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PRESS RELEASE

Neurobiology

Where does the energy come from that is needed as a carrier in neuron extensions?

The movement of molecules in the neuron extensions known as axons is a process that is vital for the survival of cells and the smooth operation of the nervous system. It is performed by vesicles that travel fast thanks to the energy-hungry molecular engines. At the "Signalling, neurobiology and cancer" Laboratory (Institut Curie/CNRS/Inserm) at the Institut Curie, the team headed by Frédéric Saudou[1], INSERM Director of Research, has shown that the vesicles have their own energy production system needed for travelling and do not depend on the mitochondria that are the main source of cell energy. This mechanism works by means of glycolysis, the first stage in the conversion of glucose and for the huntingtin protein, the protein that mutates in Huntington's Disease, a neurodegenerative condition. The results were published on 31 January 2013 in the *Cell* journal.

Unlike carcinomas in which the cell proliferates, neurodegenerative conditions such as Alzheimer's Disease, Parkinson's Disease and Huntington's Disease are due to the accelerated death of neurones. At the "Signalling, neurobiology and cancer" Laboratory (Institut Curie/CNRS/Inserm), part of the Institut Curie, the research team headed by Frédéric Saudou is studying the function of the huntingtin protein which mutates in Huntington's Disease. "*When it is altered, by a process that is still not fully understood, huntingtin causes the accelerated death of neurons in the striatum, the region of the brain in which Huntington*'s *disease first manifests*" explains Frederic Saudou.
His team has shown the essential role played by huntingtin in the swift travel of vesicles through the neuron extensions or axons. axones. Huntingtin stimulates the progress of these vesicles by interacting with molecular engines, enabling them to travel to specific regions of the brain such as the striatum, the brain structure that is attacked in victims of Huntington's Disease.

ATP, the engine essential for transporting the vesicles

So where does the cell energy come from that is vital for ensuring the transport of the vesicles in the axons over long distances, that may in some cases be as long as one metre? The adenosine triphosphate (ATP) molecule is an energy source shared by all animal and plant species. In humans, it is mostly produced by specialist organelles in the cells, known as the mitochondria. "*In this project we have shown that a process other than the mitochondria is involved in the supply of energy to the molecular engines*[2] *responsible for movement along the axons"* explains Frédéric Saudou. In fact, the inhibition of the mitochondrial function has no effect on this swift movement. On the other hand, the genetic inactivation of an enzyme that is essential for glycolysis, the first stage in the conversion of glucose into energy significantly reduces movement.

A mechanism that is dependent on the huntingtin protein

[1] Frédéric Saudou is head of the "Cell Signalling and Neurobiology" team in the Cell Signalling, Neurobiology and Cancer Unit at the Institut Curie/CNRS UMR 3306/Inserm U1005

[2] The molecular engines responsible for the movement of the molecule or cell structures throughout the cell skeleton are the proteins kinesin and dynein.

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"*The enzymes responsible for glycolysis are situated directly on the vesicle and produce the energy needed for the movement of the axons. We then tried to discover the mechanism responsible for fixing it on the vesicle membrane. Our researches have established that attachment to the vesicle is performed by the huntingtin protein. We do not yet know, however, whether this function is disrupted in Huntington's disease"* stresses Frédéric Saudou. Researchers do not exclude the existence, however, of other mechanisms that link the glycolysis enzymes to the vesicle membrane.

More about Huntington's Disease

Huntington's Disease is a rare neurological disorder that affects one person in 10,000 and only manifests in adulthood. The most typical symptoms are mental disturbance (anxiety, irritability, depression), a progressive deterioration in intellectual capacity culminating in dementia, associated with abnormal involuntary jerking movements of the limbs, head and neck.

The genetic anomaly that causes Huntington's disease is an abnormal increase in the repetition of the three nucleic acids (C, A and G – known as the CAG triplet) in the coding gene for the huntingtin protein. This results in an abnormal expansion of a repetition of an amino acid (polyglutamine or polyQ repetition) in the huntigtin protein. The mechanisms leading to the manifestation of the disease are still little understood and at present there is no treatment to prevent the emergence of symptoms inpatients. A better understanding of the cell processes that occur within the neurons should make it possible to identify new treatment strategies for this neuro-degenerative disease. Understanding these mechanisms could also help in the treatment of other conditions such as cancer.

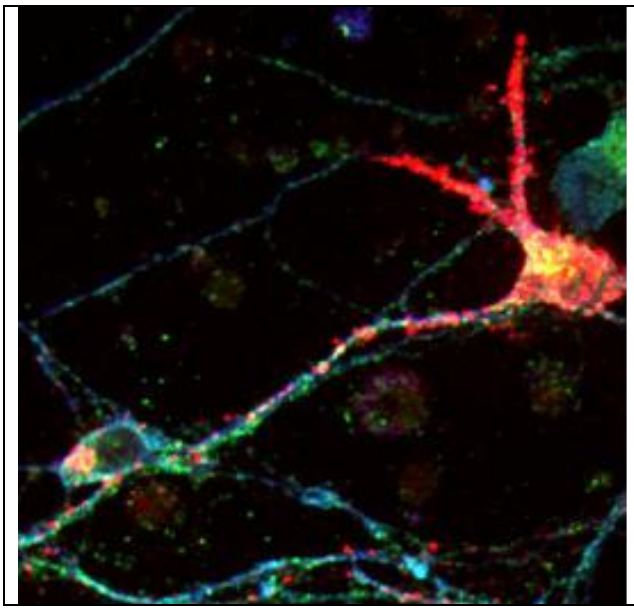

Image taken via microscopy showing the position of the vesicule of a glycolysis enzyme, the protein GAPDH (in red), with huntingtin (in green) shown in a neuron from a rat's cortex. The vesicles have been coloured blue.

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Reference

Vesicular glycolysis provides on-board energy for fast axonal transport.

Diana Zala [1,2,3], Maria-Victoria Hinckelmann [1,2,3], Hua Yu [1,2,3], Marcel Menezes Lyra da Cunha [1,4], Geraldine Liot [1,2,3], Fabrice P. Cordelières [1,5], Sergio Marco [1,4] and Frederic Saudou [1,2,3]

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