Development of the Cerebral Cortex: VI. Growth Factors: I

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Earlier columns described how neurons are born and migrate to their final destination within the cerebral cortex. In the next stage of cortical development, axons and dendrites grow and form synapses. From birth to age 6 years, the child's brain grows dramatically (Fig. 1). This growth is not due to new neurons, as the vast majority of nerve cells are present at birth. Surprisingly, two thirds of all neurons born during fetal development will die during the first decade of life in a process termed apoptosis, or programmed cell death. The remarkable growth of the brain during these first few years is due primarily to the elongation of axons and an expansion in the number of dendrites as synapses are formed. The next several Development and Neurobiology columns will describe this process and how environmental factors may influence it.

Exactly how a neuron forms its proper connections is an area of active research. The growing axonal tip interacts with its target neurons. Once a synapse has formed, the survival of both neurons depends on maintaining a close interaction. The development of synapses and the long-term survival of neurons are mediated by trophic factors that are secreted by the target nerve cells, bind to specific receptors, and signal to the nearby developing synapse.

Within the nervous system, the most extensively studied of these factors is the family of neurotrophins. Almost 50 years ago, Rita Levi-Montalcini and Stanley Cohen isolated and identified nerve growth factor (NGF). This accomplishment earned them the Nobel Prize in Medicine in 1986. Four members of this family of neurotrophins are known to affect the growth and development of cells within the CNS.

Scientists have discovered several simple rules that describe how neurotrophins influence the growth of neurons. First, neurons require trophic factors to survive. Neurons compete for the minute amounts of trophic factors that are produced. Experiments have shown that when NGF is added into tissue cultures or injected directly into the CNS, the number of neurons, as well as their axons and dendrites, increases dramatically. Antibodies that bind to and thereby inactivate NGF have the opposite effect and lead to neuronal death.

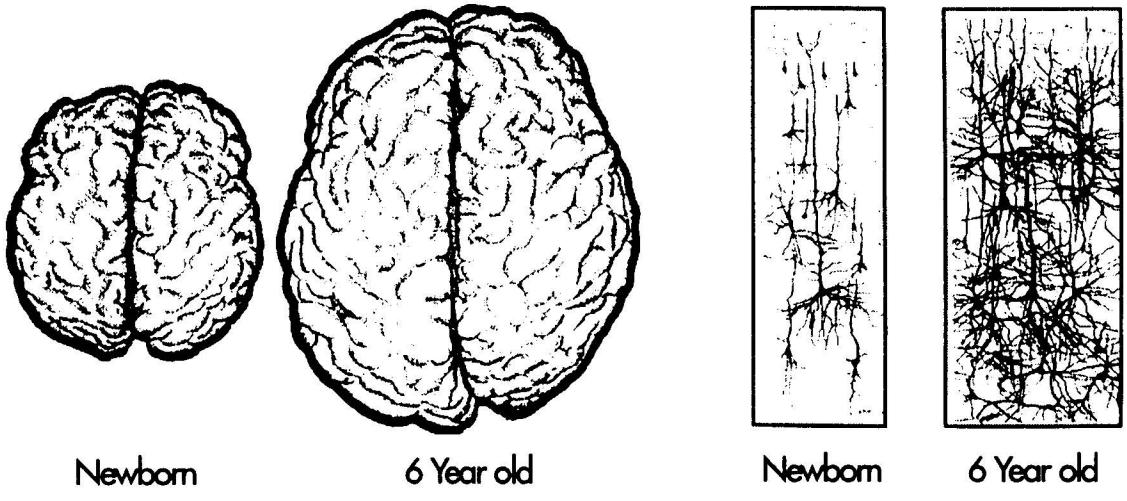

Fig. 1 The brain grows dramatically over the first decade of life. The increase in brain size is due primarily to an increase in the number and the complexity of neuronal processes rather than to an increase in the total number of neurons.

The neurotrophic hypothesis states that trophic factors are secreted by a neuron and diffuse to a nearby process of another neuron. Once they bind to receptor proteins on the nearby synapse, a cascade of signals is initiated that promotes the growth and survival of the receiving neuron. This is called retrograde signaling: the trophic factor is released by a neuron to attract a growing axon tip and establish synaptic connections. Recent work has established that neurotrophins are also secreted by the growing axon and diffuse back to the target neuron. Neurotrophins are thus required for both the target neurons and the neuron that supports the developing axon tip.

In future columns, we will discuss exactly how this signaling between neurons occurs. Disorders have been described in which mutations exist in various parts of the signaling machinery. We will also review how the environment influences the forming and strengthening of connections between neurons. This activity-dependent strengthening of synapses is also mediated by growth factors in the neurotrophin family. This is an exciting area of research that may clarify exactly how environmental factors interact with the developing infant to modulate the growth and development of the brain.

WEB SITES OF INTEREST

http://nobel.sdsc.edu/laureates/medicine-1986–2-autobio.html
http://nobel.sdsc.edu/laureates/medicine-1986–1-autobio.html

ADDITIONAL READINGS

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