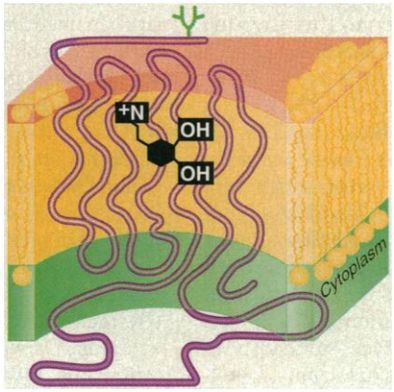
Will New Dopamine Receptors Offer a Key to Schizophrenia?



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A new suspect. The D4 receptor, threaded through the cell membrane, binds dopamine (hexagonal structure).

The search for a cause and ultimately a cure for schizophrenia has been a classic example of the street-light paradigm of scientific research, says neuropharmacologist Arvid Carlsson of the University of Gothenberg in Sweden. Carlsson is referring to the old joke about the drunk looking for his keys under the streetlight. The reason: not because he thinks he lost the keys there, but because that's where the light is best. Every so often, though, it must happen that the drunk gets lucky—and finds that his keys really were under the light.

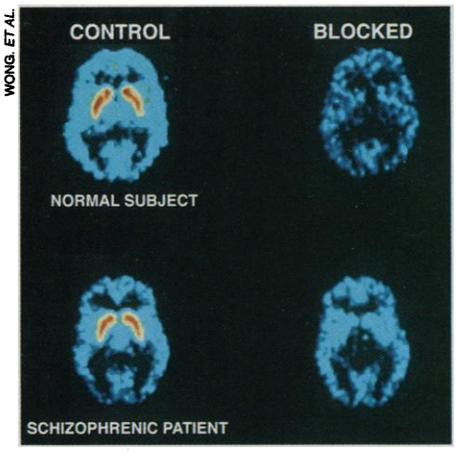
And that, says Carlsson, could be happening to neuropharmacologists working on schizophrenia. For the past 20 years, he says, the light has been shining most brightly on dopamine, because this neurotransmitter and its receptor molecules seem to play some role in the disease. Yet during all those years, researchers had very little success at showing just how the dopamine system was tied to the symptoms of the illness. Over the past four years, however, the discovery of three new receptor subtypes has rekindled hopes that a key to schizophrenia may finally have turned up—right in the street light.

The discoveries have also touched off a race by researchers and pharmaceutical companies to produce antipsychotic medications that would bind specifically to two of the most promising of the new receptors, known as D3 and D4, perhaps controlling schizophrenia more effectively and with fewer side effects than existing drugs. "If we can find a drug that works," says Carol Tamminga of the Maryland Psychiatric Research Institute, who is starting clinical trials of one of the new drugs this summer, "that will also give us additional clues to the disease."

Researchers caution, however, that the latest excitement over dopamine receptors could be just one more false dawn in research on schizophrenia—one of many in the century since the term was coined. Although one in every 100 individuals is afflicted with schizophrenia, researchers still have no universally accepted definition of the disorder, which is marked by hallucinations, delusions, eccentric or violent behavior, and social withdrawal. Suggested causes have included everything from slow viruses to "schizophrenogenic" mothers. And although the disease runs in families, searches for a schizophrenia gene or genes, says University of Toronto neuropharmacologist Phil Seeman, "have all bombed out."

In this obscurity, one highlight has been clues pointing to involvement of the dopamine system. Dopamine itself is a small, adrenaline-like molecule that acts both as a hormone, helping to regulate blood pressure, and as a neurotransmitter in the brain. Released into a synapse by one neuron, it binds to receptors on other neurons and influences their activity. One thing implicating it in schizophrenia, says Seeman, is the fact that the antipsychotic drugs that blunt symptoms have been shown to bind preferentially to dopamine receptors and block them. And the side effects of those drugs, known as neuroleptics, seem to mimic Parkinson's disease, which is caused by degeneration of dopamine-synthesizing neurons. "Everyone agrees the dopamine system is overactive" in schizophrenia, says Seeman.

But no one knows why—whether the fault lies in the receptors or in some other molecule—or how the overactivity could produce the symptoms of schizophrenia. What's more, the only dopamine receptor subtypes known until recently, called D1 and D2, had features that seemed at odds with what is known about the disease. Both subtypes are concentrated in the basal ganglia—knots of neurons involved in controlling movement. Yet schizophrenia is marked primarily by cognitive and emotional effects, not by effects on movement.



WONG *ET AL.*

Schizophrenic excess. PET scans show a higher level of dopamine receptors in a patient, even after a receptor blocker is adminstered.

What's more, the net effect of dopamine on D2 receptor–carrying neurons is to activate psychomotor pathways in the brain. Overactivation of those pathways could result in what are known as the positive symptoms of schizophrenia—hallucinations, delusions, and paranoia. But patients also exhibit negative symptoms, such as withdrawal and lack of emotional response, that are harder to explain with the D2 receptor, says Carlsson.

New clues, new targets. What may unknot these puzzles is a series of findings that began in 1990, when Pierre Sokoloff and his colleagues at INSERM in Paris identified and cloned a third dopamine receptor, D3, using a nucleic acid probe taken from D2. Oliver Civelli of the University of Oregon and Hubert Van Tol, who is now at Toronto, brought the number to four the following year. And a fifth receptor, similar to D1 in its DNA sequence and chemical activity, was cloned by groups led by Hyman Niznik in Toronto and Marc Caron at Duke.

Since then, says Caron, researchers have found that, unlike the earlier subtypes, D3 and D4 are concentrated in the part of the brain where the symptoms of schizophrenia are thought to originate: the limbic system, which controls cognition and emotion. Meanwhile Sokoloff and his colleagues have concluded that when D3 receptors bind dopamine, they tend to suppress behavior rather than stimulate it. That finding, says Carlsson, may explain how an overactive dopamine system "can give you a mixture of positive and negative symptoms" like those of schizophrenia: behavioral inhibition (that is, negative symptoms) mediated through D3 and stimulation (positive symptoms) mediated through other receptors.

The D4 subtype has its own set of circumstantial evidence pointing to a key role in the disease. In particular, the neuroleptic clozapine, the current drug of choice for schizophrenia—what Seldane is to allergies or Prozac is to depression, as one researcher put it—seems to have a high affinity for the D4 receptor. And last September Seeman and Van Tol reported that they had found six times the normal density of D4 receptors in the autopsied brains of schizophrenic patients.

Intriguing as it is, however, that result remains controversial, even among devotees of the dopamine hypothesis. Some question the technique used to measure the receptors, and Tamminga notes that the neuroleptics taken by schizophrenic patients throughout their lives could modify dopamine receptor

density. Hence the overabundance of D4 receptors might be a result of treatment rather than a cause of the disease.

Still, researchers are pressing ahead with plans to test drugs aimed at the new receptors. The D3 receptor is proving a popular target, in part because a drug specific for it might fill a gap in current therapies, which are generally more efficient at alleviating positive symptoms than controlling negative ones, says Sokoloff. "This may be a consequence of the fact that they have a preference for the D2 receptor over the D3 receptor," he explains.

Sokoloff's lab is working on compounds with the opposite preference, and Carlsson's group has devised a D3 blocker they call UH232. That experimental compound has already been tested in healthy volunteers, where, Carlsson says, "it has some kind of mixture of stimulant and depressant effects." And at the Maryland Psychiatric Research Center, Tamminga has started a clinical trial of UH232 in a small number of schizophrenic patients; if the initial results look promising, she says she will quickly increase the number of patients.

Meanwhile, Carlsson has an even more specific drug in the pipeline, one with a 20-fold higher affinity for D3 than D2, as opposed to the 3- to 5-fold preference of UH232. Other groups have their eye on the D4 receptor, hoping to devise a drug that binds to it more selectively than clozapine does. While no D4 blockers have made it to the clinical trial stage, says Dean Wong of Johns Hopkins University, a specialist in PET studies of the brain in schizophrenia, "pharmaceutical companies and universities are all now trying to get [drugs targeted to] D4 set up and running."

Cause or consequence? Even if one or another of these compounds proves superior to existing treatments, researchers are quick to point out that the mystery of schizophrenia may not be solved. The success of a drug aimed at D3 or D4 would confirm the importance of those receptors in producing the symptoms of the disease, they say, but the cause might still lie elsewhere. Indeed, studies of the D3 and D4 genes suggest that it does. Schizophrenia's tendency to be inherited implies that at least part of its cause has to lie in the genes, but the studies found no signs of abnormality in the D3 and D4 genes of schizophrenics.

One possibility is that the underlying pathology lies not in the receptors but in the molecules that regulate them—a possibility that gained ground last winter when Seeman and his colleagues turned up hints that dopamine receptors in schizophrenics are locked in a high-affinity state. Normally, he explains, regulatory molecules known as G proteins rapidly switch dopamine receptors back and forth between states of high and low affinity; in the latter state, he says, "the receptor is essentially out of business." When the group took autopsied brain tissue from schizophrenics and controls and tested the receptors' ability to switch, says Seeman, "we found that there's something wrong—only in schizophrenia—with that regulation control."

Then again, the cause might lie elsewhere in the dopamine system, says Caron at Duke—for example, in a malfunctioning of the "re-uptake" mechanism that clears dopamine from synapses after its message has been delivered. Or it might be centered in a different neurotransmitter system altogether. "The brain is so complicated," says Nancy Andreasen, a University of Iowa researcher, "that you really wouldn't expect a single neurotransmitter system to be the sole explanation of a disease process."

But Carlsson isn't discouraged by this uncertainty. "Even if the cause is not located at the dopamine receptors, we may still be able to manipulate the system in a much more precise way and avoid the side effects if we hit just the right receptor subtype." And if he and his colleagues manage to pull off that feat, the work under the streetlight will have paid off handsomely.

–Gary Taubes

Additional Reading

P. Sokoloff *et al.*, "Molecular Cloning and Characterization of a Novel Dopamine Receptor (D3) as a Target for Neuroleptics," *Nature* **347**, 146 (1990).

P. Seeman *et al.*, "Dopamine D4 Receptors Elevated in Schizophrenia," *ibid.* **365**, 441 (1993).

MATERIALS SCIENCE

Heating Up Some SQUIDs

As high-temperature superconductors get hotter, so does research in related fields. This trend started with the discovery of such superconductors in the late 1980s, which gave a major boost to the design of SQUIDs, or superconducting quantum interference devices. Incorporating high-temperature superconductors into the design of SQUIDs, sensitive magnetic detectors used to study everything from gravity waves to heart arrhythmias, raised their operating temperatures so they could be cooled with liquid nitrogen instead of liquid helium. This made them cheaper and easier to work with and opened the door to new applications in areas such as geology and medicine. Now, a research team working with the latest generation of high-temperature superconductors at IBM's Thomas J. Watson Research Center in Yorktown Heights, New York, has taken SQUIDs yet another step higher.

On page 1075, Arunava Gupta and his IBM colleagues Jonathan Sun and Chang Tsuei report making the first SQUID from a new class of mercury-based high-temperature superconductors, devices which function up to a record-setting 112 K. Commercial high-temperature SQUIDs, made of older materials, maxed out near 90 K. And researchers say the success holds out the prospect of even warmer SQUIDs down the road, since the current temperature record for superconductors—about 135 K—is held by other mercury-based superconductors.

"This is a very positive step," says John Wikswo, a physicist at Vanderbilt University in Nashville, Tennessee, who is investigating the use of SQUIDs to look for flaws in materials, such as cracks in airplane wings. "As the temperature of SQUIDs get higher, the technology gets easier to apply and cheaper."

To fabricate the new SQUID, the IBM group replaced the yttrium, barium, copper, and oxygen (YBCO) used in older superconductors with a superconducting thin film made from mercury, barium, calcium, copper, and oxygen (HBCCO). Although the new devices can function more than 20 K above those made from YBCO, both are typically operated at the same temperature, the 77 K of the liquid nitrogen coolant. But even at this operating temperature, HBCCO has the potential to improve SQUID performance over the current generation of YBCO-based devices, says Gupta, because it opens a larger window between the operating temperature and the threshold at which the material superconducts, also called the transition temperature.

When that window is small, as it is for YBCO-based SQUIDS—their transition temperature is at about 10 K above liquid nitrogen's temperature—small variations in the operating temperature can lead to cumulative measurement errors in the detectors. "We expect that this drifting will be reduced with mercury-based SQUIDs, because you're operating further from the transition temperature," says physicist Mark Ketchen, who heads IBM's SQUID research effort.

The new SQUID also represents another step toward researchers' ultimate goal of operating the devices at temperatures near 150 K. That would enable them to do away with the liquid cryogens altogether and replace them with on-chip electronic coolers, thereby making SQUIDs smaller, cheaper, and more portable. But that will take further advances in high-temperature superconductivity since neither HBCCO or any other current material operates at such high temperatures. But if this can be achieved, SQUID researchers can look for even hotter payoffs.

–Robert F. Service