Over-activity of enzyme HDAC6 exacerbates symptoms of Amyotrophic Lateral Sclerosis

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Scientists at VIB and KU Leuven have demonstrated in fruit-flies that over-activity of the enzyme HDAC6 in the nerve ends exacerbates the symptoms of the neurodegenerative condition Amyotrophic Lateral Sclerosis (ALS / Lou Gehrig's Disease). Inhibition of this enzyme could offer a protective effect against ALS.

Patrik Verstreken (VIB/KU Leuven): "Nobody wants to suffer from a degenerative condition such as amyotrophic lateral sclerosis (ALS), in which you lose coordination of all muscles through gradual damage to the nerve cells. ALS patients are conscious throughout the disease process, including death by suffocation. Any additional insight into the dysfunction of nerve cells and the defective transmission of signals to the muscles paves the way to further targeted ALS research."

Amyotrophic Lateral Sclerosis – a degenerative process

In patients with ALS, the nerve cells that allow for the synaptic transmission die off. Synaptic transmission is the transmission of signals to the muscles, which is essential for the coordination of the muscles. ALS falls under the collective term of neurodegenerative conditions, which includes diseases such as Parkinson's disease. It is a progressive, debilitating neurological disease for which there is currently no treatment available. ALS patients are very aware of the entire process. ALS patients often opt for euthanasia in order to avoid suffocating to

death as the respiratory muscles also fail in the end.

Over-activity HDAC6

Katarzyna Miskiewicz, Liya Jose and Patrik Verstreken have studied how this type of nerve cell becomes defective in fruit-flies that express a form of ALS. Fruit-flies are a very suitable model organism for neurological research. In the case of ALS, the specific defect is located at the nerve endings, where the investigators discovered an over-activity of the enzyme HDAC6. This over-activity of HDAC6 is a cause of the disrupted synaptic transmission, resulting in a symptomatic exacerbation of the disease. In order to stop this process, it would – in theory – be helpful to combat the over-activation of the enzyme HDAC6 in order to return to "normal" activity of the HDAC6 enzyme.

Not only HDAC6 defect

Although this discovery may provide a possible avenue for symptomatic ALS treatment, it should be noted that the HDAC6 defect is probably one of the many enzyme defects that play a role in ALS. Previously, Patrik Verstreken and Wim Robberecht (VIB/KU Leuven) demonstrated that another enzyme that is involved in ALS – Elp3 – acts on the same process at the nerve endings as HDAC6. Ideally, the various avenues should all be studied in the hope of finding a treatment for ALS in the future.

More information: HDAC6 Is a Bruchpilot Deacetylase that Facilitates Neurotransmitter Release, *Cell Reports*, www.cell.com/cell-reports/abstract/S2211-1247%2814%2900445-8

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