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CO₂mmon Sense

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Plants and animals sense and respond to carbon dioxide (CO₂), but the means by which they do so have not been well defined. Plants detect and respond to an increase in environmental CO₂-concentration by closing the gas valves in their leaves (thus conserving water), but the CO₂ sensing mechanism has been debated. Fruit flies, mosquitoes, and moths sense CO₂ to find food resources such as decaying fruits, human prey, and flowers, respectively, but as well, the sensing mechanisms are not yet fully characterized. Pressurized CO₂ is used in many food products, such as carbonated beverages, but it is not clear how humans sense the gas, nor what advantage this might serve. It is particularly interesting that two recent studies have unraveled, independently, how organisms as diverse as plants and mammals sense CO₂, and come up with a similar mechanism whose output triggers responses not previously linked to CO₂ detection (1,2).

Chandrashekar *et al.* (1) examined how we experience CO₂ on our tongues—a combined physical and chemical sensation. It turns out that the feel of fizz relies in part on the detection of CO₂ bubbles that stimulate somatosensory receptors on the tongue. CO₂ appears to provoke a taste response for acidity that we associate with carbonation. The authors first determined that CO₂ – induced action potentials occur in nerves that connect to taste receptor cells in the mouse tongue. When they analyzed the electrical activity of these nerves in mice lacking specific taste receptors, they made the surprising observation that the response to CO₂ disappeared only if the sour sensor cells were missing. A survey of genes in the sour sensor cells revealed that a gene encoding a carbonic anhydrase was specifically expressed in these cells. Then they showed that the enzyme is essential for mice to detect CO₂.

Carbonic anhydrase is one of the most efficient enzymes known. It facilitates the interconversion of CO₂ and water to bicarbonate and protons, with a turnover rate of up to 1 million CO₂ molecules per second. Chandrashekar *et al.* suggest that carbonic anhydrase—specifically, α -carbonic anhydrase isoform 4 (CA4)—produces a local increase in protons in response to CO₂. CA4 is anchored at the surface of gustatory cells in the mammalian tongue, where it produces protons that may acidify the immediate extra-cellular environment. The link between sour and CO₂ sensing implicates pH change as a key component of the CO₂ response (see the figure). If this is the case, then carbonic anhydrase is not a sensor in the strict sense, but a transponder that promotes the conversion of CO₂ and water into molecules that indirectly report CO₂. One could argue that the two processes together create the CO₂ sensor, although any other mechanism that leads to a local proton concentration increase (acidification by compounds such as vinegar, for example) should lead to the same response. How the proton increase is detected remains a puzzle.

Alternatively, carbonic anhydrase may have a dual function as both enzyme and sensor (a “senzyme”), as has previously been suggested for hexokinase (3). Hexokinase phosphorylates glucose in the cytosol, but also senses and responds to glucose by entering the nucleus and binding to DNA (promoters) to regulate gene expression. Dual functionality has been found for many transporters, such as the plant transporter Chl1, which senses and

transports nitrate (4). In the case of carbonic anhydrase, a conformational change of the enzyme upon binding of CO₂, as described for β -carbonic anhydrases (5), might be detected by a protein that couples to a signaling pathway. Analysis of mutants that lack enzymatic function but retain the allosteric site may indicate whether carbonic anhydrases work as sensors.

The ability to sense CO₂ gas concentrations is also crucial for plants. Plants use atmospheric CO₂ and the Sun's energy to build their biomass. They are covered with a cuticle that prevents water loss through their surface. Stomata—microscopic pores in the epidermis of leaves—act as controlled valves to take up CO₂ while limiting water loss. Thus, CO₂ is sensed by the plants to adjust the opening of these pores in response to demand. CO₂ even controls the density of stomata; as a compensatory mechanism, their numbers increase if the concentration of CO₂ drops. Similar to animals, a major puzzle has been how plants sense CO₂. Hu *et al.* (2) found that the carbonic anhydrases β CA1 and β CA4 in the model plant *Arabidopsis thaliana* function in CO₂ sensing. Plants lacking the two enzymes were greatly impaired in their response to increases in atmospheric CO₂, showing much less stomatal pore closure. In contrast to the extracellular location of the mouse carbonic anhydrase, the plant enzymes are inside the cell, both adjacent to the cell membrane and inside chloroplasts. Thus, although the enzymatic function of the enzymes—as either transponder or sensor—is conserved, the site of action is very different, implying that the sensing mechanism also may be different. Astonishingly, Hu *et al.* (2) found that expressing a structurally unrelated mammalian α -carbonic anhydrase in *Arabidopsis* plants lacking carbonic anhydrases restored CO₂ responsiveness. This supports the transponder hypothesis, as it is less probable that the downstream signaling machinery in the plant can function with this very different enzyme.

A key element of stomatal closure is the efflux of ions. Hu *et al.* (2) further showed that intracellular bicarbonate released by carbonic anhydrase activates anion channels in guard cells, allowing ions to efflux, thus triggering the closure of stomatal pores (see the figure). Plants overexpressing the β -carbonic anhydrases in guard cells also improved conservation of water, which suggests a possible means to engineer plants that use less water.

Although plants and humans diverged about 1 billion years ago, they use similar mechanisms to detect CO₂ sensing. Two main observations suggest that their common sensing mechanism must have evolved independently. There is a striking difference in the cellular location of the enzymes. Moreover, there are five classes of carbonic anhydrase enzymes that are unrelated in protein sequence and structure; plants and animals express different family members (6).

Why plants evolved this mechanism is obvious—they need to adjust the valves to optimize CO₂ uptake from the atmosphere while minimizing water loss. In humans, one may speculate that this mechanism was retained to help identify rotting food, and now serves mainly to identify carbonated drinks. The observation that carbonic anhydrase is also present in insect gustatory and olfactory cells and may cooperate with ionotropic receptors (ion channels that, when activated by a ligand, open and permit ion flow) may help to identify how insects and mammals use CO₂ sensors to discern food sources (7).

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Figure 1. Transponder or senzyme?

Carbonic anhydrase operates in CO₂ sensing in mammals (α -carbonic anhydrase at the cell surface) and plants (β -carbonic anhydrases in the cytoplasm and chloroplast). In both cases, it is possible that an increase in protons and/or bicarbonate, and/or a decrease CO₂, are detected (two possible mechanisms are shown). As a transponder, the enzyme promotes the conversion of CO₂ and water into bicarbonate and protons, and the ultimate signal that is sensed is either bicarbonate or acidification by protons. Alternatively, as a senzime, the binding of CO₂ to the enzyme may cause a conformational change that is detected by a protein that connects to a signaling cascade.