NEUROSCIENCE

Carbon Monoxide: Killer to Brain Messenger in One Step

Say the words "carbon monoxide," and most people will come up with bad images: coughing exhaust pipes, smoggy skies, suicide attempts in closed garages. But, as any good p.r. firm knows, images can be changed. Take another gas that not so long ago had a bad rep—nitric oxide. In the past 2 years nitric oxide has gone from little more than a noxious poison to one of the body's key chemical messengers (*Science*, 18 December 1992, p. 1862). And now it looks as if lowly carbon monoxide is on the verge of the same transformation. Teams led by Mahin Maines at the University of Rochester and Solomon Snyder at Johns Hopkins University have mapped the locations of a carbon monoxide-producing enzyme in the brain. Snyder's report, which appears in this issue of *Science* (page 381), goes further to show that, in at least one type of nerve cell, carbon monoxide isn't just a bystander: It regulates levels of the intracellular messenger molecule cyclic GMP. That means that carbon monoxide, like nitric oxide, could be acting as a biological signal.

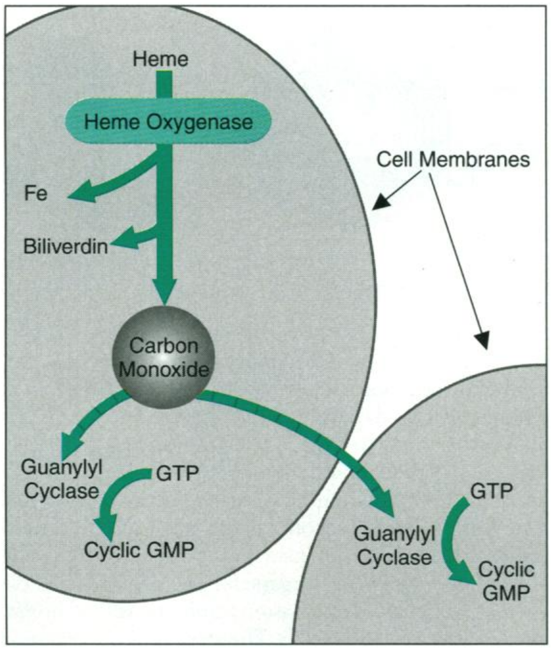
"This discovery has a lot of potential," says neuroscientist Julius Axelrod of the National Institute of Mental Health. "This is a similar story to nitric oxide, a gas generated in neural tissues that acts on a second messenger system. This seems to be a new class of neurotransmitter."

In fact, the carbon monoxide story closely follows that of nitric oxide. Both are toxic pollutants that poison by binding to the iron-containing heme group found in hemoglobin and some enzymes. Nitric oxide's more benevolent side was hinted at in 1987, when Salvador Moncada of the Wellcome Research Laboratories in England found that the gas is produced in the body and acts as a physiological signal to relax blood vessels. Other researchers found that certain nerve cells could be triggered to make nitric oxide, and soon the molecule was implicated as a messenger in functions ranging from learning to penile erection.

The idea of a gas acting as a neuronal messenger was surprising at first. Gases are nothing like classic neurotransmitters, which are made in neurons and stored in vesicles until stimulation of the neuron triggers their release. Gases, in fact, aren't contained by membranes at all; when dissolved in cell fluids, they glide right through the membranes in their path. And while classic neurotransmitters must bind to receptors to influence a cell, gases slip in through the cell's outer membrane. Yet such traits could come in handy for a messenger, says Salk Institute neuroscientist Charles Stevens—enabling messages to pass through membranes that have no vesicle-releasing machinery.

Once the idea of gaseous messengers caught on, some researchers began to suspect nitric oxide is not the only one. "If you look at neurotransmitters in general, they are [grouped] in chemical classes," says Snyder, whose lab helped reveal nitric oxide's role in the brain. "If nitric oxide is a neurotransmitter, there should be a class of analogous molecules."

Carbon monoxide was considered a likely member of that putative class for a variety of reasons. Like nitric oxide, carbon monoxide dilates blood vessels. And it gets the job done the same way: by stimulating guanylyl cyclase—the enzyme that produces cyclic GMP—in the muscle cells that surround blood vessels. Since cyclic GMP is a signal in many tissues besides smooth muscle, that meant carbon monoxide might act as a messenger elsewhere in the body.



Diffuse message. By diffusing through membranes and interacting with the enzyme guanylyl cyclase, carbon monoxide may act as a biological signal.

Carbon monoxide is made in many tissues of the body by an enzyme called heme oxygenase, which breaks down heme. Heme oxygenase is abundant in the spleen, where red blood cells are destroyed, but in 1989 Maines' group cloned a new form of the enzyme and found it in the brain. "The brain doesn't have a lot to do with heme turnover," says Snyder postdoc Ajay Verma, so the enzyme probably isn't needed to recycle heme. To some researchers, it is there to make carbon monoxide.

If that were the case, one indication would be the way the enzyme is distributed. Since the brain uses many different messenger systems, you would expect the enzyme to be present only in the areas that use carbon monoxide as a messenger. Both Maines' group and Snyder's found just that kind of patchy distribution. In a paper published last month in *Molecular and Cellular Neurosciences*, Maines and James Ewing found heme oxygenase in several brain regions. In their paper in this issue of *Science*, Snyder, Verma, and their colleagues report similar findings. One key factor links the areas that contain heme oxygenase: They also contain guanylyl cyclase, a potential target for carbon monoxide.

Those findings suggest carbon monoxide may play a functional role in these brain regions. And in one example—olfactory neurons—that seems to be true. Olfactory neurons respond to odors with a rise in cyclic GMP levels. But Snyder's group found that a drug that blocks heme oxygenase prevents that rise. "These experiments show that carbon monoxide in the olfactory neurons can use the guanylate cyclase as a target," says Columbia University neuroscientist Eric Kandel. But it isn't clear yet, he adds, just how the gas figures in odor perception.

Another brain region where carbon monoxide might be important is the hippocampus, where researchers have been searching for the "retrograde messenger," a molecule thought to be necessary for a learning-linked process called long-term potentiation, or LTP. Nitric oxide is a candidate, but there is controversy over whether the enzyme that makes nitric oxide is present in the cells that should be making the retrograde messenger. Those cells are full of heme oxygenase. And Stevens, of the Salk Institute, says he and postdoc Yanyan Wang have preliminary evidence that inhibiting heme oxygenase blocks LTP.

Despite these tantalizing snippets, many questions remain to be answered before carbon monoxide's role in the brain is clear. For one thing, if it does function as a true messenger, some signal to the neuron must trigger its production. But no one knows if such a trigger exists for carbon monoxide. If such a trigger is found, and nitric oxide and carbon monoxide turn out to represent a new class of neural messengers, there may be other members. Which means this gas is likely to provide fuel to run plenty of labs.

–Marcia Barinaga