Figure 1 Repeats in human α -synuclein.

Residues 7–87 of the 140-amino-acid protein are shown. Amino-acid identities between at least five of the seven repeats are indicated by black bars. The alanine $\rightarrow$ threonine mutation at residue 53 that is associated with familial Parkinson's disease is shown in the sequence between repeats four and five (A $\rightarrow$ T).

however, and all subsequent studies reported staining of only presynaptic nerve terminals.

Three different synuclein genes are known. Human α -synuclein has also been called NACP (for precursor of the non- β -amyloid component of Alzheimer's disease), because of the apparent association of one of its fragments with some of the extracellular β -amyloid deposits that constitute the neuropathology of Alzheimer's⁵. Human β -synuclein is 61% identical to α -synuclein and its gene maps to the long arm of chromosome 5 (refs 6, 8). Like α -synuclein, it is expressed at high levels in brain, where it localizes to presynaptic nerve terminals⁶. It also carries an alanine at position 53, suggesting that it might be worthwhile to look for mutations in β -synuclein in familial forms of Parkinson's disease. Unlike rodent and zebrafish α -synucleins, mouse, rat and bovine β -synucleins all have an alanine at position 53 (refs 9, 10). A third synuclein (synuclein-like protein) is mainly expressed in the peripheral nervous system¹¹.

Synucleins have a highly conserved amino-terminal repeat region, a hydrophobic middle section, and a less well-conserved, negatively charged carboxy-terminal region. They are modified post-translationally, but the exact modifications are not known⁶. Over half of the α -synuclein molecule is taken up by seven imperfect repeats of eleven amino acids, each having a conserved six-amino-acid core with the consensus sequence KTKEGV (in single-letter amino-acid code; see Fig. 1)^{3–5}. Core sequences of individual repeats are separated by five amino acids, with the exception of repeats four and five, which are separated by nine amino acids. The A53T change associated with FPD lies in this nine-amino-acid sequence (Fig. 1).

Although the function of the repeats is unknown, clusters of basic and acidic amino acids often mediate binding between structural proteins. Biophysical studies have shown that α -synuclein has no significant secondary structure¹². Such natively unfolded proteins frequently potentiate protein–protein interactions and become

structured when bound to other proteins¹². It will be important to identify binding partners for α -synuclein, as the A53T mutation may disrupt its normal function.

Proteins or fragments of proteins that are mutated in familial neurodegenerative disorders frequently accumulate as deposits that characterize the neuropathology of these disorders. Examples include some familial forms of Alzheimer's disease and some inherited prion diseases. It will no doubt be known soon whether or not α -synuclein is an intrinsic component of the core of the Lewy body.

Neurofilaments and ubiquitin can be detected in Lewy bodies^{13,14}, but it is unclear whether they are major components of the fibrillar and amorphous material of the core. Human recombinant α -synuclein has been shown to dimerize¹⁵, but it appears to be more soluble than the recombinant protein from the zebrafish, which aggregates in solution^{4,12}. Human α -synuclein with the A53T mutation might thus have an increased tendency to aggregate, especially if the mutation also interferes with the ability of α -synuclein to interact with its binding partner in nerve terminals. Rodent and zebrafish α -synucleins would not aggregate in nerve cells because they would be bound to other proteins and also because these species have a much shorter lifespan than humans. Lewy bodies are as much a feature of Parkinson's disease as is the dramatic loss of neuronal cells in the substantia nigra.

But Lewy bodies also occur in the brains of patients with other neurodegenerative disorders, especially in the cerebral cortex of patients with a late-life dementia that is clinically similar to Alzheimer's disease. The new work¹ brings α -synuclein to centre-stage, with the promise of new insight into the biology of the Lewy body and the pathogenesis of Parkinson's disease. □

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Daedalus

Guided lightning

Why does lightning go so far? A 100-MV spark will only bridge 20 metres or so; yet a thunder cloud at 100 MV can launch lightning flashes over 1 km long. This is because lightning travels in steps. A 'stepped leader' stroke descends about 20 m from the charged cloud, and pauses. The current ionizes the air along its track; it becomes so conducting that in a few microseconds its sharp end is raised to the 100-MV potential of its cloudy origin. A sharp point at a high potential, of course, is an ideal initiator of electric breakdown. So the stroke proceeds another 20 m, and recreates another sharp conducting point lower down, which breaks down the local air in its turn. Once begun, a stepped flash can travel indefinitely.

So, says Daedalus, with a 100-MV source we could launch our own lightning through any distance of air. But how to aim it? An ultraviolet laser has been used to ionize a path through low-pressure gas, to guide an electron beam; but air would absorb such a beam. These days, however, gyatron valves can generate brief 100-MW pulses at 150 GHz. So DREADCO plasma physicists, with some trepidation, are launching a pulsed gyatron beam from a sharp-ended hollow waveguide which has been charged to 100 MV. The intense narrow beam will energize the air along its track, so that the first 20-m lightning step will follow the beam. The skin effect of the 150-GHz modulation will preferentially ionize the outside of the discharge, forming a hollow waveguide carrying the bulk of the radiation to the end of the step. Here the process will repeat. At the next gyatron pulse, the discharge will step another 20-m step in the beam direction, and so on. Indeed, even a 5-MV source should work; its lightning would advance along the guiding beam in 1-m steps.

As a anti-aircraft weapon, DREADCO's lightning launcher could be quite humane. Most of its power will be dissipated along its track. The target will receive a shock strong enough to wreck its navigation and weapon electronics while causing little structural damage. The lightning launcher could also be useful in rain-making, by triggering potential thunderstorms — ideally from an aircraft above the clouds, to avoid receiving a prompt natural lightning blast back along the ionized channel. Religious zealots would also welcome an airborne lightning launcher. They could direct an apparent thunderbolt at York Minster or Canterbury Cathedral whenever a bishop uttered a heresy.

David Jones