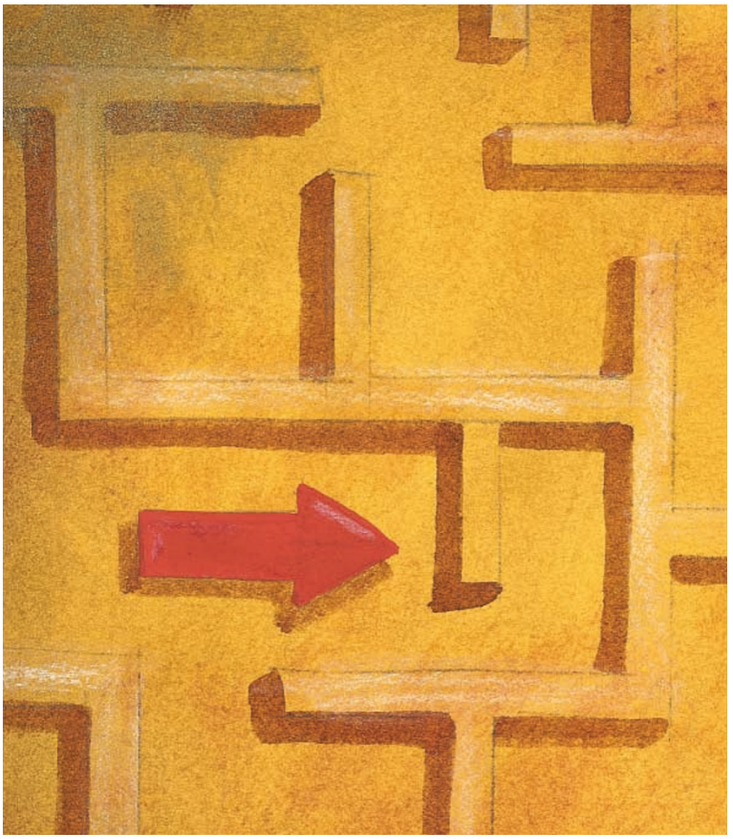

OBESITY

Dead end for NPY Y_5-receptor antagonists?

Neuropeptide Y (NPY) is thought to have a key role in stimulating feeding, and its receptors are thus viewed as attractive appetite-suppressant drug targets for treating obesity. Of the known NPY receptors, previous investigations have implicated the Y_5 and Y_1 receptors as the most probable candidates for mediating the effects of NPY on food intake, and these receptors have both been the focus of considerable drug discovery efforts. But by assessing the effects of a highly selective and potent Y_5-receptor antagonist in rats, Turnbull *et al.* have now provided strong evidence that the Y_5 receptor is not a significant regulator of feeding behaviour.

The small-molecule Y_5-receptor antagonist NPY5RA-972 is at least 1,000-fold selective for the Y_5 receptor in a commercially available panel of 129 binding assays (which included assays for NPY receptors and a wide range of other neuropeptide receptors), and has good penetration into the central nervous system. Although NPY5RA-972 inhibited the marked and dose-dependent increase in food intake induced by a selective Y_5-receptor agonist, it had no significant effect on the increase in food intake induced by NPY or by 24 hours fasting in normal or genetically obese rats. And chronic administration of NPY5RA-972 had no effect on food intake or body weight in normal rats or rats that were obese owing to their diet.

So, why are these data in such contrast to previous evidence supporting the Y_5 receptor as a promising anti-obesity target? In part, it seems that some compounds used in previous studies might have activities

ANTIBIOTIC RESISTANCE

Confronting *S. aureus* muscle

Understanding how bacterial resistance to antibiotics arises is the first step towards battling against these microorgansims. Certain strains of *Staphylococcus aureus* can survive even in the presence of powerful β-lactam antibiotics, such as penicillin and methicillin. Resistance comes from the presence of the bacterial enzyme penicillin-binding protein 2a (PBP2a), which is vital for the maintenance of bacterial cell walls. In the November issue of *Nature Structural Biology*, Lim and Strynadka report the crystal structures of one form of PBP2a, bound to several β-lactam antibiotics. Their results reveal the structural basis for the β-lactam resistance of *S. aureus*, and will be useful for designing new effective therapeutics.

β-lactam resistance in *S. aureus* first appeared with the introduction of penicillin in the 1940s, owing to the production of penicillinases. The introduction of methicillin, a semi-synthetic penicillin derivative that is resistant to digestion by penicillinases, was soon followed by the appearance of methicillin-resistant *S. aureus* strains. Penicillin and methicillin are substrate analogues of PBPs that catalyse the formation of peptide crosslinks (transpeptidation) between bacterial-cell-wall glycan chains. Covalent inhibition of PBPs by β-lactams results in a weakened bacterial cell wall, followed by lysis and death. Methicillin resistance is due to the expression of the *mecA* gene, which encodes the β-lactam-resistant PBP2a. Because of its low affinity for β-lactam, PBP2a sustains cell-wall synthesis at normally lethal antibiotic concentrations.

A soluble derivative of *S. aureus* PBP2a (SauPBP2a*) was used for structure determination. Structure-based alignments of the SauPBP2a* transpeptidase domain reveal low sequence identities and significant structural deviation from similar domains in several other bacteria. Interaction of a β-lactam inhibitor with PBP requires the formation of an acyl-PBP intermediate. Structures of SauPBP2a* reveal a distorted active site that impedes acylation by requiring energetically unfavourable conformational changes to occur for acylation. Because acylation is a key step in inhibition by all β-lactams, the reduced acylation rate of SauPBP2a* confers broad-spectrum resistance against methicillin and all other clinically relevant β-lactam antibiotics. However, as acylation is also essential for transpeptidation, the authors propose that the SauPBP2a* active site effectively balances the retention of transpeptidase activity by conserving key catalytic residues, with reduction of β-lactam affinity by distortion of the active site. An important aspect for the design of new PBP2a inhibitors will be to improve binding affinity by increasing the number of non-covalent interactions between inhibitor and active site.

Melanie Brazil

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in addition to Y_5-receptor antagonism that could be responsible for their effects on feeding behaviour. This conclusion is supported by the observation that such compounds inhibit feeding behaviour in mice that lack the Y_5 receptor, emphasizing the value of receptor knockout mice in defining the mode of action of drugs. Indeed, there is good evidence from studies in Y_1-receptor-deficient mice that the Y_1 receptor has a key role in NPY-induced feeding, and it seems likely that this is where efforts to target the activity of NPY will now be most concentrated. And in general, the study by Turnbull and colleagues serves as a warning that the effects of selective receptor activation might not necessarily be a good predictor of the importance of that receptor in more natural circumstances.

Peter Kirkpatrick

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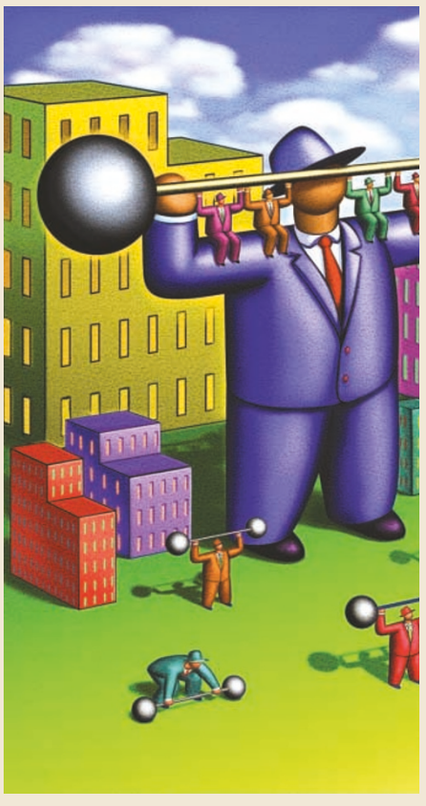

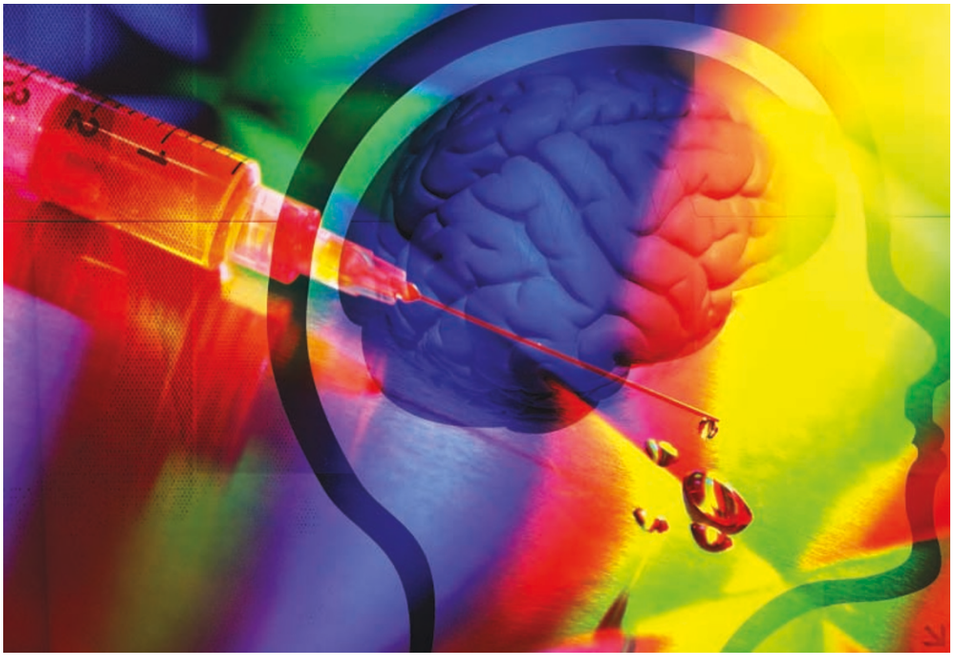

ALZHEIMER'S DISEASE

Vaccine revisited

Earlier this year, Elan Pharmaceuticals and Wyeth-Ayerst were forced to halt Phase II studies on their vaccine for Alzheimer's disease (called AN1792) after the discovery that 15 patients (out of 360) had developed severe brain inflammation. This was a huge blow, as the vaccine — a fragment of the β-amyloid precursor protein (APP) called $A\beta_{42}$ that targets the β-amyloid plaques that are a hallmark of the disease — had shown highly promising results in preclinical models and Phase I trials.

But two studies in *Nature Medicine* now reveal that there could still be hope for this strategy. Nitsch and colleagues report that they could detect a positive antibody response in patients who took part in the ill-fated trial. And McLaurin and colleagues show how refining the epitope could eliminate the harmful side effects.

In the first study, the researchers carried out immunohistochemical examinations from a subset of 30 patients who had taken part in the trial — 24 of whom received the vaccine plus booster, whereas the other 6 received placebo.

Nitsch and colleagues found that antibodies in the sera from most patients in the vaccine group recognized β-amyloid plaques, diffuse β-amyloid deposits and vascular β-amyloid in brain blood vessels from transgenic models bred to develop pronounced Alzheimer's-like β-amyloid deposits. Importantly, the antibodies did not cross-react with APP, which is found in the nerve cells of both healthy subjects and Alzheimer's sufferers. In other words, the vaccine selectively induced the desired immune response against disease-associated forms of β-amyloid — whether this mechanism can prevent cognitive decline will be the focus of future studies.

The second study assessed whether the beneficial effects of the vaccine could be separated from the inflammatory side effects. Mass spectrometry showed that the therapeutic antibodies that were raised against $A\beta_{42}$ recognized an epitope defined by residues 4 to 10 (termed $A\beta_{4-10}$). Incubating serum that contained antibodies raised against $A\beta_{42}$ with PC-12 cells showed that these antibodies could inhibit both the generation of fibrils (the long, thread-like aggregates of misfolded proteins that are associated with the formation of amyloid plaques) and cytotoxicity.

McLaurin and colleagues next investigated the immune response to $A\beta_{4-10}$. The immune system responds to antigens in two ways: it produces either T-helper type 1 (T_H1) cells, which stimulate a T-cell-based pro-inflammatory response (the response that many speculate was the cause of the side effects), or T_H2 cells, which stimulate a B-cell (antibody) response. They found that T_H2 cytokines were produced but there was no T-cell response.

Although these results will need to be tested in other models, they raise the possibility that a more refined vaccine, based on $A\beta_{4-10}$, could be effective and safe in humans. And, intriguingly, knowing the antibody–antigen interaction involved could also open the door to generating small-molecule drugs that mimic the effects of the vaccine.

Simon Frantz

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