ingly enough," Sil adds, "Nasmyth's group and our group have found that *ASH1*'s protein product, Ash1p, seems to be localized predominantly to the daughter nucleus, which is exactly the right place for a protein that's inhibiting *HO* expression in daughters" (see illustration).

This added up to a neat scenario: More Ash1p ends up in the daughter, hobbling the daughter's *HO* gene, because She proteins drag it in from the mother. At least that's what both labs guessed, until a problem cropped up. After identifying Ash1p, Nasmyth's lab found that it begins to peak in the daughter at the end of the mother's cell cycle, just before the two separate—but after the She proteins that presumably brought it there have already dispersed. So the proteins must have already ferried something into the daughter that helps Ash1p to accumulate. "The model that both Nasmyth's lab and we support is that there is another factor out there controlling the asymmetry of Ash1p synthesis," Sil says. Presumably, this factor is the one transported by the She proteins. "That's the next Holy Grail," says Sil. And both labs are now off in pursuit.

Even though this developmental chain still has a gap, "the number of missing links in yeast is probably smaller now than the number in *Drosophila* embryos" and other examples of asymmetric development, says UCSF cell biologist Andrew Murray. And Shapiro believes that it won't be long before the railwaylike mechanisms for protein localization discerned in yeast turn up in other organisms as well. "The lessons learned from yeast are going to be valuable both up and down—up to the higher mammalian cells and down to the lower bacterial cells," she says. And with those lessons, the many-stranded story of cell divergence may finally start coming together.

–Wade Roush

NEUROBIOLOGY

Rat Study Sheds Light on Cocaine Craving

To a cocaine addict, a small dose of the drug is bad news: It "primes" the brain's reward system, intensifying the craving for more cocaine. And the same effect seems to be triggered by environmental cues that an addict associates with obtaining or taking the drug. Researchers have been trying to figure out the neurobiology behind this phenomenon, because it appears to be a crucial part of the addiction process itself—and if they can understand this reward-priming mechanism, they may be able to find a way to block it with drugs and so prevent relapse of cocaine use in cocaine-dependent people. In a paper on page 1586 of this issue, a team at Yale University School of Medicine, led by Eric Nestler and David Self, reports an important step toward both goals.

The work builds on a growing understanding of how addictive drugs interact with an important neural pathway that uses the neurotransmitter dopamine to send signals between nerve cells. In research reported last month in *Nature*, for example, a team at Duke University verified that cocaine and amphetamines block the transporter molecule that normally mops up dopamine from the synapse, where it activates cell-surface receptors. Now the Yale group has shed some surprising new light on the complex role that this receptor activation plays in the priming mechanism and the processes of addiction. In fact, it appears to play two separate roles.

Dopamine interacts with two types of neural receptors, called D_1-like and D_2-like receptors. When the Yale team gave cocaine-dependent rats a shot of compounds known to stimulate only the D_2-like receptors, the rats' craving for cocaine appeared to increase. But when they administered a shot of compounds that stimulate only D_1-like receptors, they found the opposite effect: The rats no longer sought cocaine, even after they received a priming dose.

Self and his colleagues don't have a complete explanation for this dual effect—in part because it's hard to tell precisely what their experimental rats are experiencing—but it suggests that within the dopamine pathways, different biochemical routes contribute to drug-seeking behavior and other aspects of cocaine addiction. "This is the first demonstration that [different types of dopamine receptors] have qualitatively different effects on cocaine-induced behaviors," says Self, a behavioral neuroscientist. "It's provocative. ... This is extremely difficult research to do," says behavioral pharmacologist Bill Woolverton of the University of Mississippi School of Medicine.

The Yale team used a system in which rats could self-administer cocaine by pressing a lever. The animals kept up a regular routine of lever-pressing over a 2-hour period. When saline was substituted for cocaine for 2 hours, the rats began to press the lever much less frequently—presumably because their brains detected an absence of the drug. Then a "priming" injection containing either a D_1 agonist—a compound that binds and activates D_1-like receptors—or a D_2 agonist was given. Like a priming dose of cocaine, the D_2 agonist triggered a return to regular lever-pressing, but the D_1 agonist had no effect. If the rats were then given a small dose of cocaine, those that had the D_1 agonist still rarely pressed the lever, while the D_2 group pressed even more frequently. "The D_1-like receptor agonist actually blocks cocaine priming," says Self.

It is "as if the D_1 agonist makes [the rats] feel like they've had cocaine," but without making them go back for more, says neuropharmacologist Ken Johnson of the University of Texas Medical Branch at Galveston, adding "this is pretty exciting." Behavioral pharmacologist Ian Stolerman of the Institute of Psychiatry in London agrees that the work is "very interesting." Activation of the D_1-like receptors may produce a sense of gratification, he surmises, while activation of the D_2-like receptors appears to trigger the craving for more drugs.

If so, blocking the D2-like receptors should block drug-seeking behavior. But Self and his colleagues note in their paper that compounds that block dopamine receptors have been found to exacerbate symptoms of cocaine withdrawal. A better approach, they suggest, would be to work on D1-like receptor agonists in the hope that they would provide gratification in cocaine-dependent people without triggering craving for more cocaine. Woolverton says that although the work is preliminary, the results support a move to human tests of D1-like receptor agonists to see if they dampen the craving for the drug. He cautions, however, that the rat model might not correctly predict what would happen in humans. It would also be important to determine whether the agonists themselves are addictive in people.

Bad medicine.
Once touted as a tonic, small doses of cocaine are now known to intensify craving in dependent people.

If the results do hold up, Woolverton and Johnson suggest another interesting possibility: Because some other drugs, such as the opiates, also activate the "reward" pathway involving dopamine, D_1 agonists might eventually be useful in treating addiction to drugs other than cocaine.

–Claire O'Brien

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