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Advances for the Pharmacotherapy of Parkinson's Disease: Pharmacological Handling of the Ca^{2+}/cAMP Signalling Interaction

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Abstract

The sympathetic hyperactivity due to increment of catecholamine plasma levels, and tachycardia, is the main adverse effect reported since 70's by hypertensive patients that use L-type Ca^{2+} channel blockers (CCBs). Our discovery of the involvement of interaction between the intracellular signalling pathways mediated by Ca^{2+} and cAMP (Ca^{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^{2+}/cAMP interaction. In the pharmacotherapy of Parkinson's disease, this discovery may produce new paths for the understanding of the cellular and molecular mechanisms involved in the pathogenesis of this disease. In this way, novel journeys for the development of new pharmacological strategies more effective for the treatment of Parkinson's may be initiated.

Keywords

Parkinson's disease, Ca^{2+}/cAMP interaction

Introduction

Reduction of dopamine release from striatal dopaminergic neurons due to neuronal death is the main accepted concept of Parkinson's disease [1]. Parkinson's disease begins years before a clinical diagnosis can be consistently made (asymptomatic/slightly symptomatic patients). The early diagnostic phase of the disease offers an opportunity for therapies, for example: those aimed to interrupt or preventing the progression of this disease, and its many complications side effects, could be more beneficial, but no such efficient therapies are available at the present moment. Thus, revealing the mechanisms of neurodegeneration from the earliest stages, however, could lead to the development of new interventions, whose therapeutic potential will need to be assessed in adequately designed clinical trials [1].

Advances in the understanding of this early phase of Parkinson's disease will lead to the identification of biomarkers of neurodegeneration and its progression. These biomarkers will help to identify the ideal population to be included, and the most appropriate outcomes to be assessed in clinical trials of medicines. Potential 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^{2+} and cAMP (Ca^{2+}/cAMP interaction) [2-4].

Current Therapy to Treat Parkinson's Disease

The reduction of dopamine release in striatal dopaminergic neurons, due to neuronal death, outcomes in the recognizable core signs of asymmetrical bradykinesia and hypo-

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kinesia (slowness and reduced amplitude of movement), muscle rigidity (stiffness) and rest tremor, consequences from modifying motor control. Rest tremor, prominent asymmetry and a good response to levodopa are the features that most accurately predict Parkinson's disease pathology [5]. Early falls or autonomic symptoms, and a response to Parkinson's disease medicines should raise evidences about the diagnosis [5]. Medication-induced parkinsonism due to commonly prescribed dopamine-blocking medications, such as antipsychotics (eg, haloperidol, risperidone) and antiemetics (eg, metoclopramide, prochlorperazine) should be excluded in Parkinson's patients. 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. Early diagnosis will become a critical issue if effective neuroprotective drugs become available.

In fact, increasing dopamine, mainly by 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 concepts 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 limited success. In conclusion, new insights for more efficient pharmacological treatments of Parkinson's disease are clearly needed.

The Pharmacotherapy of Parkinson's Disease and 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 1960's [6]. The discovery that increase in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]c$) 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]. Although the cellular and molecular mechanisms involved in these synergistic actions of cAMP on the exocytosis of neurotransmitter and hormones remain uncertain, 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_3R) 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 cellular and molecular mechanisms involved in this apparent sympathomimetic 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 Ca^{2+}/cAMP interaction [2-4]. Then, the pharmacological manipulation of the Ca^{2+}/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]. Ca^{2+} 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 Ca^{2+}/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 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]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, scientific research also links Ca^{2+} signalling pathways with autophagy regulation, which is a very important cellular process for neurodegenerative diseases [16]. Thus, whether Ca^{2+}/cAMP interaction is involved in autophagy also deserves attention. In addition, considering $[Ca^{2+}]c$ 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 interference 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. Indeed, 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 [17]. In addition, 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 and risk of dementia in hypertensive patients, suggesting that these drugs could be clinically used to treat Alzheimer's disease [18]. Supportive findings for the neuroprotective effects of CCBs have been demonstrated in 1,241 elderly hypertensive patients with memory impairment [19]. The use of CCBs decreased the risk of cognitive impairment, and Alzheimer's disease, independently of blood pressure levels, when compared to patients not receiving CCBs [19]. These findings 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 voltage-activated Ca^{2+} channels could be an excellent pharmacological strategy to attenuate, or prevent, neuronal death in 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 [20-27].

Conclusion

The diagnosis of neurodegenerative diseases like Parkinson's disease relies 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 Ca^{2+}/cAMP interaction, could greatly contribute to enhance therapeutic strategies for increasing neuroprotection [16-27]. 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 [16-27].

Disclosure Statement

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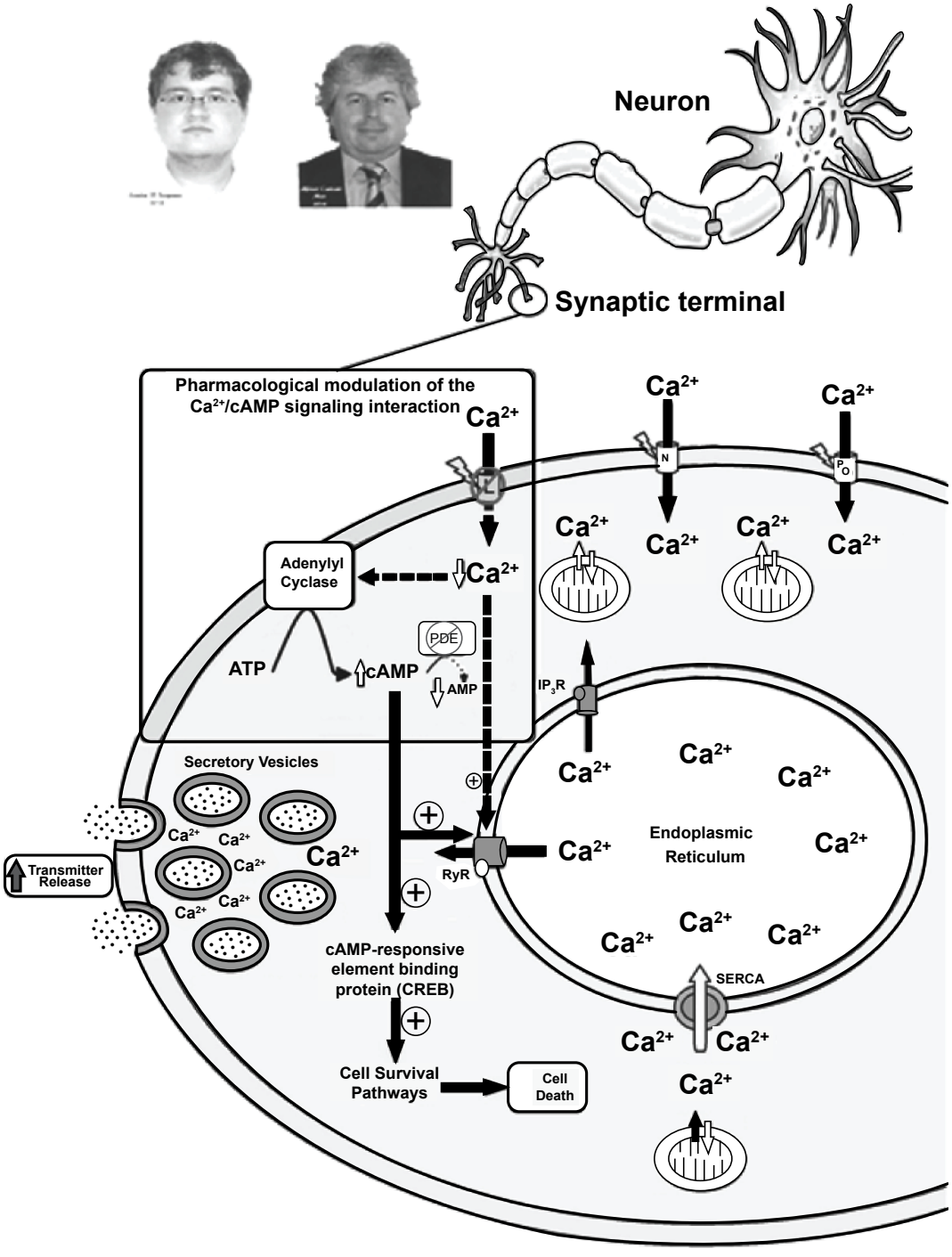

Figure 1: Increase of the neurotransmitter release and attenuation of neuronal death (neuroprotection) produced by pharmacological handling of the Ca^{2+}/cAMP signaling interaction by combined use of L-type Ca^{2+} channel blockers and cAMP-enhancer drugs. Considering our model in which increment of [cAMP]c stimulates Ca^{2+} 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 Ca^{2+} 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.

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