Determination of Cell Fate within the Telencephalon

Stewart A. Anderson

Abstract

The telencephalon (basal ganglia, septum, cerebral cortex and olfactory bulb) contains two general classes of neurons: those that project axons to distant targets and those that make only local connections. While projection neurons can be either excitatory (such as those in the olfactory bulb and cortex) or inhibitory (such as those in the striatum), local circuit neurons (interneurons) are usually inhibitory. Within these two general classes of neurons there are a myriad of cell subtypes based upon axonal and dendritic morphology, chemical markers, neurotransmitters, connectivity and physiology. A crucial issue regarding the development of the telencephalon is the molecular determination of neuronal subtypes. Since important aspects of neuronal fate determination occur within the proliferative zone, the consideration of determinants of a mature neuron’s fate requires consideration of that cell’s origin.

During development of the telencephalon, neurons become post-mitotic within the proliferative zone that lines the lateral ventricles, then migrate into the mantle zone, where they differentiate. In general, the predominant mode of neuron migration is radial, so that a given mantle region of the telencephalon is primarily derived from the underlying proliferative zone. Tangential migrations have also been identified within the developing telencephalon (Luskin, 1993; Rakic, 1995; de Carlos et al., 1996; Anderson et al., 1997). Importantly, recent evidence suggests that the mode of migration (radial or tangential) appears to distinguish between the two general classes of telencephalic neurons, projection neurons and interneurons (Anderson et al., 1999). One of the first tangential migrations to be identified, the rostral migratory stream, involves the rostral migration of interneurons from the anterior subventricular zone of the lateral ventricle into the olfactory bulb. Another tangential migration, one that could conceivably be termed the dorsal migratory stream, involves the tangential migration of GABAergic interneurons from the anlage of the basal ganglia in the ventral portion of the neural tube into the cerebral cortex. A similar tangential migration appears to carry cholinergic interneurons from the most ventral regions of the telencephalic neural tube dorsally into the striatum (Marin et al., 2000).

The relationship between neuronal type, projection neuron or interneuron, and mode of migration, radial or tangential, begs the question: why has the telencephalon developed in this fashion? The answer may relate to the restricted potential of the proliferative zone to give rise (under normal conditions) to given neurotransmitter phenotypes. Under this scenario, different regions of the neural tube, under the influences of regionally expressed factors, are normally capable of giving rise to particular subsets of cells. The dorsal region gives rise to glutamatergic cells, the middle region to GABAergic cells, and the most ventral region of the telencephalon may give rise to cholinergic cells.

In order to create mixed mantle regions containing multiple neurotransmitter phenotypes, evolution may have found it ‘easier’, for example, to import into the cerebral cortex GABAergic cells from the basal ganglia anlage, rather than give the dorsal neuroepithelium the molecular qualities necessary for generating both GABAergic and glutamatergic cells.

What evidence exists to support a dorso-ventral restriction of fate potential in the developing telencephalon? In fact, a variety of studies have suggested that when telencephalic neurons are dissociated and placed in culture, or are injected into the lateral ventricles in vivo, they are capable of evolving into many cell fates [see, for example (Brustle et al., 1995; Fishell, 1995; Götz et al., 1995)]. In these experiments, what limited fate restriction that occurs appears to mimic their final post-migratory environments, thus supporting a model that local environmental cues play a dominant role in determining a neuron’s ultimate phenotype. However, recent experiments suggest that when neurons are allowed to mature within a more ‘normal’ environment, important aspects of fate determination are restricted based upon the cell’s position of origin along the dorso-ventral axis of the neural tube. In order to study the
determination of cell fate in the cerebral cortex, I have been conducting transplant experiments using donor cells from mice that ubiquitously express green fluorescent protein. However, rather than inject the donor cells into their normal initial environment in the medial ganglionic eminence (MGE), the lateral ganglionic eminence (LGE) or the cortex, I have been injecting them directly into the normal destination of some of these cells in the neonatal cortex. Interestingly, cells from the MGE and LGE [on embryonic day (E)11.5–E16.5] injected directly into the host cortex express the inhibitory neurotransmitter GABA, but do not express markers of cortical projection neurons such as CamkII or the glutamate receptor GluR2/3. These cells frequently have morphologies consistent with interneurons. In contrast, cortical cells from donor embryos at E11.5, just prior to the initial arrival of the tangentially migrating interneurons into the cortex at E12.0, express CamkII and GluR2/3 but not GABA or other interneuron markers after transplantation into the neonatal cortex. These cells frequently have morphologies consistent with pyramidal projection neurons.

In sum, cells from the ventral embryonic telencephalon that were transplanted into the neocortex appear to have been specified to become GABAergic interneurons, whereas cells from the dorsal, cortical telencephalon were specified to become projection neurons. These results suggest that important aspects of neuronal fate, including neurotransmitter and some aspects of neuronal morphology, may normally be determined while the neurons are within their proliferative zone. What is the nature of these factors? This remains on open question, and an appropriate review of the subject is far beyond the scope of this text. However, several lines of evidence suggest that aspects of neuronal fate determination in the rostral neural tube, the telencephalon, are similar to those of the caudal neural tube, the spinal cord. In the spinal cord signaling molecules, including bone morphogenetic proteins (BMPs) dorsally, retinoids within the intermediate region, and Sonic Hedgehog ventrally, appear to pattern the expression of transcription factors which regulate cell fate (Ericson et al., 1997). These molecules are also present in the telencephalon in a similar dorsal to ventral pattern. The extent to which these molecules pattern fate-determining transcription factors in the telencephalon remains to be determined. However, Sonic Hedgehog may contribute to neuronal specification in the ventral telencephalon (Ericson et al., 1995; Kohtz et al., 1998), retinoids may affect cell fate within the intermediate level [the LGE, possibly including those cells destined for the olfactory bulb (Toresson et al., 1999)], and BMPs appear to affect cell proliferation and potentially cell fate in the cerebral cortex (Li et al., 1998).

References


