

Synapse formation and Neuronal Plasticity

Reading: 8e: Chp 13: 424-440; 9e: pp 402-409; 667-670

Learning Goals:

Describe how growth factors in general play a role in neuronal plasticity.

Describe the experiments that provided evidence for a critical time period during which activity is required for synapse maintenance.

Provide evidence that neuronal connections are maintained via a competitive process

Interpret experiments that explore neuronal plasticity

Synapse formation

Once axons and dendrites meet after pathfinding to the right "neighborhood", there must be some sort of recognition and selective adhesion process to allow specific synapse formation between the end of an axon and its target (usually another neuron, a muscle, or even a glial cell). There are many molecules known to be required for synapse formation—all of which you've heard about before: adhesive molecules like cadherins, NCAMs, and molecules that are also used for axon guidance, like the Ephrins. In addition, an adhesion protein called Neurexin, present on the presynaptic side, interacts with a protein called Neuroglian, present on the postsynaptic side. This interaction is important for recruiting and retaining cytoskeletal elements that are critical for localizing synaptic vesicles to the axon terminal, as well as localizing neurotransmitter receptors on the postsynaptic side. The details of how the molecules all fit together will not be considered in this class. Instead, we'll think more about how synapses are maintained and how they can change.

Maintenance of neuronal survival and axonal outgrowth: growth factors

The pathfinding mechanisms discussed previously can bring neurons into the vicinity of target cells but aren't solely responsible for the axon making a synapse that will be maintained. For a neuron to survive and synapse successfully, it must be stimulated by a neurotrophic factor released from the target cell. Different neurotrophic factors stimulate different neuronal types.

All neurotrophic factors are structurally related small proteins. They bind to a class of RTK receptors, encoded by genes of the Trk family, named for a proto-oncogene that was the first family member to be identified. There are several different kinds of receptors and several kinds of growth factors, and some molecules can bind to more than one receptor.

The first-discovered neurotrophic factor was called Nerve Growth Factor (NGF). It was discovered and characterized by Rita Levi-Montalcini in the 1940s. This factor is required for the survival of axonal projections from sensory neurons to the limbs, as well as by other kinds of sensory neurons. Levi-Montalcini and colleagues showed that there was extensive cell death in the neurons of the dorsal root ganglia (which are sensory neurons that send information into the spinal cord, as well as out to the musculature along the body). They noticed that the DRG neurons that projected to limbs underwent much less cell death, perhaps because their targets (the limbs) were large targets. Could there be a factor released by cells in the limbs that was responsible for the survival of the neurons back in the DRG? Yes! It took decades to actually purify the factor that is responsible for maintenance of these neurons, but once NGF was purified, other neurotrophic factors were quickly purified as well. Another commonly used neurotrophic factor is called brain-derived neurotrophic factor (BDNF), which appears to be particularly active in the central nervous system (CNS).

We now know that innervation of targets is a *competitive* process: about half of all neurons die shortly after their axons reach the vicinity of their targets! Seems wasteful, doesn't it?

Although there's a lot of coding power in the genome, it's efficient to use activity, sensory experience, and feedback to sculpt developing circuitry. This competitive process allows for selective pruning out of processes that are not needed, thus probably adding specificity and complexity to the way the nervous system can function.

In 1949, as a mechanism to explain learning and memory, the psychologist Hebb postulated that coordinated activity of a presynaptic terminal and a postsynaptic neuron would strengthen the synaptic connections between them. His ideas turned out to be true, and were refined into the so-called the **Neurotrophic hypothesis**:

- neurons are produced in excess during development
- more innervate a target tissue than needed in the adult
- The target tissues produce only limited amounts of the neurotrophic factors
- The neurons that receive a sufficient amount of the factor survive; others die.

To understand this hypothesis, and how it plays out in different parts of the nervous system, we can look at examples of synapse refinement and change. In these systems, it has been shown that when multiple axons synapse on a single cell (a muscle fiber or a cortical neuron, for example), not all will be maintained. What process selects some to survive and others to weaken?

The retinal-cortical projection

Patterning in the cortex is complicated, as you've already seen from the pathfinding mechanisms that exist from the retina to the tectum. In mammals, the retinal axons go first to the lateral geniculate nucleus (LGN), where they synapse. The LGN neurons then project to layer IV of the cortex. THEN, as if it weren't already complicated enough, the layer IV neurons project to the other layers of the visual cortex (layers 1,2,3, 5 and 6!). There are several fascinating features about this system. First of all, the target cells in layer IV of the visual cortex undergo considerable synaptic refinement. Initially, they receive inputs from both eyes. During development, this changes, such that there are bands of cells that respond only to one eye adjacent to a band of cells that respond only to the other eye (see the figures—impossible to figure out without them!).

A seminal set of experiments done by Hubel and Wiesel on cats (who have binocular vision, and a cortex like ours) in the 1970s showed that the connections made between the retina and the cortex were dependent on activity; they also showed that there is a critical period of time during development that these synapses must be made and refined. After that time, whatever damage has been done is irreparable. Briefly (again, you need to look at the ppt slides to understand this), they first showed that individual cells within the visual cortex were either primarily monocular (responded to only one eye) or were binocular (responded to light shone on both eyes). Next, they sewed shut one eye for the first 2.5 months of a kitten's life, and then opened the eye and did similar recordings from cells in the cortex to see whether light from either eye could still stimulate the cells. They found that the eye that had been closed no longer connected to any cells in the cortex! Almost no cells in the cortex now responded to light shone into that eye. All cells now responded only to light shone in the eye that had been open during those 2.5 months. In other words, the lack of activity in the closed eye resulted in that eye losing its connections to the cortex. If they did this experiment to adult cats, there was no significant change in how the cells responded to light. We'll talk about a few additional experiments in class that ultimately demonstrated that activity and competition were both critical for maintenance of cortical synapses, and that there was a short time period during development when the synapses were made and refined.

Synaptic maturation in the neuromuscular junction. When a motor axon contacts a muscle fiber, the axon releases agrin, a proteoglycan. Agrin causes the acetylcholine receptors in the fiber to cluster just under the area where the growth cone is making contact with the muscle. It is common for multiple axons to synapse onto a single muscle fiber initially. However, over time, all axons but one are eliminated from each fiber. The

pruning of connections again appears to be due to activity and competition. Activity of one axon strengthens that axon's connection to the target while inhibiting the connection of the other axons that are contacting the same muscle fiber. The synapses that fire with the same pattern as the target cell's firing are strengthened. The other synapses might be active as well, but if their pattern of firing is not coordinated with the target cell's firing, they will be weakened and eliminated.

Plasticity in adults

Scientists have recently shown that there are dividing cells still present in adult brains. This is a very exciting development, because it suggests that perhaps these cells could be stimulated to repair neuronal damage—this is an active area of research for scientists trying to help people with brain or spinal cord injuries, and also for those working on neurodegenerative diseases like Huntington's, Parkinson's and Alzheimers. It is also clear that our brains continue to change over our entire lives. Some examples of this are surprising: the brains of teenagers, for example, have a significantly different structure than adults, which may explain some of the behaviors that teenagers often exhibit. Some examples you may have heard of before: obviously our brains are constantly forming new memories, and the storage and retrieval of information requires plasticity. Two other examples are some of my favorites. Input to the somatosensory and motor cortices (where information is processed about sensation or motor activity from your body) can be rewired in certain situations. Data shows that if you lose a finger, the remaining fingers will send axons to cells in the cortex that used to get information from that lost finger—i.e., the cells now receive different input once their original source for input is gone. In addition, the area (number of cells) in the same region of the cortex can change significantly if you use any part of your body in a special way. The cortex of violinists (or violists or cellists), for example, have many more cells devoted to receiving information from the fingers of their left hand compared to the number of cells a non-musician has devoted to this input. Bottom line: your brain is constantly changing as a result of what you do. Use it well!

Summary:

After arriving at a destination, the survival of a neuron can depend on competing for a sufficient quantity of a neurotrophic factor. Activity-dependent refinement of synaptic connections may also depend upon axons obtaining neurotrophic factors in an activity-dependent manner. Ultimately, selective pathfinding, followed by activity-based refinement allows the formation of exquisitely complex and sophisticated circuitry that underly the function of the mammalian brain.