DONALD B. SHEPPARD

Figure 1 | Protective imitation. Many species of harmless snake, such as the false coral snake, *Erythrolamprus aesculapii* (left), have evolved the red–black-banded (RBB) colour pattern of highly venomous coral snakes, such as the Brazilian coral snake, *Micrurus brasiliensis* (right). Davis Rabosky *et al.*[3] show that this RBB pattern has evolved in multiple lineages of non-venomous snakes, but only after each lineage and coral snakes were present together in the New World, supporting the long-standing Batesian-mimicry hypothesis[2].

snakes occurred only after that particular lineage and coral snakes were present together in the New World. Thus, in every case, the warning signal arose first in the model, then in the mimic, which is a key prediction of Batesian-mimicry theory. These data should therefore lay to rest any doubts about whether coral-snake mimicry does occur.

The authors' work also shows that coral-snake diversity strongly predicts (and substantially increases) the number of mimic species in a given geographical area. Indeed, their data suggest that the 'mimicry excess' problem is even greater than has been historically assumed, with up to six times more mimetic than model species present in a given locality, and many more than would be expected if RBB snakes were distributed randomly across the New World. These data are at odds with the long-standing theoretical expectation that Batesian mimics should be rarer than their toxic models. However, this expectation might not apply with a highly toxic model, such as the coral snake. When the model is highly toxic, the fitness costs of mistakenly attacking it would probably be so severe that predators would be under strong selection to avoid such a model (and any lookalikes), even if the model is rare[8].

Another advance that stems from this work is the authors' proposal that mimicry might not represent an evolutionary end point. In particular, their data suggest that not only have evolutionary transitions between cryptic (non-mimetic) patterns and RBB (mimetic) patterns occurred frequently in non-venomous snakes, but so also have transitions between mimetic patterns and cryptic patterns. Most of these losses of mimicry occurred in the tropics, where coral snakes are continuously distributed, suggesting that these losses occurred even among species that live in the same area as coral snakes. This is an intriguing conclusion. Generally, mimicry has been viewed as a one-way street; it is not clear why a species should ever lose mimicry once it has evolved it, particularly if their model is still around.

This suggestion will no doubt motivate further studies to determine how transitions between mimicry and cryptic patterning occur. Evolutionary biologists have long debated whether Batesian mimicry could evolve through a gradual process of incremental evolution[9], and many of these arguments should apply equally to its loss. In particular, it is unclear how a population could transition from an ancestral cryptic colour pattern to a derived mimetic one (or vice versa) if the population must pass through a phase in which it expresses a colour pattern that is intermediate between these two extremes. Such an intermediate colour pattern would be expected to be disfavoured, because it should fail to receive the fitness benefits of either cryptic patterning or mimicry.

Batesian mimicry has been called[9] "the greatest post-Darwinian application of Natural Selection". Davis Rabosky and colleagues' study has settled some questions regarding the specific example of coral-snake mimicry, and it opens the door to answering several others. ■

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This article was published online on 25 May 2016.

PHYSIOLOGY

Microbial signals to the brain control weight

The bacteria that inhabit the rodent gut promote insulin secretion and food intake by activating the parasympathetic nervous system — a hitherto unknown mode of action for this multifaceted microbiota. SEE ARTICLE P.213

MIRKO TRAJKOVSKI & CLAES B. WOLLHEIM

We live in symbiosis with trillions of bacteria that populate our intestines, known collectively as the gut microbiota. These microbes influence many physiological processes in our bodies, from gut and immune maintenance to neurological regulation[1]. On page 213 of this issue, Perry *et al.*[2] highlight a previously unknown role for the gut microbiota in stimulating insulin secretion by signalling to the brain. Moreover, the authors report that these microbes influence appetite, providing a hint as to how the microbiota might provoke obesity.

Mammals have evolved several responses to energy scarcity. As a result of these adaptations, obesity can arise in conditions of

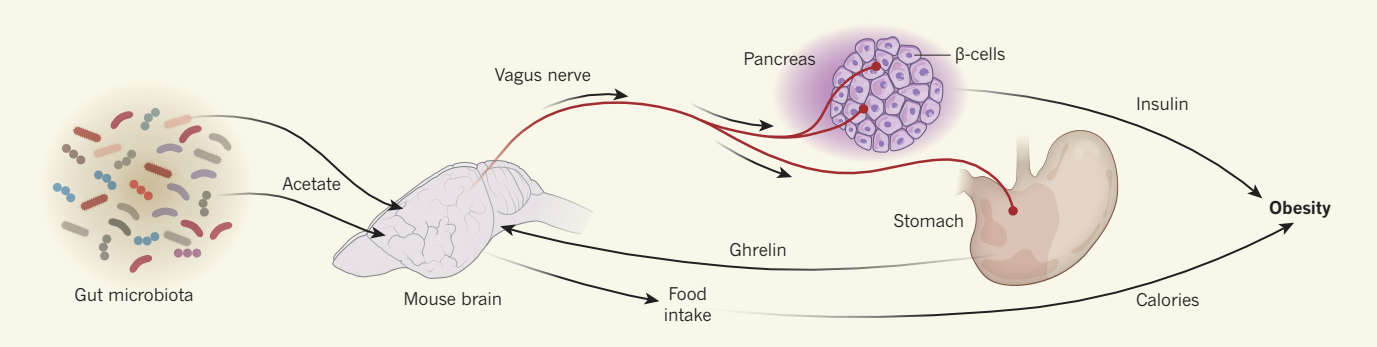

Figure 1 | A mechanism for microbiota-mediated weight gain. Perry *et al.*[2] report that, in rodents, production of acetate molecules from dietary nutrients by the bacteria that colonize the gut (the microbiota) increases the brain's stimulation of the parasympathetic nervous system, which includes the vagus nerve. Signals from the vagus nerve trigger secretion of the 'hunger hormone' ghrelin from the stomach, leading to increased food intake. The vagus nerve also potentiates glucose-stimulated insulin secretion from β-cells in the pancreas, promoting calorie storage and fat gain. In this way, the gut microbiota influences obesity.

constant food abundance. This response is mediated by the hormone insulin, which is secreted from pancreatic β-cells in response to increased blood-glucose levels. Insulin tightly controls energy balance by enhancing cellular lipid synthesis and glucose uptake, causing calorie storage.

Investigating the effects of a high-fat diet, Perry and colleagues found that production and turnover of the short-chain fatty acid (SCFA) acetate was markedly increased in rats on a high-fat diet compared with animals fed a normal diet. Moreover, infusing the stomachs of rats on a normal diet with acetate for ten days increased glucose-stimulated insulin secretion (GSIS).

Although glucose is the main stimulus for insulin secretion, the process is also under the control of the parasympathetic nervous system[3] — the part of the central nervous system that stimulates 'rest-and-digest' and 'feed-and-breed' processes. Parasympathetic activity is largely mediated by the vagus nerve, which sends motor inputs to many organs and is responsible for slowing heart rate, and for regulating gastrointestinal movement and the digestion of food, in addition to enhancing insulin secretion[4]. Perry *et al.* demonstrated that the ability of acetate infusion to increase GSIS could be blocked by administering the parasympathetic blocker molecules atropine or methylatropine, or by surgically severing one or more of the branches of the vagus nerve that connects to the gut. These results indicate that an acetate-induced increase in GSIS is controlled by the parasympathetic nervous system.

Further supporting the role of the parasympathetic nervous system in acetate-mediated GSIS, the authors demonstrated that acetate could not stimulate insulin secretion from isolated β-cell-containing pancreatic islets *in vitro*. This is consistent with some, but not all, previous investigations into a direct effect of acetate on β-cells (for a review, see ref. 5). Acetate administration into either the brain's ventricular system or a vertical column of grey matter embedded in the brainstem — both of which feed into the parasympathetic nervous system — increased GSIS, again highlighting the central-nervous effects of acetate.

Next, Perry *et al.* investigated the effects of increased acetate turnover on appetite. A chronic increase in acetate turnover promoted a constant drive to eat, known as hyperphagia, probably mediated by the 'hunger hormone' ghrelin — levels of which were elevated in the hyperphagic rats compared with controls. The hyperphagic rats developed obesity, probably owing to a combination of increased secretion of ghrelin and insulin.

Because SCFAs are products of bacterial fermentation, Perry and co-workers investigated the role of the gut microbiota in acetate turnover. The gut microbiota co-develops with the host and modulates whole-body metabolism by affecting energy balance[6–9]. The authors transplanted faecal matter from donor rats on a normal or high-fat diet into recipients on the opposing diet, and found that the acetate-turnover rate, faecal acetate levels and GSIS levels from the donor group were transferred to the recipients, implying that it is changes in the microbiota that regulate these factors. Furthermore, conditions of microbiota depletion (seen in germ-free mice, which lack a microbiota, or in rats treated with antibiotics) completely suppressed acetate turnover and decreased ghrelin levels compared to control mice — changes that were associated with two- and fivefold lower skeletal-muscle fat content, respectively.

These data suggest a mechanistic link between the onset of obesity and the gut microbiota. The microbiota-mediated increase in acetate turnover that occurs during exposure to a high-calorie diet might mediate a feedback loop between the gut microbiota and parasympathetic nervous system, promoting hyperphagia owing to increased ghrelin secretion, and increased energy storage as fat owing to increased GSIS (Fig. 1). However, this mechanism does not explain the observation[10] that microbiota-depleted mice do not show suppressed food intake. It is also intriguing that supplementation of the diets of rats with two other SCFAs, butyrate and propionate, improves host physiology and glucose metabolism, which in the case of propionate seems to be mediated by vagus-nerve stimulation by the peripheral nervous system[11]. This might indicate that the site of stimulation — central or peripheral — is relevant for SCFA-mediated effects in the parasympathetic nervous system, and points to the need for further exploration of the general role of SCFAs in regulating obesity.

For instance, follow-up work could address whether the effects in the brain are mediated by the SCFA receptor proteins FFA2 and FFA3, and clarify the controversy[5] regarding the direct effects of acetate on the β-cells. In addition, transplantation of the microbiota from rodents on a high-fat diet or from humans who are obese to germ-free rodents fed a normal diet could allow researchers to further test for a causal link between specific obesity-associated changes brought on by microbiotic acetate production and the development of metabolic syndrome (which involves obesity, insulin resistance, abnormal lipid levels in the blood and glucose intolerance). Analysis of how the genomes of the microbiota collectively change in rodents on a high-fat diet would allow researchers to identify acetate-producing microbes and to investigate their importance in the progression of diet-induced obesity.

Clinical trials[3] have shown that vagus-nerve blockade by electrodes can help to reduce body weight and improve blood-glucose control in people with obesity. Moreover, specific antimicrobials and phage therapies[12], as well as faecal or bacterial transfers, have attracted renewed interest in the past few years as potential tools to treat antibiotic-resistant enteritis (inflammation of the intestine) and ulcerative colitis[13] (long-term inflammation of the colon and rectum). In the context of the increased global prevalence of obesity, Perry and colleagues' study might inform the development of such strategies for suppressing acetate or acetate-producing microbes as a means to treat obesity and diabetes. ■

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CHEMISTRY

No turning back for motorized molecules

Two molecular motors have been developed that use chemical energy to drive rotational motion in a single direction. The findings bring the prospect of devices powered by such motors a tantalizing step closer. SEE LETTER P.235

JONATHAN CLAYDEN

The conversion of chemical energy to mechanical motion drives movement in all living things, from bacteria to whales. An intricate array of molecular ratchets and motors allows cells to extract mechanical work from chemical reactions, for example to drive muscle contraction, or to twist the helical appendages that propel some bacteria. Two papers, one by Collins *et al.*[1] in *Nature Chemistry* and another by Wilson *et al.*[2] on page 235, report the design and construction of artificial molecular motors that achieve the same outcome using much simpler, purely synthetic structures. Both pieces of work show that chemical reagents can drive the unidirectional motion of one part of a molecule (the rotor) relative to another (the stator), and thus provide direct functional analogues of biological motors.

It is not easy to design a synthetic molecular motor[3]. As was pointed out nearly 20 years ago[4,5], molecular motors are characterized by movement that must be more than random Brownian motion. Furthermore, angular momentum cannot be used to maintain a constant directionality on the molecular scale as it can in everyday electric motors. The thermodynamic landscape of a molecular system must be repeatedly altered to force concerted movement in a single direction, to prevent mere shuttling forwards and backwards between two states. The greatest successes in the field so far have used light energy to drive a molecular system away from equilibrium, followed by a directionally defined relaxation process; motors capable of megahertz rotational speeds have been designed and built using this approach[6].

The two new motors both use chemical energy to drive rotation. Collins and colleagues' motor is remarkably simple in conception. The rotor and stator are each a benzene ring, connected by a single bond that forms a rotatable axle. Systems of this sort can rotate freely about the axle, but rotation in the authors' motor is partly restricted by groups or atoms attached next to the bond that connects the two benzene rings.

Collins *et al.* added alternating sets of reagents to a solution containing their motor, which allowed first one side of the rotor ring and then the other to slip past a sulfur-containing group (a sulfoxide; Fig. 1) bonded to the stator. The alternating reagents insert a palladium atom into a carbon–hydrogen (C–H) bond on one side of the rotor, and then into a carbon–bromine (C–Br) bond on the other. Palladium's affinity for the sulfur atom of the sulfoxide (SOR) group lets it form a bridge between the rings that lowers the energy barrier to rotation, allowing the rings to slip past one another. On its own, shuttling the metal between the C–H and C–Br bonds would simply cause random rotation clockwise or anticlockwise, but the chirality (handedness) of the sulfoxide group imparts directionality to the slippage mechanism, and so also to the rotation of the motor.

The alternating C–H and C–Br insertions needed to drive this process require palladium to be in the +2 and 0 oxidation states, respectively. This means that, in its current form, the motor cannot work autonomously, because different reaction conditions are needed to

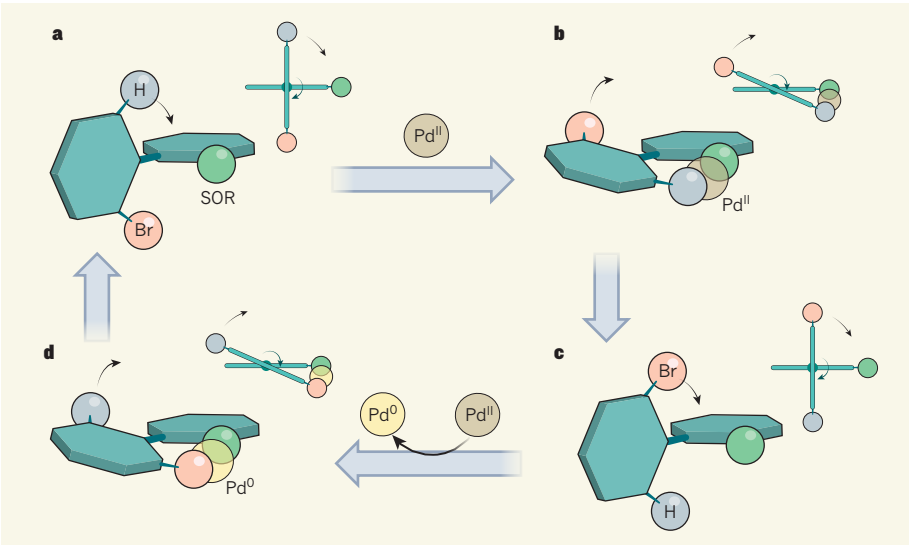

Figure 1 | A unidirectional molecular motor incorporating a rotating axle. Collins *et al.*[1] report a system consisting of two benzene rings (green hexagons) connected by a single bond. One ring acts as a rotor, and has a hydrogen atom on one side and a bromine atom on the other. The other ring is a stator and has a sulfoxide group on one side and a fluorine atom on the other (fluorine atom not shown because it is not involved in the motor mechanism). The connecting bond acts as an axle. The rings are also viewed here from above, along the axis of the axle (top right in each panel). **a**, The system's rotation cycle begins with the rotor and stator perpendicular to each other. **b**, Addition of a palladium(II) reagent allows the side of the rotor carrying the hydrogen atom to pass the sulfoxide. A palladium atom bridges the two rings. **c**, The rings then relax to the alternative perpendicular arrangement. **d**, Conversion of palladium(II) to palladium(0) allows the side of the rotor carrying the bromine atom to pass the sulfoxide group, and a palladium atom again bridges the rings. The cycle continues if reagents are added to toggle the palladium between the two oxidation states. Br, bromine; SOR, sulfoxide (where R is a benzene-ring-containing group); Pd, palladium.