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MINIREVIEWS

Diabetes and inflammatory diseases: An overview from the perspective of Ca^{2+}/3'-5'-cyclic adenosine monophosphate signaling

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Abstract

A large amount of evidence has supported a clinical link between diabetes and inflammatory diseases, *e.g.*, cancer, dementia, and hypertension. In addition, it is also suggested that dysregulations related to Ca^{2+} signaling could link these diseases, in addition to 3'-5'-cyclic adenosine monophosphate (cAMP) signaling pathways. Thus, revealing this interplay between diabetes and inflammatory diseases may provide novel insights into the pathogenesis of these diseases. Publications involving signaling pathways related to Ca^{2+} and cAMP, inflammation, diabetes, dementia, cancer, and hypertension (alone or combined) were collected by searching PubMed and EMBASE. Both signaling pathways, Ca^{2+} and cAMP signaling, control the release of neurotransmitters and hormones, in addition to neurodegeneration, and tumor growth. Furthermore, there is a clear relationship between Ca^{2+} signaling, *e.g.*, increased Ca^{2+} signals, and inflammatory responses. cAMP also regulates pro- and anti-inflammatory responses. Due to the experience of our group in this field, this article discusses the role of Ca^{2+} and cAMP signaling in the correlation between diabetes and inflammatory diseases, including its pharmacological implications. As a novelty, this article also includes: (1) A timeline of the major events in Ca^{2+}/cAMP signaling; and (2) As coronavirus disease 2019 (COVID-19) is an emerging and rapidly evolving situation, this article also discusses recent reports on the role of Ca^{2+} channel blockers for preventing Ca^{2+} signaling disruption due to COVID-19, including the correlation between COVID-19 and diabetes.

Key Words: Diabetes; Cancer; Hypertension; Dementia; Ca^{2+}/3'-5'-cyclic adenosine monophosphate signaling; Ca^{2+} channel blockers; Pharmacotherapy; Neurodegeneration; COVID-19

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Core Tip: There are several reviews in the literature on diabetes and inflammatory diseases. Nonetheless, to my knowledge, this is the first review which clearly discusses the role of Ca^{2+}/3'-5'-cyclic adenosine monophosphate (cAMP) signaling in the link between diabetes and inflammatory diseases. This article also includes a timeline of the major events in Ca^{2+}/cAMP signaling, and discusses recent reports on the role of Ca^{2+} channel blockers for preventing Ca^{2+} signaling disruption due to coronavirus disease 2019 (COVID-19), including the correlation between COVID-19 and diabetes.

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INTRODUCTION

The concept of a complex clinical link between diabetes and inflammatory diseases, *e.g.*, cancer, dementia, and hypertension, has been described in several reports[1-12]. Observational reports provided the first evidence for the link between inflammation and diabetes[11]. An interesting study correlated inflammation and diabetes by showing, in animal models, that tumor necrosis factor-alpha is correlated with both obesity and insulin resistance[13]. In addition, an epidemiologic link between inflammation and diabetes was made when circulating concentrations of markers, and mediators, of inflammation were demonstrated to be increased in these diseases[14-17], *e.g.*, white cells, interleukin (IL)-6, fibrinogen, C-reactive protein, plasminogen activator inhibitor-1, and sialic acid. Besides diabetes, the link between cancer and inflammation was proposed in 1863 by Virchow, which postulated that the etiology of cancer is related to chronic inflammation[18]. It is now clear that persistent cell proliferation at sites that are abundant in inflammatory cells, DNA-damage-promoting agents, growth factors, and activated stroma, actually increases the risk of neoplasia [19]. Inflammation also plays a central role in dementia, *e.g.*, Alzheimer's disease (AD) [20]. For instance, persistent stimulation of immune cells, and macrophages in the brain (microglia), has been shown to aggravate both amyloid and tau pathology, which then may operate as a link in the etiology of the disease[20]. Finally, recent interest has focused on studying the avenues, and inflammatory mediators, through which immune cells operate to lead to hypertension and end-organ injury[21].

Currently, it is also well-known that dyshomeostasis of Ca^{2+}, through an increase in Ca^{2+} levels within the cells $[Ca^{2+}]c$, is correlated with the pathogenesis of diabetes, cancer, hypertension, and dementia[9,10,12,22-26]. In fact, there is a clear relationship between Ca^{2+} signaling, *e.g.*, increased Ca^{2+} signals, and inflammatory responses[10,27]. Corroborating this idea, several studies have highlighted that Ca^{2+} channel blockers (CCBs), classic antihypertensive medicines, can improve cognitive function, in addition to decreasing the symptoms of both cancer and diabetes[12,28-31]. A pharmacological tenet for these exciting findings is linked with reestablishing $[Ca^{2+}]c$, in addition to modulating 3'-5'-cyclic adenosine monophosphate (cAMP) signaling pathways (Ca^{2+}/cAMP signaling)[9,10,24,25]. Due to the experience of our group in this field[9,10,12,24,25,32-36], this article discusses the contributions of Ca^{2+} and cAMP signaling in the correlation between cancer, hypertension, diabetes, and dementia. Publications involving dementia, diabetes, hypertension, and cancer were obtained by examining PubMed and EMBASE, using a search strategy with a high sensitivity for studies of etiology, as follows: (1) Searches applied the following strings: Risk (in title or abstract) odds ratio (OR) risk [as a Medical Subject Heading (MeSH) term, not exploded] OR cohort studies (as a MeSH term) OR group (as a text word). Outcomes of these searches were linked with sets conceived with diabetes OR dementia OR cancer OR hypertension OR inflammation; and (2) Bibliographies of the articles obtained were also reviewed for possible data sources.

This article included as a novelty: (1) A timeline of the major events in Ca^{2+}/cAMP signaling; and (2) As coronavirus disease 2019 (COVID-19) is an emerging and rapidly evolving situation, this article also discusses recent reports on the role of CCBs for preventing Ca^{2+} signaling disruption due to COVID-19, including the correlation

between COVID-19 and diabetes.

CANCER, HYPERTENSION, DIABETES, AND DEMENTIA: A CLINICAL LINK

Basic mechanisms

Dementia: Dementia, like AD, and aging are classically associated with each other[10,24,37,38]. Dementia is often characterized by synaptic dysfunction and death of neurons, leading to a gradual decline in cognitive abilities[24,38]. Among the hallmark features of AD, an accumulation of plaques containing the amyloid beta (Aβ) peptide is established; then in the preclinical phase of AD, Aβ is among the most prevalent pathological markers[10,24,38]. Briefly, the amyloid precursor protein (APP) undergoes proteolysis, thus producing Aβ as a product, which can be quantified from both blood and cerebrospinal fluid, and by imaging[10,24]. In addition, Ca^{2+} dyshomeostasis has also been associated with dementia, resulting in the death of neurons[10,24,33,37]. Aβ has been linked with both an increased $[Ca^{2+}]_c$ and an enhanced susceptibility to neuroexcitotoxicity[10,37]. Ca^{2+} signaling has been investigated due to modulation of neuronal death[37].

Cancer: Like dementia, cancer dramatically affects the health of individuals, and is considered an uncontrolled division of the body's cells[9,39]. Ca^{2+} dysregulations have also been observed in carcinogenesis[9,39-44]. For example, several studies corroborated the involvement of Ca^{2+} channels overexpression, or hyperactivation, in different types of cancer[40-44]. For instance, a Ca^{2+}-binding protein that exerts a protagonist role in intracellular Ca^{2+} homeostasis is regucalcin (RGN), a protein which was observed to have reduced expression in cancer of the prostate gland[45,46]. It has also been observed that an elevation of $[Ca^{2+}]c$ stimulates diverse responses to the proliferation of cells from both neoplastic and non-neoplastic cancer of the prostate gland, suggesting a correlation with RGN expression[9,45,46]. Furthermore, increased expression of RGN reduced the migration of NSCLC A549 cells from adenocarcinoma of lung *in vitro*[45,46]. The protein and mRNA expression of RGN was also decreased in (1) HepG2 cells from human hepatoma; (2) MCF-7 cells from breast cancer; and (3) LNCaP cells from prostate cancer[35,36]. Thus, reduced expression of RGN may be correlated with the stimulation of carcinogenesis[45,46]. Besides RGN, there are other Ca^{2+}-binding proteins that regulate Ca^{2+} homeostasis, which are implicated in cancer. In addition, expression levels of S100B, TM4SF3 and OLFM4 have been discovered to be highly associated with metastasis of liver cancer[9,47]. These findings confirm the participation of Ca^{2+} dyshomeostasis in cancer, opening new perspectives for the advancement of therapeutics linked to Ca^{2+} signaling.

Hypertension: Sympathetic hyperactivity, due to dysregulation of Ca^{2+} signaling as in dementia and cancer, has been correlated with hypertension. In fact, studies by Miranda-Ferreira *et al*[48,49] validated this principle by demonstrating changes in the kinetics of the release of catecholamines from spontaneously hypertensive rats (SHRs), when compared with normotensive rats. Ca^{2+} signaling is argued to be an issue involved in these differences. The authors[48,49] reinforced that Ca^{2+} dyshomeostasis might explain the increased release of catecholamines seen in SHRs, when compared with normotensive rats.

Diabetes: Like dementia, cancer, and hypertension, diabetes is also a serious medical condition. Diabetes is presently categorized according to its origin. For example, in type 1 diabetes if there is a deficiency of insulin released by the pancreas, then it can be categorized as a juvenile diabetes; while in type 2 diabetes if there is resistance to insulin, then it can be categorized as adult-onset diabetes[50]. From a cellular point of view, whereas a physiological increase in the cytoplasmic concentration of Ca^{2+} is a significant trigger for releasing insulin, an abnormal elevation of $[Ca^{2+}]c$ could stimulate β-cell apoptosis, then decrease insulin levels, contributing to diabetes[9,12,25]. Besides Ca^{2+}, cAMP modulates the release of various hormones, including insulin released from pancreatic β-cells[51,52]. Although increasing cAMP levels, *e.g.*, *via* adrenaline, might stimulate the production of hepatic glucose, increasing levels of cAMP in pancreatic β-cells may stimulate insulin release. The start signal for release of insulin is achieved by elevating $[Ca^{2+}]c$, and this signal is later amplified *via* cAMP[53]. Additionally, cAMP is also implicated in other cellular phenomena of β-cells, *e.g.*, inhibiting apoptosis[53].

Nowadays, a clinical link between these discussed diseases (hypertension, cancer, diabetes, and dementia) has been described in several reports[1-12,25,26].

A clinical link

Cancer and dementia: A link between dementia and cancer can be established through numerous cellular phenomena that are implicated in the etiology of both diseases, *e.g.*, inflammation, oxidative stress, and angiogenesis[1,3,54]. For instance, inflammatory biomarkers linked with a lower cognitive performance have been shown to be increased, including fibrinogen and IL-6[1-3]. In fact, several proteins may be involved in the etiology of this link, *e.g.*, Aβ peptide[1-3]. It is suggested that Aβ peptide overexpression is correlated with cancer as the overexpression of APP has been found in several tumors, and was then linked with cell proliferation, migration, and invasion [1]. In addition, a recognized tumor suppressor protein, the BRCA1 protein, has been linked to AD[2]. Thus, Aβ pathology can partially result from overactivation of BRCA1, and then promote neurodegeneration[2]. Converging with this concept, plasma levels of Aβ peptide have been found to be increased in patients with different cancer types[3].

In addition, a deficiency in DNA repair mechanisms and/or oxidative stress could lead to DNA damage, an issue which is also important for the etiology of both cancer and dementia[55]. A reduced capacity to repair damaged DNA due to genetic polymorphisms can be correlated to an augmented risk of both cancer and cognitive impairment. Genetic defects in DNA damage repair mechanisms could lead to syndromes such as xeroderma pigmentosum and ataxia telangiectasia, characterized by an augmented risk of cancer and cognitive problems[55]. Thus, understanding the clinical link between cancer and dementia could result in novel therapeutics for both diseases. Therefore, it is essential to determine the etiology of this link, *e.g.*, by analyzing the preclinical phases of both diseases.

Hypertension and cancer: A correlation between hypertension and a higher incidence of cancer has been established by epidemiological and clinical reports[4-8]. However, this correlation is not completely elucidated, and has been highly discussed. For example, the Metabolic Syndrome and Cancer Project assessed this issue, and included cohort studies from Norway, Austria, and Sweden[4]. The goal of the Metabolic Syndrome and Cancer Project was to study the association between metabolic issues and the increased incidence of cancer[4,5]. Patients from cohorts related to the Metabolic Syndrome and Cancer Project were enrolled in health inspections between the 1970's and 2000's[4]. The study observed a strong correlation between hypertension and an enhanced incidence of prostate, oropharynx, rectum, pancreas, bladder, lung, and kidney cancer[4]. Additionally, strong correlations between hypertension and an enhanced incidence of pancreas, breast, corpus uteri cancer and malignant melanoma were observed in women. A positive correlation was also observed for esophagus cancer in men and women[4,5]. Indeed, cancer incidence is augmented linearly by increasing blood pressure levels[4-6]. The augmentation of cancer incidence among men was 1% to 2% points higher in hypertensive patients, compared with normotensive men[4-6].

Finally, in observational reports on renal cell carcinoma, hypertension has been documented as a cancer risk factor[4-8]. A meta-analysis of 18 studies observed a 1.6-fold increase in the incidence of renal cell carcinoma in hypertensive patients[7]. Nonetheless, this positive association between hypertension and increased cancer incidence could occur in other disorders, such as obesity[7,8]. Moreover, CCBs, antihypertensive drugs which decrease the influx of Ca^{2+} into the cells, have shown anti-cancer activity[31].

Diabetes and hypertension: Diabetes is correlated with a higher risk of developing hypertension[56]. Several findings reinforce a clear interaction between diabetes and hypertension[57]. Scientific data suggest that obesity, inflammation, oxidative stress, and insulin resistance could be associated with these diseases[56,57]. Advances in the knowledge of how to prevent these diseases may provide new insights, and perspectives, for the treatment of both diseases.

In fact, hypertension and diabetes are highlighted as the leading risk factors for atherosclerosis, including heart attacks and strokes[58]. For instance, in the Hong Kong Cardiovascular Risk Factor Prevalence report, just 42% of patients with diabetes had regular blood pressure, and just 56% of patients with hypertension had regular glucose homeostasis[58]. In the United States, patients with type 2 diabetes have a prevalence of hypertension ranging from approximately 50% to 80%[59]. In fact, a prospective cohort report from the United States concluded that hypertensive patients

had an increased risk of almost 2.5-fold for developing type 2 diabetes[60]. It is clear that diabetes and hypertension are present in the same individual more often than would occur by causality, suggesting both common genetic and environmental factors in their etiology.

Diabetes and dementia: The concept of an association between diabetes and memory dysfunctions has been frequently explored[50,61-63]. Type 2 diabetes has been linked with a decrease in both processing and speed of psychomotor functioning, in addition to a memory deficit associated with speech and fluency[61-63]. Additionally, patients with diabetes have a lengthier walking pace[61-63]. In fact, mild cognitive impairment was observed in approximately 42% of diabetic patients[64]. The association between diabetes and cognitive imbalance was examined in a report[65], and the authors concluded that patients with type 2 diabetes had a lower score in the Mini-Mental State Examination[65]. An interesting study[66] assessed if lesions in the brain, associated with both vascular and degenerative disorders, could be the cause of the association between diabetes and cognitive deficit[66]. The authors concluded that memory performance in diabetic patients was significantly reduced[66].

In addition, these findings were confirmed by reports involving neuroimaging[67]. Brain atrophy was concluded to be highly correlated with type 2 diabetes[67], which usually progresses up to 3 times faster[68,69]. Patients suffering from type 2 diabetes have also demonstrated an enhanced incidence of dementia, *e.g.*, AD[70,71]. In fact, approximately 17.5% of people with type 2 diabetes have shown a modest to a serious deficiency in day-to-day activities[72,73], while 11.3% have shown a loss of cognition, and 14.2% have shown symptoms of depression[74], consequently adversely influencing cognition[75].

A decrease in brain glucose metabolism manifested before the beginning of a quantifiable cognitive decline in cohorts of patients at risk of AD[76-79]. Reports from *in vitro* and animal experiments propose that a decrease in brain glucose metabolism comes first and, therefore, may stimulate the neuropathologic cascade, finally resulting in cognitive decline in AD[76,77]. Additionally, aging is associated with an augmented risk of worsening glucose homeostasis, which, in turn, may increase the risk of decreasing brain glucose uptake[76,79]. Thus, pharmacotherapy to decrease the risk of AD could provide the following: (1) Improve insulin sensitivity, and then restore glucose homeostasis; or (2) Reduce the decline in brain glucose metabolism by applying strategies that carefully stimulate a maintainable ketonemia[76,79].

Diabetes and cancer: A relationship between diabetes and an increased risk of several types of cancer has also been described[9,18,19]. It is now clear that persistent cell proliferation in conditions with abundant inflammatory cells, growth factors, stimulated stroma, and DNA-damage-promoting molecules, increases neoplastic risk [19]. In addition, an inflammatory process is also involved in the etiology of diabetes [17], thus it could be an issue which could link both diseases.

In fact, in laboratory reports, metformin, the most frequently used drug in patients with type 2 diabetes, has been demonstrated to prevent cell proliferation and decrease colony development, causing partial cell cycle arrest in cancer cell phenotypes[9,19]; thus, it is important not to neglect the disruption of glucose homeostasis as a relevant mediator of this link between diabetes and cancer.

Hypertension and dementia: Midlife hypertension (aged 40-64 years) increases the incidence of AD in later life (≥ 65 years); and hypertension has been linked with increased amyloid deposition and neurofibrillary tangles, both hallmarks of AD[12]. Indeed, the brain of patients with hypertension, when compared with normotensive patients, had higher concentrations of β-amyloid plaques, atrophy, and neurofibrillary tangles[12,20]. Thus, hypertension has been recognized as a risk factor for the deposition of cortical fibrillar β-amyloid[12].

Diabetes and COVID-19: COVID-19, triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an emerging and rapidly evolving situation[80,81]. It is accepted that angiotensin-converting enzyme 2, which is a component of the renin-angiotensin-aldosterone system, is the key entry receptor for SARS-CoV-2[80,81].

Intriguingly, some reports have observed increased severity of COVID-19 in patients with diabetes. To assess this issue, a meta-analysis[80] was performed by conducting a literature review of Scopus, PubMed, Science Direct, and Web of Science. Observational studies, case-reports, and case-series reports that analyzed diabetes in COVID-19 patients were included in the meta-analysis[80]. It was concluded that diabetes is a risk factor, and plays a role in disease severity and the mortality of individuals with COVID-19. This study also provided suggestions, and guidelines,

which could be helpful for the prevention and treatment of diabetic patients suffering from COVID-19[80]. As already discussed in the present article, hyperglycemia may modulate both immune and inflammatory processes, thus prejudicing patients and resulting in severe COVID-19, and possible fatal consequences.

In addition, a retrospective clinical report involving hospitalized patients with COVID-19 and hypertension, concluded that therapy with the CCB amlodipine besylate was correlated with decreased mortality[82]. In fact, CCBs were described to possess antiviral activity against several evolving viruses, including bunyaviruses, arenaviruses, and flaviviruses[82]. Furthermore, CCBs were described to possess anti-inflammatory ability to control patients' intracellular Ca^{2+} levels, including decreasing the death rate in septic animal models with severe inflammatory outcomes[83,84]. Severe inflammatory outcomes are described to be linked to a critical COVID-19 result [85]. Thus, it is plausible that CCBs may operate in a synergistic way by combining their antiviral efficacy with alleviation of inflammatory responses[85].

Complementing the present discussion, and in addition to Ca^{2+} signaling, the participation of cAMP signaling (Ca^{2+}/cAMP signaling) in the correlation between cancer, hypertension, diabetes, and dementia is considered.

CANCER, HYPERTENSION, DIABETES, AND DEMENTIA: PARTICIPATION OF CA^{2+}/CAMP SIGNALING

Fundamental mechanisms

Our reports on Ca^{2+}/cAMP signaling have recognized the participation of these cellular processes in regulating the release of both neurotransmitters and hormones, as well as the death of neurons and tumor growth[9,10,12,24,25,32-36,86,87]. Our studies proved that by decreasing the influx of Ca^{2+} *via* voltage activated Ca^{2+} channels (VACCs), adenylyl cyclases (ACs) are stimulated (thus increasing the levels of cAMP, and the Ca^{2+}/cAMP signaling interaction, Figure 1).

Considering this working model, CCBs-responses can be significantly increased through their pharmaceutical association with cAMP-enhancer agents [such as phosphodiesterase inhibitors]. The working model through which the release of both transmitter and hormone can be significantly augmented by regulating Ca^{2+}/cAMP signaling is related to (1) elevating the concentrations of transmitters and hormones in the secretory apparatus; and (2) enhancing the release of transmitters and hormones [10,12]. Actually, Ca^{2+} signaling is essential for supporting the release process: *Via* rising cAMP levels, this can augment the release of Ca^{2+} from endoplasmic reticulum (ER), thus increasing the release of transmitters and hormones. The timeline of the major events in Ca^{2+}/cAMP signaling can be found below (Table 1).

Additionally, a higher $[Ca^{2+}]c$ from critical dysregulations of Ca^{2+} signaling, such as an enhanced Ca^{2+} influx, has been linked to dementia, diabetes, hypertension, and cancer[9,10,12,24,25]. For instance, it was observed that L-type Ca^{2+} channels are significantly up-regulated in different types of cancer cells, contributing to abnormal cell proliferation[9,40-44]. The pharmaceutical modulation of these channels could then improve the therapeutics for antitumor purposes.

As well as cancer, dysregulations related to aging have also been detected in Ca^{2+} signaling pathways, stimulating the death of neurons, *e.g.*, an increase in intracellular Ca^{2+} levels, an augmented Ca^{2+} influx *via* the VACC and abnormalities in Ca^{2+} regulation in ryanodine and IP_3-sensitive Ca^{2+} stores[10,12,24].

Opposing Ca^{2+} signaling, stimulation of cAMP/protein kinase/cAMP-response element binding protein pathways can reduce both neuronal death and abnormal cell proliferation, thus resulting in anti-cancer and anti-dementia effects[88-91]. Thus, both the death of neurons and abnormal cell proliferation may also be a consequence of reduced activity of signaling pathways controlled by cAMP, as well as an increase in $[Ca^{2+}]c$, resulting from disruption of Ca^{2+}/cAMP signaling interactions. Indeed, there is a clear relationship between Ca^{2+} signaling, *e.g.*, increased Ca^{2+} signals, and inflammatory responses[92]. cAMP also modulates inflammatory responses: medicines which increase intracellular levels of cAMP can diminish the generation of pro-inflammatory factors, and enhance the generation of anti-inflammatory molecules[93]. Furthermore, whereas a physiological increase in the cytoplasmic concentration of Ca^{2+} is a significant trigger to release insulin, an abnormal elevation in $[Ca^{2+}]c$ could stimulate β-cell apoptosis, then decrease insulin levels, contributing to diabetes[9,12,25]. Together with Ca^{2+}, cAMP modulates the release of various hormones, as well as insulin from the pancreatic β-cells[51,52]. Although increasing cAMP levels, *e.g.*, *via* adrenaline, might stimulate the biosynthesis of hepatic glucose, increasing cAMP

Table 1 Timeline of the major events in Ca^{2+}/3'-5'-cyclic adenosine monophosphate signaling

	1970s	1980s and 1990s	2000s and 2010s	2019-2020
Major events	Verapamil paradoxically enhanced the contractions of smooth muscles, *e.g.*, rat vas deferens	Other CCBs (besides verapamil) also paradoxically enhanced the contractions of smooth muscles, *e.g.*, rat vas deferens	2013. Bergantin *et al*[32] discovered that the paradoxical increase in the contractions of smooth muscles, produced by CCBs, was due to an interaction of Ca^{2+}/cAMP signaling 2015-2016. Bergantin *et al*[24] proposed that the pharmacological manipulation of Ca^{2+}/cAMP signaling could be a new therapeutic strategy for increasing neurotransmission in psychiatric disorders, and producing neuroprotection in neurodegenerative diseases	Bergantin[12,25,86,87] discussed the involvement of Ca^{2+}/cAMP signaling in the pathogenesis of several diseases, including hypertension, diabetes, neurodegenerative diseases, asthma, and cancer
Articles indexed in PubMed (PMID)	PMID: 1143442	PMID: 3113986; PMID: 2466518	PMID: 23849429; PMID: 26516591; PMID: 27349146	PMID: 30117399; PMID: 30639385; PMID: 30771427; PMID: 30648516; PMID: 31291877; PMID: 31456527; PMID: 31995022; PMID: 32077833; PMID: 32186273; PMID: 32026774; PMID: 32065096; PMID: 32562933; PMID: 33210037; PMID: 33176668

CCBs: Ca^{2+} channel blockers; cAMP: 3'-5'-cyclic adenosine monophosphate.

Table 2 A list of several Ca^{2+} channel blockers and 3'-5'-cyclic adenosine monophosphate signaling-enhancer compounds

CCBs	cAMP signaling (enhancer compounds)
Verapamil	Rolipram
Nifedipine	3-isobutyl-1-methylxanthine (IBMX)
Diltiazem	Forskolin
Isradipine	Aminophylline
Amlodipine	Theophylline
Nicardipine	Paraxanthine

CCBs: Ca^{2+} channel blockers; cAMP: 3'-5'-cyclic adenosine monophosphate.

levels within pancreatic β-cells can stimulate insulin release. A start signal for the release of insulin is achieved through an increase in Ca^{2+} concentration, and after this signal is amplified *via* cAMP[53]. Besides the cellular effect of increasing the biosynthesis of insulin, cAMP is implicated in other cellular processes of β-cell, *e.g.*, stimulating both proliferation and differentiation of the cell, and by rescuing the cells from death[53]. These effects are summarized in Figure 2.

A medical correlation

Ca^{2+}/cAMP signaling has been highlighted as a protagonist in hypertension, cancer, diabetes, and dementia[9,10,12,24,25,32-36,86,87]. Considering the experience of our group in this field, our reports undoubtedly show that Ca^{2+} release from the ER can be induced by an increase in $[cAMP]_c$. Therefore, considering the participation of Ca^{2+}/cAMP signaling pathways in modulating the release of both neurotransmitters and hormones, as well as tumor growth and neurodegeneration, dysregulations of these signaling pathways can result in disorders such as hypertension, dementia, diabetes, and cancer[9,10,12,24,25,32-36,86,87].

In addition, several findings have confirmed that CCBs, despite their classical antihypertensive effect, can attenuate the symptoms of dementia, diabetes, and cancer [9,10,12,29,94-96]. Similar effects could be achieved by increasing [cAMP]c[9,10,12,24,88-90]. Please see Table 2.

Undeniably, an increase in the release of neurotransmitters, and a reduction in the death of neurons in the CNS (*e.g.*, limbic brain sites), could cause as a consequence a decrease in symptoms related to dementia, a working model that can be controlled by Ca^{2+} and cAMP signaling pathways[10,12,25,33]. Analogous to dementia[10,12,33],

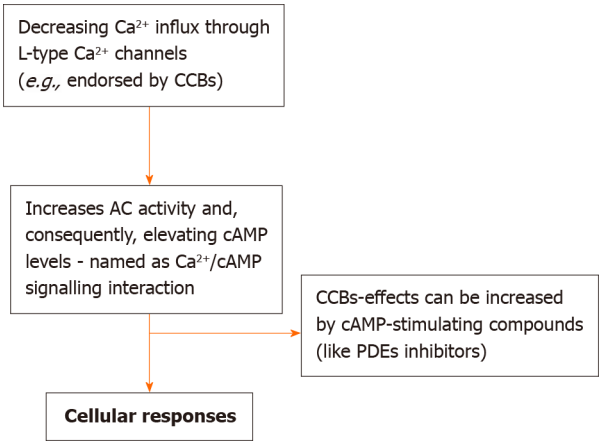

Figure 1 Pharmaceutical modulation of Ca^{2+}/3'-5'-cyclic adenosine monophosphate signaling. Decreasing Ca^{2+} influx through L-type Ca^{2+} channels, *e.g.*, endorsed by Ca^{2+} channel blockers (CCBs), enhances adenylyl cyclase activity (and consequently increases 3'-5'-cyclic adenosine monophosphate (cAMP) levels; identified as a Ca^{2+}/cAMP signaling interaction), and these effects of CCBs could be increased by cAMP-enhancer compounds (such as phosphodiesterase inhibitors). CCBs: Ca^{2+} channel blockers; cAMP: 3'-5'-cyclic adenosine monophosphate; AC: Adenylyl cyclase; PDEs: Phosphodiesterases.

Disruption of Ca^{2+}/cAMP signalling			
↑ **$[Ca^{2+}]_c$**		↓ **$[cAMP]_c$**	
Abnormal cellular consequences			
Increase of the neuronal death	Increase of the catecholamines´ release	Stimulation of abnormal cell proliferation	Increase of β-cell apoptosis and decrease of the insulin levels
Symptoms and clinical consequences			
Neurodegeneration and neuroinflammation	Sympathetic hyperactivity	Tumor growth	Dysregulations of the glucose homeostasis and stimulation of inflammatory processes
Disorders			
Dementia	Hypertension	Cancer	Diabetes

Figure 2 The Ca^{2+}/3'-5'-cyclic adenosine monophosphate signaling dysregulations and their consequences. Up arrow: Increasing; Down arrow: Decreasing. $[Ca^{2+}]_c$: Intracellular concentration of Ca^{2+}; $[cAMP]_c$: Intracellular concentration of 3'-5'-cyclic adenosine monophosphate.

discoveries have shown that CCBs can also mitigate the symptoms of both cancer and diabetes[9,12,94-96]. Reestablishing the dyshomeostasis associated with Ca^{2+} signaling is a working model for these CCBs-mentioned responses, reached due to intervening in the Ca^{2+}/cAMP signaling interactions. In fact, CCBs stimulate the activity of ACs, following an increase in $[cAMP]_c$, promoting Ca^{2+} release from the ER, ultimately inducing the release of both neurotransmitters and hormones, and decreasing the death of neurons and attenuating tumor growth. Considering that the link between diseases (cancer, diabetes, hypertension, and dementia) could be a consequence of persistent dysregulations of $[Ca^{2+}]_c$, the persistent increase in $[Ca^{2+}]_c$ might also disturb Ca^{2+}/cAMP signaling interactions.

CONCLUSION

Both Ca^{2+} and cAMP signaling pathways regulate the release of neurotransmitters and hormones, including those involved in neurodegeneration and tumor growth.

Furthermore, there is a clear relationship between Ca^{2+} signaling, *e.g.*, increased Ca^{2+} signals and inflammatory responses. cAMP also regulates pro- and anti-inflammatory responses. It is concluded that both signaling pathways play an important role in the link between diabetes and inflammatory diseases, thus impacting therapeutics including CCBs and medicines which increase the levels of cAMP. Finally, as COVID-19 is an emerging and rapidly evolving situation, it is also concluded that Ca^{2+} channel blockers could be useful for preventing Ca^{2+} signaling disruption due to COVID-19.

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