Clinical Symptoms in Parkinson's and Huntington's Diseases Reflect Loss of Connectivity Rather than Loss of Neurons

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Descriptions of neurodegenerative diseases like Parkinson's (PD) and Huntington's (HD) typically focus on the loss of specific neuronal populations, and therapeutic strategies are often based on neuroprotection (Nakamura & Lipton, 2009). Unfortunately, successful reductions in the amount of neuronal cell death have not translated to effective treatments for any neurodegenerative disease (Chiesa et al., 2005; Gould et al., 2006; Waldmeier et al., 2006). Neuronal cell death and activation of apoptotic pathways associated with loss of neurons is a late event in the pathogenesis of these and other late-onset neurodegenerative diseases (Brady & Morfini, 2010). Although neuronal apoptosis is an inevitable component of neurodegeneration, the clinical symptoms associated with these diseases are the result of synaptic dysfunction and loss of critical connections.

Clinically, the resting tremor, bradykinesia, rigidity and postural changes that are associated with parkinsonism can be produced through a variety of mechanisms including synucleinopathies and Lewy pathology (see Ch. 47), mutations in multiple genes (main text and see Ch. 41), exposure to environmental neurotoxins like MPTP and rotenone, or treatment with toxic chemicals like 6-hydroxy-dopamine. In each case, symptoms present when loss of synaptic connections between dopaminergic neurons in the substantia nigra and the striatum exceeds a threshold (loss of >80% connections and >70% of dopamine). Treatments that ameliorate parkinsonism typically increase availability of dopamine directly or indirectly to compensate for loss of functional synapses in the striatum, losing efficacy when losses become too great.

A similar early loss of neuronal connections is seen in HD, where connections made by a

population of medium spiny GABAergic projection neurons are particularly vulnerable (Han et al., 2010). As in PD, clinical symptoms precede significant loss of these neurons, suggesting that synaptic dysfunction and loss of connections is the proximate cause of functional losses. In both PD and HD, affected neurons exhibit a pattern of dying back neuropathy or distal axonopathy (Brady & Morfini, 2010; Coleman, 2005; Morfini et al., 2009). This mode of neuronal cell death exhibits an initial loss of presynaptic function and subsequent degeneration of distal axons that may be prolonged for years after the first reductions in synaptic function can be detected. Neuronal cell death only becomes a prominent feature of the disease when loss of functional synaptic connections exceeds a critical threshold.

Curiously, the sequence of events leading to neuronal apoptosis in PD and HD as well as a number of other adult-onset neurodegenerative diseases (Burns et al., 2009) exhibits striking parallels with programmed cell death during development of the nervous system (Brady & Morfini, 2010). In both cases, a failure to couple synaptic activity to uptake and return of neurotrophins to the cell body (see Chs. 8 and 29) may trigger neuronal apoptosis. Consistent with this idea, BDNF levels are reduced in affected brain regions for both PD and HD (Zuccato & Cattaneo, 2009). Similarly, evidence exists for disruption of trophic relationships due to misregulation of axonal transport of neurotrophins or neurotrophin receptors in both PD (Ittner et al., 2008; Morfini et al., 2007) and HD (Morfini et al., 2009; Zala et al., 2008). Loss of connectivity thus leads to critical loss of trophic relationships between vulnerable neurons and their targets. As a result, preservation of neuronal cell bodies through neuroprotective strategies is ineffective treatment of neurodegeneration unless appropriate functional connections are preserved or restored.

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