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Pharmacological investigation of *Trypanosoma cruzi* phosphodiesterases as drug targets. Insight into target vulnerability.

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Resumen

The intracellular cAMP and cGMP levels are regulated by cyclic nucleotide phosphodiesterases (PDEs), a group of specific cyclic nucleotide-degrading enzymes involved in the control of homeostasis. It is long been self-evident that increased knowledge of cyclic nucleotide signaling pathways can lead to the development of therapeutic agents against human diseases. The kinetoplastid PDEs are highly similar to most of the human homologs, which justifies the potential repurposing of PDE inhibitors as potential antiparasitic agents. Also, these PDEs are highly amenable to selective inhibition, due to small differences in their binding pockets. Correlating target engagement with in vivo drug activity remains a central challenge in efforts to improve the efficiency of drug treatment and discovery. Among other methods, cell-based washout experiments, in which the phenotypic consequences of target engagement are evaluated once drug is “removed” from the system, can provide direct insight into target vulnerability.

In this work, washout experiments were performed to test the effect of three commercial PDE inhibitors: Rolipram, Zaprinast and Vinpocetine. Post-washout infection inhibition was maintained for all inhibitors, but Vinpocetine showed the largest detrimental effect on *in vitro T. cruzi* infection experiments. This inhibitor also proved to be effective in trypomastigotes and amastigotes. As additional experiments in order to support target validation, we tested two other compounds from in silico studies, Terameprocol and Lasalocid. Both compounds showed to be effective at low concentrations in the amastigote stage in our experimental model. Finally, we evaluated the effect of both drugs on enzymatic activity using TcrPDEB2 and TcrPDEC recombinant *T. cruzi* enzymes. Both compounds showed activity inhibition at low concentrations. In summary, these results highlight the potential of PDEs as targets against Chagas´ disease.

Tipo de Presentación

Póster.