New research increases understanding of drug metabolism

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Research led by Wayne L. Backes, PhD, Professor of Pharmacology and Associate Dean for Research at LSU Health Sciences Center New Orleans School of Medicine, has found that drug metabolism depends not only upon which enzymes are present in an individual, but also how they interact, and that can be the difference in whether a drug is safely eliminated from the body or is converted into a toxic or carcinogenic byproduct. The paper will be published in the March 19, 2010 issue of the *Journal of Biological Chemistry*.

Dr. Backes and his LSUHSC research colleagues - J. Robert Reed, PhD, Pharmacology Assistant Professor and Marilyn Eyer, Research Associate - have been studying an enzyme called Cytochrome P450 which is responsible for the removal of the majority of drugs from the body by chemically breaking them down into inactive substances or metabolites. There are many different P450 enzymes capable of degrading many different drugs. Because there are so many, there is a high degree of variability in people's responses to a drug.

"Although most P450 reactions lead to metabolites that speed the excretion of drugs and pollutants, sometimes P450 enzymes can lead to the activation of a compound to a metabolite that can cause cancer or toxicity where the initial chemical in the drug does not," notes Dr. Backes. "This is a partial explanation of why some people are more resistant to cancer and other diseases and why it is very important to understand the reasons for the variability in drug metabolism."

The results reported in this paper show that P450 enzymes form complexes with each other in biological membranes, and that these complexes affect how the enzymes metabolize substances, making one of the P450s more active and the other less active. The researchers also showed that both of the P450 enzymes they studied (1A2 and 2B4) had to be in the same membrane inside the cell for that to happen.

"Our study shows that the P450s should not be tested alone, but need to be present in mixtures similar to those found in humans in order to better predict how rapidly a candidate drug is metabolized and eliminated or even whether it can produce toxic byproducts in some individuals," said Dr. Backes. "This information is crucial to the development of new drugs because differences in drug metabolism can lead to differences not only in potential toxicity, but also in the effectiveness of a candidate drug."

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