Disease Mechanisms in Neuroscience

Dopamine as an inactivator of parkin

Although most cases of Parkinson’s disease are sporadic, nine genes are known to be associated with inherited forms of Parkinson’s disease. PARK2, the gene which encodes the putative E3 ubiquitin ligase parkin, is the most frequently implicated, and there is evidence indicating that disease-associated mutations within PARK2 result in a loss of parkin function associated with an autosomal-recessive pattern of inheritance. It has been established that parkin mutations are sufficient to induce degeneration of catecholaminergic neurons within the pars compacta of the substantia nigra and locus coeruleus. Neurons in both of these brain regions synthesize dopamine in a constitutive manner. There is evidence implicating dopamine in a spectrum of cell-death pathways, including neurotoxicity associated with α-synuclein and the putative parkin substrate CDCrel-1. Building on this progress, LaVoie and others (2005) have now tested the hypothesis that dopamine-induced loss of parkin function can contribute to the reduced survival of dopaminergic neurons in sporadic Parkinson’s disease. They report that dopamine covalently modifies parkin within living dopaminergic cells, increasing parkin insolubility and inactivating the E3 ubiquitin ligase. They also report decreases in parkin solubility consistent with its functional inactivation within the brains of patients with sporadic Parkinson’s disease. These novel findings suggest that parkin can be modified by dopamine, a major neurotransmitter within the brain structures at risk in Parkinson’s disease, and lead the authors to propose that dopamine-induced loss of parkin activity may contribute to the selective degeneration of nigral neurons in this common and disabling disorder.


A gene for Tourette’s?

Tourette’s syndrome, which is clinically characterized by persistent and often bizarre vocal and motor tics, is present in as many as 1 in 100 individuals in societies in which it has been studied. It displays some overlap with obsessive-compulsive disorder, depression, and attention deficit hyperactivity disorder. Substantial evidence points toward a genetic contribution to Tourette’s syndrome, but to date, details of its genetic basis have been elusive. Now, a group of researchers at Yale University report an association of mutations in the SLITRK1 (Slit and Trk–like 1) gene with Tourette’s syndrome. Studying SLITRK1, which is located on chromosome 13q31.1, on the basis of its proximity to a de novo chromosomal inversion in a child with Tourette’s syndrome, Abelson and others (2005) identified a frame-shift mutation and two independent occurrences of the identical variant in the binding site for microRNA hsa-miR-189 in a sample of 174 unrelated probands, but they found that these variants were absent from 3600 control chromosomes. They observed an overlapping expression pattern for SLITRK1 mRNA and hsa-miR-189 in brain regions that have been indicted in Tourette’s syndrome, also reporting that whereas wild-type SLITRK1 enhances dendritic growth in primary neuronal cultures, the frame-shift mutant does not. Although it appears that this mutation is present in only a small subset of individuals with Tourette’s syndrome, its discovery may represent an important step forward in the search for molecular understanding of this disorder.

Narcolepsy: hypocretin (orexin) deficiency

Narcolepsy, which is clinically characterized by excessive daytime sleepiness and sleep attacks as well as irregularities in the sleep-wake cycle and cataplexy, has been associated with a loss of the hypothalamic neuropeptides orexin-A and -B (also termed hypocretin-1 and -2). However, whether this is due to a deficiency of hypocretin synthesis or to death of hypocretin-synthesizing neurons has not been determined. Now, two studies provide evidence for a specific loss of hypocretin neurons in the brains of patients with narcolepsy. Crocker and others (2005) used immunohistochemistry and in situ hybridization to examine the expression of orexin, neuronal activity-regulated pentraxin (NARP), and prodynorphin within the hypothalami of control and narcoleptic individuals. They observed that, within control hypothalami, more than 80% of the orexin-producing neurons also contained prodynorphin mRNA and NARP. In patients with narcolepsy, there was a striking reduction in the numbers of cells producing these markers, to about 5% to 10% of normal. Blouin and others (2005) also studied the distribution of NARP in normal and narcoleptic human postmortem brains using immunohistochemistry and reported that NARP colocalizes with hypocretin within the lateral hypothalamic area, dorsomedial hypothalamus, dorsal hypothalamic area, and posterior hypothalamic area within the normal brain. They observed an 89% reduction in the number of NARP-positive neurons in these areas in the hypothalami of narcoleptic patients. These two studies provide evidence that narcolepsy results from a specific loss of hypocretin neurons, representing an important step forward in the understanding of this disorder.
