

Carbon Monoxide and Dilation of Blood Vessels

In her Research News article "Carbon monoxide: Killer to brain messenger in one step" (15 Jan., p. 309), Marcia Barinaga provides only a partial account of the mechanism by which carbon monoxide may dilate blood vessels. The response in question is ascribed to activation of guanylyl cyclase, but this is one of two possibilities considered in the report "Carbon monoxide: A putative neural messenger" by Ajay Verma *et al.* (15 Jan., p. 381). In a series of investigations (1) cited by Verma *et al.*, we documented the involvement of a cytochrome P-450 hemoprotein in the vasodilation to carbon monoxide and, more recently, assigned to this hemoprotein a limiting function in the formation of the vasoconstrictor endothelin (2). In the smooth muscle preparations we used, carbon monoxide had a greater affinity than oxygen for the target heme (1), while the reverse was true of a preparation in which carbon monoxide action was linked to guanylyl cyclase (3). In our work, carbon monoxide-induced relaxation remained unchanged after treatment with methylene blue, which is inconsistent with guanylyl cyclase having a role in the response. In brief, there seem to be at least two ways for carbon monoxide to dilate blood vessels: by activation of a (guanylyl cyclase-based) relaxant mechanism and by interference with a (cytochrome P-450-based) constrictor mechanism. These two operational models are not mutually exclusive and, if carbon monoxide is indeed a biological messenger, they may be unevenly expressed throughout the body depending on the tissue and the functional state.

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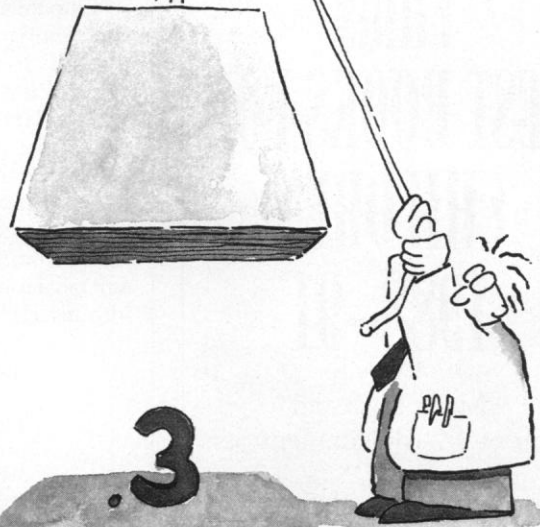
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UCSF Research Institute: No Hughes Approval

Christopher Anderson's article "Hughes' tough stand on industry ties" (News & Comment, 12 Feb., p. 884) contains an

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incorrect statement about the position of the Howard Hughes Medical Institute (HHMI) regarding a proposed new research center at the University of California, San Francisco (UCSF). At no time did I either say or imply that the HHMI had initially approved the arrangements but had later reversed itself and withdrawn its approval. The arrangements had never been approved, nor indeed could they have been, as no agreement has been finalized between the company and the university.

I should also like to point out that there is no similarity between my situation and that of Irving Weissman at Stanford. While it is accepted by both the university and the HHMI that I shall serve as chairman of the scientific advisory board of the new research center, I hold no equity in the pharmaceutical company that will support the center, I will receive no compensation from the company for my services, and no money from the center will flow into my HHMI laboratory.

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Recoverin's Role: Conclusion Withdrawn

In our Research Article of 22 February 1991, "Recoverin: A calcium sensitive activator of retinal rod guanylate cyclase" (1), our laboratories concluded that recoverin, a 23-kilodalton calcium (Ca^{2+})-binding protein, stimulates photoreceptor guanylate cyclase at submicromolar Ca^{2+} concentrations. Recent observations from our laboratories now suggest that recoverin is not the soluble activator of photoreceptor guanylate cyclase.

1) Recombinant recoverin expressed in *Escherichia coli* did not stimulate photoreceptor guanylate cyclase when it was added to washed photoreceptor membranes in submicromolar Ca^{2+} . The recombinant recoverin used in these experiments was myristoylated at its amino terminus and had a mass identical to that of one of the species of recoverin found in bovine retinas. Furthermore, polyclonal antibodies directed against both recombinant recoverin and retinal recoverin did not inhibit guanylate cyclase when they were added to rod outer segments.

2) Preparations of highly purified recoverin isolated from bovine retinas with the use of several fractionation methods did not effectively stimulate guanylate cy-

clase. In fact, guanylate cyclase stimulator activity separated from recoverin during most purification procedures.

3) Highly purified fractions of a guanylate cyclase stimulating factor that we isolated from bovine retinas contained amounts of recoverin that were nearly undetectable by immunological methods. The identity of the soluble guanylate cyclase stimulating factor in these preparations has not yet been determined.

4) The membrane-binding properties of recoverin make it seem unlikely that recoverin could stimulate membrane-associated photoreceptor guanylate cyclase (2). At the low Ca^{2+} concentrations required for cyclase stimulation, recoverin dissociated from photoreceptor membranes.

In addition, a recent study demonstrated that raising the concentration of recoverin within a rod cell slows recovery from photoexcitation (3). This result does not support our earlier view of how recoverin acts.

It remains to be determined whether recoverin plays any role in the regulation of photoreceptor guanylate cyclase. Other conclusions of our Research Article, including the sequence analysis of recoverin, its localization by immunological methods, and its Ca^{2+} -binding properties, have been confirmed.

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3. M. Gray-Keller *et al.*, *Neuron* **10**, 523 (1993).

Corrections and Clarifications

In the chart accompanying Christopher Anderson's News & Comment article "Clinton asks for a greener DOE" (9 Apr., p. 153), the budget figures for Basic Energy Science were incorrect. The correct figures are \$861 million for the 1993 appropriation and \$802 million for the 1994 request.