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Neurodegenerative Diseases: Where To Go From Now? Thought Provoking Through Ca^{2+}/cAMP Signaling Interaction

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Abstract

"Science is not always linear! Imagine this scenario: The PhD researcher and his supervisor are formulating their experiment. During the experiment course, there is on the bench a residual solution containing Verapamil, an L-type Ca^{2+} channel blocker (CCB). In a relapse, the PhD researcher decides to add this solution in an isolated smooth muscle preparation. The smooth muscle was prior relaxed with a drug that increased the cAMP cytosolic concentration. According to the classical receptor theory, addition of verapamil in the smooth muscle preparation should enhance the relaxation of the smooth muscle! To his surprise, the PhD researcher observed an incredible contraction of the smooth muscle! Perplexed with this result, the PhD researcher and his supervisor did not know how to explain this phenomenon immediately."

Keywords: Ca^{2+}/cAMP signalling interaction; Neurodegenerative diseases

An Enigma and of an Unusual History

Indeed the previous described scenario happened during my PhD studies performed in the laboratory of Prof. Afonso Caricati-Neto at EPM-UNIFESP. According to the classical concepts of neurotransmission described since Sir Henry Dale [1], the release of neurotransmitters critically depends on the Ca^{2+} influx through L-type voltage-activated Ca^{2+} channels (VACCs), thus culminating in the elevation of Ca^{2+} concentration (Ca^{2+}) [2]. In consequence, this increases the release of neurotransmitter, finally enhancing the contraction of the smooth muscle. Considering these concepts, some authors showed that verapamil reduced the contraction of the smooth muscles [3,4]. Nonetheless, science is not always linear! Surprisingly, a study published in 1970´s [5] described that, besides the classical effect of verapamil (in high concentrations) to reduce smooth muscle contractions, verapamil could also produce an apparent paradoxical increase of those contractions (in low concentrations) [5]. Isn´t it strange, puzzling, a "calcium paradox"? This apparent puzzling result was validated in 1981 by French and Scott [6]. Additionally, another study Moritoki et al. [7] described that verapamil augmented the smooth muscle contractions, whose effect was replicated by diltiazem (another L-type VACC blocker). The authors concluded that this result could be attributed to an agonist effect of verapamil on L-type VACCs! Really?! Years later [8], another outstanding study appeared revealing that L- type VACCs blocker (verapamil) elicited similar increases of the contractions of the smooth muscle; the authors did not provide an elucidation for such apparent paradoxical observation. No one could blame on them!

Since 1990´s, the Prof. Afonso´s lab has also reproduced those previous observations: at lower concentrations, CCB produced a slight increase, while at higher concentrations the VACCs blocker caused a decrease of the smooth muscle contractions. In 2013 [9], during my PhD studies, we found an exciting discovery: as the high verapamil concentrations, various cAMP-stimulating compounds classically relax the isolated smooth muscle. Surprisingly, in the presence of cAMP-stimulating compounds, the lower concentrations of verapamil caused an extraordinary augmentation of the smooth muscle contractions, instead of inhibiting them! In a "eureka minute", we concluded that the interaction between Ca^{2+} and cAMP signalling pathways (Ca^{2+}/cAMP signalling interaction) could properly solve these paradoxical results, including those observed since 1970´s [5]. The original paper published by us in Cell Calcium in the year 2013, has appeared four times in Science direct top 25 hottest articles lists, including top 1 position [9].

Which is the Relevance of this Discovery for Neurodegenerative Diseases?

The rising increment in the life expectancy of the world's population has increased the fear about the age-related neurodegenerative disorders, such as Alzheimer's (AD) and Parkinson's (PD) diseases, and others. It is now well recognized that an imbalance of intracellular Ca^{2+} homeostasis contributes to the pathogenesis of neurological diseases such as the neurodegenerative diseases, including AD and PD, and others. Our discovery of the role of Ca^{2+}/cAMP signalling interaction in the neurotransmission, and neuroprotection, has subsidized the understanding of pathophysiology, and pharmacology, of the neurological and psychiatric diseases, opening a large pathway for the advancement of new pharmacological strategies (more effective) for the treatment of these disorders. In 2013, as described above, we discovered that the "calcium paradox" resulted from the increase of transmitter release from sympathetic neurons stimulated by CCB due to its modulatory action on the Ca^{2+}/cAMP signalling interaction [9]. In addition, we discovered that this modulatory action of CCBs both increases the intracellular levels of cAMP and reduces the Ca^{2+} influx, thus attenuating the neuronal death in the neurodegenerative diseases resulted from cytosolic Ca^{2+} excess. This novel proposal involves pharmaceuticals already approved, and

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clinically safe, from non-neurodegenerative therapy indications [10-18].

Conclusion

These concepts have been extensively discussed in several cited international articles of my own authorship (>40), book chapters and in an international book [2]. Thanks Prof. Afonso Caricati-Neto for always supporting me and my career.

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