

## Sudden Unexpected Death in Parkinson's Disease and the Pharmacological Modulation of the $\text{Ca}^{2+}$ /cAMP Signaling Interaction: A Shot of Good News

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### Abstract

This discusses how pharmacological modulation of the  $\text{Ca}^{2+}$ /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:**  $\text{Ca}^{2+}$ /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 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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  overload due to

age-dependent imbalance of intracellular  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  homeostasis and attenuate cytosolic  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_c$ ) due to  $\text{Ca}^{2+}$  influx through L-type voltage-activated  $\text{Ca}^{2+}$  channels (VACC) decreases AC activity, reducing cytosolic cAMP concentration ( $[\text{cAMP}]_c$ ). In contrast, the reduction of  $[\text{Ca}^{2+}]_c$  increases AC activity, elevating  $[\text{cAMP}]_c$  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  $\text{Ca}^{2+}$  and cAMP, named by us as  $\text{Ca}^{2+}$ /cAMP signaling interaction, can have an important role in neuroprotective response and its pharmacological modulation by combined use of drugs that reduce  $[\text{Ca}^{2+}]_c$ , such as  $\text{Ca}^{2+}$  channel blockers (CCB), with drugs that increase  $[\text{cAMP}]_c$  (cAMP-enhancer compounds) could be a new therapeutic strategy for neurodegenerative diseases, including PD [16-19]. Figure 1 illustrates how the pharmacological modulation of  $\text{Ca}^{2+}$ /cAMP signaling interaction could be useful in PD therapy.

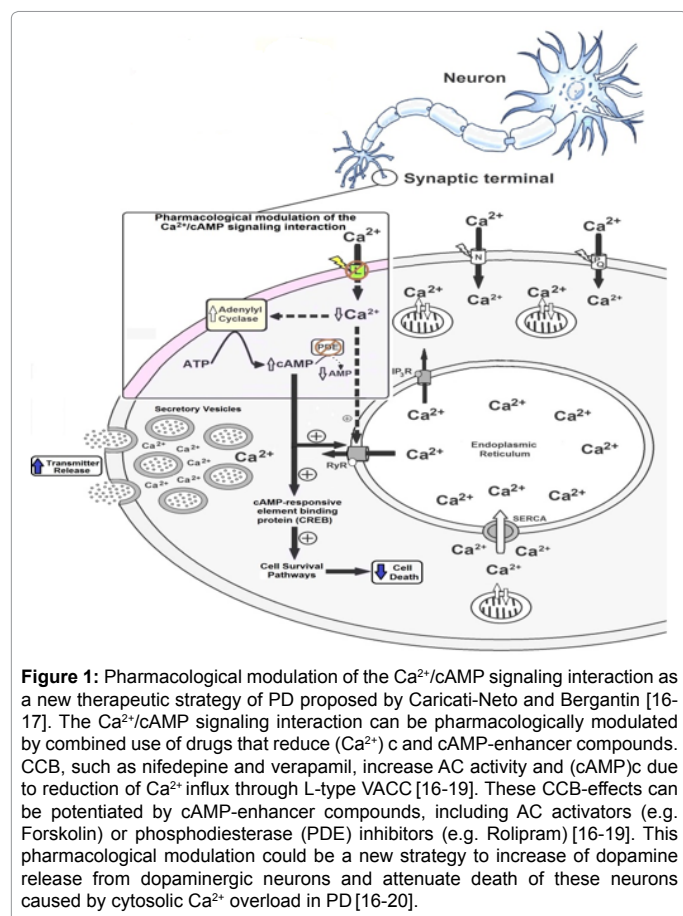
In addition to neuroprotection, the reduction of  $[\text{Ca}^{2+}]_c$  due to

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inhibition of  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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 ( $\text{K}_{\text{Ca}}$ ) channel inhibitors (e.g. iberiotoxin), suggesting the involvement of the activation of  $\text{K}_{\text{Ca}}$  by PKA in cardioprotective response [23,24]. Based on these findings, we believe that the pharmacological modulation of the  $\text{Ca}^{2+}$ /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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