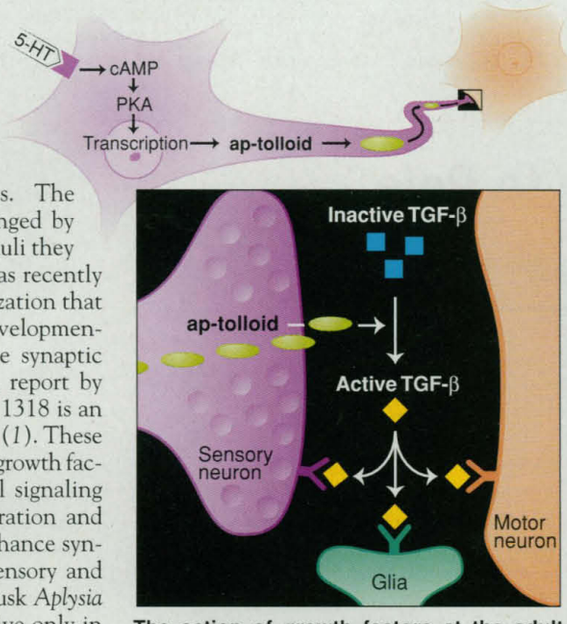
NEUROSCIENCE

# Growth Factors Sculpt the Synapse

Erin Schuman

The brain is a wonderfully adaptive organ, and much of this adaptive ability—the basis of learning and memory—resides in the plasticity of the cell-to-cell connections, the synapses. The strength of synapses can be changed by the pattern and nature of the stimuli they carry. A new class of modifiers has recently entered the picture with the realization that the adult nervous system reuses developmental growth molecules to promote synaptic changes in the mature brain. A report by Zhang *et al.* in this issue on page 1318 is an exciting example of this principle (*1*). These authors showed that transforming growth factor–β (TGF-β), a developmental signaling molecule associated with proliferation and dorsal-ventral patterning, can enhance synaptic communication between sensory and motoneurons in the marine mollusk *Aplysia californica*. Indeed, molecules active only in the embryo or only in the adult are becoming less and less frequent, suggesting that ontogeny is a continuous maturational process.




**The action of growth factors at the adult synapse.** 5-HT, serotonin.

*Aplysia* can learn to modify several of its natural behaviors, including a defensive reflex in which the animal withdraws its gill and siphon in response to a harsh stimulus. If the animal is treated with, for example, a shock to the tail, the normally brief withdrawal response becomes sensitized and can persist for hours. Underlying this sensitization is facilitated synaptic transmission between the sensory and motoneurons that mediate the reflex; these are the same synapses studied by Zhang *et al.* The primary change, which is triggered by the release of the neurotransmitter serotonin from interneurons during the sensitizing stimulus, occurs in the sensory neurons; serotonin activates a cyclic AMP cascade that has immediate effects on ionic currents and later effects on gene transcription and translation. In a related study (*2*), the same group of investigators identified, by differential display techniques and ribonuclease protection assays, an mRNA that increases in sensory neurons after exposure to serotonin; the mRNA is from an *Aplysia* homolog of the *Drosophila tolloid* and *human bone morphogenetic protein* (*BMP-1*) genes, which encode secreted metalloproteases that act on members of the TGF-cytokine superfamily. Taking their cue from the developmental association of tolloid/BMP-1 with TGF-β and its homologs, Zhang *et al.* tested whether TGF-β could alter synaptic transmission at *Aplysia* synapses (*1*). They found that the application of TGF-β to sensory motoneuron synapses caused an increase in synaptic strength, measured 24 or 48 hours later. Is TGF-β signaling actually part of the serotonin-stimulated biochemical cascade that underlies sensitization? This question is hard to address at the behavioral level, but Zhang *et al.* do show that a TGF-β receptor antagonist can block some of the actions of serotonin on sensory neurons.

An important question to answer now is how TGF-β strengthens the synapse. Zhang and colleagues propose that activated TGF-β stimulates a second round of protein translation (the first being initiated by serotonin), but the possibility remains that TGF-β acts directly at the synapse through the activity of its receptor serine-threonine kinase and local downstream signals (see figure). This question highlights a general issue for consideration: To what extent do growth factors that modulate the mature brain use the same signal transduction cascades as those used during development?

The results of Zhang *et al.* add breadth to a burgeoning area of research—the role that growth factors play in sculpting synaptic transmission in the developing and mature brain. In the developing visual cortex, for example, neurotrophins may participate in the activity-dependent strengthening of synapses conveying eye-specific information (*3*). Addition of an excess of a TrkB ligand can either block the formation of ocular dominance columns (*4*) or prevent the shrinkage of cell soma caused by monocular deprivation (*5*). It is as yet unclear whether the neurotrophins directly promote the segregation of eye-specific axons or set a threshold upon which other signals act to form the ocular dominance columns. As is true for many other synaptic signals, not much is known about how the neurotrophins, interacting with different levels of synaptic activity, might exert strengthening, weakening, or null effects on synaptic transmission. Moreover, it is not clear how the kinetics of neurotrophin release and "clearance" could subserve the function of a molecular coincidence detector that likely acts on a time scale of milliseconds.

Neurotrophins can also modulate synapses in adult animals. In many brain areas, including the hippocampus, the expression of the neurotrophins and their receptors persists well into adulthood. Long-term potentiation, a form of activity-dependent plasticity exhibited in the hippocampus and other areas, is blunted in mice that lack the gene for brain-derived neurotrophic factor (BDNF) (*6, 7*). In addition, in adult hippocampal slices and cultured neurons, the addition of either BDNF or neurotrophin-3 (NT-3) can cause a dramatic and long-lasting increase in synaptic transmission (*8, 9*). The enhancement in hippocampal slices displays a very early dependence on protein synthesis (*10*), which is not somatic in origin, raising the possibility that neurotrophins may stimulate the synthesis of proteins in dendrites and promote site-specific modifications of synaptic function.

Is the potentiation of synaptic transmission produced by growth factors due to, or accompanied by, structural changes, such as the addition of new synapses or alterations in the shape of existing synapses? There are now several instances in developing nervous systems where growth factors can cause changes in the morphology of pre- and postsynaptic elements (*11, 12*). Except for a few examples (*11–14*), however, clear demonstrations of learning-related changes in mature synaptic structures have been much harder to come by. Indeed, some recent attempts to observe directly structural changes associated with synaptic plasticity in the mature hippocampus have yielded somewhat sobering results–little or no change in synaptic morphology was observed after long-

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term potentiation (*15*, *16*). And yet, just imagining the potential for remodeling synaptic structures during learning (and in combating neurodegenerative diseases) is sufficient motivation to continue to search for structural changes in mature synaptic structures.

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VOLCANOLOGY

# Listening to Pele


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Volcanic eruptions are difficult to study rigorously for two main reasons. The first is that they are often so destructive that one cannot observe them closely and make measurements of important physical variables, such as the velocity, pressure, and proportions of gas and magma. The second reason is that they often start very suddenly after long periods of quiescence; volcanologists usually arrive after the initial phases, which are, unfortunately, often the most instructive. The new data on explosive eruptions reported on page 1290 of this issue by Morrissey and Chouet (*1*) are therefore most welcome.

Volcanic activity usually falls into two categories: (i) explosive—yielding eruptions, such as those of Mount St. Helens (1980), El Chichón (1982), and Pinatubo (1991), often associated with subduction zones—and (ii) basaltic—seen at volcanoes such as that at Kilauea Iki (Hawaii), which are often associated with hot spots, and at Stromboli. Explosive volcanoes involve very viscous magma and expel strong gas jets, called Plinian activity. The hot volcanic gas exits the volcanic vent at high velocity as a jet, then evolves into a buoyant plume into which air is dragged and heated, and finally spreads as an umbrella cloud when the density of the volcanic mixture balances that of surrounding air (see figure). Basaltic eruptions are more gentle, and the magma is much less viscous than that from explosive volcanoes, although it is still four orders of magnitude more viscous than water. The dynamical regimes of basaltic and explosive volcanoes are both directly and indirectly driven by the gas phase, and their major difference in behavior is a consequence of their large difference in viscosity (at least five orders of magnitude).

In the 1980s, the scientific community started modeling volcanic activity, both numerically and in the laboratory, first focusing on explosive volcanoes and later on basaltic activity. However, models need field observations to constrain them and to check their validity. In contrast to relatively safe basaltic eruptions, which have been monitored rather extensively, explosive volcanoes need remote, albeit precise, quantitative measurements. Therefore, the use of data obtained from several volcanoes with a network of microbarographs, such as in the report of Morrissey and Chouet (*1*), sounds very promising for estimating the exit pressure of the volcanic mixture at the very first instant of an eruption and constraining its gas concentration. It can also be used to monitor volcanic activity in a remote area (*1*).

Volcanoes inflate before an eruption, implying overpressure in the magma reservoir at shallow depths (*2*). Clearly this overpressure is part of the driving process during an eruption, making knowledge of its magnitude at depth very valuable. The first method of determining this pressure uses measurements of deformations at the surface of the volcano combined with an elastic model of the edifice and shows that tumescence and eruptive activity occur almost at the same time. The second method consists of measuring the air pressure at the eruptive vents and then combining them with a flow model to estimate the pressure in the magma reservoir.

An enhanced version of this Perspective, with live links, can be seen in *Science* Online on the Web at http://www.sciencemag.org/


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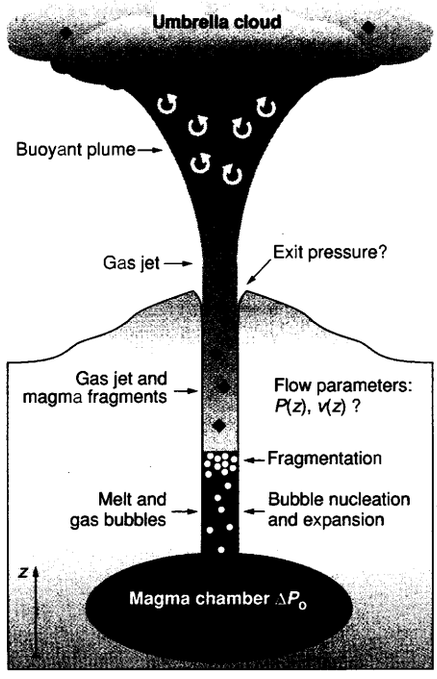


**An explosive eruption.** When magma is expelled from a volcano it undergoes fragmentation, creating a jet of gas and magma droplets. Understanding this process requires knowledge of the complex changes in pressure $P$ and velocity $v$ as a function of height $z$ in the exit channel.

When an explosive eruption starts, magma is expelled out of the magma chamber and rises, ultimately containing small gas bubbles, in the volcanic conduit (see figure). A critical change in the flow regime called fragmentation, which is still poorly understood, occurs somewhere in the conduit: the mixture is transformed into a gas jet containing magma droplets (*3*). The pressure and velocity of the volcanic mixture, which follow the equations of motion during flow in the conduit, vary together. Consequently, the volcanic mixture might reach the vent at an exit pressure different from the atmospheric value (*4*). Velocities are easier to estimate at the surface than pressures, and in the 1980s, researchers used empirical relations, derived for instance from ballistic studies, to deduce the exit pressure from the velocity. Recording pressures and velocities