

Sudden Unexpected Death in Parkinson's Disease and the Pharmacological Modulation of the Ca²⁺/cAMP Signaling Interaction: A Shot of Good News

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Abstract

This discusses how pharmacological modulation of the Ca²⁺/cAMP signaling interaction could be an important neuroprotective and cardioprotective strategy to protect the dopaminergic neurons from cell death related to Parkinson's disease (PD) and at the same time to prevent the cardiac collapse in sudden unexpected death in PD.

Keywords: Ca²⁺/cAMP; Signaling interaction; Sudden unexpected death in Parkinson's disease

Short Communication

Parkinson's disease (PD) is the second commonest age-related neurodegenerative disorder after Alzheimer's disease, affecting approximately 1% of the population over 60 years and 5% in individuals up to 85 years [1-3], and entails a major burden in PD-related in disability, stigma, costs and even mortality [1,4,5]. According to the last mentioned, data from a recent meta-analysis and systematic review clearly showed that among patients with PD, the all-cause mortality increased by 2.22-fold compared with the general population [5]. PD mortality is generally related with specific risk factors such as aspiration pneumonia, dementia, old age, male gender, cancer, cardiovascular dysfunctions and even sudden unexpected death [5-12]. Although sudden unexpected death is one of the most important causes of mortality in patients with PD, its pathogenesis and pharmacotherapy remain unknown.

Most studies suggest that the sudden unexpected death in PD (SUDPAR) appears to be intimately related to severe cardiac arrhythmias caused by collapse of cardiac excitation-contraction coupling (CECC) due to cytosolic Ca²⁺ overload resulting from autonomic and myocardial dysfunctions associated to PD [5,13-15]. Unfortunately, studies so far do not point to a specific mechanism and an effective way to minimize these dysfunctions and even SUDPAR that can affect PD patients and increase mortality rates in this population. In any case, neuroscientists are convinced that translational studies should be carefully delineated in order to reduce this gap [10].

PD is characterized by motor symptoms, such as akinesia, tremor at rest or rigidity caused mainly by neurodegeneration of dopaminergic neurons in the substantia nigra that results marked dopamine deficit in the striatum [1,3]. In 1960, the lack of dopamine in brain of patients with PD was discovered, and the use of L-Dihydroxyphenylalanine (L-Dopa) to improvement of the motor symptoms was introduced in PD therapy [1,3]. Recently, drug development for PD therapy shifted its focus from transmitters, transmitter-related receptor agonists and antagonists, and transmitter-synthesizing and -degrading enzymes to other molecular targets related to neurodegeneration of dopaminergic neurons, such as alpha-synuclein, MAP-Tau and beta-amyloid protein [1,3].

Interestingly, it was observed that cytosolic Ca²⁺ overload due to

age-dependent imbalance of intracellular Ca²⁺ homeostasis is also involved in neuronal death in several neurodegenerative diseases [1,3]. Thus, we have proposed that the use of drugs to restore intracellular Ca²⁺ homeostasis and attenuate cytosolic Ca²⁺ overload could be a new therapeutic strategy to produce neuroprotection in neurodegenerative diseases, including PD [16-19]. In addition, our studies showed that the cytosolic Ca²⁺ finely regulates adenylate cyclase (AC) activity and consequently cAMP production. Several evidences suggest that cAMP is involved in the regulation of survival cell pathways mediated by cAMP-dependent protein kinase (PKA) and cAMP-responsive element binding protein (CREB) [16-19]. The increase of cytosolic Ca²⁺ concentration ([Ca²⁺]_c) due to Ca²⁺ influx through L-type voltage-activated Ca²⁺ channels (VACC) decreases AC activity, reducing cytosolic cAMP concentration ([cAMP]_c). In contrast, the reduction of [Ca²⁺]_c increases AC activity, elevating [cAMP]_c due to degradation of ATP [16,17]. cAMP is involved in several cellular functions, including regulation of activity of the L-type VACC and other ionic channels [16-19]. We have proposed that this functional interaction between intracellular signaling pathways mediated by Ca²⁺ and cAMP, named by us as Ca²⁺/cAMP signaling interaction, can have an important role in neuroprotective response and its pharmacological modulation by combined use of drugs that reduce [Ca²⁺]_c, such as Ca²⁺ channel blockers (CCB), with drugs that increase [cAMP]_c (cAMP-enhancer compounds) could be a new therapeutic strategy for neurodegenerative diseases, including PD [16-19]. Figure 1 illustrates how the pharmacological modulation of Ca²⁺/cAMP signaling interaction could be useful in PD therapy.

In addition to neuroprotection, the reduction of [Ca²⁺]_c due to

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Received April 07, 2017; Accepted April 18, 2017; Published April 25, 2017

Citation: Caricati-Neto A, Scorza FA, Scorza CA, Cysneiros RM, Menezes-Rodrigues FS, et al. (2017) Sudden Unexpected Death in Parkinson's Disease and the Pharmacological Modulation of the Ca²⁺/cAMP Signaling Interaction: A Shot of Good News. Brain Disord Ther 6: 231. doi: 10.4172/2168-975X.1000231

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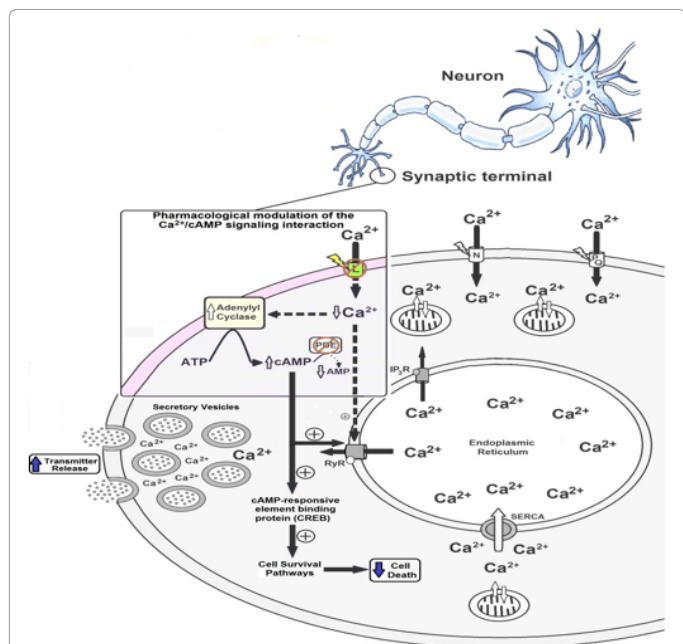


Figure 1: Pharmacological modulation of the Ca²⁺/cAMP signaling interaction as a new therapeutic strategy of PD proposed by Caricati-Neto and Bergantin [16-17]. The Ca²⁺/cAMP signaling interaction can be pharmacologically modulated by combined use of drugs that reduce (Ca²⁺)_c and cAMP-enhancer compounds. CCB, such as nifedipine and verapamil, increase AC activity and (cAMP)_c due to reduction of Ca²⁺ influx through L-type VACC [16-19]. These CCB-effects can be potentiated by cAMP-enhancer compounds, including AC activators (e.g. Forskolin) or phosphodiesterase (PDE) inhibitors (e.g. Rolipram) [16-19]. This pharmacological modulation could be a new strategy to increase of dopamine release from dopaminergic neurons and attenuate death of these neurons caused by cytosolic Ca²⁺ overload in PD [16-20].

inhibition of Ca²⁺ influx through L-type VACC by CCB and increase of [cAMP]_c can also produce cardioprotection [16-22]. These proposals emerged from studies that showed that the amlodipine (nifedipine analogous) and HO-4038 (verapamil analogous) significantly reduced myocardial damage and mortality in animal model of acute myocardial infarction (AMI) induced by cardiac ischemia and reperfusion (I/R) [21,22]. This cardioprotective effect was attributed to attenuation of cytosolic Ca²⁺ overload in cardiomyocytes combined with other beneficial cardiac effects of CCB, such as antioxidant (reduction of superoxide production) and prosurvival (increase of nitric oxide generation and Akt and Bcl-2 levels) effects [21,22]. Additionally, it was showed that the AC activator Forskolin also reduced myocardial damage in animal model of AMI induced by cardiac I/R [23,24]. This effect was completely abolished by PKA inhibitors (e.g. H-89) and mitochondrial calcium-sensitive potassium (mK_{Ca}) channel inhibitors (e.g. iberiotoxin), suggesting the involvement of the activation of mK_{Ca} by PKA in cardioprotective response [23,24]. Based on these findings, we believe that the pharmacological modulation of the Ca²⁺/cAMP signaling interaction by combined use of CCB and cAMP-enhancer compounds could be an important neuroprotective and cardioprotective strategy to protect the dopaminergic neurons from cell death related to PD and at the same time to prevent the cardiac collapse in SUDPAR [16-20].

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