Researchers use honeybee venom toxin to develop a new tool for studying hypertension

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Researchers at the University of Pennsylvania School of Medicine have modified a honeybee venom toxin so that it can be used as a tool to study the inner workings of ion channels that control heart rate and the recycling of salt in kidneys. In general, ion channels selectively allow the passage of small ions such as sodium, potassium, or calcium into and out of the cell.

The study, published in the *Proceedings of the National Academy of Sciences,* is from the laboratory of Zhe Lu, M.D, Ph.D., Professor of Physiology and a Howard Hughes Medical Institute Investigator, who looked at the action of a natural bee toxin on inward-rectifier potassium channels, Kir channels for short, to identify new approaches to treat cardiovascular disease.

The honeybee venom toxin, called tertiapin, or TPN, stops the flow of potassium ions across cell membranes by plugging up the opening of Kir channels on the outside of cells. Kir channels in kidneys are potential new targets for treating hypertension. "The clue comes from patients with genetic defects in these channels who lose a lot of sodium because it cannot be effectively reabsorbed and thus have low blood pressure," notes Lu. "An inhibitor specifically against these kidney channels will allow this idea to be tested."

Developing a specific inhibitor for one type of Kir channel has been challenging because the target site is very similar among different types of Kir channels. For example, while TPN inhibits Kir type 1 channels in

kidney cells, it also inhibits other types of Kir channels in heart cells. After more than a decade, Lu and his colleagues succeeded in bioengineering a TPN that selectively inhibits Kir channels important for salt recycling in kidneys.

By introducing two mutations into TPN, they engineered a variant, called TPNLQ, which stems the flow of potassium ions in renal Kir type 1 channels at low concentrations, and with a 250-fold sensitivity over six other types of Kir channels.

The development of TPNLQ demonstrates that a highly specific inhibitor of potassium channels can be engineered. TPNLQ can now be used as a tool to prove the concept, in animal studies, that reducing salt reabsorption by plugging up renal Kir type 1 potassium channels is a potential new way to treat hypertension.

Source: University of Pennsylvania