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/

References

1. Y. Ido *et al.*, *Science* **277**, 563 (1997).
2. J. Wahren, B.-L. Johansson, H. Wahlbert-Henriksson, *Diabetologia* **37** (suppl. 2), 99 (1994).
3. D. F. Steiner, G. I. Bell, H. S. Tager, in *Endocrinology*, L. DeGroot, Ed. (Saunders, Philadelphia, PA, 1995), pp. 1296–1328.
4. K. S. Polonsky and N. M. O'Meara, *ibid.*, pp. 1354–1372.
5. J. M. Gottesfeld *et al.*, *Nature* **387**, 202 (1997).

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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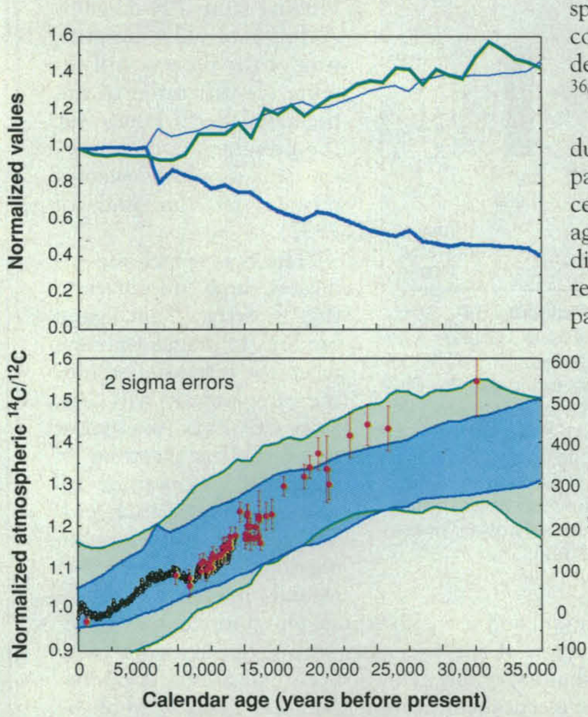
of the late 17th century, during which there were almost no sunspots (*7*). This conclusion has been recently strengthened by the analysis of ^{10}Be and ^{36}Cl in polar ice from Greenland and the South Pole (*8*, *9*).

By contrast, the long-term decrease of 400 per mil in the atmospheric ^{14}C/^{12}C ratio cannot be explained by magnetic fluctuations of the sun. One of the main arguments for this conclusion comes from the variations of ^{10}Be and ^{36}Cl measured at different latitudes. Owing to its orientation, the geomagnetic field acts as a shield against the primary cosmic-ray protons only at low and mid-latitudes. Carbon-14, being rapidly mixed in the atmospheric CO_2 reservoir, loses its latitudinal dependence. This change is fortunately not the case for ^{10}Be and ^{36}Cl, which are mainly modulated between 60°S and 60°N. Several recent results have disentangled the different processes affecting cosmogenic isotopes during the last 40,000 years: ^{10}Be and ^{36}Cl fluxes in Greenland ice cores (*8*, *9*), ^{10}Be fluxes in numerous deep-sea sediments spread at different latitudes (*10*), and now the work of Plummer *et al.* on ^{36}Cl levels in fossilized packrat urine from the Nevada desert (*2*).



Cosmic trends. (**Top**) Mean intensity of the geomagnetic field (thick blue line) (*11*), normalized to the present value, along with the cosmogenic production predicted from those changes (thin blue line) (*16*) and the global ^{10}Be flux (green line) (*10*). (**Bottom**) Changes of the atmospheric ^{14}C/^{12}C, normalized to the present value (left axis) and given in terms of Δ^{14}C in per mil (right axis). Open black dots represent the raw tree-ring data (*4*), and red dots are raw data based on paired ^{14}C and ^{230}Th ages of corals (*6*). The colored regions indicate the area predicted from the paleomagnetic reconstruction (blue) and the ^{10}Be reconstruction (green) in the top panel. Errors on each record are given at the 2σ level (except for the tree-ring data, for which the error bars are small and vary between 1 and 20 per mil).

Although there are still significant differences between individual records, in terms of timing and amplitude, a broad picture begins to emerge: a long decrease in ^{10}Be and ^{36}Cl over the last 30,000 years is present in the low and mid-latitudes records, but by contrast, the decrease is essentially absent in polar profiles. These observations strongly suggest that the long-term decrease of cosmonuclide production is indeed a response to a slow change of the global geomagnetic dipole.

Paleomagneticians have been able to reconstruct past variations of the geodynamo strength by studying volcanic rocks and lacustrine and marine sediments. As compiled recently by Guyodo and Valet (*11*) the record is mainly characterized by a twofold increase of the geomagnetic field during the period between 30,000 and 5,000 years ago. This record can be used to make theoretical predictions of the cosmonuclide production through time, which must have been significantly enhanced during periods of weak magnetic shielding. The first-order conclusion is that the twofold increase of the geomagnetic field during the last 30,000 years probably caused the 400–per mil decrease of the atmospheric ^{14}C/^{12}C ratio (*6*). A similar conclusion can be drawn for the long decreasing trend of ^{10}Be (*10*) and ^{36}Cl shown by Plummer *et al.* (*2*).

The record of global ^{10}Be flux during the past 35,000 years (top panel of the figure), compiled recently by Frank *et al.* (*10*), is in good agreement with the theoretical predictions based on the paleomagnetic record. These two records are compared with the detailed record of the atmospheric ^{14}C/^{12}C ratio based on the coral ^{230}Th and tree-ring data (*4*, *6*) (see figure, bottom panel). For this comparison, it is necessary to take into account the secondary effect of ^{14}C mixing within the global carbon cycle, which slightly smoothes fast changes and introduces a delay and a memory effect to the system (*4*). Most of the ^{14}C/^{12}C decrease can be accounted for by the long-term increase of the geomagnetic shielding strength (bottom panel).

The paleomagnetic and the ^{10}Be and ^{36}Cl records are not yet precise enough to assess the cause of second-order features of the atmospheric ^{14}C/^{12}C profile, such as the excursion centered between 13,000 and 12,000 years ago. Major changes in the rate of exchange or reservoir sizes within the carbon cycle seem to be the plausible causes of this millennium-scale event, which occurred during the last deglaciation (*4*, *5*, *12*).

Much work is still needed to fully understand and quantify the past variation of cosmonuclide fluxes. This effort is crucial because the fallout of each particular isotope is affected differently by stratospheric, tropospheric, hydrologic, and oceanic processes before it is locked into a particular archive. For example, as acknowledged by Plummer *et al.* (*2*), the ^{36}Cl fallout in Nevada was probably enhanced during the last glacial period in response to changes of the atmospheric mixing across the tropopause.

A remaining puzzle is the ~2000-year-long ^{10}Be peak centered somewhere between 35,000 and 40,000 years ago in polar ice from Antarctica and Greenland (*8*, *13*). It corresponds chronologically to the so-called Laschamps magnetic excursion, during which the magnetic field was probably no longer dipolar and was drastically reduced in intensity (*11*). This explanation remains hypothetical, and other causes have been invoked, such as an extreme solar modulation (*13*), the shock wave of a supernova (*14*), or even the combination of several of these causes (*15*).

References

1. G. M. Raisbeck and F. Yiou, in *Nuclear Methods of Dating*, E. Roth and B. Poty, Eds. (Solid Earth Sci. Library 5, Kluwer Academic, Dordrecht, Netherlands, 1990), pp. 353–378.
2. M. A. Plummer *et al.*, *Science* **277**, 538 (1997).
3. F. M. Phillips *et al.*, *ibid.* **248**, 1529 (1990); T. E. Cerling and H. Craig, *Annu. Rev. Earth Planet. Sci.* **22**, 273 (1994); E. T. Brown *et al.*, *Earth Planet. Sci. Lett.* **124**, 19 (1994); P. R. Bierman, *J. Geophys. Res.* **99**, 13885 (1994); J. R. Ritz *et al.*, *Geology* **23**, 1019 (1995).
4. M. Stuiver, T. F. Brazunias, B. Becker, B. Kromer, *Quat. Res.* **35**, 1 (1991).
5. T. Goslar *et al.*, *Nature* **377**, 414 (1995); K. A. Hughen *et al.*, *ibid.* **380**, 51 (1996).
6. E. Bard, B. Hamelin, R. G. Fairbanks, A. Zindler, *ibid.* **345**, 405 (1990); E. Bard, M. Arnold, R. G. Fairbanks, B. Hamelin, *Radiocarbon* **35**, 191 (1993); E. Bard *et al.*, *Nature* **382**, 241 (1996).
7. J. A. Eddy, *Science* **192**, 1189 (1976).
8. F. Yiou *et al.*, *J. Geophys. Res.*, in press; R. C. Finkel and N. Nishiizumi, *Eos* **77**, F428 (1996).
9. J. Beer *et al.*, *Nature* **331**, 675 (1988); E. Bard, G. Raisbeck, F. Yiou, J. Jouzel, *Earth Planet. Sci. Lett.*, in press.
10. M. Frank *et al.*, *Earth Planet. Sci. Lett.* **149**, 121 (1997); Y. Lao *et al.*, *Nature* **357**, 576 (1992).
11. Y. Guyodo and J.-P. Valet, *Earth Planet. Sci. Lett.* **143**, 23 (1996).
12. T. F. Stocker and D. G. Wright, *Paleoceanography* **11**, 773 (1996); R. L. Edwards *et al.*, *Science* **260**, 962 (1993).
13. G. M. Raisbeck *et al.*, *Nature* **326**, 273 (1987).
14. C. P. Sonett, G. E. Morfill, J. R. Jokipii, *ibid.* **330**, 458 (1987).
15. L. R. McHargue, P. E. Damon, D. J. Donahue, *Geophys. Res. Lett.* **22**, 659 (1995); C. Robinson *et al.*, *Earth Planet. Sci. Lett.* **136**, 551 (1995).
16. D. Lal, in *Solar-Terrestrial Relationships*, X. C. V. Corso, Ed. (Society Italy di Fisica, Bologna, Italy, 1988), pp. 216–233.