Metabolic disorder underlies Huntington's disease

October 19 2006

A metabolic disorder underlies the brain effects found in those with Huntington's disease, researchers report in an advance article publishing online October 19, 2006. The article will appear in the November 2006 issue of the journal *Cell Metabolism*, published by Cell Press.

Their new evidence ties a metabolic defect to the loss of neurons in the striatum, the brain's "movement control" region. That neurodegeneration leads to the uncontrollable "dance-like" movements characteristic of the fatal, genetic disorder.

The findings may help to explain other symptoms of the disease, including weight loss, and could point to new avenues for therapy, according to the researchers.

"Huntington's has been thought of primarily as a neurological disease," said Albert R. La Spada of the University of Washington, Seattle. "Our findings underscore the fact that the condition includes other, underrecognized aspects."

The findings in Huntington's disease further highlight the possibility that other neurological conditions might also have a strong metabolic component, La Spada added.

Huntington's is relentlessly progressive, the researchers said, as patients succumb to the disease 10 to 25 years after its onset. The disease is caused by a genetic defect in which a repetitive sequence of DNA in the

"huntingtin" (htt) gene gets expanded to encode an abnormally elongated protein.

Although the mutant htt protein is widely present, only certain populations of neurons degenerate and only a subset of other cell types are affected, they said. And exactly how the htt protein causes disease has remained uncertain.

The researchers made their current discovery after stumbling onto evidence that mice with Huntington's disease suffer extremely low body temperatures that worsen as the disease progresses.

"These mice have been around for at least a decade," La Spada said. "They have been the subjects of dozens, if not hundreds, of studies, but no one had checked one of their most basic vital signs.

"When you do, you find that the mice have a dramatic abnormality in temperature--which is normally tightly regulated."

Early on, the animals' temperature registered one or two degrees below normal, La Spada said. As their condition worsened, body temperatures fell substantially, he added, sometimes below 30°C. Like humans, the normal body temperature of mice is about 37°C.

To trace the causes of the animals' hypothermia, the researchers first looked to the brain region that controls body temperature. The animals brains, however, appeared to register and respond to cold normally.

The problem, they found, lay instead in fat cells known as brown adipose tissue (BAT). In rodents, BAT is the primary tissue that controls body temperature. When the brain signals that the body is cold, the gene called PGC-1б increases production of a protein in BAT that leads the cellular powerhouses known as mitochondria to generate heat instead of energy.

In the BAT of hypothermic Huntington's mice, PGC-1ϭ levels rose but failed to elicit the other events required to maintain normal body temperature, they found.

The link to mitochondria-regulating PGC-1ϭ led the team back to the brain, and specifically to the striatum. That brain region is most affected in Huntington's disease and is particularly sensitive to mitochondrial dysfunction.

The researchers found that tissue taken from striatums of Huntington's disease patients and mice showed reduced activity of genes controlled by PGC-1ϭ. They further found reduced mitochondrial function in the brains of Huntington's mice.

The findings suggest a link between two theories to explain Huntington's disease, the researchers said.

The earlier finding that the striatum is particularly sensitive to mitochondrial dysfunction suggested that the cellular powerhouses might play a role in the disease. Other evidence suggested that mutant htt might interfere with "transcription factors" that control gene activity.

"PGC-1ϭ transcription interference may provide a link between transcription dysregulation and mitochondrial dysfunction in Huntington's disease," the researchers said. "More importantly, our study underscores an emerging role for metabolic and mitochondrial abnormalities in neurodegenerative disease."

As metabolic function generally diminishes in older people, such a connection might explain why many neurodegenerative diseases--such as Lou Gehrig's, Alzheimer's, and Parkinson's diseases, for example--tend to emerge and worsen with age, La Spada said.

Source: Cell Press