gered seismicity in volcanic or geothermal areas, Hill *et al.* suggest that the specific triggering mechanism and time delay is due to the properties of the fluid systems (see abstracts from the recent meeting of the American Geophysical Union[7–9]). But there are still some mysterious aspects of this case history. Hill *et al.* show that dynamic stress levels of the Landers seismic waves at the triggered sites are larger than tidal stress levels, generated by the Sun and Moon — but are they larger than dynamic stress levels of other nearby earthquakes? The Petrolia, California, earthquake of 25 April 1992 (magnitude 7.1) did not trigger seismicity at the Mount Lassen and Mount Shasta areas, only 200 km from the Petrolia epicentre (see figure). But, just 64 days later, the Landers earthquake occurred more than 800 km to the south and did trigger seismicity at these volcanoes. Perhaps there is more to triggering than just the peak dynamic stress. But what?

In answer to the third question, I believe that the Landers observation will have a lasting influence on earthquake research. First of all, it changes our initial assumption about earthquake interaction, and allows for more serious scientific considerations of 'wild ideas' on the subject. Second, more documentation and acceptance of triggering may well provide valuable information on the detailed physics of frictional failure; further, the understanding of the final preparatory phase of frictional failure is of paramount importance for short-term earthquake prediction. Perhaps if we can listen in on earthquakes talking to each other, we may learn from the whispers that pass beneath our feet. □

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PHARMACOLOGY

Janus faces of nitric oxide

Solomon H. Snyder

NITRIC oxide (NO) has been implicated as a mediator of neuronal destruction in vascular stroke. In some studies, however, it seems to have neuroprotective effects. This paradox may be resolved by the observations of Lipton *et al.* reported on page 626 of this issue[1]. The authors find that NO might exert both of these effects, depending on its oxidation–reduction status.

Nitric oxide is rapidly emerging as one of the main neurotransmitters in the central and peripheral nervous systems[2]. For many transmitters, decades pass before their specific neural functions are elucidated. By contrast, NO, first reported in the brain only about four years ago, is already known to mediate intestinal relaxation in peristalsis, penile erection, and the actions of glutamate on cyclic GMP levels in the brain. It is also implicated in neuropathological conditions, in that it may mediate major neuronal damage in stroke and neurodegenerative diseases. Most neural destruction in stroke seems to result from a massive release of glutamate, which, acting through the *N*-methyl-D-aspartate (NMDA) subtype of receptor, somehow causes 'excess excitation' resulting in neuronal death[3]. This notion obtained strong support from demonstrations that drugs which are NMDA receptor antagonists provide marked protection against neural damage following vascular occlusion.

Recent evidence indicates that NO mediates these neurotoxic effects of glutamate. The NO-forming enzyme NO synthase (NOS) is activated by Ca^{2+} binding to the calmodulin associated with the enzyme. NMDA receptor activation triggers a massive influx of Ca^{2+} into neurons, and NO is formed and diffuses to adjacent cells to kill them. This model is supported by the ability of NOS inhibitors to block the neurotoxic actions of glutamate and NMDA in brain cultures[4]. The evidence from culture has been translated into clinically relevant models, as in several species low doses of NOS inhibitors, administered after ligating the middle cerebral artery, provide marked protection against stroke damage[5]. The clinical relevance of NO may extend to other forms of neurotoxicity. AIDS dementia, for example, may derive from neurotoxic effects of the coat protein gp120 of the HIV virus which kills neurons when acting in conjunction with glutamate at NMDA receptors. Inhibitors of NOS block this form of neurotoxicity and thus may have a role in the therapy of AIDS dementia[6].

Despite the strong evidence for NO-mediated neurotoxicity, in some studies it seems to be neuroprotective. The neuroprotective action may be explained by observations that NO can nitrosylate the NMDA receptor, thus blocking glutamate neurotransmission[7]. Insights into mechanisms for the neurotoxic and neuroprotective effects now come from Lipton *et al*[1]. who emphasize that NO can exist in distinct oxidation–reduction states which have very different biological actions. Indeed, the designation nitric oxide should be restricted to the reduced, $NO^{\bullet}$ form of the molecule, while the parent NO should be called 'nitrogen monoxide', and the oxidized form NO^{+}, the nitrosonium ion.

Lipton *et al.* present evidence that the neurotoxic actions of NO derive from the $NO^{\bullet}$ form of the molecule, which reacts with superoxide anion to form peroxynitrite, probably the final neurotoxic agent. On the other hand, NO in the form of the nitrosonium ion (NO^{+}) reacts with the thiol group of the NMDA receptor to block neurotransmission. Numerous other proteins can be S-nitrosylated, a modification which conceivably has physiological regulatory functions, akin to phosphorylation[8]. Lipton *et al.* use various NO donors in the presence or absence of reducing agents to form $NO^{\bullet}$ or NO^{+} respectively. In cerebral cortical cultures, conditions favouring $NO^{\bullet}$ give rise to neurotoxicity, whereas neuroprotective effects occur in the presence of NO^{+}. NO^{+} also blocks NMDA receptor-mediated currents.

These results may have substantial therapeutic implications. The observation that NOS inhibitors provide up to 70 per cent protection from neural stroke damage has triggered a great effort in the pharmaceutical industry to develop NOS inhibitors as antistroke drugs. Perhaps a more sophisticated approach is needed. The ideal therapeutic agent should be one that prevents the formation of $NO^{\bullet}$ while enhancing the formation of NO^{+}. Alternatively, one might seek to develop drugs that are converted to nitric oxide, but only to the NO^{+} form of the molecule. Similar considerations would apply to drugs aimed at AIDS dementia and neurodegenerative conditions, such as Huntington's and Parkinson's diseases, which may also involve excessive stimulation of NMDA receptors. □

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