photorefractive effect has been used extensively as a medium for studying nonlinear dynamical phenomena such as the breakup of solitary waves and pattern formation. Photorefractives are popular for image processing devices, such as the novelty filter, which is an optical system that displays changes in a visual scene arising from motion or some other dynamical cause. Other photorefractive-based image processing systems have been used to find edges or to otherwise spatially filter an image. Photorefractive-based systems have furthermore been used to optically implement neural network models for pattern classification and recognition of both spatial and temporal information.

Like their complex electronic circuit counterparts, complex photorefractive optical circuits often require several crystals, yet a single cube of photorefractive crystal measuring 5 mm on a side typically costs a few thousand dollars. Needless to say, a low-cost alternative can make a substantial impact on both applications and research in the field. Those of us who work with inorganic crystals appreciate the flexibility that organic synthesis provides as well: Crystal properties are mostly fixed by nature and modified only in a coarse way by the addition of dopants. Furthermore, the crystal growth process is long and tedious compared with the combine-and-stir approach of polymer chemistry. With their high-gain medium, Grunnet-Jepsen *et al.* demonstrated some of the core building blocks of photorefractive systems. Their research, along with the work of others on photorefractive polymers, suggests that organic synthesis may be a viable approach to manufacturing general purpose photorefractive materials.

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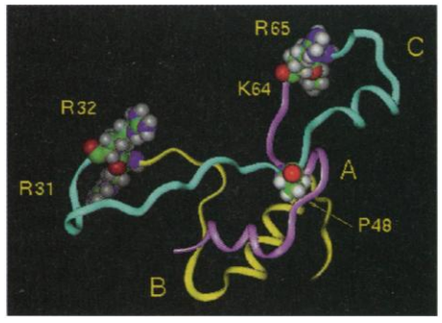
BIOMEDICINE

Proinsulin C-Peptide–Biological Activity?

Donald F. Steiner and Arthur H. Rubenstein

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.



Human proinsulin with its C-peptide. Insulin A chain (purple), B chain (yellow), and C-peptide (blue). The CA and BC junctions, the dibasic processing sites (R31-R32 and K64-R65), are shown suitably poised for interaction with the prohormone convertases (*3*). Pro^{48} (P48) corresponds to Pro^{16} [in figure 6 of (*1*)]. [Model by G. Lipkind, with Biosyn Technologies Software]

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).

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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."

An enhanced version of this Perspective with links to additional resources is available for *Science* Online subscribers at http://www.sciencemag.org/

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ISOTOPE GEOCHEMISTRY

Nuclide Production by Cosmic Rays During the Last Ice Age

Edouard Bard

The last 2 years have been exceptional for our understanding of past variations in the natural production of isotopes by cosmic rays. These cosmogenic nuclides have a wide range of applications in Earth sciences as tracers and geochronometers. Although ^{14}C is the best known of these isotopes, accelerator mass spectrometry has made it possible to use other cosmonuclides such as ^{10}Be, ^{26}Al, ^{41}Ca (*1*), and ^{36}Cl, as illustrated by Plummer *et al.* (*2*) on page 538 of this issue.

For most applications, it is extremely important to quantify the flux variations of cosmonuclides through time, especially in the time range for which the radiocarbon method is applicable (that is, the last 40,000 years). This widely used dating method requires that the initial $^{14}C/^{12}C$ ratio of a sample be known in order to calculate an accurate calendar age. The problem is thus to evaluate past variations in the atmospheric $^{14}C/^{12}C$ ratio, which is sensitive to previous production changes and, to a lesser degree, rearrangements within the global carbon cycle.

A similar fundamental problem arises with the use of ^{36}Cl, ^{10}Be, and ^{26}Al to calculate so-called surface exposure ages—which are now crucial for dating moraines, land surfaces, and faults—and quantify erosion rates (*3*). For better accuracy, the past flux variations of cosmic rays should be taken into account, to quantify the in situ isotopic buildup.

Several methods have been devised for reconstructing past fluctuations of the atmospheric $^{14}C/^{12}C$ ratio by comparing ^{14}C measurements with true ages measured in the same samples by an independent dating technique. For the Holocene period (the last 10,000 years), it has been possible to find abundant fossil pines and oaks and thus produce a high-resolution atmospheric $^{14}C/^{12}C$ curve by comparing ^{14}C levels and tree ring counts on the same tree logs (*4*). Other types of archives are currently used to continue the calibration effort: annually laminated sediments (*5*) and shallow corals from tropical islands, which can be cross-dated by high-precision ^{14}C and ^{230}Th mass spectrometry back to 40,000 years (*6*).

Altogether, these different calibration methods led to the reconstruction of significant variations of the atmospheric $^{14}C/^{12}C$ ratio through time (bottom panel of figure). These data indicate that the atmospheric $^{14}C/^{12}C$ ratio was about 400 to 500 per mil higher 20,000 to 30,000 years ago and that it essentially decreased during the period from 18,000 to 3000 years ago. High-resolution studies based on ^{14}C in tree rings (*4*) have shown that there are some high-frequency peaks that lasted on the order of a few centuries superimposed on the long decreasing trend.

Besides its fundamental use for radiocarbon dating, the atmospheric $^{14}C/^{12}C$ curve provides information on a variety of geophysical, geochemical, and astronomical phenomena. Changes of the atmospheric $^{14}C/^{12}C$ result mainly from the modulation of the flux of cosmic rays by magnetic fields in the vicinity of Earth. For example, most of the high-frequency excursions observed during the Holocene are the result of century-scale fluctuations in solar magnetic activity (*4*), similar to the Maunder Minimum period

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