cells, and what is known has not yet been used to explore new treatment strategies. The two new reports in this issue fill in some of these gaps in our knowledge.

When the first synapses in the pain pathway are stimulated, they release a bouillabaisse of neuroactive substances from their presynaptic terminals: glutamate, calcitonin gene–related peptide, substance P, and substance K. One of the most provocative consequences of this release is that the NK-1 receptor (which binds substance P), located on the plasma membrane of the second-order neurons, is rapidly internalized upon noxious stimulation (5) (see the figure). The robustness of this internalization suggested a means to biochemically manipulate the second-order nociceptive neurons: make them internalize something interesting. Coauthors Wiley and Lappi coupled substance P to the cytotoxin saporin, which inactivates protein synthesis, thus producing a selective, receptor-targeted toxin for SP-receptor expressing neurons (6). A single injection of the toxin-ligand conjugate into the cerebrospinal fluid bathing the spinal cord kills the substance P receptor–expressing neurons in the superficial lamina I of the spinal cord. The toxic effect did not extend to substance P receptor–expressing cells located deeper in the cord, possibly because the substance P ligand portion of the hybrid molecule is susceptible to degradation by a dipeptidyl carboxypeptidase in the spinal fluid, thereby limiting tissue penetration and duration of ligand-toxin uptake.

When the treated rats were tested with an acute noxious stimulus, radiant heat applied to the hindpaw, they exhibited normal withdrawal latencies; the good pain was spared. But in an experimental hyperalgesia model in which capsaicin (the active ingredient in hot chili pepper, which causes primary afferent C-fibers to release substance P) was injected into the hindpaw, the toxin-ligand treatment reduced pathological pain. In this model the massive release of substance P sensitizes the second-order spinal cord neurons to subsequent mechanical and thermal stimuli. Rats treated with the toxin-ligand showed a reduced behavioral output as a result of the capsaicin injection and reduced hyperalgesia and allodynia in response to subsequent thermal and mechanical stimuli. These results are not specific to the pain model used. In another model of neuropathic pain that also causes abnormal activation of nociceptive primary afferents—chronic constriction of the sciatic nerve—an amidated substance P–diphtheria toxin fusion protein decreases allodynia and hyperalgesia (7). Thus, bad pain is attenuated by two different toxin-ligand molecules.

In the second report, the authors analyzed mice lacking the enzyme PKCγ, revealing a potential role in establishing allodynia and hyperalgesia for another set of second-order spinal cord neurons, in a dorsally located but distinct spinal layer (lamina IIi) from the SP receptor cells in lamina I. In this study, the PKCγ mutant mice displayed an attenuation of behavioral hyperalgesia and changes in spinal cord neuropeptide and receptor levels in animals experiencing pain from both nerve injury and from inflammation. Thus, these experiments identify both a specific neuronal population and the signal transduction pathway (PKCγ-coupled phosphorylation) involved in development of the neuropathic pain state.

What wider possibilities are presaged by these studies? First, they highlight the idea of pain state–specific therapies, drugs that block the development of hyperexcitability in postinjury and chronic pain states, but leave perception of acute pain intact. Second, they predict an emerging dichotomy in therapeutic strategies for chronic neural disorders. Development of an inhibitor for PKCγ will likely conform to the traditional approach to drugs: a small organic molecule with oral bioavailability. This contrasts sharply with biologically based treatments such as noci-toxins, implantation of genetically engineered cells and tissue-engineered devices (8), or gene therapy approaches to pain control, whereby viral vectors delivered to the spinal cord (9) can be used to confer an "analgesic" phenotype to the spinal cord. Both approaches focus on controlling pain at the spinal level. Such spinal anesthesia is particularly effective, because once pain signals reach the brain, there are multiple routes to conscious perception (*10*). Thus, noci-toxins and gene transfer are on the horizon as treatments for severe chronic pain.

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GEOLOGY

Do Continents Part Passively, or Do They Need a Shove?

Richard W. Carlson

Every once in a while in geologic history, fissures form in Earth's continental crust and pour forth prodigious quantities of basalt (*1*) (Fig. 1). One way to comprehend the tremendous scale of such events is to note that the average "flood basalt" would cover the area bounded by New York City, Cleveland, Atlanta, and Charleston with a slab of basaltic magma over a kilometer thick, burying the Appalachian Mountains to form a broad flat plateau over most of the eastern United States.

Fig. 1. Flood basalt. A 2-km-thick section of the Columbia River basalts in the Grande Ronde River valley of eastern Washington.

Why such events occur has been a focus of investigation since the recognition of their huge scale. Some flood basalts, such as the Paraná-Etendeka Province of South America, are clearly connected with the opening of major ocean basins (*2*). Others, such as the Deccan Province of India, are associated with linear tracks of continuing volcanism believed to be caused by the melting of plumes of hot material rising from the deep mantle (*3*) (see Fig. 2). These associations have created a "chicken and the egg"

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problem in the understanding of the forces driving the motion of continental tectonic plates. Does the balance of forces exerted on Earth's crustal plates cause continental rifting, or are continents driven apart as huge plumes of deep mantle ascend beneath them, fueling flood basalt volcanism and causing thermal weakening of the crust?

A recent paper by Chesley and Ruiz (*4*) addresses this question with a new radiogenic isotope system to study the youngest of the flood basalt provinces, the Columbia River basalts of the Pacific Northwest. Continental crust consists of igneous rocks that are clearly distinct in chemical composition from the rocks that erupt along mid-ocean ridges or at intraplate oceanic volcanoes such as Hawaii and Iceland (*5*). This distinction is believed to reflect the formation of continental crust largely through the volcanism associated with plate subduction. Subduction of oceanic plates transports water and surficial sediments into the shallow mantle. The water lowers the melting point of the mantle, and the subducted oceanic crust contributes fluids and melts that produce the distinctive chemistry of the magmas erupted above the subduction zone (*6*).

Flood basalt events are not associated with plate subduction but rather with continental rifting. Nevertheless, flood basalts often show chemical characteristics similar to those associated with subduction-related volcanism (*7*). Some interpret this similarity as a sign that flood basalts originate through melting of the shallow mantle beneath continents that has been contaminated by past subduction along the continental margin (*8*). Others suggest that these chemical characteristics reflect the contamination of melts of deep-mantle materials by continental crust or shallow continental mantle (*9*).

In principle, the ability of isotopic studies to distinguish source chemical characteristics from those induced by melting or contamination should allow ready definition of the origin of the distinct composition of flood basalts. In practice, this effort is compromised by the fact that "average" mantle contains low concentrations of all of the elements found in the commonly applied radiogenic isotope systems, such as rubidium-strontium, samarium-neodymium and uranium-lead. Thus, the shallow mantle can easily be overprinted with these elements by interaction with the melts rising from the subducting plate. The end result is that such "contaminated" mantle will have trace element abundance characteristics and, with time, isotopic characteristics similar to those considered typical of continental crust.

Chesley and Ruiz overcame this problem by applying the isotope system based on the decay of rhenium-187 to osmium-187. The Re-Os system is unique in that Os prefers to stay with the residual solids during the melting of mantle rocks (*10*), whereas all of the elements of the more commonly applied radiometric systems strongly concentrate in the melt. As a result, the mantle has relatively high Os concentrations compared to most melts, so that melt infiltration into the mantle does not greatly modify its distinguishing characteristic of a low Re-to-Os ratio. This has been shown quite clearly by study of the Re-Os systematics of the rare samples of continental mantle brought to the surface by certain types of explosive volcanic eruptions (*11*). Thus, the mantle and melts derived from the mantle have low $^{187}Os/^{188}Os$ ratios, whereas essentially any old crustal rock has high $^{187}Os/^{188}Os$ ratios.

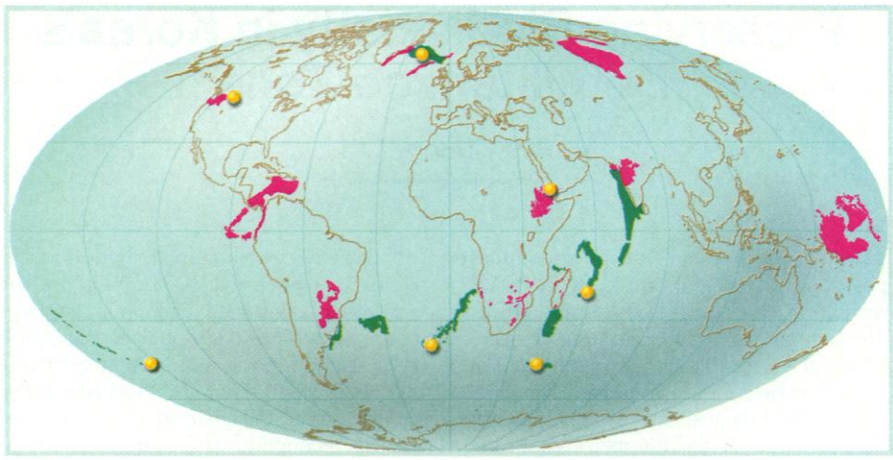

Fig. 2. Map of flood basalt provinces (red) younger than 250 million years and oldest volcanic ridges (green) together with present volcanism (yellow).

What has hampered application of the Re-Os system to these problems until recently has been the exceedingly low concentration of Os in most magmas, on the order of a few picograms of Os per gram of basalt. Chesley and Ruiz undertook tedious mineral separations of Columbia River basalts in order to analyze mineral phases with somewhat higher Os concentrations and low Re/Os ratios to reduce the uncertainty in Os isotopic composition induced by Re decay since eruption. Even with the mineral concentration, the isotopic analyses were performed on picograms of Os, roughly a factor of thousand to a million less than typically used for strontium and neodymium isotopic analysis. Through these efforts, Chesley and Ruiz were able to show that the volumetrically rare Columbia River basalts that have chemical characteristics similar to oceanic basalts also have the Os isotopic compositions expected for melts derived from deep-mantle material. In contrast, the volumetrically dominant basalt in the province has a chemical signature similar to that of continental crust. According to Chesley and Ruiz (*4*), these basalts have high $^{187}Os/^{188}Os$ ratios, well outside typical mantle values. This result confirms previous suggestions that the majority of Columbia River basalts derive their peculiar composition through contamination of deep-mantle melts by the rocks of the continental crust through which they erupted. This supports the idea that flood basalt volcanism is not the passive result of plate movement, but reflects the impingement of a plume of deep-mantle material at Earth's surface. Thus, continental breakup may well be caused by a strong shove from below.

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