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Complex regulation of dendritic transmitter release from thalamic interneurons

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Neuronal output typically involves neurotransmitter release via axonal terminals; however, a subpopulation of neurons can also release neurotransmitters through vesicle-containing presynaptic dendrites. In the thalamus, local circuit inhibitory interneurons are a class of cells that can release γ-aminobutyric acid (GABA) via both axon terminals (termed F1 terminals) as well as presynaptic, vesicle-containing dendrites (termed F2 terminals). For example, in the visual thalamus, these F2 terminals are tightly coupled to the primary sensory afferents (axons of retinogeniculate neurons) that synapse onto thalamocortical relay neurons. The F2 terminals are primarily localized to distal dendrites of the interneurons, and in certain situations the excitation/output of F2 terminals can occur independent of somatic activity within the interneuron thereby allowing these F2 terminals to serve as independent input/output components giving rise to focal inhibition. On the other hand, somatically evoked Na+-dependent action potentials can backpropagate throughout the dendritic arbor of the interneuron. The transient depolarizations, or stronger somatically initiated events (e.g. activation of low threshold calcium transients) can initiate a backpropagating Ca^{2+}-mediated potential that invades the dendritic arbor activating F2 terminals and leading to a global form of inhibition. These distinct types of output (focal versus global) could play an important role in the temporal as well as spatial roles of inhibition that in turn impacts thalamocortical information processing.

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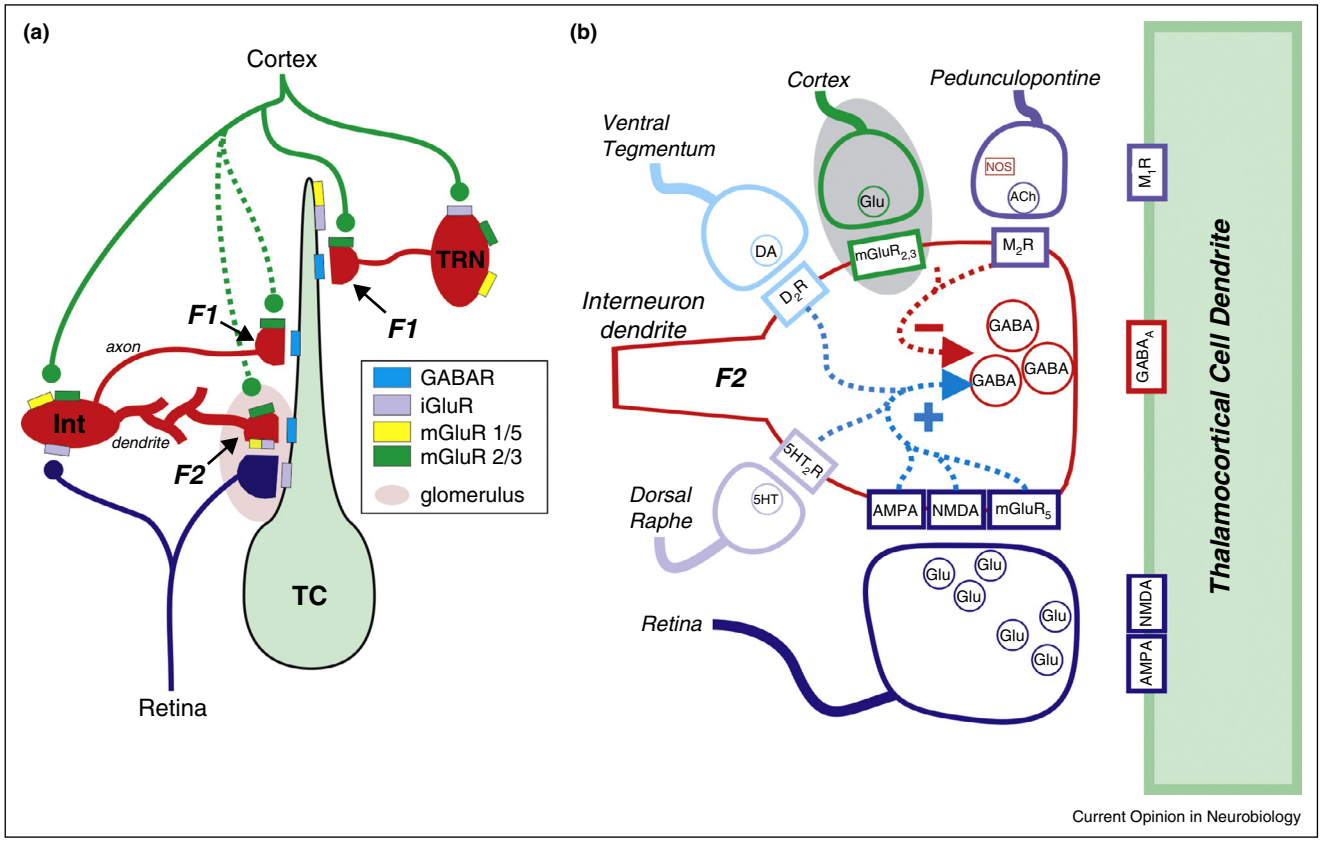
Introduction

Classic synaptic transmission within neural networks typically consists of suprathreshold excitation of the presynaptic neuron, action potential propagation through the axonal arbor, and subsequent neurotransmitter release from axonal terminals, which ultimately influences postsynaptic targets. Dendrites characteristically have the responsibility of integrating afferent synaptic activity which can be a dynamic process considering these structures may contain a wide variety of voltage dependent conductances that can influence their integrative properties [1]. In a subpopulation of neurons, there is an added complication in that the dendrites may also contain synaptic vesicles and serve to release neurotransmitters. Therefore, these local areas of integration/synaptic release may bypass the complex somatic integration and axonal output. Dendritic transmitter release has been associated with neurons found in multiple brain areas (for review, see [2]). Furthermore, there is increasing evidence that dendritic release of neurotransmitters may be regulated by a variety of modulatory systems given the convergence of multiple transmitter systems upon dendritic arbors.

The thalamus serves as the gateway through which sensory information passes before entering the neocortex. It is now widely accepted that information processing through the thalamus is a dynamic process rather than a mere passive relay of information to various neocortical areas. Primary sensory afferents entering the thalamus typically synapse onto two subtypes of neurons: thalamocortical relay neurons that subsequently project to primary sensory cortex and inhibitory local circuit neurons with axonal arbors that remain within the thalamus (Figure 1a). It is worth noting that the proportion of local interneurons within thalamic nuclei varies across species. In rodents, these local interneurons are predominantly found in visual related thalamic nuclei and are absent in many other thalamic nuclei; however in higher order mammals including cats, nonhuman primates and primates, these local interneurons are localized within most thalamic nuclei [3].

For this review, we will focus on the visual system, in which retinogeniculate neurons innervate thalamocortical neurons and local circuit interneurons within the dorsal lateral geniculate nucleus (dLGN). In addition to this bottom up circuitry, there is strong feedback circuitry originating from layer VI corticothalamic neurons that innervate: (1) thalamocortical neurons, (2) local circuit interneurons, and (3) inhibitory thalamic reticular nucleus (TRN) neurons that in turn project back into dLGN. The local circuit interneurons serve as a feedforward inhibitory circuit predominantly driven by primary sensory afferents, and functionally are thought to enhance stimulus selectivity, refine receptive fields of thalamocortical neurons, improve sensory coding, and ensure temporal

Figure 1



(a) Simplified schematic diagram of visual system thalamic circuitry depicting multiple types in inhibitory inputs. Inhibitory axonal outputs (F1 terminals) arise from both local circuit neurons in dLGN as well thalamic reticular nucleus (TRN) neurons. Presynaptic dendrites (F2 terminals) of interneurons (Int) are innervated by retinogeniculate axons, which also innervate the dendrite of thalamocortical neuron (TC). Adapted from [22]. **(b)** Schematic representation illustrating multiple transmitter systems that have been shown to alter the output of putative F2 terminals. The cortical pathway engaging mGluR2/3 (gray circle) clearly involves F1 terminals but unclear if engages F2 terminals [22].

precision of spiking [4–7]. To complicate matters, afferents from corticothalamic neurons also innervate the local interneurons providing a cortically driven feedback on inhibitory activity within the thalamus, and these inputs likely influence how subsequent retinogeniculate information is processed [8–10].

These local circuit inhibitory interneurons provide two types of GABAergic output: axonal and dendritic (Figure 1a). Similar to nearly all other neurons, the axonal arbor consists of vesicle containing terminals that form both axodendritic and axosomatic synaptic contacts onto thalamocortical relay neurons (F1 terminals). An additional feature of these neurons is that they form dendrodendritic synapses onto thalamocortical neurons, which have been named F2 terminals [11–17]. These F2 terminals are part of a triadic arrangement that includes three components: retinogeniculate axon terminal, distal presynaptic dendrite of the interneuron, and the proximal dendrite of the thalamocortical neuron (Figure 1). The retinogeniculate axon innervates the proximal dendrite of the thalamocortical neuron forming a monosynaptic excitatory synapse. In addition, the same retinogeniculate axon forms a synapse on the distal dendrite of the interneuron, which in turn is presynaptic to the dendrite of the thalamocortical neuron providing a disynaptic inhibitory pathway to the local region of the dendrite (Figure 1b). The compact localization of these multiple synaptic contacts suggests that there could be a tight regulation of retinogeniculate excitation of the thalamocortical neurons.

Regulation of dendritic outputs via multiple neuromodulators

Despite anatomical evidence depicting the presence of F2 terminals within the thalamus, their function remained hypothetical for many years [12,15]. During this time, numerous studies focused on the role of inhibition within thalamocortical processing; however, the potential contribution of F2 terminals to this inhibitory activity remained speculative. Prior studies on