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Editorial Open Access

Revisiting the Clinical Link Between Alzheimer's Disease and Depression Through the Ca^{2+}/Camp Signalling Interaction

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Editorial

This editorial brings insights for the clinical link between Alzheimer´s disease and Depression through the Ca^{2+}/cAMP signaling interaction.

The scientific literature has recently debated (more intensively) the clinical link between Alzheimer´s disease (AD) and Depression [1]. Despite the accumulation of the amyloid-β (Aβ) in the brain (amyloid cascade hypothesis) has been considered the main issue in the arena of AD, this hypothesis does not explain the fact that there must be changes that may occur during aging process that result in increased production and aggregation of Aβ, thus culminating in the status of AD. Evidences suggest that Ca^{2+} signalling dysregulation may be such an upstream issue. Environmental issues that prevent amyloid genesis (caloric restriction, cognitive stimulus and antioxidants) virtually restore the neuronal Ca^{2+} homeostasis, whereas factors that enhance amyloid genesis dysregulate Ca^{2+} homeostasis. These evidences are supported by experiments which demonstrated that exposure of cultured neurons to Ca^{2+} ionophores enhances the production of Aβ, as do conditions such as ischemia that cause sustained elevations of Ca^{2+} concentrations $[Ca^{2+}]_c$ [2].

In addition, considering that the neuron uses Ca^{2+} signals to regulate the release of neurotransmitter, and that the deficit of neurotransmitter release is causally related to the clinical signs of Depression, then Ca^{2+} signalling is also one of the main actors in the arena of Depression. Indeed, the monoamine hypothesis of Depression continues to be one actor that dominates the field, which hypothesizes that an imbalance in monoaminergic neurotransmission culminates in the deficit of neurotransmitter release. Despite this hypothesis, pre-clinical and clinical studies have also shown that Depression can lead to cell loss in limbic brain structures, which are critically involved in the status of depression, including the hippocampus [3]. Thus, if Ca^{2+} signalling dysregulation may be such an upstream issue for AD, then sustained elevations of neuronal $[Ca^{2+}]_c$ may be a reasonable clinical link between AD and Depression, because the sustained elevations of $[Ca^{2+}]_c$ may also lead to neuronal cell death in these structures (limbic brain structures and hippocampus), which are related to the development of Depression.

Furthermore, our discovery entitled "calcium paradox" due to interaction between Ca^{2+} and cAMP signalling pathways (named by us as Ca^{2+}/cAMP signalling interaction) has supported the better understanding of the pathophysiology of the neurological and psychiatric diseases [4-7]. Our proposal involves pharmaceuticals already approved, and clinically safe, from non-neurodegenerative therapy indications (hypertension). Thus, combined with improvements in the lifestyle issues (caloric restriction, cognitive stimulus and antioxidants), it may allow sustained increments in the life quality of age-related neurological patients, opening a large path for the improvement of new pharmacological strategies (more effective) for the treatment of these diseases. Then, if sustained elevations of neuronal $[Ca^{2+}]_c$ may be a reasonable clinical link between AD and Depression, then the Ca^{2+}/cAMP signalling interaction may also be disrupted in AD and Depression. We nowadays know that neuronal Ca^{2+} signalling involves an intricate interaction between Ca^{2+} influx across plasma membrane through voltage-activated Ca^{2+} channels (VACC), TRP (transient receptor potential) channels, and Ca^{2+} release from intracellular Ca^{2+} stores via IP_3R, and RyR channels in the endoplasmic reticulum (ER) [4-7]. Intracellular Ca^{2+} release via IP_3R is triggered by the second messenger IP_3, which is produced following activation of metabotropic receptors coupled to phospholipase C. In addition, neuronal RyR functions as Ca^{2+}-activated Ca^{2+} channels which further amplifies Ca^{2+} signals, originating from other sources. Mitochondria also plays a significant role in shaping neuronal Ca^{2+} signalling by utilizing potent mitochondrial Ca^{2+} uptake mechanisms. Ca^{2+} uptake into mitochondria plays an important role in neuronal physiology by stimulating mitochondrial metabolism and increasing mitochondrial energy production. Excessive Ca^{2+} uptake into mitochondria can lead to opening of a permeability transition pore (PTP) and apoptosis. Owing to its importance for neuronal function, Ca^{2+} signalling in neurons is tightly compartmentalized, and regulated within signalling microdomains which involve, for example, functional coupling between VACC and intracellular Ca^{2+} release channels, or between ER Ca^{2+} release and Ca^{2+} uptake into mitochondria. Indeed, evidences reinforce the idea that compartmentalization of adenylyl cyclases (AC) may also cause functional compartmentalization of [cAMP]c oscillations. The more exact and specific compartmentalization takes place within several AC in proximity to VACC. Thus, in excitable cells, Ca^{2+}-regulated AC are controlled by Ca^{2+} entry through VACC [4-7]. Not surprisingly, the form of regulation described in most studies is that in which AC are controlled by Ca^{2+} influx through VACC. Then, if sustained elevations of neuronal $[Ca^{2+}]_c$ may be a reasonable clinical link between AD and Depression, thus the cAMP signalling pathways may also be dysregulated through Ca^{2+}/cAMP signalling interaction. Additional experiments in this field, using fluorescent probes which target Ca^{2+} and cAMP may add interesting results for this challenge hypothesis [8-10].

References

1. Harrington KD, Lim YY, Gould E, Maruff P (2015) Amyloid-beta and depression in healthy older adults: A systematic review. Aust N Z J Psychiatry 49: 36-46.

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2. Mattson MP, Bezprozvanny I (2008) Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. Trends Neurosci 31: 454-463.

3. Duman RS (2004) Depression: A case of neuronal life and death? Biol Psychiatry 56: 140-145.

4. Bergantin LB, Caricati-Neto A (2016) Challenges for the pharmacological treatment of neurological and psychiatric disorders: Implications of the Ca^{2+}/cAMP intracellular signalling interaction. Eur J Pharmacol 788: 255-260.

5. Caricati-Neto A, Garcia AG, Bergantin LB (2015) Pharmacological implications of the Ca^{2+}/cAMP signaling interaction: From risk for antihypertensive therapy to potential beneficial for neurological and psychiatric disorders. Pharmacol Res Perspect 3: e00181.

6. Bergantin LB (2017) Neurodegenerative diseases: Where to go from now? Thought provoking through Ca^{2+}/cAMP signaling interaction. Brain Disord Ther 6: e125.

7. Bergantin LB (2017) Neurological Disorders: Is there a horizon? Emerging ideas from the interaction between Ca^{2+} and camp signaling pathways. J Neurol Disord 5: e124.

8. Caricati-Neto A, Bergantin LB (2017) Pharmacological modulation of neural Ca^{2+}/camp signaling interaction as therapeutic goal for treatment of Alzheimer´s disease. J Syst Integr Neurosci 3.

9. Caricati-Neto A, Bergantin LB (2017) The passion of a scientific discovery: The "calcium paradox" due to Ca^{2+}/camp interaction. J Syst Integr Neurosci 3.

10. Caricati-Neto A, Bergantin LB (2017) From a "Eureka insight" to a novel potential therapeutic target to treat Parkinson´s disease: The Ca^{2+}/camp signalling interaction. J Syst Integr Neurosci 4.