Medical Xpress

Protein found that regulates gene critical to dopamine-releasing brain cells

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Researchers have identified a protein they say appears to be a primary player in maintaining normal functioning of an important class of neurons – those brain cells that produce, excrete and then reabsorb dopamine neurotransmitters. These molecules command numerous body functions, ranging from management of behavior and mood to control of movement, and one day may hold the key to why and how some people develop Parkinson's and other brain diseases.

In the September 10 issue of the *Journal of Neuroscience*, the scientists say that this protein, which they call the Nurr-1 interacting protein (NuIP), interacts with, and helps regulate the activity of the Nurr1 gene. That gene has long been known to be essential to development and maintenance of dopaminergic neurons.

Efforts to control Nurr-1 have been underway by pharmaceutical drug developers, because these neurons are the ones that die in Parkinson's disease and which are, conversely, over-active in schizophrenia. Now NuIP may also provide a good drug target for these and other neurological disorders caused by faulty dopamine transmission, says the study's lead investigator, Howard J. Federoff, M.D., Ph.D., Executive Vice President for Health Sciences and Executive Dean of the School of Medicine at Georgetown University Medical Center.

"We do not know yet whether this is true, but one can speculate that small molecules that may either facilitate, stabilize, or otherwise regulate the action of NuIP on Nurr1 may be relevant in a therapeutic context,"

says Federoff, a neuroscientist who did much of this research at the University of Rochester School of Medicine and Dentistry before coming to Georgetown in 2007. His three other co-authors are from Rochester.

In this study, the researchers specifically set out to find potential "partners" of Nurr1 because no molecule had yet been found that could positively activate the Nurr1 gene or the protein receptor it produces. Crystal structures of the Nurr1 receptor show it to have an area where another protein could bind to it, but this "domain" is too small for usual binding partners, such as steroids.

Using a library of potential molecules in laboratory samples of brain cells from a developing mouse, the researchers identified a new family of gene products that interacts with and regulates the activity of Nurr1. These gene products are all derived from the NuIP gene.

They then discovered that loss of NuIP function led to decreased numbers of cells in culture and to a decreased expression of the dopamine transporter on these neurons.

The mechanism underlying the ability of NuIP to positively regulate the activity of Nurr1 is not yet clear, but the researchers suspect that "as yet unknown upstream signals impinge on NuIP which, in turn, instructs Nurr1 to become activated and thus facilitates the expression of a set of genes involved in dopamine neuron phenotypic maturation," Federoff says. "That means they become more like a dopamine neuron which manufactures, releases, and the takes up the neurotransmitter."

"The relevance of NuIP to Parkinson's disease has not been established but it is tempting to speculate that it participates in the maintenance of the mature phenotype of midbrain dopaminergic neurons which are rendered vulnerable in this neurological disease," Federoff says.

Source: Georgetown University Medical Center