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Advances for The pharmacotherapy of Alzheimer´s Disease: The Ca^{2+}/cAMP Signaling Interaction

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Published Date: February 21, 2017

ABSTRACT

It is well recognized that an imbalance of intracellular Ca^{2+} homeostasis contributes to the pathogenesis of neurodegenerative diseases, such as Alzheimer's **(AD)**. Therefore, regulation of intracellular Ca^{2+} homeostasis may represent a new target for treatment of this disease. Our recent discovery of the participation of the interaction between intracellular signaling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP signaling interaction) in the neurotransmission and neuroprotection has subsidized to the understanding of pathophysiology and pharmacology of neurodegenerative diseases. Interestingly, this discovery emerged from many clinical studies performed since 1975 that reported that L-type Ca^{2+} channel blockers **(CCBs)** used in antihypertensive pharmacotherapy decreased arterial pressure, but produced typical symptoms of sympathetic hyperactivity such as tachycardia and increment of catecholamine plasma levels. Despite these adverse effects of CCBs have been initially attributed to adjust reflex of arterial pressure, during almost four decades this enigmatic phenomenon remained unclear. In 2013, we discovered that this sympathetic hyperactivity resulted from the increase of transmitter release from sympathetic neurons and adrenal chromaffin cells stimulated by CCBs due to its modulatory

action on the Ca^{2+}cAMP signaling interaction. In addition, we discovered that this modulatory action of CCBs increases the intracellular levels of cAMP, attenuating neuronal death caused by cytosolic Ca^{2+} excess due probably to the activation of cellular survival pathways mediated by cAMP-response element binding protein **(CREB)**. Then, our discovery of the role of the Ca2+/cAMP signaling interaction in the neurotransmission and neuroprotection may open a large path for the advance of new pharmacological strategies more effective for the treatment of AD.

Keywords: Ca^{2+}/cAMP signaling interaction; Alzheimer's disease

INTRODUCTION

Several clinical studies have described (since 1970´s) that acute and chronic administration of L-type Ca^{2+} channel blockers **(CCBs)** in hypertensive patients, such as nifedipine and verapamil, decreased arterial pressure but produced typical symptoms of sympathetic hyperactivity such as tachycardia and increment of catecholamine plasma levels [1]. Despite these adverse effects of CCBs have been initially qualified as adjust reflex of arterial pressure, the cellular and molecular mechanisms involved in these CCBs-effects remained unclear for decades.

Since 1975, some studies achieved in isolated tissues richly innervated by sympathetic nerves (rodent vas deferens), to exclude the influence of adjusting reflex, showed that responses mediated by these nerves were completely inhibited by L-type CCBs in high concentrations (>1 μmol/L), but unexpectedly and paradoxically potentiated in concentrations below 1 μmol/L, characterizing CCBs-induced sympathetic hyperactivity [2-5]. During almost four decades, this paradoxical sympathetic hyperactivity produced by L-type CCBs named by us as "calcium paradox" remained unclear.

In 2013, we discovered that this paradoxical sympathetic hyperactivity produced by L-type CCBs is due to its modulatory action on the interaction between the intracellular signaling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP signaling interaction) [5]. Our studies have proposed that pharmacological modulation of the Ca^{2+}/cAMP signaling interaction by use of the L-type CCBs and compounds that increase the cytosolic concentration of cAMP (cAMP-enhancer compounds) could be effective in enhancing neurotransmission and neuroprotection in neurological and psychiatric disorders resulting from neurotransmission deficit and neuronal death [5-11].

The increasing in the life expectancy of the world's population has amplified the concern about neurodegenerative diseases such as Alzheimer's disease **(AD)**. According to a 2015 United Nations report on world population aging, the number of people aged 60 and older worldwide is predictable to more than double in the next 35 years, reaching almost 2.1 billion people. Most of this growth will come from developing regions of the world, although the oldest old, who are more than 80 years of age, are the fastest growing segment of the population in developed regions. Despite these improvements in life expectancy, AD and related neurodegenerative conditions

have arguably become the most dreaded maladies of older people. Then, in this chapter we will discuss how the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction could be a new therapeutic target to treat the neurodegenerative diseases such as AD.

PARTICIPATION OF THE CA^{2+}/CAMP SIGNALING INTERACTION IN NEUROTRANSMISSION

Many experiments studies originated decades ago, using adrenal chromaffin cells as cellular model, recognized the notion of stimulus-secretion coupling to explain transmitter release from central and peripheral neurons. In 1970´s, it was discovered that a rise in the cytosolic Ca^{2+}concentration ($[Ca^{2+}]c$) constitutes an elementary requirement to trigger release by exocytosis of secretory vesicles containing transmitter (catecholamines, purines and other substances) in adrenal chromaffin cells [12]. In 1990´s, it was discovered a direct relationship between rise in $[Ca^{2+}]c$ and rapid transmitter release from adrenal chromaffin cells [13]. In addition to Ca^{2+}, other intracellular messengers are involved in the exocytosis of neurotransmitter and hormones. In 1988, it was discovered that elevation of intracellular cAMP concentration **([cAMP]c)** mediated by activation of adenylyl cyclases **(AC)** with forskolin enhanced exocytosis of secretory vesicles in adrenal chromaffin cells [14]. Although these evidences indicated that both Ca^{2+} and cAMP participate of transmitter exocytosis from neurons, the interaction between Ca^{2+} and cAMP in this response remained unclear for decades.

In 2013, we discovery that neurotransmitter release from sympathetic neurons is finely regulated by interaction between intracellular signaling pathways mediated by Ca^{2+} and cAMP, named Ca^{2+}/cAMP signaling interaction [5]. Using isolated tissues richly innervated by sympathetic nerves (rat vas deferens) stimulated by electrical pulses, we showed that responses mediated by these nerves were reduced and completely inhibited by L-type CCBs in high concentrations (>1 μmol/L), but paradoxically increased in concentrations below 1 μmol/L, characterizing CCBs-induced sympathetic hyperactivity [5]. As the activity of AC is regulated by Ca^{2+}, the reduction of $[Ca^{2+}]c$ produced by L-type CCBs results in increase of activity of AC and elevation of [cAMP]c [5]. The elevation of [cAMP]c activates cAMP-dependent protein kinase or kinase A **(PKA)** that activates endoplasmic reticulum (ER) Ca^{2+} channels, such as ER-Ca^{2+} channels regulated by ryanodine receptors (RyR), stimulating Ca^{2+} release [5]. This Ca^{2+} release from ER enhances number of secretory vesicles docked in plasma membrane, increasing neurotransmitter release and synaptic concentration of neurotransmitters [5-11].

Then, we demonstrated that the reduction of Ca^{2+} influx through L-type voltage-activated Ca^{2+} channels **(VACC)** produced by CCBs increases synaptic transmission due to enhance of neurotransmitter release [5]. Our discovery solved the enigmatic "calcium paradox" of almost four decades involved in sympathetic hyperactivity produced by L-type CCBs due to its modulatory action on the Ca^{2+}/cAMP signaling interaction [5-11].

In addition, our studies also showed that combined use of the L-type CCBs and cAMP-enhancer compounds, such as AC activators and phosphodiesterase **(PDE)** inhibitors, produced potentiation of sympathetic neurotransmission due to additional increase of neurotransmitter release from sympathetic nerves [5]. We showed that the magnitude of contractile responses mediated by neurotransmitter released from sympathetic nerves by means electrical field stimulation in rat vas deferens (neurogenic contractions) were significantly reduced by L-type CCBs (verapamil) in high concentrations (>1 μmol/L), but paradoxically increased in concentrations below 1 μmol/L, characterizing CCBs-induced sympathetic hyperactivity (figure 1). This paradoxical increase of neurogenic contractions was significantly potentiated by pre-treatment of vas deferens with cAMP-enhancer compounds, such as AC activators (forskolin) and PDE inhibitors (rolipram and isobutyl methyl xanthine **(IBMX)**) (figure 1). These finding indicated that the pharmacological modulation of neural Ca^{2+}/cAMP signaling interaction enhances neurotransmitter release causing increase of synaptic transmission [5-11]. Then, the pharmacological modulation of this interaction could be a new strategy to increase neurotransmission in neurodegenerative disease related to aging characterized by severe deficit in central neurotransmission such as AD.

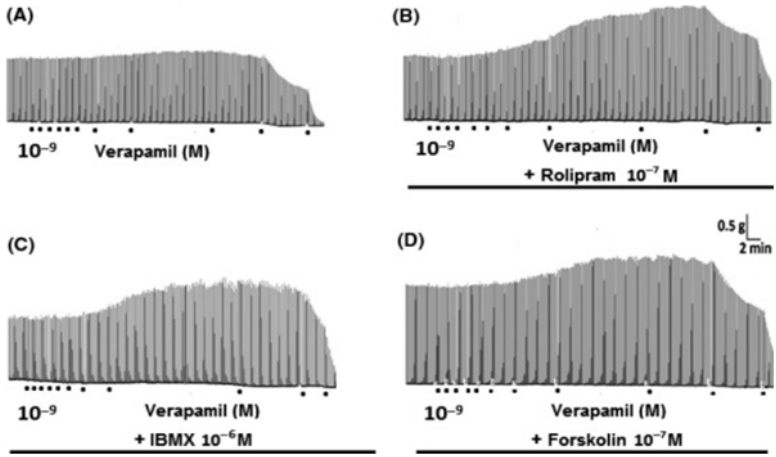

Figure 1: Increase of neurotransmission produced by pharmacological modulation of neural Ca^{2+}/cAMP signaling interaction. (A) Records showing that contractile responses mediated by neurotransmitter released from sympathetic nerves by means of electrical field stimulation in rat vas deferens (neurogenic contractions) were significantly reduced by L-type CCBs (verapamil) in high concentrations (> 10-6 M), but paradoxically increased in concentrations below 10-6 M, characterizing CCBs-induced sympathetic hyperactivity. This increase of neurogenic contractions by verapamil (< 10-6 M) was potentiated by pre-treatment of isolated tissue with cAMP-enhancer compounds, such as rolipram 10-7 M (B), IBMX 10-6 M (C) and forskolin 10-7 M (D). This potentiation by cAMP-enhancer compounds was prevented by pharmacological inhibition of AC with SQ 22536 (Data not showed). Each point below the record represents molar concentration of verapamil (interval of 0.5 log unity). Each line below the record represents incubation time with cAMP-enhancer compounds. Representative records extracted from [5].

ROLE OF THE CA^{2+}/CAMP SIGNALING INTERACTION IN NEUROPROTECTION

It is well recognized that an imbalance of intracellular Ca^{2+} homeostasis, especially cytosolic Ca^{2+} overload, decisively contributes to the pathogenesis of neurodegenerative diseases related to aging such as AD [5-11]. Therefore, regulation of intracellular Ca^{2+} homeostasis may represent a new therapeutic strategy of these diseases. As previously mentioned, blockade of the L-type VACC by CCBs attenuates Ca^{2+} influx, favoring the reduction of $[Ca^{2+}]c$ and the increase of [cAMP]c [5-11]. This functional Ca^{2+}/cAMP signaling interaction regulates various cellular responses, including neurotransmitter release [5-11].

Recently, it was showed that the treatment with L-type CCBs reduces motor symptoms and attenuates progressive neuronal death in animal model of degenerative disease, suggesting that L-type CCBs are potentially viable neuroprotective agents [15,16]. These finding reinforced the idea that attenuation of cytosolic Ca^{2+} overload produced by L-type CCBs due to blockade of Ca^{2+} influx through L-type VACC could be an excellent pharmacological strategy to attenuate or prevent neuronal death in neurodegenerative diseases such as AD.

In addition, some studies showed that increase of [cAMP]c stimulates neuroprotective response attenuating neuronal death due probably to activation of cellular survival pathways mediated by cAMP/PKA/cAMP-response element binding protein **(CREB)**-dependent intracellular signaling pathway [17-20]. In this way, the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction by combined use of L-type CCBs and cAMP-enhancer compounds could stimulate neuroprotective response due to increase of [cAMP]c and attenuation of cytosolic Ca^{2+} overload [5-11]. Thus, pharmacological modulation of this interaction could be a new neuroprotective therapeutic strategy to slow the progression of neurodegenerative diseases such as AD. Figure 2 shows how pharmacological modulation of the Ca^{2+}/cAMP signaling interaction by combined use of L-type CCBs and cAMP-enhancer compounds can produce increase of neurotransmission and neuroprotection.

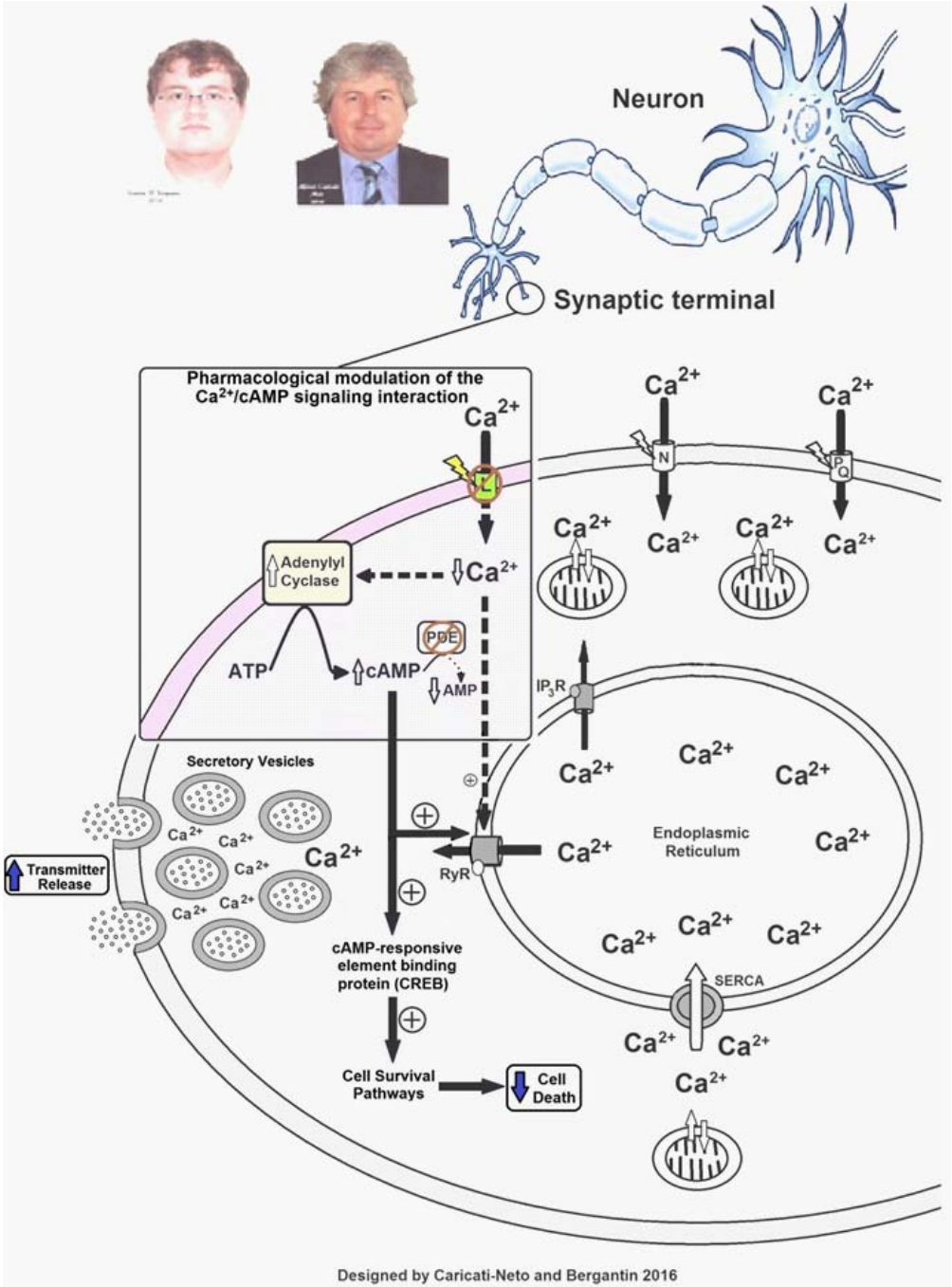

Figure 2: Increase of neurotransmitter release and attenuation of neuronal death (neuroprotection) produced by pharmacological modulation of the Ca^{2+}/cAMP signaling interaction by combined use of L-type Ca^{2+} channel blockers **(CCBs)** and cAMP-enhancer drugs. PDE - Phosphodiesterase. Figure adapted from [11].

PHARMACOLOGICAL MODULATION OF NEURAL CA^{2+}/CAMP SIGNALING INTERACTION AS A NEW THERAPEUTIC STRATEGY FOR TREATMENT OF ALZHEIMER'S DISEASE (AD)

AD is a progressive neurodegenerative disorder related to aging characterized by cognitive and memory deterioration. Neuritic plaques represent the pathological status of AD, and are respectively related to the accumulation of the β-amyloid peptide **(Aβ)** in brain tissues [21,22]. According to the amyloid hypothesis, the overproduction of Aβ is a consequence of the disruption of homeostatic processes that regulate the proteolytic cleavage of the amyloid precursor protein **(APP)**. Genetic and age-related factors could contribute to a metabolic change, favoring the amyloidogenic processing of APP in detriment of the physiological secretory pathway [21,22].

The neurotoxic potential of the Aβ results from its biochemical properties that favor aggregation. These processes, along with a reduction of Aβ clearance from the brain, leads to the extracellular accumulation of Aβ, and the subsequent activation of neurotoxic cascades that ultimately lead to cytoskeletal changes, neuronal dysfunction and cellular death [21]. Intracerebral amyloidosis development in AD patients is in an age-dependent manner, but recent evidences indicate that it may be observed in some subjects as early as in the third or fourth decades of life, with increasing magnitude in late middle age, and highest estimates in old age [21-23].

Therapies targeting the modification of amyloid-related cascades may be viewed as promising strategies to attenuate or even to prevent dementia [21]. Therefore, the cumulative knowledge on the pathogenesis of AD derived from basic science models will hopefully be translated into clinical practice in the forthcoming years. Other targets relevant to AD have also been considered in the last years for producing multitarget compounds [24,25].

In addition to what has been discussed above, acetylcholinesterase **(AChE)** is another important target to treat the pathogenesis of AD (cholinergic dysfunction hypothesis). Considering the current hypothesis of accumulation of the Aβ in AD, this relies in the reduction of neurotransmitter acetylcholine **(ACh)** release in central cholinergic nervous system involved in cognitive function. Thus, the inhibition of ACh degradation by AChE is a potential target to alleviate AD symptoms [24-26].

An imbalance of intracellular Ca^{2+} homeostasis also contributes to the pathogenesis of aging-related neurodegenerative diseases, including AD. Several evidences suggest that aging impairs ability of the brain intracellular Ca^{2+} degradation which is likely to induce cellular damage due to cytosolic Ca^{2+} overload leading to neural death and resultant cognitive dysfunction, such as AD [27]. Therefore, regulation of intracellular Ca^{2+} homeostasis may represent a new therapeutic strategy of AD.

A 10-year follow-up study (2000 to 2010), involving 82,107 hypertensive patients of more than 60 years of age, showed that use of L-type CCBs reduced blood pressure **(BP)** and risk of

dementia in hypertensives, suggesting that these drugs could be clinically used to treat AD [16]. Supportive findings for the neuroprotective effects of CCBs have been demonstrated in 1,241 elderly hypertensive patients with memory impairment [28]. The use of CCBs decreased the risk of cognitive impairment and AD independently of BP levels when compared to patients not receiving CCBs [28]. The long-term effects of antihypertensive therapy initiated with a long-acting dihydropinidine (nitrendipine) has been demonstrated in the double-blind, placebo-controlled Syst-Eur trail in which the incidence of dementia was reduced by 55 % [29].

Some studies have proposed that hybrid compounds having the moieties of tacrine, a potent inhibitor of brain and peripheral AChE, and nimodipine, a L-type CCBs could be useful to treatment of AD [24,25]. In addition, galantamine, a mild AChE inhibitor and an allosteric ligand of nicotinic receptors has been used to improve cognition and behaviour in patients with AD [26].

It was showed in AD model rats that cAMP-enhancer compounds, such as nobiletin (a polymethoxylated flavone from citrus peels) and oxyntomodulin (a proglucagon-derived peptide that co-activates the GLP-1 receptor and the glucagon receptor), produce neuroprotective effect mediated by intracellular cAMP production, activation of PKA and MAPK pathways and phosphorylation of CREB [18,20].

Our discovery of the involvement of the Ca^{2+}/cAMP signaling interaction in the neurotransmission and neuroprotection has produced important advances in the understanding of the pathophysiology and pharmacology of AD [5-11]. These advances allowed us to propose that pharmacological modulation of the Ca^{2+}/cAMP signaling interaction produced by combined use of the L-type CCBs (used in the antihypertensive therapy), such as isradipine, and cAMP-enhancer compounds (used in the anti-depressive therapy) such as rolipram, could represent a new therapeutic strategy of AD in humans.

Pharmacological modulation of the neural Ca^{2+}/cAMP signaling interaction by combined use of the L-type CCBs and cAMP-enhancer drugs could attenuate ACh release deficit, increasing central cholinergic neurotransmission involved in the control of cognitive function. In addition, pharmacological modulation of this interaction could contribute to reduce neuronal death due to attenuation of cytosolic Ca^{2+} overload, increase of [cAMP]c and stimulation of cell survival pathways probably mediated by activation of cellular survival pathways regulated by cAMP/PKA/CREB-dependent intracellular signaling pathway [17-20]. Thus, pharmacological modulation of Ca^{2+}/cAMP signaling interaction could be a new neuroprotective therapeutic strategy to slow the progression of AD [5-11, 30-33].

CONCLUSION

Our recent discovery of the Ca^{2+}/cAMP signaling interaction could promote important advances in the pathophysiology and pharmacology of the neurological and psychiatric disorders related to aging. These advances can contribute to drug development more effective and safer to prevent clinical symptoms of neurological and psychiatric disorders such as AD.

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