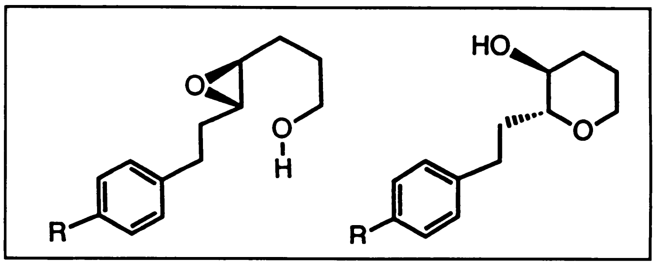
Antibody Spurs Disfavored Reaction

Baldwin said it shouldn't happen.

According to the catalog of predicted outcomes for ring-forming chemical reactions, also known as "Baldwin's rules," a molecule like trans epoxy-alcohol should not often bend into a contorted chemical creature tipped by a six-atom ring. That requires a lot of strain on the molecule's atomic scaffolding. In the "favored" reaction, such a molecule forms a five-atom ring.

But scientists at the Scripps Research Institute in La Jolla, Calif., performed the disfavored chemical maneuver anyway — with the help of a new catalytic antibody. These custom-made molecules, resembling those normally found in animals' immune systems, act like enzymes and other catalysts, throttling up the rate at which a chemical reaction occurs.

Chemists have created a new catalytic antibody that spurs the transformation of a trans epoxy-alcohol molecule (left) into an unlikely chemical creature sporting a six-atom ring (right).



Antibodies prowl the body on the lookout for bacteria and other unwanted foreign substances, or antigens. When they meet, the antibody binds to the antigen, marking it for destruction. Inspired by the immune system's creative power, chemists have found ways to harness nature's machinery — in this case, the immune systems of mice — to manufacture antibodies with a predetermined structure and electrical charge for use as catalysts in chemical reactions.

Since 1986, when scientists first created catalytic antibodies, chemists have pursued ways of using the binding properties of these laboratory-made immune-system molecules to perform diverse chemical tasks, including DNA repair and manufacturing pharmaceuticals with fewer side effects (SN: 9/2/89, p.152).

In the new research, described in the Jan. 22 SCIENCE, Scripps scientists Kim D. Janda, Charles G. Shevlin, and Richard A. Lerner announce a novel catalytic antibody that speeds the conversion of trans epoxy-alcohol molecules into tetrahydropyrans, chemical building blocks that form important, naturally occurring organic molecules. Brevetoxins, for example, the deadly by-products of a massive algae bloom popularly known as "red tide," contain tetrahydropyrans, Janda notes.

This is the first catalytic antibody shown to work in a disfavored reaction, Janda emphasizes. And at the moment, it occupies a unique niche in organic chemistry's catalytic bestiary. "There's no [other] enzyme or synthetic catalyst known that can do this," Janda notes.

Chemists can synthesize the disfavored molecules in a laborious, seven-step process. But if simply mixed with the necessary reagents, says Janda, trans epoxy-alcohol almost always forms the favored five-atom rings.

The importance of this new catalytic antibody extends beyond its novel ability to spur a disfavored chemical reaction, says organic chemist Samuel Danishefsky of Yale University. The new report, he says, suggests that chemists might, in time, design functionally unique catalytic antibodies rather than ones that simply mimic the properties of known enzymes and synthetic catalysts.

"They have created now a major challenge for themselves," Danishefsky says of the Scripps researchers. "If they meet that challenge with any degree of consistency, then it will become very important."

— D. Pendick

Fats may influence insulin sensitivity

Physicians typically recommend that patients with Type II (non-insulin-dependent) diabetes eat foods low in fat, especially saturated fat. These guidelines aim primarily at preventing obesity — a condition that can aggravate diabetes — and heart disease, which frequently accompanies the metabolic disorder. A new Australian study now indicates a more direct reason for encouraging diabetics to limit saturated fats: They may foster a diabetic's resistance to insulin.

Together with animal data, these new findings hold out the prospect of one day altering "insulin action by changing the fatty-acid composition of the diet," says Leonard H. Storlien at the University of Sydney, who led the study.

People with Type II diabetes often possess plenty of insulin, a hormone that helps transport glucose (blood sugar) into cells. However, because these diabetics develop resistance to insulin, glucose and insulin may build to unhealthy concentrations in blood, eventually promoting potentially life-threatening damage. This insulin resistance, a hallmark of Type II disease, is also common in obesity and can precede the onset of diabetes by a decade or more.

Storlien and his co-workers biopsied skeletal muscle from 20 men and seven women between the ages of 50 and 65; all were nondiabetic and undergoing coronary-bypass surgery. The researchers correlated fatty acids in the cell membranes with each patient's sensitivity to insulin. In general, they report in the Jan. 28 NEW ENGLAND JOURNAL OF MEDICINE, the more saturated fatty acids present, the more resistant a patient proved to insulin.

The Sydney team also biopsied skeletal muscle from 13 healthy men, each about 30 years old, and tested their sensitivity to insulin. Again, "we found exactly the same relationship," Storlien says: The more long-chained polyunsaturated fats in muscle-cell membranes, the more responsive these individuals were to insulin.

In earlier work with rats, Storlien says, his group found that diets rich in long-chained omega-3 polyunsaturated fatty acids — from fish oils — were the most effective in overcoming "very profound whole-body insulin resistance."

Animal and cell-culture studies show that increasing the polyunsaturated fatty acids in cell membranes not only increases the amount of insulin bound by a given tissue or cell, but also insulin's action, notes Mark Yorek of the Veterans Administration Medical Center in Iowa City, Iowa. "And this study would support that [this also occurs] in humans." However, he cautions, fishy fats are not a panacea; studies show diabetics on diets high in fish oils can experience trouble regulating glucose levels.

Indeed, the Sydney researchers point out, the fatty-acid profile of muscle-cell membranes may be due as much to some internal defect as to diet. They noted, for instance, that the reduced activity of one enzyme — a delta-5 desaturase — "was directly related to estimates of insulin resistance in this study." This suggests, they say, that some enzyme-related defect might impair insulin action by reducing levels of long-chain polyunsaturated fatty acids in cell membranes.

— J. Raloff

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