Inhibition of the gastric H,K-ATPase by potassium competitive acid blockers

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The gastric H,K-ATPase is a membrane protein found in the parietal cells of the stomach, where it couples H^+ extrusion to the uptake of K^+ , leading to the acidification of gastric juice (1). Acid-related diseases are an important public health issue where the mainstay of treatment has been the suppression of H,K-ATPase activity. As K^+ plays a vital role in this catalytic cycle, for the dephosphorylation of the H,K-ATPase and the subsequent conformational changes, acid secretion can be inhibited by agents that are competitive with respect to K^+ binding. This argument led in the past decades to the development of a new class of acid suppressants, known as potassium competitive acid blockers (P-CABs). Since a systematic investigation of enzyme-inhibition mechanisms has become a fruitful way to
design and test new drugs, the effects of P-CABs-type inhibitors have been extensively studied analyzing how the apparent Michaelis and Menten parameters are affected (2). Working with the non-compartmentalized enzyme preparation, we analyzed the interactions between K^+ , the H,K-ATPase, and two different inhibitors under steady state conditions. Our results from ATPase activity as a function of K^+ concentration was described by a rational function where the maximal exponent on $[K^+]$ is 2. Data show that K^+ , as a product, can inhibit the reaction steps that involve its release, which implies that ATPase activity would not obey the Michaelis-Menten equation. This can lead to mistakes when analysing the results according to variations in V_{max} and K_M . Here we propose a minimal model to describe
the binding of K^+ to different enzyme conformations and the inhibition by P-CABs compounds allowing a more realistic evaluation of their effects.

References

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Acknowldegments

This work was supported by Agencia Nacional de Promoción Científica y Tecnológica [PICT 2012-2018, 1053], Consejo Nacional de Investigaciones Científicas y Técnicas [PIP 11220150100250CO], and Universidad de Buenos Aires [UBACyT 2014-2017, 20020130100302BA].