glass–ceramic composite. They showed that these phonons could switch the magnetization of a thin film of gadolinium iron cobalt — a magnetic alloy — that was placed on top of the substrate. The direction of magnetization depended on the handedness of circular polarization of the exciting laser, indicating that the chirality of the phonons was preserved as they made their way through the substrate and into the thin film. Although different in nature, the two investigations both demonstrate that the angular momentum of phonons induced by circular laser pulses is intimately tied to macroscopic magnetization.

Both sets of authors excited chiral phonons in insulating, non-magnetic materials to ensure that any magnetic effects they observed came from the phonons, rather than from direct interactions between light and spin. In simple terms, the materials' magnetization can be thought of as the result of the atoms behaving like tiny electromagnetic coils. Passing an electric current through a coil of wire generates a magnetic field, and this is essentially what happens in these non-magnetic materials, albeit on an atomic scale. The pump pulses excite the materials' ions to rotate, generating a circular current that resembles a miniature electromagnetic coil, which in turn induces magnetization.

The magnetic field can be quantified by a magnetic moment carried by the chiral phonon. Staggeringly, Basini *et al.* estimated the strength of the phonon magnetic moments to be on the scale of one-tenth of the magnetic moment of the electron, which is about 10,000 times larger than that predicted[9], suggesting that more complex physics is at play than was previously thought. This creates an interesting distinction between strontium titanate and magnetic systems such as erbium orthoferrite[10] or cerium trifluoride[11–13], in which chiral phonons create magnetic moments that have strengths spanning various ranges, up to that of the electron. In those cases, the phonon-induced magnetization can be understood in terms of the way that the phonons couple to unpaired electron spins and to partially filled orbitals.

The authors' measurements of the phonon Barnett effect are therefore indicative of intriguing new physics, but they also pose questions and challenges for theoretical predictions and future experiments. For example, the physical mechanisms that are responsible for the connection between phonon angular momentum and magnetization in these non-magnetic materials are yet to be determined. Davies *et al.* showed that the induced magnetic field of chiral phonons can affect magnetic order far away from the point at which the phonons are created, suggesting that there are non-local mechanisms at play, and also that chiral phonon transport needs to be better understood. How the angular momentum propagates through the crystal and how far it travels are therefore issues worthy of investigation.

Theories as to why the induced magnetic fields are larger than predicted have already started to appear[14,15]. These ideas will need to be examined carefully with further spectroscopic experiments, especially those involving electron scattering and X-ray scattering. Such methods are able to track the motion of the atoms directly[16], and will be necessary to fully understand the dynamics of the crystal lattice and the emergent magnetization.

By inducing magnetization in non-magnetic compounds using chiral phonons excited by light, Basini *et al.* and Davies *et al.* have provided a means of generating and controlling magnetic order in a wide range of materials. Their approaches are immediately applicable to simple crystalline materials as well as to heterostructures made from thin layers of different compounds that have been stacked together. Furthermore, the methods could also be extended to molecular systems. The work therefore creates an avenue for 'chiral phonomagnetism' that could lead to fresh approaches to magnetization-based electronics and computing.

Carl P. Romao is in the Department of Materials, Swiss Federal Institute of Technology, CH-8093 Zurich, Switzerland. **Dominik M. Juraschek** is in the School of Physics and Astronomy, Tel Aviv University, Tel Aviv 6997801, Israel.
e-mail: djuraschek@tauex.tau.ac.il

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Structural biology

A bitter taste receptor activated in surprising way

Antonella Di Pizio

The sensing of bitter taste results from the complex interplay of many chemical cues and a range of receptors. It emerges that this complexity might be built-in even at the level of individual receptors. **See p.664**

More than 1,000 bitter-tasting compounds are recognized by a repertoire of 26 membrane proteins called the type-2 taste receptors (TAS2Rs), also known as the bitter taste receptors[1,2]. Our understanding of how such chemically diverse compounds activate these receptors at the molecular level has been hindered by a lack of structural data for the receptors. On page 664, Kim *et al.*[3] report a breakthrough in this field: cryo-electron microscopy structures of the human bitter taste receptor TAS2R14. The structures suggest that different molecules modulate the receptor's function at two distinct regions of the receptor, and that dual binding at these regions leads to complete activation.

TAS2Rs belong to the superfamily of G-protein-coupled receptors (GPCRs). In humans, around 800 GPCRs mediate communication between cells and the extracellular environment. When an agonist molecule binds at the extracellular region of a GPCR, the receptor undergoes dynamic conformational changes that enable it to bind to a G protein inside the cell, thereby initiating downstream signalling. The ligand-binding and activation mechanisms of several GPCRs are emerging from experimentally obtained structures of receptors in their inactive and active states[4], but structures of bitter taste receptors have been limited to just one example[5].

The TAS2R14 protein studied by Kim *et al.* binds to most known TAS2R agonists[6], and is present both in the mouth and in numerous other human tissues[7]. The authors report two structures of the receptor in the agonist-bound active state, in complex with one of two

G-protein variants. In the first, the α subunit of the G protein is gustducin, which is involved in TAS2R signalling in taste-bud cells. The α subunit in the second variant is $G\alpha_{i1}$, which is widely expressed throughout the body.

These structures reveal the presence of two binding sites for ligand molecules. One is on the extracellular part of the receptor; the other is accessible from the inside of the cell (Fig. 1). The extracellular site coincides with the location of the primary (orthosteric) binding site for agonist molecules that has been identified in other GPCRs, whereas the intracellular binding site is allosteric; in other words, it's a separate site, at which the binding of a small molecule can modulate the receptor's activity. In both structures, cholesterol — a molecule found in high concentrations in all human cell membranes — is bound to the orthosteric site, whereas a synthetic compound (cmpd28.1) is accommodated at the allosteric site. A tunnel, shaped by hydrophobic amino-acid residues, connects the two sites.

Further structures of TAS2R14 in complex with different ligands are needed to explore how this tunnel affects the affinity and selectivity of ligand binding to the receptor. However, the reported architecture potentially opens up opportunities for ligand binding along the tunnel, especially once the dynamics of the receptors are considered. Bitter sensory perception results from a complex interplay of chemical cues with a repertoire of receptors. The structures of TAS2R14 indicate that this complexity might be built-in even at the level of individual receptors.

Surprisingly, Kim and colleagues' findings show that cholesterol, which does not taste bitter, affects the function of TAS2R14. A previous study[8] had shown that bile acids — steroid compounds that are structurally similar to cholesterol — are TAS2R14 agonists, hinting at a potential physiological role for steroids at this receptor. The authors carried out experiments showing that cholesterol alone does not completely activate TAS2R14. Moreover, although cmpd28.1 alone can activate the receptor, this activation is stronger when cholesterol is also bound. The observed dual modulation of receptor activity might enhance the ability of TAS2R14 to respond to varying environmental conditions and compound concentrations, supporting its ability to react to diverse molecules.

Cmpd28.1 was synthesized as a structural analogue of flufenamic acid[9], a bitter-tasting compound that binds to TAS2R14. Kim and colleagues report that mutations to the allosteric site that abolish the binding affinity and activation ability of cmpd28.1 do the same for flufenamic acid, suggesting that the latter also binds to the allosteric site. Similar intracellular binding sites have been observed[10] in structures of other GPCRs in complex with biased modulators — compounds that cause receptors to activate specific intracellular signalling pathways. Research targeting the intracellular allosteric site of TAS2R14 might therefore guide efforts to design biased modulators for this receptor.

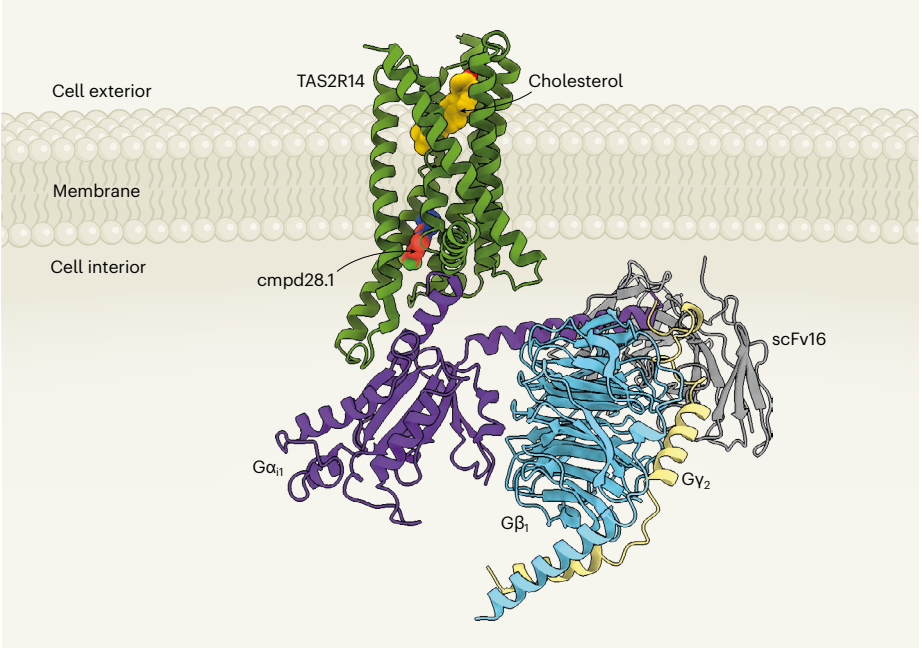

Figure 1 | Structure of a bitter taste receptor. The membrane receptor TAS2R14 is involved in sensing bitter-tasting compounds. When activated by an agonist molecule, it couples to a G protein in the cell, which then triggers cell signalling. Kim *et al.*[3] report two cryo-electron microscopy structures of activated human TAS2R14, one of which is shown here. The protein is shown in complex with a G protein, which consists of three components ($G\alpha_{i1}$, $G\beta_1$ and $G\gamma_2$). The protein scFv16 is included in the complex to stabilize the structure of the G protein. The primary (orthosteric) binding site in the extracellular region of TAS2R14 is occupied by cholesterol, whereas a second (allosteric) binding site in the intracellular part of the receptor is occupied by a synthetic agonist (cmpd28.1). The authors report that binding of both cholesterol and cmpd28.1 is needed for full activation of the receptor.

Currently, the only other TAS2R structure to have been determined[5] is that of TAS2R46. A comparison of the structures of TAS2R14 and TAS2R46 reveals some differences, particularly in the extracellular regions. This suggests that structural features identified in one TAS2R are not necessarily found in other members of the family, supporting the idea that each receptor binds to particular types of molecule. Such differences might also explain why only subsets of TAS2Rs are found in non-mouth (extra-oral) tissues: perhaps, with evolution, TAS2Rs were repurposed for the extra-oral detection of molecules similar to those of bitter-tasting compounds, and therefore only specific subsets of receptors are expressed, as needed for the molecules found in each tissue.

"Surprisingly, cholesterol, which does not taste bitter, affects the function of the TAS2R14 receptor."

Much remains to be uncovered about the ligand-binding mechanisms of TAS2R14 and their functions in various tissues. Kim and colleagues' findings point the way to future advances. For example, using the TAS2R14 structures, researchers can further explore the features that are specific to this receptor and thereby design new ligands — potentially opening up opportunities for developing therapies that target TAS2R14, such as treatments for asthma or chronic obstructive pulmonary disease.

Antonella Di Pizio is at the Leibniz Institute for Food Systems Biology at the Technical University of Munich, 85354 Freising, Germany.
e-mail: a.dipizio.leibniz-lsb@tum.de

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