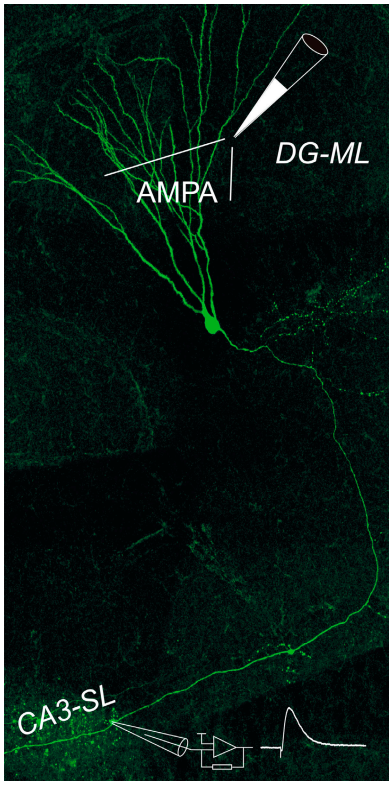
Research Roundup



GEIGER/AAAS

Subthreshold stimuli (top) propagate to distant sites in neurons (bottom).

Analogue brains

Digital computers and mammalian brains share not only a talent for computation but also a method that favors absolutes. The ones and zeros of a computer are analogous to the all-or-none character of action potentials in the brain. Neurons sum all incoming depolarizing signals until, at a threshold level of depolarization, an action potential fires along the axon. Now, however, Henrik Alle and Jörg Geiger (Max Planck, Frankfurt, Germany) show that the rat brain also uses graded signals for communication.

This analogue or subthreshold processing has been seen in invertebrates, but "in the central mammalian brain it was never shown," says Geiger. The presumption was that the all-or-none action potentials were the whole story. "To be honest," says Geiger, "I don't know how this kind of thinking developed."

Alle and Geiger looked in the hippocampus, the center of memory and learning, using tissue slices. They introduced subthreshold signals in the cell body and saw that these reached synapses up to 1 mm away. If the subthreshold signals reached the synapse just before an action potential arrived, the response in the postsynaptic neuron was increased.

Although the information in the subthreshold signal can only be communicated in combination with an action potential, it may have great power. Most synapses in the brain are close to their cell bodies— within range of the subthreshold signals. And so-called theta oscillations are a potentially crucial form of subthreshold signaling. These oscillations are thought to act as a kind of clock in the brain, helping to "bind" different sensory inputs into a single experience.

Geiger now plans to look for subthreshold signals generated by receptors in the brain, and to test whether individual axons are carrying out analogue computations. The molecular mechanisms that transduce the signal are also a mystery. "Classically one would expect it to be calcium, but we have evidence against that," says Geiger. "This is completely new territory." JCB

Reference: Alle, H., and J.R.P. Geiger. 2006. *Science*. 311:1290–1293.

Curing TB with sunlight

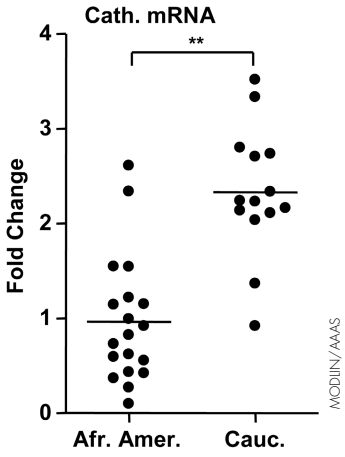
Ultraviolet (UV) light makes vitamin D, and vitamin D turns on innate immunity to tuberculosis (TB), say Steffen Stenger (Universität Erlangen, Germany), Philip Liu, Robert Modlin (University of California, Los Angeles, CA), and colleagues. The lower absorption of UV light by African Americans, leading to lower vitamin D levels, may be one reason why this group is more susceptible to TB.

Chemicals from bugs turn on the innate immune response via Toll-like receptors (TLRs). Modlin had already found that activating TLRs killed off intracellular *Mycobacterium tuberculosis*. Nitric oxide (NO) was the downstream mediator for this in mouse cells, but "we've been grasping for a decade to find a mechanism in humans," says coauthor Barry Bloom (Harvard School of Public Health, Boston, MA).

The answer came from gene arrays. Active TLR turned on production of both an enzyme (which converts 25D3 into active vitamin D) and the vitamin D receptor. The activated pathway produced an antimicrobial peptide called cathelicidin, which attached itself to intracellular *M. tuberculosis*, and is a prime suspect for causing its death.

Serum from white-skinned donors had enough of the precursor (25D3) to keep this pathway active, but serum from African Americans was short on 25D3 and supported a much lower output of cathelicidin. The shortfall was corrected by adding 25D3.

The finding may explain why Hermann Brehmer's 19th century trip to the Himalayas cured him of his TB, and why the fresh air at his sanatoria helped cure others. "Our forefathers knew a lot more about this than we give them credit for," says Modlin. Eventually, however, sanitoria coddled their patients behind glass, which would have blocked the beneficial UV light.



MODLIN/AAAS

African Americans induce less of a TB-fighting peptide.

Although pigmented skin blocks out a lot of UV light, Africans and Asians probably got their fair share before the modern age introduced clothes. Now, however, supplementation may be needed. Bloom plans to test whether vitamin D supplementation can reduce TB transmission within families, speed cures by anti-TB drugs, or slow TB reactivation. "These are not trivial studies to undertake," he says, "but it could make a big difference." JCB

Reference: Liu, P.T., et al. 2006. *Science*. doi:10.1126/science.1123933.