Revisiting the Clinical Link Between Alzheimer’s Disease and Depression Through the Ca²⁺/cAMP Signalling Interaction

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Editorial

This editorial brings insights for the clinical link between Alzheimer’s disease and Depression through the Ca²⁺/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 Ca²⁺ signalling dysregulation may be such an upstream issue. Environmental issues that prevent amyloid genesis (caloric restriction, cognitive stimulus and antioxidants) virtually restore the neuronal Ca²⁺ homeostasis, whereas factors that enhance amyloid genesis dysregulate Ca²⁺ homeostasis. These evidences are supported by experiments which demonstrated that exposure of cultured neurons to Ca²⁺ ionophores enhances the production of Aβ, as do conditions such as ischemia that cause sustained elevations of Ca²⁺ concentrations [Ca²⁺], [2].

In addition, considering that the neuron uses Ca²⁺ signals to regulate the release of neurotransmitter, and that the deficit of neurotransmitter release is causally related to the clinical signs of Depression, then Ca²⁺ 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 Ca²⁺ signalling dysregulation may be such an upstream issue for AD, then sustained elevations of neuronal [Ca²⁺], may be a reasonable clinical link between AD and Depression, because the sustained elevations of [Ca²⁺], 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 Ca²⁺ and cAMP signalling pathways (named by us as Ca²⁺/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 [Ca²⁺], may be a reasonable clinical link between AD and Depression, then the Ca²⁺/cAMP signalling interaction may also be disrupted in AD and Depression. We nowadays know that neuronal Ca²⁺ signalling involves an intricate interaction between Ca²⁺ influx across plasma membrane through voltage-activated Ca²⁺ channels (VACC), TRP (transient receptor potential) channels, and Ca²⁺ release from intracellular Ca²⁺ stores via IP₃R, and RyR channels in the endoplasmic reticulum (ER) [4-7]. Intracellular Ca²⁺ release via IP₃R is triggered by the second messenger IP₃, which is produced following activation of metabotropic receptors coupled to phospholipase C. In addition, neuronal RyR functions as Ca²⁺-activated Ca²⁺ channels which further amplifies Ca²⁺ signals, originating from other sources. Mitochondria also plays a significant role in shaping neuronal Ca²⁺ signalling by utilizing potent mitochondrial Ca²⁺ uptake mechanisms. Ca²⁺ uptake into mitochondria plays an important role in neuronal physiology by stimulating mitochondrial metabolism and increasing mitochondrial energy production. Excessive Ca²⁺ uptake into mitochondria can lead to opening of a permeability transition pore (PTP) and apoptosis. Owing to its importance for neuronal function, Ca²⁺ signalling in neurons is tightly compartmentalized, and regulated within signalling microdomains which involve, for example, functional coupling between VACC and intracellular Ca²⁺ release channels, or between ER Ca²⁺ release and Ca²⁺ 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, Ca²⁺-regulated AC are controlled by Ca²⁺ entry through VACC [4-7]. Not surprisingly, the form of regulation described in most studies is that in which AC are controlled by Ca²⁺ influx through VACC. Then, if sustained elevations of neuronal [Ca²⁺], may be a reasonable clinical link between AD and Depression, then the cAMP signalling pathways may also be dysregulated through Ca²⁺/cAMP signalling interaction. Additional experiments in this field, using fluorescent probes which target Ca²⁺ and cAMP may add interesting results for this challenge hypothesis [8-10].

References


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