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Depression at Thalamocortical Synapses: The Key for Cortical Neuronal Adaptation?

Neuronal adaptation to repetitive sensory stimuli is ubiquitous in the mammalian cortex. Despite its prevalence, the cellular mechanisms underlying this basic physiological property remain a matter of dispute. In this issue of *Neuron*, Chung et al. provide conclusive evidence that depression of thalamocortical synapses may play a significant role in the expression of neuronal adaptation in the rat somatosensory cortex.

Despite the fact that neuronal adaptation to repetitive presentations of sensory stimuli has been repeatedly observed in multiple cortical areas, the cellular and synaptic mechanisms underlying this basic phenomenon remain a matter of hot debate. The question is not simple. First, since there is a multitude of afferents that converge to cortical neurons, dissecting the potential pathways that can contribute to the phenomenon at cortical level poses major experimental challenges. Moreover, the fact that neuronal adaptation is also observed in subcortical structures, such as the thalamus and the brainstem, makes it difficult to discern whether cortical adaptation results from purely intrinsic cortical mechanisms as proposed previously. Part of the mystery in this fascinating story is unveiled in this issue of *Neuron* by Chung et al. (2002). In this very interesting manuscript, these authors provide the first clear in vivo demonstration that a decrease in the gain of thalamocortical synaptic transmission may be the main reason neurons in the rat somatosensory cortex adapt rapidly, following repetitive whisker stimulation under certain experimental conditions or behavioral states. Perhaps more surprisingly, and contrary to previous observations in primary visual cortical slices, Chung et al. report a conspicuous absence of corticocortical synapse depression in the rat barrel cortex following repetitive whisker stimulation. These findings are very significant, not only because they support the notion that short-term synaptic depression, a phenomenon commonly documented in vitro, may play a significant role in vivo, but also because they highlight the relevance of considering thalamic neurons and their efferent projections as key players in determining cortical physiology dynamics.

Chung et al. supported their conclusions by a series of very elegant experiments. First, they recorded the simultaneous extracellular activity of neurons located in both the ventral posterior medial (VPM) nucleus of the thalamus and primary somatosensory (SI) cortex. By stimulating the single facial whisker that induced the fastest and strongest sensory-evoked response in these neurons, they demonstrated that although both thalamic and cortical cells exhibit fast frequency-dependent adaptation, cortical neurons adapt more strongly and at lower frequencies than thalamic neurons to repetitive whisker stimulation. Next, in vivo whole-cell patch recordings of SI neurons located primarily in layers 2/3 and 4 revealed that cortical neuronal adaptation involved a dramatic reduction in the earliest portion of the whisker-evoked cortical synaptic potentials, which followed the same frequency-dependence observed in the extracellular recordings. The authors also observed that cortical synaptic potentials adapted faster and recovered more slowly than thalamic sensory responses, suggesting that intrinsic cortical mechanisms, in addition to thalamic adaptation, contributed to the observed attenuation of SI tactile responses.

Interestingly, rapid adaptation of cortical synaptic potentials was not paralleled by any significant change in these neurons' intrinsic membrane properties. Thus, neither the membrane resting potential nor the input resistance of neurons in the rat SI cortex changed after the induction of sensory adaptation. Further control experiments also ruled out any other potential postsynaptic factors as major contributors to the observed adaptation of cortical synaptic potentials. Perhaps the most surprising result of the present study was the observation that short-term depression of intrinsic cortical afferents to SI neurons did not contribute significantly to the adaptation of these neurons to repetitive whisker stimulation. Instead, control and testing electrical stimuli, delivered near the recorded SI neuron, produced virtually identical monosynaptic electrical responses before and after the induction of sensory-evoked adaptation. Only polysynaptic components of these responses seemed to be somewhat altered. This observation, therefore, virtually ruled out the possibility that sensory-evoked adaptation in the rat SI cortex emerged as a result of modifications in the synaptic efficacy of local excitatory corticocortical interactions.

The results were very distinct, however, when the VPM thalamus instead of the SI cortex was electrically stimulated before and after the induction of sensory cortical adaptation by repetitive whisker stimulations. In a clear contrast to the cortical stimulation experiments, electrical stimulation of VPM neurons that provide thalamocortical projections to the recorded barrel cortex neurons produced EPSPs that were significantly attenuated after the induction of sensory-evoked cortical adaptation. This attenuation manifested itself by reductions in both the magnitude and slope of the earliest components of the cortical synaptic response to the VPM electrical stimulation. By recording from SI neurons that receive monosynaptic input from VPM neurons, the authors were also able to observe that the recovery rate of thalamocortical synapses after adaptation was similar to that

of the cortical sensory-evoked responses following whisker deflection. This result provided very strong evidence that short-term depression of thalamocortical synapses played a major role in the phenomenon of neuronal adaptation in the rat SI cortex following repetitive whisker stimulation.

These findings are very significant since they provide a potential cellular explanation to account for the well-known finding that SI neurons recorded in anesthetized (Ahissar et al., 2000) animals or during awake immobility (Fanselow and Nicolelis, 1999) tend to exhibit frequency-dependent adaptation to repetitive tactile stimulation. But what role could sensory adaptation mediated by short-term depression of thalamocortical synapses play in awake and freely behaving rats? Although more experiments are necessary to address this question satisfactorily, it is conceivable that fast thalamic and cortical sensory adaptation may contribute to the ability of the thalamocortical loop to optimize the detection of small and transient tactile stimuli in awake and immobile rats (Chung et al., 2002; Nicolelis and Fanselow, 2002).

It is important to emphasize, however, that this is not the end of the story by a long shot. Whereas neuronal adaptation dominates the profile of cortical sensory-evoked responses to repetitive peripheral stimulation in anesthetized preparations, it is not necessarily present at all times in behaving animals. For instance, the physiological properties of the thalamocortical loop of the rat somatosensory system change significantly when animals engage in active exploration of their surrounding environment by producing large amplitude rhythmic whisker movements. During this behavioral state, there is a very dramatic reduction in cortical and thalamic neuronal adaptation to repetitive sensory stimulation (Fanselow and Nicolelis, 1999). These experiments suggest that, as animals sweep objects with their facial vibrissae, both VPM and SI neurons become capable of faithfully responding to fast sequences of single and multiwhisker deflections. This makes perfect sense, since it is likely that these fast sequences of whisker contacts are used by rats to discriminate the location, texture, size, and shape of objects. Although there is very little information regarding the potential synaptic modifications that may take place during exploratory whisking, recent evidence suggests that synchronous 7–12 Hz oscillations that appear in the SI cortex during awake immobility, and usually precede the initiation of whisking, could lead to long-term potentiation of corticothalamic synapses in VPM neurons (Castro-Alamancos and Calcagnotto, 1999). Corticothalamic LTP could then contribute to enhance VPM transmission of sensory-evoked information to the SI cortex during whisking by counteracting the tendency of these thalamic neurons to adapt to incoming trigeminal lemniscal inputs.

Many more studies will be required to further clarify the contribution of thalamocortical, corticocortical, and corticothalamic synapse dynamics in defining thalamic and cortical sensory responses under distinct behavioral states. However, one can safely conclude that the elegant results by Chung et al. provide further support to the notion that sensory systems must be considered as highly adaptive entities, in which fast alterations in synaptic and circuit dynamics, in addition to concurrent changes in behavioral exploratory strategy, allow animals to optimize their analysis of the surrounding environment. Indeed, one may dare to say that thinking of large brain circuits, such as the rat somatosensory system, as containing purely static and topographic representations is not tenable any longer. It is about time, literally!

Miguel A.L. Nicolelis
Department of Neurobiology
Duke University Medical Center
Durham, North Carolina 27710

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