's disease. J Physiol. 2014;592(Pt 2):281-93.
3. Ringer S. A third contribution regarding the Influence of the Inorganic Constituents of the Blood on the Ventricular Contraction. J Physiol. 1883;4(2-3):222-5.
4. Fleckenstein A. History of calcium antagonists. Circ Res. 1983;52(2 Pt 2):I3-16.
5. Garcia AG, Garcia-De-Diego AM, Gandia L, Borges R, Garcia-Sancho J. Calcium signaling and exocytosis in adrenal chromaffin cells. Physiol Rev. 2006;86 (4):1093-131.
6. Kreye VA, Luth JB. Proceedings: Verapamil-induced phasic contractions of the isolated rat vas deferens. Naunyn Schmiedebergs Arch Pharmacol. 1975;287 Suppl:R43.
7. Rosa JM, Conde M, Nanclares C, Orozco A, Colmena I, de Pascual R, et al. Paradoxical facilitation of exocytosis by inhibition of L-type calcium channels of bovine chromaffin cells. Biochem Biophys Res Commun. 2011;410(2):307-11.
8. Bergantin LB, Souza CF, Ferreira RM, Smaili SS, Jurkiewicz NH, Caricati-Neto A, et al. Novel model for "calcium paradox" in sympathetic transmission of smooth muscles: role of cyclic AMP pathway. Cell Calcium. 2013;54(3):202-12.
9. Burnstock G. Autonomic neurotransmission: 60 years since sir Henry Dale. Annu Rev Pharmacol Toxicol. 2009;49:1-30.
10. Hidalgo A, Beneit J, Lorenzo P. [Effect of calcium antagonists on the response of the rat vas deferens to noradrenaline and field stimulation]. Rev Esp Fisiol. 1983;39(2):211-5.
11. Hata F, Fujita A, Saeki K, Kishi I, Takeuchi T, Yagasaki O. Selective inhibitory effects of calcium channel antagonists on the two components of the neurogenic response of guinea pig vas deferens. J Pharmacol Exp Ther. 1992;263(1):214-20.
12. French AM, Scott NC. A comparison of the effects of nifedipine and verapamil on rat vas deferens. Br J Pharmacol. 1981;73(2):321-3.
13. Moritoki H, Iwamoto T, Kanaya J, Maeshiba Y, Ishida Y, Fukuda H. Verapamil enhances the non-adrenergic twitch response of rat vas deferens. Eur J Pharmacol. 1987;140(1):75-83.
14. Rae GA, Calixto JB. Interactions of calcium antagonists and the calcium channel agonist Bay K 8644 on neurotransmission of the mouse isolated vas deferens. Br J Pharmacol. 1989;96(2):333-40.
15. Caricati-Neto A, Garcia AG, Bergantin LB. Pharmacological implications of the Ca(2+)/cAMP signaling interaction: from risk for antihypertensive therapy to potential beneficial for neurological and psychiatric disorders. Pharmacol Res Perspect. 2015;3(5):e00181.
16. Bergantin LB, Caricati-Neto A. Challenges for the pharmacological treatment of neurological and psychiatric disorders: Implications of the Ca2+/cAMP

intracellular signalling interaction. Eur J Pharmacol 2016; 788: 255-260.

17. Errante PR, Caricati-Neto A, Bergantin LB. Insights for the inhibition of cancer progression: Revisiting Ca2+ and cAMP signalling pathways. Adv Cancer Prevention 2017; 2: e103.
18. Sommer N, Loschmann PA, Northoff GH, Weller M, Steinbrecher A, Steinbach JP et. al (1995) The antidepressant rolipram suppresses cytokine production and prevents autoimmune encephalomyelitis. Nat Med. 1:244–248.
19. Xiao L, O'Callaghan JP, O'Donnell JM (2011) Effects of repeated treatment with phosphodiesterase-4 inhibitors on cAMP signaling, hippocampal cell proliferation, and behavior in the forced-swim test. J Pharmacol Exp Ther. 338:641–647.
20. Ilijic E, Guzman JN, Surmeier DJ (2011) The L-type channel antagonist isradipine is neuroprotective in a mouse model of Parkinson's disease. Neurobiol Dis 43(2): 364-71.
21. Wu CL, Wen SH (2016) A 10-year follow-up study of the association between calcium channel blocker use and the risk of dementia in elderly hypertensive patients. Medicine (Baltimore) 95(32): e4593.
22. Hanon O, Pequignot R, Seux ML, Lenoir H et al (2006) Relationship between antihypertensive drug therapy and cognitive function in elderly hypertensive patients with memory complaints. J Hypertens 24(10): 2101–2107.