

From a “eureka insight” to a novel potential therapeutic target to treat Parkinson’s disease: The Ca²⁺/camp signalling interaction

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Abstract

Since 70’s, the sympathetic hyperactivity due to increment of catecholamine plasma levels is the main adverse effect reported by hypertensive patients that use L-type Ca²⁺ channel blockers (CCBs). Our discovery of the involvement of interaction between the intracellular signalling pathways mediated by Ca²⁺ and cAMP (Ca²⁺/cAMP interaction) revealed that the sympathetic hyperactivity was resulting of increase of transmitter release from sympathetic neurons stimulated by CCBs due to its interference on the Ca²⁺/cAMP interaction. For the pharmacotherapy of Parkinson’s disease, new paths for the understanding of the cellular and molecular mechanisms involved in the pathogenesis of this disease can be achieved through this discovery. In this way, novel pathways for the development of new pharmacological strategies more effective for the treatment of Parkinson’s may be initiated.

Introduction

Reduction of dopamine release from striatal dopaminergic neurons due to neuronal death is the main accepted concept of Parkinson’s disease [1]. The disease can be established years before a clinical diagnosis may be consistently made (asymptomatic/slightly symptomatic patients). Thus, the early diagnostic phase offers a real opportunity for therapies, for example: those aimed to prevent the progression of the disease, and its many complications side effects. However, no such efficient therapies are available nowadays. Thus, elucidating the mechanisms of neurodegeneration from the beginning stages could lead to the development of new approaches, whose therapeutic potential will need to be evaluated in adequately designed clinical trials [1].

Advances in the knowledge of this early phase of Parkinson’s disease could lead to the identification of biomarkers of neurodegeneration, and its progression. These biomarkers could help to identify the ideal population to be included, and the most appropriate outcomes to be assessed in clinical trials of medicines. Possible risks for asymptomatic patients developing Parkinson’s disease, and individuals who do not wish to know their mutation status, could pose specific ethical dilemmas in the design of clinical trials. In this review, we discuss novel strategies to treat Parkinson’s disease, throughout our recent discovery entitled “calcium paradox” phenomenon due to an interaction between the intracellular signalling pathways mediated by Ca²⁺ and cAMP (Ca²⁺/cAMP interaction) [2-4].

Current therapy to treat Parkinson’s disease

The recognizable core signs of the disease are related to asymmetrical bradykinesia and hypokinesia (slowness and reduced amplitude of movement), muscle rigidity (stiffness) and rest tremor, consequences from modifying motor control. These signs come from the reduction of dopamine release in striatal dopaminergic neurons, notable due to neuronal death. Rest tremor, prominent asymmetry and a good response

to levodopa are the features that most accurately predict Parkinson’s disease pathology [5]. Response to Parkinson’s disease medicines should raise evidences about the diagnosis, including early falls or autonomic symptoms [5]. Commonly prescribed dopamine-blocking medications, such as antipsychotics (eg, haloperidol, risperidone) and antiemetics (eg, metoclopramide, prochlorperazine) should be excluded in Parkinson’s patients because of medication-induced Parkinsonism. Functional imaging of the dopaminergic system using cerebral single photon emission computed tomography or positron emission tomography can be useful in diagnosis of early Parkinson’s disease [1,5]. Positron emission tomography studies examining the rate of decline in dopamine-producing cells suggest that humans have already lost 50%–70% of their nigral neurons, before they develop motor symptoms [5], and it has been estimated that the duration of this “presymptomatic” phase is about 5 years. Thus, a critical issue may rest in early diagnosis, turning more effective the therapeutic action of neuroprotective drugs when they become available.

In fact, increasing dopamine, mainly by using Levodopa combined with a dopa-decarboxylase inhibitor remains the most potent drug therapy for reversing motor impairment. A higher maintenance dose of Levodopa (eg, 200 mg three times daily compared with an initial dose of 100 mg three times daily) provides slightly greater benefit for reducing motor symptoms, but at the cost of earlier wearing-off

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symptoms and dyskinesias [5]. The combination of novel ideas may lead to advances in Parkinson’s disease research with the promise of finding compounds that are both effective, and fast-acting, including in patients who have tried other therapies with restricted success. In conclusion, new insights for more efficient pharmacological handling of Parkinson’s disease are clearly needed.

From a “eureka insight” to a novel potential therapeutic target to treat Parkinson’s disease: The Ca²⁺/cAMP signalling interaction

Discovery of the role of interaction of intracellular signalling pathways mediated by Ca²⁺ and cAMP in neurotransmitter release

Numerous experiments initiated sixty years ago, using catecholaminergic cells, originated the concept of stimulus-secretion coupling to elucidate neurotransmitter release and hormone secretion. This concept was initially resulted from the study of cat adrenal gland perfused with acetylcholine executed by Douglas and Rubin in the 1960s [6]. The discovery that increase in the cytosolic Ca²⁺ concentration ([Ca²⁺]_c) was a basic requirement for exocytosis in adrenal catecholaminergic cells was made by Baker and Knight in 1970’s [7]. In addition, some studies showed that cAMP raises transmitter release at several synapses in autonomic nervous system of vertebrate, including sympathetic neurons [8]. Indeed, the evidences suggest that this intracellular messenger can participate in fine regulation of exocytosis due to its modulatory action on the intracellular Ca²⁺ signals.

In fact, the hypothesis for Ca²⁺/cAMP interaction has been extensively studied in many cells and tissues. Generally, this interaction results in synergistic effects on cell functions [2-4] and occurs at the level of adenylyl cyclases (ACs) or phosphodiesterases (PDE) (Figure 1). The Ca²⁺/cAMP interaction has particularly been extensively studied at the Ca²⁺ channels [e.g.: ryanodine receptors (RyR)] of the endoplasmic reticulum (ER) [2-4]. Phosphorylation of RyR by protein kinase A (PKA), and also inositol trisphosphate receptor (IP₃R) at submaximal IP₃ concentrations, may increase the open probability of ER Ca²⁺ stores, amplifying Ca²⁺-induced Ca²⁺ release (CICR) mechanism and cellular responses [2-4] (Figure 1). Dysfunctions of cellular homeostasis of Ca²⁺ and/or cAMP in neuronal cells could result in the dysregulation of Ca²⁺/cAMP interaction, resulting in reduction of neurotransmitter release and also neuronal death. Then, Ca²⁺/cAMP interaction could be a novel therapeutic target for medicines (Figure 1).

Paradoxical effects of CCBs on neurotransmission and their pleiotropic effects in Parkinson’s disease

Since four decades ago, several clinical studies have been reporting that acute and chronic administration of L-type Ca²⁺ channel blockers (CCBs), such as nifedipine and verapamil, produces reduction in peripheral vascular resistance and arterial pressure associated with an increase in plasma noradrenaline levels and heart rate, typical effects of sympathetic hyperactivity [9]. However, the fundamental mechanisms involved in this apparent paradoxical effect of the L-type CCBs remained unclear for decades. In addition, experimental studies using isolated tissues richly innervated by sympathetic nerves showed that neurogenic responses were completely inhibited by L-type CCBs in high concentrations (>1 μmol/L), but paradoxically potentiated in concentrations below 1 μmol/L [10-12]. During almost four decades, these enigmatic phenomena remained unclear. In 2013, we discovered that this paradoxical increase in sympathetic activity produced by L-type CCBs is due to Ca²⁺/cAMP interaction [2-4]. Then, the

pharmacological handling of the Ca²⁺/cAMP interaction produced by combination of the L-type CCBs used in the antihypertensive therapy, and cAMP accumulating compounds used in the anti-depressive therapy such as rolipram, could represent a potential cardiovascular risk for hypertensive patients due to increase in sympathetic hyperactivity. In contrast, this pharmacological manipulation could be a new therapeutic strategy for increasing neurotransmission in the psychiatric disorders, such as Parkinson’s disease.

In addition, several studies have been demonstrating pleiotropic effects of CCBs. CCBs, like nifedipine, genuinely have pleiotropic effects [13]. Ca²⁺ channels are important regulators of central nervous system, and their dysfunction can give rise to pathophysiological conditions as psychiatric conditions such as epilepsy, pain and autism [13]. In the nervous system, CCBs have been emerging as potential therapeutic avenues for pathologies such as Parkinson’s disease [13]. However, the molecular mechanisms involved in these pleiotropic effects remain under debate. Different mechanisms have been proposed, but the exact mechanisms are still uncertain.

Importance of pharmacological modulation of Ca²⁺/cAMP interaction in the treatment of Parkinson’s disease

In contrast to adverse effects produced by combination of L-type CCBs with cAMP-accumulating compounds in the cardiovascular diseases, the pharmacological implications of the Ca²⁺/cAMP interaction produced by this drug combination could be used to enhance neurotransmission and neuroprotection [2-4].

Considering our model in which increment of [cAMP]_c stimulates Ca²⁺ release from ER (Figure 1), it may be plausible that the therapeutic use of the PDE inhibitor rolipram [14,15], in combination with low doses of verapamil to increase neurotransmission (Figure 1) in the areas of central nervous system involved in neurological/psychiatric disorders in which neurotransmission is reduced, including Parkinson’s disease. This new pharmacological strategy for the treatment of psychiatric disorders could increase the therapeutic efficacy and reduce the adverse effects of the medicines currently used for treating Parkinson’s disease. Considering that CCBs genuinely exhibit cognitive-enhancing abilities and reduce the risk of neurodegenerative diseases like Parkinson’s disease [13]; and that the mechanisms involved in these pleiotropic effects are largely unknown. Then, whether Ca²⁺/cAMP interaction is involved in such effects deserves special attention.

In addition, considering [Ca²⁺]_c elevation could contribute to both: negatively to neuroprotective effects and positively to exocytosis, it may be plausible the therapeutic use of the PDEs inhibitors [14,15] for antiparkinsonism purposes. Then, pharmacological handling of the Ca²⁺/cAMP interaction produced by combination of L-type CCBs and cAMP-accumulating compounds could enhance antiparkinsonism response and reduce clinical symptoms of neurodegenerative diseases. Thus, the association of currently medicines could enhance antiparkinsonism treatments. For example: the association of Levodopa with CCBs or rolipram could dramatically improve typical antiparkinsonism medicines, mainly by reducing their adverse effects and increasing their effectiveness. This new pharmacological strategy could be alternatively used for treatment of the symptoms of neurodegenerative diseases [16-23].

Conclusion

The diagnosis of Parkinson’s disease depends critically on clinical diagnosis of patients. In addition, emerging therapies may supplement

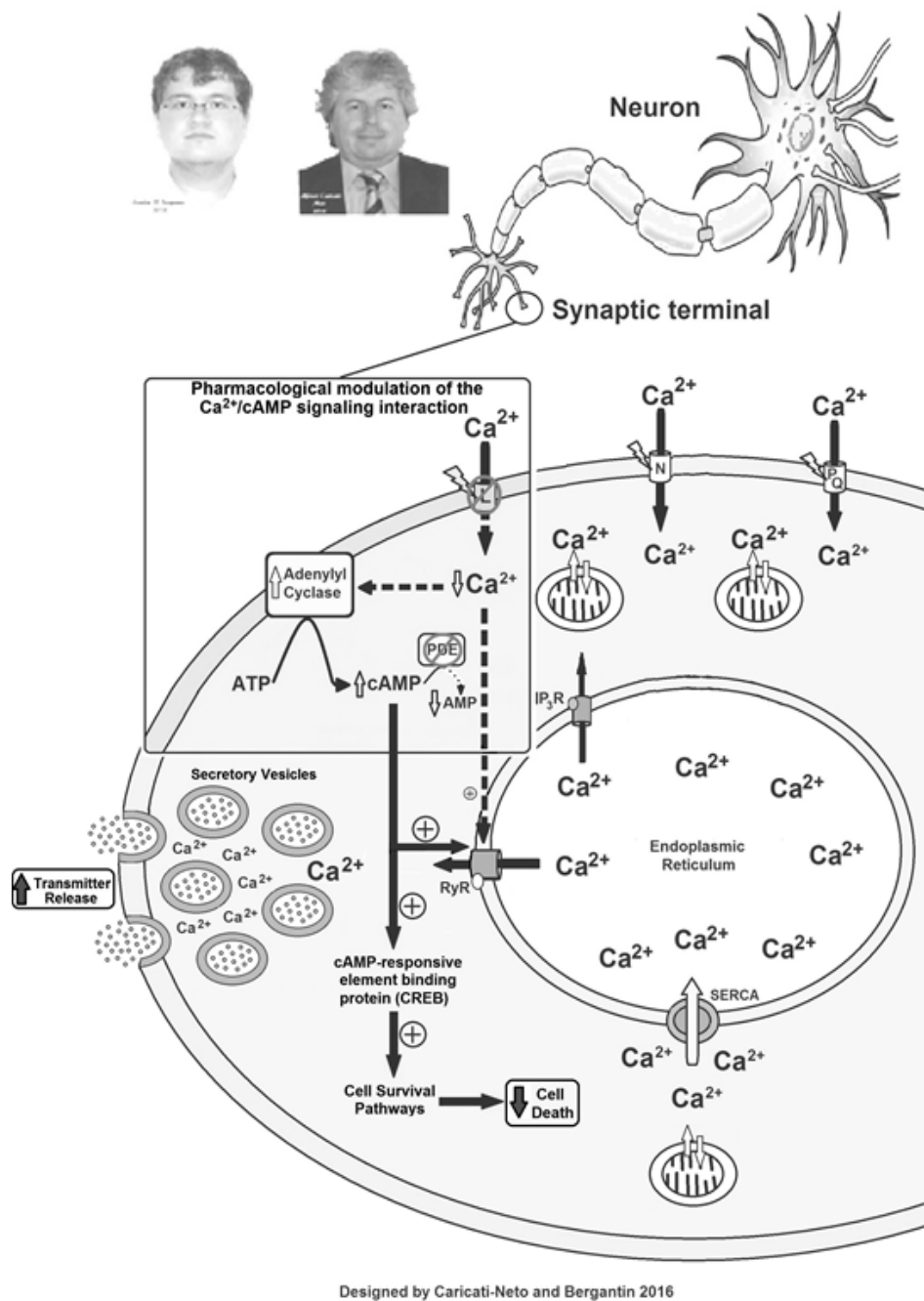


Figure 1. Pharmacological handling of the Ca²⁺/cAMP signaling interaction by combined use of L-type Ca²⁺ channel blockers and cAMP-enhancer drugs may produce increase of the neurotransmitter release, and attenuation of neuronal death (neuroprotection). Considering our model in which increment of [cAMP]_i stimulates Ca²⁺ release from endoplasmic reticulum, it may be plausible that the therapeutic use of the PDE inhibitor (rolipram) in combination with low doses of L-type Ca²⁺ channel blocker (verapamil) to increase the neurotransmission, and neuroprotection, could be a novel therapeutic strategy to treat the neurological/psychiatric disorders, including Parkinson’s disease. PDE - phosphodiesterase inhibitors.

clinical assessment in the next years. Although pharmacological therapies have been largely unsuccessful in attenuating Parkinson’s disease symptoms, targeting potential risk factors aiming to decrease incidence of this neurodegenerative disease is an important public health issue. Finally, novel strategies to treat Parkinson’s diseases, throughout our recent discovery entitled “calcium paradox” phenomenon due to Ca²⁺/cAMP interaction, could greatly contribute to enhance therapeutic strategies for increasing neuroprotection [16-23]. Thus, the association of typical antiparkinsonism medicines with CCBs

or rolipram could dramatically improve antiparkinsonism therapies, mainly by reducing adverse effects and improving effectiveness of these currently medicines [16-23].

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