A promising drug candidate for ALS prolongs lifespan and eases symptoms in rats and mice

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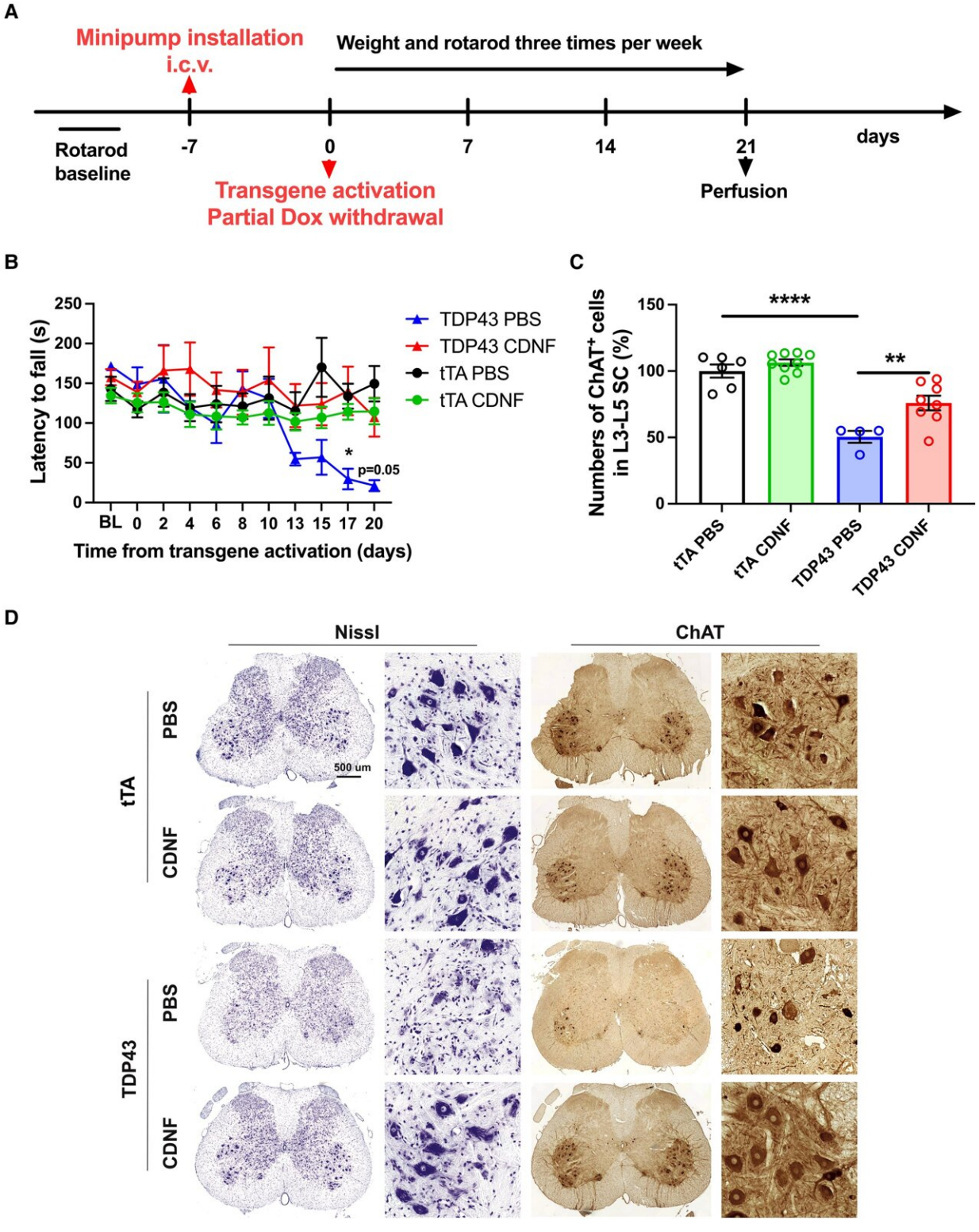

Continuous 4-week CDNF i.c.v infusion improves motor behavior and protects spinal MNs in the ChAT-tTA/TRE-TDP43-M337V rat model. (A) Experimental

design: upon reaching adult age, Alzet minipumps connected to a catheter were implanted in ChAT-tTA/TRE-TDP43-M337V and tTA rats to infuse CDNF (6 µg/day) or PBS. One week later, the activation of transgene was induced by partial withdrawal of Dox. Rats were monitored for weight and motor behavior changes until day 21 from transgene induction, when the rats were perfused. (B) Latency to fall of PBS/CDNF-treated transgenic and tTA littermates recorded three times per week. BL = baseline. (C) Quantification and comparison of the number of MNs in the lumbar (L) spinal cord, area L3–L5. (D) Representative images of Nissl and $ChAT^+$ MNs in the lumbar spinal cord. Scale bar 500 µm. Mean ± SEM, n = 4–9/group in B–D. *P Brain (2023). DOI: 10.1093/brain/awad087

A research group at the University of Helsinki and its partners have found a promising drug candidate for the treatment of amyotrophic lateral sclerosis (ALS). Cerebral dopamine neurotrophic factor CDNF prolongs the lifespan of and alleviates disease symptoms in rats and mice in animal studies.

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing fatal neurodegenerative disease that affects the nerve cells in the brain and spinal cord. Specifically, a selective degeneration of motoneurons occurs in the spinal cord, leading to muscle atrophy and paralysis. Most patients with ALS die from respiratory failure, usually within one to three years from symptom onset. There is no cure for ALS, and the only drug available in Europe, riluzole, only prolongs ALS patient survival by a couple of months.

Assistant professor Merja Voutilainen and researchers from the Regenerative Neuroscience Group, Faculty of Pharmacy and Institute of Biotechnology, University of Helsinki, together with their national and international collaborators, investigated the therapeutic effect of a protein called cerebral dopamine neurotrophic factor (CDNF) in several

cellular and animal models of ALS.

The CDNF protein, discovered by Professor Mart Saarma laboratory in 2007, is mostly found in the endoplasmic reticulum (ER) within cells. ER is an important cell organelle mainly involved in the synthesis and maturation of circa one-third of all proteins in the cell. CDNF has previously shown therapeutic potential in Parkinson's disease.

In the new study published in *Brain*, the Regenerative Neuroscience Group used three animal models that were genetically modified to express human mutations (TDP43-M337V and SOD1-G93A) affecting ALS patients. Their goal was to investigate whether CDNF can affect disease development in the rodent models of ALS and elucidate its mechanism of action.

They were particularly interested in studying ER stress, which is a cellular response to protecting cells and its proteins. If ER stress becomes chronic, as is the case in many neurological diseases, it can cause cell death.

"We found that administration of CDNF to ALS mice and rats significantly improves their motor behavior and halts the progression of paralysis symptoms. Symptom amelioration is reflected in an increased number of surviving motoneurons in the spinal cord of the animals compared to rodents that did not receive CDNF. Our experiments suggest that CDNF may rescue motoneurons by reducing the ER stress response and, therefore, cell death. Importantly, ER stress was present in all our animal models, independently of the specific genetic mutations" says Dr. Francesca De Lorenzo, lead author of the study.

Professor Michael Sendtner from the University of Würzburg, Germany, one of the world's leading researchers in the field of ALS research and co-author of the study, comments, "This study opens the way to a

rational therapy to counteract one of the most severe cellular pathologies in ALS: ER stress."

"CDNF holds great promise for the design of new rational treatments for ALS," says Dr. Merja Voutilainen, Assistant professor at the University of Helsinki and the director and senior author of the study.

More information: Francesca De Lorenzo et al, CDNF rescues motor neurons in models of amyotrophic lateral sclerosis by targeting endoplasmic reticulum stress, *Brain* (2023). DOI: 10.1093/brain/awad087

Provided by University of Helsinki