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