tosecond pulse trains was reported by Papadogiannis *et al.* (*8*). Last year, de Paul *et al.* measured a train of 250-as pulses directly in the time domain (*9*).

Can such pulse trains be used for time-resolved attosecond spectroscopy? Salières *et al.* proposed in 1996 to use them for monitoring processes that occur with the period $T_L/2$ of the train. Candidates for such processes are harmonic generation itself or above threshold ionization (*2*), a laser-induced ionization process in which electrons absorb more photons than they need to be released. All of these processes can be described by "simple man's models" (*10*). Unfortunately, today's attosecond pulses are not sufficiently intense to realize time-resolved attosecond spectroscopy of these processes.

Although HHG is now an established source for attosecond pulse trains, it has one major limitation. Applications of time-resolved spectroscopy to dynamics that do not occur with the $T_L/2$ period require single isolated attosecond pulses. But there may be a way around this problem. For laser pulses shorter than 10 fs, the resulting individual harmonics fall below the femtosecond limit. Because the laser pulse lasts for only a few T_L, the harmonics cannot develop; instead, a soft x-ray attosecond pulse should be generated.

Krausz and co-workers (*11*) generated such an isolated attosecond x-ray pulse ($\lambda \approx 14$ nm) by irradiating a very short laser pulse ($\lambda \approx 750$ nm) of ~5-fs duration on a krypton gas sample, and filtering the outgoing radiation to a 5-eV range around 90 eV. They then irradiated the target krypton sample simultaneously with the x-ray pulse and a laser pulse of visible light of a few laser cycles duration. The x-ray pulse ionized the krypton atoms. The energy spectrum of the photoelectrons depended on the phase of the laser pulse at the moment of the electron's detachment. When the authors changed the relative delay between the laser and the soft x-ray pulse, a modulation of the spectral width appeared, allowing the duration of the x-ray pulse to be estimated as ~650 as.

Krausz and co-workers now describe (*1*) the first genuine application of isolated attosecond pulses for time-resolved attosecond spectroscopy. They study the absorption and emission of laser photons by electronic wavepackets created by soft x-ray radiation. Normally, the photoelectron energy spreads as a result of the photon absorption or emission (*12*). If, however, the emitted electron wavepacket is temporally confined to a fraction of T_L, its energy spectrum may be up- or down-shifted by several laser photon energies without broadening. The laser light can then "steer" the electron wavepacket like a classical particle. The results of such "steering" depend on the timing of the attosecond x-ray pulse relative to the absolute phase of the laser (see the figure), offering a simple, single-shot tool for time-resolved attosecond spectroscopy.

Attophysics has moved from dream to reality. One can expect fruitful applications of time-resolved attosecond spectroscopy to HHG or to above threshold ionization processes induced by ultrashort laser pulses, in which the absolute phase of the laser pulse plays a crucial role (*13*). Attosecond spectroscopy will provide diagnostics and perhaps new ways of controlling these processes, in particular to obtain better ways of short x-ray coherent pulse generation.

References and Notes

1. R. Kienberger *et al.*, *Science* **297**, 1144 (2002); published online 11 July 2002 (*Science* 10.1126/science.1073866).
2. C. J. Joachain, M. Dörr, N. Kylstra, *Adv. Atom. Mol. Opt. Phys.* **42**, 225 (2000).
3. Ch. Spielmann *et al.*, *Science* **278**, 661 (1997).
4. P. B. Corkum, *Phys. Rev. Lett.* **71**, 1994 (1993).
5. K. C. Kulander, K. J. Schafer, J. L. Krause, in *Super-Intense Laser-Atom Physics*, B. Piraux, A. L'Huillier, K. Rzcàzēwski, Eds. (Plenum, New York, 1993).
6. M. Lewenstein *et al.*, *Phys. Rev. A* **49**, 2117 (1994).
7. P. Antoine, A. L'Huillier, M. Lewenstein, *Phys. Rev. Lett.* **77**, 1234 (1996).
8. N. Papadogiannis *et al.*, *Phys. Rev. Lett.* **83** 4289 (1999).
9. P. M. Paul *et al.*, *Science* **292**, 1689 (2001).
10. P. Salières *et al.*, *Science* **292**, 902 (2001).
11. M. Hentschel *et al.*, *Nature* **414**, 509 (2001).
12. N. M. Kroll, K. M. Watson, *Phys. Rev. A* **8**, 804 (1973).
13. G. G. Paulus *et al.*, *Nature* **414**, 182 (2001).

14. I thank the Deutsche Forschungsgemeinschaft, Alexander von Humboldt-Foundation, the VolkswagenStiftung, the ESF, and European Union Research Training Network "Cold Quantum Gases."

PERSPECTIVES: NEUROSCIENCE

It Takes More Than Two to Nogo

Clifford J. Woolf and Stefan Bloechlinger

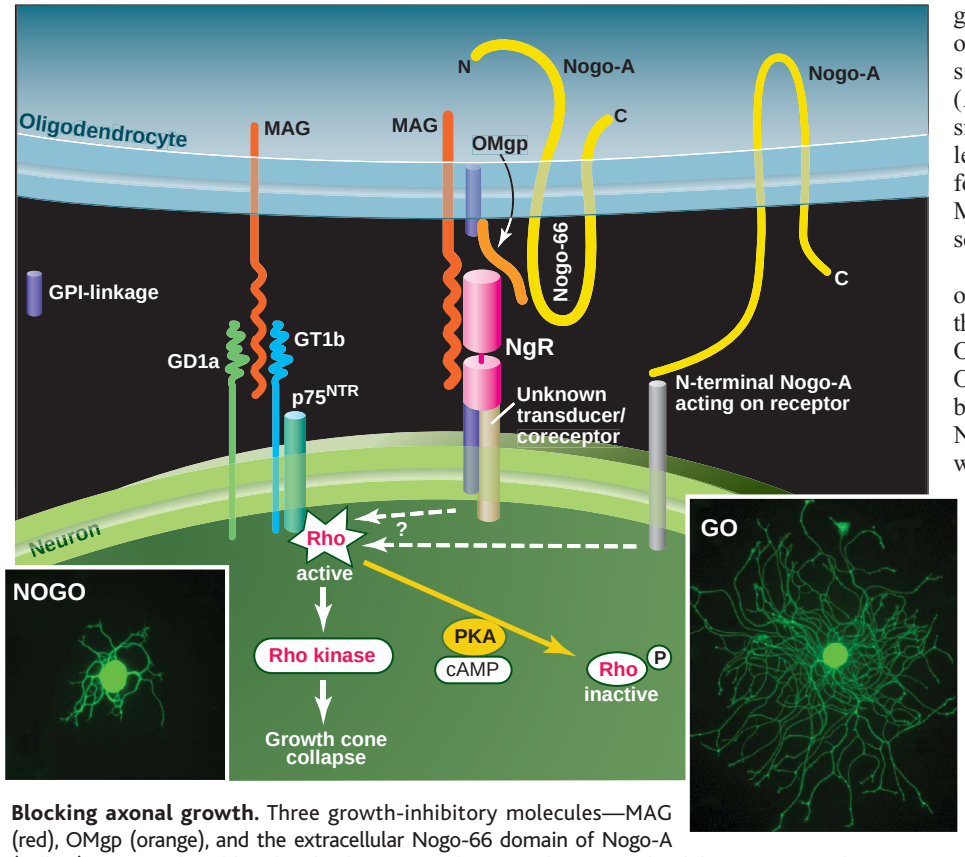
The environment of the adult mammalian central nervous system (CNS) is hostile to the growth of axons and is a major contributor to the inability of injured neurons to regenerate. Much of this inhibition is caused by myelin, the insulating lipid and protein material that is wrapped around axons, ensuring rapid transmission of electrical signals along central nerve fibers. In the CNS, myelin is produced by supporting glial cells called oligodendrocytes. These cells also make growth-inhibitory proteins that become embedded within the myelin sheath. Injured nerve fibers that make contact with CNS myelin cease to regenerate. At least three growth-inhibitory proteins have been identified so far: Nogo-A, named for its inhibitory action on axonal growth; myelin-associated glycoprotein (MAG); and oligodendrocyte myelin glycoprotein (OMgp). Although Nogo-A is known to bind to the Nogo receptor (NgR), the receptors for MAG and OMgp have remained elusive. Now, in an extraordinary and unexpected convergence reported by several groups including Liu *et al.* (*1*) on page 1190 of this issue, all three molecules appear to bind to the same receptor, NgR (*2–4*). This discovery opens up exciting new possibilities for overcoming axonal growth inhibition, a vital step in neuronal regrowth after brain or spinal cord injury.

Enhanced online at www.sciencemag.org/cgi/content/full/297/5584/1132

The authors are in the Neural Plasticity Research Group, Department of Anesthesia, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02129, USA. E-mail: woolf.clifford@mgh.harvard.edu

During the development of the nervous system and in neurons grown in culture, the extension of axons from the cell body begins with the formation of small processes whose active tips have a specialized structure called the axonal growth cone. The growth cone interacts with the environment to determine the direction and rate of axon elongation. When the growth cone contacts CNS myelin, its cytoskeletal structure is altered, causing it to collapse and resulting in cessation of axonal growth. Nogo-A, MAG, and OMgp all contribute to the inhibitory action of CNS myelin on axonal growth and regeneration.

Nogo-A, a member of the reticulon family of proteins, has two inhibitory domains: a cell surface domain called Nogo-66 (*5*), and a long amino-terminal region (*6*) (see the figure). The Nogo-66 domain on the oligodendrocyte surface binds to NgR, a leucine-rich repeat protein that is attached to the extracellular surface of the neuronal membrane by glycophosphatidylinositol (GPI) (*4*). The location of the inhibitory amino-terminal domain of Nogo-A may be cytoplasmic, although this remains unclear (*5, 6*). If this is the case, then the amino-terminal domain of Nogo-A can inhibit axonal growth only when myelin is disrupted by injury. No receptor



Blocking axonal growth. Three growth-inhibitory molecules—MAG (red), OMgp (orange), and the extracellular Nogo-66 domain of Nogo-A (yellow)—are produced by oligodendrocytes in the CNS. These growth-inhibitory proteins become embedded in the myelin sheath that surrounds axons, and they block the regeneration of nerve fibers. They all bind to the same neuronal receptor NgR (pink), resulting in the activation of signaling pathways that block axonal growth and induce growth cone collapse. NgR may require a coreceptor to transduce intracellular signals via molecules such as the Rho GTPase, but this putative coreceptor has not been identified. Activation of PKA leads to inactivation of Rho and prevents growth cone collapse. In addition to binding to NgR, MAG also interacts with a complex between the gangliosides GT1b and GD1a and the neurotrophin receptor p75, resulting in activation of Rho. The photomicrographs depict primary adult dorsal root ganglion neurons grown either on a laminin substrate that is permissive for growth (**right**) or on a CNS myelin substrate that prevents growth (**left**).

for the Nogo-A amino-terminal domain has been reported so far. Competitive inhibition of the binding of Nogo-66 to NgR by an antagonistic peptide, NEP1-40, overcomes all of the inhibitory action of Nogo-66 and much but not all of the inhibitory action of CNS myelin on cultured neurons (*7*). In vivo studies reveal similar effects on regenerative neural growth after spinal cord injury for both NEP1-40 (*7*) and IN-1, a monoclonal antibody that recognizes Nogo-A (*8*). IN-1 antibody treatment also causes rearrangement of intact fiber tracts, which suggests that Nogo-A tonically suppresses neural growth in the adult CNS (*9*).

MAG is a sialic acid–binding protein of the SIGLEC (sialic acid–dependent immunoglobulin-like family member lectin) group. It inhibits axonal growth in multiple in vitro assays, although, surprisingly, deleting the *MAG* gene does not promote neuronal regeneration in mice (*10*). OMgp is a GPI-anchored protein that was recently found to potently inhibit neurite outgrowth in culture (*3*). Both MAG and OMgp, like Nogo-66, bind to NgR with high affinity (*1, 3*). Although the NgR binding sites for OMgp and Nogo-66 appear to overlap, MAG and Nogo-66 bind to different sites on NgR (*1*). Removal of NgR by cleaving its GPI membrane anchor results in loss of the growth-inhibitory action of all three proteins. In contrast, introduction of exogenous NgR into neurons that are unresponsive to the growth-inhibitory proteins renders them responsive (*1–4*). NgR is therefore a promiscuous receptor binding to multiple inhibitory myelin proteins, and it appears to act as the major convergence point on the surface of growth cones for detecting many of the inhibitory influences of CNS myelin.

NgR has no transmembrane or intracytoplasmic domains and so must produce inhibition by binding to a membrane-bound coreceptor that transduces the extracellular signal and activates intracellular signaling cascades that lead to the collapse of the growth cone. Apparently, MAG binds not only to NgR (*1*) but also to the gangliosides GD1a and GT1b at least in some (*11*), but not all (*1*), assays. This ganglioside action requires the low-affinity nonselective neurotrophin receptor p75, which forms a complex with GT1b that binds to MAG (*12*). Thus, like Nogo-A, MAG seems to have two independent receptors.

Which signaling molecules downstream of NgR or the GT1b/p75 complex transduce the activation signals of Nogo-A, MAG, and OMgp that result in growth cone collapse? One possibility is Rho, a small membrane-bound guanosine triphosphatase (GTPase). Neurons expressing dominant-negative Rho, which cannot transduce signals, are not responsive to the growth-inhibitory properties of MAG. Blocking Rho-GTPase activity with the *Clostridium botulinum* enzyme C3 allows neurites to grow on MAG substrates in vitro (*13*). Inhibition of Rho-kinase (a downstream target of Rho that interacts with the cytoskeleton) overcomes GT1b-mediated blockade of axonal elongation. In addition, cyclic adenosine monophosphate (cAMP) blocks MAG-induced inhibition by activating protein kinase A (PKA), which inactivates Rho through phosphorylation (*14*). Recently, it has been shown that cAMP promotes neurite growth after spinal cord injury in vivo (*15, 16*).

The convergence of inhibitory influences at the level of both cell surface receptors and intracellular signaling could be the reason for the devastating suppression of neuronal growth by CNS myelin after spinal cord injury. This convergence could explain the powerful independent effects of Nogo-A, MAG, and OMgp, as well as the modest increase in regeneration that is produced by blocking the activity of each individual growth-inhibitory protein. Neuronal regeneration is likely to be improved by targeting NgR or Rho rather than by targeting Nogo-A, MAG, or OMgp independently. However, one major concern with this type of treatment is that it may enable maladaptive sprouting and growth of noninjured neurons, which could disrupt the highly organized connectivity of the CNS established during development. Indeed, the function of Nogo-A, MAG, or OMgp may be related more to preservation of the wiring of the CNS than to suppression of neuronal regeneration. In any case, myelin inhibition is not the only factor responsible for the lack of regeneration. Astrocytes, another type of CNS glial cell, also produce inhibitory molecules, including tenascin and chondroitin sulfate proteoglycan. In addition, overcoming inhibition is only half the story; an increase in the intrinsic growth capacity of the injured neurons is also re-

quired (*17*). Nonetheless, the new reports identifying the importance of NgR in preventing neuronal regeneration represent a big step forward in our understanding of the molecular pathways that impede regeneration in the CNS. The fact that these reports provide a point of convergence—and therefore a potential reduction in the number of interventions necessary to promote nerve regeneration—is also good news.

References

1. B. P. Liu, A. Fournier, T. GrandPré, S. M. Strittmatter, *Science* **297**, 1190 (2002); published online 27 June 2002 (10.1126/science.1073031).
2. M. Domeniconi *et al.*, *Neuron* **35**, 283 (2002).
3. K. C. Wang *et al.*, *Nature* **417**, 941 (2002).
4. A. E. Fournier, T. GrandPré, S. M. Strittmatter, *Nature* **409**, 341 (2001).
5. T. GrandPré, F. Nakamura, T. Vartanian, S. M. Strittmatter, *Nature* **403**, 439 (2000).
6. M. S. Chen *et al.*, *Nature* **403**, 434 (2000).
7. T. GrandPré, S. Li, S. M. Strittmatter, *Nature* **417**, 547 (2002).
8. B. S. Bregman *et al.*, *Nature* **378**, 498 (1995).
9. M. Thallmair *et al.*, *Nature Neurosci.* **1**, 124 (1998).
10. U. Bartsch *et al.*, *Neuron* **15**, 1375 (1995).
11. A. A. Vyas *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 8412 (2002).
12. T. Yamashita, H. Higuchi, M. Tohyama, *J. Cell Biol.* **157**, 565 (2002).
13. M. Lehmann *et al.*, *J. Neurosci.* **19**, 7537 (1999).
14. P. Lang *et al.*, *EMBO J.* **15**, 510 (1996).
15. J. Qiu *et al.*, *Neuron* **34**, 895 (2002).
16. S. Neumann, F. Bradke, M. Tessier-Lavigne, A. I. Basbaum, *Neuron* **34**, 885 (2002).
17. S. Neumann, C. J. Woolf, *Neuron* **23**, 83 (1999).

PERSPECTIVES: ASTRONOMY

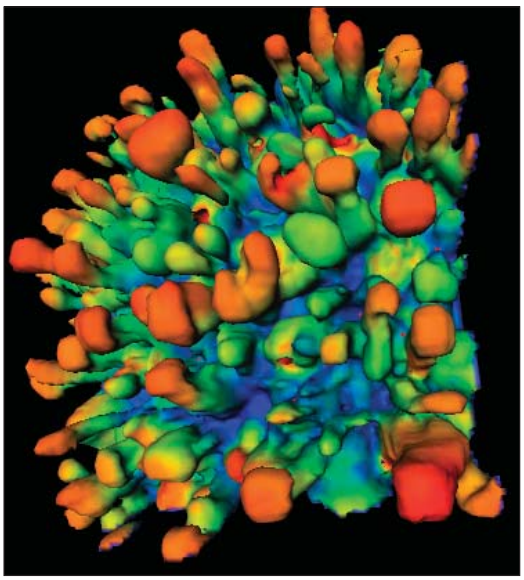
The Secrets Behind Supernovae

H.-Th. Janka

Once every second, somewhere in the universe a massive star is disrupted in a supernova explosion. Visible even at cosmic distances, these stellar catastrophes provide valuable information about the history of star formation in the universe. Ejecting several solar masses of stellar debris, they enrich the interstellar medium with heavy elements from millions of years of quiescent nuclear burning, and with radioactive nuclei that are freshly synthesized during the star's violent death.

As brilliant as it may be, a supernova explosion is only a weak side effect of a much more energetic event. Theory suggests that as the iron core of the exploding star collapses to form a neutron star or black hole, most of the gravitational binding energy is carried away by neutrinos. This prediction was confirmed by the detection of two dozen of the 10^{58} neutrinos from Supernova 1987A in the underground experiments of Kamiokande, Irvine-Michigan-Brookhaven, and Baksan. Typically, only 1% of the released energy goes into kinetic energy of the ejecta, and only a small fraction of this energy is converted to electromagnetic radiation.

How is energy transferred from the collapsing compact remnant to the matter that gets ejected? Understanding this driving force of the explosion is crucial for predicting remnant masses, explosion energies, and nucleosynthetic yields. It is thus essential for establishing the theoretical link between the properties of massive stars and the observables of supernova explosions. Unfortunately, observations have so far been unable to constrain the processes that take place in the collapsed core of a star.



Three-dimensional supernova simulation. The perspective image shows convective mixing in a newly formed neutron star. The mushroom-shaped structures are a result of hydrodynamic instabilities (*19*). The colors represent different fluid entropy values (blue, low; red, high) on a surface of constant proton-to-neutron ratio. [Adapted from (*19*)]

Future measurement platforms may provide the required data by allowing thousands of neutrinos and possibly gravitational waves to be measured in a future supernova in our Galaxy. But current knowledge is based mainly on numerical simulations and analytic analysis. Despite more than 30 years of research and increasingly detailed computer models, there is still no satisfactory understanding of the start of the explosion.

Stellar iron cores become gravitationally unstable when energetic photons begin to split iron-group nuclei into α particles and free nucleons (protons and neutrons). At the same time, electrons are captured by nuclei and free protons, thereby reducing the pressure even more and producing large numbers of electron neutrinos. The latter can leave the star unhindered until they get trapped as the density grows. Within less than a second, the inner part of the core collapses to nuclear densities and then resists further compression due to the onset of nucleon degeneracy and repulsive nuclear forces.

At this moment, a hydrodynamical shock wave is launched and propagates outward through the still supersonically infalling outer core. There is general agreement that this shock cannot cause an explosion directly. It suffers from severe energy losses by photodisintegration of iron nuclei and neutrino emission and therefore stalls at a radius of 100 to 200 km.

But just fractions of a second later, the situation has changed. The temperature behind the standing shock has dropped so much that energetic neutrinos, which leave the hot, nascent neutron star in large fluxes, are readily absorbed by free nucleons in the postshock layer (the layer right behind the supernova shock). If this energy deposition is large enough, it can revive the stalled shock and lead to a successful "delayed" explosion (*1*, *2*). Because the ultimate fate of the shock is determined by a delicate rivalry between competing processes, detailed computer models are needed to answer the question of whether the energy transfer to the shock by neutrinos is sufficient to lead to an explosion.

Wilson and Mayle (*3*) have successfully simulated such neutrino-driven explosions by making two assumptions, which are, however, not generally accepted. They assumed that convective mixing by neutron-finger instabilities (*4*) in the neutron star boosts neutrino emission. Moreover, they considered high densities of pions (strongly interacting elementary particles that are built from a quark and an antiquark) in the neutron star medium to obtain explosion energies in the observed range (*5*). Both assumptions favor an explosion because the energy transfer by neutrinos increases sensitively with higher neutrino luminosities and energies.

But important other physics was missing from the models of Wilson and colleagues, as suggested by spectral observations of

The author is at the Max-Planck-Institut für Astrophysik, Karl-Schwarzschild-Strasse 1, 85741 Garching, Germany. E-mail: thj@mpa-garching.mpg.de