Chapter 1

Challenges for the Pharmacological Treatment of Dementia: Implications of the Ca$^{2+}$/cAMP Intracellular Signalling Interaction

Leandro Bueno Bergantin* and Afonso Caricati-Neto

Department of Pharmacology, Universidade Federal de São Paulo, Escola Paulista de Medicina, Laboratory of Autonomic and Cardiovascular Pharmacology, Brazil

*Corresponding Author: Leandro Bueno Bergantin, Department of Pharmacology, Universidade Federal de São Paulo, Escola Paulista de Medicina, Laboratory of Autonomic and Cardiovascular Pharmacology, 55 11 5576-4973, Rua Pedro de Toledo, 669–Vila Clementino, São Paulo–SP, Brazil, Email: leanbio39@yahoo.com.br

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Abstract

In 2013, we discovered that the entitled "calcium paradox" phenomenon, which means a paradoxical sympathetic hyperactivity produced by L-type Ca\(^{2+}\) channel blockers (CCBs), used in antihypertensive therapy, is due to the interaction between the intracellular signaling pathways mediated by Ca\(^{2+}\) and cAMP (Ca\(^{2+}/\)cAMP interaction). In 2015, we proposed that the pharmacological manipulation of this interaction could be a new therapeutic strategy for increasing neurotransmission in psychiatric disorders, and producing neuroprotection in the neurodegenerative diseases. Besides the paradoxical sympathetic hyperactivity produced by CCBs, several clinical studies have been demonstrating pleiotropic effects of CCBs, including neuroprotective effects. CCBs genuinely exhibit cognitive-enhancing abilities and reduce the risk of dementia, including Alzheimer’s, Parkinson’s disease and others. The molecular mechanisms involved in these pleiotropic effects remain under debate. Our recent discovery that the "calcium paradox" phenomenon is due to Ca\(^{2+}/\)cAMP interaction may provide new insights for the pharmacological treatment of neurological and psychiatric disorders, including enhancement of current therapies mainly by reducing adverse effects, and improving the effectiveness of modern medicines. Whether Ca\(^{2+}/\)cAMP interaction is involved in CCBs pleiotropic effects also deserves special attention. Then, the pharmacological manipulation of the Ca\(^{2+}/\)cAMP interaction could be a more efficient therapeutic strategy for increasing neurotransmission in psychiatric disorders, and producing neuroprotection in the neurodegenerative diseases. Thus, in this chapter we summarize the current knowledge of this field, making new directions and future perspectives.

Keywords

Neurological and Psychiatric Disorders; Ca\(^{2+}/\)cAMP Signalling Interaction

Introduction

Neurological and psychiatric disorders have been considered severe global illness, becoming more and more common each decade [1]. Because of their devastating symptoms, they have been considered as a leading cause of disability all over the world [1 – 6]. Neurological disorders which result from neurodegeneration (neurodegenerative diseases) commonly begin years before a clinical diagnosis can be consistently made (asymptomatic/slightly symptomatic patients), for example Alzheimer’s and Parkinson’s diseases [2,6]. The early diagnostic phase of these diseases offer an opportunity for therapies, for example: those aimed to interrupt or preventing the progression of these diseases, and their many complications side effects could be more beneficial. However, no such efficient therapies are available at the present moment [5,6]. Thus, revealing the mechanisms of neurodegeneration
from the earliest stages could lead to the development of new interventions, whose therapeutic potential will need to be assessed in adequately designed clinical trials [2,6,7]. Advances in the understanding of this early phase of neurodegenerative diseases 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. Thus, in this chapter we discuss novel strategies to treat neurological and psychiatric disorders, throughout our recent discovery entitled “calcium paradox” phenomenon due to Ca\(^{2+}\)/cAMP interaction [8-11].

**Current Therapies to Treat Neurological and Psychiatric Disorders**

Here we discuss current therapies to treat neurological and psychiatric disorders, including Alzheimer’s and Parkinson’s diseases, and depression.

**Alzheimer’s Disease**

Neuritic plaques represent the pathological status of Alzheimer disease, and are respectively related to the accumulation of the β-amyloid peptide (Aβ) in brain tissues [2,5]. According to the amyloid hypothesis, the overproduction of Aβ is a consequence of the disruption of homeostatic processes that regulate the proteolytic cleavage of the amyloid precursor protein (APP). Genetic and age-related factors could contribute to a metabolic change, favor the amyloidogenic processing of APP in detriment of the physiological secretory pathway [2,5]. The neurotoxic potential of the Aβ results from its biochemical properties that favor aggregation. These processes, along with a reduction of Aβ clearance from the brain, leads to the extracellular accumulation of Aβ, and the subsequent activation of neurotoxic cascades that ultimately lead to cytoskeletal changes, neuronal dysfunction, and cellular death [2]. Intracerebral amyloidosis development in Alzheimer disease patients are in an age-dependent manner, but recent evidence indicate that it may be observed in some subjects as early as in the third or fourth decades of life, with increasing magnitude in late middle age, and highest estimates in old age [1,2,5]. The relevance of the early diagnosis of Alzheimer disease relies on the hypothesis that pharmacological intervention with disease-modifying compounds are more likely to produce clinically relevant benefits if started early enough in the continuum towards dementia [2,5]. Therapies targeting the modification of amyloid-related cascades may be viewed as a promising strategies to attenuate or even to prevent dementia [2]. Therefore, the cumulative knowledge on the pathogenesis of Alzheimer disease derived from basic science models will hopefully be translated into clinical practice in the forthcoming years. Other targets relevant to Alzheimer disease have also been considered in the last years for producing multitarget compounds [12,13].
In addition to what has been discussed above, acetylcholinesterase (AChE) is another important target to treat the pathogenesis of Alzheimer disease (cholinergic dysfunction hypothesis). Considering the current hypothesis of accumulation of the Aβ in Alzheimer disease, this relies in the reduction of acetylcholine release in central cholinergic nervous system involved in cognitive function. Thus, the inhibition of acetylcholine degradation by AChE is a potential target to treat Alzheimer disease [12-14]. Destructive excess Ca\(^{2+}\) influx is also another component seen in aging and neurodegenerative diseases [15]. Thus, hybrid compounds having the moieties of tacrine, a potent inhibitor of the brain and peripheral AChE, and nimodipine, a blocker of L-type CCBs have been synthetized [12]. In addition, galantamine, a mild AChE inhibitor and an allosteric ligand of nicotinic receptors have been used to improve cognition and behaviour in patients with Alzheimer’s disease [14]. Finally, N-methyl-D-aspartat (NMDA) receptor antagonist (memantine) has also been proposed to treat this disease [16].

 Besides the current medicines available nowadays in clinics, new insights for more efficient pharmacological treatments of Alzheimer disease are clearly needed.

**Parkinson’s Disease**

Dopamine loss in the substantia nigra, which results from the reduction of dopamine release in striatal dopaminergic neurons due to neuronal death, outcomes in the recognizable core signs of asymmetrical bradykinesia and hypokinesia (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 pathology [6,7]. The tremor-dominant form of Parkinson tends to run a more benign course than typical Parkinson. Early falls or autonomic symptoms, and a response to Parkinson medicines should raise evidence about the diagnosis [6,7]. 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 the diagnosis of early Parkinson. 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, and it has been estimated that the duration of this “presymptomatic” phase is about 5 years [6,7]. Early diagnoses 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 [6,7]. The combination of novel concepts may lead to advances in Parkinson 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 are clearly needed.

**Depression**

Depression is an incapacitating psychiatric condition that causes a significant problem for individuals and society by affecting their mood. There is still a lack of a clear understanding of the neuropathological changes associated with this illness, and the efficacy of antidepressants is still far from the best [3,4]. Research into antidepressant therapies have derived from observations in human trials and animal models after the first monoaminergic hypothesis emerged (about six decades ago). Nonetheless, the monoamine hypothesis of depression continues to dominate the field and clinical trials which postulate that an imbalance in monoaminergic neurotransmission is causally related to the clinical features of depression [3,4]. Antidepressants influence serotonin whose main goal consist of raising serotonin concentrations, thereby increasing serotonergic transmission at the level of the synapse, for example by inhibiting the serotonin transporter. However, the serotonin system is multifaceted. Different serotonin receptor subtypes turn the serotonergic system into a complex neurochemical arrangement that influences diverse neurotransmitters in various brain regions. Classical antidepressants, as well as other psychopharmacological agents have various crucial effects on serotonin receptors. Researchers aim to provide a useful characterization of serotonin receptor subtypes in the treatment of depression. Clarifying the mode of action, and the interplay of serotonin receptors with pharmacological agents should help elucidate antidepressant mechanisms and typical side effects to better understanding. In addition, clinical medicine featured the novel antidepressants vortioxetine, vilazodone and milnacipran/levomilnacipran with regard to their serotonin receptor targets such as the 5-HT1A, 5-HT3 and 5-HT7, which may account for their specific effects on certain symptoms of depression as well as characteristic side-effects profile [3,4].

In addition to the monoamine hypothesis of depression, glutamatergic modulators, such as ketamine also have become the forefront of antidepressant exploration, especially for treatment-resistant depression and suicidal ideation [3]. The glutamatergic hypothesis of depression is not novel, however, other NMDA receptor modulators do not seem to share the rapid and sustained effects of ketamine, suggesting that a unique combination of intracellular targets might be involved in its effect [4]. Interestingly,
inflammation can impact the glutamatergic system enhancing excitotoxicity and decreasing neuroplasticity. The points of convergence between the inflammatory and glutamatergic hypotheses of depression are not completely established, especially regarding the effects of fast-acting antidepressants [3,4].

The combination of novel ideas added to improvements on the discoveries may lead to advances in antidepressant research with the promise of finding compounds that are both effective, and fast-acting, including patients who have tried other therapies with limited success. In conclusion, new insights for more efficient pharmacological treatments of depression are clearly needed.

Challenges for the Pharmacological Treatment of Dementia: Implications of the Ca\(^{2+}\)/cAMP interaction

Implications of the Ca\(^{2+}\)/cAMP Interaction: A Brief Review

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 [17]. 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 [18]. In addition, some studies showed that cAMP rises transmitter release at several synapses in an autonomic nervous system of the vertebrate, including sympathetic neurons [19]. Although the cellular and molecular mechanisms involved in these synergistic actions of cAMP on the exocytosis of neurotransmitter and hormones remain uncertain, the evidence 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 an interaction between Ca\(^{2+}\)/cAMP signaling has been extensively studied in many cells and tissues. Generally, this interaction results in synergistic effects on cell functions, and occurs at the level of adenyl cyclases (ACs) or phosphodiesterases (PDEs) (Figure 1) [20 – 22]. 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) [8-11]. Phosphorylation of RyR by protein kinase A (PKA), and also inositol trisphosphate receptor (IP\(_{3}\)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, including neuroprotection and increase of exocytosis in neuronal cells (Figure 1).
Dementia

Figure 1: Role of Ca\(^{2+}\)/cAMP interaction in neurotransmitter release from central system nervous. Cellular homeostasis of Ca\(^{2+}\) and/or cAMP in these cells could be a novel therapeutic target for medicines. By reducing Ca\(^{2+}\) influx, CCBs may increase [cAMP]c by enhancing adenylyl cyclase activity, which increases neuroprotection. cAMP also enhances the release of Ca\(^{2+}\) from endoplasmic reticulum, which increases exocytosis; according to our previous studies [8-11]. Considering our model in which increment of [cAMP]c stimulates Ca\(^{2+}\) release from endoplasmic reticulum, it may be plausible the therapeutic use of the PDE inhibitor rolipram in combination with low doses of CCBs to stimulate neuroprotection and enhance neurotransmission by increasing neurotransmitter release in the areas of central nervous system involved in neurological/psychiatric disorders in which neurotransmission is reduced, including Alzheimer’s and Parkinson’s diseases.

Paradoxical Effects of CCBs and their Pleiotropic Effects

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 a reduction in peripheral vascular resistance and arterial pressure associated with an increase in plasma noradrenaline levels and heart rate, typical effects of sympathetic hyperactivity [23]. 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 \(\mu\)mol/L), but paradoxically potentiated in concentrations below 1 \(\mu\)mol/L [24-26]. 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 [8]. 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, in 2015 we proposed that this pharmacological manipulation could be a new therapeutic strategy for increasing neurotransmission in the psychiatric disorders, and producing neuroprotection in the neurodegenerative diseases [11]. In addition, several studies have been demonstrating pleiotropic effects of CCBs [27-29]. CCBs, like nifedipine, genuinely have pleiotropic effects [1]. 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 [1]. In the nervous system, CCBs have been emerging as potential therapeutic avenues for pathologies such as Parkinson’s and Alzheimer’s disease. In fact, apart from its classical functions, CCBs are described to have beneficiary roles on the cognitive profile of the aged population and individuals with hypertension, diabetes, Parkinson’s disease, and Alzheimer’s disease [27-29]. However, the molecular mechanisms involved in these pleiotropic effects remain under debate. Different mechanisms have been proposed, but the exact mechanisms are still uncertain.

Involvement of Ca\(^{2+}\)/cAMP Interaction: Role in CCBs Pleiotropic Effects

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 stimulate neuroprotection and enhance neurotransmission [11].

Considering our model in which increment of cytosolic cAMP concentration \([\text{cAMP}]_c\) stimulates Ca\(^{2+}\) release from ER (Figure 1), it may be reasonable to therapeutically use the PDE inhibitor rolipram, in combination with low doses of CCBs to increase neurotransmission (Figure 1) in the areas of the central nervous system involved in neurological/psychiatric disorders in which neurotransmission is reduced [30,31]. 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 neurological and psychiatric disorders. Considering that CCBs genuinely exhibit cognitive-enhancing abilities and reduce the risk of neurodegenerative diseases like Parkinson’s and Alzheimer’s diseases, and that the mechanisms involved in these pleiotropic effects are largely unknown [1,32]. Then, whether Ca\(^{2+}\)/cAMP interaction is involved in such effects deserve special attention.

In addition, considering \([\text{Ca}^{2+}]_c\) elevation could contribute to both: negatively to neuroprotective effects and positively to exocytosis, it may be plausible to therapeutically use the PDEs inhibitors for neuroprotective purposes [11]. Then, pharmacological interference of the Ca\(^{2+}\)/cAMP interaction produced by combination of L-type CCBs and cAMP-accumulating compounds could stimulate neuroprotective response and reduce clinical symp-
toms of neurodegenerative diseases. Thus, the association of current medicines could enhance neurological and psychiatric disorder treatments. For example: the association of current psychiatric/neurological medicines with CCBs or rolipram could dramatically improve typical antidepressant, antiparkinsonism and anti-Alzheimer therapies, mainly by reducing adverse effects and increasing therapeutic effectiveness. Thus, this new pharmacological strategy could be alternatively used for treatment of the symptoms of neurological and psychiatric disorders like neurodegenerative diseases.

Conclusions and Future Directions

The diagnosis of neurological and psychiatric disorders, especially neurodegenerative diseases like Parkinson’s and Alzheimer’s diseases 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 neurodegenerative diseases symptoms, targeting potential risk factors aiming to decrease the incidence of these neurodegenerative diseases is an important public health issue. Finally, novel strategies to treat theses 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 and enhancing neurotransmission, including Alzheimer’s and Parkinson’s diseases, and depression. Similarly to diseases like Alzheimer’s and Parkinson’s, this therapeutic pharmacological strategy could be used to increase neurotransmission and neuroprotection in neurodegenerative diseases like amyotrophic lateral sclerosis and myasthenia gravis. For instance, considering [Ca\(^{2+}\)]c elevation could contribute to both: negatively to neuroprotective effects and positively to exocytosis, it may be promising the therapeutic use of the PDEs inhibitors in combination with CCBs for antidepressant and neuroprotective purposes [11]. By reducing Ca\(^{2+}\) influx, CCBs may increase [cAMP]c by enhancing adenylyl cyclase activity, which increases neuroprotection [31]. cAMP also enhances the release of Ca\(^{2+}\) from endoplasmic reticulum, which increases exocytosis [8]. Thus, we have in this scenario the following targets for medicines: ACs, PDEs, L-type Ca\(^{2+}\) channels, PKA and RyR/IP\(_3\)R. In conclusion, the association of typical psychiatric/neurological medicines with CCBs or PDE inhibitor rolipram could dramatically improve psychiatric and neurological therapies, mainly by reducing adverse effects and improving effectiveness of these currently medicines [10].

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