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PERSPECTIVES

Subliminal messages in hippocampal pyramidal cells

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Synaptic activity regulates gene transcription in neurons. The coupling between synaptic transmission and transcription is accomplished by the second messenger calcium, which enters the cell through synaptic receptors and voltage-gated calcium channels and binds enzymes that activate transcription factors. In schematic diagrams showing these calcium-activated pathways, synaptic calcium influx happens conveniently close to the nucleus (West *et al.* 2001). In reality, however, synapses are distributed over an extensive dendritic tree. How then is information about synaptic activity passed on to the nucleus, which can be hundreds of micrometres from activated synapses? Passive diffusion is too slow for a long-range signalling system, especially given the high buffer capacity of the dendritic cytoplasm for calcium and the slow diffusion of these buffers (Helmchen *et al.* 1996). The report of Nakamura *et al.* (2002)in this issue of *The Journal of Physiology* takes a closer look at the properties of regenerative calcium waves in the apical dendrite of CA1 pyramidal cells (see also: Kapur *et al.* 2001; Nakamura *et al.* 1999, 2000). These waves, which depend upon activation of inositol 1,4,5-trisphosphate (IP_3) receptors, are a prime candidate for a signalling system that locally integrates synaptic activity in the dendrite and sends a binary signal to the nucleus (Berridge, 1998).

A unique property of IP_3 receptors is their sensitivity to both $[IP_3]$ and $[Ca^{2+}]$. Calcium released through activated IP_3 receptors will facilitate the opening of neighbouring receptors, providing a positive feedback loop (Nakamura *et al.* 1999). Thus, once the local cytoplasmic calcium and IP_3 concentrations have reached a critical level, a regenerative wave of calcium-induced calcium release can start to travel along the endoplasmic reticulum. Using metabotropic receptor agonists to provide global subthreshold $[IP_3]$ and backpropagating action potentials to cause global dendritic calcium influx through voltage-gated channels, the authors demonstrate that branch points of the main apical dendrite are privileged loci of wave initiation, presumably due to a high density of IP_3 receptors at these locations. Other means of elevating cytoplasmic $[IP_3]$, either by activating muscarinic acetylcholine receptors or uncaging of IP_3, can also initiate waves with very similar pharmacological and physical properties (Nakamura *et al.* 2000; Power & Sah, 2002). Waves travel inside the apical dendrite towards the soma, but fail to invade thin oblique dendrites. In summary, the results of Nakamura *et al.* (2002) suggest a compartmentalization of the dendritic tree into three functional zones: (i) input zones-oblique dendritic branches where most synapses impinge on spines; (ii) trigger zones-branch points between the large apical dendrite and oblique dendrites, where regenerative signals are initiated; and (iii) a propagation zone, consisting of the main apical dendrite (Fig. 1). IP_3 generated by phospholipase C at stimulated synapses acts as a diffusible messenger, functionally connecting the input zones to the trigger zones.

In the current study, which uses focal synaptic stimulation of single oblique branches, most calcium waves do not travel very far, but die out before they reach the soma. Similarly, if cholinergic afferents are stimulated just above threshold for wave initiation, calcium waves vary in the extent to which they invade the nucleus (Power & Sah, 2002). These observations suggest that the regenerative process involved has a low safety factor. Calcium waves invade the soma reliably if metabotropic receptors are stimulated all over the cell surface by pharmacological agonists, or when synapses are activated distributed over the dendritic tree, e.g. by placing the stimulation electrode in stratum oriens at some distance from the cell (Power & Sah, 2002). A possible explanation for the sensitivity of the waves for the spatial distribution of the stimulated synapses is that elevated $[IP_3]$ is needed not only to trigger the waves, but also as a substrate for successful wave propagation. Therefore waves are most likely to reach the soma when several synergistic factors coincide. The optimal stimulus might consist of highly localized synaptic activity, providing threshold levels of IP_3 at a trigger zone, combined with more diffuse activation to facilitate wave propagation. In addition, signal propagation to the nucleus will be sensitive to other state variables, e.g. the filling state of the intracellular stores, as well as the spatial distribution of excitatory synaptic input.

Regenerative calcium waves are well poised to serve as a signalling system, informing the nucleus about spatio-temporal features of the pattern of excitatory synaptic activity in the dendrite. Although it is well documented that many pathways for activity-dependent gene activation depend on calcium (West *et al.* 2001), most transcription assays have employed fairly severe, non-physiological stimulation (but see Mermelstein *et al.* 2000). The link between calcium waves and gene transcription remains to be demonstrated, perhaps using optical reporters of transcriptional activation in combination with local synaptic stimulation and calcium imaging. *In vivo* calcium imaging could in principle be used to search for Ca^{2+} waves in the intact brain, in response to behaviourally salient stimuli (Svoboda *et al.* 1997). Such dreams for the future notwithstanding, the similarity between stimuli that induce synaptic plasticity and stimuli that trigger calcium waves makes them an intriguing candidate for a chemical long-range signalling system.

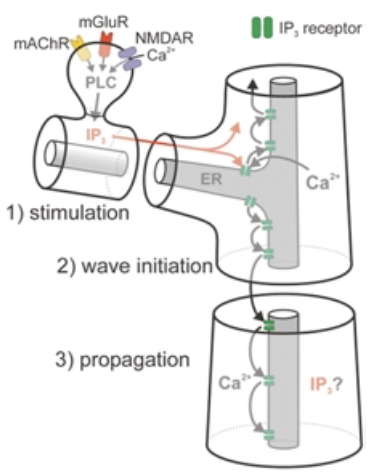

Figure 1. Functional specialization of dendritic compartments

1, in thin oblique dendrites, activation of excitatory synapses leads to generation of IP_3. The enzyme responsible for IP_3 generation, phospholipase C (PLC), can be activated by muscarinic acetylcholine receptors (mAChR), metabotropic glutamate receptors (mGluR), and is sensitive to calcium influx through NMDA receptors. 2, at branch points of the main apical dendrite, IP_3 diffusing from oblique branches activates IP_3 receptors on the endoplasmic reticulum (ER), triggering a regenerative calcium wave. Due to the calcium sensitivity of IP_3 receptors, elevated $[Ca^{2+}]$ facilitates this process. 3, in the proximal apical dendrite, the calcium wave propagates towards the soma. Elevated $[IP_3]$ might be necessary for successful long-range propagation.

Berridge, M. J. (1998). *Neuron* **21**, 13–26.

Helmchen, F., Imoto, K. & Sakmann, B. (1996). *Biophysical Journal* **70**, 1069–1081.

Kapur, A., Yeckel, M. & Johnston, D. (2001). *Neuroscience* **107**, 59–69.

Mermelstein, P. G., Bito, H., Deisseroth, K. & Tsien, R. W. (2000). *Journal of Neuroscience* **20**, 266–273.

Nakamura, T., Barbara, J. G., Nakamura, K. & Ross, W. N. (1999). *Neuron* **24**, 727–737.

Nakamura, T., Lasser-Ross, N., Nakamura, K. & Ross, W. N. (2002). *Journal of Physiology* **543**, 465–480.

Nakamura, T., Nakamura, K., Lasser-Ross, N., Barbara, J. G., Sandler, V. M. & Ross, W. N. (2000). *Journal of Neuroscience* **20**, 8365–8376.

Power, J. M. & Sah, P. (2002). *Journal of Neuroscience* **22**, 3454–3462.

Svoboda, K., Denk, W., Kleinfeld, D. & Tank, D. W. (1997). *Nature* **385**, 161–165.

West, A. E., Chen, W. G., Dalva, M. B., Dolmetsch, R. E., Kornhauser, J. M., Shaywitz, A. J., Takasu, M. A., Tao, X. & Greenberg, M. E. (2001). *Proceedings of the National Academy of Sciences of the USA* **98**, 11024–11031.