From a “eureka insight” to a novel potential therapeutic target to treat Parkinson’s disease: The Ca\textsuperscript{2+}/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 Ca\textsuperscript{2+} channel blockers (CCBs). Our discovery of the involvement of interaction between the intracellular signalling pathways mediated by Ca\textsuperscript{2+} and cAMP (Ca\textsuperscript{2+}/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 Ca\textsuperscript{2+}/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 Ca\textsuperscript{2+} and cAMP (Ca\textsuperscript{2+}/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
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 Ca\(^{2+}\)/cAMP signalling interaction**

**Discovery of the role of interaction of intracellular signalling pathways mediated by Ca\(^{2+}\) 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 Ca\(^{2+}\) concentration ([Ca\(^{2+}\)\(_{\text{c}}\)) 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 Ca\(^{2+}\) signals.

In fact, the hypothesis for Ca\(^{2+}\)/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 Ca\(^{2+}\)/cAMP interaction has particularly been extensively studied at the Ca\(^{2+}\) 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 (IP,R) at submaximal IP \(_3\) concentrations, may increase the open probability of ER Ca\(^{2+}\) stores, amplifying Ca\(^{2+}\)-induced Ca\(^{2+}\) release (CICR) mechanism and cellular responses [2-4] (Figure 1). Dysfunctions of cellular homeostasis of Ca\(^{2+}\) and/or CAMP in neuronal cells could result in the dysregulation of Ca\(^{2+}\)/cAMP interaction, resulting in reduction of neurotransmitter release and also neuronal death. Then, Ca\(^{2+}\)/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 Ca\(^{2+}\) 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 with cAMP-accumulating compounds in the cardiovascular diseases, the pharmacological implications of the Ca\(^{2+}\)/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]\(_{\text{c}}\) stimulates Ca\(^{2+}\) 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 Ca\(^{2+}\)/cAMP interaction is involved in such effects deserves special attention.

In addition, considering [Ca\(^{2+}\)\(_{\text{c}}\)] 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 Ca\(^{2+}\)/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...
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].

 Disclosure statement

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