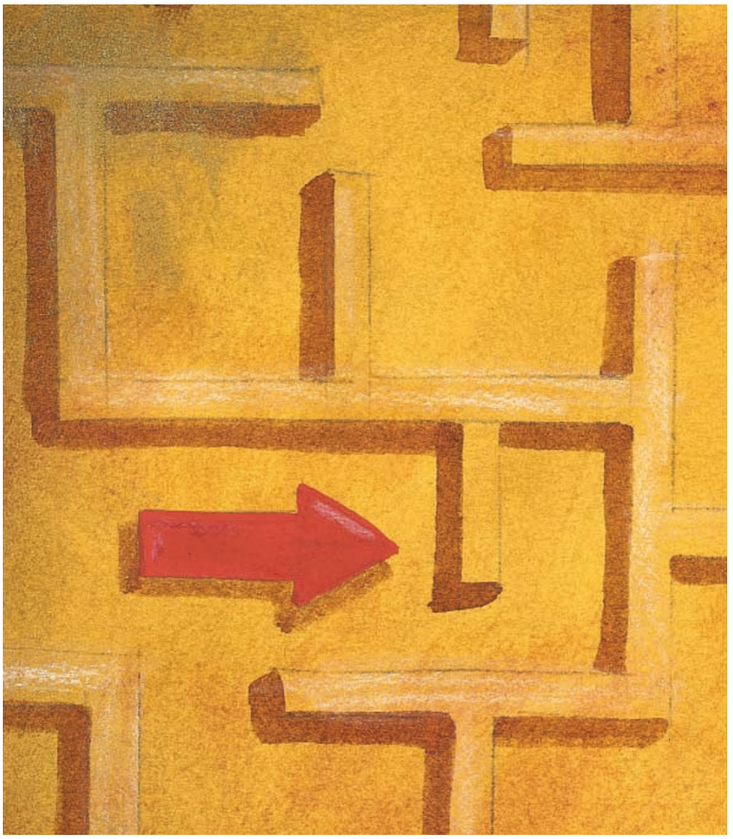

OBESITY

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.

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References and links

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WEB SITE

Strynadka's laboratory: http://byron.biochem.ubc.ca