REVIEW ARTICLE

Huntington´s disease and the interaction between Ca^{2+} and cAMP signaling pathways

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Caricati-Neto A, Bergantin LB. Huntington´s disease and the interaction between Ca^{2+} and cAMP signaling pathways. J Pharmacol Res December-2017;1(1):17-24.

Huntington disease (HD) is a neurodegenerative disease known by progressive motor, behavioral, and cognitive decline that culminates in the death. HD therapy is yet unsatisfactory. Chorea and psychiatric symptoms usually respond to pharmacotherapy. Recent advances in pathogenesis and newer biomarkers have promoted some progresses in HD therapy. It was suggested that an imbalance in the intracellular calcium (Ca^{2+}) homeostasis has a key role in neurodegenerative diseases. Recently, we showed that the interaction between intracellular signaling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP signaling interaction) plays as a key role in several cellular responses in mammalians, including neurosecretion and cell survival. Our studies showed that the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction by the combined use of the Ca^{2+} channel blockers (CCB), and drugs that increase the intracellular concentration of cAMP (cAMP-enhancer compounds), increases synaptic neurotransmission and stimulates neuroprotective response. Thus, we have proposed that this new pharmacological strategy could open a new avenue for the drug development more effective and safer for treatment of the neurodegenerative diseases, including HD. Here, we discuss the perspectives of the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction as a new therapeutic strategy for HD.

Key Words: Ca^{2+}/cAMP signaling interaction; Huntington´s diseases; Neurodegenerative disease

INTRODUCTION

General aspects of Huntington's disease

Described in 1872 by american physician George Huntington, the Huntington's disease (HD), also known as Huntington's chorea, is a progressive and fatal neurodegenerative disorder [1]. In the world, the HD prevalence was estimated in 5 to 10 cases per 100,000 persons [2]. The initial physical HD symptoms are jerky, random, and uncontrollable movements defined as chorea [1] The earliest symptoms are characterized by alterations of mood and cognitive abilities [1]. With the disease advance, the uncoordinated body movements become more apparent and cognitive abilities decline into dementia [1-3]. HD symptoms can start at any age, but generally begin between 30 and 50-year-old [1-3]. Some HD cases start before the age of 20 years (about 8%) with symptoms similar to Parkinson's disease [1]. The most common complications that reduce life expectancy are lung (pneumonia) and cardiac diseases [1]. In general, the death due to HD occurs after 15 to 20 years from initial HD symptoms [1].

Although the precise causes of HD are not totally unknown, has been proposed that this neurodegenerative disease is resultant from autosomal dominant mutation of Huntingtin (HTT) gene [1,3,4]. The HTT gene control the genetic expression of HTT protein [1,3,4]. This protein interacts with over 100 other proteins, and appears to have multiple biological functions [5]. Studies in animals genetically modified to exhibit HD showed that HTT protein is involved in embryonic development, and its absence is related to embryonic death [3,4]. Other studies indicated that the HTT protein participates in neurotransmitter vesicular transport, facilitating synaptic neurotransmission [6]. HTT protein is expressed in all mammalian cells, but its function in human cells is poorly known.

Although the behavior of the mutant HTT (mHTT) protein is not fully understood, some studies showed that mHHT is toxic to certain cell types, particularly in the brain neurons [5]. In HD patients, the brain damage likely related to mHTT protein was most evident in the striatum [5]. However, other brain areas are affected with the disease advance [5]. Initial HD symptoms appear related to abnormal function of the striatum and its cortical connections [3]. The pathways by which mHTT gene may cause neuronal death include: (1) effects on chaperone proteins; (2) interactions with caspases (apoptotic proteins); (3) the toxic effects of glutamine on neuronal cells; (4) impairment of energy production within cells; and (5) effects on the expression of genes [3,4,7].

If the expression of HTT protein is increased and more HTT produced, brain survival is improved and the effects of mHTT gene are reduced, whereas when the expression of HTT is reduced, the resulting characteristics are more typical of the presence of mHTT [6]. It was showed that the disruption of the normal HTT gene does not cause the HD in humans, but a gain of toxic function of mHTT appears to be related to HD [3]. Thus, the detection of mHTT gene has been used as a biomarker for the HD diagnosis in humans [8]. Although the HD represents the major medical, social, financial and scientific problem, only symptomatic relief drugs are available. Chorea and psychiatric symptoms usually respond to pharmacotherapy and can improve quality of life. Actually,the therapeutic strategies can be grouped into three categories: (1) reduction of the mHTT protein levels; (2) improvement of the neuronal survival; and (3) replacement of the death neurons using stem cells therapy [3,6]. Although several pharmacological agents have been used to treat HD symptoms, such as creatine, riluzole, dimebon, phenylbutyrate minocycline, ethyl-EPA, coenzyme Q10, these agentes have been ineffective to prevent or slow progression of HD in humans [1]. Tetrabenazine and benzodiazepines have showed satisfactory results in HD patients to attenuate the motor dysfunctions and chorea, respectively [1]. Serotonin reuptake inhibitors and mirtazapine have been used to treat depression in HD patients, while atypical antipsychotic drugs are used to treat psychosis and behavioral disturbances [1]. The antiparkinson drugs have been used to treat hypokinesia and rigidity [1].

Although the primary dysfunctions that lead to neurodegeneration and neuronal death in the brain of HD patients are not fully understood, recent evidences indicate that an imbalance in the intracellular calcium (Ca^{2+}) homeostasis in neuronal cells is directly involved in neurodegenerative process that cause motor and cognitive dysfunctions [9,10]. It is important

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Received: September 07, 2017, Accepted: September 22, 2017, Published: September 26, 2017

to note that the Ca^{2+} is an intracellular messenger involved in the regulation of the multiple cellular processes, including cell proliferation and differentiation, neurotransmitter release, hormone secretion, cell excitation and plasticity, and others [11-19]. However, an imbalance in the intracellular Ca^{2+} homeostasis could result in loss of cellular function and death due to cytosolic Ca^{2+} overload [9,10]. Several studies have showed that various neurodegenerative disorders are related to imbalance in the intracellular Ca^{2+} homeostasis, including Alzheimer´s (AD) and Parkinson ´s (PD) diseases [9,10]. Thus, the use of pharmacological agents to attenuate the neuronal cytosolic Ca^{2+} overload and stimulate cellular survival mechanisms has become the major focus of the therapeutic strategy in various neurodegenerative diseases, including HD.

Neurons are excitable cells that require extremely precise spatial-temporal control of Ca^{2+}-dependent processes because this ion regulates vital functions as synaptic plasticity. When these cells are depolarized, the Ca^{2+} from the extracellular fluid enters into cytosol by the voltage-activated Ca^{2+} channels (VACC), transiently increasing the cytosolic Ca^{2+} concentration ([Ca^{2+}]c [11-19]. The nervous system expresses VACC with unique cellular and subcellular distribution and specific functions. N-, P/Q- and L-type VACC are distributed at neuronal cells regulating neuronal excitability, neurotransmitter release, and gene expression [11-19]. Evidences obtained from natural mutants, knockout mice, and human genetic disorders indicate a fundamental role of some VACC in a wide variety of neurodegenerative disorders, including AD and PD [11-19]. In addition to Ca^{2+}, other intracellular messengers participate in the regulation of cellular functions, including 3′-5′-cyclic adenosine monophosphate (cAMP). cAMP regulates key cellular responses, including central metabolic events, cell growth, survival and differentiation, secretory processes, as well as inflammatory responses [11-19]. Due to importance of the cAMP in the cellular function, it is not surprising that pharmacological manipulation of the cytosolic cAMP concentration ([cAMP]c) and intracellular cAMP signaling has proven therapeutic benefit in various human diseases. Thus, drugs that produce the increase of [cAMP]c (cAMP-enhancer compounds) have proven therapeutic benefit for diseases ranging from depression to inflammation [11-19].

The efforts to understand the intracellular signaling mediated by cAMP led to the discovery of exchange protein directly activated by cAMP (EPAC) proteins. EPACs are specific guanine nucleotide exchange factors for the Ras GTPase homologues, Rap1 and Rap2, which they activate independently of the classical routes for cAMP signalling, cyclic nucleotide-gated ion channels and protein kinase A (PKA) [11-19]. Rather, EPAC activation is triggered by internal conformational changes induced by direct interaction with cAMP. Leading from this has been the development of EPAC-specific agonists, which has helped to delineate numerous cellular actions of cAMP that rely on subsequent activation of EPAC, including the regulation of exocytosis, cell adhesion, growth, division and differentiation.

Our previous studies have indicated that the functional interaction between intracellular signaling pathways mediated by Ca^{2+} and cAMP (Ca^{2+}/cAMP signaling interaction) participates in several cellular responses, including neurotransmitter/hormone exocytosis, and neuronal survival [11-19]. These studies have also indicated that the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction by the combined use of the Ca^{2+} channel blockers (CCB) and cAMP-enhancer compounds, such as phosphodiesterase (PDE) inhibitors, can increase neurotransmission and additionally stimulate neuroprotective response [11-19]. This pharmacological strategy could open a new avenue for the drug development more effective and safer for treatment of the neurodegenerative diseases, including HD.

Pharmacological modulation of the Ca^{2+}/cAMP signaling interaction as a new therapeutic strategy for the neurodegenerative diseases

For understanding the role of the Ca^{2+}/cAMP signaling interaction in the regulation of the neuronal activity initially proposed by [11-19], we should return to the past. In the 1970s, it was demonstrated that a transient increase in the [Ca^{2+}]c is a fundamental requirement to trigger the neurotransmitter release [20]. In the 1980´s, the *in vitro* studies made by Nobel laureate Erwin Neher using electrophysiological techniques showed the unquestionable direct relationship between neurotransmitter release and elevation in [Ca^{2+}]c [21]. This relationship has become more evident when was observed that the CCB in concentration above 1 μmol/L inhibited the neurotransmitter release due to blockade of the VACC and consequent reduction in the Ca^{2+} influx in neuronal cells.

Interestingly, some *in vitro* studies performed between 1975 and 1987 have demonstrated that the CCB, such as verapamil and nifedipine, produced paradoxical sympathetic hyperactivity in concentrations below 1 μmol/L [22-24]. In accordance to these *in vitro* studies, several clinical studies reported that the CCB, currently used in the antihypertensive therapy, alleviated systemic arterial hypertension due to vasodilation caused by the blockade of the Ca^{2+} influx through L-type VACC in smooth cells of the resistance arteries, but produced tachycardia and increase of catecholamine serum levels, characterizing CCB-induced sympathetic hyperactivity [25]. Despite these adverse effects of CCB have been initially attributed to adjust reflex of arterial pressure, during almost four decades the molecular mechanism involved in these paradoxical CCB-effects remained unclear for decades.

Using a smooth muscle richly innervated by sympathetic nerves (rat vas deferens) as study model of the sympathetic neurotransmission, we discovered that contractile responses mediated by sympathetic neurons were completely abolished by L-type CCB in concentrations above 1 μmol/L due to selective and effective blockade of the Ca^{2+} influx through L-type VACC in smooth cells of the vas deferens, but were paradoxically increased in concentrations below 1 μmol/L, confirming *in vitro* CCB-induced sympathetic hyperactivity [26]. Interestingly, we observed that this CCB-induced sympathetic hyperactivity was significantly potentiated by cAMP-enhancer compounds, such as PDE inhibitor (rolipram and IBMX) and AC activators (forskolin) [26].

Evidences obtained since 1980´s suggested that the increase of [cAMP]c enhances neurotransmitter release at several synapses in autonomic nervous system of mammalians [27], reinforcing the participation of cAMP in the neurotransmitter release. Our demonstration that CCB-induced sympathetic hyperactivity was significantly potentiated by cAMP-enhancer compounds was decisive to discovery that the functional Ca^{2+}/cAMP signaling interaction) is involved in several cellular responses in mammalians cells, including the regulation of transmitter release from neurons and neuroendocrine cells [11,26]. Our findings clearly demonstrated that this paradoxical sympathetic hyperactivity results from the augmentation of transmitter release from sympathetic neurons produced by L-type CCB due to its interfering on the Ca^{2+}/cAMP signaling interaction [11-19].

This nowadays accepted concept assumes that the Ca^{2+}/cAMP signaling interaction virtually exist in all mammalian cells, regulated by adenylyl cyclases (AC) and PDE [11-19]. Indeed, Ca^{2+} channels regulated by ryanodine receptors (RyR) located in endoplasmic reticulum (ER) have particularly been a forefront for the Ca^{2+}/cAMP signaling interaction field [11]. We discovered that in low concentration, the L-type CCB produces moderate blockade of the L-type VACC that reduce Ca^{2+} influx and [Ca^{2+}]c, that in turn attenuate inhibitory action of Ca^{2+} on the AC and increase the [cAMP]c synthesis, stimulating the intracellular signaling pathways mediated by cAMP [11-19]. This Ca^{2+}/cAMP signaling interaction stimulates Ca^{2+} release from ER that increases neurotransmitter release facilitating neurotransmission in sympathetic synapses [11-19]. Some evidences have suggested that increase of [cAMP]c reduces neuronal death triggered by cytosolic Ca^{2+} overload due to stimulation of the cellular survival pathways mediated by cAMP/PKA/CREB [28,29]. Then, a new pharmacological goal for increasing neurotransmission in neurodegenerative diseases resulting of neurotransmitter release deficit, and neuronal death, could be achieved by the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction [11-19]. We have proposed that the combined use of the L-type CCB, prescribed in the antihypertensive therapy such as nifedipine analogous,

and cAMP-enhancer compounds, prescribed in the antidepressive therapy such as rolipram, could be useful to achieve this purpose.

It is important to note that the effect of this combined therapy in attenuating neuronal death may be related to the genomic response, as synaptic release may be attributed to a rapid response. Indeed, pharmacological modulation of the Ca^{2+}/cAMP signaling interaction by combination of the L-type CCB, and cAMP-enhancer compounds, could increase neurotransmission [11-19]. In addition, pharmacological modulation of this interaction could subsidize the reducing of neuronal death due to attenuation of cytosolic Ca^{2+} overload, increase of [cAMP]c, and stimulation of cell survival pathways mediated by genomic response due to activation of cellular survival pathways regulated by cAMP/PKA/CREB-dependent intracellular signaling pathway [9,10,30]. Figure 1 illustrates how the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction could produce the increase of neurotransmitter release (rapid response), and the attenuation of neuronal death (genomic response) in neurodegenerative diseases.

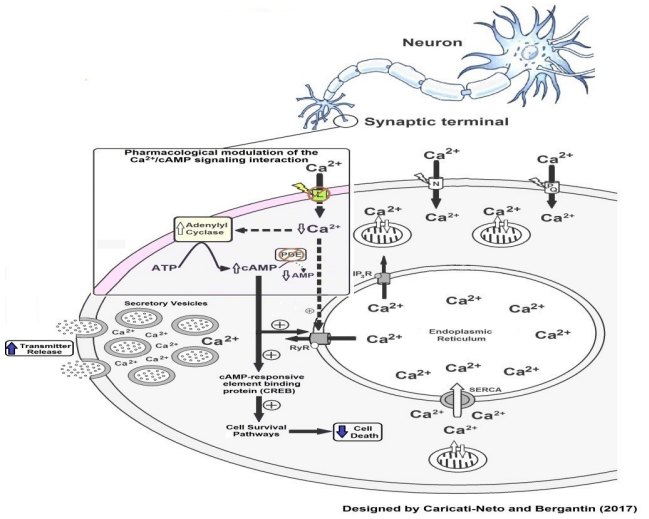

Figure 1: Increase of the neurotransmitter release and attenuation of neuronal death due to pharmacological modulation of the Ca^{2+}/cAMP signaling interaction. The moderate inhibition by L-type CCB of the Ca^{2+} influx through L-type voltage-activated Ca^{2+} channels (VACC) increases the adenylyl cyclase (AC) activity and consequently [cAMP]c. These CCB-effects can be potentiated by cAMP-enhancer compounds (like PDE inhibitors). The combined use of the CCB with cAMP-enhancer compounds could be useful to attenuate the motor and cognitive dysfunctions related to HD [11-19]. PDE - Phosphodiesterase's, RyR - Ryanodine receptors, IP3R - IP3 receptors, SERCA - Sarcoendoplasmic reticulum Ca^{2+}-ATPase.

Therapeutic perspectives of the pharmacological modulation of the Ca^{2+}/cAMP signaling interaction in Huntington´s disease

The development of new effective therapeutic strategies for HD depends on the advancement of scientific knowledge about the primary mechanisms involved in HD pathogenesis. This can take many years and cost many millions of dollars. Thus, alternative proposal for the treatment of HD symptoms could be attempted. In fact, some studies demonstrated that the use of L-type CCB reduces motor and cognitive symptoms in neurodegenerative diseases, such as AD and PD [9,10]. Studies made in animal model of PD strongly suggest that the treatment with the L-type CCB can reduce the progressive neuronal death due to its neuroprotective action [9]. It is important to note that a 1-decade study involving thousands senile hypertensive patients showed that the treatment with L-type CCB reduced arterial pressure, and risk of dementia these patients, indicating that this pharmacological strategy could be clinically used to treat neurodegenerative diseases [10]. These neuroprotective effects of CCB have been reinvestigated in thousands elderly hypertensive patients with memory deficit [30]. These studies concluded that patients treated with CCB had their risk of cognitive deficit decreased [30]. These findings reinforce the idea that the attenuation of cytosolic Ca^{2+} overload due to blockade of Ca^{2+} influx though L-type VACC blockade by L-type CCB associated to increment of [cAMP]c could be a new pharmacological strategy to reduce, or prevent, neuronal death in neurodegenerative diseases [11-19].

Like PD, the HD is a neurological disease resulting from neurodegenerative disorders that affect the motor control of skeletal muscles, producing the progressive loss of motor function [1]. It is caused by death of motor neurons. The loss of these neurons leads to weakness and wasting, atrophy, of muscles used for activities such as crawling, walking, sitting up, and controlling of head movement [1]. In severe cases of HD, the muscles involved in breathing and swallowing are dramatically affected. Deranged cellular signaling provides several tractable targets, but specificity and complexity are challenges. Thus, the preservation of neurotrophic support in HD remains a key potential therapeutic approach.

Neuronal dysfunction that affects the synaptic plasticity had been pointed out as one of the reversible causes of motor and cognitive deficit in HD. The use of the PDE inhibitors to restore neuronal function due to increment of the [cAMP]c, has progressed rapidly to human trials. Impairment of cAMP intracellular signaling and dysregulation of gene transcription mediated by the CREB are established features of HD [31,32]. The 10A-subtype PDE (PDE10A) is almost exclusively expressed in the striatum, and its activity is intimately linked to the synaptic biology of medium spiny neurons whose death is a prominent feature of HD [33]. This PDE regulates the intracellular signaling mediated by cAMP and cyclic guanosine monophosphate (cGMP) and other neuronal responses, including the synaptic plasticity and the response to cortical stimulation [34,35]. The inhibition or genetic deletion of the PDE10A induces various CREB–related gene expression changes and alterations in synaptic function, suggested that PDE10A inhibition could be beneficial in HD [35-37]. In fact, studies of the effects of PDE10A inhibition with TP-10 in the R6/2 mouse have showed the ameliorated motor deficits, reduced striatal atrophy and increased brain-derived neurotrophic factor (BDNF) levels [38]. One concern is that early death of striatal neurons might deplete PDE10A levels to the extent that the target is lost. However, clinical studies using PET imaging with the specific radioligand of PDE10A [18F]-MNI-695 suggests that PDE10A levels are sufficient even in manifest HD to expect a meaningful response [39]. Clinical studies using pharmacological inhibitors of PDE10A in HD patients are already underway, with motor and functional MRI endpoints [40]. Studies using R6/2 mouse showed that selective PDE4 inhibition with rolipram, meanwhile, improved survival and ameliorated neuropathology and motor phenotypes [41]. These findings reinforced the idea that the pharmacological modulation of the Ca^{2+} cAMP signaling interaction by combined use of the CCB and PDE inhibitor could be useful to attenuate the motor and cognitive deficit in HD [11-19].

CONCLUSION

Our studies have proposed that the pharmacological modulation of Ca^{2+}/cAMP signaling interaction by combined use of the CCB and cAMP-enhancer compounds could open a new avenue for the drug development more effective and safer for treating neurodegenerative diseases, including HD.

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