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Short Communication

The "Calcium Paradox" Due To Ca^{2+}/Camp Interaction: New Insights for the Neuroscience Field

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ABSTRACT

In the cardiovascular field, tachycardia and increment of catecholamine plasma levels (sympathetic hyperactivity) have been reported by hypertensive patients that use L-type Ca^{2+} channel blockers (CCBs) since 70´s. Our discovery of the involvement of interaction between the intracellular signalling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP interaction) revealed that this phenomenon (sympathetic hyperactivity) was resulting of increase of transmitter release from sympathetic neurons stimulated by CCBs due to its interference on the Ca^{2+}/cAMP interaction. In the neuroscience field, this discovery has produced new paths for the understanding of the cellular and molecular mechanisms involved in the pathogenesis of neurodegenerative diseases, such as Alzheimer´s and Parkinson's diseases. In this way, novel journeys for the development of new pharmacological strategies more effective for the treatment of neurodegenerative diseases may be initiated.

INTRODUCTION

Many results have shown that cAMP increases neurotransmitter release at many synapses in autonomic nervous system of vertebrate, including sympathetic neurons [1]. The notion of stimulus-secretion initially resulted from the experiments performed by Douglas and Rubin in the 1960s [2]. Using adrenal chromaffin cells, Baker and Knight revealed in 1970´s that a rise in the cytosolic Ca^{2+} concentration ([Ca^{2+}] c) is an elementary requirement to trigger transmitter release [3]. The demonstration of direct relationship between rapid neurotransmitter release and rise in $[Ca^{2+}]_c$ derived from the experiments using photo released caged Ca^{2+} in adrenal chromafin cells performed Neher and Zucker in 1990´s [4]. Although the cellular and molecular mechanisms involved in these synergistic 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.

The ca2+/camp interaction hypothesis

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. 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]. 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]. Indeed, Ca^{2+}/cAMP interaction plays a role in neurotransmitter release from neurons and

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neuroendocrine cells [5-8]. Then, novel therapeutic insights for medicines could be developed by the pharmacological modulation of the Ca^{2+}/cAMP interaction.

The ca2+/camp interaction: new insights for neuroscience

Sympathetic hyperactivity such as tachycardia, and increment of catecholamine plasma levels, have been evidenced by several medical studies dealing with CCBs [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 revealed that “calcium paradox” phenomenon resulted from the increment of transmitter release from sympathetic neurons, and adrenal chromaffin cells, stimulated by CCBs due to its interference on the Ca^{2+}/cAMP interaction [6]. 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]. Indeed, this paradoxical sympathetic hyperactivity is caused by increment of neurotransmitter release from sympathetic neurons due to its pharmacological modulation on the Ca^{2+}/cAMP interaction [5-8] (Figure 1).

Undeniably, several studies showed that neuroprotective response can be achieved by increase of cytosolic cAMP concentration ([cAMP] c) stimulation [13,14]. In this way, we could propose that a rise of [cAMP]c by interfering in the Ca^{2+}/cAMP interaction could attenuate neuronal death triggered by cytosolic Ca^{2+} overload [5-8,15,16]. Then, the pharmacological modulation of the Ca^{2+}/cAMP interaction [17,18] 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 [19,20] resulting from neurotransmitter release deficit, and/or neuronal death [5-8,15,16]. These results could open a new path for the drug development more effective and safer for the treatment of neurodegenerative diseases.

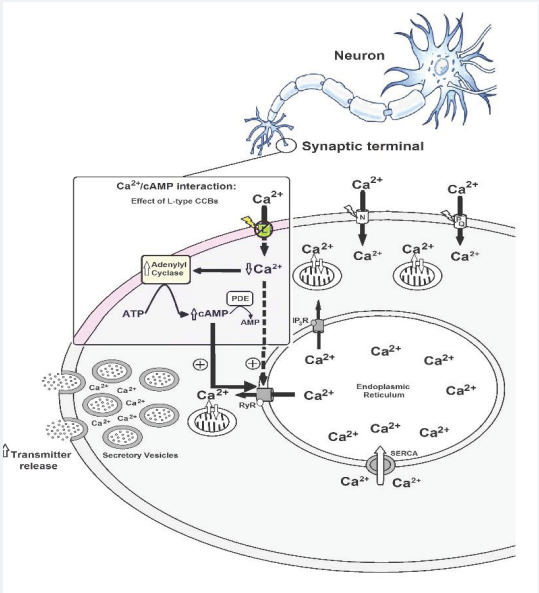

Figure 1: Increase of the neurotransmitter release due to pharmacological modulation of the Ca^{2+}/cAMP interaction by L-type CCBs [5-8].

CONCLUSION

New insights for the neuroscience field from the discovery of the "calcium paradox" due to Ca^{2+}/cAMP interaction have been emerging to treat neurodegenerative diseases. Pharmacological modulation of this interaction could be a more efficient and safer therapeutic strategy for stimulating neurotransmission compromised by neurotransmitter release deficit, and attenuating neuronal death in the neurodegenerative diseases.

DISCLOSURE STATEMENT

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REFERENCES

1. Chern YJ, Kim KT, Slakey LL, Westhead EW. Adenosine receptors activate adenylate cyclase and enhance secretion from bovine adrenal chromaffin cells in the presence of forskolin. J Neurochem. 1988; 50: 1484-1493. Ref.: https://goo.gl/D3U5F0

2. Douglas WW, Rubin RP. The role of calcium in the secretory response of the adrenal medulla to acetylcholine. J Physiol. 1961; 159: 40-57. Ref.: https://goo.gl/Lwekpm

3. Baker PF, Knight DE. Calcium-dependent exocytosis in bovine adrenal medullary cells with leaky plasma membranes. Nature. 1978; 276: 620-622. Ref.: https://goo.gl/bvf8DR

4. Neher E, Zucker RS. Multiple calcium-dependent processes related to secretion in bovine chromaffin cells. Neuron. 1993; 10: 21-30. Ref.: https://goo.gl/3fvzjy

5. Caricati-Neto A, García AG, Bergantin LB. Pharmacological implications of the Ca^{2+}/cAMP signalling interaction: from risk for antihypertensive therapy to potential beneficial for neurological and psychiatric disorders. Pharmacol Res Perspect. 2015; 3: e00181. Ref.: https://goo.gl/UiQrGs

6. Bergantin LB, Souza CF, Ferreira RM, Smaili SS, Jurkiewicz NH, et al. Novel model for "calcium paradox" in sympathetic transmission of smooth muscles: role of cyclic AMP pathway. Cell Calcium. 2013; 54: 202-212. Ref.: https://goo.gl/HHou6F

7. Bergantin LB, Jurkiewicz A, García AG, Caricati-Neto A. A Calcium Paradox in the Context of Neurotransmission. Journal of Pharmacy and Pharmacology. 2015; 3: 253-261. Ref.: https://goo.gl/ltkVhv

8. Bergantin LB, Caricati-Neto A. Challenges for the pharmacological treatment of neurological and psychiatric disorders: Implications of the Ca^{2+}/cAMP intracellular signalling interaction. Eur J Pharmacol. 2016; 788: 255-260. Ref.: https://goo.gl/u21xBi

9. Grossman E, Messerli FH. Effect of calcium antagonists on sympathetic activity. Eur Heart J. 1998; 19: F27-F31. Ref.: https://goo.gl/BQkkG1

10. Kreye VA, Luth JB. Proceedings: verapamil-induced phasic contractions of the isolated rat vas deferens. Naunyn Schmiedebergs Arch Pharmacol. 1975; 287: R43. Ref.: https://goo.gl/Z07NA4

11. French AM, Scott NC. A comparison of the effects of nifedipine and verapamil on rat vas deferens. Br J Pharmacol. 1981; 73: 321-323. Ref.: https://goo.gl/d8wrcd

12. Moritoki H, Iwamoto T, Kanaya J, Maeshiba Y, Ishida Y, et al. Verapamil enhances the non-adrenergic twitch response of rat vas deferens. Eur J Pharmacol. 1987; 140: 75-83. Ref.: https://goo.gl/OKoviM

13. Sommer N, Loschmann PA, Northoff GH, Weller M, Steinbrecher A, et al. The antidepressant rolipram suppresses cytokine production and prevents autoimmune encephalomyelitis. Nat Med. 1995; 1: 244-248. Ref.: https://goo.gl/MiganR

14. Xiao L, O'Callaghan JP, O'Donnell JM. 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. 2011; 338: 641-647. Ref.: https://goo.gl/14xO4A

15. Bergantin LB, Caricati-Neto A. Novel Insights for Therapy of Parkinson’s disease: Pharmacological Modulation of the Ca^{2+}/cAMP Signalling Interaction. Austin Neurol & Neurosci. 2016; 1: 1009. Ref.: https://goo.gl/ujivdj

16. Bergantin LB, Caricati-Neto A. Recent advances in pharmacotherapy of neurological and psychiatric disorders promoted by discovery of the role of Ca^{2+}/cAMP signaling interaction in the neurotransmission and neuroprotection. Adv Pharmac J. 2016; 1: 66.

17. Halls ML, Cooper DM. Adenylyl cyclase signalling complexes - Pharmacological challenges and opportunities. Pharmacol Ther. 2017; 7258: 30011-30016. Ref.: https://goo.gl/VDeVKV

18. Cooper DM, Mons N, Karpen JW. Adenylyl cyclases and the interaction between calcium and cAMP signalling. Nature. 1995; 374: 421-424. Ref.: https://goo.gl/OVc1JP

19. Bereczki E, Francis PT, Howlett D, Pereira JB, Höglund K, et al. Synaptic proteins predict cognitive decline in Alzheimer`s disease and Lewy body dementia. Alzheimers Dement. 2016; 12: 1149-1158. Ref.: https://goo.gl/pch8Cq

20. Clare R, King VG, Wirenfeldt M, Vinters HV. Synapse loss in dementias. J Neurosci Res. 2010; 88: 2083-2090. Ref.: https://goo.gl/5sJRu7