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RESEARCH NEWS

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Molecule Provides a Missing Link in Understanding Depression

Researchers have discovered a regulatory molecule that links faulty dopamine signaling in the brain to the neural machinery that breaks down in people who suffer from depression.

The findings may explain why commonly prescribed antidepressants can take weeks to work and why the drugs are ineffective for some people. The researchers said their findings could open the way for the development of antidepressant drugs with improved efficacy.

The researchers, led by Howard Hughes Medical Institute investigator Li-Huei Tsai at Harvard Medical School, published their findings in the July 29, 2005, issue of the journal *Cell*.

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- Li-Huei Tsai

According to Tsai, one of the longstanding puzzles in the treatment of depression has been the long lag time that it takes before antidepressants begin to work. These drugs ameliorate depression by increasing levels of the neurotransmitters serotonin and/or noradrenaline in the brain. Since the clinical effects of these drugs are usually significantly delayed, it is now believed that their efficacy depends on changes to later events in the signaling pathway resulting from adaptation to chronic treatment, said Tsai.

Neurotransmitters such as serotonin and dopamine are molecular “messengers” that neurons fire at protein receptors on the surface of neighboring neurons. Drugs that influence the levels of these neurotransmitters are central to treating a wide range of neurological disorders.

In the current research, lead author Sang Ki Park sought to understand the little-known signaling pathways in the cell that are triggered by activation of the D2 receptor. He first conducted a broad screen for proteins that interacted with a central regulatory segment of the D2 receptor.

One of the proteins that the screen revealed, surprisingly, was a regulatory molecule involved in the cell's suicide program, called prostate apoptosis response 4 (Par-4) Apoptosis is the mechanism by which the body rids itself of unneeded or damaged cells.

Further studies revealed that Par-4 was produced in the same neurons where D2 receptors function, and that it competes with another key signaling molecule, calmodulin, to bind to D2 receptors. The outcome of this competition depends on calcium, one of the most important regulators of neuronal function, said Tsai.

The researchers found that knocking out Par-4 in mouse neurons or disrupting its interaction with the receptor caused a loss of the normal inhibition of another key regulatory molecule, called cyclic AMP.

The behavioral consequences of loss of Par-4 function were striking, the researchers found. Mice deficient in Par-4 activity showed depression-like behaviors in multiple tests. When placed in a water-filled chamber, they gave up swimming as a means of escape more quickly than do normal mice. When suspended by their tails, the mutant mice try less to wriggle free and instead hung limply. When presented with food in an open space, which mice perceive as an uncomfortable setting, they showed less motivation to overcome their discomfort and obtain the food, despite hunger. Furthermore, they showed reduced motivation to explore open spaces than do normal mice, said Tsai. Other tests confirmed that anxiety was not the basis of the abnormal behaviors in the Par-4-deficient mice, she said.

Identifying Par-4's role in dopamine-mediated signaling could have important scientific and clinical implications, said Tsai. “These are very exciting results for two reasons,” she said. “First, they indicate the importance of the signaling pathway mediated by the D2 receptor in depressive behavior. While there had been interesting studies on the involvement of dopamine D2 receptor in depression, the mechanistic link at a molecular level has never been clear.”

“Secondly, this study pinpoints a specific pathway that implicates Par-4 in this process, which opens new possibilities for developing improved antidepressants,” she said. Tsai said that further studies in her laboratory would aim not only to understand the Par-4 regulatory pathway in greater detail, but also to explore drugs that could affect its normal function.