Ca\textsuperscript{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\textsuperscript{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\textsuperscript{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 proved it! Our group has been one of the pioneers in establishing that the so-called Ca\textsuperscript{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\textsuperscript{2+}/cAMP signalling interaction in the enigma of the ‘paradoxical effects produced by L-type Ca\textsuperscript{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\textsuperscript{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\textsuperscript{2+} is stored in intracellular organelles, such as endoplasmic reticulum (ER) and mitochondria [11]. Indeed, intracellular Ca\textsuperscript{2+} homeostasis is controlled by several channels and transporters of Ca\textsuperscript{2+}, as by the receptor of inositol 1,4,5-triphosphate (IP\textsubscript{3}/R) and Ca\textsuperscript{2+} ATPase pump. In addition, Ca\textsuperscript{2+} influx through cellular membrane occurs facilitated by voltage-activated Ca\textsuperscript{2+} channels (VACCs), and transient receptor potential channels (TRPs). Intracellular Ca\textsuperscript{2+} homeostasis is also controlled by the Ca\textsuperscript{2+} induced Ca\textsuperscript{2+} release (CICR) mechanism, Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger (NCX) and mitochondrial Ca\textsuperscript{2+} uniporter (MCU) [12]. Thus, the rise of expression, or activity, of Ca\textsuperscript{2+} channels in the plasma membrane mediates the increase of Ca\textsuperscript{2+} influx, endorsing Ca\textsuperscript{2+}-dependent cell proliferation, and differentiation [13]. Considering these findings, we now know that Ca\textsuperscript{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\textsuperscript{2+} channels, Ca\textsuperscript{2+} transporters or Ca\textsuperscript{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\textsuperscript{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
agents, in hepatocellular carcinoma [17]. Do you now understand how Ca²⁺/cAMP signalling interaction are correlated to cancer field? And the history goes ahead…

Ca²⁺/cAMP signalling and cancer progression: a beautiful correlation

Our group has been pioneering in establishing that the manipulation of Ca²⁺/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 Ca²⁺, the decrease of [Ca²⁺]c achieved by L-type CCBs promotes an increase of activity of ACs, and rise of [cAMP]c (Ca²⁺/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 Ca²⁺ 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 Ca²⁺/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
