Medical Xpress

Targeting drugs to reduce side effects

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(Medical Xpress)—Consider ice cream – the base of which is frozen cream. Ingredients are then added to make different flavours. All these flavours are distinctly different but are created from the same foundation.

The same goes for actions of phosphodiesterases or PDEs – enzymes that are key targets for drugs that combat various cardiovascular and respiratory diseases.

Although PDEs carry out only one reaction in cells, they inactivate small signaling molecules. As humans, we can create about 120 different "flavours" of PDEs, using the 26 different PDE genes in our genome.

After conducting a review of the drugs that act by targeting individual PDE "flavours", Donald Maurice, Director of the Cardiac, Circulatory and Respiratory Research Program at Queen's, and his international co-authors have learned that many of the drugs' side effects can be avoided.

When PDEs are inhibited, there is an increase in the rhythmic beating of the heart and blood pressure is often reduced. Common PDE-inhibiting drugs include caffeine and Viagra.

The research review aimed to study previous research on PDE's in order to position past results in the context of the recently discovered "flavours" of PDEs, which can be targeted individually by cardiovascular drugs.

"Few PDE drugs currently available have the selectivity needed to target the individual PDE "flavours" that contribute to human diseases," says Dr. Maurice, also a professor in the Department of Biomedical and Molecular Sciences. "Yes, it's important to understand drug successes, but comprehensive critical reviews give researchers the chance to understand the basis of failures and make improvements."

While PDE-inhibitors have been used in the past to treat cardiovascular illnesses, this review outlines recent advances from the laboratories of the authors that have led to an increased interest in the design of PDE-acting drugs for conditions such as Alzheimer's, schizophrenia and diabetes.

The review also found that drugs that target specific locations within a cell are more likely to be successful.

"If you can regulate individual events happening in individual locations of the cell then you can leave the normal functions of the cell unaffected while challenging the abnormal ones," says Dr. Maurice.

Dr. Maurice's review was published in *Nature Reviews Drug Discovery*. His research program is funded by the Canadian Institutes of Health Research.

More information: "Advances in targeting cyclic nucleotide phosphodiesterases." Donald H. Maurice, Hengming Ke, Faiyaz Ahmad, Yousheng Wang, Jay Chung & Vincent C. Manganiello. *Nature Reviews Drug Discovery* 13, 290–314 (2014) DOI: 10.1038/nrd4228
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