Molecular modelling to help create better, safer drugs

May 24 2013

(Phys.org) —How our bodies break down the common drugs ibuprofen, diclofenac and warfarin is the subject of a new study from the University of Bristol, published in the *Journal of the American Chemical Society*. The research should ultimately help predict how new drugs will be metabolized in the body, potentially helping avoid adverse drug reactions in future.

Professor Adrian Mulholland of the School of Chemistry and colleagues used molecular modelling to show in atomic detail how ibuprofen, diclofenac and warfarin are broken down by a group of enzymes called cytochrome P450s which play an important part in the metabolism of drugs.

Cytochrome P450s break down drugs by adding oxygen atoms to them, thus making them more soluble in water and easier to remove from the

body. It's important that drugs are broken down in this way so they don't accumulate to toxic levels. However, it's also important that the drugs aren't broken down too quickly otherwise they won't stay in the body long enough to work.

Different people have different types of P450 which mean they break down drugs more quickly or more slowly. Potentially harmful complications can also sometimes occur, for example, other drugs can 'block up' P450s thus interfering with the metabolism of a particular drug. Other substances can also interfere with the process, for example grapefruit and grapefruit juice contain a molecule that 'inhibits' some cytochrome P450s, preventing them from breaking down drugs. This can cause the drug to build up to a toxic – and possibly lethal – level.

Professor Mulholland said: "An important aim in developing a safe, effective drug is understanding how it will be broken down in the body. This process would be made quicker, cheaper and safer if we could predict reliably – for example, by using computers – how a candidate drug reacts in the body.

"This study uses molecular modelling methods which are able to describe chemical reactions in large and complex enzymes such as cytochrome P450s. Our results agree well with experiments, and point to how modelling of this sort can help in developing predictions of drug metabolism."

More information: Lonsdale, R. et al. QM/MM Modeling of Regioselectivity of Drug Metabolism in Cytochrome P450 2C9, *Journal of the American Chemical Society*. pubs.acs.org/doi/abs/10.1021/ja402016p

Provided by University of Bristol