

Emerging Concepts for Neuroscience Field from Ca²⁺/cAMP Signalling Interaction

Leandro Bueno Bergantin* and Afonso Caricati-Neto

Laboratory of Autonomic and Cardiovascular Pharmacology, Department of Pharmacology, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), 55 11 5576-4973, Rua Pedro de Toledo, 669 – Vila Clementino, São Paulo – SP, CEP: 04039-032, Brazil

*Correspondence to:

Leandro Bueno Bergantin, PhD
Laboratory of Autonomic and Cardiovascular
Pharmacology, Department of Pharmacology
Escola Paulista de Medicina, Universidade
Federal de São Paulo (UNIFESP)
55 11 5576-4973, Rua Pedro de Toledo
669 – Vila Clementino, São Paulo – SP, Brazil
E-mail: leanbio39@yahoo.com.br

Received: March 20, 2017

Accepted: May 10, 2017

Published: May 12, 2017

Citation: Bergantin LB, Caricati-Neto A. 2017. Emerging Concepts for Neuroscience Field from Ca²⁺/cAMP Signalling Interaction. *J Neurol Exp Neurosci* 3(1): 29-32.

Copyright: © 2017 Bergantin and Caricati-Neto. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY) (<http://creativecommons.org/licenses/by/4.0/>) which permits commercial use, including reproduction, adaptation, and distribution of the article provided the original author and source are credited.

Published by United Scientific Group

Abstract

The interaction between intracellular signalling pathways mediated by Ca²⁺ and cAMP (Ca²⁺/cAMP signalling interaction) is now well-accepted as a vital cellular process for mammals. In the neuroscience field, it has opened a new avenue for the drug development more effective, and safer, for the treatment of Alzheimer's and neurodegenerative diseases. It has been almost 4 years since we revealed the involvement of the Ca²⁺/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 Ca²⁺ 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 creative experiments, 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 Ca²⁺/cAMP signalling interaction. Thus, pharmacological handling of the Ca²⁺/cAMP signalling interaction could be a more efficient and safer therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and attenuating neuronal death.

Keywords

Ca²⁺/cAMP signalling interaction, "Calcium paradox", Neuroscience field

Introduction

Nowadays, the interaction between intracellular signalling pathways mediated by Ca²⁺ and cAMP (Ca²⁺/cAMP signalling interaction) is well-recognized as a vital cellular process for mammals. This interaction has opened a novel pathway for the drug development more effective, and safer, to treating diseases related to the neuroscience field, such as Alzheimer's and other neurodegenerative diseases. The results which demonstrated the involvement of the Ca²⁺/cAMP signalling interaction in the enigma of the so-called "calcium paradox" have completed a 4-years anniversary. 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 Ca²⁺ concentration ([Ca²⁺]_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 [Ca²⁺]_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 $1 \mu\text{mol/L}$, 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, including sympathetic neurons [7]. We recently showed that Ca^{2+} /cAMP signalling interaction participates in the regulation of transmitters release from sympathetic neurons, and adrenal chromaffin cells [8-11].

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

The Ca^{2+} /cAMP signalling interaction is well-recognized as a vital cellular process for mammals. This nowadays accepted concept assumes that these signalling pathways virtually exist in all mammalian cells, regulated by adenylyl cyclases (ACs) and phosphodiesterases (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 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 neuroscience field

Several medical studies have been evidencing that prescription of L-type CCBs in the antihypertensive pharmacotherapy decreased arterial pressure arterial, but produced typical clinical 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 creative experiments, 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 sympathetic-mediated contractions of the vas deferens were completely inhibited by L-type CCBs in high concentrations ($>1 \mu\text{mol/L}$), but unpredictably, and paradoxically, potentiated in concentrations below $1 \mu\text{mol/L}$, characterized by CCBs-induced sympathetic hyperactivity [4-6, 9]. Our studies showed that this 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 [8-11]. Briefly, the reduction of Ca^{2+} influx through L-type voltage-activated Ca^{2+} channels produced by CCBs enhances the adenylyl cyclase activity (and consequently elevating cAMP levels, please see figure 1). These CCBs-effects can be potentiated by cAMP-enhancer compounds (like PDEs inhibitors). In fact, the fundamental mechanisms by which Ca^{2+} /cAMP signalling interaction may increase the transmitter release are due: increasing of

content of transmitter in the secretory vesicles (please see figure 1) and enhancing of rate of transmitter release. Thus, by elevating cAMP levels, this second messenger may enhance the release of Ca^{2+} from ER. Indeed, Ca^{2+} 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. Figure 1 shows how the pharmacological modulation of the Ca^{2+} /cAMP signalling interaction could produce increase of neurotransmitter release.

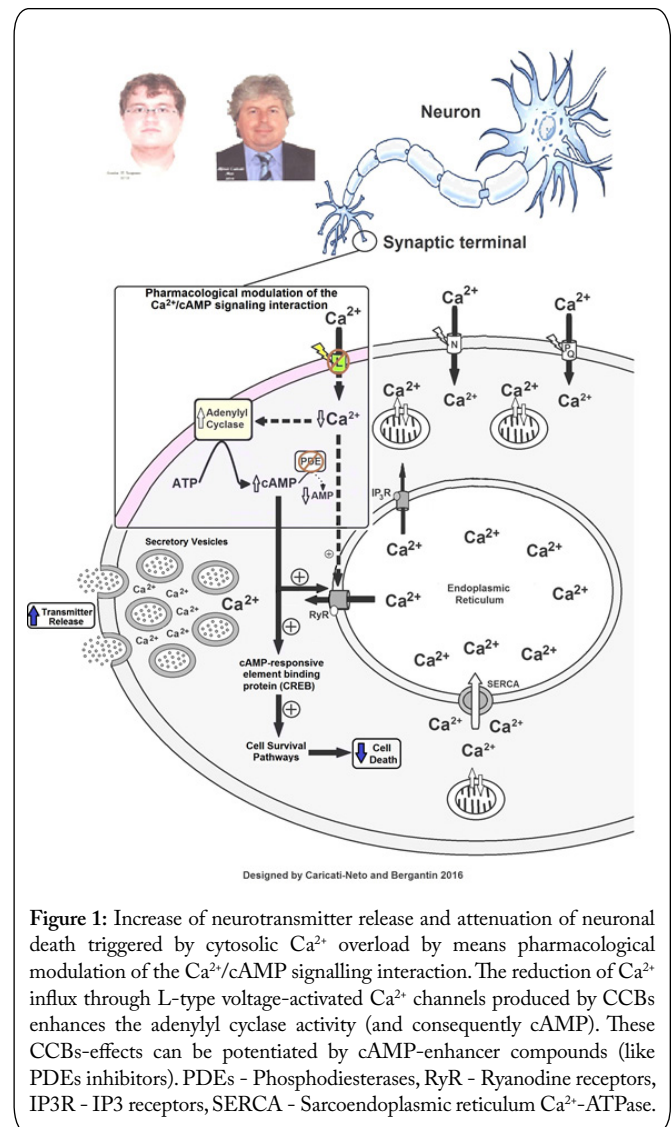


Figure 1: Increase of neurotransmitter release and attenuation of neuronal death triggered by cytosolic Ca^{2+} overload by means pharmacological modulation of the Ca^{2+} /cAMP signalling interaction. The reduction of Ca^{2+} influx through L-type voltage-activated Ca^{2+} channels produced by CCBs 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, IP3R - IP3 receptors, SERCA - Sarcoendoplasmic reticulum Ca^{2+} -ATPase.

Indeed, many reports have shown that increase of cytosolic cAMP concentration ($[cAMP]_c$) stimulates neuroprotective effects [13, 14]. Thus, elevating $[cAMP]_c$ by handling Ca^{2+} /cAMP signalling interaction could reduce neuronal death triggered by cytosolic Ca^{2+} overload [8-11]. 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 novel 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 attenuation of neuronal death.

In fact, it was showed that the prescription of L-type CCBs reduces motor symptoms, and reduces progressive neuronal death in animal model of Parkinson's disease, suggesting that L-type CCBs are potentially viable neuroprotective pharmaceuticals [15]. Additionally, 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 during antihypertensive therapy reduces risk of dementia in these patients, indicating that these pharmaceuticals could be clinically used to treat Alzheimer's disease [16]. These findings for the neuroprotective CCBs-effects 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 Ca²⁺ overload produced by L-type CCBs due to blockade of Ca²⁺ influx could be a successful pharmacological strategy to reduce, or prevent, neuronal death in neurodegenerative diseases. Finally, these findings could open a new way for the drug development more effective, and safer, for the pharmacotherapy of Alzheimer's and other neurodegenerative diseases [18-24].

Conclusion

This work proposes that pharmacological interference on the Ca²⁺/cAMP signalling interaction could be a more efficient, and safer, therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and reducing 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

References

- Douglas WW, Rubin RP. 1961. The role of calcium in the secretory response of the adrenal medulla to acetylcholine. *J Physiol* 159: 40-57. <https://doi.org/10.1113/jphysiol.1961.sp006791>
- Baker PF, Knight DE. 1978. Calcium-dependent exocytosis in bovine adrenal medullary cells with leaky plasma membranes. *Nature* 276(5688): 620-622. <https://doi.org/10.1038/276620a0>
- Neher E, Zucker RS. 1993. Multiple calcium-dependent processes related to secretion in bovine chromaffin cells. *Neuron* 10(1): 21-30. [https://doi.org/10.1016/0896-6273\(93\)90238-M](https://doi.org/10.1016/0896-6273(93)90238-M)
- Kreye VA, Luth JB. 1975. Proceedings: verapamil-induced phasic contractions of the isolated rat vas deferens. *Naunyn Schmiedebergs Arch Pharmacol* 287(Suppl): R43.
- French AM, Scott NC. 1981. A comparison of the effects of nifedipine and verapamil on rat vas deferens. *Br J Pharmacol* 73(2): 321-323. <https://doi.org/10.1111/j.1476-5381.1981.tb10424.x>
- Moritoki H, Iwamoto T, Kanaya J, Maeshiba Y, Ishida Y, et al. 1987. Verapamil enhances the non-adrenergic twitch response of rat vas deferens. *Eur J Pharmacol* 140(1): 75-83. [https://doi.org/10.1016/0014-2999\(87\)90636-4](https://doi.org/10.1016/0014-2999(87)90636-4)
- Chern YJ, Kim KT, Slakey LL, Westhead EW. 1988. Adenosine receptors activate adenylate cyclase and enhance secretion from bovine adrenal chromaffin cells in the presence of forskolin. *J Neurochem* 50(5): 1484-1493. <https://doi.org/10.1111/j.1471-4159.1988.tb03034.x>
- Caricati-Neto A, García AG, Bergantin LB. 2015. Pharmacological implications of the Ca²⁺/cAMP signalling interaction: from risk for antihypertensive therapy to potential beneficial for neurological and psychiatric disorders. *Pharmacol Res Perspect* 3(5): e00181. <https://doi.org/10.1002/prp2.181>
- Bergantin LB, Souza CF, Ferreira RM, Smali SS, Jurkiewicz NH, et al. 2013. Novel model for "calcium paradox" in sympathetic transmission of smooth muscles: role of cyclic AMP pathway. *Cell Calcium* 54(3): 202-212. <https://doi.org/10.1016/j.ceca.2013.06.004>
- Bergantin LB, Jurkiewicz A, García AG, Caricati-Neto A. 2015. A calcium paradox in the context of neurotransmission. *J Pharm Pharmacol* 6: 253-261. <https://doi.org/10.17265/2328-2150/2015.06.001>
- Bergantin LB, Caricati-Neto A. 2016. Challenges for the pharmacological treatment of neurological and psychiatric disorders: Implications of the Ca²⁺/cAMP intracellular signalling interaction. *Eur J Pharmacol* 788: 255-260. <https://doi.org/10.1016/j.ejphar.2016.06.034>
- Grossman E, Messerli FH. 1998. Effect of calcium antagonists on sympathetic activity. *Eur Heart J* 19(Suppl F): F27-F31.
- Sommer N, Loschmann PA, Northoff GH, Weller M, Steinbrecher A, et al. 1995. The antidepressant rolipram suppresses cytokine production and prevents autoimmune encephalomyelitis. *Nat Med* 1(3): 244-248. <https://doi.org/10.1038/nm0395-244>
- 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(2): 641-647. <https://doi.org/10.1124/jpet.111.179358>
- 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): 364-371. <https://doi.org/10.1016/j.nbd.2011.04.007>
- 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. <https://doi.org/10.1097/MD.0000000000004593>
- Hanon O, Pequignot R, Seux ML, Lenoir H, Bune A, et al. 2006. Relationship between antihypertensive drug therapy and cognitive function in elderly hypertensive patients with memory complaints. *J Hypertens* 24(10): 2101-2107. <https://doi.org/10.1097/01.hjh.0000244961.69985.05>
- Bergantin LB, Caricati-Neto A. 2016. Insight from "calcium paradox" due to Ca²⁺/cAMP interaction: novel pharmacological strategies for the treatment of depression. *Int Arch Clin Pharmacol* 2(1): 007.
- Bergantin LB, Caricati-Neto A. 2016. Novel insights for therapy of parkinson's disease: pharmacological modulation of the Ca²⁺/cAMP signalling interaction. *Austin Neurol & Neurosci* 1(2): 1009.
- Bergantin LB, Caricati-Neto A. 2016. Recent advances in pharmacotherapy of neurological and psychiatric disorders promoted by discovery of the role of Ca²⁺/cAMP signaling interaction in the neurotransmission and neuroprotection. *Adv Pharmacol* 1(3): 66-70.
- Bergantin LB, Caricati-Neto A. 2016. From discovering "calcium paradox" to Ca²⁺/cAMP interaction: Impact in human health and disease. Scholars' Press.
- Caricati-Neto A, Bergantin LB. 2016. New therapeutic strategy of

- Alzheimer's and Parkinson's diseases: pharmacological modulation of neural Ca²⁺/cAMP intracellular signaling interaction. *Asian Journal of Pharmacy and Pharmacology* 2(6): 136-143.
23. Bergantin LB, Caricati-Neto A. 2016. Impact of interaction of Ca²⁺/cAMP intracellular signalling pathways in clinical pharmacology and translational medicine. *Clin Pharmacol Transl Med* 1-4.
24. Bergantin LB, Caricati-Neto A. 2016. Challenges for the pharmacological treatment of dementia: implications of the Ca²⁺/cAMP intracellular signalling interaction. *Avid Science* 2-25.