PERSPECTIVES: NEUROBIOLOGY

Does BDNF Have Pre- or Postsynaptic Targets?

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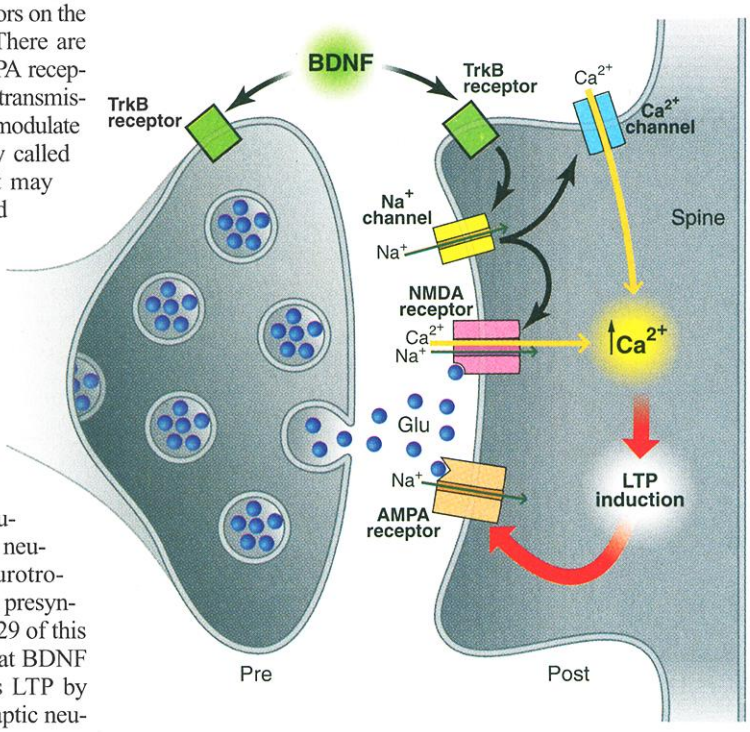
Learning and memory depend on the persistent modification of synapses between brain neurons. New memories are formed in the hippocampus, which is situated beneath the cerebral cortex, and damage to the hippocampus impairs certain kinds of learning in humans and animal models. In this brain region, excitatory synaptic transmission depends on glutamate, the most common excitatory amino acid neurotransmitter in the central nervous system (CNS). This neurotransmitter is released into the synapse by the presynaptic neuron and binds to glutamate receptors on the postsynaptic neuronal membrane. There are two sorts of glutamate receptor: AMPA receptors, which regulate basal synaptic transmission, and NMDA receptors, which modulate a specific type of synaptic plasticity called long-term potentiation (LTP) that may form the cellular basis of learning and memory (*1*). NMDA receptor activation increases the Ca^{2+} concentration in the postsynaptic neuron, activating intracellular biochemical pathways that result in persistent modification of postsynaptic AMPA receptor numbers and activity. In addition to AMPA and NMDA receptors, many other molecules localized at synapses regulate LTP induction. For example, a neurotrophin called brain-derived neurotrophic factor (BDNF) is thought to act presynaptically to induce LTP. On page 1729 of this issue, Kovalchuk *et al.* (*2*) reveal that BDNF in concert with glutamate induces LTP by binding to receptors on the postsynaptic neuronal membrane.

BDNF and other neurotrophins such as nerve growth factor (NGF) are trophic substances that promote the survival or differentiation of neurons. They are also crucial for synaptic transmission and plasticity (*3*). In contrast to their slow effect on neuronal survival or differentiation (hours or days), their modulation of synaptic transmission is much faster (seconds or minutes). A pioneering study by Lehof *et al.* (*4*) showed that treating cultured neurons and muscle cells with exogenous BDNF potentiates synaptic transmission at the developing neuromuscular junction within minutes by enhancing neurotransmitter release from presynaptic terminals. Subsequently, similar acute effects of exogenous BDNF on synaptic transmission in the CNS were reported. BDNF potentiates excitatory synaptic transmission in the CA1 region of the hippocampus (*5*) and has acute effects on both excitatory and inhibitory synapses in the CNS, although BDNF's effects on excitatory synapses are still controversial (*3*).

Several lines of evidence indicate that these actions of BDNF are mediated by the TrkB receptor tyrosine kinase. It has been shown pharmacologically and genetically that binding of BDNF to TrkB receptors is essential for LTP induction in the hippocampus. Mice engineered to lack BDNF have impaired hippocampal LTP (*6*), and conditional knockout mice that lack TrkB receptors in the forebrain during the postnatal period show reduced hippocampal LTP and impaired learning behavior (*7*). Furthermore, LTP is blocked when endogenous BDNF is reduced by a TrkB–immunoglobulin G fusion protein that scavenges BDNF (*8*). These findings strongly suggest that when endogenous BDNF binds to TrkB receptors, permissive and/or instructive signals are generated that induce LTP. It has been presumed that these actions of BDNF are mediated presynaptically, leading to modulation of neurotransmitter release (although LTP in the CA1 hippocampal region and dentate gyrus is known to be induced postsynaptically). However, because the manipulations in these studies should have affected both pre- and postsynaptic BDNF-TrkB pathways equally, it is unclear whether the action of BDNF is solely due to presynaptic modification.

Enter Kovalchuk *et al.* (*2*) with their study showing that the postsynaptic BDNF-TrkB pathway is crucial for regulation of excitatory synaptic transmission and LTP induction. Using electrophysiology in mouse hippocampal slices, the authors show that exogenously applied BDNF induces depolarization of postsynaptic dentate granule cells, presumably through activation of Na^+ channels (*9*) and Ca^{2+} ion influx through Ca^{2+} channels. In contrast, BDNF has no effect on presynaptic perforant path fibers originating from cortical neurons, which form synapses with the dentate granule cells. An increase in Ca^{2+} concentration in dentate granule cells induced by BDNF, but not their depolarization, is blocked by a Ca^{2+} channel inhibitor D890. Postsynaptic voltage clamping, which prevents depolarization



Postsynaptic modulation by BDNF. The neurotrophin BDNF postsynaptically modulates hippocampal synaptic transmission and plasticity (*2*). Activation of postsynaptic TrkB receptors by BDNF causes depolarization of the postsynaptic neuron, presumably through opening of Na^+ channels (*9*) and concomitant activation of Ca^{2+} channels, resulting in an increase in the Ca^{2+} concentration. During synaptic transmission, postsynaptic cell depolarization caused by the activation of TrkB receptors enhances NMDA receptor opening by removing a Mg^{2+} block from the receptor channel, which then facilitates the induction of LTP in the postsynaptic cell.

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of dentate granule cells, also blocks an increase in Ca^{2+} concentration in response to BDNF. These findings suggest that the primary action of BDNF is to induce postsynaptic depolarization of dentate granule cells leading to voltage-dependent opening of Ca^{2+} channels (see the figure). BDNF application alone has no effect on synaptic transmission. However, when it is combined with a weak burst of presynaptic activity that itself has little effect on synaptic transmission, persistent enhancement of synaptic transmission is induced, similar to that seen with tetanic stimulation. Furthermore, this persistent enhancement is blocked by the D890 inhibitor or by an NMDA receptor antagonist, demonstrating that BDNF-mediated LTP is induced postsynaptically.

The Kovalchuk *et al.* study clearly shows that TrkB receptors are present on the postsynaptic neuron and that exogenous BDNF has some effect on postsynaptic excitability and Ca^{2+} signaling in the dentate granule cell. Furthermore, the authors point out that the BDNF-TrkB pathway can regulate the induction of NMDA receptor–dependent LTP. Their work provides concrete evidence for the importance of BDNF in postsynaptic regulation of LTP. However, because the investigators only examined TrkB receptor activity by applying BDNF exogenously, it will be important to show in future experiments that the same phenomenon is induced by endogenous BDNF, and to identify the site of BDNF release. Although this study strongly suggests that the target of BDNF is TrkB receptors in the postsynaptic neuronal membrane, it remains possible that presynaptic TrkB receptors are also involved in synaptic transmission and plasticity. This puzzle could be solved by engineering conditional knockout mice that do not express BDNF or TrkB receptors in specific brain regions, such as the dentate gyrus or the CA1 and CA3 regions of the hippocampus.

References

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PERSPECTIVES: ASTRONOMY

Blood Out of a Stone

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Almost 50 years ago, radio astronomers showed that the powerful radio emission associated with many giant elliptical galaxies is not centered on the stars that optical astronomers record. Instead, it is localized in two giant "lobes" on opposite sides of the galaxy, millions of light years from the stars (see the right panel in the figure) (*1*). In one of the great detective stories in astronomy, the prime movers of these radio displays have been identified (*2*). The lobes are continuously supplied with power by a pair of jets emanating from a spinning black hole in the galaxy's nucleus, which may be no more than a few light hours in size. But how does the black hole generate the jets? On page 1688 of this issue, Koide *et al.* (*3*) present numerical computations that may take us a step closer to solving this mystery.

Radio astronomers have long been responsible for almost all jet observations. They found that the flow speed is typically 99% of the speed of light (*4*) and that the jets are formed on scales smaller than a hundred times the radius of the black hole. However, recently, optical, x-ray (*5*), and gamma-ray (*6*) astronomers have been observing jets and have shown that they are even more powerful and energetic than previously thought. They appear to have very small gas densities, with electrons and positrons accelerated to energies of 10^{12} eV (*2*). These observations provide powerful clues as to what jets contain and how they are generated and focused.

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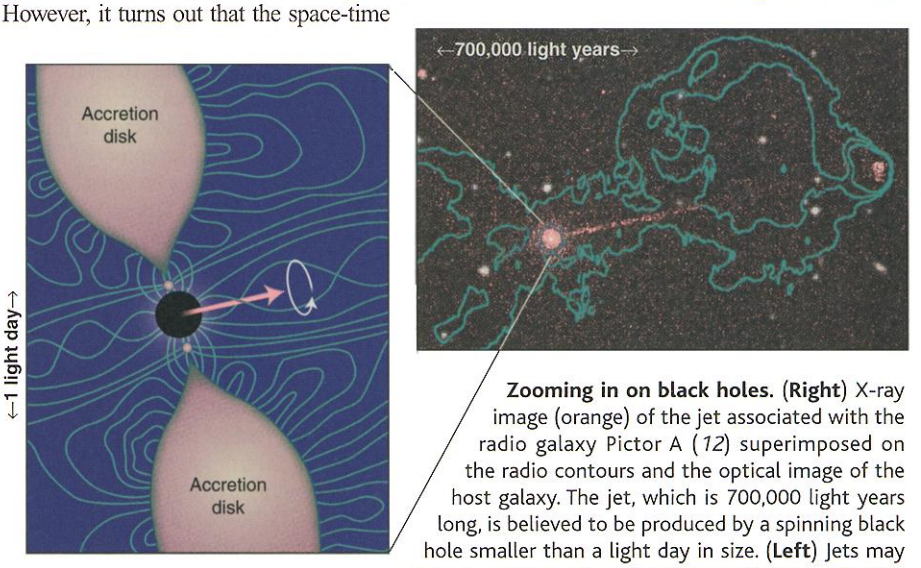
The black holes found at the centers of most galaxies are infinitely deep gravitational potential wells. When matter falls into such a hole through an accretion disk, it can release a substantial fraction of its rest mass, providing ample fuel for even the most powerful radio sources. However, there have long been doubts about whether these disks can be responsible for the speed and composition of the observed jets given that they are not located very deep in the potential well.

Attention has therefore turned to the black hole itself (*2*). This may seem unpromising at first because black holes are energy sinks. However, it turns out that the space-time around spinning black holes stores a substantial amount of rotational energy, which can be tapped directly by an electromagnetic field (*7*) and used to power a pair of jets.

Black holes are very good at removing matter from their surroundings. The power that they release is therefore most likely to be in an electromagnetic form. This allows the jets to achieve the high speeds that are observed. The magnetic field that is attached to the accretion disk (*8*) may also have a function as it can be twisted up to create a sort of magnetic sleeve, which surrounds and collimates the jets (see the left panel in the figure). In addition, there is now evidence for another type of magnetic connection, between the hole and the disk, from observations of active galactic nuclei, which suggest that the hole's spin energy must be tapped to power the x-ray emission (*9*).

The idea of an electromagnetic connec-



Zooming in on black holes. (Right) X-ray image (orange) of the jet associated with the radio galaxy Pictor A (*12*) superimposed on the radio contours and the optical image of the host galaxy. The jet, which is 700,000 light years long, is believed to be produced by a spinning black hole smaller than a light day in size. **(Left)** Jets may be powered through a direct magnetic connection to the black hole or through an indirect connection via gas that swirls around just outside the event horizon, as Koide *et al.* simulate. They could also be powered magnetically by the accretion disk.