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THALAMOCORTICAL SYNAPSES

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Abstract—Thalamocortical synapses inform the cerebral neocortex about the external and internal worlds. The thalamus produces myriad thalamocortical pathways that vary in morphological, physiological, pharmacological and functional properties. All these features are of great importance for understanding how information is acquired, integrated, processed, stored and retrieved by the thalamocortical system. This paper reviews the properties of the afferents from thalamus to cortex, and identifies some of the gaps in our knowledge of thalamocortical pathways. © 1997 Elsevier Science Ltd. All Rights Reserved.

CONTENTS

1. INTRODUCTION

The thalamus and neocortex are two highly organized and complex brain structures that are responsible for some of the most sophisticated of mammalian behaviors. Two features are salient about the relationship between these structures. First, they are recurrently and extensively interconnected with one other and, second, the processing power of the neocortex can access specific information about the external world only via its afferent connections from the thalamus. Although a few diffuse pathways originating in several brain stem nuclei also project to the cortex, the thalamus is the main gateway to the neocortex. Therefore, the properties of the connections between these structures are of great importance in understanding how information is acquired,

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cessed, stored and retrieved by the thalamocortical system. The aim of this paper is to review the functional properties of the afferents from thalamus to cortex. We will discuss general principles governing the morphology, physiology, pharmacology and function of thalamocortical connections, focusing mainly on data derived from rodents and, when appropriate, cats and primates. We will not deal with the recurrent pathways feeding back from cortex to thalamus, nor with the general properties of the thalamus and neocortex. The transmission, coding and transformation of sensory information by the thalamocortical system is beyond the scope of this review.

2. ANATOMY OF THALAMOCORTICAL PATHWAYS

The thalamus can be divided into three regions according to the relationship of each with the cerebral cortex: epithalamus, ventral thalamus and dorsal thalamus (Jones, 1985). The epithalamus (e.g. habenular nuclei) does not receive or send fibers to the cerebral cortex. The ventral thalamus (e.g. reticular nucleus) receives fibers from the cerebral cortex but does not send fibers to it. Finally, the dorsal thalamus includes numerous nuclei that both send and receive fibers from the cerebral cortex. The dorsal thalamus is divided into three compartments by the internal medullary lamina, a bifurcating sheet of myelinated fibers. Thus, the dorsal thalamus has anterior, medial and lateral nuclear groups (Table 1; see Faull and Mehler, 1985, for details). This is a useful classification based on purely descriptive anatomy. An alternative way to classify the dorsal thalamic nuclei is based on their ascending projections. This allows the dorsal thalamic nuclei to be differentiated into two groups: the intralaminar nuclei, which project to the striatum and cortex, and the non-intralaminar nuclei, which project only to the cortex.

Other classifications of the dorsal thalamic nuclei take into consideration other features, such as the structure of their terminations in the cortex, the information transmitted, and the cortical layer of termination (Lorente de Nó, 1938; Macchi, 1983; Frost and Caviness, 1980; Herkenham, 1986). In 1938, Lorente de Nó (Lorente de Nó, 1938) described two types of thalamocortical fibers that he observed in Golgi-stained preparations, and accordingly suggested the existence of two groups of thalamic nuclei that could be differentiated by the spread of their cortical projections. The first type of fiber he called the "*specific*" *thalamocortical afferent*, which terminates in a dense plexus within a single cortical area. The second type of thalamocortical axon he called the "*unspecific*" *fiber* (or *non-specific fiber*), which has more frequent intracortical branching and terminates in several cortical areas. The two types of thalamocortical fibers define two types of thalamic nuclei: the *specific thalamic nuclei* form restricted and dense arborizations, while the *non-specific nuclei* form more widespread and sparse projections. In a more recent and detailed classification, also based on differences in the spread of the thalamocortical projections (Macchi, 1983), thalamic nuclei can be classified into four distinctive groups according to the spread of their projections to the cortex: nuclei projecting densely into single cortical fields, nuclei projecting densely into one area and diffusely into another, nuclei projecting diffusely into several cortical fields but with regional concentrations, and nuclei projecting diffusely over widespread areas.

A functional classification of the thalamic nuclei relies on the type of information relayed to the cortex. Simplistically, thalamic nuclei can be classified according to the modality of information that they provide to the cortex: visual, somesthetic, motor, auditory, etc. More rigorously, a functional classification should distinguish between nuclei that convey specific information of one modality from nuclei that convey information of multiple modalities, or relatively non-specific information about modulatory or state-dependent processes. The nuclei conveying specific information could be classified further as *primary* or *secondary*, depending on the quality of the information transmitted. Although both might transmit information of a particular modality, e.g. a sensory one, the activity from the *primary* nucleus would reflect more precisely the environmental stimulus presented, while the activity in the *secondary* nucleus would be the result of more elaborate higher-order processing. An example of a primary specific nucleus in the somatosensory system is the ventroposterior medial (VPM) nucleus, and a secondary specific thalamic nucleus is the rostral sector of the posterior complex (Pom). Both of these nuclei provide sensory information to the vibrissae representation of the somatosensory cortex, but the quality of this information is quite different. The activity of Pom neurons is much more strongly dependent upon processed corticothalamic influences than is the activity of VPM neurons (Diamond, 1995). Examples of nuclei that convey information about different modalities or no sensory information at all would be the ventromedial nucleus (VM) and the intralaminar nuclei (e.g. parafascicular nucleus), respectively.

A particularly useful classification, which arose from studies of the rat, is based on thalamocortical lamination patterns (Herkenham, 1986). Thus, according to the main layer(s) of termination of the thalamic projections, the thalamic nuclei can be divided into three groups (Fig. 1). The first group consists of the *specific nuclei*, and their cortical projections terminate mainly in layers IV and lower III, with a separate and less dense set of collaterals in upper layer VI. The second group is the *non-specific deep-layer projecting nuclei*, or *intralaminar nuclei*, and their cortical projections terminate densely in layers V and VI, and perhaps layer I as well. The third group is the *non-specific layer I — projecting nuclei*, or *paralaminar nuclei*, and their cortical projections terminate in layer I, often with additional terminations in other laminae, depending on cortical area. See Table 1 for a grouping of the various thalamic nuclei into these three categories.

2.1. Specific Thalamic Nuclei

The specific thalamic nuclei have received considerable attention since they provide sensory information (i.e. auditory, visual, somesthetic) to the sensory

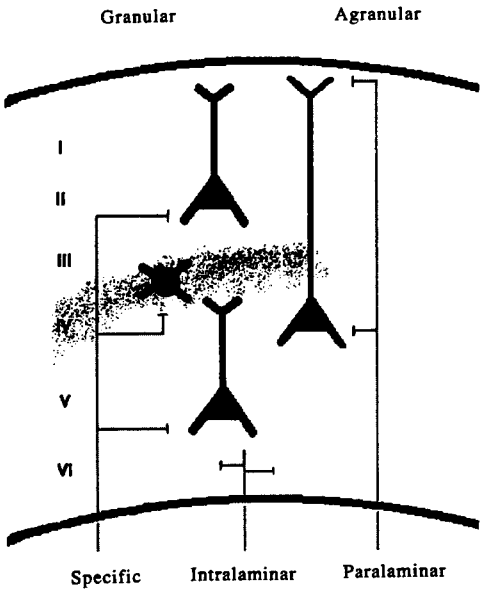

Fig. 1. Schematic diagram illustrating the three main types of thalamocortical pathways classified according to their lamination patterns in the cortex. Specific nuclei contact layer VI pyramidal cells, layer IV spiny stellate cells, and the basal dendrites of layer III pyramidal cells in granular cortex. Paralaminar nuclei project to layer I, and a majority of them also have connections in layer V of agranular cortex. Intralaminar nuclei project mainly to infragranular layers, and currently it is unclear if they project also to layer I. Connections with inhibitory interneurons are not illustrated.

cortex of the modality they represent. It is well established that these nuclei project densely and in a topographically organized manner to the primary sensory areas of the neocortex, with their main terminations in layers IV–III, and with collaterals mainly in upper VI (Bernardo and Woolsey, 1987; Jensen and Killackey, 1987; Lu and Lin, 1993; Keller *et al.*, 1985; Chmielowska *et al.*, 1989; Romanski and LeDoux, 1993; Freund *et al.*, 1985). However, it is important to recognize that the classification of specific thalamic nuclei based on lamina of cortical termination is not without problems (Steriade *et al.*, 1990). One major problem is that a single specific thalamic nucleus may have two or more populations of neurons, each projecting to different layers of the same cortical area. For example, the lateral geniculate nucleus (LGN), the ventral posterior lateral nucleus (VPL) and the medial geniculate nucleus (MGN) each has a population of small neurons that project to layer I of their respective primary sensory cortical areas (Ferster and LeVay, 1978; Rausell and Avendaño, 1985; Mitani *et al.*, 1987).

A second problem is that while one population of cells may project topographically to a single cortical area, other cells in that same nucleus can project to several cortical areas. Hence, important interareal and interspecies differences have been described in the patterns of branching for specific nuclei projections. For example, in the visual cortex of the monkey and cat, one geniculate afferent can form multiple patches of terminals in layer IV (Blasdel and Lund, 1983; Ferster and LeVay, 1978) while, in the barrel cortex of the rat, each afferent from VPM terminates within a single barrel hollow (Jensen and Killackey, 1987). In addition, in the barrel cortex individual fibers form thalamocortical axon terminals throughout the height of a layer IV barrel (Jensen and Killackey, 1987), while thalamocortical fibers originating in the LGN terminate in specific and restricted sublaminae of the visual cortex (Blasdel and Lund, 1983). The interareal differences of the specific nuclei projections may arise from, or be relevant to, the functional specializations of the different areas.

Table 1. Thalamocortical Nuclei

Descriptive anatomy	Nuclei	Laminar projection
Anterior and mediodorsal group	Anterodorsal (AD)	Paralaminar
	Ventroanterior (VA)	
	Anteromedial (AM)	
	Mediodorsal (MD)	
Midline group	Parataenial (PT)	Paralaminar
	Paraventricular (PV)	
	Intermediodorsal (IMD)	
	Rhomboid (Rh)	
Intralaminar group	Central medial (CM)	Intralaminar
	Paracentral (Pc)	
	Central lateral (CL)	
	Parafascicular (Pf)	
Geniculate group	Lateral geniculate (LG)	Specific
	Medial geniculate (MG)	
	Medial geniculate magnocellular (MGm)	Paralaminar
Ventral group	Ventroposterior medial (VPM)	Specific
	Ventroposterior lateral (VPL)	
	Ventrolateral (VL)	
	Ventromedial (VM)	Paralaminar
Posterior group	Rostral (Pom)	Paralaminar
	Caudal (Poc)	
Lateral group	Lateroposterior (LP)	Paralaminar
	Laterodorsal (LD)	

A third problem is that one specific thalamic nucleus may project fibers solely to cortical layers IV–III, while others may have additional axon collaterals that terminate in other layers (i.e. mainly upper layer VI). This may be a source of functional heterogeneity for the different afferent populations. Despite these caveats, it is clear that the main feature of these nuclei is their topographically organized, dense and restricted arborizations within layers IV–III of the primary cortical areas they innervate.

The layers of axonal termination only begins to tell the story, and it is important to consider the finer structure of the projections from specific thalamic nuclei. In what layers are synapses made? Which types of cortical cells receive synapses from specific nuclei? On what part of the neurons are the synapses formed? What are the morphological characteristics of these synapses?

One general principle of the thalamocortical projections from specific nuclei seems to be that every neuron with a dendrite traversing layer IV of a primary cortical area makes synaptic contact with thalamic afferents (White, 1986; Peters and Payne, 1993). In addition, the majority of these specific thalamocortical synapses are formed on spines. However, both spiny and non-spiny cells of the cortex make synapses with specific thalamic afferents, and the dendrites of different neuron types form markedly different numbers of thalamocortical synapses. Thus, cortical cells defined by the projection sites of their axons receive distinct densities of thalamocortical synapses (White, 1986). Spiny stellate cells, which are often the major cell type in the dense, granular layer IV, are the principal recipients of specific thalamocortical synapses. These cells in turn project strongly to other spiny stellate cells of layer IV, and to layer III pyramidal cells (Anderson *et al.*, 1994). Despite the fact that layer IV spiny stellate cells are the principal recipients of synapses from the specific thalamic nuclei (White, 1986), it has been suggested that thalamocortical synapses represent a very small percentage (i.e. 6%) of the total number of excitatory synapses formed upon these cells (Ahmed *et al.*, 1994). Thus, synapses established by thalamocortical projections corresponding to the specific nuclei are only a minority of cortical synapses, even in thalamic recipient layers (see White, 1986; Peters and Payne, 1993; Ahmed *et al.*, 1994).

Structurally, thalamocortical synapses originating from the specific nuclei are larger than corticocortical synapses (Fig. 2; Kharazia and Weinberg, 1994; Ahmed *et al.*, 1994). Thalamocortical synapses contain abundant mitochondria and loosely packed clear vesicles, while corticocortical synapses are smaller, and with sparser mitochondria and more densely packed clear vesicles (Kharazia and Weinberg, 1994). Since synaptic size has sometimes been correlated with efficacy (Pierce and Lewin, 1994), it is possible that individual thalamocortical synapses produce a stronger synaptic drive than intracortical synapses (see point 4.2 below). Indeed, the size of synaptic boutons has been used to classify synaptic inputs onto spiny stellate cells in layer IV as of presumed thalamic or intracortical origin (e.g. Ahmed *et al.*, 1994).

The fact that different cell types receive different numbers of synapses from each specific thalamic nucleus raises the interesting possibility that cortical neurons may differ in their immediate responsiveness to thalamic activity. This issue has been studied in the somatosensory cortex using the thalamocortical slice preparation (Agmon and Connors, 1991). A correlation between the intrinsic firing patterns of cells in the cortex and the probability of activation by thalamocortical synapses was observed (Agmon and Connors, 1992). Monosynaptic connections were restricted to infragranular regular-spiking cells and to fast-spiking (presumed inhibitory) cells, while disynaptic potentials were observed in supragranular regular-spiking and intrinsically bursting cells. A more recent study, also using slices, showed that intrinsically bursting neurons in layer V also receive monosynaptic input (Gil and Amitai, 1996a). In the unanesthetized cat, all neuron types recorded (i.e. bursting, regular-spiking and fast-spiking) received monosynaptic inputs in the motor cortex from the ventrolateral nucleus (VL) of the thalamus, although different cell types did differ in the strength of activation (Baranyi *et al.*, 1993).

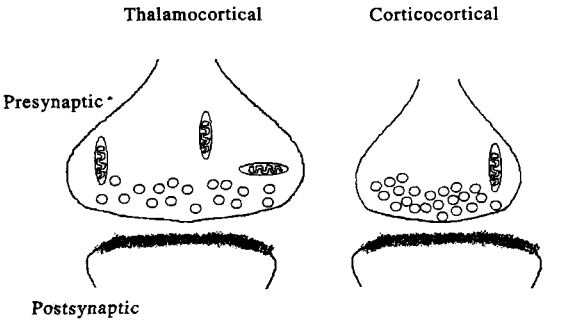

Fig. 2. Schematic ultrastructure of thalamocortical and corticocortical synapses. Thalamocortical synapses originating in specific nuclei are larger than corticocortical synapses, and contain more mitochondria and loosely packed vesicles. Based on Kharazia and Weinberg (1994).

To summarize the characteristics of the thalamocortical pathways from specific nuclei:

1. The main cortical projections from specific nuclei end in layers IV and III, forming dense, topographically organized arbors that synapse mainly with dendritic spines. Some of these layer IV–III-terminating fibers have collateral branches that innervate upper layer VI.

2. A distinct group of thalamic cells (i.e. usually with relatively small somata) may be present, and these project diffusely to other cortical laminae (in particular layer I).

3. All cells traversing layer IV in the cortical projection area of the specific afferents receive thalamocortical synapses, but in different amounts correlated with their projection site and possibly their intrinsic physiology.

4. Synapses formed by axons originating in the specific nuclei are a minority of the total asymmetric synapses (i.e. $< 10\%$) in the principal lamina of their projection (i.e. layer IV). Thalamocortical synapses are larger in size, and contain more mitochondria and loosely packed clear vesicles than intracortical asymmetric synapses.

2.2. Non-specific Thalamic Nuclei: Intralaminar Nuclei

The most distinctive characteristic of the intralaminar nuclei is that they have a dense projection to the striatum, in addition to their cortical projection. This striatal projection is more dense than that to the cortex, and each projection seems to originate from different sets of cells contained within the same nuclei. Thus, separate populations of specific cortex- or striatum-projecting cells intermingle to form the intralaminar nuclei, while a small subpopulation of cells has been claimed to project to both targets (Royce, 1983). Under our functional classification, the intralaminar nuclei would not be related to any particular modality.

It is still not clear which layer(s) of the cortex the intralaminar nuclei terminate in. Jones (1975) first proposed that they terminate in layer I. Herkenham (1986) later suggested that the most likely projection site was layer VI, and that previous claims of layer I projections were due to the spread of axonal tracers to the adjacent VM nucleus, which clearly projects to layer I (Glenn *et al.*, 1982; Herkenham, 1980; Rieck and Carey, 1985). Retrograde labeling with tracer injections restricted to layer I also indicate that the projection to layer I is specifically from VM, and not from the intralaminar nuclei (Glenn *et al.*, 1982; Rieck and Carey, 1985). Others have suggested that the intralaminar nuclei may terminate in *both* layers I and VI (Cunningham and LeVay, 1986).

Differences between species studied may account for some of these contradictory conclusions. However Herkenham's (Herkenham, 1986) investigation of the rat indicates that the main projection sites of the intralaminar nuclei are layers V and VI, while a more recent report, also in the rat, indicates that in addition to the infragranular layers, layer I is a target for the fibers originating in some intralaminar nuclei (Berendse and Groenewegen, 1991). Moreover, a recent study in the cat and monkey indicates that injections of HRP in the posterior parietal cortex only label the intralaminar nuclei when the deep layers are injected with the tracer (Avendaño *et al.*, 1990). Anterograde tracers placed in the intralaminar nuclei of the monkey show widespread projections to layer I and to layers V and VI of the visual cortex (Towns *et al.*, 1990). We must conclude that the exact cortical projection laminae of the intralaminar nuclei remain controversial.

Recent work has shown that the intralaminar nuclei have more restricted projections to the cerebral cortex than previously thought. In fact, axons from these nuclei terminate in circumscribed parts of the cerebral cortex and striatum, and these targets are interconnected through corticostriatal projections (Groenewegen and Berendse, 1994). As a whole, the midline–intralaminar nuclear complex projects to widespread, mainly frontal cortical areas, but each individual nucleus has a restricted cortical field of termination that overlaps only slightly with the projection fields of adjacent nuclei (Groenewegen and Berendse, 1994).

The finer aspects of the intralaminar projection to the cortex have been largely neglected so far. Very little is known about the specific cortical cell types receiving intralaminar synapses, the part of the cell that receives them, or the ultrastructural characteristics of these synapses.

To summarize the general characteristics of the thalamocortical pathways from intralaminar nuclei:

1. They project to the striatum and cerebral cortex, arising largely from separate subpopulations of thalamic cells; the striatal projection is denser than the cortical projection.
2. Cortical terminations are mainly in layers V and VI, and it is still unclear whether or not they have additional sparse projections to layer I.
3. As a whole, the intralaminar nuclei have widespread projections mainly to the frontal cortex, but each individual nucleus has a restricted cortical field of termination.

2.3. Paralaminar Nuclei

All thalamic nuclei that are not "specific" or "intralaminar" may be placed into the broad category of paralaminar. According to Herkenham (1986), all paralaminar nuclei have in common that they project to layer I, but they vary in their projections to other cortical laminae. A typical example of a layer I-projecting nucleus is VM, and some studies suggest that it projects exclusively to layer I (Glenn *et al.*, 1982; Herkenham, 1986). In addition, VM's terminations in layer I seem to be widespread (Rieck and Carey, 1985). The posterior nucleus (Po) also is a paralaminar nucleus with area-dependent lamination patterns (Herkenham, 1986). The anterior nuclear group is an example of a paralaminar system that projects to layer I in addition to other layers (i.e. III, IV, V and VI), depending on the cortical area (Shibata, 1993; Wannier *et al.*, 1992). The adjacent mediodorsal nucleus projects to layers I and III of different areas in the prefrontal cortex (Krettek and Prince, 1977). Other paralaminar nuclei include the most medial portion of VL, which has a widespread projection to layer I and shows area-dependent lamination (Herkenham, 1986).

The VL deserves special consideration within the paralaminar nuclei. This nucleus has been shown to project with topographic specificity onto the primary motor cortex of the rat (Donoghue *et al.*, 1979). Most of the rat primary motor cortex corresponds cytoarchitectonically to the lateral agranular cortex (Donoghue and Wise, 1982), which means that most of the motor cortex lacks a densely cell-packed layer IV. Accordingly, the main projection of VL cannot go to layer IV, as most specific nuclei do. Instead, anatomical results show that rat VL axons terminate mainly in cortical layers I, III and V (Herkenham, 1980), or layers I and V (Yamamoto *et al.*, 1990a). The main terminal layer might depend on cortical area; hence layer III might be the principal lamina of termination in prefrontal areas, while layer V would be the principal lamina in motor cortex (Jacobson and Trojanowski, 1975). Moreover, Herkenham (1986) has proposed that the VL nucleus of the rat can be divided into two regions. A lateral region has specific projections to the primary motor cortex, while a more medial region (i.e. VLm) provides

paralaminar input to a much more widespread area of the cortex. Other species may show different termination patterns for their VL fibers. For instance, in the cat it has been shown that VL fibers are densest in layers I and III of the motor cortex (Shinoda and Kakei, 1989), and that the terminations of VL afferents in layer III form multiple patches of innervation, similar to the LGN fibers in the visual cortex of the cat (Shinoda *et al.*, 1993). A recent study in the cat comparing the VL and VM pathways has emphasized the different degrees of spread of these projections in the cortex (Steriade, 1995).

The cortical projections from the Pom nucleus (a paralaminar nucleus) and VPM nucleus (a specific nucleus) were compared recently using anterograde tracing methods in the rat (Koralek *et al.*, 1988; Lu and Lin, 1993). These two nuclei project to the same cortical area, i.e. the barrel cortex, in a distinct and complementary fashion. The specific nucleus showed its characteristic projection by densely innervating layers IV and III and, more sparsely, upper layer VI, deep layer V and layer I. However, the paralaminar nucleus densely innervated layers I and V of both the barrel and the interbarrel area (i.e. the dysgranular portion of the barrel cortex which lacks a densely cell packed layer IV). For the purposes of a functional classification, the paralaminar nuclei can be considered to provide secondary information to the cortex of the modality they represent. Therefore, it seems that the specific and the paralaminar nuclei may have complimentary projections and functions in thalamocortical processing (Diamond, 1995).

The comparison between VPM and Pom projections fits well with the general differences between paralaminar and the specific nuclei (Lu and Lin, 1993). First, the fibers originating in the Pom tend to avoid the granular layer IV. Second, these Pom fibers tend to be distributed over a larger area than those originating in specific nuclei. Third, the average distance between synapses formed by an axon of Pom seems to be more than twice as large as those of VPM. Fourth, at the ultrastructural level it seems that no differences exist between both types of synapses (Lu and Lin, 1993), and thus the main difference might be in the synaptic density and not in synaptic morphology (or efficacy) of each nucleus innervation of cortex. Further research will be necessary to establish the generality of these characteristics among other paralaminar nuclei.

To summarize the general characteristics of the paralaminar thalamocortical pathways:

1. They always have a dense and widespread projection to layer I, and they may or may not have projections to other layers.
2. The projections to laminae other than I are variable between nuclei, and area-dependent for each nucleus, and tend to avoid the primary projection lamina of the specific nuclei (i.e. layer IV in granular cortex); synaptic contacts are also sparser from paralaminar than from specific nuclei.
3. Usually, a particular paralaminar nucleus projects to the same cortical area as another specific nucleus, providing complimentary, parallel thalamocortical pathways to that area.

2.4. Convergent Thalamic Projections to the Cortex

An important principal of thalamocortical connectivity is that a particular cortical area receives convergent projections from a variety of thalamic nuclei. This can be best demonstrated by infusing a retrograde tracer (e.g. horseradish peroxidase, HRP) into a cortical area and investigating the thalamic location of stained neurons. Although not well suited to tracing the lamina of termination of axons, retrograde tracers have been the most popular approach to the study of thalamocortical connectivity, providing invaluable information. For instance, an infusion of HRP into a restricted topographic region (but across many layers) of the primary motor cortex produces retrograde labeling in a variety of thalamic nuclei, including VL, VM, the posterior nucleus (Po), and all the intralaminar nuclei (Donoghue and Parham, 1983; Aldes, 1988; Cicirata *et al.*, 1986; Asuncion-Moran and Reinoso-Suarez, 1988). The most strongly labeled nuclei are VL and Pom, while the intralaminar nuclei are sparsely labeled. In the vibrissae representation of the somatosensory cortex, HRP injections label the same thalamic nuclei as they do in the primary motor cortex, but the labeled nucleus providing primary information changes from VL (motor cortex) to VPM (somatosensory cortex; Diamond, 1995). The connections of the rat posterior parietal cortex also have been examined with retrograde tracers, and they show that it receives projections from the lateral posterior (LP) and lateral dorsal (LD) nuclei, but not from the ventrobasal thalamus (i.e. VPL and VPM) which project to frontoparietal areas (Chandler *et al.*, 1992). The infralimbic cortex, or ventral portion of the medial frontal cortex, receives projections from the mediodorsal, intralaminar and midline thalamic nuclei (Freedman and Cassell, 1991). Thus, different cortical areas receive independent projections from the specific nuclei, and share projections from the non-specific nuclei. This allows the arrival of primary information specific to the modality of the cortical area, as well as secondary information related to other aspects of processing.

3. ELECTROPHYSIOLOGY OF THALAMOCORTICAL PATHWAYS

The area of neocortex activated by a particular thalamic nucleus varies according to the cortical region and laminae of fiber terminations; as we described above, termination patterns vary among nuclei. The thalamocortical pathways also respond differentially to different frequencies of stimulation. The pioneering studies of thalamocortical responsiveness were carried out by Morison and Dempsey over 50 years ago (Morison and Dempsey, 1942, 1943; Dempsey and Morison, 1942a, 1942b, 1943). Their work demonstrated three basic responses from the cortex following thalamic stimulation. The first type, called the *primary response*, consists of a short-latency, biphasic extracellular potential (surface positive–negative) which is most prominent when the specific nuclei are stimulated (Figs 3 and 4). The second type, called the *augmenting response*, is evoked by

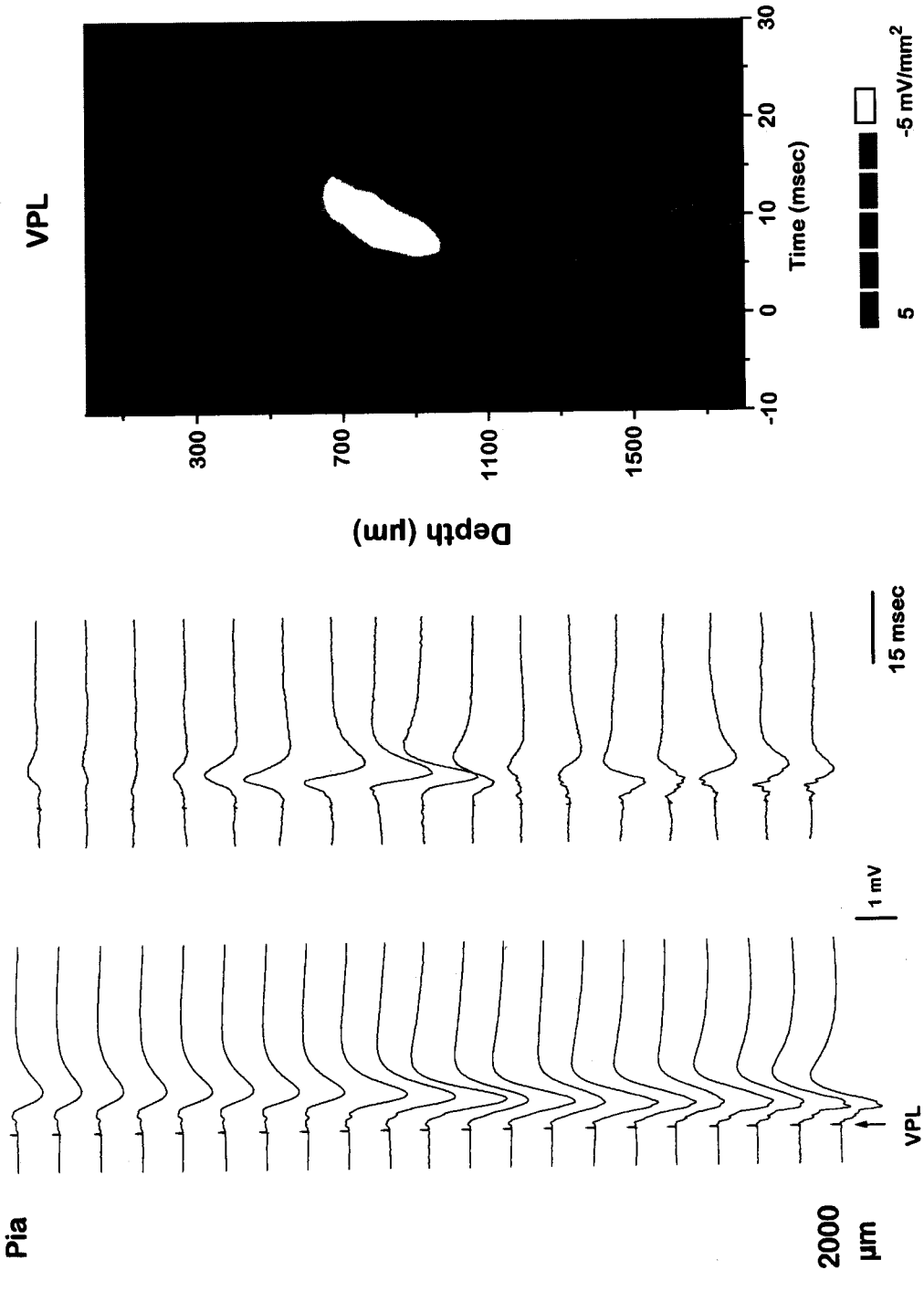

Fig. 3. Primary response evoked in neocortex by stimulating a specific thalamic nucleus. Laminar analysis of response to VPL stimulation. Field potentials (left), CSD analysis (middle), and contour plot of the CSD (right) after VPL stimulation while recording in the somatosensory cortex of the rat. In the contour plot, white represents current sinks, black represents current sources, and grays are around zero. Note the two short-latency current sinks in layer IV and upper layer VI, and the very effective spread of activity from layer IV into the upper layers. From Castro-Alamancos and Connors (1996b).

low-frequency stimulation (i.e. 7–14 Hz) of some of the thalamic nuclei (Figs 4, 6). It is evident as an increment in the amplitude of the second pulse of a series of pulses, and reaches a steady-state of augmentation by the third pulse. The augmenting response is characterized by its surface positivity and middle layer negativity, and was described as being specific to certain restricted cortical areas. The third response type, called the *recruiting response*, is characterized by monophasic surface negativity and middle layer positivity. It has a relatively long latency when elicited from the intralaminar nuclei, but it can be evoked with short latencies from certain other nuclei (e.g. VM; ventroanterior, VA). The recruiting response appears over widespread areas of the cortex in response to low-frequency stimulation delivered within the same frequency range as the augmenting response (i.e. 6–12 Hz). The primary, recruiting and augmenting responses imply that the effects of afferent activity entering the neocortex are highly sensitive to frequency.

3.1. The Primary Response

Primary and augmenting responses typically are considered together, since they can be elicited from the same thalamic location by different stimulus frequencies (e.g. Morin and Steriade, 1981; Ferster and Lindstrom, 1985a). However, we will consider them separately, because recent data indicate that they involve independent response systems (Castro-Alamancos and Connors, 1996b). The primary response is the cortical response evoked by the direct, monosynaptic projections of the thalamus to the cortex. The most widely studied is the primary response induced by stimulation of specific nuclei, which is biphasic, surface positive–negative; the negativity apparently occupies a larger cortical region than the positivity (Steriade *et al.*, 1990). The surface-negative phase of the response has been attributed to the layer I terminations of the small-sized thalamocortical projection cells that occur in each specific thalamic nucleus (Ferster and LeVay, 1978; Penny *et al.*, 1982; Rausell and Avendaño, 1985). These are said to be more extensive and profuse than the layer IV projections. A relatively more profuse layer I projection would also explain the larger spread of the surface negativity over the cortex, as compared to the surface positivity. In addition, the surface negativity arises from the polysynaptic activation of upper layer (i.e. I, II and III) dendritic processes by axons from layer III and IV neurons that are activated monosynaptically by the thalamic fibers (Mitzdorf and Singer, 1978). Using electrophysiological procedures, it is possible to investigate the laminar projections of the different thalamic nuclei by calculating the current-source density (CSD) from extracellular cortical field potentials (Castro-Alamancos and Connors, 1996b). The CSD analysis reveals the locations of the underlying current generators of these potentials,

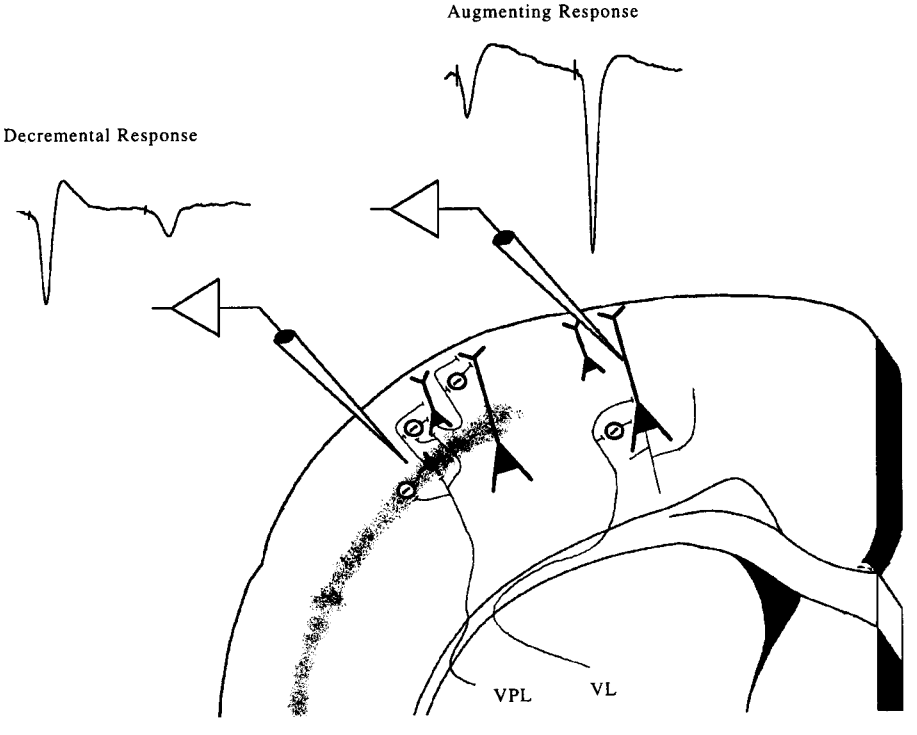

Fig. 4. Schematic diagram showing the thalamocortical connections responsible for the generation of decremental and the augmenting responses in VPL and VL pathways, respectively. The VPL thalamocortical pathway projects mainly to layers IV and lower III of granular cortex and produces a decremental response. The VL thalamocortical pathway projects to layer V of agranular cortex and produces an augmenting response. Open circles with a minus sign represent inhibitory interneurons. Based on Castro-Alamancos and Connors (1996b, 1996c, 1996d).

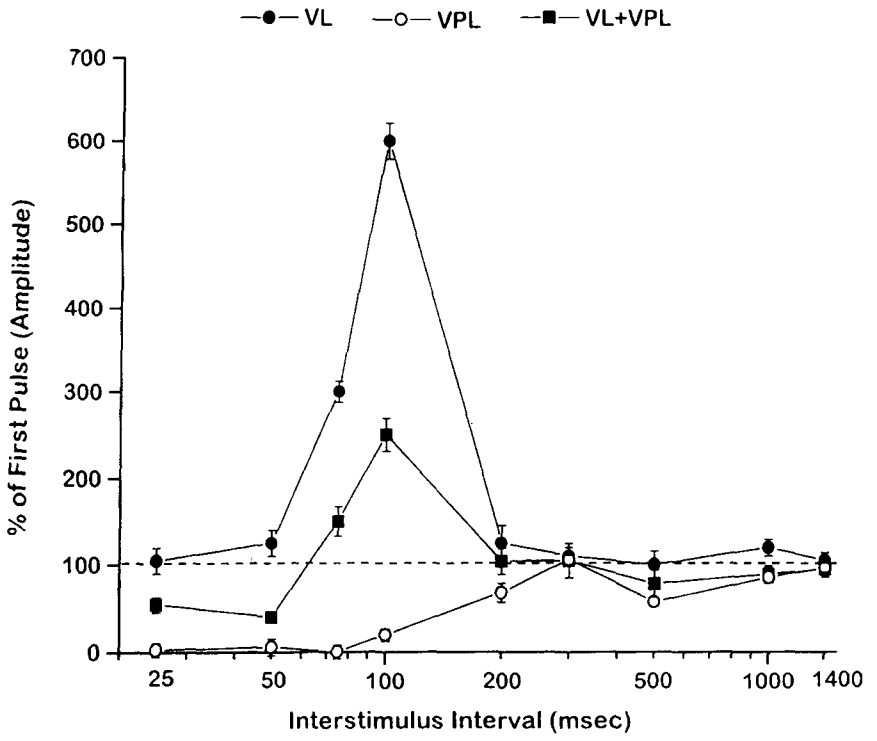

Fig. 5. Effects of paired-pulse stimulation applied in VL, VPL or both while recording in the sensorimotor cortex of the rat. Data are expressed as the percentage of change in the amplitude of the second response, compared to the first response. The interval between stimuli is represented on a semi-logarithmic scale. Stimulation to VL produces an augmenting response at interstimulus intervals between 50 and 200 msec, while stimulation to VPL produces a decremental response at interstimulus intervals below 200 msec. Stimulation to both nuclei simultaneously produces intermediate effects. From Castro-Alamancos and Connors, (1996b).

with good spatial resolution (Nicholson, 1979; Mitzdorf, 1985). Figure 3 shows a CSD analysis derived from stimulation of a specific thalamic nucleus (i.e. VPL) with one pulse while recording in the primary somatosensory cortex of the rat. Two short-latency current sinks are observed (white). The largest is located in layer IV, and has a corresponding current source (black) in layers II–III. The layer IV sink spreads strongly into layers II–III over the next 10 msec or so. The second short-latency current sink originates in upper layer VI and has a corresponding source in lower layer VI. The locations of the short-latency current sinks correlate very well with the results of numerous anterograde tracer studies, which show that the fibers of the specific nuclei terminate mainly in layers IV–III, with axon collaterals in upper VI (see Section 2.1).

The primary response evoked from specific thalamic nuclei shows strong depression to paired stimuli applied at frequencies above 5 Hz (Figs 4 and 5). We call this response depression the *decremental response* (Castro-Alamancos and Connors, 1996b). Its mechanisms have not been investigated, and there are several candidates. In a variety of other brain regions, paired-pulse depression often has been attributed to the actions of a modulator or neurotransmitter acting on presynaptic receptors, and diminishing transmitter release (e.g. Mott and Lewis, 1994). In neocortical slices, paired-pulse depression of both inhibitory postsynaptic potentials (IPSPs) (Deisz and Prince, 1989) and excitatory transmission (Kang, 1995) may be due, at least in part, to the action of GABA on presynaptic $GABA_B$ receptors. Other potential mechanisms of the decremental response are that the strong postsynaptic inhibition recruited by thalamic input shunts subsequent excitatory input within the course of the hyperpolarization (Metherate and Ashe, 1993a), or that the intrinsic neurotransmitter release properties of thalamocortical synapses are responsible for the strong depression (see Section 4.2; Castro-Alamancos and Connors, 1997). This interesting property of thalamocortical responsiveness deserves further investigation.

The responses of neocortical neurons to stimulation of specific thalamic nuclei also has been studied with intracellular recording methods. The initial response in a pyramidal neuron is typically a monosynaptic excitatory postsynaptic potential (EPSP), which is immediately followed by a disynaptic, strong and long-lasting IPSP. Inhibition occurs because both excitatory and inhibitory cells of the cortex are monosynaptically activated by specific thalamocortical fibers. However, intracellular responses may differ according to the laminar position of the recorded neuron. For example, in the cat, LGN stimuli monosynaptically activate cells in layers III, IV, upper V and VI of primary visual cortex (Ferster

and Lindstrom, 1983), which agrees with the pattern of terminal boutons formed by specific thalamocortical fibers (Landry *et al.*, 1987). But infragranular cells in the cat visual cortex apparently receive a stronger EPSP than upper layer cells (Douglas and Martin, 1991). When activated from VPL, pyramidal cells of the cat somatosensory cortex located in layers IV and III receive short-latency (i.e. 1–1.5 msec) EPSPs, while cells of layer V and VI respond with longer latencies (2.9 msec; Yamamoto *et al.*, 1990b). These studies suggest a common sequence of cellular activation following stimulation of specific nuclei: upper layer cells (layers I–IV; i.e. corticocortical cells) fire first, followed by layer V and VI cells (i.e. output cells).

Using a thalamocortical slice preparation it was shown that specific fibers from the VPM nucleus produce monosynaptic EPSPs mainly onto fast-spiking and regular-spiking cells in the infragranular layers (Agmon and Connors, 1992). Intracellular recordings *in vivo* suggested that thalamic EPSPs differ from intracortical EPSPs mainly in their voltage-dependent properties (Baranyi *et al.*, 1993). While corticocortical EPSPs had late components that increased in amplitude during depolarizing current injections and decreased by hyperpolarization, thalamocortical EPSPs increased during hyperpolarization and decreased during depolarization (see Section 4.3.2).

The conduction velocity of the thalamocortical axons is of fundamental importance to characteristics of the thalamocortical primary response. Axonal conduction velocity is correlated tightly with the diameter of the fibers, and their myelination. In the cat, geniculocortical projection axons differ greatly in conduction velocity (see Lennie, 1980). The Y cells in the dorsal layers of the LGN have faster conducting axons than X cells, and the axons that activate these cells from the optic tract also display this difference. In the somatosensory system of the cat, VPL cells with the fastest projection fibers are also connected with faster medial lemniscus fibers, with a range of conduction velocities for the thalamocortical fibers of 13–44 m/sec (Tsumoto and Iwama, 1972). In the rabbit somatosensory system, cells can be activated by tactile stimulation with a latency range of about 5.7–13 msec; the total conduction time through the thalamocortical fibers originating in VPM is about 1 msec (Swadlow, 1995). In the cat, conduction through the thalamocortical fibers originating in VL ($\sim$ 2 msec) was found to be 1 msec faster than those originating in VM ($\sim$ 3 msec), and these differences also matched the conduction velocities of the cerebellar fibers projecting to these thalamic nuclei, interpositus-dentate and fastigial, respectively (Steriade, 1995). In the rat, a comparison of the conduction velocities of VL and VPL thalamocortical fibers revealed no significant differences (Dutar *et al.*, 1985).

3.2. The Augmenting Response

When certain thalamic nuclei are stimulated at frequencies ranging from 7–14 Hz, an augmenting response develops with the second pulse and grows quickly to a steady-state. In addition to its incremental nature, the most distinctive characteristic of the augmenting response is its surface positivity and middle layer negativity. Morison and Dempsey attributed the augmenting response to a purely thalamic locus and a very speculative mechanism (Morison and Dempsey, 1943). Subsequent studies have indicated that cortical processes are responsible (Morin and Steriade, 1981; Castro-Alamancos and Connors, 1996b, 1996c, 1996d).

Although the augmenting response has been widely studied (e.g. Spencer and Brookhart, 1961a; Purpura and Shofer, 1964; Purpura *et al.*, 1964; Sasaki *et al.*, 1970), the mechanisms responsible for its generation remained elusive. Morin and Steriade (1981) proposed that the augmenting response is due largely to the intrinsic organization of the cerebral cortex and not due to a thalamic mechanism. Ferster and Lindstrom (1985a, 1985b) proposed that the augmenting response arose from the unusual synaptic properties of the intracortical axon collaterals of antidromically activated corticothalamic neurons (i.e. corticothalamic layer VI cells that project collaterals to layer IV). However, the hypothesis proposed by Ferster and Lindstrom cannot account for most of the defining characteristics of the augmenting response; such as, the restricted frequency dependence of the augmenting response and its correlation with hyperpolarization of cortical cells, or the importance of a long-latency potential which delimits the effective temporal interval for augmenting (see below and Castro-Alamancos and Connors, 1996d, for discussion). There seems to be general agreement that the phenomenon does not require the thalamus (but see Mishima and Ohta, 1992), although some contributory role for the thalamus has not been ruled out.

Recently, Metherate and Ashe (1994) studied an incrementing response very similar to the augmenting response, although they did not refer to it as such (see their Fig. 1). They concluded that its mechanisms depended on the facilitation of *N*-methyl-D-aspartate (NMDA) receptor-mediated EPSPs by the frequency-dependent depression of GABAergic IPSPs (Metherate and Ashe, 1994). However, this is inconsistent with observations that blockade of NMDA receptors does not abolish the augmenting response (Addae and Stone, 1987; Salt *et al.*, 1995; Castro-Alamancos and Connors, 1996b). Moreover, in slices *in vitro*, the facilitation of NMDA receptor-mediated EPSPs due to the depression of IPSPs occurs at a frequency range that does not parallel the frequency range that is effective for the generation of the augmenting response (see Castro-Alamancos and Connors, 1996d, for discussion).

Our recent work has inspired a new hypothesis for the cortical mechanisms of the augmenting response (Castro-Alamancos and Connors, 1996b, 1996c, 1996d). The first issue is whether the thalamus is responsible for generating this response, and ineffectiveness of thalamic lesions has suggested that this cannot be the case (Morin and Steriade, 1981; Ferster and Lindstrom, 1985a). Consistent with this, the reversible inactivation of the thalamic circuitry with microinjections of GABA or kynurenic acid did not

impair the augmenting response (Castro-Alamancos and Connors, 1996b). These results mean that it is very unlikely that the augmenting response is due to a polysynaptic intra-thalamic process that is relayed to the cortex.

How does the cortex generate augmenting? Stimulation of the VL nucleus of the rat induces an augmenting response in the primary motor cortex, consistent with the well-known thalamocortical projections of this system (Donoghue *et al.*, 1979; Donoghue and Parham, 1983). Anterograde tracers show that the main terminations of the VL projection are layers I and V (Yamamoto *et al.*, 1990a) or layers I, III and V (Herkenham, 1980) in the rat motor cortex. The CSD analysis in response to VL stimulation (Fig. 6) shows two current sinks located in layers V and I. Moreover, the augmenting response develops from the sink located in layer V; upon repeated stimulation the layer V sink becomes much stronger, concurrent with a similar increase in a current source located in the upper layers. This dipolar arrangement suggests that the elongated pyramidal cells of layer V are the primary generators of the currents of the augmenting response. It further suggests that thalamic nuclei projecting to layer V, but not those projecting to layer IV, are likely to be responsible for generating augmenting responses. A corrolary of this hypothesis is that specific (layer IV-projecting) thalamic nuclei may be less capable of triggering augmenting responses, as compared to paralaminar nuclei with projections to layer V (e.g. VL, Po, LP). Indeed, augmenting responses are only evoked by stimulating specific thalamic nuclei with very strong currents (Ferster and Lindstrom, 1985a; Castro-Alamancos and Connors, 1996b). In these cases, augmenting may be caused by current spread in the thalamus, which could activate adjacent paralaminar nuclei.

An intriguing property of the augmenting response is the very narrow frequency range that is effective in triggering it: stimulus intervals of about 50–200 msec (see Fig. 5). The intracellular correlate of this interval is a prominent hyperpolarization of layer V cells, generated by IPSPs evoked by the strong thalamocortical recruitment of inhibitory interneurons and terminated by a long-latency depolarizing event (Fig. 7). Furthermore, layer V has a subpopulation of pyramidal cells with specific membrane conductances that can be activated or deinactivated by hyperpolarization [Fig. 8(A); Castro-Alamancos and Connors, 1996d]. These apparently mediate low-threshold calcium currents (I_T) and hyperpolarization-activated cationic currents (I_H). At resting membrane potential levels, these currents are largely inactivated, and thus the response to the first pulse is modest. However, when the cells are transiently hyperpolarized due to the strong inhibitory input that they receive during afferent stimulation, the I_H is activated, and I_T is deinactivated. A subsequent excitatory input will trigger a larger depolarizing response [Fig. 8(B)] that will spread through the cortex by means of the extensive intracortical axon collaterals of the layer V pyramidal cells (Castro-Alamancos and Connors, 1996d). Once generated, the augmenting response spreads very effectively horizontally into adjacent cortical territory, but also propagates from layer V to the upper layers (see Figs 6,9). Interestingly, this upward propagation involves active dendritic conductances (Fig. 9; Castro-Alamancos and Connors, 1996d), which are evoked in the upper layer dendrites by the augmenting response generated in layer V.

The augmenting response also is very strongly influenced by the awake behavioral state of the animal (see Section 5), which suggests that the cellular mechanisms involved in its generation may be modulated by brain mechanisms governing behavioral state (Castro-Alamancos and Connors, 1996c). This modulation may arise from activation of the reticular formation, which is known to modulate the augmenting response (Steriade and Morin, 1981), by means of certain neurotransmitter systems (Castro-Alamancos and Connors, 1996e).

3.3. The Recruiting Response

Dempsey and Morison were also the first to describe the recruiting response (Dempsey and Morison, 1943). Subsequent investigators attributed the recruiting response to the depolarization of distal dendrites of pyramidal neurons by layer I thalamocortical projections (e.g. Herkenham, 1986; Steriade *et al.*, 1990). The nuclei that best induce recruiting responses (i.e. VM, VA) indeed project densely to layer I (Herkenham, 1979, 1986). This explains why the recruiting response is surface-negative, reflecting the inward flux of synaptic current and depolarization of terminal apical dendrites located in layer I. The fact that the recruiting response is observed over widespread areas of the cortex is consistent with the evidence that layer I projections usually have a longer lateral range than middle layer projections (Herkenham, 1986). Recruiting responses have been described as having long latencies, although they can be elicited with short latencies from several nuclei (Sasaki *et al.*, 1970). In some cases, the long latency of the recruiting response has been attributed to the slower conduction velocities of the axons originating in the nuclei producing recruiting responses (Glenn *et al.*, 1982; see Section 3.5). In other cases, long latency was said to arise from the intrathalamic disynaptic activation of certain nuclei elicited by stimulating the intralaminar nuclei (Jibiki *et al.*, 1986); thus, stimulation of intralaminar nuclei would specifically activate certain layer I projecting nuclei (e.g. VA, VM), through an intralaminar-to-VA pathway that has been observed anatomically (Steriade *et al.*, 1984). This hypothesis accounts for the capacity of intralaminar nuclei to generate long-latency recruiting responses, despite the apparent paradoxical lack of intralaminar projections to cortical layer I (Herkenham, 1986).

The cellular mechanisms of recruiting responses are not understood. It is interesting that recruiting responses are elicited at the same frequency as the augmenting response, and suggests that similar mechanisms might be involved. One possible scenario is that thalamocortical fibers reaching layer I produce augmenting-like responses in this layer through the

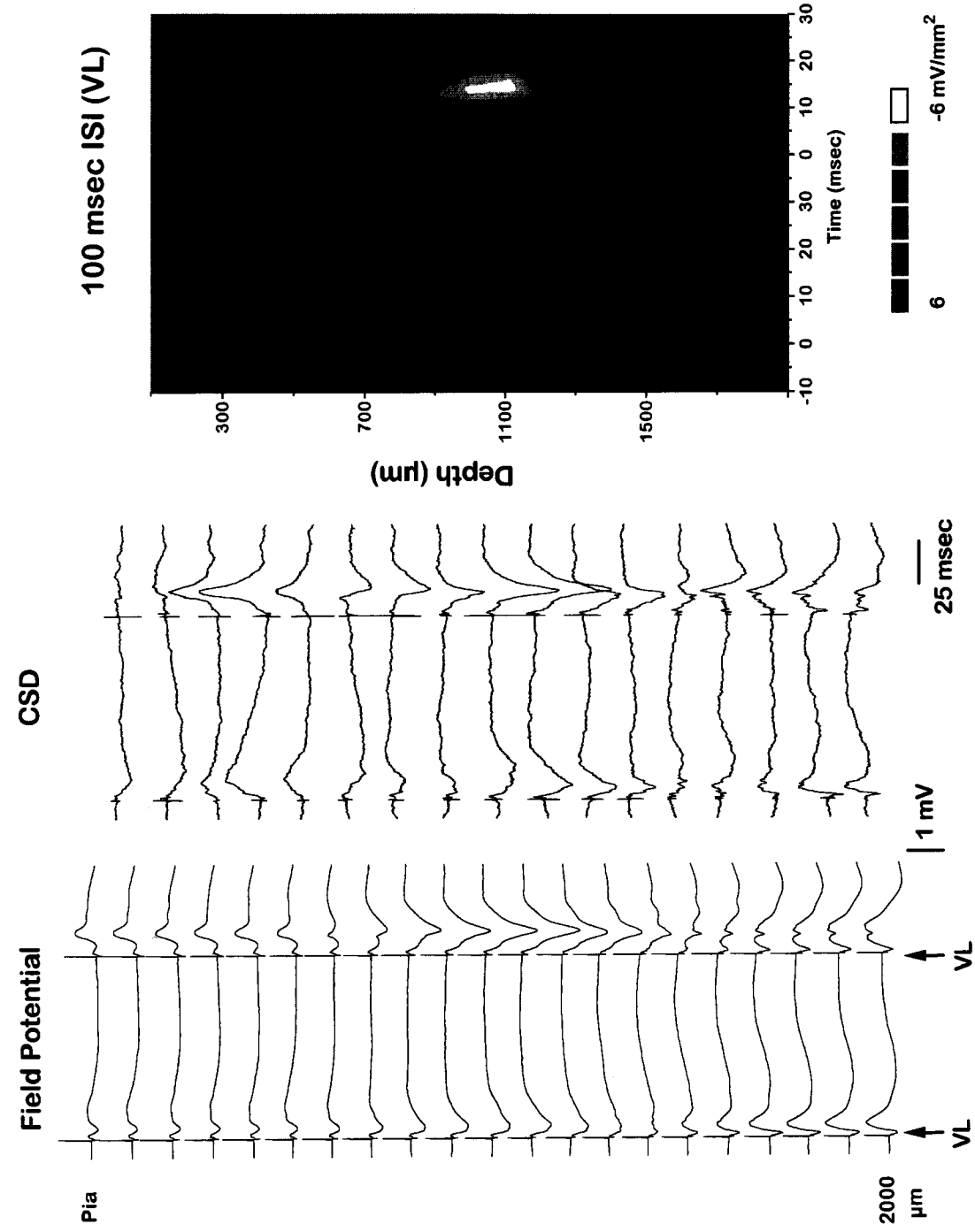

Fig. 6. Augmenting response evoked in neocortex by a pair of stimuli delivered in a paralaminar nucleus. Laminar analysis of responses evoked by a pair of VL stimuli delivered with an interstimulus interval of 100 msec. Field potentials (left), CSD analysis (middle), and contour plot of the CSD (right) after VL stimulation while recording in the primary motor cortex of the rat. In the contour plot, white represents current sinks, black represents current sources, and grays are around zero. The contour plot is interrupted, showing only 30 msec after and 10 msec before each stimulus. Note that the response to the first pulse is a small sink in layer V which is transformed into an augmented response by the second pulse delivered 100 msec later. See also Castro-Alamancos and Connors (1996b, 1996c, 1996d).

activation of hyperpolarization-activated or deinactivated conductances in apical dendrites. These responses then could be propagated actively along apical dendrites toward the somata of layer V pyramidal neurons. In fact, there is evidence for low-threshold calcium channels in the apical dendrites of pyramidal neurons (Markram and Sakmann, 1994). Further, active currents in apical dendrites serve to amplify the synaptic inputs arriving in layer I at the distal tufts of pyramidal neurons (Kim and Connors, 1993; Cauller and Connors, 1994). These active currents are evoked in neocortical

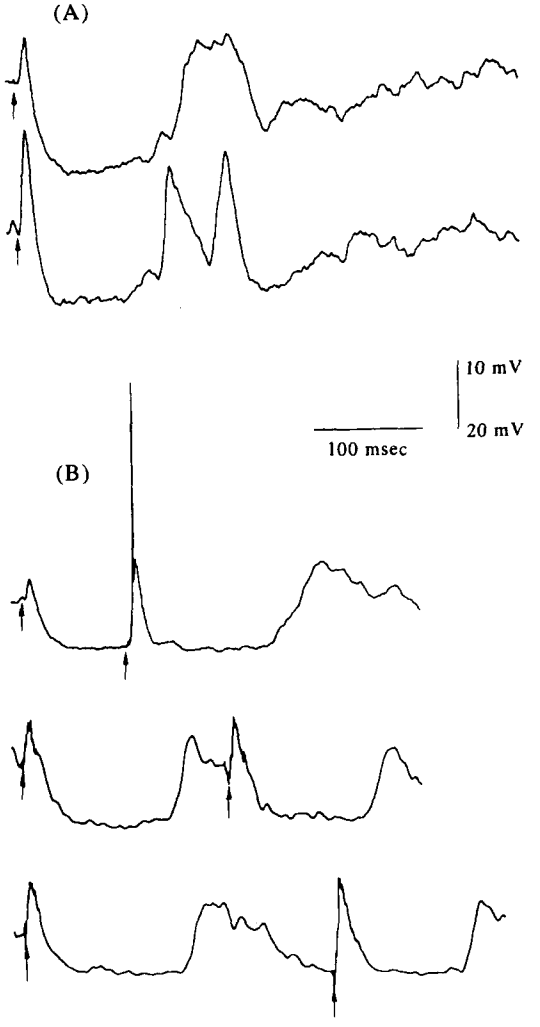

Fig. 7. Intracellular correlates of the augmenting response. (A) Effect of applying one stimulus to VL and recording from a cell in layer V of the primary motor cortex of the rat. One stimulus (arrow) applied to VL evokes a small excitatory postsynaptic potential, which is followed by a strong hyperpolarization lasting several hundreds of milliseconds. The hyperpolarization is interrupted at about 200 msec by a wave of depolarization. Bottom trace was hyperpolarized by about 20 mV from resting potential. (B) When a second stimulus is delivered during the hyperpolarization, an augmenting response is produced (100 msec), but not when the stimulus occurs during (200 msec) or after (300 msec) the long-latency depolarization. See also Castro-Alamancos and Connors (1996c, 1996d).

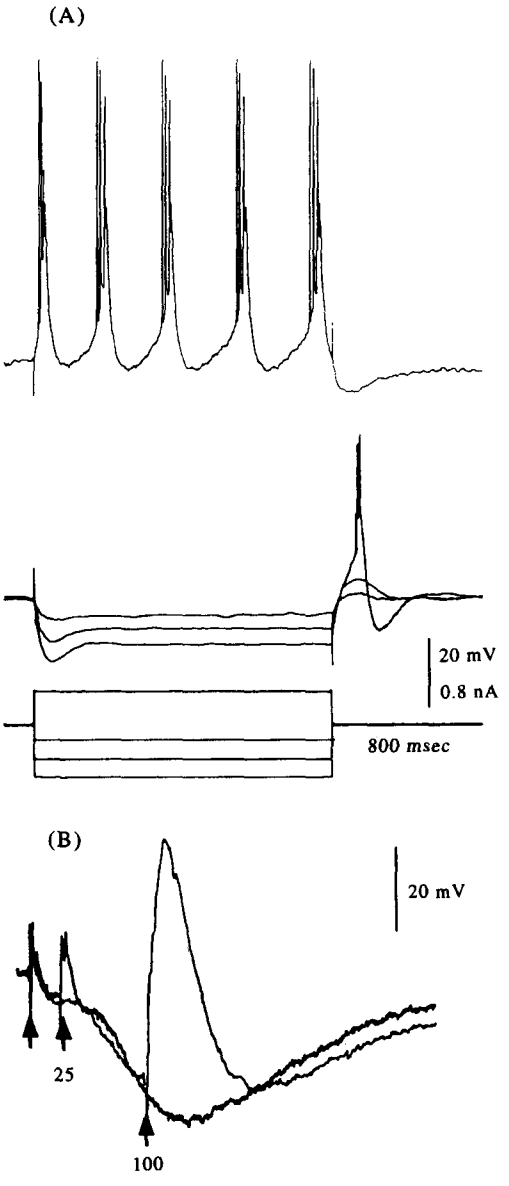

Fig. 8. Intrinsic membrane properties of layer V cells that contribute to the generation of augmenting responses. (A) Recording from a layer V pyramidal cell which has the intrinsic ability to burst repetitively upon current injection. These cells have currents which are activated or deinactivated by hyperpolarization. Note the depolarizing sag that occurs after the onset of hyperpolarizing current injection, and the rebound depolarization occuring after current offset, which can trigger a burst (spikes truncated). (B) Layer V cells in the slice produce augmenting responses. One stimulus delivered in the slice to layer V produces a small excitatory postsynaptic potential, which is followed by a hyperpolarization. When a second stimulus is delivered during the strong hyperpolarizing phase (100 msec), but not before (25 msec), an augmented response is generated. See Castro-Alamancos and Connors (1996c, 1996d).

apical dendrites by thalamic stimulation that triggers augmenting responses (Fig. 9; Castro-Alamancos and Connors, 1996d), and this could be the basis for recruiting response generation.

3.4. Rhythmic Activity of the Cortex: The Roles of Thalamocortical Synapses in their Generation and Modulation

Recordings from the neocortex during different behavioral states reveal a variety of electrical activities that can be differentiated by their frequency and pattern. Some of these clearly are generated by the thalamus, and therefore use thalamocortical pathways to access the neocortex. Others are thought to be generated entirely in the neocortex, but may be modulated and triggered by afferent activity from the thalamus. Thalamus and cortex are so intimately interconnected that, in most cases, probably we must consider both for a complete picture of the underlying rhythmic processes.

The functional significance of the various rhythms of the cerebral cortex is almost entirely unknown, and most research has concentrated on the more straightforward question of the cellular mechanisms involved. The following is a summary of the most widely investigated rhythms in the neocortex, in order of increasing frequency.

3.4.1. *Slow Waves* (< 1 *Hz*: 0.3–0.8 *Hz*)

These are observed mainly during drowsiness and slow-wave sleep (see Fig. 10). The mechanisms involved have been investigated recently (Steriade *et al.*, 1993a, 1993b, 1993c). At the single neuron level, slow waves parallel a prolonged depolarizing component that gives rise to repetitive action potentials (5–40 Hz), followed by a long-lasting hyperpolarization (0.5–1.5 sec). Slow waves are generated intracortically, since thalamic lesions and brainstem transections do not prevent their occurrence, and they are relayed by descending projections to the thalamus, where they can induce synchrony among the dorsal and ventral thalamus. Stimulation of the thalamus can transform this slow rhythm into faster rhythms, including seizure-like forms of activity (Steriade, 1994).

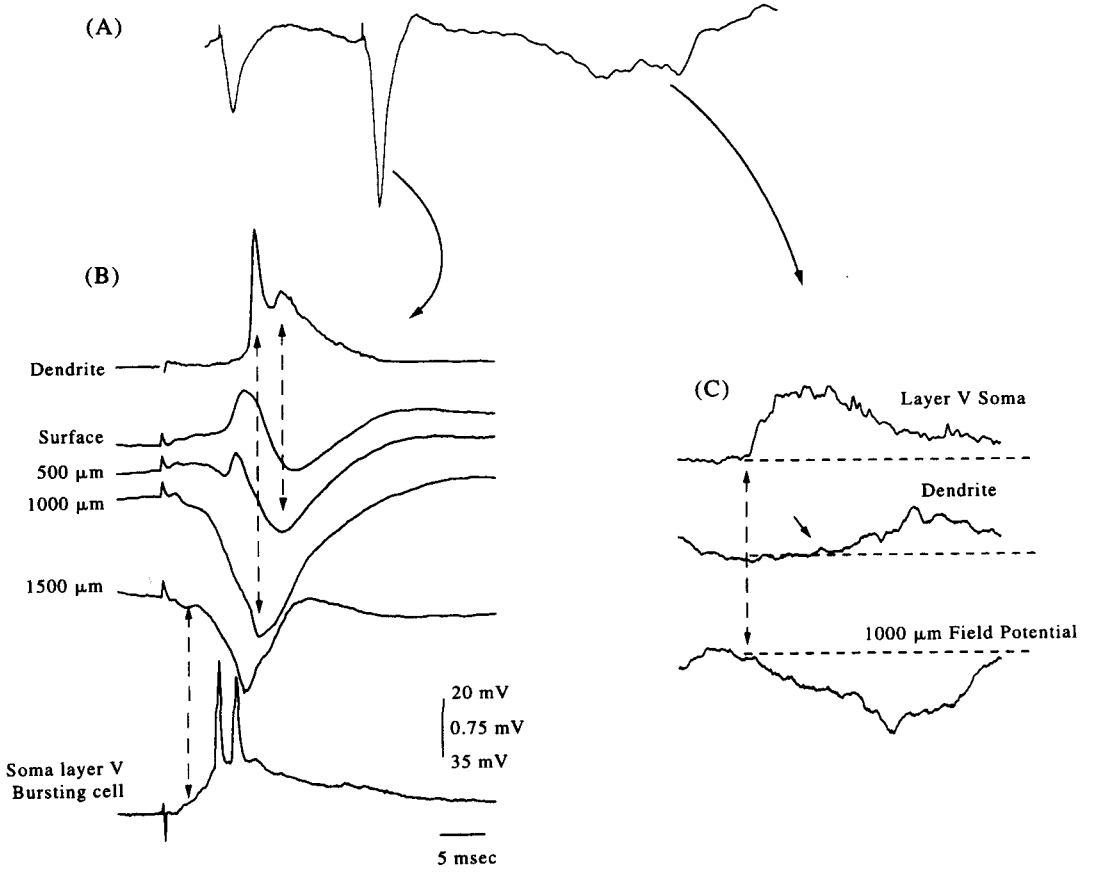

Fig. 9. Augmenting responses propagate to upper layers. (A) Extracellular recording from layer V showing an augmenting response evoked by VL stimulation; it consists of a primary response, an augmented response and a long-latency reponse. (B) Shown is the the augmented response corresponding to the second of a pair of stimuli delivered to VL. Sequential intracellular recordings from neuronal elements in different layers are phase-locked to different components of the field potentials recorded extracellularly. Responses from layer V correpond to the earlier component of the augmenting response recorded extracellularly between 1000 and 1500 μm, whereas recordings from a dendrite located in layer III corresponds to later components of the field potentials recorded in the upper layers. (C) The long-latency potentials occuring 200 msec after the augmenting response also originate in layer V and spread to the upper layers. See Castro-Alamancos and Connors (1996c, 1996d).

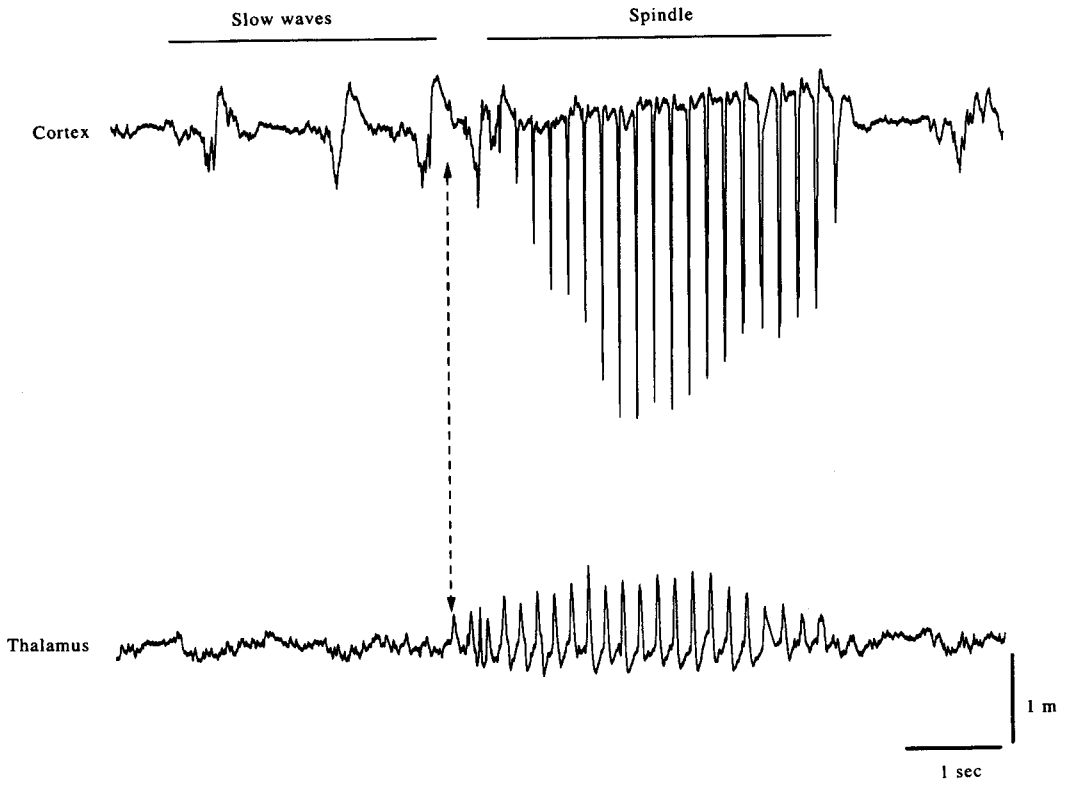

Fig. 10. Slow waves and spindle waves. Recordings were obtained from the neocortex (upper; primary motor cortex) and thalamus (lower; VL) of a ketamine-anesthetized rat. Slow waves are observed in the cortex, and periodically the slow waves are interrupted by spindle waves which originate in the thalamus.

3.4.2. *Delta Waves* (1–4 *Hz*)

These are prominent during slow-wave sleep, and are believed to involve at least two components, one cortical and one thalamic. Delta waves are observed in athalamic cats (Villablanca and Salinas-Zeballos, 1972), indicating that the cortex is capable of generating these oscillations independently. Cortical cellular mechanisms responsible for delta waves have been proposed (Metherate and Ashe, 1993a). However, thalamocortical cells in the specific thalamic nuclei also can generate an intrinsic oscillation in the delta range through the interplay of two of their voltage-gated conductances (McCormick and Pape, 1990), and this activity can be synchronized by corticothalamic volleys (Steriade *et al.*, 1991). Thus, inextricable interplay between the cortex and thalamus may be responsible for generating delta oscillations in the normal, intact brain.

3.4.3. *Spindle Waves* (7–14 *Hz*)

These are waxing and waning rhythms with dominant frequencies of 7–14 Hz, grouped in sequences that last 1–3 sec and recur periodically at 0.1–0.2 Hz (see Fig. 10). Spindle waves are prominent at sleep onset, during loss of awareness, during slow-wave sleep, and are prevalent during barbiturate anesthesia. The basis for the generation of spindles is particularly well understood (see Steriade *et al.*, 1990; Bal *et al.*, 1994). Spindles are generated in the thalamus (see Fig. 10) through interactions between the reticular nucleus and thalamocortical relay neurons (von Krosigk *et al.*, 1993), from which they are projected onto the neocortex. Interestingly, spindle waves can be triggered by corticothalamic volleys arising from slow-wave activity generated in the cortex (Contreras and Steriade, 1995), and when transmitted back to the cortex from the thalamus they can activate augmenting and recruiting responses (Spencer and Brookhart, 1961a, 1961b).

3.4.4. *Theta Waves* (5–7 *Hz*)

These can be observed in the parietal neocortex during certain behavioral states (e.g. motor activity). However, their presence in neocortex is due to volume conduction from the hippocampus (Buszaki *et al.*, 1988), where they have been studied extensively. Theta waves also can be observed in the entorhinal cortex (Chrobak and Buzsaki, 1994), which is believed to play an important role in their generation (Alonso and Llinás, 1989) by its interplay with the hippocampus.

3.4.5. *Alpha Waves* (8–12 *Hz*)

These have the same frequencies as spindles. However, each has several distinct characteristics. First, alpha waves are observed during restful attentiveness, while spindles are observed during unconscious states. Second, alpha waves form trains that are not rhythmic, while spindles wax and wane

in long sequences that recur periodically. Third, each has different topographies; while spindles are more prevalent in the frontoparietal areas, alpha waves have been more systematically observed in occipital cortex. The mechanisms involved in the generation of alpha waves are not known, but it is believed that the cortex plays an essential role (Lopes da Silva *et al.*, 1980). In fact, a subpopulation of layer V pyramidal cells has intrinsic properties that allow them to oscillate individually within the alpha range (Silva *et al.*, 1991). Again, the frequencies of alpha rhythms are similar to those that induce augmenting and recruiting responses in thalamocortical pathways. This suggests that they might share similar cellular mechanisms.

3.4.6. *Mu Waves* (12–18 *Hz*)

These occur in the sensorimotor cortex of awake cats during behavioral immobility, and are blocked by active movement (Bouyer *et al.*, 1983). In felines, this oscillation has been called the "sensorimotor rhythm", and it has been postulated that the ventrobasal thalamus is involved in the generation of mu waves over the sensorimotor cortex (Rougeul-Buser *et al.*, 1983). The analogous rhythm in humans occurs at a lower frequency range (8–13 Hz) than in cats. Interestingly, the sensorimotor rhythm has been considered to be anticonvulsive, and its enhancement by training has been considered as a potential therapeutic approach for the treatment of some forms of epilepsy.

3.4.7. *Beta Waves* (15–30 *Hz*)

These are observed in humans during states of focused attention and, as with mu waves, they tend to disappear during movement. A 35–45 Hz rhythm, also called a *beta rhythm*, has been observed in the frontoparietal cortex of cats and in the visual cortex of monkeys during periods of awake immobility, while exploring the environment, and especially during periods of focused attention on a visible target (Rougeul-Buser, 1994). Thalamocortical pathways have been proposed to generate this rhythm in the parietal cortex of the cat. Cell firing in the Pom precedes the beta waves recorded in the neocortex, and this activity is under the control of dopaminergic cells from the ventral tegmental area (Rougeul-Buser, 1994).

3.4.8. *Gamma Waves* (30–80 *Hz*)

These are the highest-frequency EEG signals commonly recorded. During active behavioral states, the usual EEG pattern is a low-amplitude, high-frequency (so-called "desynchronized") state. However, recently a variety of high-frequency activities that are well synchronized across specific regions of cortex have been observed during freely moving conditions and stimulus processing states (Singer, 1993). It has been proposed that rhythmic cortical activity in the gamma range is responsible for the binding of sensory responses into coherent percepts (Gray and Singer, 1989). Synchronous activity at around 40 Hz has been recorded within a column of visual cortex when light bars of optimal displacement and orientation are presented. These oscillations can become synchronized across widely separated cortical columns when components of a visual stimulus corresponding to a singular, extended object are presented (Gray and Singer, 1989). Interestingly, synchronization of this activity is enhanced by activating the reticular formation, an event that desynchronizes the EEG (Munk *et al.*, 1996). A population of pyramidal cells in superficial layers of the cat visual cortex that intrinsically generate repetitive bursts in the gamma range, have been proposed to be major participants in the generation of synchronous oscillations evoked by visual stimuli (Gray and McCormick, 1996). Gamma oscillations also have been observed throughout the cortical mantle of awake human subjects by using magnetoencephalography (Llinás and Ribary, 1993). These rhythms were proposed to mediate temporal conjunctions of rhythmic activity over a large ensemble of forebrain neurons (Llinás *et al.*, 1994). The notion is that sparsely spiny stellate (inhibitory) interneurons in the cortex, some of which have the intrinsic membrane properties necessary to oscillate around 40 Hz (Llinás *et al.*, 1991; Whittington *et al.*, 1995), entrain such oscillations in corticothalamic neurons, which in turn induce 40 Hz oscillations in the reticular neurons of the ventral thalamus. Reticular nucleus neurons then would entrain the specific and intralaminar nuclei in this oscillation, giving rise to a 40 Hz resonant oscillation in the entire thalamocortical network (Llinás *et al.*, 1994). In a recent series of studies, high-frequency stimulation delivered to the posterior intralaminar nucleus, but not to the dorsal or ventral MGN, evoked synchronized gamma oscillations in the primary and secondary auditory cortices (Barth and MacDonald, 1996). These oscillations occurred independently in sensory cortices representing different modalities, were intracortically generated and seemed to originate in the primary sensory areas (MacDonald and Barth, 1995; Barth and MacDonald, 1996).

4. PHYSIOLOGY AND PHARMACOLOGY OF THALAMOCORTICAL SYNAPSES

4.1. The Neurotransmitter at Thalamocortical Synapses

There is extensive evidence that, at least for the specific thalamic nuclei, the neurotransmitter used at thalamocortical synapses is one of the excitatory amino acids glutamate or aspartate. Thus, intracellular and extracellular recordings demonstrate that local application of glutamate antagonists block the response of cortical neurons induced by sensory stimulation or electrical stimulation of thalamocortical axons (Hagihara *et al.*, 1988; Tsumoto *et al.*, 1986; Salt *et al.*, 1995; Hicks *et al.*, 1991). Glutamate is released in the cortex by thalamic stimulation in a Ca^{2+}-dependent manner (Tamura *et al.*, 1990). Thalamocortical neurons are immunoreactive for a phosphate-activated glutaminase, which is a major synthesizing enzyme in glutamatergic synapses (Kaneko and Mizuno, 1988). In addition, thalamo-

cortical synapses are enriched in glutamate in all sensory cortical areas (Kharazia and Weinberg, 1994). A problem with the idea that glutamate is the thalamocortical transmitter of the specific nuclei is that ^{3}H-amino acids injected into the cortex are not retrogradely transported to the specific thalamic nuclei, although they are transported to the intralaminar nuclei and VM (Baughman and Gilbert, 1980; Ottersen *et al.*, 1983). This might be due to the fact that glutamate, as well as the injected ^{3}H-amino acids, are taken up by the cortical postsynaptic membranes. Consistent with this is recent evidence that glutamate is enriched in the postsynaptic spines of thalamocortical synapses (Kharazia and Weinberg, 1994). A further problem is that glutamate has not been observed in the release vesicles of thalamocortical synapses, although technical issues might readily account for this result (see Kharazia and Weinberg, 1994).

4.2. The Properties of Transmitter Release at Thalamocortical Synapses

The functional properties of chemical synapses can be described by the principles of quantal theory and its variants (Fatt and Katz, 1952; Bekkers, 1994). The morphological characteristics displayed by thalamocortical synapses indicate that their physiology might differ from corticocortical synapses. Unfortunately, a detailed electrophysiological analysis of single, confirmed thalamocortical synapses has not been performed to date. In recent studies, using neocortical slices, a portion of the presumed single-fiber EPSPs evoked in the cortex by local cortical stimulation were of large amplitude (i.e.1.5–2 mV), showed a very high probability of release (i.e. about 1) and a very low coefficient of variation (e.g. Volgushev *et al.*, 1995), but there is no evidence for the origin of these synaptic events. Single-axon EPSPs between cortical cells also have been found to have such large amplitudes, sometimes, but usually have a large coefficient of variation (e.g. Stern *et al.*, 1992). In addition, such EPSPs displayed a strong paired-pulse depression (Volgushev *et al.*, 1995), which would be consistent with the paired-pulse depression displayed by specific thalamocortical pathways *in vivo* (see Figs 4 and 5, and Section 3.1). Thus, the properties of these single-axon EPSPs would seem to be compatible with the morphological characteristics of thalamocortical synapses (e.g. large size; see Section 2.1). A recent study (Stratford *et al.*, 1996) in slices of cat visual cortex described a class of minimal synaptic events in layer IV spiny stellate cells that were evoked by intracortical stimuli to deep layers or white matter. These EPSPs had particularly large amplitudes, strong paired-pulse depression, and a low coefficient of variation. The authors argued that these EPSPs might be generated by thalamocortical synapses arising from the LGN, although confirmation of this was not provided. Paired-pulse depression is also observed in intracortical synapses (i.e. layer IV to layer III pathways), and this is due to a shunt by IPSPs, the high release probability of these synapses and the action of substances that decrease release presynaptically (Castro-Alamancos and Connors, 1997). Detailed biophysical study of thalamocortical synapses will be invaluable to mechanistic interpretations of modulator effects and plasticity.

4.3. Receptors Bound by the Thalamocortical Neurotransmitter

Since there is considerable evidence that the neurotransmitter used by thalamocortical synapses is an excitatory amino acid, a central issue is the classification of glutamate receptors that are activated at these synapses. Three different subtypes of ionotropic glutamate receptors have been pharmacologically defined (Dingledine and Bennett, 1995). These include the D,L-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (*AMPA*) *receptors*, which have low affinity for the agonist kainate, the high-affinity *kainate receptors*, and the *NMDA receptor*. In addition, a family of G protein-coupled receptors known as the *metabotropic glutamate receptors* also have been identified (Dingledine and Bennett, 1995). All of these receptor types are present on cortical cells and therefore might be activated by glutamate released from thalamocortical synapses (Huntley *et al.*, 1994). There is a voluminous literature concerning the subtypes, modulation and cellular actions of these receptors in the cerebral cortex, but very little is based on the thalamocortical system. A study correlating the type of thalamocortical pathways with glutamate receptor subunit localization at the level of the synapse would be particularly valuable, but has not been attempted.

4.3.1. *The AMPA and Kainate Receptors*

Non-NMDA (i.e. AMPA) receptors are the major contributors of the synaptic response of mature cortical cells activated by thalamocortical fibers. Application of non-NMDA receptor antagonists blocks most of the thalamocortical transmission *in vivo* or in the mature slice (Agmon and O'Dowd, 1992; Armstrong-James *et al.*, 1993; Crair and Malenka, 1995; Salt *et al.*, 1995), as well as most of the transmission at corticocortical synapses (Jones and Baughman, 1988). Recent results show that in thalamo-recipient layers of the monkey cerebral cortex the density of kainate receptors is low (Vickers *et al.*, 1993). The roles of kainate receptors are largely unknown since the excitatory effects of kainate are mediated by AMPA receptors; however, recent results from hippocampus indicate that presynaptic kainate receptors regulate the release of glutamate from central synapses (Chittajallu *et al.*, 1996). Corticocortical projection neurons in layer III seem to have a selective parcellation of kainate receptor subunits, since apparently none of the layer V pyramidal cells of the same area have kainate receptors (Vickers *et al.*, 1993; Huntley *et al.*, 1994). In contrast, the barrel cortex of the rat shows no obvious density or distribution differences in AMPA receptors between layers (Jaarsma *et al.*, 1991).

4.3.2. *The NMDA Receptors*

Several recent studies have shown that NMDA receptors are prominent in neocortex, but that the

density and the receptor subtypes vary greatly between cortical areas (Huntley *et al.*, 1994). In the primary visual cortex of the monkey, NMDA receptor subunits are distributed equally across the different cortical layers, which contrasts with the distribution of other glutamate receptors (Huntley *et al.*, 1994). In the barrel cortex of the rat, NMDA receptors are located throughout the supragranular layers and upper layer V, while in layer IV they are confined to the barrels, which are the sites of termination of the specific thalamocortical fibers (Jaarsma *et al.*, 1991).

By using the thalamocortical slice preparation, it has been shown that thalamocortical synapses activate NMDA currents with great efficacy in young rats. As the cortex matures, synaptic inhibition reduces the effectiveness of NMDA activation (Agmon and O'Dowd, 1992). The degree of activation of NMDA currents at thalamocortical synapses also decreases with age independent of the maturation of inhibition, apparently due to changes in the kinetics of NMDA channels (Crair and Malenka, 1995). In contrast, another report indicates that NMDA receptors still contribute to transmission in adult thalamocortical synapses, though the contribution of NMDA receptors to corticocortical synapses is much stronger (Gil and Amitai, 1996b). *In vivo*, the infusion of NMDA receptor antagonists during intracellular recordings suggests that the contribution of these receptors to the monosynaptic input from thalamus is low or non-existent (Salt *et al.*, 1995). A study of the voltage dependency of the NMDA component in unanesthetized cats also implies that the thalamocortical synapses have a much smaller NMDA contribution than corticocortical synapses (Baranyi *et al.*, 1993).

The contribution of NMDA receptors to visually evoked responses decreases between 3 and 6 weeks of age for cells in layers IV, V and VI of the kitten visual cortex (Fox *et al.*, 1991). In the barrel cortex of the mature rat, extracellular unit recordings suggest that NMDA receptors do not contribute to the monosynaptic thalamocortical responses of layer IV cells, which appear to be mediated entirely by non-NMDA receptors. However, longer latency activity from the same cells is dependent mostly on NMDA receptors (Armstrong-James *et al.*, 1993). The site of NMDA receptors contributing to the long-latency activity is not clear, and could arise from recurrent intracortical synapses activated by the thalamic input.

4.3.3. *Metabotropic Glutamate Receptors*

Agonists of the metabotropic glutamate receptor have a variety of effects on cortical cells. A subpopulation of layer V cells is depolarized when a metabotropic glutamate agonist (i.e. ACPD) is applied, and there is a consequent change in firing mode from bursting to regular-spiking (Wang and McCormick, 1993). The effects of ACPD are layer-specific in the cortex, which may have implications for their possible role in thalamocortical transmission (Cahusac, 1994). However, it is unclear whether thalamocortical synapses are influenced by metabotropic glutamate receptors either pre- or postsynaptically.

4.4. Inhibitory Interneurons Activated by Thalamocortical Synapses

Immunohistochemical studies of GABA immunoreactivity in axonal boutons have revealed laminar differences in distribution in the rat visual cortex, in particular a high density in layer IV, the recipient layer of specific thalamic inputs (Beaulieu *et al.*, 1994). Inhibitory interneurons recorded intracellularly, identified by their fast-spiking firing pattern, have been shown in slices and *in vivo* to be monosynaptically activated by thalamocortical synapses (Agmon and Connors, 1992; Baranyi *et al.*, 1993). This is consistent with extracellular recordings *in vivo*, where action potentials with very short durations in layer IV (i.e. putative fast-spiking GABAergic cells) respond powerfully at very short latencies to sensory stimulation (Swadlow, 1995), and with slice and *in vivo* studies where postsynaptic inhibition is activated strongly by thalamic stimulation (Agmon and Connors, 1992; Castro-Alamancos and Connors, 1996c, 1996d). Intracellular recordings from cortical excitatory cells reveal that inhibition activated by these interneurons is mediated by $GABA_A$ and $GABA_B$ receptors (Connors, 1992; Douglas and Martin, 1991). In excitatory cells, the monosynaptic EPSP is followed immediately by a strong hyperpolarization due to the inhibitory drive [see Figs 7 and 8(B)]. The $GABA_A$ component of the IPSP occurs immediately after the initial EPSP and lasts about 50 msec, while the $GABA_B$ component occurs in the late phase of the response as a prolonged hyperpolarization of some 200–300 msec. These inhibitory components appear in all cortical pyramidal neurons, but $GABA_A$ components have been described as either more (Douglas and Martin, 1991) or less (Chagnac-Amitai *et al.*, 1990) powerful in layer V neurons than in supragranular neurons of the visual cortex.

Typically, the GABA-mediated hyperpolarization that follows the excitatory response *in vivo* is terminated or interrupted by a rebound depolarization at long latency (see Figs 7,9; Steriade, 1984; Douglas and Martin, 1991; Baranyi *et al.*, 1993). These rebound depolarizations are thought to be generated by a combination of currents from the activation of certain voltage-dependent conductances in layer V cells, and recurrent synaptic excitation (Castro-Alamancos and Connors, 1996c, 1996d).

4.5. Presynaptic Modulation of Thalamocortical Activity

A variety of neurotransmitter systems are able to modulate thalamocortical activity. The postsynaptic modulation of neuronal firing in thalamocortical pathways has been reviewed elsewhere (McCormick, 1992), and here we focus on presynaptic effects. The most widely studied modulator is acetylcholine. Cholinergic neurons of the nucleus basalis are the primary source of acetylcholine to the neocortex, and tetanic stimulation applied to this nucleus strongly facilitates thalamocortical transmission through the activation of muscarinic receptors (Metherate and Ashe, 1993b). The site of action of acetylcholine can be either pre- or postsynaptic. Receptor-binding

techniques coupled with lesions of specific thalamocortical fibers suggest that muscarinic receptors are located postsynaptically on cortical cells, while a subset of nicotinic receptors is located on the thalamocortical fibers (Sahin *et al.*, 1992). The neocortex also has nicotinic acetylcholine receptors (McGehee and Role, 1996). Both α-7 nicotinic receptors and the α-bungarotoxin binding sites are present in the rat and mouse barrel cortex during early postnatal development, but are only present in high amounts in rat thalamocortical afferents (Bina *et al.*, 1995). After postnatal day 14, expression of α-7 subunits declines dramatically in thalamus and cortex, but remains high in certain thalamic nuclei of the rat (i.e. LGN, MGN) into adulthood (Broide *et al.*, 1995). In addition, thalamocortical axons projecting to layer I of the posterior cingulate cortex (i.e. originating in VA and VM) of the rat have M2-muscarinic and serotonin-1B receptors (Vogt *et al.*, 1992). Serotonin-1B receptors also are expressed transiently during development in specific thalamocortical fibers (Bennett-Clarke *et al.*, 1993), and thalamocortical neurotransmission is depressed by serotonin (Rhoades *et al.*, 1994). Other receptors observed on thalamocortical terminals include neurotensin, mu-opioid and beta-2-adrenoceptors (Vogt *et al.*, 1992; Sahin *et al.*, 1992).

These studies suggest that thalamocortical transmission may be modulated presynaptically by a wide range of neurotransmitter systems. Considering the long list of putative presynaptic modulators and receptor types in the forebrain, this is not surprising. But the actions of modulators vary greatly between synapse types, so further research on the specific characteristics of thalamocortical terminals is necessary.

5. FUNCTIONS, SYNAPTIC PLASTICITY AND SEIZURES IN THALAMOCORTICAL PATHWAYS

At the risk of oversimplifying, we can consolidate the functional roles of thalamocortical pathways into two basic groups. First, they transfer information from the periphery and other major brain circuits to the neocortex, and mediate intercommunication between areas of cortex (Sherman and Guillery, 1996). Second, they participate in the generation of dynamic modes of activity that regulate the access of information to the neocortex during different behavioral states. Obviously, different nuclei will have different capacities for each function; projections originating in the specific nuclei will have the primary role of transferring information, while other nuclei (paralaminar in particular) will provide more highly processed information from other brain processing centers, including the neocortex (Sherman and Guillery, 1996; Diamond, 1995). However, it seems clear that at the level of the thalamocortical synapse itself, very important transformations of sensory input occur. For instance, direction selectivity in the visual system might arise through the organization of these synapses (Hubel and Wiesel, 1962; Reid and Alonso, 1995). An example of information provided to the cortex through the thalamus by non-sensory brain systems is the motor information originating in the cerebellum, and the role of the thalamocortical pathway in the control of movement has been studied intensely (Horne and Butler, 1995).

Despite the importance of thalamocortical pathways in transferring information to the cortex, it has been proposed that the main function of the thalamocortical system is to generate internal functional modes that operate both in the presence and absence of external sensory activation (Llinás and Pare, 1991). In this scheme, the transfer of information would be secondary to the generation of these internal modes, which depend on the behavioral state. While there has been great interest in the generation of different oscillatory modes in the thalamocortical system (Steriade *et al.*, 1993d), and their ability to regulate information flow to the cortex, a greater challenge will be to understand the functional significance of these modes. A recent study suggested how behavioral state might affect the response properties of thalamocortical pathways by showing that the capacity to generate an augmenting response (see Section 3.2) depended on the behavior of the animal (Castro-Alamancos and Connors, 1996c). Previous work had shown that augmenting changed between sleep and awake states (Steriade *et al.*, 1969) but, more surprisingly, the response also is affected by different awake behavioral states (see Fig. 11). This indicates that thalamocortical pathways may dynamically shift their responsiveness depending on immediate behavioral contingencies.

Some have suggested that thalamocortical pathways are involved in several forms of learning, including classical conditioning of the forepaw-withdrawal reflex (Meftah and Rispal-Padel, 1994), contact-placing reactions (Amassian *et al.*, 1972), receptive field plasticity induced by classical conditioning (Weinberger, 1995) and operant conditioning of limb movements (Fabre-Thorpe and Levesque, 1991; Bornschlegl and Asanuma, 1987). The case for an involvement of thalamocortical pathways in learning would be strengthened by demonstrations that these synapses are plastic, i.e. that they show long-term, activity-dependent changes in efficacy. The most widely studied cellular model for learning and memory is a form of synaptic plasticity called long-term potentiation (LTP). The basic idea is that long-lasting changes in the efficacy of synapses are the underlying substrate responsible for the storage of information (for review of LTP, see Bliss and Collingridge, 1993).

Long-term potentiation has been investigated in several neocortical areas (Kirkwood and Bear, 1994; Castro-Alamancos *et al.*, 1995). The probability of its induction varies widely among areas, perhaps due to differences in the responsiveness of NMDA currents to afferent stimulation (Castro-Alamancos and Connors, 1996a). A similar difference might also exist among different thalamocortical pathways. Figure 12 shows the effect of applying high-frequency stimulation (i.e. theta-burst stimulation pattern — TBS) in VPM and recording in the upper layers of the primary somatosensory cortex of the pentobarbital-anesthetized rat. Note that, after TBS, the size of the cortical response is increased. Whether this involves

an enhancement of efficacy at the thalamocortical synapses or the intracortical synapses activated by this pathway (see Figs 3 and 4) is currently unknown.

The first study that clearly described a lasting change in the efficacy of a thalamocortical pathway was carried out in anesthetized cats by Baranyi and Feher (1978). When activity in the VL-to-motor cortex pathway was paired with the antidromic firing of infragranular pyramidal cells (by stimulating the pyramidal tract), the synaptic efficacy of the VL input increased in 14% of the recorded cells. This procedure was repeated in several subsequent studies, which showed that the convergence of two inputs (i.e. thalamocortical and corticocortical) and the time interval between the two inputs (less than 100 msec) were critical variables to produce long-lasting changes (Baranyi and Feher, 1981). More recent studies also have shown that, while corticocortical pathways may have the capacity to induce LTP, at least some thalamocortical pathways are not capable of expressing LTP unless high-frequency activity in the thalamocortical pathway is coupled with high-frequency activity in the corticocortical pathway (Iriki *et al.*, 1989, 1991). Another early study was conducted in kitten visual cortex by Tsumoto and Suda (1979). They showed that low frequency (2 Hz) stimulation applied to the optic nerve for protracted periods (15–60 min) induced a long-lasting enhancement of field potentials recorded in the visual cortex. This change could only be induced in kittens during the critical period of postnatal development. Interestingly, they also observed a long-lasting heterosynaptic depression of the cortical field potential to stimulation of the non-tetanized optic nerve. Recently, Crair and Malenka (1995) used the thalamocortical slice preparation to study the induction of LTP in whisker-barrel cortex of developing mice. They observed that thalamocortical synapses are capable of generating LTP only during the critical period during which the barrel neurons can be

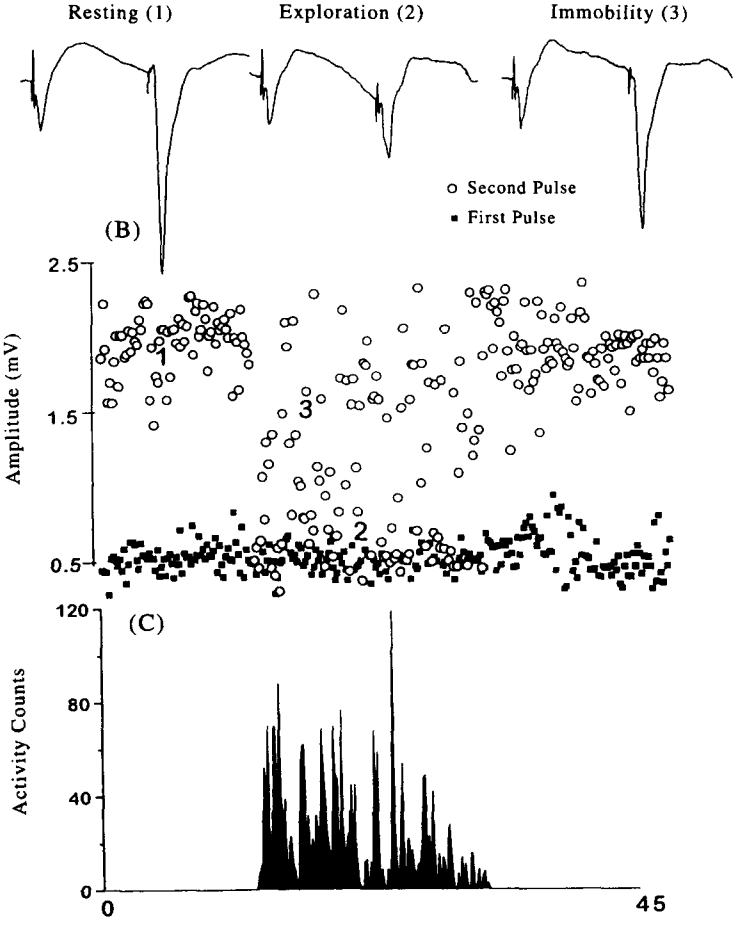

Fig. 11. Dynamic modulation of the augmenting response with behavioral state in awake, freely moving animals. (A) An augmenting response is induced during periods of resting and immobility, but is inactivated during periods of exploration. The numbers in (A) indicate the location of the trace in (B). (B) An animal was allowed to explore freely an open field while motor activity was monitored by using photobeam detectors. Paired pulses at a 100 msec interval were applied to the VL nucleus at 0.1 Hz and responses were recorded in the sensorimotor neocortex. The amplitude of the first (closed squares) and second (open circles) responses were measured and plotted with respect to the animal's motor activity, which is indicated by the number of photobeam interruptions (activity counts) per 10 sec bins in (C). From Castro-Alamancos and Connors, (1996c).

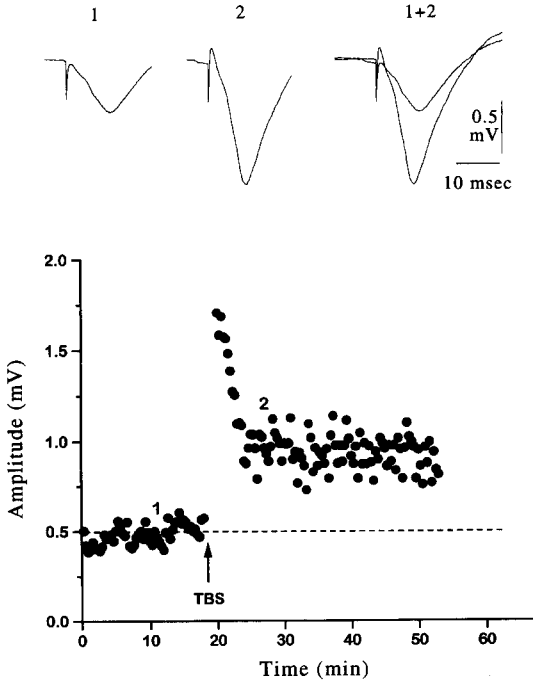

Fig. 12. Long-term potentiation in a thalamocortical pathway. A rat was anesthetized with sodium pentobarbital, and stimulation (0.2 Hz) was delivered to the VPM while recording in the upper layers of the the somatosensory cortex. After a period of stable recording, a theta-burst stimulation (TBS) was applied in the VPM and the size of the evoked response was enhanced. The numbers shown above the traces indicate their location in the plot below. See Castro-Alamancos *et al.* (1995); Castro-Alamancos and Connors, (1996b) for details about TBS.

modified by sensory experience (i.e. within 1 week after birth), which suggests the potential participation of this process in developmental plasticity.

The capacity of thalamocortical pathways to synchronize neocortical activity can become problematic during certain pathological states, such as epileptic seizures. Seizures are defined, in fact, by abnormally widespread and synchronous activity, and can be generated by a variety of processes (Schwartzkroin, 1993; McNamara, 1994). Disinhibition is effective especially in generating seizure-like synchrony both in isolated neocortical (Connors and Amitai, 1995) and thalamic (Bal *et al.*, 1994) slices, and *in vivo*. Indeed, thalamocortical circuits appear to be essential elements in the genesis of certain generalized seizures (Gloor and Fariello, 1988; Snead, 1995; Jefferys, 1994; Steriade and Contreras, 1995), though some investigators have emphasized the role of the neocortex (McLachlan *et al.*, 1984; Kostopoulos and Avoli, 1983), while others stress the role of the thalamus (Vergnes *et al.*, 1987).

Thalamocortical pathways are affected differentially in a model of generalized epilepsy (Kostopoulos, 1982; Kostopoulos and Avoli, 1983). Neurons from some thalamic nuclei and not others are involved in generating the spike-wave discharges typical of generalized epilepsy (McLachlan *et al.*, 1984). Thus, it has been proposed that during the spike-wave type of generalized epilepsy, spindles generated in the thalamus activate the cortex, which leads the thalamus in the generation of the widespread 3 Hz activity characteristic of this type of epilepsy (Avoli *et al.*, 1983; Steriade and Contreras, 1995). The thalamus subsequently is entrained in the spike-wave activity through the corticothalamic pathway (Avoli and Kostopoulos, 1982), and cortically projecting cells are strongly hyperpolarized during spike-wave paroxysms; this may underlie the loss of consciousness characteristic of spike-wave seizures (Steriade and Contreras, 1995). The neocortical mechanism responsible for the transformation from normal spindles to spike-wave activity has not been identified. An increase in excitability of cortical neurons and in GABA-mediated IPSPs accompanies the generation of spike-wave patterns, while a subsequent breakdown of synaptic inhibition might cause the convulsive form (i.e. 10 Hz) of generalized seizures (Gloor and Fariello, 1988).

6. CONCLUSIONS

Thalamic nuclei produce a large array of parallel projections to neocortex that differ in their lateral spread, lamina of projection, evoked responses, functional roles, modifiability, and involvement in pathological states. There are wide gaps in our knowledge of thalamocortical pathways, in particular about the physiological properties of single thalamocortical synapses, and the functional role of these pathways during behavior.

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