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Neurodegenerative diseases and clues to their cause provided by plant toxins

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Neurodegenerative diseases affect all parts of the nervous system but most are of unknown cause. For many of these illnesses, the pathology is well described and major alterations in neurotransmitters have been detected, but why neuronal cell loss occurs remains a mystery as do the mechanisms underlying cell death. Current knowledge has reached a point where clues are starting to emerge and one source of this information has come from the actions of naturally occurring toxins, in particular those derived from plants.

Alzheimer's disease is primarily associated with a loss of cholinergic neurones arising in the nucleus basalis of Meynert and which innervate the cerebral cortex. Neuronal loss is associated with the appearance of senile plaques and neurofibrillary tangles. The pathological and biochemical changes occurring in Alzheimer's disease are very complex but current therapeutic strategies have attempted to restore cholinergic tone, largely through the use of cholinesterase inhibitors. In contrast, Parkinson's disease is primarily due to a loss of dopamine containing neurones in substantia nigra accompanied by the appearance of intracellular inclusions known as Lewy bodies. Dopamine replacement therapy with L-DOPA or dopamine agonist drugs is highly effective in controlling this disorder but does not prevent its progression. In Huntington's chorea, Cell death occurs primarily in the striatum and largely affects cholinergic interneurones and GABA-containing output pathways. Currently, there is no effective treatment for Huntington's disease as a primary biochemical defect has not been identified. Motor neurone diseases which affect both upper and lower motor neurones is also currently untreatable because there is no clear indication of the transmitter defect which leads to its symptomatology.

All of these illnesses have been extensively investigated with current interest centring on the mechanisms responsible for neuronal loss. There is no precise indication of what processes are involved but there is much interest in the role played by free radicals and oxidative stress ensuing from mitochondrial dysfunction, excitotoxicity and the actions of nitric oxide (or peroxynitrite), cytokines or mutant proteins. However, clues to their cause have been provided by a range of naturally occurring toxins, some of which are known to be responsible for specific neurological syndromes.

For example, amyotrophic lateral sclerosis occurring on the Pacific island of Guam may be related to ingestion of the non-protein amino acid BMAA found in the seeds of cycads. Similarly, motor neurone degeneration characterizing lathyrism may be due to the related amino acid BOAA found in the chickling pea. Both compounds may act through excitatory amino acid mechanisms to cause toxicity. The role of excitotoxic mechanisms in Huntington's chorea has been explored using the seaweed derived toxin, kainic acid and other related naturally occurring molecules. These substances mimic the pathological changes occurring in Huntington's disease when injected into the striatum. A role for mitochondrial dysfunction in Huntington's disease has similarly been suggested by the action of another plant derived toxin; dystonia in a Chinese population was found to be due to ingestion of mildewy sugar cane contaminated with 3-nitropropionic acid, an inhibitor of complex II of the mitochondrial respiratory chain, and its administration to experimental animals leads to pathology closely resembling that of Huntington's chorea. In Parkinson's disease, the discovery of the selective nigral toxicity of MPTP led to a search for related molecules and the discovery that simple isoquinolines and β-carbolines from natural sources including also appear to inhibit mitochondrial function but at the level of complex I.

Other toxins also occur in plants and cause neurological damage although at present their direct relevance to human disease is not clear. For example, horses grazing on the yellow star thistle develop equine pallidonigromalacia associated with degeneration of the striatum and globus pallidus. Cattle grazing on the Russian knapweed develop a similar syndrome. While the exact toxin has not been identified it would seem to relate to the presence of sesquiterpene lactones found in these plants. How these toxins produce such focal pathology in brain may help explain the susceptibility of specific brain areas to degeneration in human disease.