Nature-derived peptides as molecular tools to study cellular signaling

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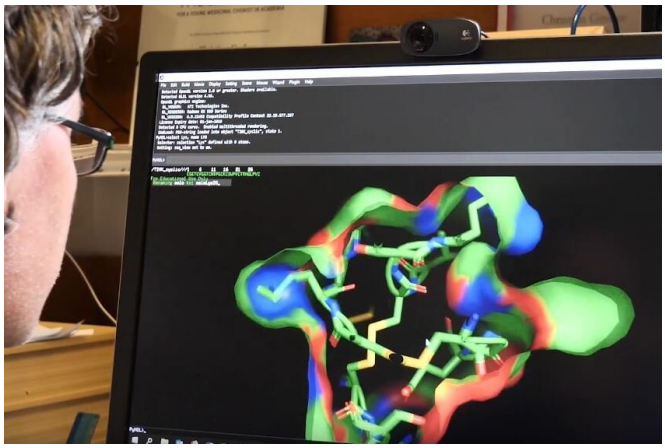

Credit: Medical University of Vienna

A group of researchers of the Institute of Pharmacology at the Medical University of Vienna in collaboration with the University of Vienna and different institutions in Australia, has shown that a certain peptide hormone derived from a mite activates selectively a specific secondary messenger molecule on the human vasopressin 2 receptor (V2R). This is all the more astonishing since drugs normally activate several different molecular signaling pathways via this class of receptors—belonging to the group of G protein-coupled receptors. This evokes desirable, but also adverse effects. Such peptides can now be used as chemical tools to gain a better understanding of the mechanisms of signal transmission in cells, hence facilitating the more targeted use of drugs in the future—with fewer side-effects.

"The results of our study show that peptides isolated from arthropods are highly suitable for the exploration of targeted, molecular tools or drugs for this class of human receptors," says Principal Investigator Christian Gruber from MedUni Vienna's Institute of Pharmacology. Around 30% of all drugs act on the so-called G protein-coupled receptors, but various molecular signaling pathway are activated in the cell simultaneously, and not selectively, which, in rare cases, can lead to fatal side-effects. Gruber: "An example of this would be respiratory depression after using opiates for pain control, which is currently a major problem in the U.S., known as 'opiate crisis.'"

However, the Viennese scientists (largely due to the contribution of the two Ph.D. students Edin Muratspahi? and Leopold Dürrauer) now seem to have discovered a possible way of using drugs more specifically and stopping non-selective activation of the signaling pathways, namely with peptide hormones derived from Nature—in this case from a mite—that act specifically on a signaling pathway of the human vasopressin 2 receptor (V2R).

Vasopressin-like drugs for example are used in the clinic to treat diabetes insipidus. This condition is characterized by the large amount of dilute urine which is excreted via the kidneys, either because the vasopressin hormone is no longer being produced or the vasopressin receptor in the renal tubules is no longer functional, so that the filtered water cannot be returned to the body. Other applications are, e.g. enuresis or particular forms of hemophilia. "In the future, it might be possible to use synthetically optimized peptide hormones to treat diseases very specifically and eliminate adverse side-effects.", says Gruber.

Exploring evolution & Nature's blueprints

"And all this with the aid of naturally occurring peptides from animal venoms, insect hormones, fungi or plants, which are based on evolution and some of which have evolved over millions of years, to act as defense or messenger substances on similar receptors. This means that we can skip many of the synthesis steps normally required in drug development via combinational chemistry. We are directly using the blueprints of Nature, which

has preselected the drug candidates for us so that we can develop optimized signaling molecules and potential drug candidates," explains Gruber.

Multiple sclerosis: Plant peptide a highly promising medication

This is also the basis for this research group's highly promising research in the battle against Multiple Sclerosis (MS). A few years ago, they were able to show in an animal experiment that, following administration of a special synthetically recreated plant peptide (cyclotide), there was no further development of the usual clinical signs of multiple sclerosis. This discovery offers hope that the disease can be halted at a very early stage or, at the very least, its progression can be greatly retarded.

In the meantime, the Swedish company Cyxone has conducted a successful Phase I trial with the drug candidate T20K. However, further clinical trials will be required before the potential approval of the drug and its availability to patients.

More information: Edin Muratspahi? et al. Nature-Derived Peptides: A Growing Niche for GPCR Ligand Discovery, *Trends in Pharmacological Sciences* (2019). DOI: 10.1016/j.tips.2019.03.004

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