New Drugs and the Brain

Discoveries in brain chemistry are leading to a more rational search for new psychotropic drugs

The pharmaceutical industry's search for new psychotropic drugs has moved from animal testing to the world of molecular biology. Only a few years ago, laboratory scientists would tinker with the structure of a drug known to have, for instance, some antianxiety activity, and then inject the "new" drug into animals to determine its effects on behavior. Today, new drugs first are screened for their biochemical actions on isolated brain cells.

The recent development of rational biochemical assays for drugs that affect behavior rests on a quantum leap in the understanding of brain chemistry. The previous method of injecting substances into animals in hope of producing the desired effect was crude, expensive, and not very successful. Almost all the drugs used now to treat mental disorders were discovered in "ridiculously accidental" ways, says Solomon Snyder, of Johns Hopkins University School of Medicine.

The revolution in psychotropic drug development has come surprisingly swiftly. Although they know some general principles, researchers are still profoundly ignorant of the details of the molecular biology of the brain. Yet their meager knowledge has allowed them to gain some understanding of how drugs alleviate several of the major mental disturbances.

The story of the search for drugs to treat mental disorders began in the early 1950's, when antischizophrenia drugs were found quite unexpectedly. The French surgeon Henri Laborit was looking for drugs to calm patients before surgery. He tried giving them chlorpromazine, a drug that the French pharmaceutical firm Specia had synthesized when it was developing antihistamines. Chlorpromazine literally had been banished to basement storerooms because it was so sedating. For Laborit's purposes, however, chlorpromazine was ideal, and he suggested to some of his colleagues that they try giving it to patients in mental hospitals to make them more manageable. Much to these doctors' surprise, the drug seemed not only to calm schizophrenic patients but also to relieve their symptoms.

Although the notion that chlorpromazine is an antischizophrenia drug originally met with skepticism, it eventually won acceptance. But it was some time before anyone could discover how it worked. The first clue came in 1963, when Arvid Carlsson of the University of Göteborg in Sweden found that chlorpromazine and haloperidol, a related compound, increase the amount of the metabolites of dopamine in rats' brains. Dopamine is a neurotransmitter, a hormonelike chemical that carries signals between nerve cells. Carlsson proposed that the antischizophrenia drugs prevent nerve cells from responding to dopamine by blocking specific receptors on cell surfaces that bind it. The nerve cells that release dopamine would sense that the cells that were supposed to respond to it were not responding. So they would release more and more dopamine to provoke a response, causing the brain to be swamped with dopamine and its metabolites.

Carlsson's hypothesis was especially intriguing because it could explain a major effect of the drugs. Patients tend to become very rigid and to have difficulty in moving. They have symptoms identical to those of Parkinson's disease, which is caused by a lack of brain dopamine. If the antischizophrenia drugs block dopamine receptors, their effects could be the same as those caused by an actual lack of the neurotransmitter, even though the brain was overwhelmed with it. The hypothesis remained untested, however, because no methods were available for deciding whether neurotransmitter receptors were blocked. Then, more than 10 years later, two discoveries were made that not only confirmed the Carlsson hypothesis but paved the way for the new drug assays.

The first discovery was a way to measure indirectly whether dopamine receptors are blocked. Paul Greengard of Yale University School of Medicine and John Kebabian, now at the National Institute of Neurological and Communicable Diseases and Stroke, noticed that brain cells from the caudate nucleus make the regulatory substance adenosine 3′,5′-monophosphate (cyclic AMP) immediately after they are exposed to dopamine. They found that the dopamine receptors on these cells are linked to an adenylate cyclase, an enzyme that catalyzes the synthesis of cyclic AMP. When the cells bind dopamine, the enzyme is activated. But if cells from the caudate nucleus are first exposed to antischizophrenia drugs, they no longer respond to dopamine by making cyclic AMP.

There was, however, one drawback to Greengard and Kebabian's work. They did not find the predicted correlation between the drugs' potencies in treating schizophrenia and their abilities to prevent cells from making cyclic AMP in response to dopamine. This discrepancy was cleared up when investigators discovered that there are two kinds of dopamine receptors—one that is linked to an adenylate cyclase and one that is not. "Antipsychotic drugs hit both kinds of dopamine receptors but some have better affinities for one than the other," Greengard explains. There is now a simi-

This is the first of a series of occasional articles on recent developments in neurobiology. Future stories will discuss sex hormones and sexual behavior, the role of peptides as possible neurotransmitters, and the development of the nervous system.

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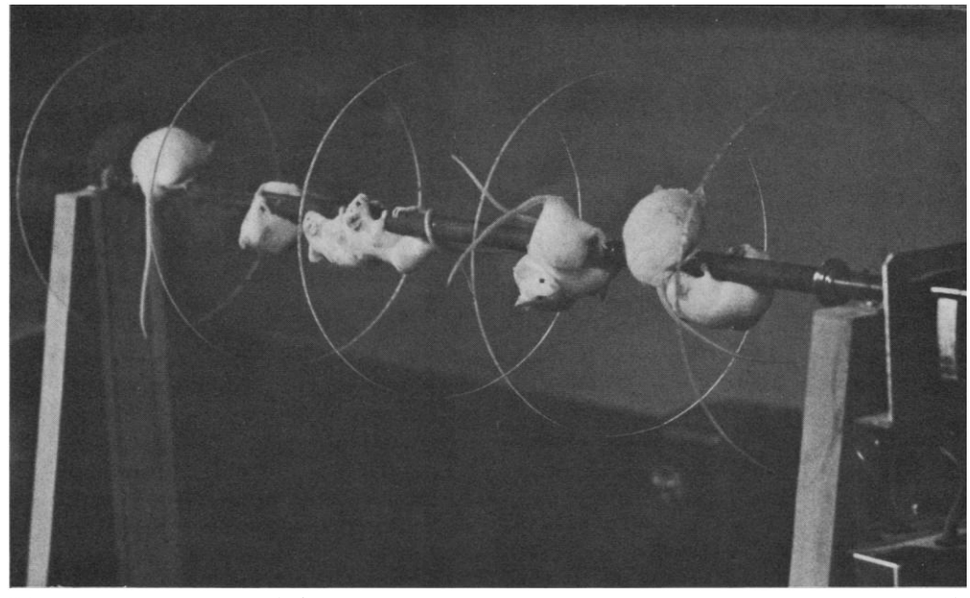
lar indirect assay for cells whose dopamine receptors are not linked to an adenylate cyclase. The assay involves pituitary cells that respond to dopamine by ceasing to make the hormone prolactin. Antischizophrenia drugs also block this response.

These two indirect assays of dopamine binding had an immediate practical application in the search for better antischizophrenia drugs. Drug companies are now searching for, and at least one company, Smith Kline and French, says it has found, a compound that blocks one kind of dopamine receptor but not the other. A drug that blocked the receptors in the caudate nucleus but not those in the pituitary would be quite valuable, as long as it still alleviated the symptoms of schizophrenia. Current antischizophrenia drugs, because they block dopamine receptors of pituitary cells, cause the cells to secrete excessive amounts of prolactin. Excess prolactin causes menstrual abnormalities, and it is also known to cause mammary tumors in animals.

The second discovery confirming Carlsson's hypothesis was a direct demonstration that the drugs block dopamine receptors. At first, researchers found it difficult to measure binding to any receptors on brain cells. The problem is that neurotransmitters tend to bind nonspecifically to all sorts of sites on cells; in fact, the number of nonspecific binding sites is far greater than the number of receptor sites for a neurotransmitter.

In 1973, three groups of investigators overcame this hurdle and found a way to measure specific binding of drugs to receptors for opiates such as heroin and morphine. The trick is to use low concentrations of highly radioactive drugs and to wash the brain tissue thoroughly to remove the opiates bound nonspecifically (and more loosely) to other sites. (The ability to measure binding to opiate receptors led to the finding that the brain makes its own substances, called enkephalins, that bind to these receptors and cause analgesia. It also led to a search, as yet unsuccessful, for new drugs that bind to these receptors, relieve pain, but are not addicting.)

Then, in 1975, Ian Creese and Snyder and, independently, Philip Seeman of the University of Toronto used the same method to measure specific binding of dopamine to its receptors. They found not only that antischizophrenia drugs bind to dopamine receptors but that the tenacity with which they bind is related to the potencies of the drugs. Thus, according to Snyder, "If you want to screen drugs for antischizophrenia activity, all you need is a very simple dopamine binding technique. This is much cheaper than previous testing techniques in animals where you need 100 grams of the drug and 100 rats. Now you need only about 1 milligram of the drug and a couple of test tubes."



White mice balance on a turning rod in a psychopharmacology laboratory. This is one of a battery of tests of the behavioral effects of drugs. [*Source: Pfizer, Inc.*]

But the binding assays, too, have a drawback. It is usually impossible to distinguish between substances that bind to a receptor and block the actions of a neurotransmitter and those that bind and mimic the actions of a neurotransmitter. To decide between these possibilities, researchers must give the substances to animals and observe their behavior. The binding assays, however, are quick and easy screens for substances that are likely to affect behavior.

In recent years, investigators have progressed to where they can not only screen for antischizophrenia drugs that block dopamine receptors but at the same time search for drugs with fewer side effects than those on the market. And they can use these techniques to screen for antianxiety and antidepressive drugs.

One of the side effects of antischizophrenia drugs that can be nearly eliminated is the parkinsonian effect. The clue to its elimination is the discovery that the drugs also bind to a class of receptors, called muscarinic receptors, for the neurotransmitter acetylcholine. Snyder and, independently, Richard J. Miller and C. Robin Hiley, then at Cambridge University, found that the better the drugs are at binding to muscarinic receptors, the less likely they are to cause parkinsonian side effects. This finding agrees with the old, but poorly understood, observation that atropine, which binds to muscarinic receptors, alleviates symptoms of Parkinson's disease. Apparently, nerves that use dopamine and nerves that use acetylcholine are close together and interact in the corpus striatum—the part of the brain that specifically malfunctions in Parkinson's disease.

Other serious side effects of antischizophrenia drugs are sedation and blood pressure lowering. David U'Prichard and Snyder found that these side effects can be predicted by comparing a drug's ability to bind to a class of receptors (α-receptors) for the neurotransmitter norepinephrine with its ability to bind to dopamine receptors. Drugs that have high affinities for α-receptors relative to dopamine receptors are likely to cause these effects.

Thus in their screening test for new antischizophrenia compounds, drug companies now employ three binding assays. They look for drugs that bind well to dopamine receptors and that also bind well to muscarinic receptors and that bind poorly to α-receptors relative to dopamine receptors. In addition, they often screen drugs for their affinity for the dopamine receptors linked to adenylate cyclases but not the receptors on pituitary cells that trigger prolactin synthesis.

The relatively tidy picture of the molecular actions of antischizophrenia drugs does not yet extend to other classes of drugs. But there are some good clues to the actions of other drugs. The antidepressants, for example, were thought for years to act by increasing the brain's supply of the neurotransmitters serotonin and the catecholamines. The earliest antidepressants, the monoamine oxidase inhibitors, seemed to act that way, and so did the more recently discovered tricyclic antidepressants. The

antihypertension drug reserpine, which causes depression in a number of patients, sedates rats, and depletes the brain of serotonin and catecholamines. Moreover, every clinically effective antidepressant blocks the sedating effects of reserpine in rats. This was taken as evidence that the drugs act by increasing brain serotonin and catecholamine concentrations, thereby negating reserpine's actions in depleting the brain of these neurotransmitters.

But the theory that antidepressants act by increasing the brain's supply of serotonin and catecholamines has now fallen by the wayside. The problem was that it could not explain how the more recently discovered antidepressants, such as iprindole and mianserin, work. These drugs do not seem to affect serotonin and catecholamine supplies, yet they block reserpine's actions in rats and they are chemically related to the tricyclic antidepressants.

Recently, Philip Kanof and Greengard discovered that antidepressants may act by blocking receptors for the neurotransmitter histamine. Histamine, like dopamine, has two kinds of receptors, one linked to an adenylate cyclase and one not. The Yale researchers found that a large number of chemically diverse antidepressants block the histamine receptors that are linked to an adenylate cyclase. Independently, Ray Chang, Vinh Tran, and Snyder discovered that the antidepressants block both kinds of histamine receptors, as measured by binding assays. According to Snyder, the antidepressants are 100 to 1000 times more potent in blocking histamine receptors than are the antihistamine drugs.

What these discoveries mean is that companies can look for new antidepressants by looking for drugs that block histamine receptors. "But catecholamines and serotonin must fit in somewhere," Snyder says. "Perhaps by blocking histamine receptors, the drugs secondarily influence serotonin and the catecholamines."

Still other drugs whose actions are beginning to be understood are the benzodiazepines (Valium and Librium). For many years, biologists debated how these drugs act. There was little doubt that the drugs shared something with meprobamate (Miltown), alcohol, and barbiturates since patients develop cross-tolerances. And it is well known that tranquilizers and sedatives potentiate the effects of alcohol. The question often asked was, Do benzodiazepines do anything that barbiturates do not do, or are they just less toxic barbiturates?

Two years ago, Claus Braestrup of Ferrosan Research Laboratories in Switzerland and Richard Squires, now at Lederle Laboratories, discovered that the brain has its own specific receptor for benzodiazepines. Their work was soon confirmed by Hans Mohler and T. Okada of Roche Pharmaceuticals in Switzerland. No drugs other than benzodiazepines bind to this receptor and no known neurotransmitters bind to it. And the affinities of benzodiazepines for their receptor reflect their relative clinical potencies in relieving anxiety. For this reason, most investigators believe that the benzodiazepine receptor is somehow related to the actions of these drugs and that the benzodiazepines really are different from barbiturates.

The discovery of the benzodiazepine receptor gave rise to another question: What is this receptor doing in the brain? A number of laboratories began looking for a naturally occurring substance in the brain that tightly binds to this receptor, but so far they have met with no success. Meanwhile, John Tallman of the National Institute of Mental Health and, independently, Squires' laboratory and Michael Williams' laboratory at Merck Sharp & Dohme have found that the benzodiazepine receptor is closely linked to receptors for the neurotransmitter γ-aminobutyric acid (GABA). When they add GABA, they increase the binding of benzodiazepines. What this may mean is that the search for a new substance in the brain that binds to benzodiazepine receptors could be in vain. There may not be a distinct benzodiazepine receptor that binds only the drugs and some as yet unknown antianxiety substance in the brain; the receptor may be part of the GABA system instead.

To further complicate matters, there now seem to be not one but several chemically distinct benzodiazepine receptors. "I think we are dealing with a group of different benzodiazepine receptor complexes," Squires says. "We can develop drugs that act on some but not all of these receptors." He explains that Lederle and other companies have already found some drugs that are good at reducing anxiety and are good anticonvulsants, as are Valium and Librium, but are not sedating. According to Squires, the Lederle compound is chemically quite different from Valium and Librium. It was synthesized in the company's cardiovascular program and its effects on the benzodiazepine receptors were completely unexpected.

So far, it looks as if all the pieces are fitting together and that the molecular actions of all the major drugs affecting behavior are beginning to make sense. But most investigators think that their current picture of how the drugs work is a gross oversimplification. According to Greengard, only 1 to 5 percent of the brain's neurotransmitters are known. Thus, he says, it would be almost inconceivably fortuitous if this handful of neurotransmitters happened to be the only ones involved in mental disorders and drug actions. What is much more likely is that the brain's chemistry is in a delicate balance and that almost anything that upsets that balance is likely to alter behavior.

Snyder gives the analogy of an electrical circuit. "The fact that a dangerous short circuit can be abolished by tripping a circuit breaker does not mean that the short is in the breaker—it may be anywhere in the circuit." For example, the fact that blocking dopamine receptors may alleviate schizophrenia symptoms does not mean that the fundamental defect in schizophrenia is an excess of dopamine.

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Yet, although they are oversimplifications, the new theories of drug actions promise to lead to much better new drugs. Since the assays are so quick and easy far more substances can be screened, and inevitably there are far more surprises. But since it takes at least 10 years from the time a drug is discovered until the time it is marketed, the new drugs discovered with the quick assays will not be available for quite some time.—GINA BARI KOLATA

Additional Readings

1. S. H. Snyder, *J. Contin. Educ. Psychiatry* **39**, 21 (1978).
2. P. Greengard, *Trends Pharmacol. Sci.* **1**, 21 (1979).