Changing the perspective on the origin of enzymatic catalytic power
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The enzymes found in living organisms have impressive catalytic power. Thanks to enzymes, the chemical reactions that sustain life happen millions of times faster than they would occur without them. Enzymes speed up reactions by helping to lower the activation energy needed to start them, but for more than 70 years, how enzymes achieve this has been the subject of intense debate.

Dr. Tor Savidge, professor of pathology and immunology at Baylor College of Medicine and Texas Children's Microbiome Center, and his colleagues are changing the way to look at this old argument. In their work published in Chemical Science, they investigated the similarities and differences between the two mechanisms currently under debate by characterizing catalytic reactions at a detailed molecular level.

"At present time, two major different reaction mechanisms are proposed to explain enzymatic catalytic power," Savidge said. "One proposes that enzymes lower the reaction's activation energy via stabilization of transition states (TS) and the other that they do it by destabilizing the ground state (GS) of enzymes. The current idea is that these mechanisms are mutually exclusive."

First author Dr. Deliang Chen at Gannan Normal University in China and his colleagues took a theoretical approach, taking into consideration previous findings from the Savidge lab showing that the noncovalent interactions of substrates and enzymes with water are important in terms of the mechanism of the enzymatic reactions.

"In a biological environment you have to consider the water—that it is going to interfere with the very complex atomic interactions occurring in the enzyme's active site. We need to consider all of them to understand where exactly you need to have electrostatic interactions that are going to favor that enzymatic process," Savidge said. "When you take that into consideration, you can understand how these mechanisms are operating."

Their analyses led the team to propose something new: that TS and GS are not that different after all. They use a similar atomic mechanism to boost the enzymatic reaction forward. The mechanism involves water in altering the charge of important residues within the catalytic site in a way that favors the formation of an energetically favorable state that drives the enzymatic reaction to occur.

"The important, new point here is not how this is achieved but when it is achieved," Savidge said. "We have shown that in stabilization of transition states, the charges that drive the reaction forward are formed before the substrate enters the active site. While in the destabilization ground state this also occurs, but after the substrate enters the active site."

The researchers also proposed that the common mechanism between TS and GS is universal; it can be applied to many enzymatic reactions.

Their findings have important implications not only to help researchers better understand the catalytic power of enzymes, but also for practical drug design applications.
"We use our findings to more deeply explore microbial enzymatic catalysis in different environments and to design artificial enzymes," Savidge said.

Yibao Li, Xun Li, Xiaolin Fan, at Gannan Normal University, and Xuechuan Hong at Wuhan University School of Pharmaceutical Sciences also contributed to this work.


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