New Valiums and Anti-Valiums on the Horizon

It is now possible to find drugs with some, but not all of Valium's effects, to find drugs that block Valium, and to find drugs that produce anxiety

A few years ago, it was discovered that benzodiazepines, such as Valium and Librium, act by binding to specific receptors in the brain. Since these drugs are not just anti-anxiety substances but also are sedatives, muscle relaxants, and anticonvulsants, researchers immediately began asking if there were one or several kinds of benzodiazepine receptors. Are all the actions of the benzodiazepines inextricably linked or can drugs be found that reduce anxiety, for example, without causing sedation? Are there drugs that may antagonize the benzodiazepines—drugs that may make people more alert, for example? The surprising answers that came out of a recent conference* are yes, it seems possible to separate out the benzodiazepine effects and yes, it is possible to antagonize the actions of benzodiazepines. With the new drugs as research tools, it may be possible to at last understand the biochemistry of anxiety and also perhaps to understand sleep and epilepsy.

The way to find benzodiazepine antagonists is to look for substances that bind in vitro to the benzodiazepine receptor, whether or not those substances bear any resemblance to benzodiazepines, and then test the substances' actions in animals. With this technique, several major drug companies have, within the past year, found benzodiazepine antagonists. And, with one exception, none of these antagonists have chemical structures similar to benzodiazepines.

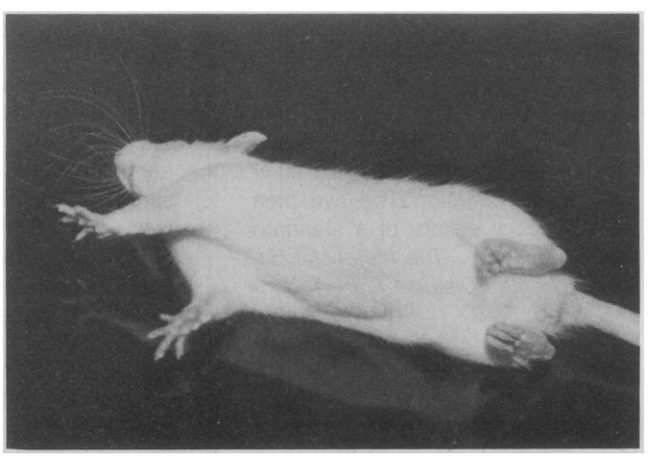
One of the most-studied antagonists is RO 15-1788, an imidazobenzodiazepine that is a Hoffmann–La Roche product. According to Willy Haefly and Hans Mohler of Hoffmann–La Roche in Basel, Switzerland, the compound blocks benzodiazepine but does not seem to produce any other effects at moderate doses. One possible use for this compound is as an adjunct in the treatment of schistosomiasis. Patients with this tropical disease sometimes are given 3-methylclonazepam, a clonazepam derivative that acts directly to kill the parasite. Unfortunately, the clonazepam derivative also acts on the brain, sedating patients to such an extent that they often find it difficult to function. Recently, a group of British researchers found that if these patients are given RO 15-1788 at the same time as they are given clonazepam, the clonazepam actions on their brains are blocked but the drug can still kill the schistosomiasis parasites.

Other drugs, the β-carbolines, which also were found by receptor binding assays, produce effects opposite to those of the benzodiazepines. For example, a β-carboline derivative studied by the Danish drug company A/S Ferrosan seems to produce anxiety in animals and its effects are canceled by the benzodiazepine lorazepam. Claus Braestrup of A/S Ferrosan reported at the meeting on a small pilot study in which he gave this β-carboline derivative to four human volunteers. The volunteers became anxious—they didn't want to stay alone in the room. One became so anxious that the researchers had to physically restrain him and inject him with a benzodiazepine. In less than 1 minute, his symptoms were reversed.

Wallace Mendelson of the National Institutes of Health (NIH) used another β-carboline derivative to induce wakefulness in rats. The more of the drug he gave, the longer the animals stayed awake. Unlike the amphetamines, which also keep people and animals awake, the β-carboline derivative did not increase the animals' motor activity.

"Now we are looking to see if the animals become more anxious when we give them this β-carboline," says Mendelson. His group tried one test of anxiety, devised by Jacqueline Crawley of E. I. Du Pont de Nemours and Co., in which rats or mice are put in a dark chamber connected by a doorway to a chamber that is brightly lit. The animals prefer the dark chamber—the bright light frightens them. But when they are given Valium, they are more likely to wander into the lighted chamber.

According to this test of anxiety, the β-carboline derivative did not make mice more anxious at doses that keep them awake. Mendelson, and Steven Paul and Phil Skolnick of NIH are now using other animal models of anxiety to further test their results. "We'll feel better about saying the drug does not produce anxiety when we try different models," says Mendelson.



This rat is having convulsions after being given Metrazol. Metrazol's actions are completely blocked if it is given with Valium. [*Reginald L. Dean, Lederle Laboratories*]

Of course, if the β-carboline derivative does turn out to enhance wakefulness without producing anxiety, it could be an important drug. "It's possible that it could be used in cases of daytime sedation. This is a common phenomenon—people tend to get tired and sleepy during the day," says Skolnick. "The drug could be like an energizer."

Skolnick cautions, however, that the drug is far from clinical tests. The proposed uses, he remarks, are ones "we are fantasizing about." Mendelson adds that "The β-carbolines would have to be

*The conference, called The Pharmacology of Benzodiazepines, was held on 12 to 14 April at NIH.

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tested very very carefully because a related group of compounds [the Harmala alkaloids] are hallucinogens."

Paul and Skolnick described at the meeting another kind of benzodiazepine antagonist, an imidazopyridine, that selectively blocks only the anxiety-reducing actions of these drugs. It does not affect the sedative, muscle-relaxant, or anticonvulsant activities of benzodiazepines. The drug, says Skolnick, "may not have any practical value but it does suggest that you can separate the action of benzodiazepines."

Bernard Beer, Claire Klepner, and Arnold Lippa of American Cyanamid's Lederle Laboratories have direct evidence that the actions of benzodiazepines are separable. They have found a compound, a triazolopyridazine, that counteracts anxiety and is an anticonvulsant without being a muscle relaxant or a sedative, and without interacting with alcohol. Beer explains that the Lederle group now believes there are two types of benzodiazepine receptors. Drugs that bind to "type 1" but not "type 2" will counteract anxiety without having the other benzodiazepine effects. The benzodiazepines themselves are indiscriminate, binding equally well to both receptor types.

Finally, John Tallman of NIH, Skolnick, and Paul suggest a way to speed up the screening for benzodiazepine antagonists. At the present time, researchers must test compounds in vitro to see if they bind to the benzodiazepine receptors and then must test them in animals to see if they affect behavior. But, Tallman found, benzodiazepines bind better to their receptors in the presence of the neurotransmitter GABA. In contrast, substances that block or antagonize benzodiazepines bind to benzodiazepine receptors equally well when GABA is present as when it is not. Thus, it looks like researchers may be able to use the receptor binding assay in the presence and absence of GABA to decide if a compound will mimic or antagonize benzodiazepines before ever testing the compounds in animals.

The search for drugs having some, but not all, effects of the benzodiazepines and the search for drugs to block or antagonize effects of benzodiazepines is just beginning. But, predicts Skolnick, "soon I suspect that we'll have compounds that will disrupt or mimic each of the actions of benzodiazepines." At the very least, these compounds should be invaluable research tools in probing the basis of human anxiety and it is likely that they will be clinically important as well.—GINA KOLATA

Neutrinos: No Oscillations?

Opening another chapter in a continuing controversy, a team of American, German, and Swiss physicists have reported new evidence casting doubt on the idea that neutrinos exhibit a bizarre phenomenon called "oscillation." The results of the new experiment were discussed by California Institute of Technology physicist Felix Boehm at the annual meeting of the American Physical Society in Washington, D.C.

They thus bring the controversy full circle. Neutrinos, ghostly particles released in certain nuclear reactions, have no electric charge and very little propensity to interact with matter. They do, however, come in three varieties, known as the electron, mu, and tau neutrinos. Since 1931, when Enrico Fermi first postulated the particles' existence, physicists have also assumed that neutrinos are massless, like the photon.

In 1980, however, experiments in the Soviet Union indicated that neutrinos might indeed have a small mass. At the same time, physicists from the University of California at Irvine reported evidence for oscillations: one type of neutrino can turn into another as it moves along, rather as if a swallow were to metamorphose into a hawk. The two experiments were considered mutually supportive, since for mathematical reasons it is impossible for neutrinos to oscillate unless they also have mass.

The massive neutrino concept was immediately taken up in other disciplines. Cosmologists hoped that swarms of massive neutrinos might account for the invisible "missing mass" which seems to exert gravitational effects on individual spiral galaxies and on clusters of galaxies (*Science*, 30 January 1981, p. 470). Astrophysicists believed that the oscillation phenomenon might solve the solar neutrino problem: that nuclear reactions in the core of the sun should produce far more neutrinos than are observed. The detectors used to date look only for electron-type neutrinos, however, so if electron neutrinos emitted in the sun have changed to something else by the time they reach Earth, then the paucity is explained.

But now researchers from the California Institute of Technology, the Technical University of Munich, and the Swiss Institute of Nuclear Research have searched for neutrino oscillation with a much more sensitive apparatus than the Irvine group's and have found no evidence for the phenomenon. Their work does not directly contradict the Soviet experiment, however, so neutrino mass is still quite possible.

For a neutrino source, Boehm and his colleagues used a 2800-megawatt power reactor near Gösgen, Switzerland. (Fissioning uranium atoms emit electron-type neutrinos.) Their detector was set up near the containment building, 38 meters from the reactor core. Since neutrinos so rarely pay attention to ordinary matter—they can easily sail through the core of the earth without slowing—the intense flux of neutrinos from the reactor yielded only about three events per hour in the detector. Still, this setup represented about ten times the sensitivity of the group's previous experiment using a 57-megawatt research reactor at Grenoble, France.

The detector responded only to electron neutrinos. Thus, the difference between the number of events expected from calibration measurements made at the core, and the number actually found at the detector, represented the number of electron neutrinos that had oscillated away and changed to some other type as they traveled the intervening distance.

That number, the group concluded after running the experiment from June 1981 to February 1982, is consistent with zero. In technical terms, the physicists were able to exclude the possibility of neutrino oscillations down to a mixing angle of 0.16 and a mass-squared difference of 0.02 square electron volts. This represents a very large region of parameters where oscillations could possibly be found, said Boehm.

In May, the researchers will begin an effort to set still more stringent limits by moving the detector back to a distance of 48 meters from the reactor core. If the neutrinos are going to oscillate at all, they will then have another 10 meters in which to do it. Moreover, comparison of the two sets of data will eliminate calibration uncertainties.—M. MITCHELL WALDROP

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