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Local Gating of Information Processing through the Thalamus

Inhibitory sculpting of afferent signals in the thalamus is exerted by two types of neurons using γ-amino butyric acid (GABA) as neurotransmitter. Of them, local-circuit neurons exert their functions via two outputs: axons and presynaptic dendrites. In this issue of *Neuron*, Govindaiah and Cox reveal that synaptic activation of metabotropic glutamate receptors selectively increases the output of presynaptic dendrites of local interneurons in rat visual thalamus, without affecting the axonal output.

It is now firmly established that the thalamus is not just an anteroom for relaying signals to the cerebral cortex, but a structure actively implicated in shaping afferent information through inhibitory processes, thus participating in highly integrative functions during adaptive states of behavior. A large set of data using extra- and intracellular recordings from thalamic and neocortical neurons in vivo revealed that, although long-lasting inhibitory periods are reduced or erased upon awakening from sleep, the short-lasting inhibition is preserved or even enhanced (see Steriade, 2003). This reinforcement in short-lasting inhibitory processes during waking, compared to states of sleep, provides a mechanism subserving accurate discrimination of incoming signals and leads to improvement in directional selectivity (Livingstone and Hubel, 1981). Two types of inhibitory GABAergic neurons operate in the thalamus: reticular and local-circuit neurons. Both have been implicated in discrimination functions. Although thalamic reticular neurons may play a role in attention, which is impaired following large lesions of the reticular nucleus (Weese et al., 1999), and activation of some thalamic reticular sectors is observed following exploration of a novel environment (Montero, 1997), the cellular mechanisms underlying the attentive function of thalamic reticular neurons are not elucidated. Moreover, thalamic reticular neurons are mainly implicated in the generation of global oscillations in thalamocortical systems, which characteristically define the states of slow-wave sleep and some types of paroxysmal discharges during which conscious processes are suspended (Steriade, 2003). On the other hand, local-circuit interneurons have been implicated in processes related to focused attention and local discrimination processes. The latter neuronal type is confined within virtually all dorsal thalamic nuclei of felines and primates as well as the dorsal lateral geniculate nucleus (dLGN) of rats but is absent in other thalamic nuclei of rodents. The output of local interneurons arises from axon terminals that form inhibitory synapses onto somata and dendrites of thalamocortical neurons but also, importantly, from the dendritic appendages of interneurons that are equipped with presynaptic vesicles, known as F2 terminals, which contact the dendrites of thalamocortical neurons and form symmetrical (inhibitory) profiles within the triadic circuitry of synaptic aggregations called glomeruli (Jones, 1985).

In this issue of *Neuron*, Govindaiah and Cox (2004) used parasagittal slices from rat dLGN to preserve the optic tract (OT) input, recorded intracellularly from relay cells and local interneurons, and revealed that OT tetanic stimulation activated metabotropic glutamate receptors (mGluRs) located on presumed presynaptic GABA-containing dendrites of interneurons, which led to increased inhibition in target thalamocortical neurons. The contrast between these very interesting results and some previous data indicating that OT stimulation does not produce mGluRs-mediated synaptic responses in thalamocortical neurons might be explained by differences between the recording technique in the present paper (whole-cell configuration) and the sharp-electrode recordings used previously. In about 25% of thalamic relay cells, the increased incidence of inhibitory postsynaptic potentials (IPSPs) resulting from strong tetanic OT stimulation was independent of the slow depolarization. Using a series of pharmacological manipulations in the bath, the authors concluded that the increased IPSPs in thalamic relay cells was not due to suprathreshold depolarization of the interneurons at the somatic level but to OT-induced activation of mGluRs that are presumably localized on presynaptic dendrites of dLGN interneurons. The reason behind this assumption was that the OT-elicited increase in IPSPs recorded from thalamic relay cells was independent of action potentials fired by local interneurons, as would have been the case within the conceptual frame of feed-forward inhibition. Also, changing the site of stimuli showed that the increased IPSPs were selectively due to OT stimulation, since this increase was not obtained using stimuli applied to optic radiation that contains corticothalamic axons. Govindaiah and Cox hypothesized that synaptic activation of mGluRs on presynaptic dendrites of dLGN interneurons increases the release of GABA from these dendrites, without influencing the axonal output, and may modulate synaptic transmission at retino-dLGN synapses, thus representing a focal form of information integration.

Of course, any attempt toward deciphering the function of presynaptic dendrites of local thalamic interneurons is of tremendous interest since direct recordings from presynaptic dendrites in thalamic glomeruli are not yet feasible. This technical difficulty (say impossibility, at least nowadays) is combined with the fact that axons arising from thalamic reticular neurons have access not only to thalamocortical cells, but also to local interneurons, in both dLGN (Montero and Singer, 1985) and ventroposterior nuclear complex (Liu et al., 1995). Although this connection to interneurons arising in the thalamic reticular nucleus is numerically less important than that contacting relay cells, its effects may be dramatic. Indeed, following interruption of the input from thalamic reticular neurons, there is a release from inhibition of local interneurons, which results in greatly increased incidence of IPSPs in thalamic relay cells (Steriade et al., 1985). To safely circumvent the possible interven-

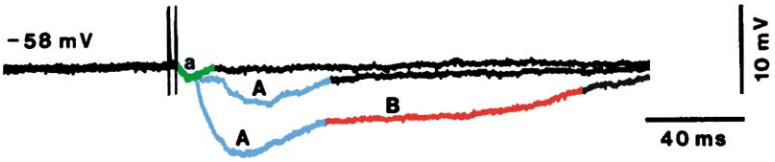

Figure 1. Intracellular Recording of Cat Anterior Thalamocortical Neuron In Vivo

Different stimulation parameters that gave rise to $GABA_a$-, $GABA_A$-, and $GABA_B$-IPSPs are provided in the text. Modified from Paré et al. (1991).

tion of inhibitory processes arising in thalamic reticular nucleus and exclusively deal with the action of local interneurons, the strategy was used to investigate the sequence of IPSPs in thalamocortical neurons induced by inhibitory local-circuit cells (Paré et al., 1991) in the few thalamic sectors (such as anterior nuclei) that, in felines, are naturally devoid of inputs from the reticular nucleus (Steriade et al., 1984). In that condition, stimulation of afferent (prethalamic) pathways gives rise, in addition to the classic biphasic sequence of $GABA_{A\text{-}B}$-IPSPs, to a Cl^--dependent IPSP that has the shortest latency and very small amplitude, whence the term "miniature" or $GABA_a$-IPSP (Paré et al., 1991). One of the reasons behind ascribing the $GABA_a$-IPSP to its generation by presynaptic dendrites is the fact that it is selectively elicited by axons arising in the mammillary body, which have access to presynaptic dendrites, whereas it is not evoked by setting into action corticothalamic axons whose overwhelming majority do not contact presynaptic dendrites. Another reason is that, when Cl^- is injected into neuron, $GABA_A$-IPSP reverses before $GABA_a$-IPSP, thus indicating that the synaptic sites responsible for the former are closer to the soma than those responsible for the latter. The presence of $GABA_a$-IPSP was subsequently also revealed in dLGN (Soltesz and Crunelli, 1992).

The failure of detecting the $GABA_a$-IPSP in other studies is probably due to the fact that minimal stimulation strength has to be used to reveal this "miniature" IPSP in isolation because, with slightly increased stimulation intensity, $GABA_a$-IPSP is immersed in the following $GABA_A$-IPSP that has a much greater amplitude. As shown in Figure 1, taken from a decorticated cat, an isolated $GABA_a$-IPSP could be evoked by a single stimulus, with the lowest intensity, applied to the mammillary body; two stimuli evoked both $GABA_a$- and $GABA_A$-IPSPs; and only by increasing the stimulation strength of the two stimuli was the full sequence ($GABA_{a\text{-}A\text{-}B}$) evoked.

Why are the data by Govindaiah and Cox interesting and why is the evidence of "miniature" $GABA_a$-IPSP important? Presynaptic dendrites of local inhibitory interneurons provide a mechanism for focal forms of integrative processes and thus play a crucial role in local gating of information processing through the thalamus. A series of previous studies, both in vivo and in vitro, have focused on the cholinergic (muscarinic) suppressing effect on axonal as well as presumed dendritic outputs of thalamic inhibitory neurons. However, during states, such as wakefulness, that are associated with significantly increased brainstem-thalamic cholinergic output (Steriade et al., 1990), inhibitory processes are not completely blocked. Indeed, such adaptive states are associated not only with increased responsiveness of neurons in thalamocortical systems but also with fine tuning and precise discrimination, which imply increased inhibitory sculpting. Although prolonged inhibitory periods, which characterize slow-wave sleep oscillations, are suppressed upon arousal, the $GABA_a$-IPSP is preserved and may even be enhanced by conditioning stimulation applied to brainstem cholinergic nuclei (Curró Dossi et al., 1992). Further studies are needed in chronically implanted, naturally awake animals to assess the presence of IPSPs generated by presynaptic dendrites of local inhibitory thalamic interneurons and to investigate their behavior during states of inattention and complex tasks during sensory stimulation.

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