Insulin—a hormone critical for the control of blood glucose—is first synthesized as a longer prohormone. During its maturation, a peptide, C–peptide, is cleaved from the protein, but has been thought to be biologically inert. Defying the rule that peptide hormones act only by binding to stereospecific receptors, Ido et al. (1) report on page 563 of this issue that C–peptide not only produces biological effects, but does so by an unusual mechanism that depends on structural features of the C–peptide related to its sequence but independent of its direction or chirality. These effects include a restoration toward normal of the diabetes–induced decrease in cellular sodium–potassium adenosine triphosphatase (ATPase) activity and impaired nerve conduction, and reductions in the diabetes–induced increase in vascular permeability and blood flow, changes that are concomitants of the hyperglycemia associated with diabetes. These beneficial effects are seen after prolonged treatment of diabetic rats with pharmacological doses of C–peptide, as well as in specially designed skin chambers in which granulation tissue can be exposed to various agents while blood flow is maintained to supply nutrients and endogenous hormones. Normalization of these parameters, argue the authors, could prevent or slow the progression of some of the complications of this chronic and often debilitating disorder.

The C–peptide seems to accomplish these effects without reducing hyperglycemia. It has no insulin–like action and so acts without changing any of the usual metabolic parameters that are deranged in diabetes. In addition to hyperglycemia and hyperlipidemia, these include elevation of sorbitol in tissues, a consequence of hyperglycemia that can lead to cataracts and degenerative changes. C–peptide administration also does not prevent the increased nonenzymatic glycation of proteins, which has also been implicated in retinal, nerve, kidney, and general vascular degenerative processes in diabetes. [In support of these results, in diabetic humans (2) C–peptide shows beneficial effects on microcirculation, vascular permeability, and sodium–potassium ATPase, but in contrast it also improves glucose utilization and glycemia.]

What is even more remarkable about this action of C–peptide is that it seems not to follow the usual rules of ligand and receptor chemistry. Its action does not require the normal chirality of the peptide, a property that may be attributable to the glycine–rich central portion. A C–peptide made up of D–amino acids is equally active, as is a peptide synthesized with amino acids in the reversed order, carboxyl terminal to amino terminal. The central glycine–rich region is largely achiral, is extremely flexible, and is well conserved in most, but not all, of the mammalian C–peptides. Both the rat and the human peptides are active in their systems, whereas the porcine (and possibly also bovine) peptides, which have deletions in the central region, appear to be inactive or less active. It should be noted that
complications in type II diabetes, in which insulin and C-peptide secretion are significantly retained, do not differ from those of insulin-dependent diabetes, characterized by absent C-peptide (endogenous and exogenous).

How can these new observations be explained? The authors suggest that C-peptides may function like some antibiotic peptides, which assemble into bacterial membranes to form pores or channels that disrupt normal ion flow and membrane integrity and thereby inhibit cellular function. The C-peptides, however, differ significantly in their structure from these antibiotic peptides. It seems unlikely that they could form membrane channels, especially since the C-peptides show no tendency to self-associate and are rather polar (negatively charged).

The C-peptide serves several functions as part of the precursor of insulin. Its main function is to bring the A and B chains together into a single molecule so that the process of folding and interchain disulfide bond formation necessary for generating mature insulin can be accomplished as an intramolecular event. However, simply linking the B and A chains together in series, without a C-peptide spacer, also will accomplish this goal and produce a normally folded miniproinsulin. Although such molecules can be transported and stored, they are biologically inactive because the carboxyl-terminal part of the B chain, by virtue of its covalent linkage to the amino-terminal glycine of the A chain, is not free to move to assume the appropriate conformation necessary for productive interaction with insulin receptors. The C-peptide overcomes this problem by providing a spacer sequence that can be removed by proteolytic processing. Evolutionary studies suggest that a length of approximately 30 amino acids is ideal for the dual role of promoting the folding of proinsulin and then permitting its efficient processing. Modeling studies on proinsulin indicate that a C-peptide of this length provides sufficient flexibility in the dibasic cleavage sites at either end of the connecting segment for their appropriate interaction with the prohormone convertases, PC2 (SPC2) and PC1/PC3 (SPC3), which carry out this conversion in the maturing secretory vesicles (see the figure). Once this goal is accomplished, the excised C-peptide is stored with insulin in the mature granules and secreted along with it into the bloodstream (3).

Is it indeed possible, then, that in the course of evolution these “shavings from the carpenter’s bench,” derived from the formation of the indispensable insulin molecule, have taken on a life of their own, one which might independently complement the role of insulin by affecting specific cellular processes? The C-peptide might also exert effects that are not within the repertoire of insulin itself. Although at present there is no known paradigm for a molecule to function in such a manner, it is conceivable that C-peptide can interact either with membranes or with some proteins within membranes in a transient manner to modify their functional properties. Receptors for the C-peptide have not yet been isolated, and its relatively slow metabolism suggests that it diffuses freely into the extracellular space, but is not associated with cell membranes (4). Alternatively, the glycine-rich central domain might function as a scavenger, binding noxious agents, ions, or metabolic by-products. An interesting analogy might be the recent discovery that certain polyamides can hydrogen bond to specific DNA sequences to modify gene expression in cells (5). These tantalizing possibilities certainly deserve further study, especially with the objective of improving the therapy of diabetes by a judicious (and more physiological?) combination of C-peptide and insulin—possibly closer to “nature’s own way.”

**HyperNotes Related Resources on the World Wide Web**

- [The Dictionary of Cell Biology](http://www.sciencemag.org/content/277/5325/531.long) (London, Academic Press, 1995) defines some of the terms used in this article.
- [Online Mendelian Inheritance in Man (OMIM)](http://www.sciencemag.org/content/277/5325/531.long) includes basic information on insulin and diabetes
mellitus in several chapters. For example, *Insulin* provides basic information on insulin and its allelic variants. Links to MEDLINE records are included.

*The American Peptide Society* provides a list of links to *Protein and Peptide Related Sites*. The list includes a link to *A Compendium of Information on Individual Amino Acids*, which provides molecular formulas, structures, and physical data for the common amino acids.

*Introduction to Endocrine Physiology* by Peggy Neville provides a brief introduction to hormones including insulin.

*The National Institute of Diabetes and Digestive and Kidney Diseases* provides a general description of diabetes and a *Diabetes Dictionary*.

*The MIT Biology Hypertextbook*, developed by the Experimental Study Group at the Massachusetts Institute of Technology, provides background information on the biology of cells. *Receptors* describes the action of ligands and receptors. *Central Dogma* describes the process of translation and the biosynthesis of peptides.

The *ExPASy World Wide Web (WWW)* molecular biology server of the Geneva University Hospital and the University of Geneva is dedicated to the analysis of protein and nucleic acid sequences. It provides access to SWISS-PROT, the annotated protein sequence database; PROSITE, the dictionary of protein sites and patterns; SWISS-3DIMAGE, a database of three-dimensional images of proteins and other biological macromolecules; and other databases.

*The World Wide Web Virtual Library: Biosciences* points to virtual library pages for *Biochemistry* and *Molecular Biology*, and other topics related to this article. Each of these pages presents a long list of Web resources.

*The World Wide Web Virtual Library: Biosciences: Medicine* is a list of Web resources in medicine, including endocrinology.

*CSUBIOWEB*, the California State University Biological Sciences Web server, provides links to other Web sites on genetics, cell biology, and molecular biology.

1. Donald F. Steiner's *Web page* describes his research.
2. *Insulin Biosynthesis and its Hormonal Functions* by Ying-Yin Cheng describes the functions of insulin and provides illustrations of C-peptide and the A and B chains.
5. *Organic Chemistry Online* by Paul R. Young includes a section on *Chirality*, providing a basic description of molecular handedness.
6. *Hyperlipidemia* is one of the many topics covered by the *American Heart Association*.
7. Howard Hughes Medical Institute, the *University of Chicago*

References

4. K. S. Polonsky, N. M. O'Meara, *ibid*. 1354–1372. [Google Scholar](http://www.sciencemag.org/content/277/5325/531.long)
5. J. M. Gottesfeld *et al.*, *Nature* 387, 202 (1997). [CrossRef](http://www.sciencemag.org/content/277/5325/531.long) [Medline](http://www.sciencemag.org/content/277/5325/531.long) [Web of Science](http://www.sciencemag.org/content/277/5325/531.long) [Google Scholar](http://www.sciencemag.org/content/277/5325/531.long)

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