Dynamics of sensory thalamocortical synaptic networks during information processing states

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Abstract

The thalamocortical network consists of the pathways that interconnect the thalamus and neocortex, including thalamic sensory afferents, corticothalamic and thalamocortical pathways. These pathways are essential to acquire, analyze, store and retrieve sensory information. However, sensory information processing mostly occurs during behavioral arousal, when activity in thalamus and neocortex consists of an electrographic sign of low amplitude fast activity, known as *activation*, which is caused by several neuromodulator systems that project to the thalamocortical network. Logically, in order to understand how the thalamocortical network processes sensory information it is essential to study its response properties during states of activation. This paper reviews the temporal and spatial response properties of synaptic pathways in the whisker thalamocortical network of rodents during activated states as compared to quiescent (non-activated) states. The evidence shows that these pathways are differentially regulated via the effects of neuromodulators as behavioral contingencies demand. Thus, during activated states, the temporal and spatial response properties of pathways in the thalamocortical network are transformed to allow the processing of sensory information.

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Abbreviations: BRF, brainstem reticular formation; VPM, ventroposterior medial thalamus; POm, rostral sector of the posterior complex; nRt, thalamic reticular nucleus; CO, cytochrome oxidase; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential; GABA, gamma-aminobutyric acid; LTP, long-term potentiation; LTD, long-term depression; CSD, current source density analysis; TTX, tetrodotoxin; VL, ventrolateral nucleus of the thalamus

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1. Introduction

Understanding how the brain acquires, analyzes, stores and retrieves sensory information is one of the most compelling questions in neuroscience. Central to information processing, are neural networks that interconnect the thalamus and the neocortex. Rather than being static, these neural pathways are highly dynamic and modifiable on a moment to moment basis. These dynamic changes occur in response to behavioral demands to allow information processing. The neocortex is the most highly evolved area in the brain; it is the location where the most complex brain activities take place, such as perception and consciousness. The thalamus is the gate to the neocortex; all sensory information, excluding olfaction, must pass through the thalamus before reaching the neocortex. It is widely accepted that the main function of the thalamus is to control the flow of sensory information to the neocortex during different behavioral states. The thalamus and neocortex are highly organized and complex structures that work in concert with each other. The importance of their relation is evident in that they are recurrent and extensively interconnected with one another, the neocortex accesses information about the external world primarily via the thalamus, and the largest input to the thalamus arrives from the neocortex. I will refer to the system of different pathways that interconnect the thalamus and cortex as the thalamocortical network.

The goal of the present review is to describe the properties of pathways in the sensory thalamocortical network using rodent vibrissae as a model system; reference will also be made to studies from other sensory modalities and species when necessary. A number of reviews and books exist on the properties of the thalamocortical network (e.g. Sherman and Guillery, 1996, 2001; Steriade et al., 1997; Jones and Diamond, 1995). The present review focuses on the basic properties of the three major pathways in the thalamocortical network, and particularly on how they are modified by behavioral state. The pathways are: (1) the primary sensory thalamic afferents that originate in the trigeminal nucleus and via the medial lemniscus tract innervate cells in the ventroposterior medial thalamus (VPM); for simplicity, termed here the lemniscal pathway; (2) the massive corticothalamic pathway that originates in layer VI of neocortex and innervates VPM; and (3) the thalamocortical pathway originating in VPM cells. The role of the lemniscal pathway is to provide direct sensory information from the peripheral receptors, while the thalamocortical pathway relays that information to the neocortex. The role of the corticothalamic pathway is less understood but among other things it is thought to regulate sensory inputs. The main interest here is to describe how these pathways operate during information processing states (see below Section 1.2).

The underlying theme of this review is that the properties of the inputs to the thalamus (corticothalamic and lemniscal) and its output (thalamocortical) are differentially regulated via the effects of neuromodulators as behavioral contingencies demand. In other words, neuromodulators change the properties of these pathways during behavior to allow effective information processing. Understanding how a pathway operates requires intimate knowledge of the intrinsic membrane properties of the pre- and postsynaptic
cells forming the pathway, and particularly of the synaptic connections that those cells produce. There is an ample literature on the intrinsic membrane properties of neurons in the thalamocortical network. However, the properties of synapses in this network have been less intensely studied. Deciphering the properties of these synapses is vital for understanding the thalamocortical network. Both, intrinsic membrane and synaptic properties contribute to the fact that the excitability of the thalamocortical network is not static but highly dynamic. The pioneering studies of thalamocortical responsiveness were carried out by Morison and Dempsey over 60 years ago (Dempsey and Morison, 1942a,b, 1943; Morison and Dempsey, 1942, 1943). Their work showed that pathways in the thalamocortical network are highly sensitive to frequency (for review see Castro-Alamancos, 1997; Castro-Alamancos and Connors, 1997b).

An important subject is to understand how these temporal properties are involved in sensory information processing during different behavioral states.

1.1. The vibrissae thalamocortical network

The thalamocortical network discussed here is the representation of vibrissae in rodents (Woolsey and Van der Loos, 1970; Bernardo and Woolsey, 1987). This system shares many properties with the other major models used to study sensory processing, such as the visual system (Miller et al., 2001). Most rat strains have relatively poor visual abilities, and instead use their whiskers to navigate and to locate and identify objects (Carvell and Simons, 1990; Guic-Robles et al., 1989; Brecht et al., 1997). The tactile skills of their whiskers are in some ways comparable to primates using their fingertips (Carvell and Simons, 1990; Simons, 1995), employing active touch strategies common throughout mammalian sensory/motor systems (Simons, 1995). For a whisker deflection that drives a mechanoreceptor on the sensory axon of a trigeminal (V) ganglion cell there are three levels of processing up to the neocortex. The first level occurs in the trigeminal complex (i.e. trigeminal (V) brainstem nuclear complex), where groups of cells representing primarily one whisker form cell clusters, called barrelettes (Henderson and Jacquin, 1995). The axons of these trigeminal cells produce the lemniscal pathway that innervates clusters of cells in VPM, called barreloids (Land et al., 1995), which represent the same principal whisker. Finally, the axons of these VPM cells produce a thalamocortical pathway that innervates clusters of cells in layer IV called barrels (Woolsey and Van der Loos, 1970), which also represent the same principal whisker. By definition the whisker thalamocortical network consists of the pathways received and produced by VPM cells, including lemniscal, corticothalamic and thalamocortical (see Fig. 1).

Notably, the number of corticothalamic fibers is one order of magnitude larger than the number of thalamocortical axons (Sherman and Guillery, 1996), and cortical afferents are the most abundant input to the thalamus (Guillery, 1971). In the vibrissae somatosensory network, primary and secondary thalamic nuclei can be distinguished based on the characteristics of the sensory information that they process (Diamond, 1995). The primary thalamic nucleus is the VPM, and the secondary nucleus is the rostral sector of the posterior complex (POm). In addition, there are two types of corticothalamic pathways (see Fig. 1) that differ in the layer of cortex from where they originate (for review Guillery, 1995). One pathway originates in layer VI and sends reciprocal connections to both primary and secondary thalamic nuclei, leaving collateral fibers in the thalamic reticular nucleus (nRt) (Zhang and Deschenes, 1997). The nRt sends inhibitory fibers (GABAergic) to VPM and POm. The other pathway originates in layer V, from neurons whose axons run toward the brainstem and give rise to collaterals that enter the thalamus and terminate exclusively in secondary thalamic nuclei, such as POm (Bourassa et al., 1995), and thus avoid the nRt and VPM. The corticothalamic fibers that originate in layer VI and innervate VPM produce glutamatergic synapses that act on distal dendrites (for review Guillery, 1995; Deschenes et al., 1998; Sherman and Guillery, 1996). The VPM receives its primary sensory input from the principal trigeminal nucleus through the lemniscal pathway (for review Diamond, 1995). Lemniscal terminals form glutamatergic synaptic contacts with the soma and proximal dendrites of VPM neurons (Spacek and Lieberman, 1974; Williams et al., 1994b). Thus, corticothalamic synapses contact distal dendrites, while lemniscal synapses occur more proximal to the cell body of thalamocortical neurons (Liu et al., 1995a; Spacek and Lieberman, 1974; Williams et al., 1994b; Erisir et al., 1997a), and corticothalamic fibers have smaller diameters than lemniscal fibers and consequently conduct slower (Sherman and Guillery, 1996; Robson, 1983). In conclusion, VPM thalamocortical neurons are contacted close to their somata by principal trigeminal nucleus fibers (lemniscal pathway) and by nRt fibers (inhibitory pathway), and at distal portions of their dendrites by fibers from neurons in layer VI of neocortex (corticothalamic pathway). Moreover, VPM thalamocortical neurons lack recurrent axon collaterals between them, and are not innervated by local interneurons since these do not exist within rodent ventrobasal thalamus (Ohara and Lieberman, 1993).

There are different types of thalamocortical pathways (for review Castro-Alamancos and Connors, 1997b), but the main thalamocortical pathway we will discuss here is the primary thalamocortical pathway that originates in VPM and innervates the barrel cortex. Thalamocortical cells in VPM project to the neocortex via the thalamic radiation and as they do, they leave collateral fibers in the nRt and in upper layer VI of neocortex before arriving at their destination in layer IV (Jensen and Killackey, 1987). In addition, the POm also generates a thalamocortical pathway, usually termed secondary thalamocortical pathway, which is much sparser and innervates different cortical regions and layers than the
primary thalamocortical pathway (Koralek et al., 1988; Lu and Lin, 1993).

1.2. Activated versus quiescent states

Several decades ago (Moruzzi and Magoun, 1949), it was shown that electrical stimulation of the brainstem reticular formation (BRF) transforms the slow and large amplitude electroencephalographic activity typical of anesthetized or sleeping animals into the fast and low amplitude activity typical of activated or aroused states. Indeed, the activity measured extracellularly in the neocortex and thalamus during states of vigilance, alertness and attention (i.e., behavioral arousal) is very similar from that observed after BRF stimulation in anesthetized animals, and we use the term *activation* to refer to this activity. This contrasts with the activity measured during sleep or quiescent states, which is very similar to that observed in anesthetized animals not subjected to BRF stimulation. Commonly, these two distinct states are referred to as desynchronized and synchronized states, respectively. However, these terms should be avoided since during activated states cell activity may be more tightly synchronized than during non-activated (quiescent) states. For example, cortical neurons responding to a sensory input may do so more tightly synchronized during activated states than during quiescent states (Munk et al., 1996). Thus, the use of the term desynchronized to refer to activated states seems inaccurate. Instead, we commonly use the terms activated and quiescent states to refer to these two distinct states of electrographic activity. Thus, to further clarify these terms, it should be noted that activation is the electroencephalographic sign of behavioral arousal, which can be produced in anesthetized animals by BRF stimulation, and that behavioral arousal per se can only be studied in behaving un-anesthetized animals.

The thalamocortical network serves a basic function, to acquire, analyze, store and retrieve sensory information; a process called information processing. Sensory information processing mostly occurs during behavioral arousal, a state characterized by vigilance, alertness and attention. During arousal the discharge rate of cells in several brainstem neuromodulatory systems (e.g. norepinephrine, acetylcholine) increases significantly (Aston-Jones et al., 1991, 1994; Steriade et al., 1990; Buzsaki et al., 1988), and since these systems project to the thalamocortical network (Hallanger et al., 1990; Simpson et al., 1997; Bennett-
Clarke et al., 1999; Liu et al., 1995b) the levels of these neuromodulators increase during arousal (Williams et al., 1994a). In general, neuromodulators can affect the response properties of isolated synapses (Thompson et al., 1993; McGehee and Role, 1996; Wu and Saggau, 1997; Miller, 1998), they can alter the intrinsic properties of neurons (McCormick, 1992; Steriade et al., 1993), or they can act at multiple sites in a neural network producing complex effects. There is an ample literature on the effects of these neuromodulators on the intrinsic membrane and firing properties of thalamic neurons. Briefly, application of a variety of neuromodulators to thalamocortical cells results in their depolarization. In contrast, nRt cells are differentially affected by neuromodulators, so that noradrenaline depolarizes these cells while acetylcholine hyperpolarizes them (McCormick, 1992; Steriade et al., 1993). In neocortex, neuromodulators have shown to have different effects depending on the cell type (McCormick and Prince, 1985; Xiang et al., 1998). Interestingly, many of the effects produced in the thalamus and neocortex by neuromodulators released during arousal in behaving animals can be reproduced in anesthetized animals by using BRF stimulation. For example, electrical stimulation in the area of the laterodorsal and pedunculopontine tegmentum in rats (termed here BRF stimulation), which are the main source of cholinergic inputs to the thalamus from the brainstem (Hallanger et al., 1987), transforms thalamocortical activity similarly to application of acetylcholine in the thalamus (Castro-Alamancos, 2002a). Moreover, since neuromodulatory activating systems in the brainstem and basal forebrain are interconnected, electrical stimulation of one of those systems is likely to recruit other neuromodulatory systems, which may also occur during behavior.

Fig. 2 shows a typical example of simultaneously recorded field potential and single-unit activity in VPM and barrel cortex. The activity of two cortical cells from layers IV-III and a VPM cell are shown before, during and after activation or arousal caused by BRF stimulation (100 Hz, 1 s; gray box) in a urethane anesthetized rat. During activation the VPM cell (cell 3) robustly enhanced its firing rate, which is typical of all VPM cells. Meanwhile the simultaneously recorded cortical cells either suppressed (cell 1) or enhanced their spontaneous firing rate (cell 2). Also, the high amplitude slow activity characteristic of field potentials during quiescent states is transformed into low amplitude fast activity during activation. Based on Castro-Alamancos and Oldford (2002).
One way to conceive the functioning of thalamocortical cells with regards to the transmission of sensory information is like an electrical relay, in which the primary sensory inputs from thelemniscal pathway are regulated by the other afferents, such as the fibers from the nRt and from BRF. Electrical relays allow the transmission of a signal when another current activates the relay at a different input, thus regulating the output of the relay. This seems to be the operation of thalamocortical cells. Thus, the main role of thalamocortical neurons is to relay sensory inputs to the neocortex according to the regulations dictated by behavioral state. These regulations are imposed by neuromodulators that are released in the thalamus mainly by afferents from the BRF. Traditionally, the state-dependent relay of sensory information to the neocortex through the thalamus has been studied within the context of two firing modes of thalamocortical cells, the bursting mode and the tonic mode (Steriade et al., 1997; Sherman and Guillery, 1996). The bursting mode is mainly associated with states of slow-wave sleep (Guido and Weyand, 1995) and deep anaesthesia (although its relevance during awake states is also hotly debated (Sherman, 2001; Steriade, 2001)). In contrast, the tonic-firing mode is mainly associated with waking and alertness. The significant work that has lead to establishing the dichotomy between bursting and tonic firing as modes of thalamocortical relay function has placed little relevance on the properties of thalamic and cortical synapses. Nevertheless, computational studies indicate that synaptic properties (e.g., short-term plasticity) are crucial in determining the mode of processing in neural networks (Tsodyks et al., 1998; Abbott et al., 1997). In fact, while thalamocortical cells are in the tonic-firing mode synaptic mechanisms may be essential to set the thalamocortical network in different information processing modes.

In the last few years we have studied how the different connections of the thalamocortical network are affected by the state of the subject, and in particular how they are affected by activated states. In the long term, the major question to decipher is what differences exist in the thalamic and neocortical pathways between being awake and being attentive. An initial question is how the different pathways in the thalamocortical network are affected by activation and behavioral arousal. This review discusses recent work illustrating the changes in temporal and spatial response properties that take place during transitions between quiescent and information processing states in the three main pathways received or produced by thalamocortical neurons of the rodent vibrissae system: lemniscal, corticothalamic and thalamocortical pathways.

2. Primary sensory lemniscal pathway

The rodent whisker thalamus receives its primary sensory input from the principal trigeminal nucleus through the medial lemniscus tract. In addition, the spinal trigeminal nucleus also sends a projection to the thalamus (Spacek and Lieberman, 1974; Feldman and Kruger, 1980; Chiaia et al., 1991a; Williams et al., 1994b; Diamond, 1995; Veinante and Deschenes, 1999; Veinante et al., 2000). Between 70 and 90% of the axons originating in the principal trigeminal nucleus innervate the upper two thirds of VPM. The other 10–30% of fibers originating in the principal nucleus innervates PoM and the colliculus. Cells in the three spinal trigeminal nuclei (i.e. oralis, interpolaris and caudalis) also project to the whisker thalamus. Few axons from oralis innervate the thalamus, and those that do go to PoM. Two types of axons originate in interpolaris; fast conducting thick axons go to PoM while slowly conducting thin axons go to VPM. The caudalis nucleus also produces axons projecting to VPM that are similar to the slow conducting axons of interpolaris. Interestingly, despite the fact that the principal trigeminal nucleus and two of the spinal nuclei (interpolaris and caudalis) project to VPM, these axons do not overlap so that there seems to be no convergence of principal and spinal information in the VPM as discussed ahead.

Cytochrome oxidase (CO) staining in VPM reveals rod-like structures that transverse the dorsal part of the nucleus and are called barreloids (Land et al., 1995). Retrograde labeling of thalamic barreloids by tracer injections in a single cortical barrel reveals rod-like structures consisting of a core, which corresponds to the rod structures revealed with CO staining, plus a tail that extends ventrolaterally in VPM and is lightly CO stained (Saporta and Kruger, 1977). The principal trigeminal nucleus projects mainly to the dorsomedial portions of VPM, to the core of barreloids, while spinal axons project to ventrolateral portions of VPM, to the tails of barreloids, where projections from the principal nucleus are sparse (Williams et al., 1994b; Pierret et al., 2000; Veinante et al., 2000). Thus, in the core of a thalamic barreloid, a VPM neuron receives its sensory input primarily from cells in the principal trigeminal nucleus and this VPM cell projects to a corresponding barrel in cortex. In contrast, the spinal projection to VPM forms a parallel stream because it does not innervate cells in the core of a barreloid; instead these axons contact a population of cells in the tail of a barreloid. Moreover, the thalamocortical cells in these barreloid tails do not project to a cortical barrel; instead they project sparsely to areas outside a barrel column (i.e. dysgranular zones or septal regions) and more heavily to the secondary somatosensory area (Pierret et al., 2000). The present review deals with the properties of lemniscal synapses contacting VPM cells in barreloid cores, which are formed by fibers that originate in the principal trigeminal nucleus.

2.1. Morphology of lemniscal synapses

Lemniscal terminals form glutamatergic synaptic contacts with the soma and proximal dendrites of VPM
neurons (De Biasi et al., 1994; Williams et al., 1994b). At the electron microscope level, lemniscal synapses form complex synaptic connections called synaptic glomeruli (Fig. 3) consisting of a synaptic arrangement in which axonal and dendritic components are ensheathed by glial cell processes (Spacek and Lieberman, 1974). Several elements are involved (see Fig. 3): (1) a postsynaptic dendrite (D) which produces prominent excrescences (E) or protrusions; (2) a large axon terminal (A) deeply invaginated by the excrescences that contains spherical synaptic vesicles and makes multiple synaptic contacts or release sites (R) on the dendritic excrescences but no synaptic contacts with the dendritic shaft; (3) a small number of synaptic terminals (F) that contained flattened synaptic vesicles and make contacts with the dendritic shafts at the periphery and immediately adjacent to the glomerulus, which likely consist of inhibitory inputs from the nRt and modulatory inputs from the brainstem reticular formation; (4) the postsynaptic excrescences-presynaptic lemniscal fiber complex is surrounded by glial processes (G), which may serve to limit the spread of glutamate and may also limit the influence of other neurotransmitters on lemniscal synapses. A fully reconstructed glomerulus of the rat somatosensory thalamus was found to be 5 μm in diameter, in which two dendrites produced a total of 10 excrescences receiving a total of 44 synaptic contacts (Spacek and Lieberman, 1974). Thus, each lemniscal synaptic glomerulus forms a large number of closely spaced synaptic contacts or release sites. This, in combination with the proximal location on the dendrite, combines to produce a very powerful synaptic input.

2.2. Electrophysiology of lemniscal synapses

Lemniscal synapses of adult rodents studied in vitro (Fig. 4) produce short latency, fast-rising, large amplitude, highly secure all-or-none EPSPs, which depress in response to repetitive stimulation at frequencies above 2 Hz (Castro-Alamancos, 2002b). Although further work is needed to decipher the reasons why lemniscal synapses present these specific properties, current knowledge of synaptic transmission and lemniscal synapses suggests the following scenario:

1) The short latency of lemniscal EPSPs is likely due to fast conducting large-caliber myelinated lemniscal axons, and also presumably due to the optimization of the molecular steps responsible for fast synaptic transmission at these synapses.

2) The rise time of the EPSP for synapses that are electrotonically close to the soma, such as lemniscal synapses, is a function of the rate of rise of glutamate release.
4) Synapses display a wide range of activity-dependent response properties. At many synapses, when two action potentials depolarize a presynaptic terminal in rapid succession, the second action potential releases more neurotransmitter than the first producing synaptic facilitation (Zucker, 1989). In contrast, other synapses display decreased efficacy with repeated use that lasts from several hundred milliseconds to seconds, called short-term synaptic depression (Zucker, 1989). The mechanisms by which synapses produce short-term depression are not entirely elucidated, and different synapses may have different mechanisms involved, such as inhibition of Ca$^{2+}$ channels through metabotropic receptors (Takahashi et al., 1996), depletion of docked vesicles (Stevens and Tsujimoto, 1995), and desensitization of postsynaptic receptors (Trussell et al., 1993). Repetitive stimulation of lemniscal fibers at frequencies above 2 Hz produces robust frequency-dependent depression of lemniscal EPSPs (Castro-Alamancos, 2002b). The depression of lemniscal synapses may be related to their high release probability. In fact, several lines of evidence suggest that this may be the case. First, evidence from other systems indicate that synapses with high release probability tend to display synaptic depression (Zucker, 1989; Debanne et al., 1996; Castro-Alamancos and Connors, 1997a; Gil et al., 1999). Second, the structure of synaptic terminals usually correlates with release probability, so that the volume of the presynaptic terminal correlates with the size and number of its active zones, docked vesicles and release probability (Korn and Faber, 1991; Pierce and Lewin, 1994; Schikorski and Stevens, 1997). As described above, lemniscal synapses form large size terminals with numerous closely spaced release sites (Spacek and Lieberman, 1974), which is suggestive of a high release probability. As discussed below, these specialized properties of lemniscal synapses serve to endow the lemniscal pathway with useful mechanisms for the transmission of sensory inputs through the thalamus.

2.3. Effects of neuromodulators on lemniscal synapses

Neuromodulators are involved in a broad range of brain functions. They have been implicated in the control of arousal states and they may be important for attentive and memory processes (e.g. Buzsaki et al., 1988; Singer, 1977; Aston-Jones et al., 1991; Sillito et al., 1983; Steriade et al., 1997; Hasselmo and Bower, 1993; Bakin and Weinberger, 1996). Apart from the excitatory glutamatergic synaptic connections in the thalamus (corticothalamic and lemniscal), there are several major regulatory systems.

Among them are the noradrenergic and cholinergic fibers originating in the brainstem (Simpson et al., 1997; Hallanger et al., 1987; Satoh and Fibiger, 1986), and the GABAergic fibers originating in the nRt (Ohara and Lieberman, 1985). GABA is released in the VPM by the nRt terminals and produces well-characterized postsynaptic effects. Receptor proteins corresponding to different neuromodulatory systems have been found on these pathways (Vidnyanszky et al., 1996; Broide et al., 1995; Vogt et al., 1992), providing a site for neuromodulation.

A recent study found that lemniscal synapses are insensitive to acetylcholine and norepinephrine (Castro-Alamancos, 2002b). That is, application of these neuromodulators, or the respective receptor agonists, do not affect the amplitude of lemniscal EPSPs evoked in thalamocortical cells that are recorded with intracellular solutions used to block the postsynaptic actions produced by these neuromodulators. On the other hand, activation of GABA$\_B$ receptors seems to depress lemniscal synapses (Emri et al., 1996). Although the site of GABA effects (pre- or postsynaptic) has not been established, these observations suggest that lemniscal inputs are quite selective about the neuromodulators that affect them. Despite the apparent absence of presynaptic effects, neuromodulators such as norepinephrine and acetylcholine have profound effects on the efficacy of the lemniscal pathway because of the postsynaptic actions produced by these neuromodulators on thalamic cells. Thus, the postsynaptic depolarization produced by these neuromodulators influences how effective lemniscal EPSPs are in driving thalamocortical neurons. This depolarization allows the relay of lemniscal inputs at high-frequency rates by bringing the depressed lemniscal EPSPs close to firing threshold (Castro-Alamancos, 2002b), which has important
consequences for the transmission of sensory information in vivo as discussed below.

2.4. Sensory responses mediated by lemniscal synapses

The properties displayed by lemniscal EPSPs in slices (Castro-Alamancos, 2002b) are also present in vivo (Castro-Alamancos, 2002a). Intracellular recordings in vivo reveal that whisker stimulation produces a short latency, fast-rising, large amplitude EPSP followed by a longer latency GABAergic IPSP in some VPM cells, and only an IPSP in other VPM cells (see Fig. 5) (Castro-Alamancos, 2002a; Brecht and Sakmann, 2002). In rodent VPM, the IPSPs are generated by feedback inhibition from the nRt because there seem to be no inhibitory interneurons within the ventrobasal thalamus of rodents (Spacek and Lieberman, 1974; Barbaresi et al., 1986; Harris and Hendrickson, 1987; Ohara and Lieberman, 1993). The EPSP–IPSP sequence occurs in cells that are contacted directly by lemniscal fibers representing the stimulated whisker, while the IPSP-alone responses correspond to cells that are in a different barreloid and are not directly innervated by the lemniscal fibers for the stimulated whisker but that receive recurrent inhibition from nRt (cross-inhibition) as a consequence of the whisker stimulation. nRt cells seem to project to VPM in a closed-loop pattern, meaning that they project back to the barreloid from where they receive excitation (Desilets-Roy et al., 2002). Thus, nRt axons entering adjacent barreloids do not seem to provide the source for cross-inhibition between barreloids. However, VPM cells extend their dendrites into adjacent barreloids where they can sample recurrent inhibition evoked by adjacent whiskers and this may well be a substrate for cross-inhibition (Varga et al., 2002; Lavallee and Deschenes, 2004). In addition, it is likely that the excitation received by a population of nRt cells from a barreloid spreads within nRt by means of intra-nRt connections (Sohal and Huguenard, 2003; Shu and McCormick, 2002) and gap junctions (Landisman et al., 2002), leading to the stimulation of nRt cells that project to other barreloids, which could also explain cross-inhibition between barreloids and, thus, between whiskers.

Generally, whisker stimulation evokes few large amplitude unitary lemniscal events (~2) on a given VPM neuron, suggesting that VPM neurons are contacted by few lemniscal fibers (Castro-Alamancos, 2002a,b; Deschenes et al., 2003). These events usually have a slight difference in latency and sum to produce a larger composite lemniscal EPSP that very effectively drives a VPM neuron during low frequency stimulation. The characteristics of lemniscal EPSPs endow the lemniscal pathway with a powerful capacity to drive thalamocortical neurons, so that in deeply anesthetized animals receiving low frequency stimuli (<2 Hz), the principal whisker is able to drive a VPM cell on ~80% of trials. Interestingly, during activated states caused in anesthetized animals by BRF stimulation or by the application of neuromodulators to the thalamus, the same
sensory stimulus is able to drive the thalamocortical cell on 100% of the trials (Castro-Alamancos, 2002a; Castro-Alamancos and Oldford, 2002). Differences in sensory transmission through the lemniscal pathway during different behavioral states are more dramatic for the transmission of high frequency sensory inputs, as described ahead.

2.4.1. Temporal response properties

In anesthetized rats, thalamocortical neurons follow high frequency whisker stimulation with great difficulty; thalamocortical neurons are low-pass filtered. Only low frequency inputs are relayed to the neocortex in anesthetized rats. This process is also called rapid sensory adaptation and it is a property shared by other sensory systems, such as for example the visual system (Nelson, 1991a). However, there are significant differences among studies regarding the cut-off frequency for this low-pass filter or sensory adaptation. Some studies report strong frequency-dependent depression at frequencies above 5 Hz (Diamond et al., 1992b; Lee et al., 1994b), others at 2 Hz (Ahissar et al., 2000), while others report the ability to follow frequencies of up to at least 12 Hz (Simons, 1985; Simons and Carvell, 1989; Hartings and Simons, 1998). In urethane-anesthetized rats, thalamic neurons are low-pass filtered so that whisker stimulation above 2 Hz is not relayed to neocortex (Castro-Alamancos, 2002a). However, when the thalamus of anesthetized rats is aroused by BRF stimulation or by applying acetylcholine to the thalamus, the lemniscal low-pass filter is significantly opened allowing the relay of sensory inputs at much higher frequencies. Indeed, during activated states VPM cells can follow whisker stimulation fairly efficiently at frequencies of up to 40 Hz, and even 100 Hz (Fig. 6). Thus, during activated states of the thalamus typical of information processing, the low-pass filtering of sensory inputs is largely eliminated (Castro-Alamancos, 2002a).

The underlying cause of this low-pass filter during quiescent states has been studied in the VPM both in vivo and in vitro. Intracellular recordings in vivo in urethane anesthetized rats revealed that lemniscal synapses present robust frequency-dependent depression, so that whisker stimulation at frequencies above 2 Hz depresses lemniscal EPSPs (Castro-Alamancos, 2002a,b). The activity-dependent synaptic depression is translated into the low-pass filtering of sensory inputs through the thalamus (Castro-Alamancos, 2002a). Sensory inputs at frequencies above 2 Hz reduce the efficacy of lemniscal synapses, which drives the lemniscal EPSP away from the discharge threshold of the cell resulting in a low probability of firing for thalamocortical cells. These properties are likely shared by other primary sensory afferents in the thalamus, such as retino-geniculate synapses (Turner and Salt, 1998), and the sensory adaptation observed in the visual thalamus may also be caused by the activity-dependent synaptic depression of retina-geniculate synapses.

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**Fig. 6.** Effects of acetylcholine on whisker evoked responses in VPM neurons. (A), Upper plots correspond to counts per 2-ms bins evoked by 15 whisker stimuli (30 trials) at different frequencies during quiescent states in urethane-anesthetized rats. Lower plots correspond to the same stimuli during application of acetylcholine in VPM. Note the strong low-pass filtering of VPM responses at frequencies above 2 Hz, but not during application of acetylcholine. (B) Example of whisker stimulation delivered at 66 Hz and at 100 Hz during acetylcholine. Notice that the cell is able to follow these high frequencies during application of acetylcholine in VPM. (C) Population data showing a spectrum analysis of whisker evoked responses in VPM neurons before and during the application of acetylcholine. Based on Castro-Alamancos (2002a).
The reason why this low-pass filter is eliminated during activated states could be that the activity-dependent depression of lemniscal EPSPs (i.e., synaptic depression) is eliminated by neuromodulators that are released during arousal. This hypothesis was examined using thalamic slices in vitro. As discussed above (see Section 2.3), lemniscal EPSPs are insensitive to the effects of acetylcholine and norepinephrine, and thus this hypothesis is not supported (Castro-Alamancos, 2002b). However, these modulators have well recognized postsynaptic actions on thalamocortical neurons; they depolarize thalamocortical neurons (McCormick, 1992; Steriade et al., 1997). The postsynaptic depolarization of thalamocortical neurons produced by these neuromodulators is sufficient to eliminate the effect of synaptic depression on the relay of high frequency inputs (Fig. 7). Indeed, synaptic depression is effective at suppressing the transfer of lemniscal inputs when neurons are sufficiently hyperpolarized within the tonic firing mode. In contrast, if the neuron is depolarized closer to its firing threshold it can overcome the depression and relay sensory inputs at high frequency. Thus, because of synaptic depression the relay of sensory information through the lemniscal pathway requires sufficient postsynaptic depolarization to overcome synaptic depression (Castro-Alamancos, 2002b). When these two events coincide (lemniscal release and postsynaptic depolarization) the relay of sensory information is warranted for high frequency inputs. This interaction between synaptic depression and postsynaptic depolarization was also demonstrated in vivo using whisker stimulation (Castro-Alamancos, 2002a). These results serve to explain why in anesthetized rats some studies have shown that thalamocortical neurons can follow whisker stimulation up to 12 Hz (Simons, 1985; Simons and Carvell, 1989; Hartings and Simons, 1998), while other studies report strong frequency-dependent depression at frequencies above 5 Hz (Diamond et al., 1992b) or 2 Hz (Ahissar et al., 2000). These discrepancies are explained by the anesthetic state of the preparation, and in particular the membrane potential of thalamocortical neurons. The more efficient frequency following of lemniscal sensory inputs during activated states as compared to quiescent states would result from the depolarization of thalamocortical neurons caused by the release of neuromodulators in the thalamus, which serves to bring depressed lemniscal EPSPs close to firing threshold.

It is worth mentioning that, in anesthetized cats, lateral geniculate nucleus (LGN) cells have been reported to show a strong paired-spike facilitation to fast incoming retinal inputs (Usrey et al., 1998). That is, when two retinal spikes arrive in close succession the second one discharges the LGN cell with high probability. This phenomenon seems to occur when the first retinal spike generally fails to discharge the LGN cell and when the second retinal spike occurs rapidly after the first retinal spike (<30 ms). This time course reflects the time constant of the EPSP produced by primary sensory afferents (lemniscal or retinal-geniculate) (Castro-Alamancos, 2002b; Turner and Salt, 1998). In this case, the first retinal spike produces a large EPSP in the LGN cell that is just subthreshold for spike generation, and a second EPSP caused by the second retinal spike will be strongly depressed due to synaptic depression, but because it arrives during the time course of the first EPSP (temporal summation) both sum and reach firing threshold only in response to the second retinal spike. This phenomenon might be less common during activated states, when thalamic cells respond with very high reliability to stimulation of their receptive fields, and thus would be unlikely to fail to the first retinal spike.

Thalamocortical cells operate mainly in two different firing modes: bursting and tonic firing (Steriade et al., 1997; Sherman and Guillery, 1996). In the bursting mode, neurons respond robustly to low frequency lemniscal stimuli with a burst of action potentials (see Fig. 7) but are unable to follow at frequencies above 2 Hz. In contrast, in the tonic mode, the firing of thalamic neurons is highly reliable for every stimulus delivered at frequencies up to 100 Hz (Fig. 6). Thus, in the tonic mode, lemniscal inputs seem to be able to overcome synaptic depression because the membrane potential is placed close to firing threshold. Thalamocortical neurons are unable to follow high frequency lemniscal

![Fig. 7. Voltage-dependency of the low-pass filtering of lemniscal inputs within the tonic firing mode in slices. Four lemniscal stimuli are applied at 10 Hz. The neuron is placed at different membrane potentials in the bursting mode (bottom trace) or in the tonic mode (upper traces). Note that due to lemniscal synaptic depression the cell only responds with an action potential to the first stimulus unless the cell is sufficiently depolarized within the tonic firing mode. Based on Castro-Alamancos (2002b).]
inputs in the burst mode because of the properties of the currents involved in burst generation (McCormick and Feeser, 1990; Sherman, 1996). It is important to note that the suppression of high frequency lemniscal inputs does not require thalamocortical neurons to be in the bursting mode. Indeed, synaptic depression is effective at suppressing the transfer of lemniscal inputs when neurons are sufficiently depolarized so they are not in the bursting mode (Castro-Alamancos, 2002b). Within the tonic mode, the suppression of lemniscal inputs is expressed when the neuron is sufficiently hyperpolarized so that the depressed lemniscal EPSPs do not reach action potential generation threshold. When the neuron is depolarized closer to the firing threshold it can overcome the depression and relay sensory inputs at high frequency (Fig. 7). Within the tonic firing mode, the relay of sensory information through the lemniscal pathway requires sufficient postsynaptic depolarization to overcome synaptic depression. Thus, neuromodulators play an essential role in the transmission of inputs through the lemniscal pathway by setting the level of postsynaptic depolarization within the tonic firing mode.

Since IPSPs mediated by the nRt follow lemniscal EPSPs (Castro-Alamancos, 2002a; Brecht and Sakmann, 2002), an important issue relates to the role played by the nRt in the relay of high-frequency sensory inputs. The long duration of IPSPs may affect the responses to trains of stimuli delivered at relatively high frequencies. This is supported by finding that lesions of nRt (Lee et al., 1994a) or blocking GABA receptors in the thalamus (Lee et al., 1994b; Castro-Alamancos, 2002a) alter the responses of VPM neurons to sensory inputs. Hence, the nRt must play an important role in defining the response properties of VPM neurons. nRt neurons produce responses to sensory stimuli that are different from those of VPM neurons; nRt neurons respond to a single whisker deflection (Fig. 8) with a stronger and longer lasting response than VPM neurons (Hartings et al., 2000). VPM neurons respond weakly to sustained deflections, and responses to maintained deflections are only unmasked in VPM by the application of GABA receptor antagonists (Hartings and Simons, 2000).

Recent work has also shown that the responses of nRt neurons to sensory stimuli during tonic and burst firing...
mocortical neurons is not suf- 


circumstances postsynaptic depolarization alone of thala-


neurons alone produced by current injection is insuf-


tions could last for up to one second and are caused by the oscillatory activity of nRt neurons (Fig. 8). Thus, a single whisker deflection causes nRt neurons to oscillate at the spindle oscillation frequency (≈10 Hz). Consequently, VPM neurons are bombarded by IPSPs at ≈10 Hz for ≈500–1000 ms after a single whisker stimulus (Fig. 8). These IPSPs can successfully filter successive sensory inputs arriving during the initial ≈800 ms after the first stimulus, even if the VPM neuron is depolarized by current injection. This indicates that during quiescent states, in which nRt neurons respond to a sensory stimulus with a spindle oscillation, subsequent sensory input at high frequencies (the interval corresponding to the duration of the spindle sequence) can be shunted by feedback inhibition from the nRt. This, together with lemniscal synaptic depression, may well serve as a mechanism that disconnects thalamocortical neurons from high frequency sensory activity in the external world during quiescent states and certain stages of sleep, while still allowing a low frequency communication line with the external world.

Notably, the robust and sometimes oscillatory feedback IPSPs from the nRt only occur during deep anesthesia and not during activated states (Fig. 9). During activated states, such as those caused by BRF stimulation, IPSPs are strongly reduced but not absent (Castro-Alamancos, 2002a). This is caused by several factors: (1) nRt neurons change their state from burst to tonic firing, resulting in the consequent reduction in IPSP amplitude and duration (Kim and McCormick, 1998); (2) GABAergic IPSPs are suppressed in the ventrobasal thalamus by acetylcholine (Fig. 9) and norepinephrine (Castro-Alamancos, 2002b); (3) Certain neuromodulators such as acetylcholine hyperpolarize nRt neurons (Ben Ari et al., 1976; McCormick and Prince, 1986), and thus would inhibit their discharge. Thus, the amplitude and duration of feedback IPSPs is strongly reduced during activated states and consequently, they do not oppose the relay of sensory inputs by lemniscal EPSPs during arousal. The changes in response properties of nRt neurons (Hartings et al., 2003) and the change in size and duration of evoked IPSPs in VPM work favorably for the relay of sensory inputs through VPM. When this occurs the only obstacle for sensory transmission of high frequency sensory inputs to the neocortex is lemniscal synaptic depression, which can be overcome by postsynaptic depolarization of VPM neurons caused by the release of neuromodulators during arousal. Thus, the sharper IPSPs that occur during activated states may well serve to sharpen the excitatory response and allow the transmission of high frequency sensory inputs.

2.4.2. Spatial (receptive field) response properties

Recent studies in vivo and in slices indicate that VPM neurons are contacted by few (1–3) lemniscal fibers (Castro-Alamancos, 2002a,b; Deschenes et al., 2003), each of them giving rise to a large amplitude EPSP with the properties described above. Early studies that recorded from VPM neurons in anesthetized rats indicated that they respond solely to a single whisker (e.g. Chiaia et al., 1991a; Rhoades et al., 1987; Waite, 1973; Shosaku, 1985). However, more recent work has revealed that under light anesthesia VPM cells respond to deflections of multiple whiskers (Arm-
Sakmann, 2002), and therefore may be especially susceptible to a modulation by feedback IPSPs from the nRt.

The origin of the principal whisker responses in VPM cells is the principal nucleus of the trigeminal complex, but the origin of the longer latency adjacent whisker responses is less clear. There are several possible sources for the origin of adjacent whisker responses found in VPM during activated states:

1) One explanation may be that the dendrites of VPM neurons, which extend beyond the area of a single barreloid (Chiaia et al., 1991b; Varga et al., 2002; Harris, 1986; Ohara and Havton, 1994) integrate information from lemniscal inputs arriving at adjacent barreloids. The major problem with this hypothesis is that recent work has revealed that lemniscal synapses are absent on extra-barreloid dendrites (Varga et al., 2002).

2) Corticothalamic feedback may contribute to adjacent whisker responses in VPM. A large percentage of adjacent whisker responses occur at latencies that would allow for the signal to travel to cortex and return to thalamus via corticothalamic fibers (Minnery et al., 2003). The major problem with this hypothesis is that recent work indicates that corticothalamic feedback seems to form a closed loop somatotopically-precise barrel-to-barreloid connectivity (Temereanca and Simons, 2004), which cannot account for the origin of adjacent responses because according to this connectivity scheme VPM neurons primarily receive cortical information from the whisker they represent.

3) Several studies have proposed that the longer latency adjacent whisker responses in VPM reflect an input from the spinal trigeminal nucleus, and in particular, from the subnucleus interpolaris (Armstrong-James and Callahan, 1991; Friedberg et al., 1999; Lee et al., 1994a; Rhoades et al., 1987). It is well established that cells in the subnucleus interpolaris project to VPM (Chiaia et al., 1991b; Erzurumlu and Killackey, 1980; Pierret et al., 2000; Veinante et al., 2000; Williams et al., 1994b), have multiwhisker receptive fields (Jacquin et al., 1989, 1986) and have slower conducting axons than those originating in the principal trigeminal nucleus (Veinante et al., 2000). However, the major problem with this hypothesis is that, as discussed above (see Section 1.1), the spinal and principal trigeminal inputs to VPM do not overlap (Pierret et al., 2000; Williams et al., 1994b). Inputs to VPM from the subnucleus interpolaris are sparse and target the tails of barreloids in the ventral lateral region of VPM, while inputs from the principal nucleus target the core of barreloids in the dorsomedial portion of VPM. Thus, a direct pathway from the spinal nucleus to VPM is unlikely the origin of multiwhisker receptive fields in most VPM neurons.

4) Recent work has demonstrated that, in lightly anesthetized rats, cells in the principal trigeminal nucleus have multiwhisker receptive fields just like cells in VPM (Minnery and Simons, 2003), and that principal nucleus responses can fully account for the multiwhisker receptive fields found in VPM (Minnery et al., 2003). Thus, the question now becomes what is the origin of multiwhisker receptive fields in the principal trigeminal nucleus? Morphological studies have identified a dense plexus of intersubnuclear connections linking the different spinal trigeminal subnuclei with the principal trigeminal nucleus (Jacquin et al., 1990). It is possible that these connections provide the substrate for multiwhisker responses in the principal trigeminal nucleus, and recent evidence indicates that this is the case (Timofoeva et al., 2004).

A related question is: why do multiwhisker responses emerge in VPM during activated states? A major problem with answering this question is that there are no studies comparing the responses of principal trigeminal nucleus neurons and those of VPM neurons during different behavioral states. Thus, it is not currently possible to ascertain if the large receptive fields of VPM neurons arise during activated states as a consequence of thalamic mechanisms or because those same receptive fields also appear in the trigeminal nucleus during activated states and are absent during non-activated states. One possibility is that principal trigeminal receptive fields respond to one whisker during quiescent states and only during activated states do multi-whisker receptive fields arise. Alternatively, multiwhisker receptive fields may be present in the principal trigeminal cells during both quiescent and activated states, with little changes between these states. In this case, the origin of large receptive fields in the VPM would be caused by thalamic mechanisms that suppress multiwhisker responses during quiescent states while enhancing them during activated states. Further work should explore these issues.

Feedback inhibition mediated by the nRt should affect thalamocortical receptive fields. In particular, these long latency IPSPs are well suited to modulate the longer latency adjacent whisker responses. A recent study performed intracellular recordings from VPM cells of urethane-anesthetized young rats (P16–24) and mapped their...
subthreshold receptive fields (Brecht and Sakmann, 2002). Under these conditions, VPM neurons respond to a principal whisker with action potentials while the surrounding whiskers produced either subthreshold excitatory or inhibitory responses. One possibility is that the excitatory responses of adjacent whiskers are strongly shunted by inhibition, and so a mechanism of recurrent inhibition would lead to single whisker receptive fields.

In lightly anesthetized animals, when VPM cells respond to multiple whiskers, recurrent inhibition from the nRt is also present in VPM as determined using single-unit extracellular recordings but it is a weak phenomenon that does not seem to counteract excitation (Minnery et al., 2003). This may be due to the fact that during activated states, VPM IPSPs driven by whisker deflections are strongly reduced (Fig. 9) both in vivo and in vitro (Castro-Alamancos, 2002a,b). One possible scenario is that during quiescent states, strong recurrent IPSPs serve to suppress adjacent whisker responses by shunting EPSPs from adjacent whiskers. During activated states, because of the postsynaptic depolarization and the reduction of inhibition, the excitatory responses of adjacent whiskers would remain unchallenged and receptive fields would consequently enhance. Further work should explore this possibility.

2.5. Functional relevance during behavior

These results indicate that synaptic depression of lemniscal EPSPs and the level of depolarization of thalamocortical neurons work together in thalamic primary sensory pathways to suppress high-frequency sensory inputs during non-activated (quiescent) states while permitting the faithful relay of high-frequency sensory information during activated (processing) states. Work conducted in awake behaving animals indicates that this in fact occurs during behavior. Poggio and Mountcastle (1963) demonstrated that the capacity for frequency following of tactile stimuli is dramatically different for thalamic cells in the waking as compared to the anesthetized monkey. More recent work in the freely behaving rat using electrical stimulation of the infraorbital nerve has shown that pairs of stimuli delivered at frequencies above 10 Hz were suppressed during quiescent states, but not during active exploration (Fanselow and Nicolelis, 1999). In unanesthetized rabbits, arousal measured as increased hippocampal theta has been shown to markedly facilitate the sustained responses of LGN neurons to constant stimulation of the center of the receptive field (Swadlow and Weyand, 1985). If the reduction of the sustained responses is caused by retinogeniculate depression, then these results could also indicate the elimination of retinogeniculate depression during arousal.

Taken together, these results suggest that one way the thalamus gates the flow of sensory inputs to the neocortex is by filtering high-frequency sensory inputs during quiescent states, while allowing them to flow through during activated states. It is noteworthy that this gating occurs during the tonic-firing mode of thalamocortical neurons. In the tonic mode, the interaction between postsynaptic depolarization (within the membrane potential range of tonic firing) and synaptic depression serves to regulate the flow of sensory inputs through the thalamus. On a speculative note, this mechanistic interaction occurring within the tonic firing mode could underlie the differences between being awake and being attentive. In the bursting mode, during deep sleep and deep anesthesia, low frequency sensory inputs trigger low-threshold calcium spikes in thalamocortical neurons that either completely fail to discharge the cell or trigger a burst of action potentials, while high frequency sensory inputs are unable to trigger repetitive bursting because of both synaptic depression and the properties of the currents involved in generating low-threshold calcium spikes.

3. Corticothalamic pathway

The thalamus receives a massive input from the neocortex via corticothalamic fibers. The number of corticothalamic fibers is one order of magnitude larger than the number of thalamocortical axons, and cortical afferents to the thalamus largely outnumber the primary sensory input from peripheral receptors (Guillery, 1969; Sherman and Guillery, 1996; Steriade et al., 1997). Considering the massiveness of the corticothalamic pathway it must serve an important function. However, detailing a clear role for corticothalamic activity has been difficult. In fact, most studies have found small effects on thalamic responsiveness when the neocortex was inactivated (e.g., Baker and Malpeli, 1977). As discussed later, this may be due to the frequency-dependent properties of the corticothalamic pathway; this pathway is expressed strongly only when high frequency activity flows through it. Some processes believed to be mediated by corticothalamic activity are: (1) corticothalamic activity could serve as a modulatory system that serves to change the firing rate, mode, and excitability of thalamic neurons. For instance, glutamate released by corticothalamic fibers may serve to shift the firing between burst and tonic modes of firing by affecting the membrane potential of thalamic neurons (Sherman, 1996; McCormick and von Krosigk, 1992). It is also possible that corticothalamic activity regulates the firing of thalamocortical cells by activating the nRt, resulting in a tonic inhibition of TC cells via feedforward inhibition; (2) corticothalamic activity may specifically affect the spatial and temporal properties of thalamocortical receptive fields (e.g. Murphy et al., 1999; Singer, 1977; Diamond et al., 1992a; Yuan et al., 1985; Krupa et al., 1999). For instance, there is evidence that corticothalamic activity serves to spatially focus thalamocortical receptive fields, presumably by enhancing the inhibitory surround through activation of the nRt and/or by
enhancing the excitatory center (Murphy and Sillito, 1987; Temereanca and Simons, 2004; Ergenzinger et al., 1998). There is also evidence that the gain and timing of thalamic sensory responses may be affected by corticothalamic activity (reviewed in Sherman and Koch, 1986; Singer, 1977). In the somatosensory system, thalamocortical cells follow more effectively repetitive stimulation in the presence of corticothalamic activity (Yuan et al., 1985). In the visual system, corticothalamic activity may also serve to synchronize thalamocortical cells in the LGN as cells respond to single elongated stimuli (Sillito et al., 1994). There is no doubt that further work is required to clarify the functional role of corticothalamic activity.

3.1. Morphology of corticothalamic synapses

Corticothalamic pathways arise from pyramidal cells in layers V and VI of neocortex (Fig. 1). Corticothalamic fibers originating from layer V consist of fiber collaterals from long range axons projecting to the brainstem and/or spinal cord. These collaterals do not contact the nRt or VPM. Instead they project to intralaminar and higher order associational nuclei, such as POM in the vibrissa system, where they form small clusters of large terminals (Deschenes et al., 1998; Sherman and Guillery, 1996). The large terminals innervate proximal dendrites of thalamic neurons and form complex synaptic glomeruli that are similar to those formed by primary sensory (lemniscal) synapses (Jones and Powell, 1969; Li et al., 2003b). In contrast, the corticothalamic fibers originating from layer VI leave a fiber collateral in the nRt on their way into VPM (i.e., primary sensory nuclei) where they produce small terminals that innervate the distal dendrites of thalamic neurons (Robson, 1983; Li et al., 2003b; Bourassa et al., 1995; Zhang and Deschenes, 1997; Erisir et al., 1997b; Jones and Powell, 1969). The small terminals formed by layer VI corticothalamic fibers have a small postsynaptic density that is consistent with the presence of a single release site. On nRt cells, these synapses are formed in more or less equal numbers over proximal and distal dendrites, while on thalamocortical cells they occur preferentially at distal dendrites (Jones, 2002). On nRt cells, as many as 70% of all the synapses are corticothalamic, while the remaining 30% are about equally distributed between GABAergic synapses and synaptic collaterals of thalamocortical cells; synapses from the brainstem and basal forebrain form a very small number of contacts (Liu and Jones, 1999). In primary thalamic nuclei, approximately 44% of the synapses are corticothalamic, while about 16% originate from primary sensory afferents and the rest correspond primarily to inhibitory synapses from the nRt plus a portion of neuromodulatory afferents from the brainstem (Liu et al., 1995a; Erisir et al., 1997b).

It has been estimated that about half of the pyramidal cells in layer VI project to the thalamus (Eydin et al., 2003), and there seems to exist two distinct populations of corticothalamic cells within layer VI. In the barrel cortex, cells in the upper part of layer VI of a barrel column project exclusively to VPM where they form rod-like terminal fields in a thalamic barreloid. Thalamocortical cells in VPM and upper layer VI cells in a barrel form closed-loops for the flow of information between a thalamic barreloid and a cortical barrel column (Bourassa et al., 1995). In contrast, the corticothalamic cells located in deep layer VI exclusively innervate large sectors of secondary thalamic nuclei and intralaminar thalamic territories such as POM in the vibrissa system (Deschenes et al., 1998). A similar segregation between upper and lower layer VI cells has been found in the visual cortex of monkeys; upper layer VI cells project to the parvocellular LGN layers, while lower layer VI cells project to the magnocellular LGN layers (Lund et al., 1975).

Recent work has also found differences between the corticothalamic projections depending on the type of sensory cortex from where the corticothalamic fibers originate (Fig. 1), so that granular and dysgranular fields project differentially to the thalamus (Killackey and Sherman, 2003). The major difference is that the dysgranular zones of the barrel cortex (e.g., the area between the barrel columns) project from upper layer VI to the secondary thalamic nucleus (i.e., POM), while the granular zone (barrel area) does not, projecting only to the primary thalamic nucleus (i.e., VPM). This indicates that for the primary sensory thalamus recurrent loops with the neocortex only occur in the granular (barrel) zones of the sensory cortex within the upper part of layer VI. While for the secondary thalamic nuclei (POM), recurrent loops (not necessarily monosynaptic) with the dysgranular (non-barrel) zones of the sensory cortex involve pathways from all three thalamic projecting layers (i.e., layer V, upper layer VI and lower layer VI). Thus, the primary sensory thalamocortical network would consist of a barrel column and its corresponding barreloid in VPM, while a secondary sensory or higher order thalamocortical network would involve a non-barrel area or septa and POM (Killackey and Sherman, 2003). In addition to these recurrent closed loop circuits, corticothalamic fibers form open loop connections that could serve to link different cortical and thalamic areas. For example, layer V and lower VI cells of barrel columns project to POM (but not to VPM), providing a potential mechanism for cortico-cortical communication (Guillery, 1995; Killackey and Sherman, 2003). By means of these pathways, information from a cortical area could arrive at a different cortical area via the thalamus.

Since the main types of corticothalamic connections originate from distinct cell types in neocortex and project in a different pattern, it is quite feasible that the type of information they carry, and thus their functional roles, are quite distinct. It has been proposed that layer V corticothalamic fibers provide the primary driving input to cells in the secondary (higher order) thalamic nuclei (Sherman and Guillery, 1996), much like the primary sensory afferents do in the primary thalamic nuclei. The function of this powerful input originating in layer V would be to provide a way for
cortico-cortical communication via the thalamus (Guillery, 1995). Here we will focus on the properties of the corticothalamic fibers that originate from layer VI and innervate the primary thalamic nuclei, such as VPM. Reference will also be made to the layer V corticothalamic pathways when appropriate for comparison purposes. In the following sections, unless otherwise indicated, corticothalamic refers to neurons originating in layer VI, particularly in its upper part.

3.2. Electrophysiology of corticothalamic synapses

The largest group of excitatory synapses received by a thalamocortical neuron are corticothalamic synapses originating from layer VI cells (Erisir et al., 1997b, 1998; Liu et al., 1995a). However, these synapses occur at the distal portions of thalamic cells and structurally are relatively small, which usually corresponds to synapses that have a low release probability and a single release site. Thus, it is possible that despite the massiveness of the corticothalamic pathway it may have little impact on thalamocortical cells because the small excitatory responses they generate are filtered by the dendritic cable and shunted by the feedforward inhibition produced by nRt fibers.

Corticothalamic synapses activate both NMDA and non-NMDA receptors (Turner and Salt, 1998; Scharfman et al., 1990; Kao and Coulter, 1997). In addition, glutamate released by these synapses may activate metabotropic glutamate receptors (Turner and Salt, 1999). At many synapses, usually those with a low release probability, when two action potentials depolarize a presynaptic terminal in rapid succession the second action potential releases more neurotransmitter than the first (Zucker, 1989). This short-term enhancement of release that persists for tens to hundreds of milliseconds following a conditioning pulse is known as facilitation. Facilitation has long been believed to reflect a transient increase in the probability of neurotransmitter release and several studies have provided evidence that this is the case (Stevens and Wang, 1995; Debanne et al., 1996). It is thought that residual presynaptic Ca\textsuperscript{2+} contributes to the increased probability of release that is responsible for the observed facilitation (Katz and Miledi, 1968; Zucker, 1989; Kamiya and Zucker, 1994). Several studies have shown that corticothalamic pathways display some form of facilitation in vivo (Lindstrom and Wrobel, 1990; Tsumoto et al., 1978; Hu, 1993; Scharfman et al., 1990). Recently, it was realized that isolated corticothalamic EPSPs display strong synaptic facilitation (von Krosigk et al., 1999; Turner and Salt, 1998; Castro-Alamancos and Calcagnotto, 1999) that contrasts with the synaptic depression produced by primary sensory synapses (e.g. lemniscal) onto the same thalamocortical neurons (Turner and Salt, 1998; Castro-Alamancos, 2002b) (Fig. 10A).

Fig. 10. Facilitation of corticothalamic EPSPs in vivo and in vitro. (A) Corticothalamic EPSPs evoked by stimulating corticothalamic fibers in a slice preparation show synaptic facilitation. For comparison, EPSPs evoked by a pair of stimuli at 20 Hz in the corticothalamic pathway are overlaid with the EPSPs evoked by a pair of stimuli in the lemniscal pathway. (B) Extracellular field potential recordings in VPM evoked by thalamic radiation stimulation display strong facilitation, especially at frequencies above 5 Hz. Based on Castro-Alamancos and Calcagnotto (2001).

Stimulation of corticothalamic fibers produces a small amplitude and slow rising EPSP that can be graded in amplitude with increases in stimulation current reflecting the recruitment of fibers and release sites. The slow rise time of the EPSPs is likely a consequence of the low pass filtering exerted by the dendrites on corticothalamic EPSPs, and the small amplitude of the events may be related to the possibility that corticothalamic synapses have a low release probability (Granseth and Lindstrom, 2003). Thus, despite the large number of synapses formed on thalamocortical cells by corticothalamic fibers, the amplitude of corticothalamic EPSPs is relatively small during low frequency corticothalamic activity because corticothalamic synapses have a low release probability and occur at distal portions of the dendritic tree (Fig. 10). However, during high frequency corticothalamic activity (>5 Hz) the probability of release at these synapses sharply increases due to synaptic facilitation producing large amplitude EPSPs that can be as powerful or more than those produced by primary sensory afferents (Turner and Salt, 1998; Castro-Alamancos, 2002b).

Interestingly, not all corticothalamic EPSPs are created equal. Corticothalamic EPSPs produced on nRt cells differ from those produced on thalamocortical cells (Golshani et al., 2001; Gentet and Ulrich, 2004). Corticothalamic EPSPs produced by fiber collaterals on nRt neurons are fast-rising and activate both NMDA and AMPA receptors (Warren and Jones, 1997). The amplitude of EPSPs evoked in nRt neurons by stimulating single corticothalamic fibers are...
rodent slices in vitro showed that acetylcholine and norepinephrine, on corticothalamic responses. Results from the effects of two neuromodulators, acetylcholine and synaptic inputs to the thalamus (Erisir et al., 1997), and it is corticothalamic synapses may provide the two most numerous in fact, neuromodulatory synapses from the brainstem and changes by the actions of several neuromodulatory systems.

3.3. Effects of neuromodulators on corticothalamic synapses

In addition to activity-dependent changes, corticothalamic synapses may be subject to neuromodulator-dependent changes by the actions of several neuromodulatory systems. In fact, neuromodulatory synapses from the brainstem and corticothalamic synapses may provide the two most numerous synaptic inputs to the thalamus (Erisir et al., 1997), and it is possible that they modulate each other. Recent work has tested the effects of two neuromodulators, acetylcholine and norepinephrine, on corticothalamic responses. Results from rodent slices in vitro showed that acetylcholine and norepinephrine depress the efficacy of corticothalamic synapses while enhancing their frequency-dependent facilitation (Castro-Alamancos and Calcagnotto, 2001). This produces a stronger depression of low frequency responses than of high frequency responses. The effects of acetylcholine and norepinephrine are mimicked by muscarinic and α2-adrenergic receptor agonists and blocked by muscarinic and α-adrenergic antagonists, respectively. Thus, acetylcholine acting on muscarinic receptors and norepinephrine acting on α2-adrenergic receptors depress corticothalamic synapses. This contrasts with the lack of effects of these same neuromodulators at primary sensory afferents (lemniscal synapses) (Castro-Alamancos, 2002b). It has also been shown that group III metabotropic glutamate receptors depress corticothalamic synapses (Turner and Salt, 1999). In addition, glutamate released by corticothalamic fibers may activate metabotropic glutamate receptors and lead to the depolarization of thalamocortical neurons via cellular mechanisms similar to those activated by other neuromodulator systems (McCormick and von Krosigk, 1992).

3.4. Corticothalamic responses during information processing states

The firing properties of corticothalamic neurons have been extensively studied in awake rabbits (Swadlow, 1989, 1990, 1991, 1994; Swadlow and Weyand, 1987). In general, many of these neurons are described as virtually unresponsive to sensory stimuli and display very little spontaneous activity. Moreover, corticothalamic cells may be sensitive to changes in arousal (Livingstone and Hubel, 1981; Swadlow and Weyand, 1987), and corticothalamic responses evoked by sensory stimuli are clearly observed in the thalamus in lightly anesthetized animals (Temereanca and Simons, 2004). Changes in corticothalamic activity during information processing states would affect thalamic processes that corticothalamic connections mediate such as thalamic neuromodulation exerted by corticothalamic fibers, and the spatial and temporal properties of thalamic receptive fields. Thus, understanding the firing properties of corticothalamic cells during activated states is an essential step to comprehend the functional role of corticothalamic pathways.

A few technical details about corticothalamic stimulation are worth mentioning. First, electrical stimulation of the cortex or thalamic radiation can stimulate intracortical circuits that can feed their activity back to the thalamus. This effect can be eliminated by inactivating the cortex with muscimol or TTX and stimulating in the radiation. Second, electrical stimulation of the thalamic radiation or of the neocortex will inevitably lead to the antidromic discharge of some thalamocortical cells. Generally, it is quite feasible to record thalamocortical cells that are only orthodromically driven by corticothalamic stimulation, and not antidromically. This does not mean that other thalamocortical cells are not being antidromically stimulated, they surely are. One main consequence of this effect is that those cells could activate the nRt via their recurrent collaterals and produce recurrent inhibition in the thalamus. However, this effect is basically also produced by orthodromic stimulation of corticothalamic synapses in nRt. Third, stimulation of cortex and thalamic radiation leads to an additional potential confound in vivo. This stimulation can discharge cortico-
bulbar cells that would stimulate brainstem nuclei (e.g. principal trigeminal nuclei) that feed back to the thalamus. This problem can be eliminated by inactivating the brainstem nucleus, and it is not a concern in corticothalamic slices.

### 3.4.1. Temporal response properties

An interesting proposal is that corticothalamic activity is merely a modulator of thalamocortical activity (Sherman and Guillery, 1998). This would agree with the small amplitude EPSPs produced by corticothalamic synapses, and thus primary sensory inputs would be the main drivers of thalamocortical activity. This seems to be the case during low frequency corticothalamic activity, but not during high frequency (>5 Hz) corticothalamic activity (see Fig. 11). Indeed, low frequency stimulation of corticothalamic fibers rarely drives VPM cells in vivo (Fig. 11B) or in slices (Fig. 11A). In contrast, during stimulation at frequencies above 5 Hz corticothalamic activity is a very effective driver of thalamocortical neurons. Thus, the corticothalamic pathway is an activity dependent driver of thalamocortical activity. When layer VI neurons fire at frequencies above 5 Hz they drive thalamocortical cells as effectively as primary sensory (lemniscal) inputs. It is also noteworthy that corticothalamic fibers on nRt neurons lead to strong feedforward inhibition, and consequently corticothalamic activity produces profound inhibitory effects on thalamocortical cells, especially during quiescent states.

Indeed, inhibition may be the predominant effect of corticothalamic activity in the thalamus during low frequency corticothalamic activity and during quiescent (non-activated) states. However, during high frequency corticothalamic activity, inhibition will tend to depress while excitation will enhance due to facilitation and there will be a net excitatory effect at thalamocortical neurons. Moreover, as described in the previous section, during activated states the large amplitude and long-lasting IPSPs characteristic of quiescent states will be reduced.

During activation caused by BRF stimulation, corticothalamic responses are depressed, and this result is consistent with the effects of neuromodulators on corticothalamic synapses in slices (Castro-Alamancos and Calcagnotto, 2001). The suppression of corticothalamic responses by neuromodulators or activation is strong for low frequency corticothalamic activity, which does not produce synaptic facilitation, but mostly absent for high frequency corticothalamic activity, which triggers facilitation. The net effect is the high-pass filtering of corticothalamic activity during arousal. These effects of arousal seem to be mediated by the activation of muscarinic and α-adrenergic receptors because application of muscarinic and α-adrenergic antagonists into the thalamus in vivo abolish the suppression of corticothalamic responses induced by BRF stimulation (Castro-Alamancos and Calcagnotto, 2001). Thus, cholinergic and noradrenergic activation during arousal serves to high-pass filter corticothalamic activity. When these neuromodulators are released in the thalamus the flow of low-frequency activity from the neocortex is suppressed, while high frequency activity is allowed. This suggests that during activated states the corticothalamic pathway becomes a more selective activity-dependent driver of thalamic neurons; only activity at frequencies above 5 Hz will be allowed to reach thalamic cells.

### 3.4.2. Functional relevance during behavior

The results discussed above indicate that during arousal only high frequency inputs from the neocortex are allowed to reach the thalamus. The thalamocortical network undergoes dramatic functional changes between sleep and arousal (Steriade et al., 1997). For example, during slow wave sleep the neocortex and thalamus are engaged in low frequency
oscillations, while during arousal they engage in high-frequency gamma oscillations (Steriade et al., 1993). Gamma oscillations at 20–40 Hz coincide with the frequencies that are effective in triggering short-term synaptic facilitation in corticothalamic synapses. Interestingly, BRF stimulation enhances both gamma oscillations (Steriade et al., 1991; Steriade and Amzica, 1996) and corticothalamic facilitation (Castro-Alamancos and Calcagnotto, 2001). Thus, an important role for this corticothalamic high-pass filter during arousal may be to permit the flow of gamma oscillations between neocortex and thalamus, while impeding low frequency oscillations. It would serve as a gate that allows the flow of low frequency and gamma activity during sleep, while allowing only gamma activity during arousal.

4. Thalamocortical pathway

There are several types of thalamocortical pathways, which are differentially sensitive to activity and arousal (for reviews of their morphology and physiology see Castro-Alamancos, 1997; Castro-Alamancos and Connors, 1997b). A particularly useful classification of the thalamic nuclei relies on the type of information relayed to the neocortex. This classification distinguishes between thalamocortical pathways that convey information of multiple modalities or relatively non-specific information about modulatory or state-dependent processes and thalamocortical pathways that convey specific information about a particular modality. Nuclei that convey specific information can be classified further as primary and secondary depending on the information transmitted. Although both might transmit information of a particular modality, the activity from the primary nucleus would reflect more precisely the stimulus presented at the peripheral receptors, while the activity in the secondary nucleus would be the result of more elaborate higher order processing. A good example of a primary specific nucleus in the somatosensory system is VPM, while the corresponding secondary or higher order nucleus is POM. Both of these thalamocortical pathways provide sensory information about the vibrissae, but the quality of this information is quite different. For instance, the activity of POM neurons is much more processed and strongly dependent upon corticothalamic influences (Diamond et al., 1992a), while the activity of VPM neurons reflects more faithfully the sensory input. In the following sections, the focus is on the properties of primary thalamocortical pathways, and in particular the pathway originating in VPM.

4.1. Electrophysiology of thalamocortical synapses

An important question relates to the response properties of thalamocortical synapses formed by VPM neurons in neocortex. Specifically, the question is: what is the excitatory response produced by thalamocortical synapses, in the absence of recurrent cortical excitation or inhibition and thalamic feedback? It is important to recognize upfront that such isolation is difficult to accomplish because of several major caveats. The most notable problem is that it is difficult to block recurrent cortical excitation without also affecting thalamocortical excitation. A second major problem is that complete block of inhibition in the neocortex produces seizures making it complicated to interpret cortical responses under those circumstances. A third problem in the thalamocortical system that is mainly encountered when using extracellular electrical stimulation to drive thalamocortical fibers is that such stimulation almost inevitably leads to stimulation of corticothalamic fibers, which produces two unwanted consequences: (1) corticothalamic activity can synaptically drive thalamocortical cells (see Fig. 11), and consequently this activity will be fed back to the cortex. Fortunately, this unwanted consequence of electrical stimulation can be surmounted by inactivating the thalamus and stimulating thalamocortical fibers in the thalamic radiation (Castro-Alamancos and Oldford, 2002); (2) the second unwanted consequence of electrical stimulation is recurrent cortical excitation and inhibition mediated by the intracortical axon collaterals of corticothalamic cells. There are several potential ways to bypass this major problem such as using intracellular stimulation of thalamocortical cells or fibers, using sensory stimulation instead of electrical stimulation to drive thalamocortical cells or using chemical instead of electrical stimulation of thalamocortical cells. Each of these alternatives presents their own challenges. It is also noteworthy that because thalamocortical fibers leave collaterals in the nRt as they ascend to the neocortex, thalamocortical activity will lead to recurrent inhibition of thalamocortical cells which may affect subsequent thalamocortical activity or produce rebound excitation of thalamocortical cells. These intrathalamic recurrent effects can be eliminated by inactivating the thalamus. With this in mind we consider the data about the response properties of thalamocortical synapses.

A major contributor to the study of thalamocortical synapses has been the development of a thalamocortical slice preparation (Agmon and Connors, 1991). Using this preparation, it has been possible to record cortical responses evoked by thalamic electrical stimulation. An interesting property of these responses is that they show frequency-dependent depression (Castro-Alamancos, 1997; Gil et al., 1997) similar to what is observed in the previous and subsequent synapses in this ascending axis; i.e., both primary sensory (lemniscal) synapses of the thalamus (Castro-Alamancos, 2002b) and layer IV-to-layer III synapses in the cortex (Castro-Alamancos and Connors, 1997a) show frequency-dependent depression. A further characterization of thalamocortical responses evoked by minimal electrical stimulation has revealed that quantal events from thalamocortical and intracortical fibers onto layer IV cells were indistinguishable (Gil et al., 1999). However, thalamocortical fibers have about three times more
release sites than intracortical axons, and the mean release probability at thalamocortical synapses was about 1.5 times higher than that at intracortical synapses. These differences in innervation ratio and release probability make the average thalamocortical connection several times more effective than the average intracortical connection, and may allow small numbers of thalamocortical axons to dominate the activity of cortical layer IV cells during sensory inflow. It has also been found that thalamocortical synapses excite a population of inhibitory interneurons called fast-spiking cells, and the response evoked on these cells is also stronger than that observed on excitatory cells of layer IV (Gibson et al., 1999).

Consequently, in addition to exciting the neocortex and depressing in response to activity, an important property of thalamocortical synapses is that they recruit strong feedforward inhibition mediated by fast-spiking interneurons, a property also observed in vivo (see Section 4.4).

In addition to short-term changes in efficacy caused by activity, thalamocortical synapses may be able to undergo long-term changes in efficacy, such as LTP and LTD. Indeed, thalamocortical synapses can produce LTP in slices, but only up to postnatal day 9 (Crair and Malenka, 1995). This time seems to coincide with the critical period for development alterations in the barrel cortex caused by sensory perturbations, and also with the time when silent synapses (i.e., synapses devoid of AMPA receptors, but containing NMDA receptors (Liao et al., 1995; Isaac et al., 1995)) disappear from thalamocortical connections (Isaac et al., 1997). However, high-frequency thalamocortical stimulation in adult rodents in vivo seemingly causes LTP of thalamocortical evoked responses (Heynen and Bear, 2001) (see also Fig. 12 in Castro-Alamancos and Connors, 1997b). Further work is needed to reconcile these in vitro and in vivo results.

4.2. Effects of neuromodulators on thalamocortical synapses

It appears that the most likely consequence of acetylcholine release in neocortex during behavior is selective enhancement of the sensory thalamocortical pathway through activation of nicotinic receptors. This is based on the effects of cholinergic receptor agonists and antagonists in slices and in vivo. Thus, application of neuromodulators to thalamocortical slices has revealed that thalamocortical responses are depressed by activating muscarinic receptors, but not by activating GABAergic receptors. In contrast, intracortical responses evoked on the same neurons by cortical stimulation are depressed by activating either muscarinic or GABAergic receptors. In addition, activation of nicotinic receptors selectively enhances thalamocortical but not intracortical responses (Gil et al., 1997; Hsieh et al., 2000). Similarly, in vivo, application of cholinergic receptor agonists in neocortex differentially affects sensory and intracortical responses (Oldford and Castro-Alamancos, 2003). In fact, increasing endogenous acetylcholine by cortical application of an acetylcholinesterase inhibitor selectively enhances the sensory evoked response in neocortex, while leaving the intracortical response unchanged and this effect is mimicked by nicotine (Oldford and Castro-Alamancos, 2003). These results suggest that the main effect of acetylcholine in the neocortex during behavior may be a selective enhancement of the sensory thalamocortical pathway relative to intracortical pathways.

Neuromodulators can affect a neural network by both presynaptic and postsynaptic actions, and dissociating these actions is not a simple feat. The site of action of acetylcholine on thalamocortical pathways has not yet been established, but it is noteworthy that at least some of its actions are input specific. That is, they selectively modify one pathway but not a second pathway innervating a cell population. This is the case for the cholinergic effects mediated by nicotinic receptors (Oldford and Castro-Alamancos, 2003; Gil et al., 1999; Gioanni et al., 1999), which suggests a presynaptic action of acetylcholine at nicotinic receptors localized on thalamocortical fibers (Bina et al., 1995; Sahin et al., 1992; Lavine et al., 1997) or a selective localization of nicotinic receptors at postsynaptic cortical targets innervated by thalamocortical synapses (Clarke et al., 1985). The preferential distribution of nicotinic receptors in the vicinity of synapses relaying sensory information (i.e. thalamocortical) would modulate thalamic inputs in neocortex while not affecting others.

The importance of selectively modulating the thalamocortical pathway is noticeable when considering that the majority of synapses in thalamocortical recipient layers of the neocortex (e.g. layer IV) originate from cortical neurons. In particular, only a minority of synapses on layer IV thalamocortical-recipient cells are thalamic in origin (i.e., approximately 5–10%), whereas the remaining are intracortical in origin (Peters and Payne, 1993; Ahmed et al., 1994; White, 1989). Note that other work has suggested significantly higher numbers of thalamocortical synapses (i.e., approximately 25%), but these are still fewer than intracortical synapses (LeVay and Gilbert, 1976). This suggests that under normal conditions, intracortical pathways could dominate cortical processing because of their larger numbers. Therefore, acetylcholine release during various behaviors may serve to facilitate the numerically inferior thalamocortical pathway in order to maximize transfer of information from the periphery to the cortex.

The effects of other neuromodulators on thalamocortical pathways have also been investigated. For example, it has been shown that norepinephrine can depress sensory evoked responses in neocortex (Foote et al., 1975; Waterhouse et al., 1980), but whether such an effect is specific for thalamocortical pathways is unclear. Serotonin receptors are expressed transiently at thalamocortical synapses, and accordingly, thalamocortical neurotransmission is depressed by serotonin during development (Rhoades et al., 1994).
4.3. Thalamocortical responses during information processing states

Stimulation of different thalamic nuclei leads to different cortical responses. In rodents, low frequency (<0.3 Hz) stimulation of VPM produces a large field potential response in neocortex that is almost indistinguishable from the response produced by a sensory stimulus (i.e. whisker deflection) (Castro-Alamancos and Oldford, 2002; Castro-Alamancos, 1997; Castro-Alamancos and Connors, 1997b). This large amplitude response is also observed in other species (e.g. cat), and was termed the primary response by the pioneering studies of thalamocortical pathway excitability (Dempsey and Morison, 1942a). The pattern of cortical activity produced by the primary response can be best observed by performing current source density analysis (CSD) in neocortex (Castro-Alamancos and Connors, 1996; Castro-Alamancos and Oldford, 2002; Mitzdorf and Singer, 1978; Di et al., 1990). The primary response consists of short latency inward current flow (current sinks) in the thalamocortical recipient layers of neocortex, in layers IV and upper layer VI. The initial short-latency current flow in layer IV very effectively spreads into the upper layers because layer IV cells are strongly synaptically coupled with layer III cells (Silver et al., 2003). Thus, the primary response consists of the current flow produced in neocortex by thalamocortical synapses plus all the intracortical current flow triggered by the thalamocortical input recipient cells.

As mentioned above (see Section 4.1) electrical stimulation of the thalamus or thalamic radiation produces several effects in addition to activation of thalamocortical synapses, which make it difficult to interpret data obtained after electrical stimulation of the thalamus or thalamic radiation. The two most noticeable unwanted effects are the stimulation of corticothalamic fibers and their intracortical collaterals, and the stimulation of recurrent collaterals of thalamocortical fibers in the nRt. Stimulation of thalamocortical recurrent collaterals in the nRt robustly excites nRt neurons (Gentet and Ulrich, 2003) leading to recurrent inhibition and possibly rebound excitation of thalamocortical cells, which would be relayed to the cortex. Note that this effect would also occur during sensory stimulation. More importantly, corticothalamic fibers are also stimulated by electrodes placed within the thalamus or thalamic radiation. This will lead to direct excitation of nRt and thalamocortical cells by corticothalamic synapses, plus the excitation of cells in neocortex that are targeted by the intracortical collaterals of corticothalamic cells. Fortunately, the effects produced by direct excitation of nRt and thalamocortical cells caused by the electrical stimulation of thalamocortical and corticothalamic fibers can be eliminated by inactivating the thalamus. Fig. 12 shows the effect of stimulating the thalamic radiation during control conditions and during thalamic inactivation with TTX (Castro-Alamancos and Oldford, 2002). When the thalamus is intact a single stimulus at low frequency produces a primary response that is followed by a rebound oscillation at 10 Hz (asterisks in Fig. 12). This rebound oscillation is completely abolished by thalamic inactivation with TTX, and reflects the stimulation of nRt cells by the axon collaterals of VPM cells, which triggers a thalamic spindle oscillation. The other usual effect of thalamic inactivation with TTX is the enhancement of the primary thalamocortical response evoked by low frequency stimulation. This occurs because of the abolishment of spontaneous thalamocortical activity which normally tends to depress thalamocortical synapses. As discussed below (see Section
4.3.1), additional effects are observed during high frequency thalamic radiation stimulation.

After the thalamus is inactivated with TTX, there is really only one confound in the primary response evoked by thalamic radiation stimulation: the intracortical fiber collaterals of corticothalamic cells (for Discussion see Castro-Alamancos and Oldford, 2002). Thus, an important question relates to the relative contribution of these synapses to the primary response, as compared to thalamocortical synapses. There are several arguments that suggest that during low frequency stimulation, the contribution of the collaterals of corticothalamic cells is quite small (i.e., <5% of total current flow). First, the neocortical primary response produced by low frequency sensory stimulation and by electrical stimulation of the thalamic radiation when the thalamus is inactivated is almost indistinguishable. This suggests that these two methods pretty much produce the same effect in neocortex; namely, the stimulation of thalamocortical synapses. Second, although intracortical fiber collaterals of corticothalamic cells may be stimulated, they will contribute minimally to the primary response during low frequency stimulation because these collaterals, like corticothalamic synapses, have a very low release probability while displaying strong facilitation at high frequencies (Stratford et al., 1996). Indeed, even when the responses of these synaptic collaterals are maximized by high frequency stimulation their contribution to the cortical response is relatively small when compared to the primary response (Castro-Alamancos and Oldford, 2002). This is because both thalamocortical (Gil et al., 1999) and layer IV-to-layer III synapses (Silver et al., 2003; Castro-Alamancos and Connors, 1997a) have a very high release probability which contributes to the large amplitude of the primary response. For example, if the release probability of thalamocortical synapses were 0.9 while the release probability of the intracortical collaterals of corticothalamic cells were 0.1, then an action potential arriving at these synapses would produce (release) a postsynaptic EPSP at 90% of the thalamocortical synapses, but only at 10% of the intracortical corticothalamic synapses. Without further assumptions, this indicates that the cortical response evoked by electrical stimulation will be at least 90% caused by thalamocortical synapses. In conclusion, it is safe to say that in sensory cortex the primary response produced by low frequency electrical stimulation, when the thalamus is inactivated, is mostly caused by thalamocortical synapses and the intracortical network that these synapses engage.

Recent work has shown that the primary thalamocortical response is strongly suppressed during natural arousal or activation induced by BRF stimulation (Castro-Alamancos and Oldford, 2002). BRF stimulation robustly suppresses whisker-evoked responses in the neocortex, but not in the thalamus. BRF stimulation also suppresses the cortical response evoked by electrically stimulating thalamocortical fibers. This same suppression of the thalamocortical pathway is observed in freely behaving rats during natural arousal. For instance, suppression occurs when animals transition from slow-wave sleep to waking (Castro-Alamancos and Oldford, 2002; Castro-Alamancos, 2004). Current-source density analysis revealed that sensory suppression in the neocortex caused by BRF stimulation occurs at the thalamocortical recipient layers (layers IV and VI); the earliest current sinks in those layers are suppressed. Thus, sensory suppression during arousal occurs at the thalamocortical connection.

But what causes the suppression of the thalamocortical primary response during arousal? During natural arousal or after BRF stimulation, thalamocortical neurons display significantly enhanced spontaneous firing rates (see Fig. 2). Synapses are sensitive to activity and, in particular, thalamocortical synapses display robust depression when stimulated at high rates (Castro-Alamancos, 1997; Gil et al., 1997). These properties suggest that differences in the tonic firing rates of thalamocortical neurons between quiescent and aroused states could change the gain of thalamocortical synapses and significantly impact the mode of sensory transmission at the thalamocortical connection. The prediction would be that during aroused states, the enhanced activity of thalamocortical neurons results in the depression of thalamocortical synapses. Thus, during aroused states, sensory inputs traveling to the neocortex would encounter a depressed thalamocortical synapse due to the activity-dependent depression caused by enhanced activity of thalamocortical neurons. This is supported by the fact that blocking the thalamocortical activity by application of TTX in VPM completely eliminates the suppression of the thalamocortical pathway caused by BRF stimulation (Castro-Alamancos and Oldford, 2002). Thus, thalamocortical sensory suppression is mainly a consequence of the activity-dependent depression of thalamocortical synapses caused by increased thalamocortical tonic firing during arousal (Swadlow and Gusev, 2001; Castro-Alamancos and Oldford, 2002). It is also noteworthy that increased thalamocortical activity will lead to a strong recruitment of intracortical inhibition due to the fact that thalamocortical cells and some inhibitory interneurons (fast-spiking cells) in neocortex are very effectively coupled (Bruno and Simons, 2002; Swadlow, 1995). Thus, enhanced tonic inhibition in neocortex driven by enhanced thalamocortical activity may also contribute substantially to sensory suppression of primary responses during arousal.

4.3.1. Temporal response properties

Repetitive stimulation at high frequencies of different thalamic nuclei leads to different effects in the cortex (for reviews see Castro-Alamancos and Connors, 1996, 1997b; Castro-Alamancos, 1997). For example, stimulation of the VL thalamus at 7–14 Hz produces augmenting responses in the motor cortex. These augmenting responses evoked primarily in motor cortex by VL stimulation are clearly distinct from the responses evoked in sensory cortex by stimulating VPM (Castro-Alamancos and Connors, 1996).
As discussed above, low frequency stimulation of thalamocortical fibers from VPM produces large amplitude primary responses. When the thalamus is intact, the primary response evoked by thalamic or thalamic radiation stimulation is usually followed by oscillatory activity at \( \sim 10 \text{ Hz} \) (Fig. 12, asterisks). This oscillatory activity is a spindle oscillation generated in the thalamus, and thus, is abolished by inactivating the thalamus. Higher frequency stimulation of thalamocortical fibers leads to different effects depending on whether or not the thalamus is intact. When the thalamus is inactivated with TTX, repetitive stimulation of the thalamic radiation at frequencies above 0.3 Hz leads to the activity-dependent depression of the primary thalamocortical response (see Fig. 12). When the thalamus is intact, electrical stimulation of the thalamic radiation or thalamus produces a primary response in neocortex which depresses at frequencies above 0.3 Hz, but an additional slightly longer latency response appears at stimulation frequencies above 2 Hz, which we call here incremental response (Castro-Alamancos, 1997). As shown in Fig. 12, the cortical incremental response is completely abolished by inactivating the thalamus with TTX (Castro-Alamancos and Oldford, 2002), and reflects the facilitation produced in thalamocortical cells by stimulating corticothalamic synapses at frequencies above 2 Hz (Castro-Alamancos and Calcagnotto, 2001) (see also Section 3; Fig. 10). Thus, this incremental response is generated in the thalamus by corticothalamic facilitation and is fed back to the cortex via thalamocortical fibers.

The primary response, but not the incremental response, is evoked in neocortex by sensory (whisker) stimulation (Chung et al., 2002; Castro-Alamancos, 2004; Castro-Alamancos and Oldford, 2002). The activity-dependent depression of the primary response leads to a well known phenomenon in sensory physiology, called rapid sensory adaptation, which basically means that sensory inputs reaching the cortex are low-pass filtered. Sensory adaptation has been described in virtually all sensory modalities (Ohzawa et al., 1982; Nelson, 1991b; Wilson, 1998; Hellweg et al., 1977). The functional role of sensory adaptation is unclear, but it has been suggested to serve as a means to enhance sensory coding and as a mechanism to affect perception of subsequent stimuli (Adorjan et al., 1999; Fairhall et al., 2001; Kohn and Whitsel, 2002). As discussed above (see Section 2.4.1), during quiescent states, the responses of thalamocortical cells to sensory inputs are also low-pass filtered due to the activity dependent depression of primary sensory (lemniscal) synapses (Castro-Alamancos, 2002a). Thus, during quiescent states the sensory adaptation observed in the neocortex is a consequence of depression at both lemniscal and thalamocortical pathways.

During activated states produced by BRF stimulation in anesthetized animals or when animals are alert (i.e. actively exploring the environment or actively expecting stimuli), sensory evoked responses in the neocortex are suppressed and rapid sensory adaptation is reduced (Fig. 13). In contrast, during quiescent states such as slow-wave sleep or awake immobility, sensory evoked responses are strong in neocortex and adaptation is present (Castro-Alamancos, 2004). Thus, during the processing of sensory inputs, the thalamocortical pathway is already in an adapted state. These properties change rapidly and dynamically to meet information processing demands imposed by behavioral contingencies. The potential functional role of these changes is discussed below (see Section 4.3.3).

### 4.3.2. Spatial (receptive field) response properties

During anesthesia or quiescent states, sensory inputs spread through large areas of neocortex giving rise to large receptive fields and large sensory representations (Armstrong-James and Fox, 1987; Armstrong-James et al., 1991; Chen-Bee and Frostig, 1996; Sheth et al., 1998; Moore and Nelson, 1998; Brett-Green et al., 2001; Petersen and Diamond, 2000; Ghazanfar et al., 2000). Hence, during quiescent states, the neocortex favors the spread of activity. In contrast, other studies find a great spatial contrast between adjacent whiskers in the barrel cortex (Simons and Carvell, 1989; Goldreich et al., 1999) primarily mediated by locally recurrent inhibition (Simons, 1995). The more restricted
receptive fields and barrel independence may be attributed to different levels of brain activation (Armstrong-James and George, 1988; Simons et al., 1992). Indeed, recent work has shown that receptive fields and cortical representations change size depending on the level of arousal (Fig. 14), so that they are more focused during aroused states (Castro-Alamancos, 2002c). As shown in Fig. 14B, the area of neocortex excited by a single whisker deflection is much larger during quiescent states as compared to activated states. This was determined by placing a 16-channel linear array silicon probe in the horizontal plane within layer IV to determine the extent of activity spread. Likewise, individual cortical cells respond to more whisks during quiescent states than during activated states (Fig. 14C). The focusing of thalamocortical receptive fields during arousal seems to be a consequence of the factors that cause thalamocortical sensory suppression. Namely, the activity-dependent depression of thalamocortical synapses and enhanced recurrent inhibition during arousal. Locally recurrent inhibition has been proposed as the means to achieve selectivity in the neocortex (Simons, 1985; Miller et al., 2001; Pinto et al., 2003). In fact, thalamocortical neurons produce a very powerful connection with cortical inhibitory interneurons (Swadlow, 1995), much more so than with excitatory neurons of layer IV (Gibson et al., 1999). Although the efficacy of thalamocortical connections with interneurons is reduced during aroused states (Castro-Alamancos and Oldford, 2002; Swadlow and Gusev, 2001), it should still be effective in producing inhibitory potentials and reducing the spread of activity. In fact, one of the main consequences of BRF stimulation is a reduction of the spontaneous firing rate of a large percentage of cortical neurons (Castro-Alamancos and Oldford, 2002). This is consistent with the hyperpolarization of cortical neurons via the activation of GABA<sub>A</sub> receptors. One possibility is that the enhanced firing rates of thalamocortical neurons during arousal increase the firing of cortical inhibitory interneurons that are strongly innervated by thalamocortical inputs (White and Rock, 1981). This would result in an enhanced tonic level of recurrent inhibition in the neocortex during activated states. Therefore, thalamocortical synaptic depression and enhanced cortical inhibition during arousal, which are both a direct consequence of enhanced thalamocortical firing, result in increased selectivity (focusing) of cortical receptive fields and sensory representations. In conclusion, increased thalamocortical tonic firing during activation reduces the strength of the thalamocortical connection and may increase tonic cortical inhibition. Under these conditions the response of cortical neurons to sensory inputs becomes more selective for their principal input. Thus, cortical representations and receptive fields become focused during arousal.

4.3.3. Functional relevance during behavior

During arousal or activated states, neuromodulators are released in the thalamus and they increase the discharge rate of thalamocortical neurons as compared to quiescent states. Enhanced thalamocortical activity leads to two consequences, the activity dependent depression of thalamocortical synapses and the recruitment of inhibition in neocortex. As a result of these changes, thalamocortical sensory

![Fig. 14. Focusing of sensory inputs in neocortex during arousal. (A) Schematic representation of the location of the 16-channel silicon probe placed at a 135° angle in the barrel cortex to record field potential responses through an extension of layer IV–III of the barrel neocortex. (B) Contour-plot of the amplitude of the negative field potential recorded from 16-sites (100-um intervals) along layer IV–III of the barrel cortex in response to stimulation of a single whisker. Note the spread of activity under control conditions and the suppression of spread and focusing of the representation after BRF stimulation (RF stim). (C) Enhanced selectivity of a neuron in layer IV–III of barrel cortex during activation. Effect of activation induced by BRF stimulation on single-unit response to stimulation of the principal whisker and of an adjacent whisker. Single-unit responses are displayed as the probability of firing per 2-ms bins before (upper) and during (lower) activation (RF stim). The whisker stimulus is delivered at time zero. Based on Castro-Alamancos (2002c).](https://example.com/fig14)
suppression occurs, which means that primary thalamocortical responses are strongly suppressed during arousal. As a consequence of this suppression, rapid sensory adaptation is no longer observed because the thalamocortical pathway is already in an adapted (depressed) state, and thus cannot be further depressed by activity. Thus, two major functional consequences occur during arousal as a result of thalamocortical sensory suppression: the focusing of sensory inputs in neocortex (Castro-Alamancos, 2002c) and the absence or reduction of sensory adaptation to high frequency sensory inputs (Castro-Alamancos, 2004).

Thalamocortical suppression may be functionally useful as a gain regulator of activity reaching the neocortex (Abbott et al., 1997; Tsydyks and Markram, 1997). Thus, when a sensory input reaches the neocortex during behaviorally activated states it encounters a depressed thalamocortical synapse and likely enhanced tonic inhibition. This produces the suppression of primary thalamocortical responses during arousal. By reducing the impact of thalamocortical inputs sensory representations may become focused in neocortex. At a functional level this may well serve as a mechanism to focus sensory inputs to their appropriate representations (barrels) in neocortex, which may be helpful for the spatial processing of sensory information. This is important because in studies of sensory representation mapping in anesthetized animals the area of neocortex that responds to a focal peripheral stimulus is extremely large. For instance, several barrels respond in the neocortex to deflection of a single whisker in anesthetized rodents (Armstrong-James et al., 1992; Masino et al., 1993; Ghazanfar and Nicolelis, 1999; Moore et al., 1999; Petersen and Diamond, 2000). In fact, in anesthetized rodents stimulation of whiskers with corresponding barrels located in the border of the barrel cortex revealed that activity spreads from these border barrels into adjacent non-sensory cortex (Brett-Green et al., 2001). This suggests that the strong spread of sensory-evoked activity through cortex during anesthesia, and consequently the large representations and receptive fields attained during quiescent states, are not the norm during information processing states. However, because of thalamocortical sensory suppression during arousal, sensory inputs (i.e. whiskers) may become significantly focused in neocortex to their appropriate representations (i.e. barrels). This could be particularly helpful for spatial processing, such as stimulus location, because the topographic arrangement at the morphological level is maintained at the physiological level. Also, focusing may be helpful for sensory processing because the lack of selectivity observed during quiescent states seems to hinder information processing. For example, simple tasks performed by the somatosensory system (e.g. two-point discrimination) are more difficult to conceive with such overlapping and large cortical representations and receptive fields. Obviously, these behavioral capacities are possible only during brain-activated states typical of alertness, attention and arousal, and not during quiescent states typical of drowsiness, inattentiveness and sleep. Cortical sensory suppression during arousal may serve to focus sensory inputs in order to allow a more discrete and segregate representation of sensory information in the neocortex. Thus, activation typical of arousal provides enhanced sensory selectivity via thalamocortical suppression (Castro-Alamancos and Oldford, 2002; Castro-Alamancos, 2002c).

Sensory adaptation caused by repetitive sensory stimulation has been proposed as a way to focus sensory representations in neocortex (Sheth et al., 1998; Moore et al., 1999; Kohn and Whitsel, 2002). Thus, it is logical that during alert and expectant states, typical of active information processing and learning, sensory suppression is prevalent and adaptation is mostly absent. In contrast, the functional role of the large unadapted (non-suppressed) responses that occur at low frequencies during quiescent states is not obvious. They have been proposed to serve as a mechanism of heightened sensitivity for detecting transient stimuli (Moore et al., 1999; Fanselow and Nicolelis, 1999; Chung et al., 2002; Sherman, 2001). Thus, these large evoked responses could serve to alert quiescent animals of the presence of a stimulus. For instance, when animals perform a behavioral task in which they learn to use a sensory stimulus (CS) to avoid an aversive stimulus, dramatic changes occur in the size of the primary thalamocortical response evoked by the CS. When the animal is very alert the primary thalamocortical response is strongly suppressed. Thus the thalamocortical pathway is in the adapted state because thalamocortical activity is high and consequently, thalamocortical synapses are depressed. However, when the animal has learned the task and the level of alertness and attentiveness is lessened, the primary thalamocortical response becomes large as in sleeping or quiescent animals, and thus the thalamocortical pathway is in the unadapted state (Castro-Alamancos, 2004). There are several potential interpretations of this observation. As already mentioned, one possibility is that the animals may be using the unadapted (large amplitude) responses as a wake-up call of the presence of the CS. When a stimulus reaches the neocortex during an alert state it encounters a depressed thalamocortical synapse, and probably also enhanced inhibition, both leading to sensory suppression, which places the thalamocortical pathway in the adapted state. Although fewer cells in neocortex respond to the sensory stimulus during activated states, current knowledge is consistent with the idea that these fewer responding cells are better synchronized (see Castro-Alamancos, 2004). These effects may well serve to focus sensory inputs to their appropriate cortical representations, as a means of enhancing selectivity while also allowing for enhanced synchronization between responding neurons, which seems to be a hallmark of attention (Steinmetz et al., 2000; Fries et al., 2001) and of activation (Munk et al., 1996). These two effects, enhanced selectivity and synchronization, may serve to produce salient responses in higher order cortical areas.
leading to a behavioral outcome. In conclusion, during alertness and attentive states the thalamocortical pathway is in the adapted (i.e. suppressed) state, which leads to enhanced selectivity by focusing sensory inputs and the absence of rapid sensory adaptation to high frequency inputs. In addition, the fewer and more selective responding cells are much better synchronized leading to a stronger output to the next stage of processing. This occurs dynamically to meet information processing demands dictated by behavioral contingencies. Thus, sensory responses at even the earliest stage of cortical processing are strongly regulated by behavioral state and attention.

5. Conclusions

The thalamocortical network consists of the pathways interconnecting the thalamus and neocortex. Three major pathways are involved: lemniscal, corticothalamic and thalamocortical. The present review considered how these...
different pathways operate during aroused and quiescent behavioral states. During arousal or activated states electroencephalographic activity consists of low amplitude fast activity, which is displayed when subjects are vigilant, alert and attentive. During quiescent states electroencephalographic activity consists of large amplitude slow activity, which is typical of drowsiness and sleep. The response characteristics of the thalamocortical network to a sensory input ascending via the lemniscal pathway will depend on two main variables, the behavioral state and the recent activity history of the network.

As depicted in Fig. 15, during quiescent states, the lemniscal and thalamocortical pathways are low-pass filtered due to synaptic depression and recurrent inhibition, leading to sensory adaptation. Meanwhile, the corticothalamic pathway amplifies high frequency inputs due to synaptic facilitation, but also allows low frequency corticothalamic responses. In contrast, during activated states the low-pass filtering is eliminated at both lemniscal and thalamocortical pathways, but this occurs via two distinct mechanisms. For the lemniscal pathway, neuromodulators depolarize VPM cells and suppress recurrent inhibition so that cells that previously did not discharge to high frequency lemniscal inputs during quiescent states are able to do so during activated states. For the thalamocortical pathway, neuromodulators depolarize VPM cells enhancing their spontaneous firing rate. This enhancement of thalamocortical activity depresses thalamocortical synapses so that both low and high frequency sensory inputs reaching the neocortex during this state generally encounter a depressed thalamocortical synapse. Consequently, the thalamocortical pathway is already suppressed and does not lead to sensory adaptation because it is already adapted. For the corticothalamic pathway, neuromodulators released in the thalamus depress corticothalamic synapses, and this leads to the suppression of low frequency corticothalamic activity because facilitated corticothalamic responses are less affected by this depression. The net effect is a high-pass filtering of corticothalamic activity, so that during activated states corticothalamic responses at low frequencies are suppressed while those at high frequencies are not.

5.1. Dynamics of the thalamocortical network during an ascending input

During quiescent states, when an action potential (caused by a low frequency sensory stimulus) ascends toward the thalamus via a lemniscal fiber there is a fairly good chance (≈80%) that it will trigger an action potential in a VPM cell contacted by the lemniscal fiber. The ≈20% failure occurs because the VPM cell is somewhat hyperpolarized during quiescent states (although still within the tonic firing mode), and thus the large amplitude lemniscal EPSP on occasion fails to reach the action potential generation threshold. Then the VPM action potential is relayed to the neocortex via the thalamocortical pathway resulting in the stimulation of at least three major cell populations: nRt cells, layer VI corticothalamic cells and layer IV cells. Thalamocortical collaterals discharge nRt cells, leading to recurrent inhibition that feeds back to VPM, and possibly causing full blown spindle oscillations lasting up to 1 s in duration that bombard VPM cells with IPSPs at ≈10 Hz. Thalamocortical collaterals discharge corticothalamic cells in upper layer VI, leading to the stimulation of corticothalamic synapses providing feedback recurrent excitation to VPM and nRt cells. Finally, the action potential ascending via the thalamocortical fiber depolarizes both excitatory and inhibitory cells in layer IV (in particular, fast spiking inhibitory cells) resulting in strong excitation that is curtailed by strong feed forward inhibition. The action potentials produced in layer IV excitatory cells depolarize cells in layer III, and these pyramidal cells distribute the activity to other layers in the same cortical column as well as horizontally to adjacent cortical territory. Thus, during quiescent states the thalamocortical network is in a condition that favors the spread of low frequency activity through all of its connections.

Also, during quiescent states, if an additional action potential (caused by a high frequency sensory stimulus) travels shortly after the previous one (e.g., 100 ms later) toward VPM via the same lemniscal fiber it will have a very low chance of triggering an action potential in the contacted VPM neuron, and thus the sensory input is low-pass filtered; i.e., effectively blocked. This blockage is caused by lemniscal synaptic depression and also by the recurrent feedback inhibition from the nRt that was recruited by the first sensory stimulus. The few VPM cells that do respond to the lemniscal action potential relay this activity to neocortex where they encounter synapses that are depressed by the previous action potential. The ascending thalamocortical action potential encounters depressed synapses at its major targets, producing smaller amplitude EPSPs than it did in response to the previous (low frequency) action potential. Many of the targeted cells that reached firing threshold in response to the previous action potential will not be able to reach threshold to this action potential. The net effect will be the suppression or adaptation of the responses to high frequency sensory inputs in neocortex during quiescent states (i.e., rapid sensory adaptation).

During activated states typical of information processing, when an action potential (caused by a low frequency sensory stimulus) ascends toward the thalamus via a lemniscal fiber there is an excellent chance (≈100%) that it will trigger an action potential in a VPM cell contacted by the lemniscal fiber. This effectiveness occurs because the VPM cell is more depolarized during activated states than during quiescent states allowing the large amplitude lemniscal EPSP to reach threshold with great certainty. The fact that the VPM cell is more depolarized implies that its spontaneous firing rate is greater than during quiescent states, and the enhanced activity inevitably leads to the
activity-dependent depression of the synapses formed by thalamocortical fibers in the nRt, upper layer VI and layer IV. It may well also lead to enhanced tonic inhibition in neocortex because thalamocortical cells and cortical fast-spiking interneurons are very effectively coupled. The ascending thalamocortical action potential encounters depressed synapses at its major targets, producing smaller amplitude EPSPs than it did during quiescent states. Thus, many of the targeted cells that reached firing threshold during quiescent states will not during activated states. As during quiescent states, thalamocortical collaterals depolarize nRt cells leading to recurrent inhibition in VPM, but these IPSPs are smaller in size and duration because they are suppressed during activation. Thalamocortical collaterals depolarize corticothalamic cells in upper layer VI that produce feedback recurrent excitation of VPM and nRt cells. However, corticothalamic synapses are depressed by neuromodulators released in the thalamus during activation resulting in the suppression of the excitatory corticothalamic feedback. Finally, the action potential ascending via the thalamocortical fiber produces smaller EPSPs in both excitatory and inhibitory cells in layer IV. The suppressed excitation leads to fewer layer IV cells producing action potentials and fewer cells in layer III that are stimulated. Overall, the result is the focusing of the cell population that is stimulated by the ascending input as compared to quiescent states. Interestingly, despite the fact that the number of cells firing in the neocortex may be reduced during activated states, this cortical activity is nevertheless more tightly synchronized, surely to allow an effective discharge at the target cell populations.

Also, during activated states, if an additional action potential travels shortly after the previous one (e.g. 100 ms later) toward VPM via the same lemniscal fiber it will have an excellent chance of producing an action potential in the contacted VPM neuron, and thus it will be effectively relayed to the neocortex. This effectiveness occurs despite the fact that lemniscal synapses were depressed by the previous action potential, and thus the lemniscal EPSP that follows is quite small. But during activated states the VPM cell is depolarized and much closer to firing threshold than during quiescent states, and even depressed lemniscal EPSPs can reach firing threshold. Moreover, recurrent inhibition from the nRt is strongly suppressed, which also further favors the effectiveness of high frequency (i.e. depressed) lemniscal EPSPs to produce an action potential in the VPM cell. The response properties of the VPM action potential at the targets of thalamocortical fibers will be similar to that of the previous (low frequency) action potential with one notable exception at corticothalamic synapses. Since corticothalamic synapses display frequency-dependent facilitation they will produce a much larger EPSP to an action potential that occurred shortly after (<200 ms) a previous one. Thus, during activated states recurrent corticothalamic feedback will be enhanced but only for high frequency inputs. It is possible that corticothalamic activity caused by high frequency sensory inputs during activated states has a strong impact on VPM cells. Regarding the responses produced in cells targeted by thalamocortical fibers in layers VI and IV, their properties should be quite similar to those produced by the previous action potential occurring at low frequency. Thus, during activated states thalamocortical responses do not depress or adapt as during quiescent states because the thalamocortical network is already in an adapted state.

5.2. In conclusion

Sensory inputs from the whiskers reach the thalamus via the medial lemniscus tract, which originates in the brainstem trigeminal nucleus. The lemniscal synapses are quite specialized producing fast-rising, large amplitude all-or-none events that are very secure (i.e., high release probability) when stimulated at low frequencies (<2 Hz), but that significantly depress upon stimulation at high frequencies (>2 Hz). Thus, during quiescent states, sensory stimuli delivered at frequencies above 2 Hz are not relayed to the neocortex despite the fact that thalamocortical cells are firing in the tonic mode. However, during activated states the low pass filtering of sensory inputs is eliminated, and TC cells are able to relay sensory inputs to the neocortex at high frequencies. The low-pass filter is eliminated during activated states because of the postsynaptic depolarization exerted by neuromodulators on thalamocortical neurons, which places the depressed lemniscal EPSPs closer to firing threshold allowing them to trigger action potentials. While this happens at the lemniscal pathway significant changes are also occurring at the other major thalamic synapses; corticothalamic synapses. During activated states, corticothalamic activity is high-pass filtered; i.e., low frequency cortical inputs to the thalamus are depressed while high-frequency inputs, which trigger presynaptic facilitation in corticothalamic synapses, are unaffected. The high-pass filtering during activated states is due to the synaptic effects of neuromodulators acting on muscarinic and α2-adrenergic receptors, which depress corticothalamic synapses and enhance their facilitation. Thus, during activated states, sensory inputs are allowed through the thalamus at low and high frequencies with enhanced effectiveness, but activity from the cortex is high-pass filtered so that only high frequency cortical activity is allowed to reach the thalamus.

Most interesting is that the neocortex is simultaneously undergoing dramatic changes. A notable change is that during activated states, occurring naturally in behaving animals or induced by BRF stimulation, the thalamocortical pathway is depressed, so that sensory inputs reaching the cortex are suppressed. The suppression is primarily caused by the activity-dependent depression of thalamocortical synapses. During activated states, thalamocortical neurons increase their spontaneous firing rates and consequently their thalamocortical synapses become depressed. Therefore, when a sensory input reaches the neocortex during
behaviourally activated states it encounters a depressed thalamocortical synapse. The functional implications of this sensory suppression are intriguing. It eliminates rapid sensory adaptation because thalamocortical responses are already adapted, and serves to focus sensory inputs to their appropriate cortical representation while also allowing for enhanced synchronization between responding neurons, which seems to be a hallmark of attentive states. As a consequence of the suppression, the size of cortical representations and receptive fields are reduced during activated states providing enhanced selectivity, which may be advantageous for sensory processing, such as for example two-point discrimination in the somatosensory system.

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