GAS SENSING

CO_2 speaks for itself

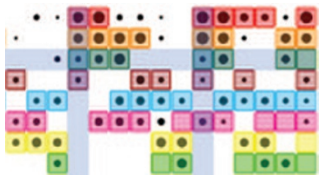
eLife **2**, e01213 (2013)

CO_2 is a common byproduct of basic metabolism and affects cellular pH via its interconversion with bicarbonate. Thus, changes in pH are generally assumed to serve as a cellular proxy for CO_2 concentration. However, recent research on the gap junction proteins connexin 26, 30 and 32 revealed changes in connexon channel opening in response to varying CO_2 concentrations at constant pH. In their efforts to explain this behavior, Meigh *et al*. found that, unlike the previous connexins, connexin 31 was CO_2 insensitive. The authors suspected this could be due to protein carbamylation—modification of an amino acid by CO_2—at a lysine present in the sensitive proteins but not connexin 31. Bioinformatic analysis pointed to Lys125 within a KVREI motif as a possible carbamylation site that could create a salt bridge with a neighboring arginine. The authors confirmed that insertion of this motif into connexin 31 made the resulting mutant protein sensitive to CO_2. Mutation of either Lys125 or the neighboring arginine eliminated CO_2 sensitivity, whereas mutation of either residue to glutamate created a constitutively open channel. A coarse-grained elastic network model further suggested that the salt bridge decreased the population of the closed state substantially. Although the authors did not directly observe the carbamylated species, these results provide exciting evidence for the second case of mammalian carbamylation and the first in which CO_2 regulates cellular signaling. *CG*

OLFACTION

Computational transformation

Neuron, doi:10.1016/j.neuron.2013.08.026



ELSEVIER

Most natural odors are mixtures that can be perceived as wholes (for instance, 'grapefruit') or in categories with degrees of refinement ('citrusy'). Humans can usually distinguish up to three components of a mixture, but insects and rodents frequently do better. Because of odorant mixing, the process of olfaction involves several object recognition problems. These include discrimination and generalization (shared features define a new group). Shen *et al*. used locusts to study how odors are represented and computed by different parts of its olfactory system. The authors tested the responses to various mixtures of two monomolecular odors by 168 antennal lobe projection neurons (PNs) and the responses to mixtures of up to eight diverse monomolecular odors by 174 PNs and 209 mushroom body Kenyon cells (KCs, the direct targets of PNs and the site for associative memory) in 61 animals. Although PNs tended to respond strongly to many of the odors tested, KC responses were much sparser and showed higher odor specificity, with many KCs signaling the presence of single odor components in mixture. The responses of both populations could be decoded over short time windows to perform odor identification, categorization and generalization. The collective results suggest that dense PN odor representations are reformatted by the KCs into sparse ones to better effect discrimination and generalization further downstream. *MB*

NATURAL PRODUCTS

Sweet dreams are made of this

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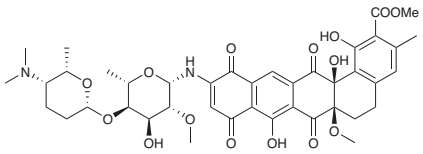

Secondary metabolites are produced by a broad range of microorganisms, and many of these 'natural products' are used clinically as antibiotics or anticancer agents. The discovery and characterization of a therapeutically useful natural product can be challenging, especially if it is glycosylated, as there are >100 different sugars found in microbial glycosylated natural products (GNPs). Most GNPs are inactive if the carbohydrates are missing, so knowing the structures of these sugars and understanding how they are attached to the natural product scaffold can help unravel how the GNP elicits its biological effect. Kersten *et al.* now report a new method—'glycogenomics'—that can be used to identify GNPs and the gene clusters responsible for their biosynthesis. The authors first used tandem MS to generate fragmentation data for 83 microbial monosaccharides; using the resulting glycogenetic code, they were able to link 18 of the 20 GNPs in a 'test set' to the correct biosynthetic gene cluster. The methodology was then used to show that an anthracycline polyketide was produced by a strain of *Streptomyces* that was not previously known to do so and to determine that *Salinispora arenicola* CNB-527, a marine actinobacterium, makes a new arenimycin derivative that can kill multidrug-resistant strains of *Staphylococcus aureus*. This approach should facilitate the rapid identification of other biologically active GNPs and the biosynthetic gene clusters that assemble them. *JMF*

METABOLIC REGULATION

Glucose balancing act

Nature; doi:10.1038/nature12724

Blood glucose levels must be carefully regulated in response to nutritional status, as disruption of this homeostasis can result in hyperglycemia, a hallmark of type II diabetes. Glucose production and utilization are controlled by enzymes such as glucokinase (GK), which phosphorylates glucose and promotes glucose uptake into tissues. Under fasting conditions, GK is sequestered in the nucleus and rendered inactive through direct interactions with glucokinase regulatory protein (GKRP). A rise in blood glucose concentration triggers GK activation by promoting cytoplasmic translocation. Stimulating GK activity in cases of rampant hyperglycemia could therefore relieve the metabolic defects associated with type II diabetes through lowering of blood glucose levels. However, the compounds that have been developed to directly activate GK reduce blood glucose to dangerously low levels, making them unsafe for use. An alternative approach is to target GKRP activity. Lloyd *et al.* identified two small molecules (AMG-1694 and AMG-3969) that disrupt GK-GKRP interactions by binding an allosteric site on GKRP, resulting in redistribution of GK to the cytoplasm to promote cellular glucose uptake. Interestingly, treatment of diabetic rats and mice with either compound could reduce blood glucose levels but had no effect on normoglycemic animals. These compounds represent a new strategy to treat type II diabetes by lowering the amount of blood glucose to a manageable level. *GM*

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