Protein can nurture or devastate brain cells, depending on its 'friends'

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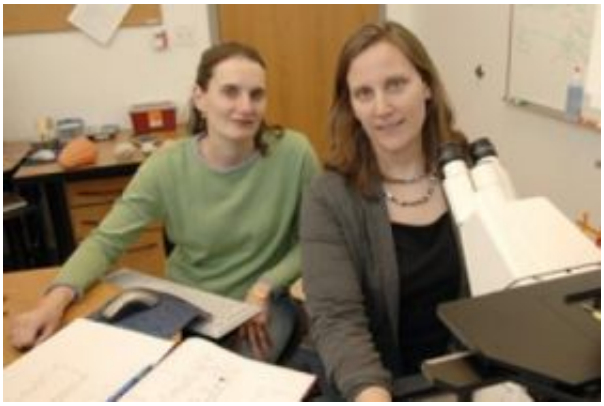

Dr. Amelia Eisch (right) and colleagues from psychiatry, including Dr. Diane Lagace, uncovered a beneficial mechanism of the Cdk5 protein, which is also thought to kill brain cells and contribute to diseases such as Alzheimer's. The researchers found that Cdk5, together with its activating partner molecule p35, helps immature nerve cells become fully functional. Credit: UT Southwestern Medical Center

Researchers at UT Southwestern Medical Center have uncovered new insights into the "Dr. Jekyll and Mr. Hyde" nature of a protein that stimulates stem-cell maturation in the brain but, paradoxically, can also lead to nerve-cell damage.

In two separate studies in mice scheduled to appear online this week and in an upcoming issue of the *Proceedings of the National Academy of Sciences*, UT Southwestern research teams studied the protein Cdk5 and

discovered both helpful and detrimental mechanisms it elicits in nerve cells.

Dr. Amelia Eisch, assistant professor of psychiatry at UT Southwestern, and her colleagues uncovered a beneficial mechanism of the helpful "Dr. Jekyll" side of the Cdk5 protein, which is also thought to kill brain cells and contribute to neurodegenerative diseases such as Alzheimer's. In the current study, Dr. Eisch found that Cdk5, together with its activating partner molecule p35, helps immature nerve cells become fully functional.

In a separate study, Dr. James Bibb, associate professor of psychiatry at UT Southwestern, found yet another harmful action of the Cdk5 protein. It can stunt learning and reduce motor control.

Cdk5 is a kinase, which means its job is to interact with all sorts of other proteins inside cells and modify them through a process called protein phosphorylation. Whether Cdk5 nurtures or devastates depends on the state of its partner and the proteins it modifies.

"Like all of us, Cdk5 can influence others, in this case other proteins," Dr. Eisch said. "When Cdk5 messes with hooligans, it causes big trouble. When it hangs with the straight-A students, it actually helps other cells reach their full potential."

Dr. Eisch studied different stages of neurogenesis, or the formation of new nerve cells, in the brains of adult mice and found that the absence of Cdk5 prevents neural stem cells from maturing. She and her group used advanced genetic engineering to create mice in which they could turn off Cdk5 within nerve cells in a specific region of the brain where new neurons are born.

Dr. Eisch found that when Cdk5 is removed from immature nerve stem

cells, normal cell division occurs, but the nerve cells never reach maturity. Researchers also removed Cdk5 from neighboring mature nerve cells and discovered that this removal resulted in the production of fewer immature nerve cells.

"The techniques we used have moved us several steps beyond what is usually done in the field," Dr. Eisch said. "We're beginning to assemble a dictionary of what regulates neurogenesis. By understanding what's vital at each stage of development, we hopefully can one day manipulate human nerve cells so that the brain can withstand neurodegenerative diseases such as Alzheimer's."

Dr. Bibb studied the "Mr. Hyde" component of Cdk5. Using a different but equally advanced set of genetic approaches, his team studied the effects of turning Cdk5 to the "dark side" by expressing a shortened form of the Cdk5 activating partner called p25. The group found that when paired with p25 in deep brain structures, Cdk5 had destructive effects on motor coordination and learning in the mice.

Neuropsychiatric illnesses such as schizophrenia, attention deficit hyperactivity disorder and drug addiction involve similar brain pathways as the ones studied and implicated in the "Mr. Hyde" aspect of Cdk5, Dr. Bibb said.

Dr. Bibb also used new technology to reach deeper inside the brain and explore regions beyond those typically examined in conjunction with neurodegenerative diseases. His team used a green fluorescent protein to trace Cdk5's activity in mice, allowing the researchers to examine precisely what was happening in the brain when the Cdk5/p25 pairing was overexpressed.

They found that the overexpression damaged circuitry in the area of the brain that controls movement and reward-based learning. The brain cells

lost about half of their connections, or synapses, with other brain cells. This was accompanied by inflammation usually associated with neurodegeneration.

"Once we saw the loss of synapses, we understood why the mice experienced problems with movement and learning," Dr. Bibb said. "Surprisingly, despite the negative effects of putting Cdk5 with p25 in this part of the brain, the cells didn't die. Researchers now have the tools to delve deeper into the brain to study disease. Being unable to control movement, or having psychiatric illness, can be as devastating as memory loss."

Dr. Eisch will next study why immature cells need Cdk5/p35 and why the loss of Cdk5 in neighboring mature nerve cells stopped development.

Dr. Bibb's work will focus on blocking Cdk5 from causing negative reactions and trying to determine how Cdk5/p25 is created.

Source: UT Southwestern Medical Center