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Editorial

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Ca^{2+} and Camp: Do these Intracellular Messengers 'Work' Independently? Of Course Not, and the History Goes Ahead…

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Abstract

Our group has been pioneering in exploring that the pharmacological handling of Ca^{2+}/cAMP signalling interaction could be a better therapeutic method for increasing neurotransmission in psychiatric disorders, and stimulating neuroprotection for combating neurodegenerative diseases, such as Alzheimer´s disease. Indeed, Ca^{2+} is a classic intracellular second messenger, now well recognized as a ubiquitous molecule that controls several processes, including gene transcription, cell cycle regulation, mobility, apoptosis, neurotransmitter release and muscle contraction. In addition, cAMP, another vital intracellular messenger, modulates since cardiac contraction to neurotransmitter release. Do these intracellular messengers ´work´ independently? Of course not, and we demonstrated it! Through groundbreaking experiments (including one by accident!), our group discovered that the paradoxical effects (e.g. reduction of intracellular Ca^{2+} concentration, and enhancing of neurotransmitter release?!) produced by L-type Ca^{2+} channel blockers (CCBs) resulted from interferences on the Ca^{2+}/cAMP signalling interaction. Considering the widely use of CCBs as antihypertensive drugs, and for combating arrhythmia, the elucidation of these paradoxical effects proved to be very important (specially for clinical reasons). How does this history correlate to cancer field? Considering the notion that Ca^{2+}/cAMP signalling interaction is a fundamental cellular process, which exists in many cell types, whether this interaction may be a novel therapeutic target to alter cancer tumor growth, angiogenesis and metastasis, without affecting normal cell physiology deserves special consideration. Thus, this editorial article highlights the latest advances made by our group in the field of Ca^{2+}/cAMP signalling interaction.

Keywords

Therapeutics outcomes; Ca^{2+}/cAMP signalling interaction

Introduction

Ca^{2+}, a classic intracellular second messenger, is now well documented as a ubiquitous molecule that controls several processes, including since gene transcription to cell cycle regulation, also mobility and apoptosis. In addition, cAMP, another important intracellular messenger, modulates since cardiac contraction to neurotransmitter release. Do these intracellular messengers 'work' independently? Of course not, and we proved it! Our group has been one of the pioneers in establishing that the so-called Ca^{2+}/cAMP signalling interaction is a fundamental cellular process for mammalians [1-10]. This interaction has 'unlocked' a new 'paradigm' to the drug development for the treatment of diseases like Alzheimer's and others, related to the neurotransmitter release deficit, now including possible cancer. It has been completed 4 years, since our group came across with the pioneer discovery of the involvement of the Ca^{2+}/cAMP signalling interaction in the enigma of the 'paradoxical effects produced by L-type Ca^{2+} channel blockers (CCBs)', the so-called calcium paradox [9]. Interestingly, these 'paradoxical effects' have been reported by decades without a proper solution. Indeed, numerous clinical studies have documented that prescription of CCBs for hypertensive patients decreased arterial pressure, but also produced paradoxical increases in plasma noradrenaline levels. For four decades, or even more, this 'paradox' remained a mystery [10]. Through innovative experiments (including one by accident), our group discovered that this unexpected result was coming from rises of neurotransmitter release from sympathetic neurons, and adrenal chromaffin cells, endorsed by CCBs due to its interference on the Ca^{2+}/cAMP signalling interaction. Considering the widely use of CCBs as antihypertensive drugs, and for combating arrhythmia, the elucidation of this enigma proved to be very important (especially for clinical reasons). How does this history correlate to cancer field?

From basic science, we know that Ca^{2+} is stored in intracellular organelles, such as endoplasmic reticulum (ER) and mitochondria [11]. Indeed, intracellular Ca^{2+} homeostasis is controlled by several channels and transporters of Ca^{2+}, as by the receptor of inositol-1,4,5-triphosphate (IP_3R) and Ca^{2+} ATPase pump. In addition, Ca^{2+} influx through cellular membrane occurs facilitated by voltage-activated Ca^{2+} channels (VACCs), and transient receptor potential channels (TRPs). Intracellular Ca^{2+} homeostasis is also controlled by the Ca^{2+} induced Ca^{2+} release (CICR) mechanism, Na^{+}/Ca^{2+} exchanger (NCX) and mitochondrial Ca^{2+} uniporter (MCU) [12]. Thus, the rise of expression, or activity, of Ca^{2+} channels in the plasma membrane mediates the increase of Ca^{2+} influx, endorsing Ca^{2+}-dependent cell proliferation, and differentiation [13]. Considering these findings, we now know that Ca^{2+} is decisive for the cancer progression. How does this occur? Carcinogenesis is a progressive process that can be reached by the action of environmental agents, such as chemical substances, radiation or viruses, or can be inherited in the germ line. This suggests alterations in proto-oncogenes, genes that regulate apoptosis, and genes involved in DNA repair. Most antineoplastic chemotherapeutic compounds performance their action through cell division, affecting both normal and neoplastic cells. Indeed, there is a consensus that carcinogenesis process is associated with an increase of expression, or abnormal activation, of Ca^{2+} channels, Ca^{2+} transporters or Ca^{2+} ATPases [12], making these paths possible therapeutic targets for preventing cancer growth. For example, this issue can be observed by the use of selective SERCA pump inhibitor, thapsigargin [14] and of course, CCBs prescribed in anti-hypertensive therapy [15,16].

In addition to Ca^{2+}, cAMP has been emerging as playing a role in cancer progression [17]. Isn't it fantastic? From this concept in mind, phosphodiesterase IV inhibitors like rolipram, which enhance cAMP, have been anticipated as potential adjuvant, or chemotherapeutic

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agents, in hepatocellular carcinoma [17]. Do you now understand how Ca^{2+}/cAMP signalling interaction are correlated to cancer field? And the history goes ahead…

Ca^{2+}/cAMP signalling and cancer progression: a beautiful correlation

Our group has been pioneering in establishing that the manipulation of Ca^{2+}/cAMP signalling interaction could be a better therapeutic 'cellular method' for increasing neurotransmission in psychiatric disorders, and stimulating neuroprotection for combating neurodegenerative diseases, such as Alzheimer's disease. As the activity of adenylyl cyclase (AC) is controlled by Ca^{2+}, the decrease of $[Ca^{2+}]c$ achieved by L-type CCBs promotes an increase of activity of ACs, and rise of [cAMP]c (Ca^{2+}/cAMP signalling interaction) [1-10]. Isn't it spectacular? Thus, whether this interaction may be a novel therapeutic goal to alter cancer tumor growth, angiogenesis and metastasis, without affecting normal cell physiology deserves special reflection [18-21]. So, the current information about modulation of the homeostasis of Ca^{2+} and cAMP in cancer tumor cells, and the search for new drugs to regulate these intracellular messengers, may be able to lead the progress (in the future) of novel pharmacological strategies that specifically alter tumor growth, angiogenesis and metastasis, possible without affecting normal cell physiology. Don't you agree? Finally, the pharmacological handling of the Ca^{2+}/cAMP signalling interaction could be a more efficient therapeutic 'cellular method' to inhibit cancer tumor progression, a new hope to treat cancer tumor progression (in the future). Indeed, oncological patients deserve it.

References

1. Bergantin LB, Caricati Neto A (2016) Challenges for the pharmacological treatment of neurological and psychiatric disorders: Implications of the Ca^{2+}/cAMP intracellular signalling interaction. Eur J Pharmacol 788: 255-260.
2. Bergantin LB, Caricati Neto A (2016) Insight from "Calcium Paradox" due to Ca^{2+}/cAMP interaction: novel pharmacological strategies for the treatment of depression. Int Arch Clin Pharmacol 2: 007.
3. Bergantin LB, Caricati Neto A (2016) Novel insights for therapy of parkinson's disease: pharmacological modulation of the Ca^{2+}/cAMP signalling interaction. Austin Neurol Neurosci 1: 1009.
4. Bergantin LB, Caricati Neto A (2016) Recent advances in pharmacotherapy of neurological and psychiatric disorders promoted by discovery of the role of Ca^{2+}/cAMP signalling interaction in the neurotransmission and neuroprotection. Adv Pharmac J 1: 66.
5. Bergantin LB, Caricati Neto A (2016) From discovering "calcium paradox" to Ca^{2+}/cAMP interaction: Impact in human health and disease. Global Congress on Biochemistry, Glycomics & Amino Acids, San Antonio, USA.
6. Bergantin LB, Caricati Neto A (2016) New therapeutic strategy of Alzheimer's and Parkinson's diseases: Pharmacological modulation of neural Ca^{2+}/cAMP intracellular signalling interaction. Asian J Pharmacy and Pharmacol 2(6): 136-143.
7. Bergantin LB, Caricati Neto A (2016) Impact of interaction of Ca^{2+}/cAMP intracellular signalling pathways in clinical pharmacology and translational medicine. Clinical Pharmacology and Translational Medicine 1: 1-4.
8. Bergantin LB, Caricati Neto A (2016) Challenges for the pharmacological treatment of dementia: implications of the Ca^{2+}/cAMP intracellular signalling interaction. Avid Science.
9. Bergantin LB, Souza CF, Ferreira RM, Smaili 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: 202-212.
10. Caricati Neto A, Garcia AG, Bergantin LB (2015) 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 3: e00181.
11. Berridge MJ, Lipp P, Bootman MD (2000) The versatility and universality of calcium signalling. Nat Rev Mol Cell Biol 1: 11-21.
12. Cui C, Merritt R, Fu L, Pan Z (2017) Targeting calcium signalling in cancer therapy. Acta Pharma Sin B 7: 3-17.
13. Roderick HL, Cook SJ (2008) Ca^{2+} signalling checkpoints in cancer: remodeling Ca^{2+} for cancer cell proliferation and survival. Nat Rev Cancer 8: 361-375.
14. Gu J, Liu H, Fu T, Xu Y (1995) Thapsigargin increases apoptotic cell death in human hepatoma BEL-7404 cells. Cell Res 5: 59-65.
15. Yoshida J, Ishibashi T, Nishio M (2007) G1 cell cycle arrest by amlodipine, a dihydropyridine Ca^{2+} channel blocker, in human epidermoid carcinoma A431 cells. Biochem Pharmacol 73: 943-953.
16. Krouse AJ, Gray L, Macdonald T, McCray J (2015) Repurposing and rescuing of mibefradil, an antihypertensive, for cancer: a case study. Assay Drug Dev Technol 13: 650-653.
17. Massimi M, Cardarelli S, Galli F, Giardi MF, Ragusa F, et al. (2016) Increase of intracellular cyclic AMP by PDE4 inhibitors affects HepG2 cell cycle progression and survival. J Cell Biochem 118: 1401-1411.
18. Errante PR, Caricati Neto A, Bergantin LB (2017) Insights for the inhibition of cancer progression: Revisiting Ca^{2+} and cAMP signalling pathways. Adv Cancer Prevention 2: e103.
19. Errante PR, Francisco S, Caricati-Neto A, Bergantin LB (2017) The pharmacological modulation of Ca^{2+}/camp intracellular signalling pathways and traditional antitumoral pharmaceuticals. J Clin Exp Oncol 6: 4.
20. Errante PR, Leite AA, Menezes-Rodrigues FS, Caricati Neto A, Bergantin LB (2017) A novel potential therapeutic target as adjuvant treatment for cancer: the pharmacological interference on the Ca^{2+}/cAMP cellular signalling pathways. Enliven: Chall Cancer Detec Ther 1: 1-2.
21. Errante PR, Menezes-Rodrigues FS, Leite AA, Caricati Neto A, Bergantin LB (2017) The second messengers Ca^{2+} and cAMP as potential therapeutic targets for the control of cancer progression. Adv Cancer Prev 2: 1-2.

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