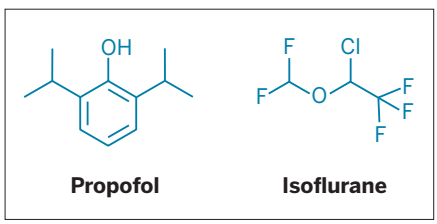
VANADIUM-B-12 BIOCONJUGATES LOWER BLOOD GLUCOSE

Nicola E. Brasch and Derek S. Damron of Kent State University and colleagues report the synthesis of the first vanadium-vitamin B-12 bioconjugates (*Chem. Commun.*, DOI: 10.1039/b806598e). These complexes could lead to novel orally active therapeutics for lowering high blood glucose levels associated with diabetes, the researchers suggest. Diabetics who must take insulin to regulate carbohydrate and lipid metabolism are often reluctant to inject the protein hormone several times per day, and even when they take their injections, they may still experience swings in blood sugar levels. Researchers are therefore trying to develop alternative oral treatments to work around these problems. Over the past decade, vanadium salts have shown promise in lab studies, but toxicity due to their poor absorption in the body became evident during clinical trials with type 1 and type 2 diabetics. Brasch's team reasoned that attaching a vanadium complex to a common vitamin should improve absorption by taking advantage of the body's vitamin uptake mechanisms. With this approach other B-12 conjugates have been successfully developed for medical uses, including chemotherapy and imaging. The researchers combined sodium metavanadate with a derivative of vitamin B-12 to make a mixture of mono and bis conjugates. The mixture was more effective at reducing glucose levels in diabetic rats than sodium metavanadate alone, they found.

WHY ANESTHETICS SOMETIMES CAUSE PAIN

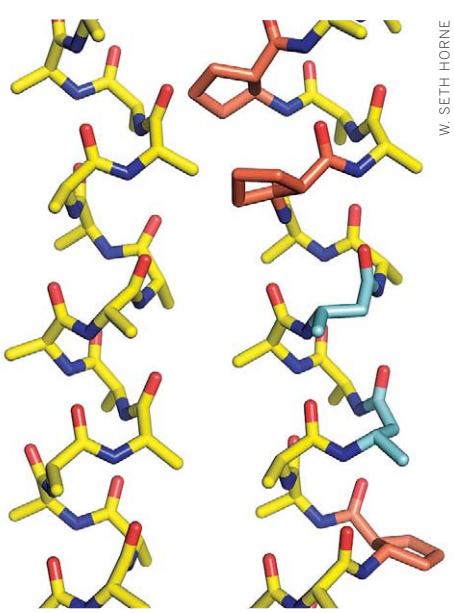
General anesthetics are welcomed for their ability to banish pain during surgery, but some of these drugs increase postsurgical pain and inflammation. Pharmacologist Gerard P. Ahern of Georgetown University and colleagues believe they have found a possible explanation (*Proc. Natl. Acad. Sci. USA* **2008,** *105,* 8784). Using cell cultures and mouse studies, the researchers discovered that certain anesthetics activate the TRPA1 receptor on nerve cells. This ion channel protein, which also responds to irritants found in hot peppers and mustard, plays a key role in the biochemical pathways for pain and inflammation. The researchers showed that intravenous anesthetics such as propofol and inhaled anesthetics such as isoflurane activate and sensitize nerve cells. This activation can lead to nerve-mediated inflammation. Although some general anesthetics don't activate the TRPA1 receptor, they might not be as effective as the irritating anesthetics, Ahern says. "This tells us that there is room for improvement in these drugs," he adds. "We hope these findings are ultimately helpful in providing more comfort to patients."



Propofol **Isoflurane**

PEPTIDE BACKBONE'S FOLDING ROLE

Modifying elements of a peptide's backbone yields nonnatural peptides that reproduce the three-dimensional structure of the original amino acid sequence, a strategy that could help in designing protein mimics (*Proc. Natl. Acad. Sci. USA*, DOI: 10.1073/pnas.0801135105). Researchers have long studied how the side chains of amino acids affect peptide folding, but little is understood about the influence of a peptide's backbone. To gain new insight on the backbone's role, Samuel H. Gellman and coworkers at the University of Wisconsin, Madison, substituted selected α-amino acid residues in a very stable four-helix protein with β-amino acid counterparts without changing the side-chain sequence. Despite the extra atoms introduced into the backbone with the β-residues, several substitution patterns closely approximated the original protein's helical structure, as determined by X-ray crystallography. The best replicas contained cyclic β-residues to make certain segments of the backbone more rigid. "Gellman and coworkers have taken another important step in the development of an expanded set of building blocks to engineer proteins," says William F. DeGrado, a protein design expert at the University of Pennsylvania.



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Nonnatural peptide with a backbone containing cyclic β-amino acids (right) mimics an α-helix (left).

ACCELERATED ELECTRON TRANSFER OBSERVED IN MODEL PROTEIN

In biological systems, electron flow often occurs very quickly between distant redox centers in electron-transfer proteins. Researchers have proposed that charge transfer in such proteins is accelerated by redox-active amino acid residues that act as donors or acceptors to relay electrons between the redox centers. But experimental evidence for this proposal has been indirect and inconclusive. A collaborative team based at Cornell University, California Institute of Technology, and the University of London has now obtained the best direct experimental evidence for the proposal so far by assessing the influence of an intervening tryptophan residue on the rate of electron transfer between redox centers in a semisynthetic model protein (*Science* **2008,** *320,* 1760). The team found that electron transfer between distant redox centers in an azurin protein mutant occurs about 300 times faster when the tryptophan residue is present than when it is absent. Researchers believe such expedited electron transfers can potentially be exploited in the design of new energy-yielding devices, among other applications.