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Neurological Disorders: Is There a Horizon? Emerging Ideas from the Interaction between Ca^{2+} and Camp Signaling Pathways

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Editorial

Our discovery that the interaction between Ca^{2+} and cAMP signalling pathways plays a role in the synaptic transmission, including protection against neurodegeneration, has supported thoughtful ideas about the neurobiology of the neurological disorders, opening a large pathway for the improvement of new pharmacological approaches for handling with these disorders [1-10]. The augmentation in the lifetime quality of the global population has amplified the prevalence of senile people. Nonetheless, it has increased the incidence of neurological disorders, such as Alzheimer's disease (AD) and Parkinson's (PD) disease.

From elementary science, we now know that a disbalance of intracellular Ca^{2+} homeostasis is correlated with the neurobiology of neurological disorders, such as AD and PD. Four years ago, we revealed that the interaction between Ca^{2+} and cAMP signalling pathways plays a role in the modulation of neurotransmitters release from sympathetic neurons [9]. In addition, we revealed that the manipulation of the interaction between Ca^{2+} and cAMP signalling pathways could be used to attenuate the degeneration of neurons in the neurological disorders, resulted from cytosolic Ca^{2+} excess [10]. This novel proposal involves medicines already approved, and clinically safe, from non-neurodegenerative treatment indications. These ideas have been widely debated in numerous cited international articles of my own authorship (>40), book chapters and in a worldwide-recognized book [5].

Briefly, we revealed that L-type Ca^{2+} channel blockers (CCBs) increase cAMP levels. These CCBs-effects can be enhanced by cAMP-stimulating compounds (like phosphodiesterase inhibitors). Indeed, the essential mechanisms by which the interaction between Ca^{2+} and cAMP signalling pathways may rise the neurotransmitter release are due: increasing the amount of neurotransmitter in the secretory vesicles, and enhancing the frequency of neurotransmitter release. Thus, by increasing cAMP levels, this intracellular messenger may augment the release of Ca^{2+} from endoplasmic reticulum. Indeed, Ca^{2+} is vital for the neurotransmitter release process, participating in virtually all the earlier mentioned steps [1-10]. In fact, the pioneering work of Katz and collaborators in the early 1950s has demonstrated that an increase in $[Ca^{2+}]$ is the immediate trigger for neurotransmitters/hormones release from neurons, and neuroendocrine cells. Physiologically, this increase of $[Ca^{2+}]c$ is primarily started by activation of nicotinic cholinergic receptors on surface of neuronal body of sympathetic neurons (postganglionic), and adrenal chromaffin cells, by ACh from ending nerves of preganglionic neurons, derived from thoracolumbar portion of medulla [11,12]. In the adrenal chromaffin cells, this event triggers release of adrenaline, and noradrenaline, from adrenal chromaffin cells into the bloodstream. In the postganglionic sympathetic neurons, this event triggers release of noradrenaline in the sympathetic neuro-effector synapse. In these synapses, the adrenaline and noradrenaline interact with adrenoceptors on surface of effector cells (smooth and cardiac muscle cells, and exocrine cells) producing a series of physiological reactions characterized as "fight or flight" responses, such as elevation of blood pressure, acceleration of heart rate and hyperglycemia. In mammals, the catecholamines synthesized by the adrenal chromaffin cells (adrenaline and noradrenaline) are storage in vesicles. The catecholamines are stored and released by exocytosis, together with several substances, including ATP, neuropeptide Y, enkephalins, chromogranins and others. There are two main kinds of controlled exocytosis: LDCV exocytosis (neuroendocrine, endocrine and exocrine cells) and SV exocytosis (neurons). In certain neurons and endocrine cells, both LDCV and SV exocytosis are found. They can be separated by morphological appearance of secretory vesicles, and by kinetics of release. Basic mechanisms of the controlled exocytotic apparatus are very preserved among different secretory cell kinds, allowing to readily demonstrate the initial process of exocytosis in both sympathetic neurons, and adrenal chromaffin cells [11,12]. Despite variances in the time course, Ca^{2+} dependency, and signal input between LDCV and SV exocytosis, both involve shared steps: (1) vesicle recruitment to the cellular membrane, (2) docking of vesicles at the cellular membrane, (3) priming of fusion machinery, and (4) fusion of vesicles with the cellular membrane. The fusion of vesicles is a critical step in regulated exocytosis in multicellular organisms, and is closely controlled to release vesicle amounts in response to specific signals, often in a focused region of the cellular membrane. The final step of exocytosis process consists in the release of vesicles containing neurotransmitters. This release is carried out for the most part by proteins identical, or very similar to those functioning at synapses.

Leaving from elementary science, ang going through clinical data, it was reported that L-type CCBs reduce characteristics motor signs of PD, suggesting that L-type CCBs are potentially workable neuroprotective medicines [13]. Additionally, a 1-decade follow-up study, involving more than eighty thousand old hypertensive patients, concluded that treatment with L-type CCBs during antihypertensive therapy decreased the risk of Alzheimer´s disease, demonstrating that these medications could be clinically prescribed to treat Alzheimer´s disease [14]. These discoveries for the neuroprotective CCBs-effects have also been demonstrated in an independent study, with thousand hypertensive patients with memory loss [15]. This study concluded the same: the treatment with CCBs reduced the risk of cognitive loss, Alzheimer´s disease, independently of pressure levels. These discoveries strengths the notion that the decrease of cytosolic Ca^{2+} excess shaped by L-type CCBs could be an effective pharmacological approach to decrease, or prevent, degeneration of neurons in neurological disorders. Finally,

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these discoveries could open a new 'method' for the drug development to treating Alzheimer´s, and other neurological disorders related to the decrease of neurotransmitter release.

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