NEUROSCIENCE

Key Protein Found for Brain's Dopamine-Producing Neurons

Just as a delicious entree can be marred by too much or too little seasoning, the brain needs exactly the right amounts of all its chemical signaling molecules. Take the neurotransmitter dopamine. People who have too little because they have lost the brain neurons that make this chemical develop the debilitating symptoms of Parkinson's disease. Conversely, too much may contribute to the mental disorder of schizophrenia. Now, researchers have identified a molecular chef that may play a key role in controlling how much dopamine the brain makes.

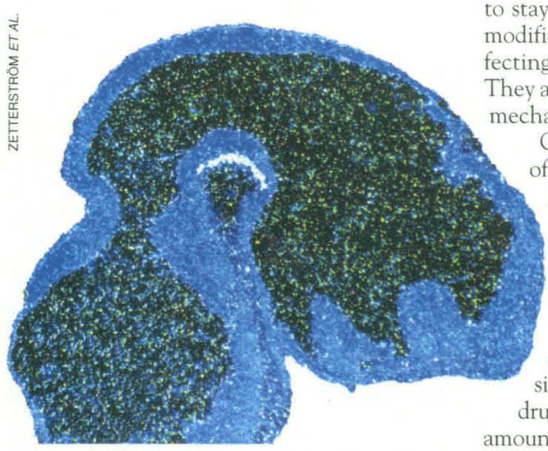
On page 248, a team led by Thomas Perlmann of the Ludwig Institute for Cancer Research and Lars Olson of the Karolinska Institute, both in Stockholm, reports that a molecule called Nurr1 plays a critical role during embryonic development in the formation of the group of dopamine-producing brain cells that are lost in Parkinson's disease. Nurr1 also appears to help keep those cells active throughout life.

Neuroscientists are intrigued by the discovery because it may help explain why that particular set of neurons degenerates in Parkinson's patients. The problem might, for example, result from a defect in Nurr1 activity. "It's a very good candidate to play a role in the pathology of Parkinson's disease," comments cell molecular biologist Orla Conneely of Baylor College of Medicine in Houston, whose team originally discovered Nurr1 and now has unpublished findings supporting the current work. The finding also raises the tantalizing possibility that boosting or restoring Nurr1 activity in failing nerve cells may delay or prevent the onset of Parkinsonian symptoms. "Finding a [protein] that affects such a specific [section] of the brain is very exciting," comments neurobiologist Ron McKay of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. "The potential for pharmacology is very interesting."

Conneely and her colleagues discovered Nurr1 in 1992 while they were screening mouse tissues for nuclear receptors, molecules in the nucleus that bind to hormones or hormonelike substances and then regulate gene expression. Among their finds was a gene they called *Nurr1* because its protein resembles a previously discovered nuclear receptor called Nur77. Both bind DNA, and because their DNA-binding domains are almost identical, it is likely that they control some of the same genes, Conneely says. But unlike Nur77, which is present in tissues throughout the body, Nurr1 was found by Conneely primarily in the brain.

That location caught molecular biologist Perlmann's eye, particularly when he realized that the gene encoding Nurr1 is most active in the dopamine-producing cells. Working with Rolf Zetterström in Olson's lab, he went on to create knockout mice lacking either one or both copies of the *Nurr1* gene.

As they now report, the mice with no copies of the gene failed to suckle and died a day or so after birth. The major physical difference the Swedish group could detect between these mice and normal animals of the same age was in the midbrain region, which contains the neurons that degenerate in Parkinson's. The cells there were poorly organized, suggesting that they had never specialized into dopamine-producing neurons.



ZETTERSTRÖM *ET AL.*

At work. Nurr1, shown in white in this embryonic mouse brain, prompts the development of midbrain dopamine nerve cells.

The team confirmed this suspicion by testing for the presence of proteins known to be produced by these particular neurons. Nurr1, tyrosine hydroxylase (an enzyme critical for dopamine production), and the other proteins they screened for were all absent. With no Nurr1, Perlmann says, "that cell type is clearly missing." Conneely, whose group has seen the same changes in the Nurr1 knockout mice they made, agrees: "Clearly this [result] suggests that Nurr1 has a selective, essential role in neurodevelopment," she says.

In addition, although mice lacking one copy of the gene develop normally, as adults they don't make as much dopamine as do mice with two intact copies of the *Nurr1* gene, Perlmann notes. The Swedish team's preliminary experiments suggest that this is because the animals' dopamine-producing cells make less of the neurotransmitter, not because they have fewer of these cells. Thus, the group thinks that Nurr1 plays two roles: Not only does it cause dopamine cells to form in the first place, but it also helps them produce the right amounts of dopamine.

That idea still needs to be confirmed, however. Indeed, neuroscientist Clifford Saper, of the Beth Israel Deaconess Medical Center in Boston, cautions that "a number of different pieces of the puzzle need to go into place" before researchers will understand just what Nurr1 does. He notes, for example, that it is unlikely that Nurr1 affects only the midbrain dopamine-producing neurons. McKay and Conneely agree. They note that Nurr1 and related nuclear receptors are unusual because their genes are turned on very early when cells receive signals to grow. They then tend to stay on, although their activities may be modified by their natural ligands, in turn affecting which genes the receptors activate. They are "part of a very generalized signaling mechanism that cells use," says McKay.

One critical missing piece is the identity of the natural molecule that binds to Nurr1. It will be the target of an intensive search, because it is needed to fully understand Nurr1 function, and it might provide clues to therapies for dopamine-related disorders. If Nurr1 is indeed essential for dopamine production in adults, then it may be possible to treat those disorders by finding drugs that either increase or decrease the amount of Nurr1 activity, suggests Olson.

Alternatively, researchers may be able to transfer active *Nurr1* genes into undifferentiated nerve cells growing in culture, converting them into dopamine-producing cells that could be used to replace those damaged in Parkinson's, Perlmann adds. The use of cultured nerve cells for this purpose is currently being studied (*Science*, 4 April, p. 66).

Even better, though, would be a way to prevent Parkinson's disease before it develops, and Conneely thinks the Nurr1 discovery could help here as well. Because this disease does not usually seem to run in families, experts have long sought an external cause, such as an environmental toxicant. It may now be possible to narrow the search by looking at how potential toxicants affect Nurr1. And that could lead to a treatment, she adds: "If we find [toxicants] that inhibit the activity of Nurr1, we may then be able to identify drugs that can counteract that."

Perlmann cautions that any applications are mere speculation now, but he hopes that eventually clinicians can learn to keep the brain seasoned with just the right amount of at least one important neurotransmitter.

–Elizabeth Pennisi