

A 4-Decade Enigma, Two Researchers and a Wonderful History

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Editorial

Without a doubt, we decided to initiate our first editorial article in this journal with the transcription of the “prologue” of our book from discovering “calcium paradox” to Ca²⁺/cAMP interaction: Impact in human health and disease [1].

In that rainy afternoon, the young researcher and his supervisor were preparing their daily experiment. On its course, there was a remaining solution containing Verapamil, a classical L-type CCB. In a relapse, the young researcher decided to add this solution (containing CCB) in the isolated smooth muscle neurogenic contraction system. There was no apparent reason for it! The smooth muscle was prior relaxed with a drug (rolipram) that increases the cAMP cytosolic concentration. Putatively, addition of verapamil in the isolated smooth muscle should enhance (much more) the relaxation of muscle contractions sympathetically-mediated! To his surprise, it was like that: the young researcher witnessed a drastic contraction of smooth muscle! Puzzled with what he had observed, the young researcher and his supervisor did not know the impact and the magnitude of their discovery until that time."

A 4-Decade Enigma: A Wonderful History

Typically, both release and postsynaptic actions of sympathetic neurotransmitters, such as noradrenaline and ATP, depend on Ca²⁺ entry through L-type voltage-activated Ca²⁺ channels (VACCs), resulting in increasing of [Ca²⁺] [2]. Considering this concept in mind, some authors showed that verapamil, a classical L-type VACCs blocker, abolished the contractions of the smooth muscle richly innervated by sympathetic nerves (vas deferens) [3,4]. Interestingly, however, a 4-decade study [5] described that, besides the classical effect of verapamil (in high concentrations) to block smooth muscle contractions, verapamil can also produce an apparent paradoxical increase of those contractions in low concentrations [5]. It is an artefact, you may say. This apparent paradoxical effect was corroborated by French and Scott [6], also in the rat vas deferens contractions. Furthermore, an independent third study [7] reported that verapamil increased the rat vas deferens contractions, whose effect was mimicked 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, thus increasing Ca²⁺ entry and neurotransmitter release [7]. Does this explanation convince you?

Two years later [8], another remarkable study appeared revealing that L-type VACCs blocker (verapamil) elicited similar augmentations of the contractions of the smooth muscle (vas deferens); the authors

did not provide an explanation for such apparent paradoxical observation (now already entitled by us as “calcium paradox”). In a report from our laboratory [9], we could reproduce those previous observations in the contractions of the smooth muscle (rat vas deferens): at lower concentrations, verapamil produced a small increase, while at higher concentrations the VACCs blocker caused full inhibition of the vas deferens contractions [9]. The exciting finding was that, as the high verapamil concentrations, various cAMP-enhancer compounds such as phosphodiesterase inhibitors rolipram and IBMX (isobutyl methyl xanthine), and adenylyl cyclase (AC) activator forskolin, reduced the neurogenic smooth muscle contractions; however, in the presence of cAMP-enhancer compounds, the lower concentrations of verapamil caused an extraordinary increase of the neurogenic contractions! The inhibition of AC by SQ 22536 decreased the enhanced contractions. In a “eureka moment”, we concluded that a Ca²⁺/cAMP signalling interaction could properly explain the paradoxical results of combined verapamil plus cAMP-enhancer compounds, and also the so-called “calcium paradox” [9]. Thus, these findings can indeed dramatically impact the antihypertensive pharmacotherapy in the current days. The original paper published by us in Cell Calcium has appeared four times in ScienceDirect TOP 25 Hottest Articles lists [9].

Which is the Importance of this Discovery for General Medicine?

Indeed, since many decades ago, several clinical studies have reported that the use of L-type VACCs blockers (by hypertensive patients) produces reduction in arterial pressure associated with a sympathetic hyperactivity. Despite this sympathetic hyperactivity has been initially described as the adjust reflex of arterial pressure, this apparent paradoxical result of the L-type VACCs blockers remained without further explanation for decades. Then, this sympathetic hyperactivity produced by L-type VACCs blockers can properly be due to Ca²⁺/cAMP signalling interaction, thus indeed providing new pharmacological insights for the control of blood pressure [10]. In contrast, the pharmacological handling of the Ca²⁺/cAMP signalling interaction could be a more efficient therapeutic approach for increasing neurotransmission in psychiatric disorders, and producing neuroprotection in the neurodegenerative diseases [11].

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