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.

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PERSPECTIVES: ASTRONOMY

Blood Out of a Stone

R. D. Blandford

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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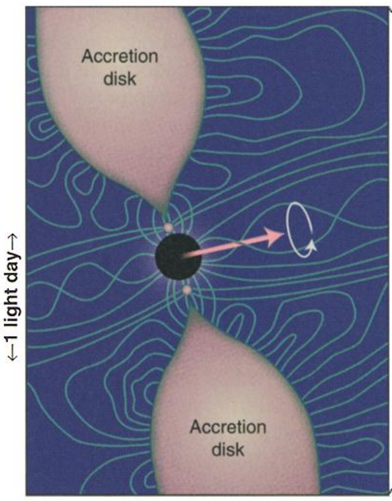
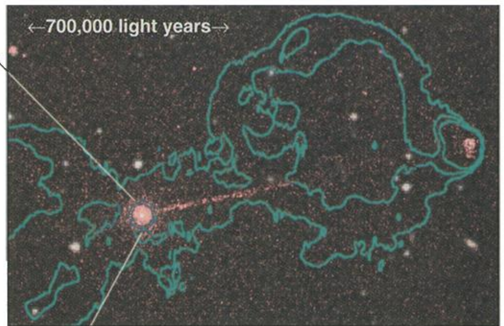
The black holes found at the centers of most galaxies are infinitely deep gravitational potential wells. When matter falls into such a hole through an accretion disk, it can release a substantial fraction of its rest mass, providing ample fuel for even the most powerful radio sources. However, there 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.

tion between the hole and the jet has proven to be somewhat controversial. Part of the problem is that several distinct mechanisms may be operating simultaneously. Electromagnetic energy may not only be transferred directly from the hole to the jet; there may also be an indirect transfer, with the jets being connected magnetically to the gas that swirls around just outside the black hole's event horizon (the "point of no return" from a black hole). In this case, the extracted energy can still be charged to the black hole because the gas is forced onto lower energy orbits by the magnetic field. When we balance the books after the gas crosses the event horizon, we find that the hole has a lower mass than if there had been no magnetic action.

It is this indirect process that Koide *et al.* are simulating. The study provides the most complete numerical calculation to date that demonstrates the extraction of energy from a spinning black hole. The numerical challenge is considerable. Not only do the equations of magnetohydrodynamics have to be solved, but this must be done within the framework of general relativity, where clocks appear to tick more slowly close to the event horizon. As a consequence, the calculation can only be followed for at most a couple of orbits and the system never reaches an equilibrium configuration.

Much remains to be explored numerically (the calculations are intractable analytically). We need to understand how much power is removed directly and indirectly from the black hole and compare this with the magnetic power released by the disk. In addition, Koide *et al.*'s axisymmetric calculation may hide serious instabilities associated with twisting magnetic field lines, rather like what happens when you twist a rope under tension. It will also be interesting to see whether the outflow evolves to a steady state or is intrinsically episodic. The necessary computing power is now available, but more robust algorithms must be developed to address these questions.

Observational astronomers are homing in on black holes, especially at x-ray wavelengths, and the next generation of space satellites, in tandem with major upgrades to existing radio telescopes, should transform our view of black holes over the next few years. Electromagnetic effects around black holes may turn out to play an important role in gamma-ray bursts (*10*) and "galactic microquasars" (*11*) and are similar to the processes that underlie pulsar wind nebulae such as the famous Crab Nebulae (*12*).

Much attention has been paid, in recent years, to the quest to reconcile quantum mechanics with gravity. The observational considerations above also motivate a more modest theoretical program to unify classical electromagnetism and gravity.

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PERSPECTIVES: CELL BIOLOGY

A Pit Stop at the ER

Gordon N. Gill

When ligands such as hormones, growth factors, or neurotransmitters bind to their cell surface receptors, a signal transduction cascade is initiated. Although signaling pathways activated by ligand are well understood, less is known about how these pathways are switched off. In general, "off" switches are spatially separated from "on" switches, providing a necessary time delay during which the biological response takes place. The off switch for activated receptor tyrosine kinases (RTKs) has three parts: dissociation of the activating ligand, removal of phosphate groups (dephosphorylation) from tyrosine residues of the RTK (where the signaling machinery is assembled), and degradation of both ligand and receptor. The imaging study by Haj *et al.* (*1*) on page 1708 of this issue provides an important and unexpected insight into the journey taken by an activated RTK as it goes through the steps to be switched off. The authors found that after internalization (endocytosis) of RTKs from the cell surface, these receptors travel to the endoplasmic reticulum (ER) where the protein tyrosine phosphatase PTP1B resides. This enzyme removes phosphate groups from tyrosine residues in the cytoplasmic domain of RTKs, which then continue on to their final destination, the lysosomes (see the figure).

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Ligand-activated receptors are internalized at a rate that is about 10-fold greater than that for receptors not occupied by ligand (*2*). The enhanced endocytosis rate for epidermal growth factor receptor (EGFR) requires both intrinsic tyrosine kinase activity and endocytic sequence "codes" located in the cytoplasmic domain of the receptor. Subsequent trafficking of endocytosed receptors to lysosomes also depends on specific receptor sequence codes (*3*). Endocytosis removes RTKs from further exposure to ligands in the extracellular milieu. The endocytic vesicles (endosomes) containing RTK cargo are progressively acidified so that the receptors become dissociated from their ligands. The differential pH sensitivity for dissociation of EGF from EGFR versus dissociation of transforming growth factor–α from EGFR accounts for the different signal strengths of these two ligands (*4*).

In their study, Haj and co-workers address the spatial and temporal features of RTK dephosphorylation. They engineered immortalized mouse fibroblasts, derived from embryos lacking the tyrosine phosphatase PTP1B, to express a mutant phosphatase in which Asp^{181} is replaced by an Ala residue, resulting in an enzyme that traps RTK substrate. Dephosphorylation involves formation of a cysteinyl phosphate intermediate (generated by attack of the active-site Cys on the phosphorus atom) followed by cleavage of the P-O bond by the acidic residue Asp^{181} (*5*). Thus, the Asp^{181} to Ala transition creates a mutant phosphatase that favors formation of stable RTK-phosphatase complexes. The authors needed to use this mutant phosphatase because the turnover of wild-type PTP1B is too great to allow visualization of the interaction between the enzyme and RTKs. Haj *et al.* used fluorescence resonance energy transfer (FRET) to visualize the interactions of ligand-activated EGFR and platelet-derived growth factor receptor (PDGFR) with mutant PTP1B. It had been presumed that PTP1B interacts with EGFR only during EGFR biosynthesis, because PTP1B is localized on the cytoplasmic face of the ER (through a hydrophobic carboxyl-terminal anchor sequence). Haj *et al.* first verified the ER localization of wild-type and mutant PTP1B and then discovered that mutant PTP1B clustered in specific regions of the ER after growth factor stimulation of cells. Direct enzyme-receptor interactions were visualized by tagging EGFR and PDGFR with green fluores-