The specificity by which neurological degenerative disorders can ravage one population of neurons, and yet leave the adjacent groups of cells undamaged, far exceeds the capability of even the smartest laser-guided bomb. The mechanism for this extraordinary specificity has long fascinated neurologists, but real progress has often come only with the development of chemical markers for specific subsets of neurons that degenerate in particular diseases. In the absence of such markers, the first attempts to identify the specific neurons whose loss results in the symptoms of Parkinson’s disease were largely unsuccessful. Lewy, for example, described the intracellular inclusion that bears his name in degenerating neurons in the basal forebrain, but never focused upon the substantia nigra as playing a special role in the disease (Lewy, 1913). It was only by carefully studying the fate of neurons bearing a chemical marker, neuromelanin (which is a non-enzymatic condensation product of catecholamine metabolism; Graham, 1979), that Foix and Nicolesco were first able to identify the loss of neurons in the pars compacta of the substantia nigra as critical in Parkinson’s disease (Foix and Nicolesco, 1925).

Their discovery was based upon the examination of brains from patients dying with post-encephalitic Parkinson’s disease in the great pandemic that swept Europe and the United States after World War I, but in fact most of their classic book was devoted to the description of the pattern of melanin pigmentation of neurons in the normal human brain. Their work was extended by Hassler, whose detailed studies of the same chemical marker demonstrated that the pars compacta is not uniformly affected by the disease (Hassler, 1938). He identified certain dense clusters of neurons in the ventral part of the pars compacta that consistently showed the greatest amount of degeneration. However, his methods involved intense analysis of serial sections through the substantia nigra and a complex system of terminology, so they were not widely applied for identifying neurons at risk of degeneration in Parkinson’s disease.

In the 1960s and ’70s, a new generation of histochemical and immunohistochemical markers allowed the measurements and visualization of neurons that contain catecholamines and their synthetic enzymes. It was soon confirmed that Parkinson’s disease included a deficit in dopaminergic innervation of the striatum (Lloyd and Hornykiewicz, 1970). Immunocytochemical studies allowed confirmation of Hassler’s observation that the more ventral tier of neurons in the pars compacta is more vulnerable in Parkinson’s disease, whereas the most medial neurons in the ventral tegmental area are the least likely to degenerate (Uhl et al., 1985; German et al., 1989, 1992; Dymecki et al., 1996). Other studies showed that noradrenergic neurons in the locus coeruleus are also consistently lost in Parkinson’s disease, leading to an alternative hypothesis that perhaps all catecholaminergic neurons are at risk (Marsden, 1983; German et al., 1992b; Zweig et al., 1993). However, this turned out not to be the case. Studies of the dopaminergic neurons in the hypothalamus found no evidence of cell loss (Matzuk and Saper, 1985), and there is only minimal involvement of the medullary catecholaminergic neurons in Parkinson’s disease (Saper et al., 1991; Gai et al., 1993). Moreover, non-catecholaminergic neurons, such as basal forebrain cholinergic neurons, are regularly involved in Parkinson’s disease (Tagliavini et al., 1984).

Against this background, the finding of a new chemical marker that might identify neurons that are marked for death in Parkinson’s disease could be a welcome entree to understanding the molecular pathophysiology of the disorder. The two papers by Damier and colleagues (Damier et al., 1999a, b) in this issue provide such a needed tool. Calbindin D28K is a well known member of the class of calcium-binding proteins, and the neuropil of the substantia nigra, pars compacta contains a dense accumulation of calbindin-positive axons. Most nigral dopaminergic neurons are interspersed within this neuropil. However, a sizeable minority (~40%) are located within five distinct and reproducible dense clusters that exclude calbindin-positive neuropil. In congruence with Graybiel and colleagues’ (Graybiel and Ragsdale, 1978; Graybiel et al., 1987) earlier work on chemical compartmentalization of the striatum into striosomes and matrix, the calbindin-positive background of the pars compacta is termed the ‘matrix’ and the calbindin-poor cell clusters are designated as ‘nigrosomes’. Moreover, nigrosome 1, the largest cluster in the ventrolateral pars compacta, was found to be the most severely depleted of neurons in Parkinson’s disease.

These findings agree closely with Hassler’s original description of regional cell loss in the pars compacta (Hassler, 1938), as well as an earlier report that the loss of dopaminergic neurons is greatest in the calbindin-poor regions of the substantia nigra (German et al., 1992a). However, the recognition that these regions form discrete and identifiable units brings chemical parcellation of the nigral cell loss in parkinsonian syndromes within the range of application by
most neuropathologists. It is not feasible to apply the complex Hassler terminology without a series of evenly spaced sections through the substantia nigra. Immunocytochemistry, however, can be performed in most neuropathology laboratories today, and the nigrosomes appear to be readily identifiable from individual to individual using calbindin staining. Extensive loss of neurons within nigrosonome I may be a sensitive criterion pathologically for the diagnosis of Parkinson’s disease. However, the patterns of cell loss in other conditions that affect the pars compacta, such as striatonigral degeneration, progressive supranuclear palsy, and corticobasoganglionic degeneration, must first be studied to determine their patterns of nigral degeneration, and whether the Parkinson pattern is specific.

Finally, we are left with the question of whether the low levels of calbindin in the nigrosomes could account in some way for the damage to the nigral dopaminergic neurons. Excess intracellular calcium can damage neurons, and low levels of calcium-binding proteins may reduce buffering capacity. But the calbindin in the pars compacta is thought to reside mainly in the axons of striatognial axons. Hence, it is not likely to contribute to the calcium homeostasis of the nigral dopaminergic neurons. However, the exclusion of calbindin-containing axons from the nigrosomes may reflect a concentration of some other type of input to these dopaminergic neurons. That input may either itself be toxic (e.g. if it releases an excess of an excitotoxic amino acid), or perhaps may simply drive the dopaminergic neurons harder, making them more susceptible to energy failure (e.g. by a mitochondrial enzyme abnormality).

One thing is clear: the chemical markers in the brain were not put there for the convenience of neuropathologists. They reflect functional organization, and it always hopeful to see that disease follows such patterns, raising the prospect that we can understand (and perhaps one day combat) its pathophysiology. It is reasonable to hope that the new generation of chemical markers in the substantia nigra will disclose for us both secrets of the organization of the pars compacta and clues to its vulnerability in Parkinson’s disease.

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References


