

# Cancer and hypertension: Debating the clinical link through the Ca<sup>2+</sup>/cAMP signaling

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## Abstract

The incidence of cancer and hypertension is dramatically increasing in worldwide population, costing millions and millions from governments into expenditures related to the medical health systems. Interestingly, hypertension has been clinically linked to an increased risk for developing cancer. However, the mechanisms involved in this possible link are still under intensive debate. In addition, a Ca<sup>2+</sup> homeostasis dysregulation has been intensively debated as an issue involved in both cancer and hypertension. Furthermore, calcium (Ca<sup>2+</sup>) channel blockers (CCBs), prescribed for treating hypertension, have been showing anti-cancer effects beyond their property of reducing blood pressure. A debated mechanism of action could rest in the fact that CCBs may maintain, or restore, the Ca<sup>2+</sup> homeostasis. Our discovery entitled “calcium paradox” due to the Ca<sup>2+</sup>/cAMP signaling may put some new light in this arena! Then, in this short communication, I have debated the possible involvement of the Ca<sup>2+</sup>/cAMP signaling in the anti-cancer effects of CCBs, including a role of the Ca<sup>2+</sup>/cAMP signaling in the clinical link between hypertension and higher risk for the development of cancer.

## Introduction

Cancer and hypertension have become a problematic topic for medical health systems around the world, then costing millions and millions from governments worldwide. Interestingly, hypertension has been associated with a higher risk for developing cancer [1]. Then, debating this clinical link might improve our understanding of the risk factors involved in developing cancer [1]. Indeed, an imbalance of intracellular Ca<sup>2+</sup> homeostasis (e.g. intracellular Ca<sup>2+</sup> excess) is now being intensively debated as an issue involved in cancer progression, then contributing to the pathogenesis of cancer [2-6].

In addition, and in accordance with the concept described above, calcium (Ca<sup>2+</sup>) channel blockers (CCBs), medicines typically prescribed for treating hypertension, have been demonstrating anti-cancer effects [6-8]. A possible mechanism of action could rest in the fact that these pharmaceuticals may restore the dysregulation of Ca<sup>2+</sup> homeostasis [9-13]. Furthermore, the phenomenon entitled as ‘calcium paradox’, which has been elucidated by us in 2013, has also been associated with the CCBs [14]. In fact, this ‘paradox’ effect consists in CCBs paradoxically enhancing the release of neurotransmitters (a ‘paradox’ because intracellular Ca<sup>2+</sup> concentration is being decreased by these medicines), very often when these medicines have been used in low doses/concentrations. The reports which describe this ‘paradox’ have included cellular models as adrenal chromaffin cells, isolated organ bath experiments such as vas deferens, strips of arteries, and most importantly clinical data. Our pioneer study which associates the involvement of the Ca<sup>2+</sup>/cAMP signalling in this ‘paradox’ has shown to be very significant, considering the broadly use of CCBs as antihypertensive medicines. Then, in this short communication, I have discussed the possible involvement of the Ca<sup>2+</sup>/cAMP signalling in the anti-cancer effects of CCBs, including the role of the Ca<sup>2+</sup>/cAMP signalling in the clinical link between hypertension and higher risk for the development of cancer.

## Hypertension and higher risk for the development of cancer, and anti-cancer effects of CCBs

A clinical link between hypertension and a higher risk for the development of cancer has been reported by epidemiological and clinical studies [1,15-17]. However, this clinical link is not fully elucidated, and has been intensively debated. For instance, the Metabolic Syndrome and Cancer Project includes 7 population-based cohorts from Norway, Austria, and Sweden. Briefly, the aim of the Metabolic Syndrome and Cancer Project was to examine the relationship between metabolic factors and cancer risk. Patients in Metabolic Syndrome and Cancer Project cohorts participated in health examination(s) between 1972 and 2005. As main results, a significant positive association per 10-mmHg increment was shown for cancers risk of the oropharynx, rectum, pancreas, lung, prostate, bladder, and kidney [15]. In addition, positive associations per 10-mmHg increments in women were found for cancer risk of the pancreas, breast, corpus uteri, and malignant melanoma. A positive association was also found for esophagus cancer in men and women [15]. In fact, cancer risk has increased linearly by increasing blood pressure levels [1,15]. Among men, a risk of cancer incidence or mortality, at age 50 years, was 1% to 2% points higher with hypertensive systolic or diastolic blood pressures, compared with normotensive men [1,15].

Furthermore, hypertension has been recognized as a risk factor for cancer in observational reports from renal cell carcinoma [16,17]. A

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meta-analysis, based on 18 studies, showed a 1.6-fold increase in the risk of renal cell carcinoma in participants with hypertension [17]. Then, abnormal blood pressure might be an issue for cancer risk; nonetheless this association between high blood pressure and cancer risk may exist combined with other factors, such as central obesity [15]. In addition, CCBs, antihypertensive medicines which reduce the influx of Ca<sup>2+</sup> into the cells, have been demonstrating anti-cancer effects [6-8]. Then, how could Ca<sup>2+</sup>/cAMP signaling help to explain this effect, including the association between hypertension and higher risk for cancer?

### Hypertension and cancer: the relevance of the Ca<sup>2+</sup>/cAMP signaling

Considered as vital cellular processes for mammals, the Ca<sup>2+</sup>/cAMP signaling are assumed to virtually exist in almost all mammalian cells, controlled by adenylyl cyclases (ACs), phosphodiesterases (PDEs), Ca<sup>2+</sup> channels and so on [18-25] (Figure 1).

In this arena, endoplasmic reticulum (ER) Ca<sup>2+</sup> channels have particularly been a vanguard for the field, such as ryanodine receptors (RyR) [18-25]. Through our studies, we have recognized that the Ca<sup>2+</sup>/cAMP signaling performance an essential role in: controlling the neurotransmitter release from neurons, and neuroendocrine cells, including modulating the neuronal death [18-21], and in the development of cancer [9-13].

For instance, hypertension has been classically correlated to a sympathetic hyperactivity: reports from Miranda, *et al.* [26-28] confirmed this idea by observing pronounced differences in the kinetics of catecholamine release from spontaneously hypertensive rats (SHRs), comparing with normotensives. Such differences could be debated on the basis of different mechanisms of Ca<sup>2+</sup> signaling. The authors [26-28] concluded that dysregulations of intracellular Ca<sup>2+</sup> signaling could elucidate the greater catecholamine release responses observed in SHRs, compared with normotensive rats.

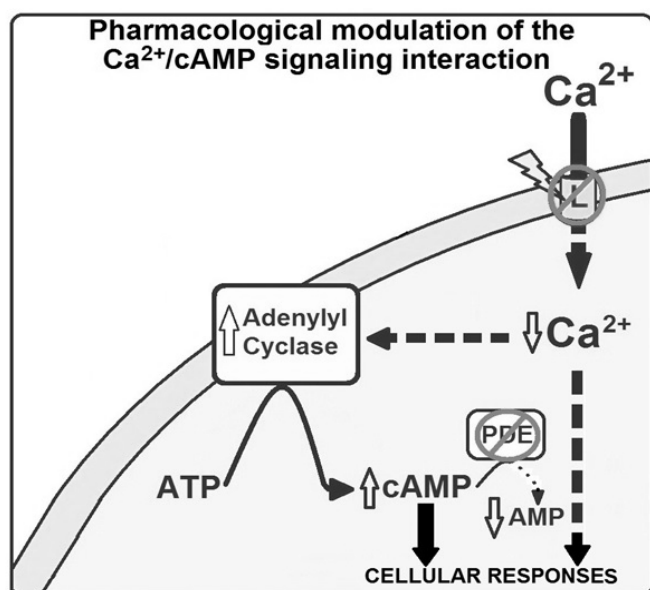
In addition, Ca<sup>2+</sup> dysregulations, such as L-type Ca<sup>2+</sup> channels up-regulations, have also been implicated in the development,

and progression, of cancer; for instance, a recent meta-analysis of microarray datasets showed a mRNA gene profile of the L-type Ca<sup>2+</sup> channels in different types of cancer [29-34]. For example, it was shown that the L-type Ca<sup>2+</sup> channels are significantly up-regulated in colon and esophageal cancer [29-34]. Thus, the pharmacological blockade of these channels could be used as a therapeutic strategy for antitumor therapy. In fact, some studies showed that the L-type CCB, such as amlodipine, mibefradil and NNC-55-0396, inhibited the proliferative response in different tumor cells [6-8].

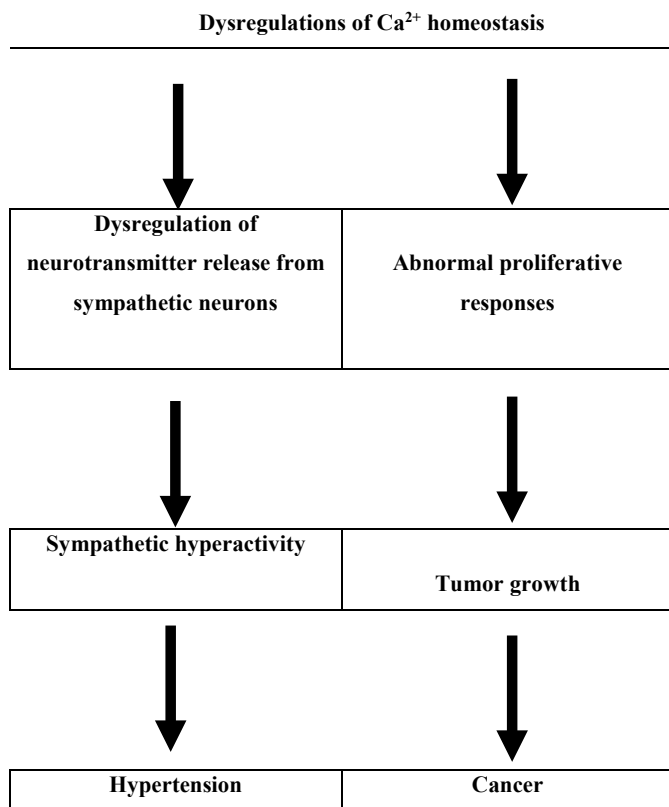
Furthermore, it was shown that the increase of cAMP, induced by ACs activator, produced significant antitumor effects [9,35]. The 8-Cl-cAMP, and the PKA -selective cAMP analogs, 8-piperidinoadenosine - 3',5'-cyclic monophosphate (8-PIP-cAMP) and 8-hexylaminoadenosine - 3',5'-cyclic monophosphate (8-HA-cAMP), produced significant antiproliferative effects in human cancer cell lines [9,35]. The anti-proliferative effect of the PKA -selective cAMP analogs was attributed to a growth arrest, while the 8-Cl-cAMP appears to be due to a pro-apoptotic effect [9,35]. These findings suggest that the cAMP analogs, such as 8-Cl-cAMP and the PKA -selective cAMP analogs, could be used in human tumor therapy. Thus, considering that our studies have shown that the reduction of Ca<sup>2+</sup> influx through L-type Ca<sup>2+</sup> channels, produced by CCBs, increases the AC activity (and consequently elevating cAMP levels; named as Ca<sup>2+</sup>/cAMP signaling interaction) [9-13], and that these CCBs-effects can be potentiated by cAMP-stimulating compounds (like PDEs inhibitors), then the pharmacological modulation of the Ca<sup>2+</sup>/cAMP signaling could be a new therapeutic strategy for the tumor therapy. In addition, our discovery, which demonstrated the role of Ca<sup>2+</sup>/cAMP signaling in the neurotransmitter release and neuroprotection [18-21], may put some new 'light' in the association between hypertension and higher risk for the development of cancer! Moreover, if the dysregulation of the Ca<sup>2+</sup> homeostasis may be an issue for the pathogenesis of cancer [9-13]; then, in this scenario, the Ca<sup>2+</sup>/cAMP signaling interaction may be disrupted as a consequence of elevations of [Ca<sup>2+</sup>]<sub>i</sub> in the development of cancer process [9-13]. For instance, considering ACs5 and ACs6 isoforms can be inhibited by increases of Ca<sup>2+</sup> concentrations [18-25]; then a rise of [Ca<sup>2+</sup>]<sub>i</sub> may dramatically disturb the cAMP signaling pathways. Indeed, up-regulations of cAMP signaling have been correlated to anti-cancer effects [9,13,35]. Thus, besides its own effect in enhancing the cancer progression, a rise of [Ca<sup>2+</sup>]<sub>i</sub> may also probably result in a cancer-excitotoxic effect by reducing anti-cancer responses due to a down-regulation of cAMP signalling pathways (due to a disruption of Ca<sup>2+</sup>/cAMP signaling interaction). In addition, CCBs, as well reducing the influx of Ca<sup>2+</sup> into the cells, could exert their anti-cancer effects [6-8] through the Ca<sup>2+</sup>/cAMP signalling interaction. Indeed, novel methodologies will allow researchers, in the future, to explore these hypotheses!

Furthermore, similarly to cancer, hypertension has also been linked to dysregulations of Ca<sup>2+</sup> signalling. Miranda, *et al.* [26-28] discovered definite differences in the kinetics of catecholamine release from spontaneously hypertensive rats (SHRs), comparing with normotensives. Such differences might be explained on the basis of different mechanisms of Ca<sup>2+</sup> signalling. Then, in this scenario, the Ca<sup>2+</sup>/cAMP signalling interaction may be disrupted as a consequence of hypertension development process, like in cancer. Thus, similar to cancer, novel methodologies will allow researchers to solve this conundrum!

Then, dysregulations of Ca<sup>2+</sup> signalling could provide a 'clinical link' between cancer and hypertension. The following diagram summarizes the previous discussion (Figure 2).



**Figure 1.** Cellular responses induced by the pharmacological modulation of the Ca<sup>2+</sup>/cAMP signalling pathways. Briefly, the reduction of Ca<sup>2+</sup> influx through L-type Ca<sup>2+</sup> channels, produced by CCBs, increases the AC activity (and consequently elevating cAMP levels; named as Ca<sup>2+</sup>/cAMP signalling interaction), and these CCBs-effects can be potentiated by cAMP-stimulating compounds (like PDEs inhibitors)



**Figure 2.** The Ca<sup>2+</sup> homeostasis dysregulations and their endpoint consequences: cancer and hypertension

## Conclusions and future directions

Ca<sup>2+</sup> signaling and its dysregulations have been implicated in the development of hypertension [26-28] and cancer [29-34]. In addition, CCBs, despite their antihypertensive effect, have been demonstrating anti-cancer effects [6-8]. Furthermore, the Ca<sup>2+</sup>/cAMP signaling interaction has now been emerging as a possible new therapeutic target for treating cancer [9-13]. If the Ca<sup>2+</sup>/cAMP signaling are involved, in part, in the CCBs anti-cancer effects deserves more consideration, including additional experiments with modern methodologies, and in clinical trials.

## Conflict of interest

None declared.

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