

Review of: "The Fundamental Problem With Enzyme Inhibition Theory"

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Review

The author claims fundamental problems with enzyme inhibition theory. His solution is to introduce a “delta” K_m and “delta” V_{max} term into kinetic equations.

The further claim that the new equations can also account for activation is suggested as a complete overhaul of an incorrect theory.

I found this submission itself contained fundamental flaws and the derivation confusing.

The idea that enzyme inhibition is *defined* by the term $1 + [I]/K_i$ is not correct. That term does arise from a derivation of a steady-state enzyme kinetic mechanism in which an inhibitor is in equilibrium with an enzyme form. The author somehow indicates an error in using equilibrium at all, but the derivation used in this paper does not discard that idea.

However, it does advance an erroneous notion of how to approach enzyme inhibition. This notion has been perpetuated in some elementary biochemistry textbooks but is not committed by experts in enzyme kinetics such as Cornish-Bowden and Cleland.

The K_m is not an affinity, as the author simply assumes. An affinity term is in fact an equilibrium constant, and K_m is instead a steady-state constant. It is popularly cited because it is sometimes a useful approximation, but not in the context of enzyme inhibition. Here, the critical parameters are V_{max}/K_m and V_{max} , not V_{max} and K_m . How an inhibitor modifies K_m is not only unimportant but seriously misleading. For example, an uncompetitive inhibitor will decrease the K_m . Does that mean it can improve the affinity of a substrate for an enzyme? Of course not; K_m is not an affinity constant. Others have made this error in print, suggesting an uncompetitive inhibitor can activate (D. Fell, *Understanding the Control of Metabolism*, Portland, London, 1997).

The backwards approach of starting with an equation and trying to interpret enzyme inhibition is different but does not lead to insight. The derivation itself is unusual. It starts with well-known derivations for binding equilibrium and the Michaelis-Menten equations and then throws in the “delta” terms.

In order to make sense of enzyme kinetics, it is important to start with a model. It can include simple terms to model inhibition, and it would clarify what the types of inhibition really are. The author does not seem to have those clearly here.

Competitive inhibition is not, as the author suggests, a competition for the active site. That is a popular notion as well, but not correct. Competitive inhibition is a competition for the free form of the enzyme, E. Uncompetitive is a binding of the inhibitor to an intermediary form, i.e., not the free form. In the simplest case, that would be ES. Finally, noncompetitive means it binds both. What the author calls “noncompetitive” is simply a special case of noncompetitive where both binding constants (K_i values) are the same. What the author calls “mixed” is just another name for noncompetitive, in the general case where the two K_i values are not equal.

As for the argument that only the manipulation of the equation can model activation, that is simply not true, and again, a backwards approach. Adding in an equilibrium between EI and ESI in a simple noncompetitive model can provide activation depending on the value of the (now three) equilibrium constants.