Triggering bitter taste receptors could someday treat asthma, COPD

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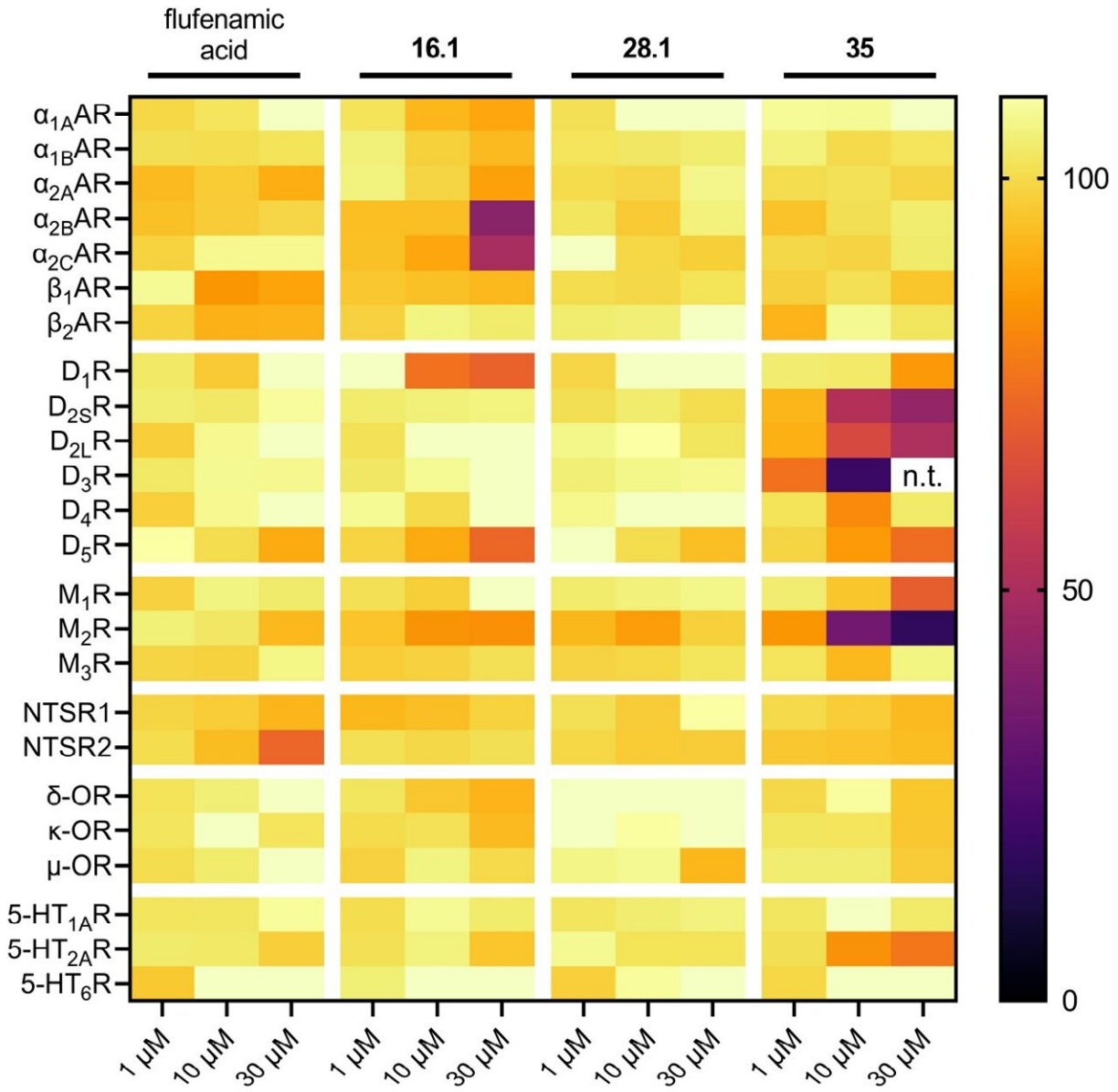

Selectivity of the test ligands was assessed with a panel of 24 class A GPCR by radioligand competition at a ligand concentration of 1, 10 and 30 μM. Color code shows the mean relative amount of the remaining bound radioligand relative to control conditions (buffer, 100% and non-specific binding 0%) out of two independent experiments, each performed in triplicates. n.t.: not tested. Credit: *Journal of Medicinal Chemistry* (2023). DOI: 10.1021/acs.jmedchem.2c01997

Surprisingly, bitter taste receptors are not only located in the mouth, but also elsewhere in the body, including the airways. Activating those receptors opens up lung passageways, so they're a potential target for treating asthma or chronic obstructive pulmonary disease (COPD). Now, researchers report in the *Journal of Medicinal Chemistry* that they have designed a potent and selective compound that could lead the way to such therapies.

Among the 25 different types of bitter taste receptors, the TAS2R14 subtype is one of the most widely distributed in tissues outside the mouth. Scientists are uncertain about the structure of the receptor, and they haven't identified the particular compound or "ligand" in the body that activates it. However, a few synthetic compounds, such as the nonsteroidal anti-inflammatory drug (NSAID) flufenamic acid, are known to bind to and activate TAS2R14s.

But these compounds aren't very potent, and they don't have similar structural features. These difficulties make it challenging to create a better ligand. Nevertheless, Masha Niv, Peter Gmeiner and colleagues used flufenamic acid as a starting point to design and synthesize analogs with improved properties. Next, the team wanted to extend that work to develop a set of even better TAS2R14 ligands.

Building on their earlier findings that certain types of structures

enhanced potency, the researchers made several new variations. They tested these compounds in a cell-based assay that measures receptor activation. This approach revealed that replacing a phenyl ring with a 2-aminopyrimidine and substituting a tetrazole for a carboxylic acid group was a promising strategy.

One of the new ligands was six times more potent than flufenamic acid, meaning less of the compound was needed to produce a similar response as the NSAID. This ligand was also highly selective for TAS2R14 compared to non-bitter taste receptors, which could potentially minimize side effects. The new compounds will help shed light on the structure, mechanism and physiological function of bitter taste receptors and guide development of drug candidates to target them, the researchers say.

More information: Lukas Waterloo et al, Discovery of 2-Aminopyrimidines as Potent Agonists for the Bitter Taste Receptor TAS2R14, *Journal of Medicinal Chemistry* (2023). DOI: 10.1021/acs.jmedchem.2c01997

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