Neurons Find Strength Through Synchrony in the Brain

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For any touch, sound, or image to be perceived, our senses have to activate neurons at the very center of the brain, in the thalamus. In turn, thalamic neurons must activate neurons in the cerebral cortex, where most complex brain functions take place. One would think that, given their role in sensory processing, the connections between the thalamus and cortex would be strong and reliable. After all, the primate brain is able to detect a skin indentation of less than 20 µm and the reflection of just a few photons in the darkness. How could our senses be so remarkably sensitive if thalamocortical connections linking these two regions were weak? Well... they are weak, and on page 1622 of this issue, Bruno and Sakmann (1) provide the first intracelluar measurements in an intact brain to prove it.

Bruno and Sakmann focused on layer 4 of the mouse sensory cortex, a main target for thalamic inputs. By using an impressive and extremely difficult technical approach, the authors were able to measure the excitatory electrical activity generated in a single cortical neuron by a single thalamic neuron. They noted that the median amplitude of the thalamocortical excitatory potential was 0.5 mV (range 0.1 to 4.1 mV), which is smaller by a factor of 30 than the average synaptic potential generated by a sensory stimulus in the cortex (~15 mV).

Neurons connect with each other through small junctions called synapses. On average, a layer 4 neuron receives 20% of inhibitory synapses and 80% of excitatory synapses from other neurons. Surprisingly, most of the excitatory synapses do not originate in the thalamus but in the cortex itself (see the figure). In layer 4 neurons of the mouse somatosensory cortex, only 10 to 23% of the excitatory synapses are formed with thalamic neurons (2), and similar percentages (5 to 25%) have been found in layer 4 neurons of the cat visual cortex [the similar percentages hold if the estimates from different research groups are taken as opposite ends of a common range instead of opposite views of thalamocortical function (3)]. This remarkable intracortical predominance in synapse number led to the idea that the input from thalamic neurons is not strong enough to elicit, or “drive,” neuron activity in the cortex.

Therefore, it’s been thought that thalamic inputs need to be amplified by recurrent intracortical connections (4). Even though layer 4 intracortical connections can be relatively strong, estimates obtained from cortical slices indicate that thalamocortical connections are stronger, if fewer in number. According to these estimates, thalamic synapses are not only larger in size (and have more active zones where neurotransmitter molecules are released) than intracortical synapses, they are also more effective at driving the cortex by a factor of 4.8 (5). Although measurements in the intact brain using techniques such as cross-correlation analysis (6, 7) or single-axon current source density analysis (8) are consistent with the idea of a dominant thalamic input to the cortex, a crucial piece of information has been missing: We have not known the amplitude of the thalamocortical postsynaptic potential in an active and intact brain.

Bruno and Sakmann now provide this measurement and show that the input from a single thalamic neuron, in isolation, cannot activate a single cortical neuron, because it generates a postsynaptic potential usually smaller than 1 mV, which is below the threshold needed for neuronal activation. On the basis of this finding, the authors conclude that thalamocortical connections are weak—a conclusion that is very consistent with the anatomy. For example, whereas a single retinal neuron makes more than 100 synapses per thalamic target [one of the strongest connections within the visual pathway (9)], a thalamic neuron makes fewer than eight synapses per cortical neuron (10). Even if thalamocortical connections are weak, they are unlikely to be weaker than intracortical connections (5). Unfortunately, there are no measurements of intracortical connections in the intact sensory cortex that could serve as comparison, despite heroic attempts to obtain them (11).

Regardless of the differences at the level of single connections, a major conclusion from Bruno and Sakmann is that thalamic inputs do not need a “cortical amplifier” to reach threshold. Although any thalamic input in isolation is weak, thalamic inputs are strong as a group. A group of just 30 synchronized inputs (out of 85 inputs available) will generate a postsynaptic potential very similar to the one generated by a sensory stimulus such as a light touch. Groups of thalamic neurons can generate many synchronized electrical discharges, or spikes, in response to sensory stimulation, and these synchronized spikes are very effective at driving cortical cells to threshold (12). Consistently, it has now been reported, in at least three different sensory systems (7), that the response properties of layer 4 cortical neurons are largely explained by the response properties of the thalamic inputs (1).

The experiments from Bruno and Sakmann will surely raise an old question: What are all the intracortical synapses doing in layer 4 neurons? The answer may not be far from the cortical amplifier idea (4). In recent years, it has become clear that intracortical inhibition plays...
a major role in normalizing the gain of intracortical responses while keeping stimulus selectivity constant (13). Like intracortical inhibition, intracortical excitation may provide gain adjustments that are far more specific and sophisticated than what we can currently imagine (14). In the meantime, the thalamocortical connections seem to be doing their job just fine, leaving the cortical amplifier available for other interesting functions that remain to be discovered.

References

Natural sulfide. Cracked open, a clump of gelatinous mud from the seaside is seen to be rich in black iron sulfide. Any hydrogen sulfide that does not react with iron is available to react with organic matter. The sulfide is produced by bacteria that oxidize organic matter at the expense of sulfate, which is abundant in seawater. The process occurs only after molecular-oxygen supplies have been exhausted. The light-colored margin of the clump marks the depth to which molecular oxygen can diffuse in the mud.

A complex web of reactions leads from primary biological products to the organic debris found in sediments and rocks. A new study shows that abiotic reactions play an important role.

The Pathway of Carbon in Nature

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Late in his exceptional career, well after he had received the Nobel Prize in 1961 for elucidating the pathway of carbon in photosynthesis, Melvin Calvin turned his attention to organic geochemistry. The progression was logical: from the pathway of carbon in a cell to the pathway of carbon in nature. In the former, there is an array of precise, enzymatic catalysts. The latter is actually a web of reactions that leads from primary biological products to the organic debris accumulating in Earth’s crust. What mechanisms control the flow of carbon within this web? The answer is worth knowing because, among other things, these mechanisms modulate Earth’s levels of CO₂ and O₂. On page 1627 of this issue, Hebting et al. (1) provide striking new information about one of the web’s most general features.

In his book Chemical Evolution (2), Calvin discusses “molecular paleontology” and makes a key point: Hydrocarbons are particularly long-lived. Petroleum is a key example. In contrast, proteins, carbohydrates, and nucleic acids—the abundant and information-rich components of biomass—are rarely preserved for more than a few million years (3). Clues about ancient biochemistry must therefore be extracted from sedimentary hydrocarbons derived mainly from lipids and other aliphatic products.

The rocks contain cholestane rather than cholesterol, carotane rather than carotene. The structural relationships are unmistakable, but the molecules are very different. Somehow, carbon skeletons are preserved, double bonds and functional groups are lost, and a saturated hydrocarbon survives to carry the root of its precursor’s name with an “-ane” suffix.

How does all this happen? The hydrocarbons—called biomarkers if their structures are distinct enough—are produced by reaction pathways within sediments. For years, organic geochemists have been disentangling those pathways, just as Calvin, Benson, and their co-workers determined the photosynthetic route from CO₂ to carbohydrates.

The time scales differ markedly, however. In photosynthesis, the problem was to stop reactions quickly so that the earliest products could be observed. In sediments, even the faster reactions require decades to produce readily analyzable quantities. Moreover, if a system is manipulated—to speed it up or to add a tracer—the pathways are likely to change. The most useful results have been based on analyses of natural materials at identifiable points in the pathway.

Sterols, which are abundant in oceanic algae and for which structurally related steranes can be found in marine sediments and petroleum, have been favored as tracers within the web of reactions (4). Even within particles that have not yet sunk to the seafloor, we find hydrogenated products, stanols, rather than the original algal products. Evidence for microbial catalysis of this process is strong (5). Double bonds within the ring system are the first to go, and the process is stereoselective. If the process were abiotic, all double bonds, not just those in the ring system, should be attacked, and there would be no stereoselectivity.

The hydrogenated products are more abundant in environments that are deficient in oxygen (such as interiors of particles or poorly ventilated waters). Apparently, microorganisms are extending their oxidative metabolism by using unsaturated lipids as electron acceptors. Microorganisms also dehydrate sterols to produce conjugated steradienes (6). In the dehydration of carotenoids, formation of an acetylenic intermediate that would not be favored in abiotic processes also suggests microbial catalysis (7). As such results have accumulated, a new conventional wisdom has emerged: If the temperature is not too high and a reaction could be microbiologically catalyzed, it probably is.

Or is it just hard to prove that a low-temperature, organic-chemical alteration is abiotic? It’s not as if sedimentary environments are chemically benign. Concentrations of hydrogen sulfide (H₂S), a potential reductant, can be appre-