Implications of the Calcium Paradox Finding on Translational Research

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Opinion

The term "translational research" has recently gained popularity in the biomedical research field. The core idea basically involves "translating" current information from basic science to methods for treating human disease - from bench to bedside. The "calcium paradox" that we discovered fits this idea well. In mammals, changes in the amount of free Ca2+ ions in the cytosol (Ca2+c) work as a messenger signal to relate the stimulus to muscle contraction or neurosecretion, among countless other physiological reactions, according to basic research. Since the discovery of the function of Ca2+ in the regulation of heartbeat, a vast array of studies has established the dogma that in excitable cells, the enhanced Ca2+ entry through Voltage-Activated Ca2+ channels (VACCs) elicited by depolarizing stimuli, triggers muscle contraction and the release of neurotransmitters and hormones. On the other hand, VACCs blockers' reduction of Ca27 entry results in a reduction of those responses. According to the aforementioned theories, increased Ca2+ entry during cell depolarization and/or increased Ca2+ release from the sarco-Endoplasmic Reticulum (ER) increase [Ca2+]c and elicit contraction or secretion responses. However, a study conducted over 40 years ago revealed that verapamil at low concentrations paradoxically increased the vas deferens contractions in rats through sympathetic neurotransmission. Nifedipine, on the other hand, has recently been discovered to paradoxically increase the exocytosis of catecholamine brought on by double-pulse depolarizations from voltageclamped bovine adrenal chromaffin cells rather than decrease the Ca2+ dependent responses of contraction and secretion? In 2013, we successfully responded to this "calcium conundrum" by using the Ca2+/cAMP signalling relationship. Noradrenaline (NA) and ATP are released in the vas deferens, and their postsynaptic activities are dependent on Ca2+ entry through VACCs and the resulting increases in [Ca2+]. As a result, according to some scientists, verapamil stopped the vas deferens from contracting when it was stimulated electrically. However, in a previous investigation, it was noted that verapamil prevented the sympathetically-mediated contractions of the rat vas deferens, as was expected; however, same study also noted that the lower concentrations of verapamil induced an unexpected increase of those contractions. French and Scott confirmed this paradoxical outcome in 1981, also in rat vas deferens contractions brought on by nerve stimulation. In addition, a third study published six years later found that verapamil and diltiazem increased the twitch response of nerve-stimulated rat vas deferens contractions. This finding was explained by the agonist effect of verapamil on L-type VACCs, which raised Ca2+ entry and neurotransmitter release. A second study that was published two years later found that the L-type VACCs blockers and the activator BAY K 8644 both increased the neur-ogenic contractions of the vas deferens, albeit the authors did not explain this paradoxical finding. In a study conducted in our lab, we were able to confirm those earlier findings regarding the neurogenically induced contractions of the rat vas deferens: at lower concentrations, verapamil only slightly increased the contractions, whereas at higher concentrations, the VACCs blocker completely inhibited the contractions. The intriguing discovery was that while forskolin and other Adenylyl Cyclase (AC) activators as well as PDE inhibitors rolipram and IBMX (isobutyl methyl xanthine) all reduced neurogenic vas deferens contractions in the presence of high verapamil concentrations, the lower concentrations of verapamil significantly increased the neurogenic contractions. The Ca2+/cAMP connection may adequately explain the contradictory results of coupled verapamil and cAMP enhancers, as well as the so-called "calcium paradox," as the suppression of AC by SQ 22536 reduced the increased contractions. These discoveries can therefore have a significant impact on cancer, neurological/psychiatric problems, hypertension, and other ailments. Based on these results, we hypothesised that increasing neurotransmission in neurological and psychiatric disorders caused by neurotransmitter release deficit and neuronal death could be achieved by pharmacologically regulating the Ca2+/cAMP interaction by combining the use of L-type VACCs blockers and [cAMP]c-enhancer compounds. This pharmacological approach presents a fresh avenue for the creation of drugs that are more effective in the treatment of neurodegenerative illnesses like Alzheimer's. In fact, it has been shown that prescribing L-type CCBs lowers motor symptoms and slows down progressive neuronal death in animal models of neurodegenerative disease, suggesting that L-type CCBs may be useful as medications for neuroprotection. Intriguingly, a decade-long study involving thousands of senile hypertension patients showed that prescribing L-type CCBs to hypertensive patients decreased blood pressure and risk of dementia, suggesting that these drugs could be used clinically to treat neurodegenerative illnesses. These findings regarding the neuroprotective properties of CCBs have been reexamined in hundreds of elderly hypertensive patients who suffer from memory loss. These investigations came to the conclusion that patients who took CCBs had a lower risk of cognitive impairment, including Alzheimer's disease. These results support the hypothesis that cytosolic Ca2+ excess caused by L-type CCBs could be reduced or prevented by pharmacological means in neurodegenerative disorders. Additionally, it has been demonstrated that deregulation of intracellular signalling pathways controlled by Ca2+ and cAMP has a role in the development, progression, metastasis, invasion, and angiogenesis of tumours. Ca2+ channels and cAMP-dependent protein kinase (PKA), two proteins implicated in these processes, are thus promising therapeutic targets for the treatment of cancer. With this idea in mind, certain investigations revealed that proliferative responses in various cancer cells are inhibited by medications that can interfere with intracellular Ca2+ signalling, such as selective VACCs blockers like amlodipine. PDE 4 inhibitors, for example, have been suggested as potential adjuvant, chemotherapeutic, or chemopreventive medicines in several cancer forms, including hepatocellular carcinoma. These medications have the ability to boost intracellular cAMP levels. Therefore, pharmacologically altering intracellular communication in cancer cells that is mediated by Ca2+ and cAMP may be a fresh approach to treating the disease. In conclusion, the "calcium paradox" may have a significant impact on translational research, spurring the creation of novel medications for the pharmacotherapy of cancer, neurological and mental disorders, hypertension, and many other illnesses.

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