

AD, suggesting that the drug traps the aggregates in an intermediate state. But the researchers still didn't know whether that state was less toxic to cells.

To find out, Graef exposed cultured rat neurons to  $\beta$  amyloid with and without the new drug and FKBP. As expected,  $\beta$  amyloid alone killed the cells. But the drug, along with FKBP, prevented much of the cell death, indicating that the smaller bundles are indeed more benign.

Whether this protection can be extended

to animals, let alone humans, remains to be seen. "They've played a creative chemical trick that clearly could be practical," says Peter Lansbury, a chemist at Harvard Medical School in Boston, "but the path from this to an Alzheimer's drug is going to be extremely difficult." One huge problem, Lansbury says, will be finding an alternative to Congo red—which doesn't enter cells or cross into the brain—that targets  $\beta$  amyloid.

The strategy might be easier to employ in other diseases, Lansbury suggests, in which

the protein targets are more rigid and stable than  $\beta$  amyloid, which has a floppy, disordered structure. Some oncogenes, for example, work as dimers, so blocking the dimer from forming might lead to a cancer therapy. Viruses and bacteria also enter cells through protein-protein interactions. Says Briese-witz: "If we could use small molecules to disrupt protein-protein interactions, we could target many more biological processes to fight disease."

—INGRID WICKELGREN

## NEUROSCIENCE

# Prozac Treatment of Newborn Mice Raises Anxiety

The U.S. Food and Drug Administration this month ordered drugmakers to put strong new labels on serotonin-based antidepressants, warning that they may raise the risk of suicidal behavior in children. Now a study by researchers at Columbia University indicates that fluoxetine (the generic name for Prozac), paradoxically, seems to raise anxiety levels in newborn mice.

The study, published on page 879 of this issue, "suggests that fluoxetine and probably other SSRIs [selective serotonin reuptake inhibitors] may have additional unexpected problems," says Miklos Toth, a pharmacology professor at Cornell University's Weill Medical College in New York City. Some scientists caution, however, that the mice in this study were at a much younger developmental age than children likely to be treated for depression.

Fluoxetine is the oldest of the SSRIs and the only one approved for pediatric use. It operates primarily on the serotonin transporter (5-HTT), which is responsible for helping neurons vacuum back up excess serotonin that they have released. By blocking the transporter, the drug enables serotonin to linger in synapses, making more available to be taken up by target receptors.

Previous animal research had shown that in early life serotonin acts as a growth factor in the brain, modulating nerve cell growth, differentiation, and migration. Interfering with this function can have behavioral consequences. Mice who have had their serotonin transporters genetically knocked out—and thus reuptake disrupted—exhibit increased depression- and anxiety-related behaviors.

The Columbia researchers, led by

psychobiologist Mark S. Ansorge, sought to determine whether fluoxetine would have the same effect as knocking out the two copies of the transporter gene. They bred sets of mice with one, two, or no functioning copies of the *5-HTT* gene. Then they randomly gave either saline injections or fluoxetine—at doses equivalent to therapeutic ones for humans—to newborn mice between 4 and 21 days old in each group. Nine weeks after the last injection, mice were given tests that revealed their emotional states.

As expected, the drug had no effect on the mice lacking any 5-HTT; they already exhibited anxiety. But the two other groups started acting like the 5-HTT-deficient group when they were treated with fluoxetine. In comparison to the saline-treated

with stress response. Co-author René Hen explains that when serotonin reuptake is blocked, the increased levels in the synapse lead to "abnormal activation [of] a bunch of receptors" during a critical phase of development. "Overstimulation could result in abnormal development" in areas of the limbic system, he says.

The scientists believe that their work could help explain a noteworthy finding announced last year from a longitudinal study of New Zealanders (*Science*, 18 July 2003, p. 386): that people with a polymorphism that reduced their 5-HTT activity were more likely than others to become depressed in response to stressful experiences.

Another implication, of course, is for those exposed to SSRIs at a tender age. The authors say the period of brain development studied in the mice corresponds roughly to the last trimester of pregnancy through age 8 in humans. So, they conclude, "the use of SSRI medications in pregnant mothers and young children may pose unsuspected risks of emotional disorders later in life."

Both notes that in contrast to humans, a partial deficit (having one defective *5-HTT* allele) is not enough to adversely affect mice's behavior. So "it is possible that humans are more sensitive than rodents to the adverse effect of fluoxetine." But he agrees with Harvard child psychiatrist Timothy Wilens, who says that the "very early exposure calls into question the generalizability [of these results] to children." Columbia psychiatrist John Mann, who was not associated with this study, adds: "This has nothing to do with the issue of SSRIs in kids because they get the SSRI well after the equivalent period in this study."

Mann says, however, that "this is an important study" because it shows that even transient loss of transporter function during a critical period in brain development may lead to depression in adulthood.

—CONSTANCE HOLDEN



**Chemical imbalance.** Mice treated with Prozac as newborns showed reduced exploratory behavior when tested on an elevated maze.

pups, they showed reduced exploratory behavior in a maze test. They also took longer to start eating when placed in a novel setting and were slower to try to escape a part of the cage that gave them mild foot shocks. All these behaviors are regarded as signs of anxiety and depression in animals.

The authors conclude that disruption of 5-HTT early in brain development affects the development of brain circuits that deal