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Differential Survival after Innervation: The Role of Neurotrophins

The target tissue regulates the number of axons innervating it by limiting the supply of neurotrophins. In addition to their roles as chemotrophic factors described in Chapter 17 of the textbook, neurotrophins regulate the survival of different subsets of neurons (Figure 1). NGF, for example, is necessary for the survival of sympathetic and sensory neurons. Treating mouse embryos with anti-NGF antibodies reduces the number of trigeminal sympathetic and dorsal root ganglion neurons to 20% of their control numbers (Levi-Montalcini and Booker 1960; Pearson et al. 1983). Furthermore, removing these neurons' target tissues results in the death of the neurons that would have innervated them, and there is a good correlation between the amount of NGF secreted and the survival of the neurons that innervate these tissues (Korsching and Thoenen 1983; Harper and Davies 1990). In contrast, another neurotrophin, BDNF, does not affect sympathetic or sensory neurons, but it can rescue fetal motor neurons in vivo from normally occurring cell death and from induced cell death following the removal of their target tissue. The results of these in vitro studies have been corroborated by gene knockout experiments in which the deletion of particular neurotrophic factors results in the loss of only certain subsets of neurons (Crowley et al. 1994; Jones et al. 1994).

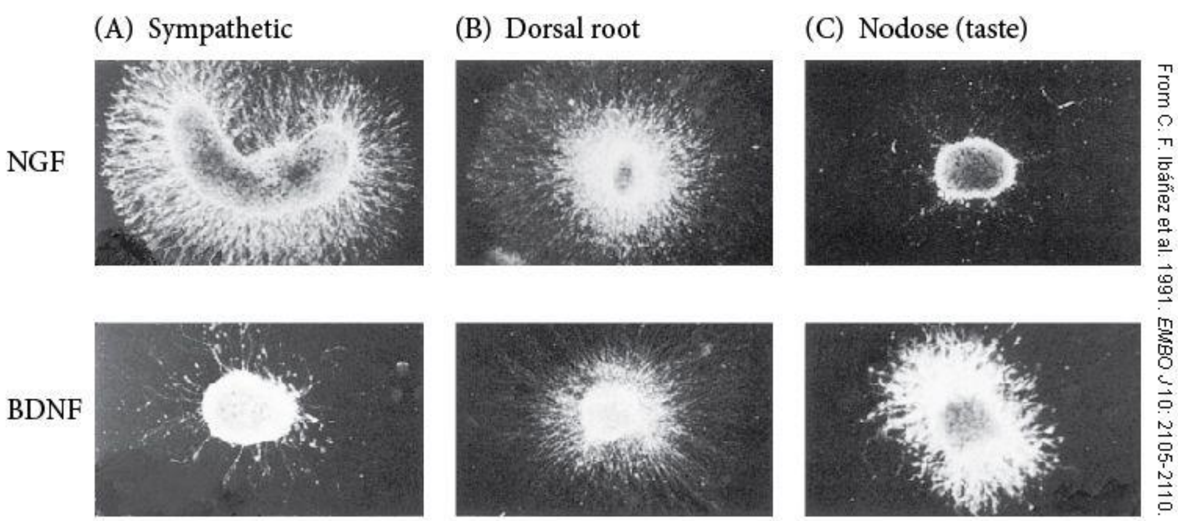

Figure 1 Effects of nerve growth factor (NGF; top row) and brain-derived neurotrophic factor (BDNF; bottom row) on axonal outgrowths from (A) sympathetic ganglia, (B) dorsal root ganglia, and (C) nodose (taste perception) ganglia. Although both NGF and BDNF had a mild stimulatory effect on dorsal root ganglia axonal outgrowth, the sympathetic ganglia responded dramatically to NGF and hardly at all to BDNF; the converse was true of the nodose ganglia.

Neurotrophic factors are produced continuously in adults, and their loss may produce debilitating diseases. BDNF is required for the survival of a particular subset of neurons in the striatum (a region of the brain involved in modulating the intensity of coordinated muscle activity such as movement, balance, and walking), and enables these neurons to differentiate and synthesize the receptor for dopamine. BDNF in this region of the brain is upregulated by huntingtin, a protein that is mutated in

Huntington disease. Patients with Huntington disease have decreased production of BDNF, which leads to the death of striatal neurons (Guillin et al. 2001; Zuccato et al. 2001). The result is a series of cognitive abnormalities, involuntary muscle movements, and eventual death. Two other neurotrophins—glial-derived neurotrophic factor (GDNF, discussed in Chapter 15 in terms of neural crest migration) and conserved dopamine neurotrophic factor (CDNF)—enhance the survival of the midbrain dopaminergic neurons, whose destruction characterizes Parkinson disease (Lin et al. 1993; Lindholm et al. 2007). The midbrain dopaminergic neurons send axons to the cells of the striatum, whose ability to respond to dopamine signals is dependent on BDNF. Drugs that activate the neurotrophic factors are being tested for the ability to cure Parkinson and Alzheimer diseases (Youdim 2013).

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