New model offers insights into how stress in neurons connects to cardiovascular disease

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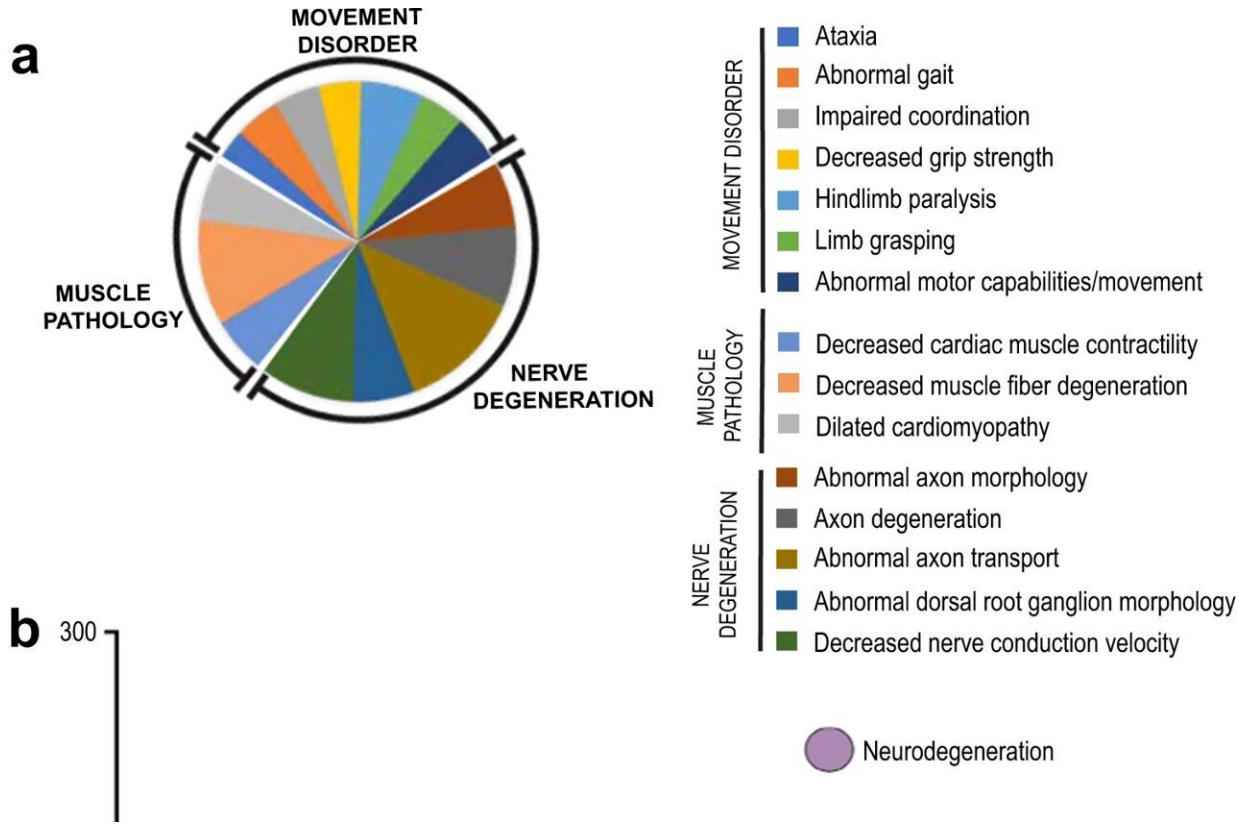

Proteomic analyses of isolated DRG from D-alanine-fed DAAO-TG^{Cdh5} and Cre^{+}/TG^{-} control mice. **a** shows the results of phenotypic enrichment analysis using GeneCodis 4.0 to assign proteomic patterns to mouse phenotypes[20,21]. The legend on the right lists the principal phenotypes detected by GeneCodis, which we have then assigned post hoc to three major phenotype classes represented by these abnormalities: movement disorder; nerve degeneration; and muscle pathology. Each color represents a separate subgroup under each class, with the size of each slice corresponding to the corresponding percent enrichment for that

phenotype, calculated with respect to the total enrichment score. **b** shows pathway enrichment analysis with KEGG by GeneCodis 4.0[22,23] shown in a bubble plot indicating significant enrichment of neurodegeneration, metabolic, and oxidative stress-related pathways, as well as diverse signaling and inflammation-related pathways. In this plot, the number of genes covered in each pathway is represented by the size in the bubble position as well as its position on the abscissa; the total number of genes present in the pathway is shown on the ordinate; the color of the bubble corresponds to the *p* value, as noted. For the KEGG pathway analyses hypergeometric test was used to calculate the enrichment and *p* value of each pathway. Adjustment for the multiple comparison was performed to obtain adjusted *p* values for each pathway enriched from the data. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-38961-0

Oxidative stress—characterized by elevated levels of unstable molecules called reactive oxygen species—is associated with neurodegeneration and cardiovascular disease. However, until recently it has not been possible to demonstrate a causal relationship between oxidative stress and disease states.

A new study used "chemogenetics" to activate a recombinant yeast protein expressed in mouse tissues to manipulate levels of oxidative stress in living mice. Researchers from Brigham and Women's Hospital, Harvard Medical School, and the Novartis Institutes for Biomedical Research applied chemogenetic approaches in a new transgenic mouse model to introduce oxidative stress into blood vessels and neurons.

The researchers initially set out to use this new transgenic mouse model to identify pathways through which oxidative stress might cause dysfunction of blood vessels and lead to diseases like hypertension and aortic aneurysms. But they were surprised to find that these mice rapidly developed profound ataxia, characterized by an inability to walk.

Probing further, they found that specific sets of sensory neurons in peripheral nerve cells had undergone degeneration from oxidative stress caused by the transgene. And when the researchers looked at the hearts of these animals, they found that heart muscle had developed cardiac hypertrophy.

This combination of sensory neuron degeneration and cardiac hypertrophy is associated with Friedreich's ataxia (FA), a progressive neurodegenerative disease that is the most common form of hereditary ataxia found in patients. Researchers also characterized specific inflammatory cell types involved in these responses, offering a more complete understanding of the mechanisms through which FA causes cardiac hypertrophy.

"Our team followed up on an unexpected phenotype that we uncovered in a new transgenic mouse line and found surprising new connections between peripheral nerves and the heart," said Thomas M. Michel, MD, Ph.D. of the Brigham Division of Cardiovascular Medicine. "Our findings may help us understand the cardiac remodeling seen in the hearts of patients with neurodegenerative diseases."

The study is published in the journal *Nature Communications*.

More information: Shambhu Yadav et al, Sensory ataxia and cardiac hypertrophy caused by neurovascular oxidative stress in chemogenetic transgenic mouse lines, *Nature Communications* (2023). DOI: 10.1038/s41467-023-38961-0

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