NEURODEGENERATIVE DISORDERS

The future in crystals

DOPA decarboxylase (DCC) is responsible for the conversion of L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine. Parkinson's disease involves a progressive loss of dopamine-producing cells in the midbrain, and L-DOPA, given orally, remains the most effective treatment for the symptoms of this disorder. Because L-DOPA is rapidly converted to dopamine in the bloodstream, it is routinely administered with a DCC inhibitor (for example, carbiDOPA), allowing greater amounts of L-DOPA to reach the brain. The treatment of patients with Parkinson's disease could be greatly improved by the design of more effective inhibitors of this enzyme. This prospect seems increasingly likely, as Burkhard *et al.* report the crystal structures of ligand-free DCC, and its complex with carbiDOPA.

X-ray crystallography can be used to obtain high-resolution, three-dimensional models of the structures of proteins and other macromolecules. X-rays are diffracted by electrons of molecules in the crystallized protein, and this diffraction pattern can be used to calculate an electron density map. A model of the protein, which has a known amino-acid sequence, can then be built to fit the map. Using this method, Burkhard and co-workers obtained structures of ligand-free DCC and the DCC–carbiDOPA complex. Several features of DCC were evident in these models: the overall structure of the protein (an α_2-dimer), the way in which the cofactor pyridoxal-5′-phosphate (PLP) is anchored to the enzyme, how the inhibitor binds (by forming a hydrazone linkage with PLP), and which amino-acid residues might be involved in the catalytic activity of DCC. Importantly, on the basis of these structures, the authors were able to suggest ways in which the binding of inhibitors of DCC might be improved.

The decrease in forebrain dopamine levels that follows dopaminergic cell loss in Parkinson's disease leads to muscle tremor, and to difficulty in initiating and sustaining locomotion. Although L-DOPA is effective in treating these symptoms, this therapy is associated with side effects that result, in part, from relatively high concentrations of L-DOPA itself, and from the production of dopamine in the bloodstream. The use of more-potent inhibitors of DCC would allow smaller amounts L-DOPA to be used in alleviating the symptoms of Parkinson's disease; the crystal structures reported by Burkhard *et al.* offer a way forward in the design of such treatments.

Rebecca Craven

References and links

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CELL BIOLOGY OF THE NEURON

The latest stuff on the Web

Many of us who started to study neurobiology before the domination of the molecular approach will surely remember the classic electron micrographs of synaptic contacts, which taught us about their asymmetry, and about the distinction between pre- and postsynaptic compartments. The electron-dense postsynaptic density (PSD) characterized the postsynaptic bouton, whereas the presence of synaptic vesicles was indicative of the presynaptic element. In addition, a conspicuous element of the presynaptic terminal was always present in the diagrams of that age: a series of 'pyramids' linked by some kind of web, which were supposed to dock synaptic vesicles near their fusion sites. Many years later, the morphological analysis gave way to the identification of the molecular components of the synapse, and those old textbook diagrams were replaced by more detailed depictions that incorporated the actual molecules of the PSD and the synaptic vesicles. But the pyramids faded into the background and were never really incorporated into our modern view of the synapse, mainly because little was learned about them during that period. Phillips *et al.* might trigger a revival of the interest in the presynaptic web after their report in *Neuron* on new data about its molecular composition.

In synaptosomal preparations, the pre- and postsynaptic elements can remain attached by links that are poorly characterized. Phillips *et al.* identified conditions in which this macromolecular complex remained assembled after membrane solubilization. The resulting particles contained presynaptic material with the characteristics of the presynaptic web, which was connected to the PSD through protein filaments. They went on to show that it was possible to disassemble and reconstitute the presynaptic web by varying pH. Using this system, the authors identified some of the proteins that formed the web, and found several molecules known to participate in synaptic vesicle fusion and recycling — clathrin, dynamin, UNC18 and NSF. They also found that it contained adhesion and adhesion-related molecules, such as N-cadherin and β-catenin; these molecules might mediate the physical interaction between the presynaptic web and the PSD.

So, the synaptic junction is much more than just two membranes in close proximity; it is a complex protein assembly in which pre- and postsynaptic elements are bridged by a discrete molecular scaffold. Just as the molecular analysis of the PSD has shaped our understanding of the postsynaptic compartment, the findings of Phillips *et al.* should help us to develop a more sophisticated view of the presynaptic terminal. We can finally start to do justice to a familiar figure that appears in some of our oldest textbooks.

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