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A tale of two spikes

Yves Frégnac

Backpropagating action potentials amplify the response to weak dendritic inputs. A new study suggests that this may serve to link simultaneous inputs to different dendritic compartments.

Since the discovery that action potentials initiated at the soma can propagate back into dendrites, the role of these spikes in shaping the cell's response to its inputs has been of intense interest. In a forthcoming issue of *Nature*, Larkum, Zhu and Sakmann[1] show that backpropagated action potentials in cortical pyramidal neurons can interact with weak synaptic inputs in the apical dendrites, triggering a dendritic calcium spike. The calcium wave is in turn propagated to the soma, causing the neuron to fire a burst of action potentials. This mechanism allows for the all-or-none amplification of weak inputs, and may have important implications for how information impinging on distal dendrites is processed at the cellular level within the cortex.

In the classic view of synaptic integration, excitatory postsynaptic potentials (EPSPs) are transmitted passively through the dendritic tree to the cell body and axon hillock, where sodium action potentials are generated. The EPSPs are summed at this 'decision point', and if the total depolarization reaches threshold, the neuron fires an action potential, which is then propagated along the axon to the rest of the network. In this model, which has often been applied to pyramidal cells of the hippocampus and neocortex, the dendrites are treated as passive cables, and the effect of a given synapse depends on its location within the dendritic tree.

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Inputs from more distant synapses take longer to reach the cell body and are more attenuated than inputs originating at synapses closer to the cell body. Such a neuron is predicted to behave as a spatiotemporal correlator; it is more likely to fire an action potential if all the EPSPs reach the axon hillock simultaneously. For this to occur, the inputs must arrive in an appropriate temporal relationship to compensate for their different locations and the resulting delays in reaching the site of action potential generation.

In reality, however, dendrites are not passive cables. They express a variety of voltage-dependent ion channels that modify their biophysical properties, allowing them not only to transmit synaptic inputs to the cell body, but also to perform considerable local processing. Recently, refined techniques, such as the use of multiple simultaneous patch electrodes at different points on a single neuron, have revealed a complex picture of neuronal function that differs in several important respects from the classical model. First, 'hot spots' of excitability within the apical dendrites are thought to modify the propagation of EPSPs from synaptic sites to the cell body, so as to reduce the differences of timing and amplitude that result from their different locations on the dendritic tree[2–4]. Second, sodium action potentials originating at the soma–hillock region can propagate not only along the axons, but also backward into the dendritic tree[5]. Third, there exists at least one other site for action potential generation, which is distinct from the soma–axon region. This second site, described in layer-V cortical neurons, is in the tuft of the apical dendrite. This region, which is rich in voltage-dependent calcium and sodium channels, gives rise to calcium spikes[6,7]. Calcium spikes are typically of much longer duration than sodium action potentials, but these regenerative events involving voltage-gated channels are normally attenuated as they spread to the soma.

The new study in *Nature* from Larkum *et al.*[1] is a logical continuation

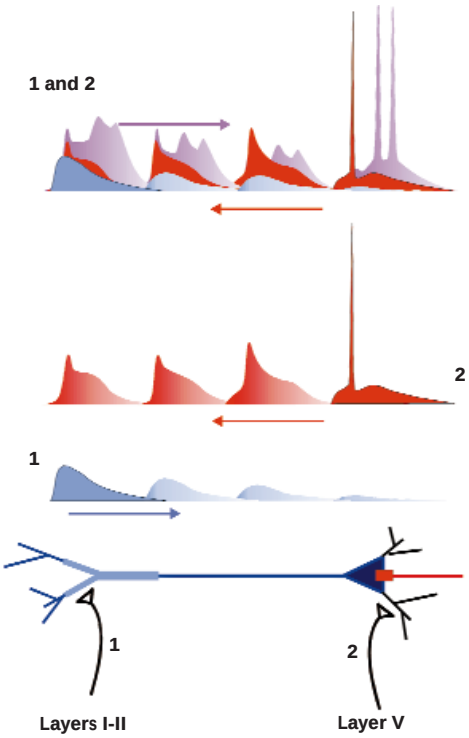

Fig. 1. The association of a subthreshold distal dendritic input (1) with a backward propagating somatic action potential (2) generates a wide dendritic calcium spike (1+2) sufficient to reactivate the soma and cause a burst of firing. Courtesy of Dr. Thierry Bal (IAF, CNRS, France).

of previous work from Sakmann and colleagues, who for several years have been studying the role of backpropagating spikes in neocortical neurons. When spikes initiated in the soma are propagated backward into the dendrites, they evoke an activity-dependent influx of calcium[7,8]. It was suggested as early as 1995 that these dendritic calcium transients might affect both the receptive and the integrative properties of the dendrites[8], providing the cell with a way to regulate dendritic processing, and hence its own inputs. Subsequent work[9] showed that if the backpropagating action potential coincided with EPSPs in the distal dendrites, a long-lasting (several hundred ms) calcium wave could be evoked within the dendrite, which could not be triggered by either the action potential or the EPSPs alone.

The new findings of Larkum and colleagues advance this story in several ways. First, they show that this effect has a very precise time dependence in that the backpropagated action potential must arrive within about ten milliseconds of the EPSP to trigger a calcium spike within the dendrite. More importantly, they show that the dendritic calcium spike is then propagated to the soma, where it produces a short burst of sodium action potentials riding on the back of the slower calcium wave. The dendritic EPSP alone produces no response without the backpropagating action potential, so this mechanism represents a large amplification of the response to the dendritic input (Fig. 1).

What might be the functional significance of this behavior? Larkum and colleagues suggest that it may allow layer V pyramidal neurons to detect associations between two types of cortical inputs. The weak input to the apical dendrite (input 1 in Fig. 1) originates from cortical layers I-II, which receive descending information from higher cortical areas, as well as ascending neuromodulatory subcortical inputs. The stronger inputs that trigger the backpropagating action potentials (input 2 in Fig. 1) would carry sensory information, which reaches layer V cells via the deeper cortical layers in which some of the thalamocortical sensory afferents terminate. Such a mechanism might allow for perceptual binding of sensory inputs based on their modulation by contextual information from higher cortical areas.

This idea, although attractive, must still be considered speculative. For one thing, the amplification effect has only been shown for inputs to the apical tuft of the dendrite, and it remains to be determined whether it will generalize to other inputs and dendritic compartments. Another caveat is that the effect was much more robust when the authors used a dendritic patch electrode to mimic the EPSC (by injecting an appropriate current waveform) than when they used extracellular stimulation to produce true synaptic input. The likely explanation for this discrepancy is that the stimulating electrode activates not only excitatory but also inhibitory inputs to the dendrite under study, and that inhibition weakens or cancels the effect. Indeed, the authors provide two lines of evidence that dendritic amplification is very sensitive to inhibition. First, amplification was only found reproducibly in their slice preparations when inhibition was partially blocked by low concentrations of GABA antagonists. Second, in an elegant experiment using paired recordings from interconnected pyramidal cells and inhibitory interneurons, they show that a single inhibitory PSP (IPSP) is sufficient to block the calcium wave for 150 ms, and that a burst of IPSPs can produce a block that lasts for as long as 400 milliseconds. Cortical pyramidal neurons *in vivo* receive strong tonic inhibition, which significantly reduces their input resistance[10] and should certainly affect the propagation of both sodium and calcium spikes back and forth along the dendrite. In addition, excitation and inhibition are coordinated *in vivo*[11], and the balance between the two is likely to be a critical determinant of whether dendritic amplification occurs in any given case.

Another interesting possibility, which the authors surprisingly do not discuss, is that dendritic amplification may be related to associative learning and to Hebbian synaptic plasticity (see ref. 12 for review). In classical long-term potentiation, a strong depolarizing stimulus acts as an unconditioned reinforcing stimulus, which strengthens a weaker synaptic input (corresponding to the conditioned stimulus) when the two inputs are paired. Similarly, action potentials initiated at the cell body can regulate plasticity at synapses on the distal dendrites via backpropagation[13]. In this latter study, synapses between reciprocally connected layer-V pyramidal neurons were strengthened or weakened depending on whether the backpropagating action potential arrived before or after the EPSC. The process was highly sensitive to the exact relative timing, with 20 milliseconds making the difference between a positive and negative effect. A similar dependence on the relative timing of pre- and postsynaptic activity has also been described in the electrosensory lobe of the electric fish[14].

The calcium spikes described by Larkum and colleagues show an obvious parallel with these examples of synaptic plasticity. Both processes show a similarly strong dependence on the relative timing of pre- and postsynaptic activity, and it is well known that increases in intracellular calcium are involved in many forms of synaptic plasticity. The graphs for the time dependence are qualitatively similar in both cases, with the input being amplified/strengthened if the dendritic EPSP occurs coincident with or immediately before the backpropagating action potential, and depressed if the order is reversed, although the graphs do not superimpose perfectly (compare Fig. 2 of Larkum *et al.* with Fig. 3 of ref. 13).

Leaving aside the possible relationship to long-term synaptic plasticity, the associative process uncovered by Larkum and colleagues has one immediate and remarkable consequence for understanding the input–output relationships of pyramidal cells: it implies that the same cell can produce two different outputs in response to the same input—single spikes or bursts, depending on whether the the somatic action potential produced by a strong proximal input is accompanied by a distal input to the apical dendrite. It is even possible that dendritic amplification underlies most bursting behavior in cortical pyramidal neurons, given that they do not normally fire bursts even in response to prolonged somatic depolarization (and are thus very unlikely to fire bursts in response to a single synaptic input). What about the functional implications for information coding? Much of the information content in neuronal spike trains is thought to be carried by the first spike rather than by bursts, but there is some evidence that bursts may have a special role in the computational process. For instance, in the primary visual cortex of behaving monkeys, visually evoked bursts have been found to correlate with the oculomotor context in which the visual stimulus occurs (S. Martinez-Conde, S. Macknik and D.H. Hubel, personal communication).

At a more abstract computational level, the transition between single spikes and bursts may reflect a multiplexing process in which the cell pro-

duces different outputs depending on when and where in the dendritic tree the input occurred. This in turn could allow the cell to recognize specific input patterns[15]. When such patterns (giving rise to subthreshold inputs at the apical dendrites) are associated with a strong input (sufficient to trigger a backpropagating action potential), the cell would signal this by firing a burst. One can speculate that such transformations—in which an irregular temporal pattern of presynaptic spikes is transformed into a pattern of bursts by the postsynaptic neuron—might form the cellular basis for the emergence of large functional assemblies of neurons. The dominance of synchronized bursting of neurons in different layers and different columns produced during intense association of ascending and descending information may underlie episodic perceptual binding at the cortical level. Burst behavior, in turn, may extend the temporal window during which a given cortical cell can detect the arrival of a combination of inputs in distinct dendritic compartments and promote the boosting and eventually the strengthening of otherwise subliminal synaptic influences.

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BMPs: time to murder and create?

Gordon Fishell

The olfactory epithelium produces new neurons throughout life. Shou ***et al.*** show that BMPs can inhibit this process by inducing degradation of the transcription factor MASH1.

When it comes to proliferation in the mature organism, neurons on the whole are a timid bunch. During embryogenesis, massive proliferation occurs in both the central and peripheral nervous system, but this ends by or soon after birth, and there is very little neurogenesis in the adult. One exception, however, is the olfactory epithelium, where new olfactory receptor neurons (ORNs) continue to be formed throughout life[1,2]. Work from many laboratories has suggested that the generation of new ORNs is a dynamically regulated process. For instance, their rate of production is dramatically increased in response to injury[3,4] suggesting that neurogenesis in the intact epithelium may normally be repressed. The signal mediating this repression has so far remained elusive, but a paper on page 339 of this issue suggests that the culprit may be a bone morphogenic protein (BMP).

BMPs are a large family of secreted growth factors, the original members of which were identified by their ability to promote bone growth. Our view of their myriad functions continues to expand, and BMPs have now been shown to act on most tissues of the body. In the developing nervous system, for instance, BMPs inhibit neural induction, dorsalize the spinal cord and promote cell death in the hindbrain[5].

Their presence in the olfactory epithelium and their inhibitory effects in other parts of the nervous system suggested to Shou and colleagues that BMPs might also be promising candidates for mediating the inhibition of ORN development. To test this possibility, the authors used a neuronal colony-forming assay, in which the various steps of ORN proliferation and differentiation are recapitulated in culture. If left unperturbed for six days, olfactory epithelial cultures give rise to mixed colonies containing both neuronal progenitors and differentiated ORNs; the cells from which the colonies arise are thought to be the stem cells that give rise to new neurons *in vivo*[6]. The authors found, remarkably, that the addition of BMP2, 4 or 7 to these cultures completely blocks the appearance of colonies.

The progression from stem cell to differentiated neuron is a multi-step process with at least two defined intermediate stages[2]. To determine where in this process BMPs might act, the authors added BMPs at different times and found that the block to ORN production occurred within the first twenty-four hours. This is at least three days before differentiated ORNs begin to appear, suggesting that BMPs must block a relatively early stage in the ORN lineage. Consistent with this, early exposure to BMPs greatly reduced the level of proliferation (as measured by incorporation of [^{3}H]thymidine by neuronal progenitor cells), suggesting that BMPs act on a still-proliferating precursor rather than on postmitotic neurons. BMPs do not cause an immediate increase in cell death, although apoptotic cell death does occur later.

How might BMPs inhibit development of ORN precursors? The authors investigated the possibility that it might act through the transcription factor MASH1 (mammalian achaete-scute homolog 1), which is expressed at an early stage in the olfactory receptor lineage[7]. MASH1 was an attractive candidate because mutant mice lacking this protein show a phenotype that is very reminiscent of the BMP-treated cultures; mature ORNs are almost totally absent from the olfactory epithelium, which instead shows a high level of apoptotic cell death[8]. The authors therefore examined the effect of BMP treatment on MASH1 expression in their cultures. Within sixty minutes of exposure to BMPs, the number of MASH1-expressing cells fell by fifty percent, with a maximal decrease seen after

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