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From discovering calcium paradox to Ca^{2+}/cAMP interaction: Impact in human health and disease

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The hypothesis of the so-called calcium paradox phenomenon in the sympathetic neurotransmission has its origin in experiments done in models of neurotransmission since 1970's. Historically, calcium paradox originated several clinical studies reporting that acute and chronic administration of L-type Ca^{2+} Channel Blockers (CCBs), drugs largely used for antihypertensive therapy such as verapamil and nifedipine produces reduction in peripheral vascular resistance and arterial pressure, associated with a paradoxical sympathetic hyperactivity. Despite this sympathetic hyperactivity has been initially attributed to adjust reflex of arterial pressure, the cellular and molecular mechanisms involved in this paradoxical effect of the L-type CCBs remained unclear for four decades. Also, experimental studies using isolated tissues richly innervated by sympathetic nerves showed that neurogenic responses were completely inhibited by L-type CCBs in high concentrations but paradoxically potentiated in low concentrations, characterized as a calcium paradox phenomenon. We discovered in 2013 that this paradoxical increase in sympathetic activity produced by L-type CCBs is due to Ca^{2+}/cAMP interaction. Then, the pharmacological manipulation of this interaction could represent a potential cardiovascular risk for hypertensive patients due to increase of sympathetic hyperactivity. In contrast, this pharmacological manipulation could be a new therapeutic strategy for increasing neurotransmission in psychiatric disorders such as depression and producing neuroprotection in the neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

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Moving forwards towards personalized medicine in lysosomal disorders

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Understanding phenotypic variability in rare genetic diseases, such as Gaucher disease (GD), is challenging because it is hard to recruit large cohorts of patients with different symptoms to perform association studies. To overcome this problem GD was chemically induced in 15 inbred mouse strains because they SNPs profile is known, followed by GWAS. GD-induced strains mimicked the divergent phenotypes observed in patients, which range from neuropathic disease with short lifespans to others with no evident CNS involvement and longer survival times. GWA analysis identified a small collection of candidate loci underlying the variable strain phenotypes, which successfully allowed to predict the severity of the disease in other strains upon GD induction and to identify a novel therapy for the neuropathic forms of GD.

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