Parkinson's Disease: Search for Better Therapies

More specific drugs, without the adverse side effects of L-dopa, are one of the goals of the research

Treatment with the drug L-dopa has not solved the problem of Parkinson's disease, a degenerative brain disorder that afflicts some 200,000 people in the United States. When L-dopa therapy first came into widespread use in the late 1960's, hopes were high that Parkinson's disease could be permanently controlled by the drug. More than 10 years of clinical experience has taught another lesson, however. Although most—about 80 percent—of the patients respond well to L-dopa for about the first 3 years of treatment, almost all of them eventually develop disabling problems. Some of the problems may result from the progression of the disease, but others appear to be caused by L-dopa itself. Consequently, neurobiologists are reevaluating the manner in which the drug is used in therapy.

In addition, they are searching for better drugs that will correct the neural deficiencies underlying Parkinson's disease without causing the disturbing side effects associated with L-dopa. Some new agents have already been tested in human patients—but only with mixed results. Investigators are hopeful, however, that they will be able to devise more effective agents with the help of new information about the way dopamine acts in the brain. Dopamine is a neurotransmitter that is deficient in the brains of parkinsonian patients as a result of the degeneration of certain nerve cells producing it.

Neurotransmitters are chemicals that carry nerve impulses from one nerve cell to the next. Neurobiologists think that the lack of dopamine in the brains of parkinsonian patients and the consequent disruption in the transmission of nerve impulses causes the neurological symptoms of the disease. The main symptoms are difficulty in initiating voluntary movements, slowness of movement, muscular rigidity, and tremors.

To exert its effects on a nerve cell, a neurotransmitter must first bind to receptors on the cell surface. Recently, John Kebabian and Donald Calne of the National Institute of Neurological and Communicative Diseases and Stroke suggested that there are at least two kinds of receptors for dopamine in the brain. Paul Greengard of Yale University Medical School and Kebabian, who was then working in Greengard's laboratory, identified the first kind of dopamine receptor (now designated the D1 receptor) a few years ago. Binding of dopamine to this receptor activates an enzyme that synthesizes adenosine 3′,5′-monophosphate (cyclic AMP). Cyclic AMP in turn induces changes in the activity of the nerve cells bearing the receptors. The second type of receptor, designated the D2 receptor by Kebabian and Calne, differs from the first in that dopamine binding does not stimulate a cyclic AMP-synthesizing enzyme.

Kebabian and Calne think that insufficient dopamine at the D2 receptor may contribute to the development of the neurological features of Parkinson's disease. Bromocriptine and lergotrile are two new drugs that have been tested—with some success—for the treatment of Parkinson's disease in human patients. These drugs are potent mimics of dopamine's effects at the D2 receptor but not at D1 receptors. In fact, lergotrile blocks the action of dopamine at the D1 receptor, according to the NINCDS investigators. Another indication that inadequate dopamine activity at the D2 receptor is involved in the development of Parkinson's disease is that some drugs known to induce or exacerbate the symptoms of the disease also block dopamine's action at D2 receptors, but have much less effect at D1 receptors.

Kebabian and Calne think that it may be possible to identify drugs for treating Parkinson's disease by looking for agents that specifically mimic the action of dopamine at the D2 receptor.

Such new agents are certainly needed. Dopamine itself cannot be given to patients because it does not pass from the blood into the brain. Thus, L-dopa, which is the abbreviation for levodihydroxyphenylalanine, is given instead. This chemical can enter the brain where it is enzymatically converted to dopamine. A drug that inhibits the enzymatic reaction outside the brain is usually administered to the patients together with the L-dopa.

This method of replenishing the brain dopamine concentrations of parkinsonian patients works dramatically when they are first given L-dopa. But after they have been on the therapy for about 3 years, the drug begins to lose its effectiveness for many patients. In addition, they often develop distressing and incapacitating problems, including abnormal involuntary movements (dyskinesias), hallucinations and other psychiatric disturbances, and abrupt losses of response to doses of L-dopa that formerly controlled the symptoms. Sometimes the responses of the patients fluctuate abruptly between symptom control—which is usually accompanied by dyskinesia—and no control. These abrupt fluctuations are called the "on-off" phenomenon because the control is switched on and off like a light.

Although high doses of L-dopa can cause hallucinations, the psychiatric disturbances and intellectual decline seen late in treatment may be the result of the progression of Parkinson's disease. But there is a growing consensus among clinical neurobiologists that the other problems, the dyskinesias and on-off effects, are the result of long-term L-dopa therapy. Exactly how L-dopa causes these side effects is still not clear.

One problem may be that L-dopa is converted to compounds other than dopamine that are also neurotransmitters in the brain. Moreover, the enzyme that transforms L-dopa to dopamine is gradually lost as Parkinson's disease progresses.

In any event, the researchers think that an agent that mimics the action of dopamine directly without first having to be activated may give better control of Parkinson's disease without evoking as many unwanted side effects as L-dopa. Bromocriptine and lergotrile, for example, mimic the effects of dopamine in animal models of Parkinson's disease and do not require activation.

Clinical trials* have shown that the drugs improve the conditions of some parkinsonian patients. The clinicians are unanimous in their opinions that the agents will not solve all the problems of therapy, however. Lergotrile and

*Among the investigators conducting the clinical trials are: W. Birkmayer of the Ludwig-Boltzmann-Institut für Neurochemie in Vienna; Donald Calne of NINCDS; Stanley Fahn of the Neurological Institute in New York; Harold Klawans of Rush Presbyterian-St. Luke's Medical Center; Abraham Lieberman and Menek Goldstein of New York University School of Medicine; C. David Marsden of the University of London; Gerald Stern of University College Hospital Medical School in London; and Melvin Yahr and Roger Duvoisin of Mt. Sinai School of Medicine.

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Bromocriptine also produce serious side effects. In addition, they are expensive to use in the doses needed. Bromocriptine treatment may cost $15 per day just for the drug.

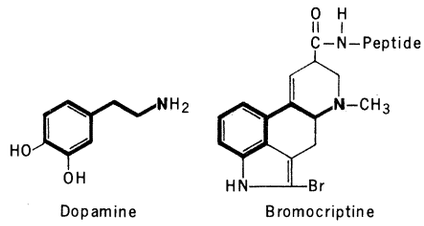
Lergotrile is no longer being tested in human patients because it produced liver damage in about one-third of the people who took it, even though animal tests gave no indication that the drug would be toxic to the liver. The damage was not permanent, however.

The clinicians testing Bromocriptine in humans think that this drug will be of at least limited use in the treatment of Parkinson's disease. They find improvement in the condition of one-third to one-half of the patients taking it, either alone or in combination with L-dopa. But there has been some disagreement over which types of patients are most likely to benefit from Bromocriptine. For example, Calne and Abraham Lieberman and Menek Goldstein of New York University School of Medicine find that the drug often alleviates on-off effects. In contrast, Stanley Fahn of the College of Physicians and Surgeons of Columbia University says that Bromocriptine helped less than half of the patients afflicted with this condition in his study and worsened the problem in some of them.

The side effects caused by Bromocriptine include nausea, dizziness, and psychiatric disturbances, which are more of a problem with this drug than with L-dopa. According to Lieberman and Goldstein, one-third of the patients in their study suffered from hallucinations. Nevertheless, they agree with the general consensus that Bromocriptine may help some patients who do not do well on L-dopa or who cannot tolerate it.

Bromocriptine and lergotrile are derivatives of the ergot alkaloids, a group of natural products made by a fungus that produce a variety of effects in animals. The structure of these ergot compounds includes a lysergic acid residue that may help to explain their hallucinagenic potential. Other ergot derivatives also have antiparkinsonian effects in animal test systems. Efforts to obtain therapeutic compounds without the untoward side effects of Bromocriptine are now under way in a number of laboratories, including those of the Eli Lilly Company.

In addition, other kinds of drugs are being tested as adjuncts to be used with L-dopa in the hope that they will alleviate L-dopa's side effects. One such agent is deprenyl, an inhibitor of an enzyme (monoamine oxidase B) that breaks down dopamine in the brain. The idea is that the inhibitor, by preventing dopamine breakdown, will help to maintain effective concentrations of the neurotransmitter in brain and prevent the sudden reappearance of parkinsonian symptoms.



Structures of dopamine and Bromocriptine. The heavy lines show the structural similarities between the two molecules.

Investigators, including W. Birkmayer of the Ludwig-Boltzmann-Institut für Neurochemie in Vienna, Gerald Stern of University College Hospital Medical School in London, and Melvin Yahr of the Mt. Sinai School of Medicine have tested the effects of deprenyl in human patients. They find that it enhances the effects of L-dopa, so that L-dopa dosages can be reduced. Moreover, Yahr says that deprenyl ameliorated on-off reactions in 21 of the 29 patients he studied who experienced the problem.

Another enzyme that attracks dopamine is catechol-*O*-methyl transferase, which adds a methyl group to the dopamine molecule. The matter is somewhat controversial but, in some studies, high concentrations of the methylated dopamine derivative have been correlated with the dyskinesias induced by L-dopa.

Early in this decade, Arthur Ericsson of Baylor College of Medicine found that an inhibitor of the methylating enzyme enhanced the therapeutic effects of L-dopa in the small number of patients tested. Ericsson's finding has never been confirmed by other researchers, however, and the inhibitor he used, and other, related compounds are considered too toxic for further tests in humans.

Currently, Fahn and his colleagues are investigating a different kind of inhibitor of catechol-*O*-methyl transferase as a possible adjunct to L-dopa. This compound, designated U-0521 by the Upjohn Company which makes it, has already been tested in humans as a drug for preventing spontaneous abortions. It was not effective for this purpose, but apparently was not toxic, either. Thus far, Fahn has only tested the agent in rats. He finds that it blocks the formation of the methylated derivatives of L-dopa and dopamine in these animals and increases the concentrations of L-dopa and the neurotransmitter in their brains.

Compounds other than inhibitors of the enzymes that break down dopamine are also being tested for use in the treatment of Parkinson's disease. A few years ago, André Barbeau of the Clinical Research Institute of Montreal and Abba J. Kastin of Tulane University Medical School and the Veterans Administration Hospital in New Orleans found that a small peptide called MIF decreased the tremors and rigidity of parkinsonian patients. Used in conjunction with L-dopa, it potentiated L-dopa's beneficial effects but not its side effects. How MIF produced these improvements in the patients is unclear.

Because MIF has to be injected intravenously for the best results, its widespread use is not practical and it is no longer being manufactured. Barbeau is now beginning to test in human patients a derivative of MIF that can be taken orally. He says that the derivative is just as effective in animal models of Parkinson's disease as MIF itself.

It is still too early to tell whether the MIF derivative or the other new drugs now being tested will prove valuable in treating Parkinson's disease. Meanwhile, by all accounts, L-dopa is still the best drug available for treating the condition. Because the benefits of L-dopa therapy generally decline after 3 years, however, some clinicians, including Calne and Fahn are now recommending a very cautious approach to institution of the therapy. They suggest that individuals who can function adequately in their occupations and in social situations not be given L-dopa until their condition begins to deteriorate. There are other drugs that are less effective than L-dopa that can be prescribed in the early stages of the disease. In this way, the beneficial effects of L-dopa, which are of limited duration, may be saved until they are truly necessary.

Caution is required, however, because L-dopa therapy has been shown to prolong the lives of Parkinson's disease patients when begun early enough. Thus, too much deterioration cannot be allowed before the drug is given. Moreover, the idea of withholding therapy may not be popular with patients—who usually want the doctors they consult to "do something." But in the view of Calne and Fahn and a growing number of other clinicians, delaying L-dopa therapy may enable the Parkinson's disease patient to function better for longer.

—JEAN L. MARX