replenishes the surface liquid (Fig. 1a). An alternative is that the surface liquid comes from a 'liquid-methane' table that fills in the topographic lows of the surface (Fig. 1b). By comparison with the morphologies of terrestrial lakes, the authors suggest that the depressions could be impact craters, volcanic calderas or the sinkholes (dolines) characteristic of karst landscapes. Such landscapes are formed on Earth by the dissolution of carbonate rocks by rainwater.

The fact that lakes are found only at high latitude in Titan's northern hemisphere seems to indicate that they expand during the winter and shrink in the summer as a result of increased evaporation (it is winter in Titan's northern hemisphere at the moment). This cycle is linked to the 29.5 years it takes Saturn to orbit the Sun. On longer timescales, Titan's atmosphere might also be replenished in methane by cryovolcanic activity, as geomorphological features observed by Cassini imply[6].

The Cassini mission is now halfway to the end of its nominal mission, and the detailed morphology of Titan's surface is becoming steadily clearer at each fly-by. Like a giant puzzle, our understanding of Titan's dynamics is coming together as we connect the pieces. There will undoubtedly be other discoveries during the next 22 Titan fly-bys, the next of them due on 13 January. By the end of the planned mission, however, Cassini's radar will have covered only 15% of Titan's surface, and its Visual and Infrared Mapping Spectrometer just a few per cent, at a resolution of less than a kilometre per pixel. An extended mission, currently under discussion, is necessary to gain better coverage of Titan's surface. Cassini's optical and infrared instrumentation could then also be used to monitor the evolution of the northern lakes — currently shrouded in the darkness of the titanian winter — as they enter the Saturn system's summer season next year.

Stofan and colleagues' findings[1] add to the weight of evidence that Titan is a complex world in which the interaction between inner and outer layers is controlled by processes similar to those that must have dominated the evolution of any Earth-like planet. Indeed, as far as we know, there is only one planetary body that displays more dynamism than Titan. Its name is Earth. ■

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NEUROBIOLOGY

Scent secrets of insects

Rachel I. Wilson

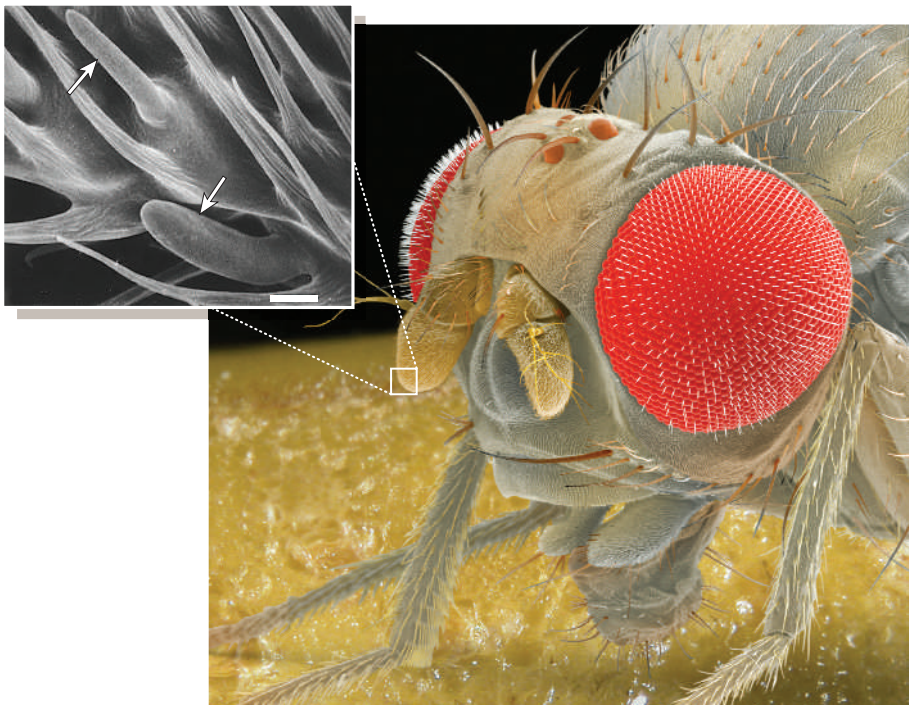
The perception of carbon dioxide provides insects with sensory data on their environment, and informs many insect behaviours. It seems that this sense relies on two dedicated neural receptors.

We inhabit a different sensory universe from that of many of the animals around us. We are deaf to high-pitched sounds that dogs perceive, blind to ultraviolet light that honeybees see, and numb to electric fields that sharks feel. And there is a world of chemicals swirling around us that we cannot smell, but that carry pungent signals for other species.

One such signal is carbon dioxide, which many insects sense through specialized neurons. At very high concentrations, CO_2 can be perceived by the human nose — recall the last time you opened a can of carbonated soda and sniffed before sipping. But many insects are exquisitely sensitive to concentrations we never notice, and monitoring CO_2 levels in the environment is crucial to many insect lifestyles. For example, some ticks can detect CO_2 fluctuations as small as 20 parts per million[1]; for a blood-sucking insect, elevated CO_2 means that a potential host animal might be nearby. Inside a beehive, high CO_2 levels mean that ventilation is needed to improve air quality[2]. But the molecular basis of CO_2 sensing in insects has remained a mystery.

On page 86 of this issue, Jones *et al.*[3] report the identification of two receptor proteins that together are required for CO_2 perception in the fruitfly *Drosophila melanogaster*. This advance contributes to our understanding of the way in which very small volatile molecules such as CO_2 are sensed by cells, and it has the potential to facilitate innovative insect control strategies.

The perception of volatile chemicals begins when molecules in the air interact with receptor proteins on the surface of olfactory neurons. In fruitflies, these neurons reside in two specialized organs, the antennae and the maxillary palps (Fig. 1). Among the approximately 1,200 olfactory neurons in each antenna are 45 CO_2-sensitive neurons. Whereas most other antennal neurons are activated by several different volatile chemicals, CO_2-sensing neurons in fruitflies respond to just this one stimulus[4]. These neurons do not express any of the olfactory receptor genes that are responsible for sensing other odours. Instead, previous work showed that they express a receptor that is similar to taste receptors, so it was classed as a gustatory receptor (GR)[5,6], even though it is evidently unrelated to taste. The gene encoding



J. RIESGO-ESCOVER & J. CARLSON

A. SYRED/SPL

Figure 1 | Sensing carbon dioxide. The fruitfly *Drosophila* has carbon dioxide-sensitive neurons on its antennae (inset, arrows). Inset: scale bar, 0.2 μm; reproduced from ref. 12.

this receptor, *Gr21a*, was shown to be expressed only in CO_2-sensitive neurons[7,8]. This suggested that *Gr21a* might be involved in CO_2 sensation. However, *Gr21a* alone was insufficient to confer sensitivity to CO_2 when it was expressed in other neurons, implying that an essential factor in the process was still missing.

Jones *et al.*[3] reasoned that the missing partner might also be similar to gustatory receptors. They discovered that one such gene, *Gr63a*, is indeed expressed with *Gr21a* in CO_2-sensitive neurons. Moreover, when these two genes were expressed together in another antennal neuron (a conventional olfactory neuron), they conferred robust responses to CO_2 on that cell. However, neither gene alone was sufficient to produce CO_2 sensitivity.

Next, the authors genetically engineered flies that lacked the *Gr63a* gene. In these 'knockout' flies, the neurons that normally respond to CO_2 were completely unresponsive. And whereas fruitflies normally avoid CO_2, the knockout flies were indifferent to this odour. This state of affairs was reversed by adding back a *Gr63a* gene to the knockout flies, demonstrating that loss of this gene was indeed responsible for the sensory deficit.

Together, these results demonstrate that both *Gr21a* and *Gr63a* are required for CO_2 perception in *Drosophila*. The simplest scenario is that the two receptors form a complex that binds to CO_2. It is possible, however, that other molecules are also required. If so, these components must be present in conventional olfactory neurons, because *Gr21a* and *Gr63a* were together sufficient to confer CO_2 sensitivity when expressed in an arbitrary olfactory neuron elsewhere in the antenna.

Another open question is whether this putative receptor complex actually binds to CO_2. In vertebrates, elevation of CO_2 excites neurons that modulate breathing rhythms, increasing respiration and helping to clear CO_2 from the blood. This response is not, however, mediated by a direct action of CO_2. Instead, the neurons involved are activated by changes in pH that are secondary to CO_2 elevation[9]. A similar process might be occurring in the *Drosophila* antenna. If the receptor complex does bind to CO_2 directly, it will be interesting to discover what this binding site looks like. Many cellular responses to gases are mediated by metalloproteins, suggesting that a metal cofactor might have a role in this complex.

Understanding how this receptor complex interacts with CO_2 should also shed light on the unusual response properties of CO_2-sensitive neurons in insects[10,11]. Compared with conventional olfactory neurons, these neurons are unusually insensitive to the velocity of air flow around the antenna. They signal concentration steps independently of background CO_2 levels, and respond to CO_2 increases and decreases in a remarkably symmetric way. Their concentration–response function is also nearly linear at concentrations near the typical ambient level of CO_2. Considered as tiny chemical sensors, these neurons are wonders of natural engineering.

Finally, the discoveries reported by Jones *et al.*[3] have the potential to contribute to disease prevention. The most dangerous animals on Earth are in fact mosquitoes — mosquito-borne diseases cause more than a million deaths annually around the world. And like other blood-sucking insects, mosquitoes use CO_2 to locate their hosts. Jones *et al.* show that the mosquito relatives of *Gr21a* and *Gr63a* are co-expressed in the mosquito maxillary palp, a structure known to be the locus of CO_2 sensation in these insects. If this molecular insight permits the design of novel mosquito deterrents, it could have a major impact on global health. ■

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BIOORGANIC CHEMISTRY

A sweet synthesis

Linda C. Hsieh-Wilson

Peptides and proteins with sugars attached have many desirable biological properties, but their chemical synthesis is a technical challenge. An ingenious take on an old idea might simplify things considerably.

Part of what distinguishes us from bacteria is that the proteins in our bodies are decorated with elaborate arrays of sugars. Protein glycosylation — the attachment of sugars to the amino-acid building-blocks of proteins — plays a crucial role in such diverse processes as protein folding, cell–cell communication and viral invasion of cells. Yet it is conspicuously absent in many simple, unicellular organisms. Understanding the roles of these sugars and how their complex, disparate structures modulate the activities of proteins has been a long-standing challenge. Reporting in the *Journal of the American Chemical Society*[1], Brik and colleagues bring us a step closer to this goal by devising a clever strategy for generating glycopeptides — short sequences of amino acids with sugars attached — that may one day permit the tailored synthesis of glycoproteins.

Glycopeptides and glycoproteins are notoriously difficult to obtain as pure compounds, because they are naturally expressed as inseparable mixtures of different structures (glycoforms) that bear various sugars. This complexity makes it difficult to study how any specific glycoform affects a protein's function, which in turn complicates efforts to generate protein-based medicines. Indeed, most therapeutic glycoproteins are sold as mixtures of glycoforms, the active components of which are often unknown. One approach to solving this problem is to use chemical synthesis to create single structures.

Brik and colleagues[1] have now developed a strategy for assembling glycopeptides using a process known as peptide ligation. In their method, one peptide is attached to another that incorporates a modified sugar. A unique feature of this approach is that the sugar assists the process by positioning the two peptides in close proximity to each other. Traditional glycopeptide synthesis is cumbersome, requiring excesses of reagents to drive reactions to completion, and often producing low yields of the desired products. Furthermore, strategies involving 'protecting groups' have been necessary to mask reactive chemical groups that do not participate directly in the reaction sequence. These requirements increase the complexity and the cost of glycopeptide synthesis. But by actively engaging a sugar in the ligation process, Brik *et al.* demonstrate that a variety of glycopeptides can be made in just a few steps and in high yield, without the need for protecting groups.

The authors' strategy is a clever twist on a well-established method for peptide synthesis known as native chemical ligation[2]. In this process, two peptide fragments are joined together to form a larger fragment via a two-step mechanism. The first step involves the transient formation of a thioester bond between the two fragments (Fig. 1a), mediated by a reactive sulphur atom on one of the fragments. The resulting intermediate then undergoes a rapid, spontaneous rearrangement to form a peptide bond. The net result is the direct connection of two peptide fragments to form a