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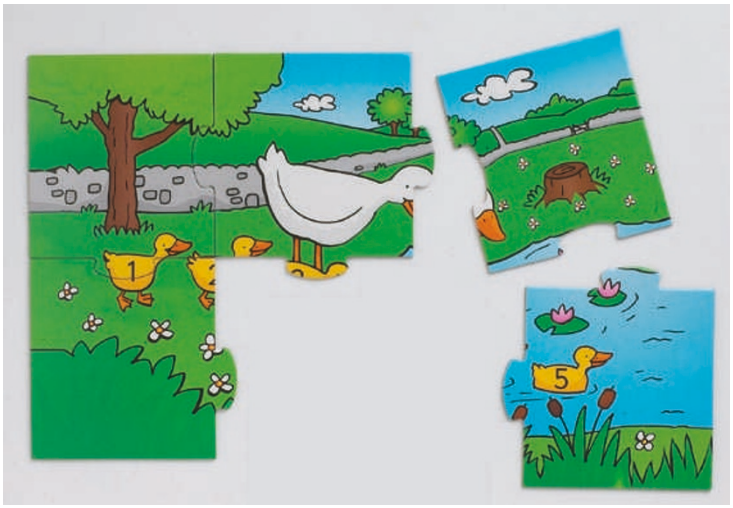
NEURODEGENERATIVE DISEASE

Pieces of the Parkinson's puzzle



MACMILLAN/Paul Bricknell

Many pathogenic molecules underlying rare, mostly autosomal-dominant forms of Parkinson's disease have been identified. However, less is known about pathogenic pathways that lead to the common, 'sporadic' form. Now, Lewandowski *et al.* show that defects in the polyamine pathway are involved in the pathogenesis of Parkinson's disease.

The authors focused on the brainstem as this region, particularly the dorsal motor nucleus of the vagus (DMNV), is thought to be affected early in the disease. Measuring cerebral blood volume using functional MRI provided high-resolution functional maps of the brainstems of human subjects. These showed that patients with Parkinson's disease had decreased cerebral blood volume in the DMNV, suggesting metabolic alterations in this region. By contrast, the inferior olivary nucleus (ION) — a neighbouring region — did not show such changes. Post-mortem analysis of Parkinson's disease brains also showed the DMNV to be positive for aggregates of the protein α-synuclein, which are associated with Parkinson's disease pathogenesis.

Next, using microarrays, the authors showed that ten transcripts were downregulated in the DMNV of Parkinson's disease brains. Of these, the authors further investigated spermidine/spermine N1-acetyltransferase 1 (SAT1). This enzyme — a component of the polyamine pathway — catabolizes spermine and spermidine, which are polyamines that increase α-synuclein aggregation *in vitro*. Parkinson's disease brains showed decreased SAT1 expression in the DMNV but not in the ION.

The authors then examined the effects of exogenous spermine on yeast strains expressing human α-synuclein. Spermine slowed and reduced growth in yeast expressing α-synuclein compared with a strain carrying the empty vector. In addition, overexpression of the yeast polyamine transporter (Tpo4) increased cell death in yeast expressing α-synuclein and caused more rapid formation of intracellular α-synuclein foci. Together, these findings suggest a relationship between polyamines and the cellular toxicity of α-synuclein.

To investigate whether altered SAT1 activity is associated with α-synuclein histopathology, the authors used transgenic mice that expressed wild-type human α-synuclein and developed α-synuclein inclusions. Reducing SAT1 activity with diminazene (Berenil; Intervet) increased neuronal accumulation of α-synuclein in the basal ganglia. Furthermore, α-synuclein pathology was worsened with diminazene but partially rescued by increasing SAT1 activity with the drug N1, N13-diethylnorspermine (DENSPM).

Finally, the authors sequenced *SAT1* and identified a rare variant in the 3□UTR of the gene found exclusively in patients with Parkinson's disease and that might therefore be associated with the disorder.

Taken together, these studies provide new insight into the common form of Parkinson's disease that could be important for early diagnosis and highlight SAT1 as a possible therapeutic target.

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ORIGINAL RESEARCH PAPER Lewandowski, N. M. *et al.* Polyamine pathway contributes to the pathogenesis of Parkinson disease. *Proc. Natl Acad. Sci. USA* **107**, 16970–16975 (2010)