Developmental Anatomy and Molecular Identity of Intra-telencephalic Corticostriatal Projection Neurons

Abstract

Many neurodegenerative, developmental, and acquired diseases of the central nervous system affect forebrain projection neurons. Corticostriatal projection neurons (CStrPN) have been implicated in the pathophysiology of specific neurological disorders including Huntington's disease and cerebral palsy. These neurons are the cortical input into the basal ganglia circuitry and underlie such functions as motor cognition and planning.

The goal of this thesis is to examine the anatomic development of CStrPN in mice. Previous studies have mainly focused on the anatomy of CStrPN at the adult stage, but none have considered the detailed anatomy of the main class of CStrPN, the intra-telencephalic CStrPN (CStrPNi), across development. Determining the normal patterns of CStrPN anatomic development will lay the foundation for future study of molecular-genetic controls over the lineage-specific differentiation of CStrPN. Such efforts carry important clinical implications for future regenerative therapies for neurological disease.

At distinct stages of mouse development, CStrPNi were retrogradely labeled from the striatum with fluorescent latex microspheres or anterogradely labeled from the cortex with the carbocyanine dye DiI. Pulse-labeling with BrdU from embryonic day 10.5 (E10.5) to El6.5 indicates that a majority of these neurons are born between EI2.5 and E14.5. CStrPNi, begin innervating the contralateral striatum between postnatal day 3 (P3) and P4, expand projections until P7, and refine connections with the striatum until P14. CStrPNi distribution is greatest in rostral sections of the brain near the motor strip, with fewer retrogtadely labeled cells in caudal sections. In areas where laminar organization is present, most CStrPNi localize to layer Va, but they are also contained in layer Vb, with occasional presence in layers II/III and very rare occurrence in layer VI. Consistent with their anatomical projections through the corpus callosum and their innervation of the striatum, CStrPNi exhibit a dual molecular identity as both callosal and corticofugal neurons. CStrPNi also extend collaterals to both striata in mice.

This understanding of the developmental anatomy of CStrPNi provides critical insight into the timing of CStrPNi maturation as well as the formation of corticofugal and commissural neuron projections. Most importantly, it enables further study of the molecular-genetic development of these cells.