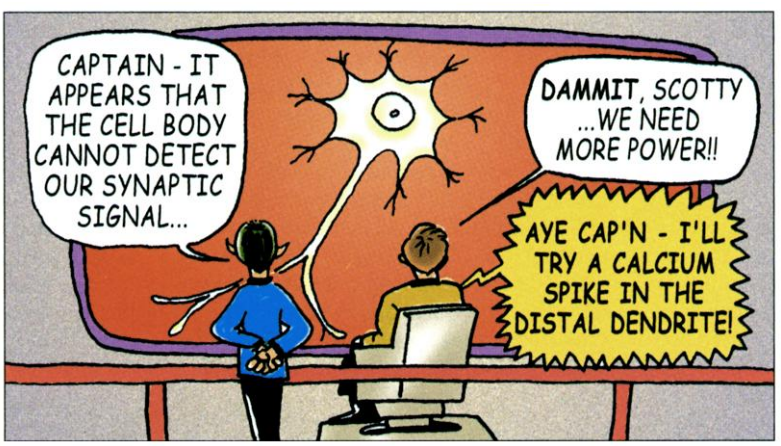
PERSPECTIVES: NEUROBIOLOGY

What the Synapse Tells the Neuron

Bartlett W. Mel

After more than a century of neuroscience research, a remarkably simple question remains unanswered: What do nerve cells in the brain do? Most of these nerve cells (neurons) have dendritic trees—finely branched extensions emanating from the cell body—that receive tens of thousands of synaptic inputs from other neurons. At any given time, tens or hundreds of these synapses may be "firing" at a rate of tens or hundreds of times per second all across the dendritic tree. How does the neuron integrate these widely scattered synaptic inputs to generate an overall response? Neurophysiologists have frequently approached this larger question by first tackling a smaller question: What is the effect on a target neuron when one synapse on one dendrite is activated once? Experiments in rat brain slices described by Williams and Stuart (*1*) on page 1907 of this issue, help to answer this question for a key population of neurons, the pyramidal cells of the mammalian neocortex.



CREDIT: JOE SUTLIFF

The great majority of synaptic contacts on pyramidal cells are excitatory. The stereotyped electrical response elicited by an excitatory synapse is called an excitatory postsynaptic potential (EPSP). Interest in the brain's 10^{15} excitatory synapses runs high, in part because they make up the bulk of the brain's massive interconnection network, in part because changes in excitatory connections between neurons are believed to mediate most forms of neural learning and memory.

Although it is well established that synaptic strengths can change, it is not clear whether the baseline strength of a synaptic contact is the same everywhere within a neuron, or whether it varies systematically across the dendritic tree. Why is this important? In the case of a neocortical pyramidal cell, the dendritic tree can extend for more than a millimeter from end to end. Common sense, backed by cable theory, tells us that synapses in the more remote regions of the apical dendritic tree ought to exert only a tiny, perhaps even a negligible, influence on the main output spike generator located near the cell body (*2*). The concern arises because signals traveling along electrical cables tend to decay with distance from their source, similar to the voltage drop one expects when using an excessively long household extension cord. However, in an intriguing recent report, Magee and Cook (*3*) show that in pyramidal cells of the hippocampal CA1 region, excitatory synapses grow progressively stronger with distance from the cell body—almost exactly counteracting the distance-dependent signal attrition one would expect to find. The implication is that these neurons may be striving to equalize the effectiveness of their synaptic inputs, regardless of where those inputs are located.

This theoretically attractive idea, if valid in the hippocampus, evidently does not reflect a general principle of neuronal design, even within the close-knit family of pyramidal cells. Using triple intracellular electrode recordings, Williams and Stuart found that in rat neocortical pyramidal cells, synaptic currents did not increase with distance, but rather remained essentially constant over a 750 μm span of the apical dendritic tree (*1*). In keeping with this, they report that EPSPs generated in the dendrites were by no means constant when measured at the cell body—instead they varied many fold depending on their site of origin "as one might expect." This inconsistency between hippocampal and neocortical pyramidal cells, in what would seem a very basic feature of neuronal design, highlights both a danger and an opportunity. The danger lies in assuming that different neurons all perform the same job, even within a family of closely related cells. The opportunity arises because contrary to expectations, the new work suggests that the spatial distribution of synaptic efficacies is a flexible design feature that the brain uses to accommodate its various information-processing goals. Theoretical and computer-modeling studies seem ideal avenues for further exploration of this issue.

In something of a twist, Williams and Stuart also found that in contrast to the uniform peak synaptic current recorded up and down the trunk of the dendritic tree, other features of the synaptic response were strongly site dependent. In particular, EPSPs originating at more distal synapses had slower rise times and showed greater paired-pulse depression than did proximal synapses (*1*). The Williams and Stuart study is capped, however, by the finding that EPSPs generated in the distal apical tree, diminutive as they may appear at the cell body when recorded as isolated events, nonetheless wielded serious power over the cell's final common output (*4*). They did this by triggering dendritic calcium spikes, heavy guns that are capable of eliciting whole bursts of action potentials in the cell body (see the figure) (*5*). Williams and Stuart found that when a stimulus to the distal part of the dendritic tree was large enough to trigger a dendritic calcium spike, it was even more potent than a stimulus of the same size delivered directly to the cell body. Perhaps, this result seems to say, the thousands of synapses populating the apical dendritic tree are not just there for decoration after all.

While affirming the value of Williams and Stuart's work and that of many other "dendriticians" who have contributed to our understanding of what neurons do (*6*), it is important to bear in mind that the rules that pyramidal cells follow in combining their many synaptic inputs over space and time remain largely obscure. A major stumbling block is that the vast majority of synaptic contacts made with pyramidal neurons lie on dendrites that are too thin to access with intracellular recording electrodes. Given this, conclusions regard-

The author is in the Department of Biomedical Engineering and Neuroscience Graduate Program, University of Southern California, Los Angeles, CA 90089, USA. E-mail: mel@usc.edu

ing the properties of these synapses, their interactions with each other and with the resident voltage-dependent membrane currents, rest on a bed of untested inferences and assumptions. In the near term, computer models should help us to see further into these hard-to-reach places, and the rapid evolution of imaging technologies could plug the dendritic recording gap in the next few years (*7*–*9*). Methods are also needed that permit selective activation of many synaptic sites, not just one or two, under flexible experimental control. Here again, technological advances, such as multisite laser uncaging of glutamate and other neurotransmitters, will free experimentalists to test hypotheses they would like to test, rather than those they are able to test. The elegant work of Williams and Stuart has moved us one step closer to that exciting day when our neurons finally lay bare the secrets of their internal lives.

References and Notes

1. S. R. Williams, G. J. Stuart, *Science* **295**, 1907 (2002).
2. A. M. Zador, H. Agmon-Snir, I. Segev, *J. Neurosci.* **15**, 1669 (1995).
3. J. C. Magee, E. P. Cook, *Nature Neurosci.* **3**, 895 (2000).
4. L. J. Cauller, B. W. Connors, *J. Neurosci.* **14**, 751 (1993).
5. M. E. Larkum, J. J. Zhu, B. Sakmann, *Nature* **398**, 338 (1999).
6. G. Stuart, N. Spruston, M. Hausser, *Dendrites* (Oxford Univ. Press, Oxford, 1999).
7. B. Lendvai, E. A. Stern, B. Chen, K. Svoboda, *Nature* **404**, 876 (2000).
8. J. Schiller, G. Major, H. J. Koester, Y. Schiller, *Nature* **404**, 285 (2000).
9. M. Zochowski *et al.*, *Biol. Bull.* **198**, 1 (2000).

PERSPECTIVES: RADICAL CHEMISTRY

From Reactive Intermediates to Stable Compounds

Curt Wentrup

More than 100 years ago, Gomberg prepared the first stable free radical, triphenylmethyl, **1** (see the figure) (*1*, *2*). Carbon-based free radicals are trivalent compounds with one unpaired (nonbonding or "free") electron that usually renders them highly reactive and short-lived. Triphenylmethyl is stable because the free electron is delocalized and the radical center is shielded from reaction by the three phenyl groups, which are arranged in a propellerlike fashion.

Enhanced online at www.sciencemag.org/cgi/content/full/295/5561/1846

Since this pioneering work, numerous free radicals, both fleeting intermediates and stable compounds, have been prepared (*3*). However, when it comes to di- or higher radicals, which contain more than one nonbonding electron, stability decreases drastically. The most stable localized singlet (*4*) diradical known to date, **2**, has a lifetime of microseconds at room temperature (*5*). On page 1880 of this issue, Scheschkewitz *et al.* (*6*) report the synthesis of a diradical, **3**, that is stable indefinitely at room temperature. The work may open the door to new types of molecular magnetism and conductivity.

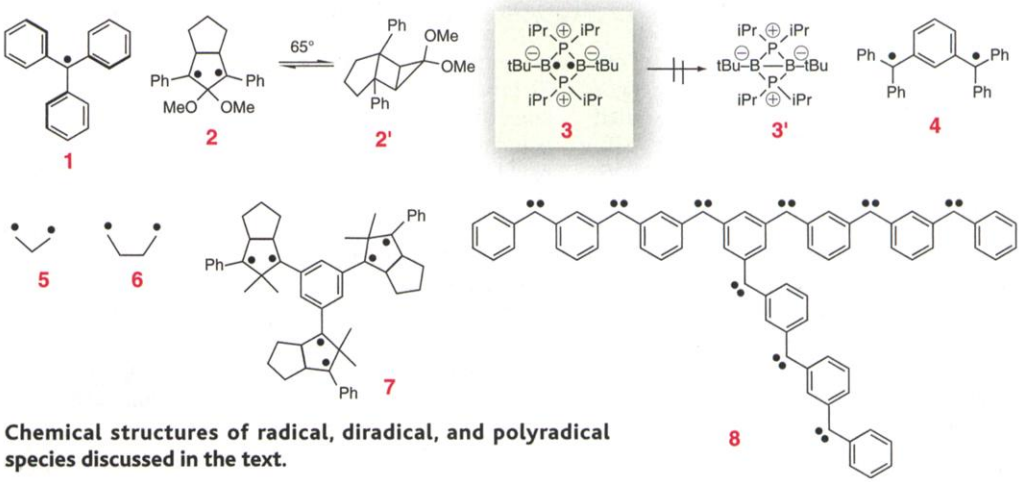
There is much current interest in generating molecules containing many nonbonding electrons. Free electrons in half-filled and high-lying nonbonding molecular orbitals could form a conduction band similar to that in metals (*7*) and may even lead to new superconducting materials. Furthermore, such molecules may show ferromagnetic or antiferromagnetic properties depending on spin and topology (*8*).

The first stable carbon-based diradical, Schlenk's hydrocarbon **4**, was prepared in 1915. It is stabilized by delocalization of the two free electrons over the aromatic rings, just as in **1** (*9*) and has a triplet ground state (*4*). Simple diradicals such as trimethylene **5** and tetramethylene **6** are involved in the thermal chemistry of hydrocarbons (*10*). Their singlet states are extremely short-lived intermediates that have only recently been observed directly by femtosecond spectroscopy (*11*, *12*). Triplet states of 1,3-diradicals have been observed by electron spin resonance (ESR) spectroscopy, but only in matrices at very low temperatures. Thus, four- and five-membered cyclic triplet diradicals have been observed below 20 K (*13*, *14*). Di-, tri-, and hexaradicals of the type **7** were remarkably long-lived at 77 K: Their ESR spectra were observable for months (*15*).

Diradical lifetimes can be influenced by substituents. The dimethoxy-substituted diradical **2** has a singlet ground state and is observable in solution at room temperature by ultraviolet spectroscopy. However, the room temperature lifetime of **2** is only 3.73 μs in chloroform (*5*). In a common reaction of hydrocarbon diradicals, the two radical electrons in **2** recombine to form a C–C single bond, resulting in the formation of **2′**. In contrast, Scheschkewitz *et al.*'s diradical **3** does not show any tendency to form an analogous bicyclic compound **3′** containing a B–B bond. Such a compound would be nonplanar. The x-ray structure of **3** clearly shows a planar four-membered ring with a B–B distance some 30% longer than the longest known B–B bond.

Magnetism requires the coupling of many electrons. High-spin molecules linked via appropriate "couplers," such as **7**, may have interesting magnetic properties. However, to be practical, these materials should be stable at room temperature.

Much valuable information on the magnetic properties of high-spin molecules has been gained from studying polycarbenes such as the nonacarbene **8**, which has 18 unpaired spins (*16*, *17*). A carbene can be regarded as a diradical where the two radical electrons are centered on the same carbon atom (*18*). However, polycarbenes are usually only stable at temperatures near 0 K.



Chemical structures of radical, diradical, and polyradical species discussed in the text.

The author is at the Department of Chemistry, School of Molecular and Microbial Sciences, The University of Queensland, Brisbane, Queensland 4072, Australia. E-mail: wentrup@chemistry.uq.edu.au