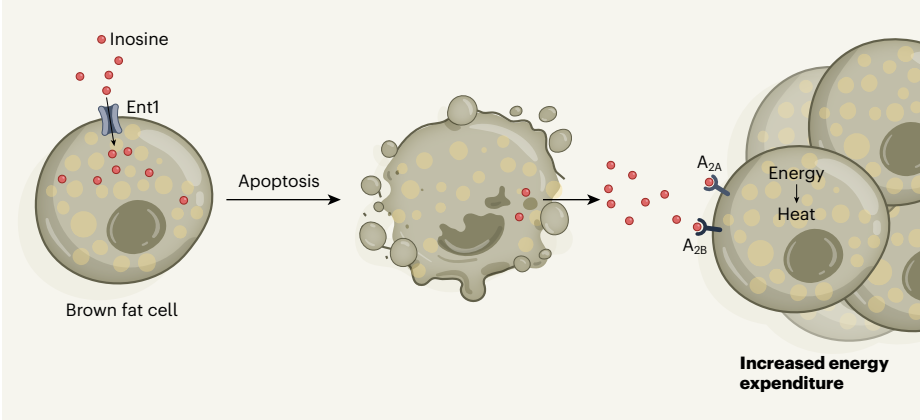

Figure 1 | A regulatory pathway in brown adipose tissue (BAT). Brown fat cells convert energy to heat. Niemann *et al.*[3] provide evidence that this process, known as thermogenesis, is regulated by the molecule inosine. Levels of extracellular inosine are maintained in normal BAT by the protein Ent1, which transports inosine into brown fat cells. But if the cells die through apoptosis — as occurs when they are moved from cold to warm conditions — the inosine is released. It binds to A_{2A} and A_{2B} receptor proteins on neighbouring cells, triggering the formation of new brown fat cells (not shown) and activating thermogenesis, thus increasing energy expenditure.

pandemic, it is essential to discover new strategies to induce weight loss. One potential branch of therapies involves small gut molecules such as GLP1, which drive weight loss mainly by restricting energy intake[5]. But a concern is that this restriction could be compensated for by a reduction in overall energy homeostasis. In this context, the action of molecules that modulate BAT function have gained prominence. Indeed, several molecules have already been shown to control the activity of BAT[6,7]. Now inosine enters the stage.

The fact that the pathway uncovered by Niemann *et al.* has a rapid response time (15 minutes) makes it highly versatile as a drug target. But it also means that the pathway must presumably be tightly regulated, to keep a lid on energy expenditure. The substantial expression of Ent1 that the authors observed indeed suggests that inosine uptake might be crucial to maintaining energy expenditure at normal levels. The pathway could play into a person's basal metabolic rate (the number of calories burnt performing life-sustaining functions), which varies widely between individuals[8]. Perhaps certain mutations in the *ENT1* gene predispose people to have a higher basal energy expenditure. Whether people with the reported Ile216Thr mutation derive their metabolic benefits from an increase in basal metabolic rate is a key question for future studies.

Another question is whether the effects of inosine are exclusively mediated by signalling through A_{2A} and A_{2B}, or partly result from intracellular changes in inosine content caused by Ent1-induced uptake, where inosine could act as a precursor for the synthesis of metabolic compounds[9], rather than as a signalling molecule. Similarly, it should be noted that Ent1 transports other compounds, too. Although Niemann and colleagues' data suggest that inosine is the main regulator of BAT induction, the possibility cannot be excluded that other Ent1 substrates are activators of A_{2A} and A_{2B}.

Inosine might also have immune modulatory effects in BAT that play into the weight-loss pathway. It has been shown to have immunosuppressive properties in several other cell types[10]. Furthermore, Niemann *et al.* found that ultraviolet irradiation triggers the release of inosine from endothelial cells, which line blood vessels in BAT. Inosine might therefore affect the microenvironment of BAT in multiple ways, thereby indirectly influencing tissue function.

Finally, before considering how this pathway could be harnessed to treat obesity, some key concerns should be addressed. First and foremost, BAT activation is driven by the sympathetic nervous system, which also increases heart rate and blood pressure, two factors linked to the risk of cardiovascular disease. In addition, A_{2A} activation in the heart increases the basal heart rate[11]. Furthermore, inosine is a precursor of urate, which has been implicated in the development of gout and rheumatoid arthritis — well-documented co-morbidities of obesity. Mitigating these risks will be essential if inosine-mediated BAT activation is to be used safely to combat obesity.

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Chemistry

Synergistic active sites observed in a solid catalyst

Tiefeng Wang

A solid catalyst has been prepared in which pairs of active sites work synergistically to promote an industrial chemical reaction, and the mechanism has been determined — a breakthrough for 'pair site' catalysis. **See p.287**

More than 80% of globally produced chemicals are made using solid catalysts[1], which are easy to separate from products formed in fluid states — a key practical advantage that lowers manufacturing costs. The improvement in solid catalysts (known in the field as heterogeneous catalysts) is therefore a dominant theme in academic and industrial-chemistry research. However, some important industrial processes still use soluble (homogeneous) catalysts, because the best available heterogeneous catalysts do not promote the formation of the desired products with sufficiently high selectivity for commercial applications[2]. On page 287, Ro *et al.*[3] report a solid catalyst that might change this situation for a widely used industrial process: the reaction of ethylene (CH_2=CH_2) with hydrogen and carbon monoxide to produce propanal (CH_3CH_2CHO), a process known as hydroformylation. More broadly, the findings herald a new era of research into a class of heterogeneous catalysts known as pair-site catalysts, in which different

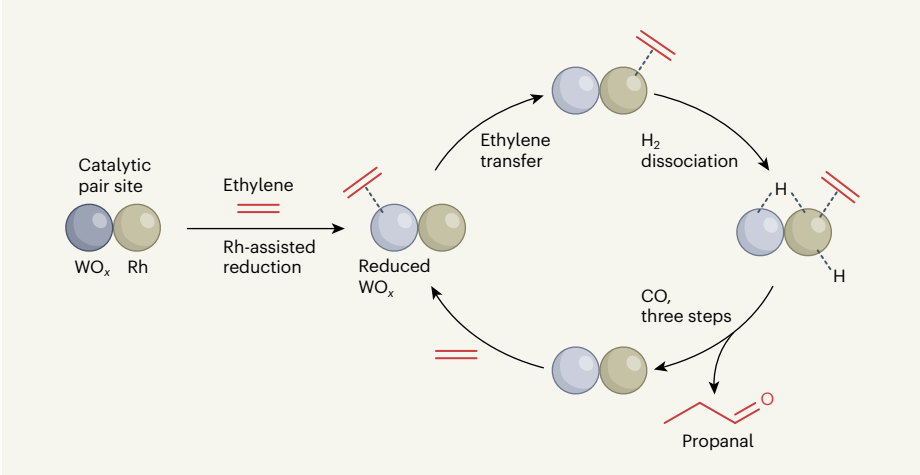

Figure 1 | Catalytic pair sites promote a hydroformylation reaction. Ro *et al.*[3] report a solid catalyst in which well-separated pair sites — which consist of pairs of different catalytic agents — promote the reaction of ethylene with carbon monoxide (CO) and hydrogen. This industrially important 'hydroformylation' reaction is used to manufacture propanal. The active sites in each pair site are a tungsten oxide species (WO_x) and a rhodium (Rh) atom. The process begins with the rhodium-assisted chemical reduction of the WO_x species, which binds to a molecule of ethylene. The ethylene is transferred to rhodium, and then a molecule of hydrogen dissociates into two hydrogen atoms, one of which binds at the Rh–WO_x interface. A molecule of carbon monoxide is then inserted into the ethylene molecule to produce propanal in three steps. A new ethylene molecule binds to the pair site, initiating a fresh catalytic cycle.

active sites work together synergistically.

The authors' work is a crucial step beyond the use of single-atom catalysts[4] (SACs), which have been actively studied in the past decade. SACs consist of individual metal atoms or chemical species (the active sites) dispersed on a non-catalytic solid (the support). Ro and colleagues' catalyst is similar to a SAC but involves two types of active site, which can promote distinct steps in a catalytic cycle and co-localize to form isolated pairs known as pair sites. Each pair site is thus bifunctional — its two active centres work cooperatively to catalyse different steps of a reaction[5].

Bifunctional active sites in supported catalysts can be made in other ways — for example, at the interfaces formed when a metal oxide is deposited on a metal nanoparticle[6], or by controlling the loading and positioning of metal nanoparticles in a composite catalyst formed from the nanoparticles, alumina (an aluminium oxide) and a zeolite (an acidic porous material)[7]. However, it is often hard to elucidate the reaction mechanisms. This is partly because the potential structures of the active sites are not well defined, and also because the active sites can undergo structural changes during reactions.

Ro *et al.* show that it is possible to overcome these limitations by making pair sites. The authors focused on heterogeneous catalysts for ethylene hydroformylation, in which the active agents are rhodium (Rh) atoms and tungsten oxide species (WO_x) deposited on a support of alumina. Different versions of the catalyst were made by varying the loading of WO_x on the support, keeping the rhodium loading at 0.23–0.29% by weight (wt%). The resulting materials were then characterized using spectroscopy and microscopy techniques.

The authors found that the catalyst structure depends on the WO_x loading. At a loading of 0.7 wt%, WO_x exists as isolated species; at a loading of 2 wt%, two-dimensional oligomers (clusters of small numbers of WO_x species) also form; and 3D WO_x structures form at loadings greater than 8 wt%. Crucially, the authors' characterization showed that atomically dispersed Rh–WO_x pair sites are produced at 0.7 wt% WO_x. The various catalyst structures each exhibited a different catalytic performance for ethylene hydroformylation. The Rh–WO_x pair sites were the best — they promoted a much higher reaction rate and product selectivity than did the catalysts with 2D oligomers and 3D structures, as a result of the rhodium and WO_x active sites working together synergistically.

Because the structure of these pair sites is well defined and relatively simple, Ro *et al.* were able to deduce the catalytic mechanism by correlating experimental kinetics data with computational modelling. The mechanism involves a series of steps: rhodium assists the chemical reduction of WO_x, which binds to a molecule of ethylene; the ethylene is transferred to the rhodium atom; and a hydrogen molecule (H_2) dissociates into two hydrogen atoms at the interface between the rhodium and WO_x (Fig. 1). This sequence of events primes the pair site to enable the insertion of a carbon monoxide molecule into the bound ethylene, leading to propanal formation.

The authors show that changes of pair-site coordination (chemical bonding to the metal atoms in the pair site) during the catalytic cycle are crucial for the synergy between rhodium and WO_x. The bifunctional behaviour of the catalyst also depends on the geometry of the Rh–WO_x interface, the energetics of reconfiguring pair-site coordination during the reaction, and the ability to transfer molecules between the active centres in the pair site.

Ro and colleagues' work has several broad implications. First, it shows that pair sites consisting of metals and metal oxides can enable bifunctional catalytic mechanisms that provide high reaction rates and product selectivity. Second, it demonstrates that it is possible to prepare pair sites that have well-defined structures, which can then be used as model systems to clarify bifunctional catalytic mechanisms. To put the value of this into perspective, our understanding of the mechanisms of heterogeneous catalysts advanced considerably when SACs that had well-defined structures were developed; the advent of model pair-site catalysts can be expected to provide similar breakthroughs. Third, Ro and co-workers' strategy of developing a controllable synthesis of Rh–WO_x pair sites, characterizing the catalyst at the atomic level and working out the bifunctional mechanism provides a template for future catalyst design.

Nevertheless, it will be challenging to develop a general approach for the synthesis of pair-site catalysts formed from metals and metal oxides. Maintaining long-term stability is even more demanding than it is for SACs or for conventional supported catalysts, because the structure of the pair site needs to be maintained during reactions.

In terms of applications, one issue with the Rh–WO_x pair-site catalyst is that its activity is still much lower than that of the best homogeneous hydroformylation catalysts. Moreover, when reactants other than ethylene are used, a mixture of linear and branched isomers of the products will form. It is therefore crucial to know whether the pair-site catalyst provides as high a ratio of linear-to-branched products as the homogeneous catalysts do. These issues should be addressed in future work. In the meantime, Ro and colleagues' groundbreaking design of a pair-site catalyst opens up fresh avenues of investigation into synergism in heterogeneous catalysis.

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