

A Life-Altering Chemical

Researchers are beginning to get a handle on dopamine's role in depression and addiction.

ALTHOUGH LESS THAN 1 PERCENT OF THE BRAIN'S NEURONS PRODUCE dopamine, the neurochemical exerts powerful effects on motivation, reward, learning, memory, sexual desire, and pleasure. "To a large degree, dopamine is what makes us human," says HHMI investigator Li-Huei Tsai. Yet, scientists know relatively little about how this neurotransmitter is so vital for many different behaviors.

>> Neurotransmitters such as dopamine and serotonin are molecular messengers released by neurons to communicate information to neighboring neurons. Studies by two independent HHMI research teams are

helping to clarify the molecular events that occur after dopamine binds to its receptors. Their findings may lead to new treatment strategies for depression, Parkinson's disease, and addiction.

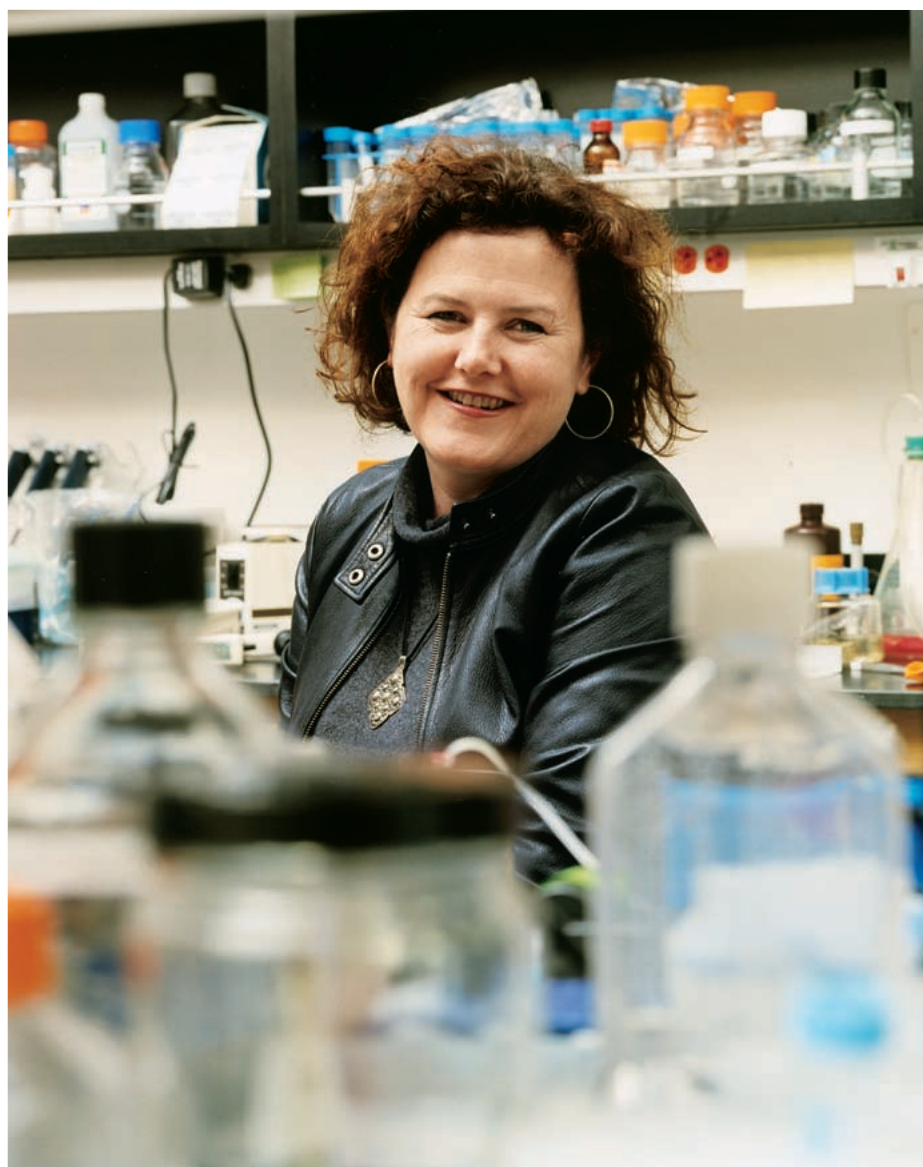
In studies published in the July 27, 2005, issue of *Cell*, a research group led by Tsai at Harvard Medical School discovered a molecule that links faulty dopamine signaling in the brain to the neural machinery that breaks down in people with depression. The findings may explain why commonly prescribed antidepressants are ineffective for some people and why, for others, they can take weeks to work.

That long lag time has been one of the enduring puzzles in the treatment of depression, says Tsai. Antidepressants work by increasing levels of the neurotransmitters serotonin and/or noradrenaline in the brain. The efficacy of antidepressants, however, may depend more on changes to much later events that occur in the dopamine-signaling pathway.

Tsai and lead author Sang Ki Park wanted to know more about those downstream events—which may involve little-known signaling pathways that are triggered when one type of dopamine receptor, D2, is activated. Park launched

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ERIN SCHUMAN



Local stimulation of protein synthesis by dopamine may also modify synapses in the brain during learning, says Erin Schuman.

Misha Gravenor

Li-Huei Tsai believes her lab's findings may lead to antidepressant drugs with improved efficacy.

the studies with a broad screen that turned up surprising information: A cell suicide molecule, prostate apoptosis response 4 (Par-4), interacted with a central regulatory segment of the D2 receptor.

The researchers then showed that Par-4 was produced in neurons where D2 receptors function. By knocking out Par-4 in mouse neurons or disrupting its interaction with the receptor, Tsai and Park caused striking behavioral changes in the mice. The knockout mice showed depression-like behaviors in multiple tests, easily giving up when faced with ordinary challenges.

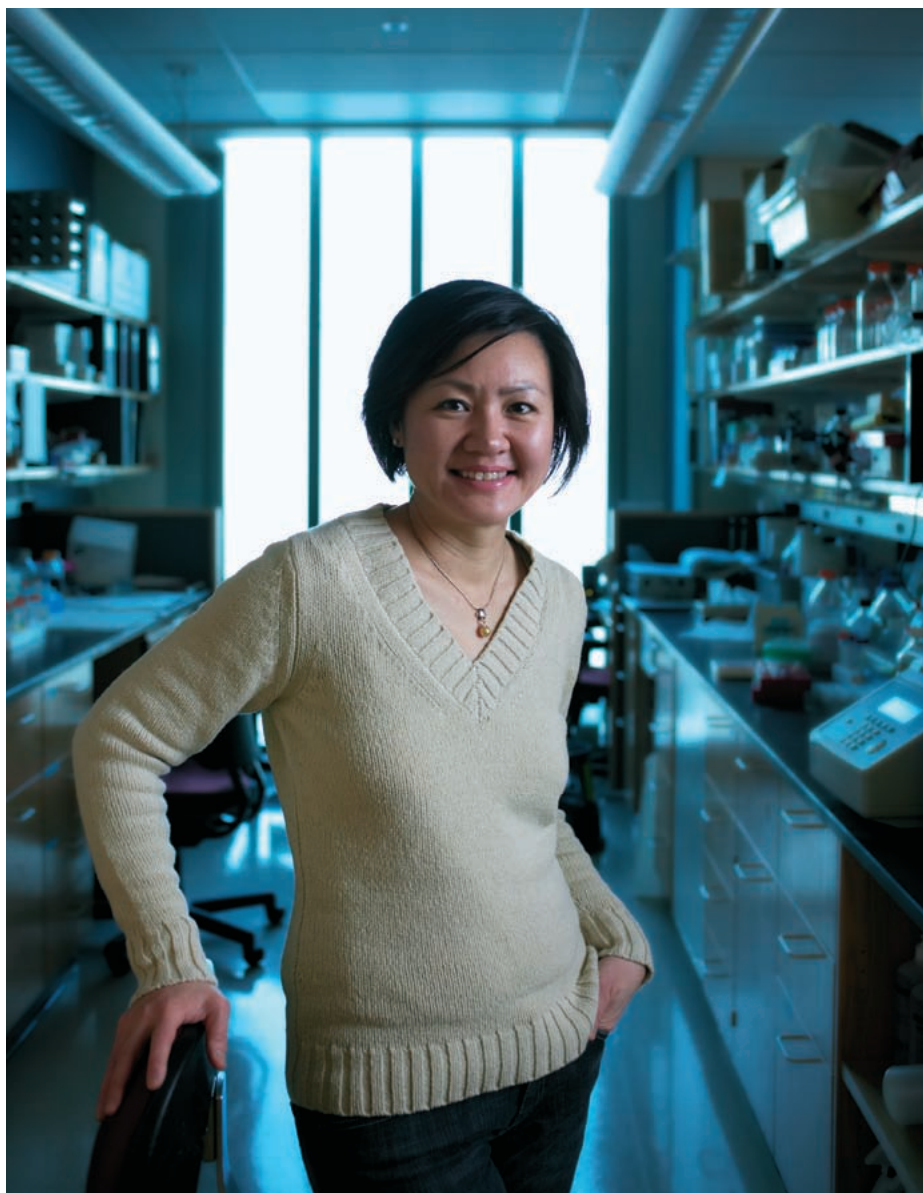
"These are very exciting results for two reasons," Tsai says. "First, they indicate the importance of the signaling pathway mediated by the D2 receptor in depressive behavior. And second, this study pinpoints a specific pathway that implicates Par-4 in this process, which opens new possibilities for developing improved antidepressants."

Synthesize Locally, Act Globally

Approaching dopamine from a different direction, HHMI investigator Erin M. Schuman and her colleague Bryan Smith, both at the California Institute of Technology, discovered how dopamine stimulates the synthesis of proteins in neuronal processes, which may in turn modify synapses in the brain during reward-related learning. The brain's reward circuitry is the top target of addictive drugs.

According to Schuman, scientists knew that dopamine influenced the strengthening of synaptic connections among neurons. This strengthening, or plasticity, causes activation of protein synthesis in the dendrites, which somehow leads to enhanced activity of other kinds of neurotransmitter receptors. However, Schuman says, no one knew how dopamine influences local protein synthesis and triggers plasticity.

Schuman, Smith, and their colleagues introduced the gene for a fluorescent reporter molecule into cultured rat



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LI-HUEI TSAI

neurons, so that the neurons glow during protein synthesis. When the researchers activated dopamine receptors on the dendrites, they detected the glow in the dendrites, revealing that dopamine activated local protein synthesis and, thus, promoted plasticity.

Additional experiments indicated that activation of dopamine receptors triggered immediate enhancement of synaptic transmission in the neurons. "That's a result that people have been seeking for years," says Schuman. "It's a very rapid effect on synaptic transmission

that is protein synthesis-sensitive." The findings were published in the March 3, 2005, issue of *Neuron*.

According to Schuman, this research could have implications for understanding and treating drug addiction. "Over the past few years, investigators have begun to focus on the dendrite and its spines as potential sites that are altered during reward and addiction," she says. "This raises the possibility that some of the signaling that goes awry during addiction may have to do with local protein synthesis." —Susan Gaidos and Jim Keeley ■