Pharmaconutrition: Modern drug design for functional studies

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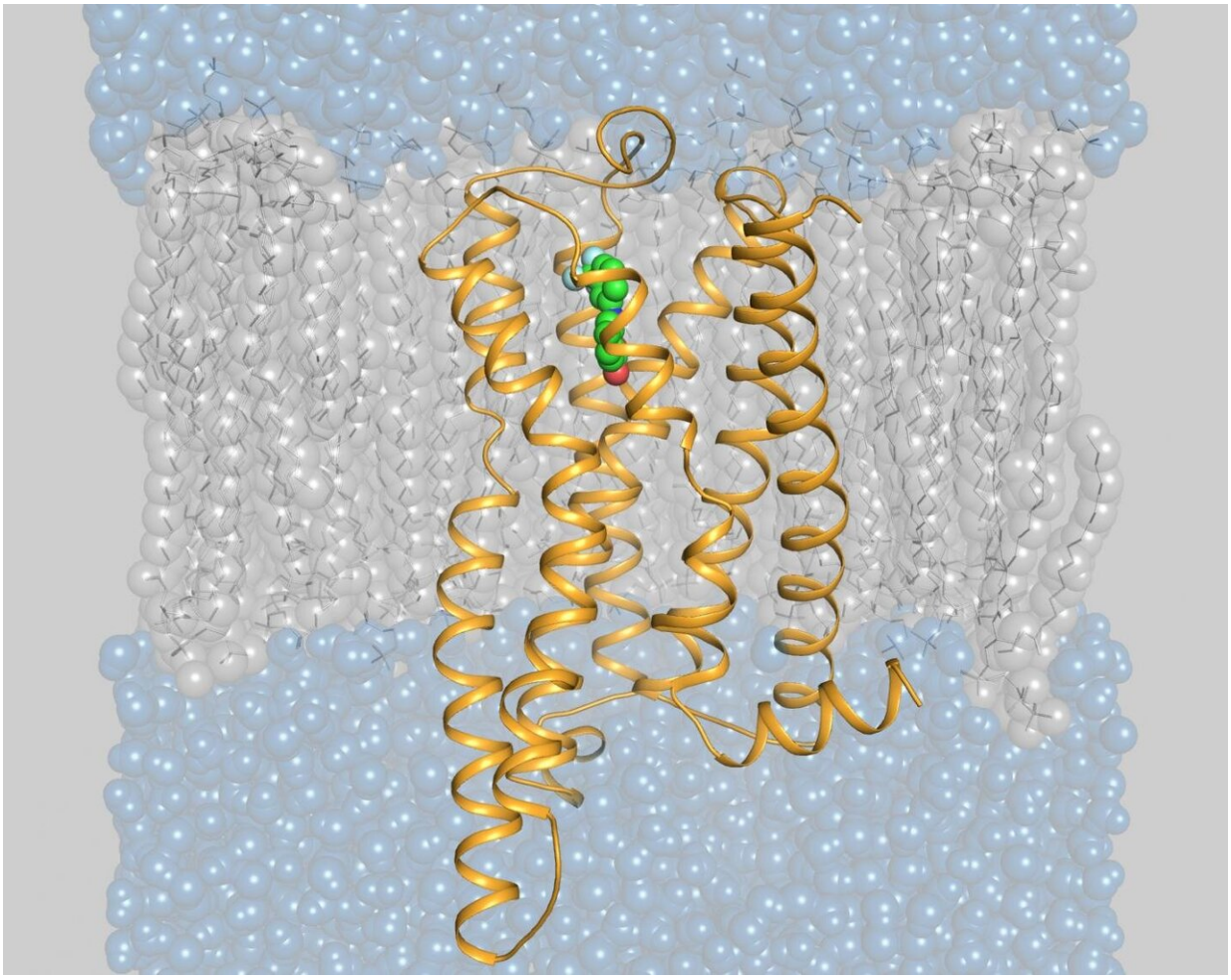

Model of the bitter receptor TAS2R14 with one of its activators (ligands), the flufenamic acid. Credit: Antonella Di Pizio/Leibniz-LSB@TUM

Antonella Di Pizio and Maik Behrens of the Leibniz-Institute for Food Systems Biology at the Technical University of Munich, together with their cooperation partners, have developed highly effective activators for the bitter receptor TAS2R14 in a German-Israeli research project. The new substances are used to investigate the as yet unknown physiological functions of the receptor, for example, in the human immune system.

The team of scientists published their results in the journal *Cellular and Molecular Life Sciences.*

Bitter (taste) receptor with health effect?

It has only been known for approximately 15 years that humans detect bitterness with the aid of 25 different receptor variants. TAS2R14 is one of these. However, unlike most of the other bitter receptors, it detects a broad spectrum of bitter substances. In addition to secondary plant substances, such as caffeine, its activators also include medications. However, the bitter receptor is not just relevant for taste perception. Recent findings indicate that it provides other physiological functions that are important for our health. It is found on lung and testicle cells and plays a role in the innate immune response.

Old drug substance as the basis for modern drug design

In order to specifically investigate the manifold functions of TAS2R14 in different organs and tissues, among other things, highly effective (potent) activators of the receptor are necessary. Using a structure-based computer-aided modeling approach, the German-Israeli team of scientists has now succeeded for the first time in synthesizing three such highly potent substances. The original substance for the drug design was the drug flufenamic acid. The well-known active ingredient is one of the

non-steroidal anti-inflammatory drugs and is contained in muscle and joint salves. It has an anti-inflammatory and analgesic effect, in that it blocks enzymes that promote the release of prostaglandins.

Photo shows Dr. Antonella Di Pizio, lead author. Credit: C. Schranner/Leibniz-LSB@TUM

"We chose this active ingredient as the basis for our investigations because it stimulates the receptor even in the most minute concentrations. This means that approximately eight millionths of a gram of the substance per liter are already sufficient for this purpose," explains bioinformatician and lead author, Antonella Di Pizio. The new derivatives are extremely potent activators, more effective than the

known drug, and in the future they will be used as tools in functional studies.

A new research area "pharmaconutrition" with a systems biology approach

"Due to the many new findings, we no longer regard bitter substances exclusively as pure flavoring components, but also as medically effective nutritional components," says molecular biologist Maik Behrens. "Likewise, today bitter receptors must no longer be viewed as just sensors that warn us of potentially toxic substances before swallowing." To research the correlations between bitter substances, bitter receptors and the human organism a new, far-reaching systems biology approach is required, the biologist continued. The Leibniz Institute is pursuing this approach by combining basic molecular research with the latest methods of bioinformatics and high-throughput technologies.

More information: Antonella Di Pizio et al, Rational design of agonists for bitter taste receptor TAS2R14: from modeling to bench and back, *Cellular and Molecular Life Sciences* (2019). DOI: 10.1007/s00018-019-03194-2

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