fibers of thick and thin diameters, some ending in the reticular nucleus and others in the dorsal thalamus. He did not visualize branches of the same corticothalamic fiber ending in both sites and, although identifying collaterals of thalamocortical axons, he did not discover their terminations in the reticular nucleus. These collateral projections of the thalamocortical and corticothalamic fiber systems to the reticular nucleus have come to occupy a prominent place in modern studies of the thalamus. Together with the reticular nucleus cells, they serve to synchronize the activities of large constellations of thalamic and cortical neurons during forebrain operations that underlie sleep, wakefulness and directed attention. In what follows, I will attempt to summarize where we stand today in our understanding of thalamic circuitry at morphological and physiological levels. In a brief overview of this type, it will not be possible to reference all the primary literature but reference to major reviews should provide a basis for identifying primary sources.

The reticular nucleus is a key structure in thalamic circuitry

The reticular nucleus is a sheet of GABAergic neurons covering the dorsal thalamus anteriorly, laterally and to some extent ventrally (Fig. 1). Although morphological variants have been described, its cell population is essentially a homogeneous one, non-GABA cell types only becoming evident in the other two elements of the ventral thalamus, the ventral lateral geniculate nucleus and the zona incerta. When stained in full, reticular nucleus cells exhibit an elongated shape with long dendrites spreading over the surface of the dorsal thalamus for several hundred microns (Yen et al., 1985b; Mulle et al., 1986; Uhlrich et al., 1991; Liu and Jones, 1999). In virtually all cases, the dendritic branches also extend across the full thickness of the reticular nucleus and commonly out into the internal capsule as well. The cells are joined by synapses made by their intranuclear axonal collaterals. Although these synapses are relatively few in number, they are profoundly influential in ways that will be described later. In some species, notably cats, but perhaps not others, the peripheral dendritic branches of reticular nucleus cells are joined by dendrodendritic synapses, the effects of which have not been the subject of physiological investigation (Deschênes et al., 1985; Williamson et al., 1994; Yen et al., 1985b).
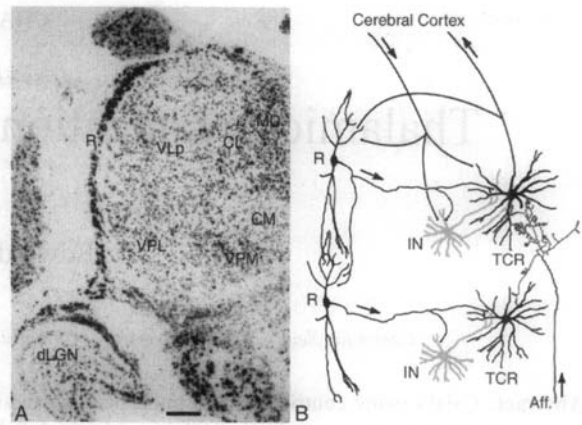

Fig. 1. **A.** Autoradiogram of a frontal section through the thalamus of a macaque monkey showing *in situ* hybridization of a radioactive RNA probe complementary to the mRNA coding for the 67 kDa form of glutamic acid decarboxylase, the enzyme involved in GABA synthesis. Intrinsic GABAergic interneurons can be identified in the nuclei of the dorsal thalamus (VLp, VPL, VPM, CM, CL, MD, L, dLGN). A second set of GABAergic neurons occupies the reticular nucleus (R). Bar 500 μm. **B.** Schematic drawing showing synaptic circuitry involving relay cells (TCR), intrinsic interneurons (IN), reticular nucleus cells (R), and subcortical afferents (Aff.), and the two-way interactions with the cerebral cortex.

The main axonal trunk of a reticular nucleus cell enters the underlying dorsal thalamus and terminates in a relatively concentrated zone, mainly in a single dorsal thalamic nucleus (Uhlrich et al., 1991; Liu et al., 1995b; Pinault et al., 1995; Cox et al., 1996). The synapses are typically symmetrical in form, release GABA and are associated with both GABA$_A$ and GABA$_B$ receptors (Fig. 2). The GABA$_A$ receptors are exclusively located in or near the postsynaptic density, while the GABA$_B$ receptors, like other metabotropic receptors, tend to be extrajunctional in location (Fig. 2). Quantitative studies indicate that in species in which intrinsic interneurons are present, the vast majority (80%) of the reticular nucleus synapses are located on dendrites of thalamocortical relay neurons (Fig. 2). This has important implications to be discussed below.

Reticular nucleus cells are innervated by collaterals of corticothalamic and thalamocortical axons

As corticothalamic and thalamocortical fibers traverse the reticular nucleus, they give off a series of two or three

CHAPTER 27

Thalamic organization and function after Cajal

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Abstract: Cajal's many contributions to understanding the thalamus have been hidden by his body of work on the cerebral cortex. He delineated many thalamic nuclei in rodents, defined afferent fibers, thalamocortical relay neurons and interneurons, was first to demonstrate thalamocortical fibers and their terminations in the cortex, and recognized the feed-back provided by corticothalamic fibers. This presentation outlines modern methods for identifying classes of thalamic neurons, their chemical characteristics, synaptology and differential connections, and describes the intrinsic circuitry of the thalamus, showing how interactions between GABAergic cells of the reticular nucleus and glutamatergic relay cells underlie rhythmic activities of neurons in the thalamo-cortico-thalamic network, activities associated with changes in the conscious state, and which are generated and maintained by the corticothalamic projection. Corticothalamic fibers interact with reticular nucleus cells and relay cells through NMDA, AMPA and metabotropic receptors while interactions between reticular nucleus cells and relay cells are mediated by $GABA_A$ and $GABA_B$ receptors. Differing strengths of synaptic input to the two cell types, from which oscillatory behavior commences, depend upon differential expression at individual synapses of specific AMPA receptor subunits which modulate excitatory postsynaptic conductances. Two classes of relay cells can be distinguished by differential staining for calbindin and parvalbumin. The first forms a matrix in the thalamus, unconstrained by nuclear borders; the second is concentrated in certain nuclei in which it forms the topographically organized core. In projecting diffusely to the cortex, calbindin cells provide a substrate for binding together activities of multiple cortical areas that receive focused input from single thalamic nuclei. This, and the presence of specific and diffuse corticothalamic projections may serve to promote coherent activity of large populations of cortical and thalamic neurons in perception, attention and conscious awareness.

Introduction

Santiago Ramón y Cajal's numerous contributions to the structure of the thalamus have tended to be overshadowed by his much greater body of work on the cerebral cortex. His thalamic contributions, however, are not only considerable but also fundamental. Apart from delineating a number of thalamic nuclei several years before the publication of Nissl's definitive (1913) paper that gave us the basis for most of the names and delineations of these nuclei that we use today, Cajal is to be credited with the

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discovery of the cortical terminations of afferent fibers (1891, 1899a,b), which he gradually came to recognize as having a thalamic origin, and with the discovery of virtually all the elements that go to make up the intrinsic circuitry of the thalamus. Reported in a short series of publications between 1900 and 1903, and republished as part of the *Textura del Sistema Nervioso*, his discoveries included descriptions of the terminations of the principal afferent fibers, of thalamocortical relay cells and intrinsic interneurons. Significantly, he reports being unable to identify intrinisic interneurons in rodents, and we now know that they are absent from most thalamic nuclei in these species (Benson et al., 1992). He also demonstrated the cells of the reticular nucleus with axons projecting into the dorsal thalamus, and he identified corticothalamic
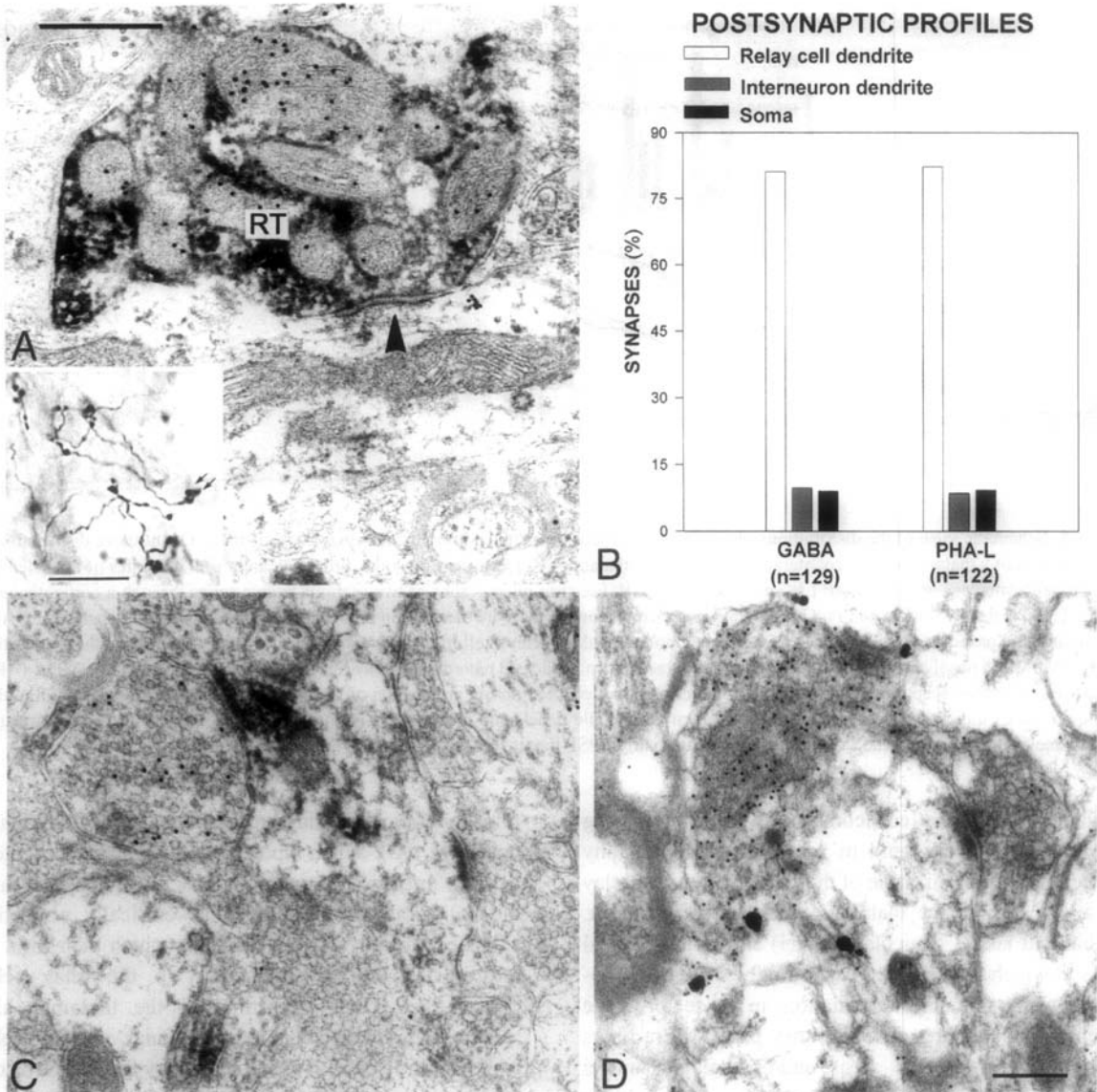
Fig. 2. A. Electron micrograph showing a terminal (RT) of a reticular nucleus axon labeled by immunoperoxidase for transported PhAL and by immunogold particles for GABA, ending (arrowhead) on the dendrite of a relay cell in the VP nucleus of a cat. Bar 1 μm. Inset: light micrograph of labeled terminal branches of the axon. Bar 10 μm. **B.** Distribution of GABA immunoreactive terminals on relay cell dendrites, dendrites of interneurons and on neuronal somata in the ventral posterior nucleus of a cat (left) is identical to that of specifically identified reticular nucleus axon terminals, labeled by transported PhAL. From Liu et al. (1995a).

short collaterals that terminate in glutamatergic synapses on the underlying neurons (Figs. 1, 3). Because fibers passing to and fro between a particular dorsal thalamic nucleus and the cortical area with which it is functionally connected traverse the same general sector of the reticular nucleus, that sector becomes associated with a particular functional system. In the case of the principal sensory systems, therefore, somatic sensory, auditory and visual sectors can be identified and the neurons of each sector can often be driven by a relevant peripheral stimulus, although usually with less specificity then relay cells in the sensory nuclei (reviewed in Steriade et al., 1997a).
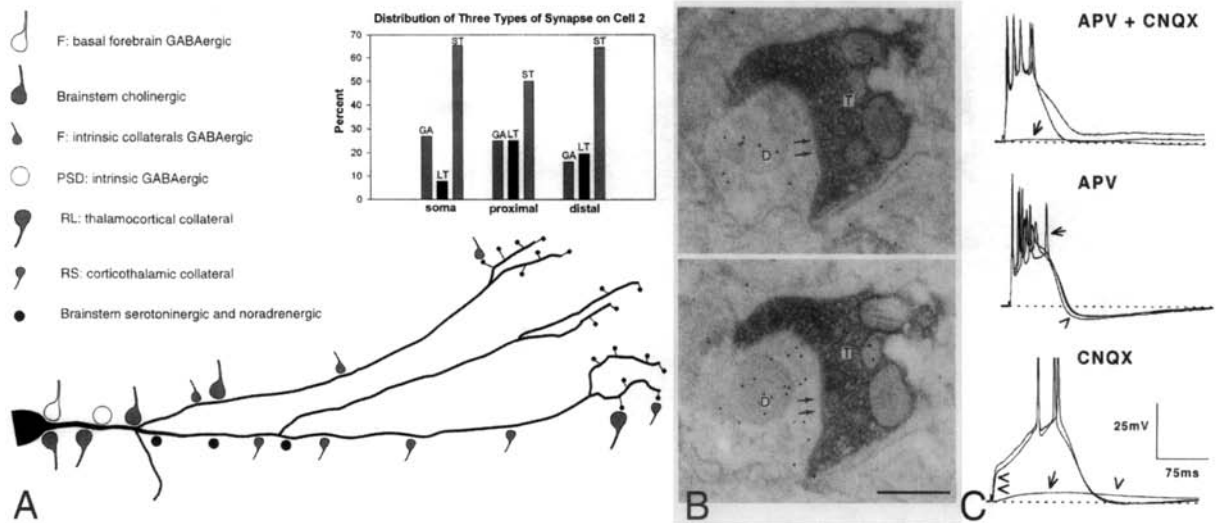
Fig. 3. **A.** Schematic view of the distributions of synapses of various types innervating the reticular nucleus. Inset: Quantitative distribution of GABAergic (GA), thalamocortical collateral (LT) and corticothalamic (ST) terminals on soma, proximal, and distal dendrites of a labeled cell in the reticular nucleus of a rat. From Liu and Jones (1997). **B.** Electron micrographs of two sections from a series through a corticothalamic terminal (T) labeled by transported PhAL and synapsing (arrows) on the dendrite of a neuron in the reticular nucleus of a rat, labeled for GABA by immunogold particles. Bar 1 μm. **C.** EPSPs induced in a reticular nucleus cell in the ventral posterior nucleus of a mouse thalamocortical slice *in vitro*. Each panel consists of three superimposed traces from whole cell recordings before, during and after application of NMDA-(APV) and AMPA-(CNQX) receptor antagonists. Arrow indicates trace recorded during application of the antagonists. Single arrowheads in middle and lower traces indicate increased after-hyperpolarization (middle panel) and overlap of remaining slow EPSP and after hyperpoarization (lower panel). Double arrowhead in lower panel indicates early EPSP that is blocked by CNQX. From Warren and Jones (1997).

Thalamocortical and corticothalamic fibers traversing the reticular nucleus tend to preserve the topography inherent in the organization of the principal sensory relay nuclei of the dorsal thalamus (the ventral posterior, medial and lateral geniculate nuclei) and in the cortical areas to which they project. Accordingly, there is a topography of the collateral terminations in the sector of the reticular nucleus through which they pass. Where fibers related to two cortical areas and/or thalamic nuclei traverse the same sector of the reticular nucleus, their collateral terminations may show differential laminations (Crabtree, 1992, 1996, 1998). Whether this topography is significant functionally is debatable: because of the extensive overlap in the long dendrites of the reticular nucleus cells, it is likely that cells located throughout a sector of the nucleus receive synapses from the localized concentrations of terminals related, for example, to a connected pair of cortical barrel and thalamic barreloid in the rodent.

The bidirectional collateral input to the reticular nucleus and the specific projection of the reticular nucleus cells back to the dorsal thalamus give us the fundamental circuit diagram of the thalamus in all mammals (Fig. 1B). When inputs coming from the periphery or from intrinsic brain structures activate relay neurons, the collaterals of these neurons' cortically projecting axons excite reticular nucleus cells which then form an inhibitory feedback connection to the relay cells. Corticofugal fibers returning to the thalamus also activate, via their collaterals, reticular nucleus cells, which in this case provide an inhibitory feedforward connection to the relay cells. Below we shall see how these two components interact in inducing and maintaining thalamocortical synchrony.

Other inputs to the reticular nucleus come largely from the brainstem and include cholinergic, serotoninergic and noradrenergic components. These are part of the nonspecific modulatory systems innervating the thalamus (reviewed in Steriade et al., 1997b). Cholinergic inputs engaging muscarinic M_2 receptors on the reticular nucleus cells tend to hyperpolarize the cells. Nicotinic effects tend to be depolarizing and to promote tonic discharges. A similar slow depolarization induced by noradrenaline acting via α_1 receptors and by serotonin

acting via $5HT_2$ receptors depends upon suppression of a potassium leak current (I_{KL}) (Steriade et al., 1997b).

A small GABAergic input of unknown function arising in the cells of the basal forebrain and ventral pallidum innervates certain parts of the reticular nucleus (Asanuma, 1992, 1994; Bickford et al., 1994).

Reticular nucleus cells are dominated by cortical inputs

When examined quantitatively, synapses in the reticular nucleus derived from corticothalamic axon collaterals exceed by far those derived from other sources (Liu and Jones, 1999). The terminals are consistently small, with a single small postsynaptic density, and are distributed over most of the extent of the dendritic tree of a reticular nucleus cell (Fig. 3). They are associated with fast rising EPSPs with NMDA and nonNMDA components (Fig. 3C). Synapses derived from collaterals of thalamocortical fibers, although in a minority, can be distinguished by their larger size and the presence of

large perforated postsynaptic densities, indicative of multiple vesicle release sites (see below). They tend to be located on the proximal dendrites of the reticular nucleus cells. Synapses derived from brainstem sites, also in a minority, are widely distributed over the dendritic tree. Many of the monoamine containing terminals do not possess the membrane contacts typical of glutamatergic and GABAergic synapses (Liu and Jones, 1991).

Corticothalamic axons that give rise to collateral terminations in the reticular nucleus invariably arise from cells in layer VI of the related cortical area (reviewed in Steriade et al., 1997a) (Fig. 4). They are thin in diameter and the principal axon, continuing into the dorsal thalamus, usually ramifies only in the principal dorsal thalamic nucleus that provides the input to the parent cortical area. A second set of corticothalamic axons, of larger diameter, arises from cells in layer V of the cortex. In this case the axon innervating the dorsal thalamus is normally a branch of a principal axon trunk that descends to midbrain, hindbrain or spinal cord. Although the branch to the thalamus may traverse the reticular nucleus en route to the dorsal thalamus, it does not give off
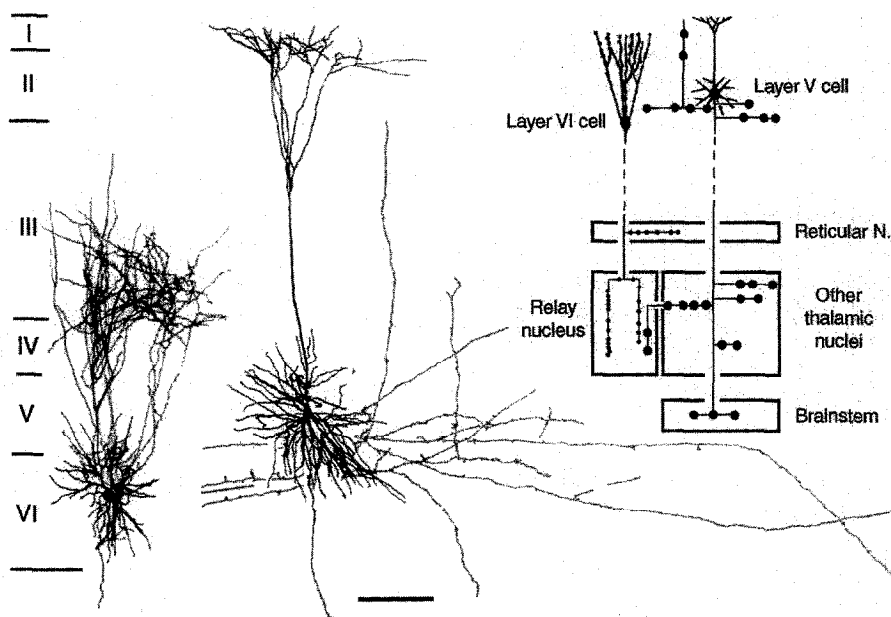

Fig. 4. Left: Corticothalamic cells in the auditory cortex of the cat, intracellularly labeled with horseradish peroxidase or biocytin, showing vertical organization of intracortical axon collaterals of layer VI cell and horiontal dispositon of intracortical collaterals of layer V cell. Right: Terminal distribution of axons of layer VI and layer V corticothalamic cells in the thalamus. Based on Ojima et al. (1992) and Ojima (1994).

collaterals in the reticular nucleus (Fig. 4). In the dorsal thalamus, it tends to have relatively widespread terminations extending across more than one nucleus. It is highly likely that the two kinds of corticothalamic fiber are those originally identified by Cajal on the basis of differences in diameter.

Because of the differences in the diameter of corticothalamic and thalamocortical fibers that provide collateral inputs to the reticular nucleus, it is possible to identify the two kinds of collateral synapse physiologically. A brief electrical stimulus applied to the cerebral cortex or underlying white matter elicits short latency EPSCs in reticular nucleus cells due to antidromic invasion of thalamocortical collaterals, and longer latency EPSCs due to orthodromic activation of the slower corticothalamic fibers (Golshani et al., 2001; Liu et al., 2001). In species in which all thalamocortical fibers emanating from a single nucleus are more or less the same size, the differentiation of the two EPSPs is usually clear-cut. Where thalamocortical fibers show a range of diameters from thick to thin, such as those arising from different cell populations in the dorsal lateral geniculate nucleus of the cat (Tsumoto and Suda, 1981), the distinction may be less easy to make.

In the somatosensory sector of the rodent reticular nucleus *in vitro*, EPSCs generated by a minimal stimulation paradigm and attributable to collateral corticothalamic synapses, have a consistent amplitude, reflecting the presence of a single vesicle release site, but a wide range of rise times, reflecting their wide distribution over the dendritic tree (Liu et al., 2001). Unitary EPSCs attributable to collateral thalamocortical synapses tend to have large, although more variable amplitudes, reflecting the presence of multiple release sites, but very consistent rise times, reflecting their proximal location on the dendritic tree. Below we will see the significance of this in the generation of thalamocortical synchrony.

Relay cells, overall, display a consistency of form and synaptic organization

With one highly significant exception, thalamocortical relay cells exhibit a commonality of structure across nuclei and across species. The cells typically have a number of radiating primary dendrites that devolve into two generations of daughter branches, giving the cells a symmetrical, bushy appearance first noted by Kölliker (1896)

who called them Buschzellen (Fig. 5). Commonly, the dendrites possess a variable number of bulbous appendages. Variations in the overall size of relay cells occur and the greatest range of sizes is found in the human thalamus. On the whole, however, relay cells have a consistency of form and variations in the bushy symmetry are commonly those imposed by boundary conditions at borders between nuclei and at white matter interfaces such as the internal and external medullary lamina.

The most significant morphological variations appear to be confined to the dorsal lateral geniculate nucleus of carnivores where relay cells show a di- or tri-morphic variation associated with their forming the specific synaptic relays for inputs from different morphological and functional classes of retinal ganglion cells (Friedlander et al., 1979, 1981; Stanford et al., 1981). The larger Y cells and the less well-characterized W cells, innervated by the α and the broad "γ" class of retinal ganglion cells, respectively, possess morphological features similar to those of relay cells in other nuclei and in other species. The X cells, innervated by the β class of retinal ganglion cells, are small with a less bushy form, the dendrites being oriented across the geniculate lamina in which the cell lies, and characterized by an unusual abundance of dendritic protrusions. These are indicative of synaptic arrangements, especially with the processes of inhibitory interneurons, that are more highly elaborated than in Y cells or in relay cells of other nuclei. Modest variations in the basic bushy morphology of relay cells can be found in the somatosensory relay nucleus of the cat (Yen, et al. 1985a). Rapidly adapting neurons have stouter dendrites and fewer protrusions than slowly adapting neurons and nociceptive neurons are small and pauci-dendritic. These differences, however, are by no means as dramatic as those among relay cells in the feline dorsal lateral geniculate nucleus. The functional differences among relay cells in the magno-, parvo- and intercalated laminae of the monkey dorsal lateral geniculate nucleus are, similarly, not accompanied by such profound differences in neuronal morphology as in the cat (Wilson, 1989).

By combining intracellular injection of physiologically identified relay cells with serial electron microscopic reconstruction of the injected cells, commonly also with co-labeling of specific synaptic inputs, it has been possible to build up a picture of the synaptic geography of thalamic relay neurons. The laborious nature of these studies has ensured that relatively few cells have been examined in this manner—4 in the ventral posterior
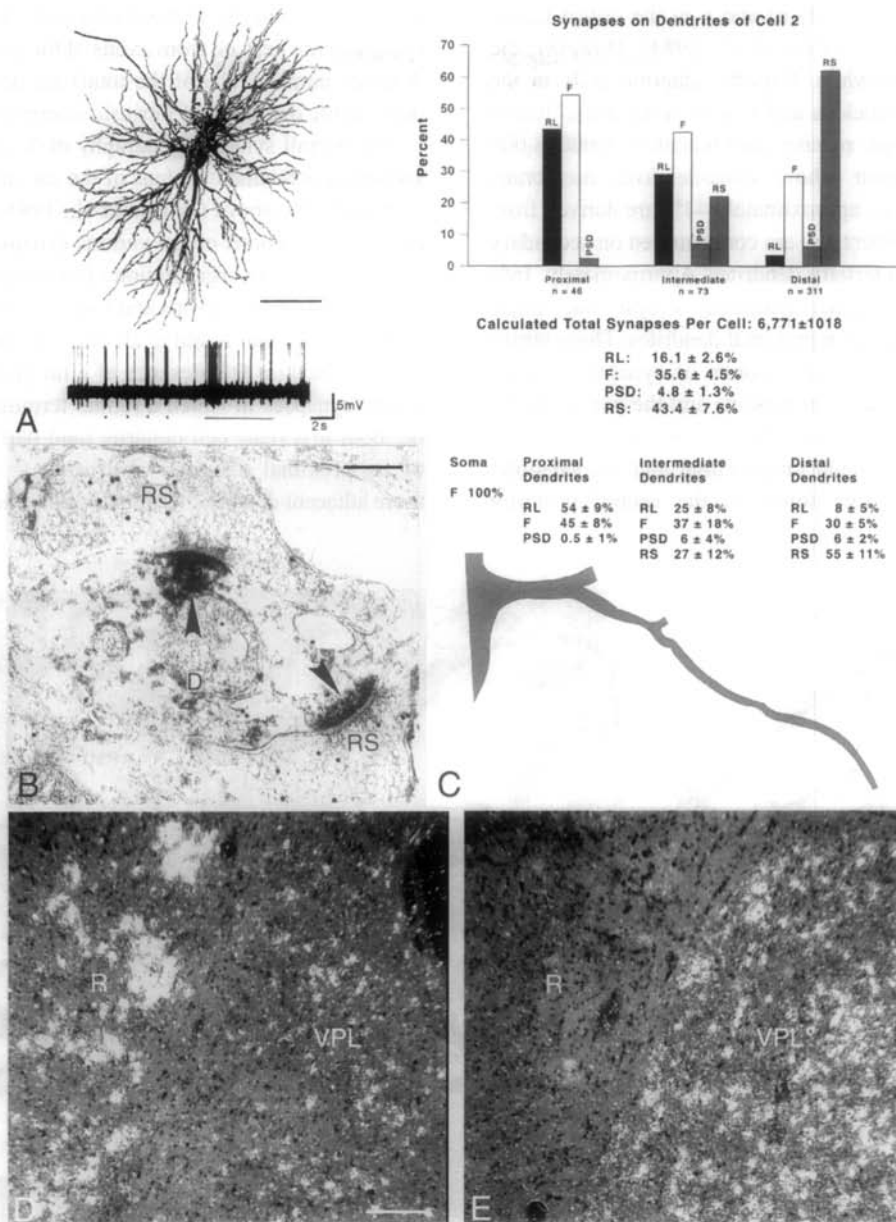
Fig. 5. **A.** Physiologically identified and intracellularly injected relay cell from the ventral posterior nucleus of a cat, showing the typical bushy form and responses to transient (dots) and maintained stimuli (line) applied to its peripheral receptive field. Bar 50 μm. From Yen et al. (1985a). **B.** Corticothalamic terminals (RS) labeled for glutamate by immunogold particles, ending on a dendrite (D) of a relay neuron at synapses in which the postsynaptic density shows strong immunoperoxidase labeling (arrowheads) for alpha-type II calcium/calmodulin-dependent protein kinase. Bar 1 μm. **C.** Quantitative distribution of medial lemmiscal (RL), GABAergic (F), and corticothalamic (RS) axon terminals, and presynaptic dendrites (PSD) of interneurons on the dendrites of an identified thalamocortical relay cell from the VP nucleus of a cat and subjected to extensive electron microscopic reconstruction. From Liu et al (1995a). **D,E.** Dark field autoradiograms from adjacent sections of a macaque monkey thalamus showing location of cells expressing GAD_{67} mRNA in reticular nucleus neurons (R) and in intrinsic interneurons of the VPL nucleus (D), but expression of α-CAMKII only in relay neurons (E). Bar 100 μm.

nucleus (Liu et al., 1995a,b) and 6 in the dorsal lateral geniculate nucleus (Wilson et al., 1984). However, the rewards are worthwhile. Rapidly adapting cells in the ventral posterior nucleus and Y cells in the dorsal lateral geniculate nucleus, receive approximately 5,000–8,000 synapses over their whole soma-dendritic membrane (Fig. 5C). Of these, approximately 44% are derived from corticothalamic fibers and are concentrated on secondary and especially on tertiary dendrites. Approximately, 16% are derived from medial lemmiscal or optic tract fibers and are concentrated on proximal dendrites. These terminals tend to have multiple points of synaptic contact, including on dendritic protrusions and the parent shafts. The remaining 40% of synapses are inhibitory and tend to be concentrated on proximal and second order dendrites and on the soma. In the ventral posterior

nucleus, the majority of these terminals (36% of the total synapses) are derived from axons of the reticular nucleus. A lesser number (5% of the total) are derived from the presynaptic dendrites of intrinsic interneurons (Fig. 5C).

The overall synaptic geography of X cells in the dorsal lateral geniculate nucleus of the cat stands in marked contrast to the above (Wilson et al., 1984). Although the relative proportions of the various synapses are more or less the same, the organization of synapses derived from retinal ganglion cell axons and from interneurons is more elaborate than that found in all other thalamic relay cells. This is based on the presence of a far greater number of triadic synapses in which a retinal terminal is presynaptic, both to a relay cell dendrite (and particularly to one of its proximal dendritic protrusions), and to one or more adjacent dendritic terminals of interneurons (Fig. 6).
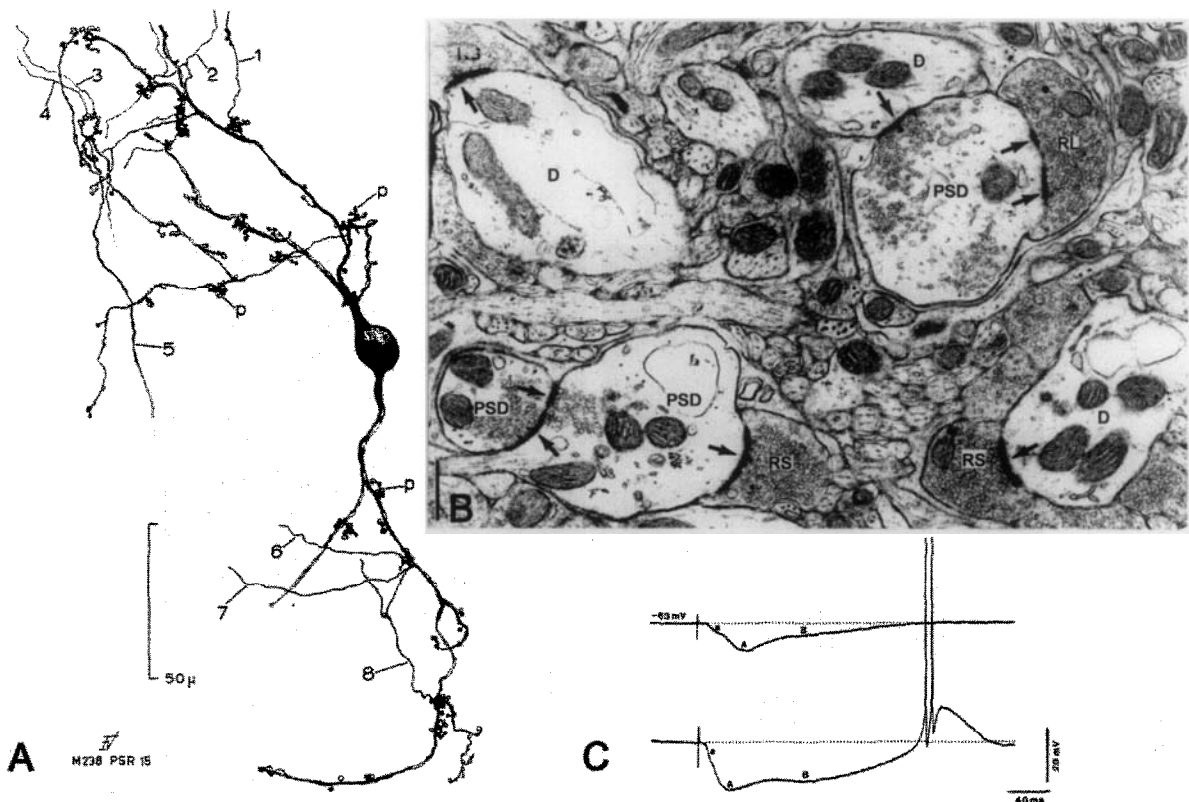

Fig. 6. **A.** Golgi-stained intrinsic interneuron from the dorsal lateral geniculate nucleus of a mouse. P indicates presynaptic dendritic appendages. From Rafols and Valverde ((1973). **B.** Electron micrograph from the ventral posterior nucleus of a cat showing profiles of presynaptic dendrites (PSD), medial lemmiscal (RL) and corticothalamic (RS) axon terminals ending in synapses (arrows) on dendrites (D) and on one another. Bar 0.25 μm. **C.** Intracellular recordings from a relay cell in the anterior nuclei of a cat, showing three IPSPs (a, A, B) induced by electrical stimulation of the mamillo-thalamic tract. a is considered to reflect local action of presynaptic dendrites, A GABA$_A$-receptor based effect of discharges of interneurons, B later GABA$_B$-receptor based effect. From Steriade et al. (1997a).

The dendritic terminals of the interneurons are themselves presynaptic to the same relay cell dendrite or protrusion—and are commonly reciprocally connected to one another as well. The massed aggregation of retinal terminals, dendritic protrusions and interneuronal terminals is commonly partially or completely ensheathed by astrocyte processes, warranting the name "glomerulus". A single X cell can be associated with multiple glomeruli. Although triadic synapses and synaptic glomeruli can be found in other thalamic nuclei (Jones and Powell, 1969) and can even be found in association with Y cells, they tend to be less common and less elaborate than those found in association with X cells. In rodents, nuclei other than the dorsal lateral geniculate, in lacking intrinsic interneurons, lack glomeruli (Spacêk and Lieberman, 1974).

A word about corticothalamic terminals and terminals that resemble them: the density of nerve terminals arising from nonspecific brainstem afferents, particularly the cholinergic group, is significantly higher in the dorsal lateral geniculate nucleus and adjoining sector of the reticular nucleus than in other nuclei and other sectors of the reticular nucleus. It has been calculated that such terminals may account for as much as 50% of the small synaptic terminals in the dorsal lateral geniculate nucleus of the cat, and they therefore pose the risk that the number of corticothalamic terminals is over estimated (Erisir et al., 1997). This does not appear to be a problem of any significance in other thalamic nuclei where the density of nonspecific terminals is low and many do not terminate in overt synaptic thickenings (Liu and Jones, 1991). When in doubt, type II calcium/calmodulin-dependent protein kinase will confirm the corticothalamic nature of small terminals on relay cells (Fig. 5B). This kinase is, however, not expressed in GABA cells, including those of the reticular nucleus (Fig. 5D, E).

Intrinsic interneurons remain less well-characterized

Intrinsic interneurons are GABAergic and found in all dorsal thalamic nuclei of carnivores and primates but are largely restricted to the dorsal lateral geniculate nucleus of rodents and a number of other small mammals (Montero and Zempel, 1986; Hunt et al., 1991; Sawyer et al., 1991; Benson et al., 1992; Spreafico et al., 1994). In cats and monkeys, they form approximately 30% of

the neuronal populations in all nuclei, including those of the intralaminar system. Golgi studies and the small number of intracellular studies in which they have been identified by injection of intracellular tracers, reveal that these small neurons have relatively few dendrites but from these dendrites a considerable number of unusual processes emerge. These are thin, commonly branched and with numerous bulbous dilatations resembling axonal boutons (Fig. 6A). On electron microscopic observation, these dilations can be seen to contain synaptic vesicles, to form symmetrical synapses on dendrites of relay cells and on one another as well as being postsynaptic to the principal afferent fiber terminals, as described above (Fig. 6B).

It has sometimes been questioned whether these presynaptic dendritic terminals of interneurons, because of their apparent segregation by the thinness of their parent processes, can ever be invaded by depolarizion spreading from the soma and principal dendrites. If this is so, they may release GABA under local depolarizing influences and therefore serve, in the complex glomeruli described above, to regulate local excitability of relay cell dendrites contacted by afferent fibers (Bloomfield and Sherman, 1989).

There is still some debate as to whether the intrinsic interneurons possess conventional axons and even if they are capable of supporting action potentials. Axons have been reported in some Golgi preparations, but here the presynaptic dendritic processes could have been mistakenly interpreted as axons. A few injected interneurons in the dorsal lateral geniculate nucleus of the cat have been reported to possess conventional axons as well as presynaptic dendritic processes (Sherman and Friedlander, 1988). Their terminals, present in small numbers, are said to resemble those of reticular nucleus axons. It is conceivable that these cells represent reticular nucleus cells displaced into the interlaminar plexuses of the lateral geniculate nucleus (Montero, 1989; Sanchez-Vives et al., 1996).

When a principal afferent input to a dorsal thalamic nucleus is stimulated electrically while recording from a relay cell in nuclei putatively lacking connections with the reticular nucleus or in in vitro preparations in which reticular nucleus input is absent, the cell shows an initial excitatory postsynaptic potential succeeded at short latency (~ 2 ms) by a deep and long lasting (~ 100 ms) inhibitory postsynaptic potential in which three principal components can be detected (Fig. 7C): a very early
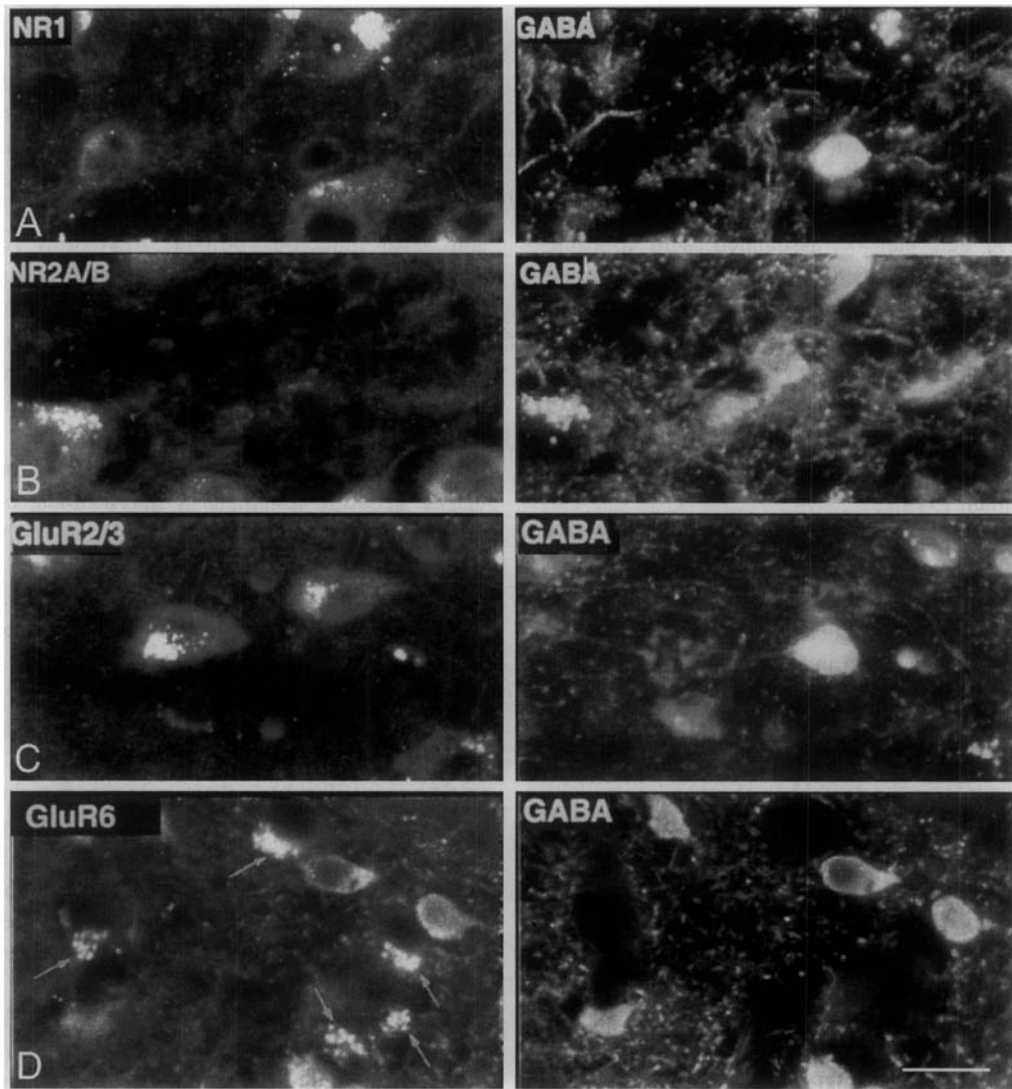
Fig. 7. **A–D**. Pairs of fluorescence photomicrographs from the same microscopic fields of the ventral posterior nucleus in a monkey, showing immunoreactivity for NMDA (NR$_1$, NR2A/B) and AMPA (GluR 2/3) receptor subunits in relay cells but not in GABA-immunoreactive cells (A–C), but strong Kainate-receptor (GluR 6) immunoreactivity in the GABA cells (D). From Jones et al. (1998).

GABA$_A$ receptor-mediated component attributable to the presynaptic dendritic terminals of interneurons, a slightly later and larger GABA$_A$-mediated component attributable to the firing of interneurons and a late GABA$_B$-mediated component also attributable to the interneurons. When inputs from the reticular nucleus are intact, longer latency (~ 3–5 ms) IPSPs with both GABA$_A$ and GABA$_B$ components overlap the IPSPs generated by the intrinsic inhibitory interneurons, representing the

feedback inhibition from reticular nucleus neurons excited by collaterals of the thalamocortical relay cells.

The fundamental properties of intrinsic interneurons, to the extent that they have been studied (in the dorsal lateral geniculate nucleus of carnivores), set them aside from relay neurons. Intracellular recordings from morphologically identified interneurons in the laminae of the dorsal lateral geniculate nucleus reveal a diversity of properties but perhaps the most distinctive is their usual

failure to show rebound burst discharges on recovering from a hyperpolarized state (McCormick et al., 1997). In this, they are clearly different from relay cells, although they do possess the low threshold Ca^{2+} current (I_t) responsible for bursting in relay cells (see below). These studies also confirm earlier observations that the interneurons are indeed capable of discharging action potentials. These are typically of short duration and occur at higher frequency for a given injection of depolarizing current than in relay cells (McCormick et al., 1997).

Thalamic interneurons can generally be shown to generate EPSPs in response to stimulation of cortical or subcortical glutamatergic afferents. As in relay cells, these EPSPs depend upon activation of both AMPA and NMDA receptors, although the NMDA-based component is described as weaker than in relay cells (McCormick et al., 1997). This is not surprising, given the lack of NMDA receptor expression in the interneurons (Jones et al., 1998; Fig. 7). A metabotropic glutamate receptor-based EPSP is reported to be absent in interneurons (Pape and McCormick, 1995), as is a GABA$_B$-based response (Williams et al., 2001).

Relay cells have two modes of functional operation

One of the most important of modern contributions to the understanding of the thalamus appeared in 1983 when Jahnsen and Llinás (1983a,b) reported that individual thalamic cells in *in vitro* slices of guinea pig thalamus showed two different patterns of discharge, depending on their resting membrane potential (Fig. 8). When a cell is depolarized by injection of a small amount of current, from a relatively depolarized (–55 mV) membrane potential, it typically fires a continuous train of action potentials and the cell is said to be in tonic firing mode. Tonic mode is characteristic of the alert state *in vivo*, when thalamic relay cells are relatively depolarized under the influence of cholinergic inputs from the brainstem. When a relay cell is depolarized from a relatively hyperpolarized (– 70 mV) membrane potential, a voltage-dependent calcium conductance is released from inactivation, leading to a low threshold calcium current (I_t), and the discharge of a calcium-based action potential. If this reaches threshold for discharge of typical Na^+/K^+ action potentials, the calcium potential has superimposed upon it a short, high frequency burst of discharges.
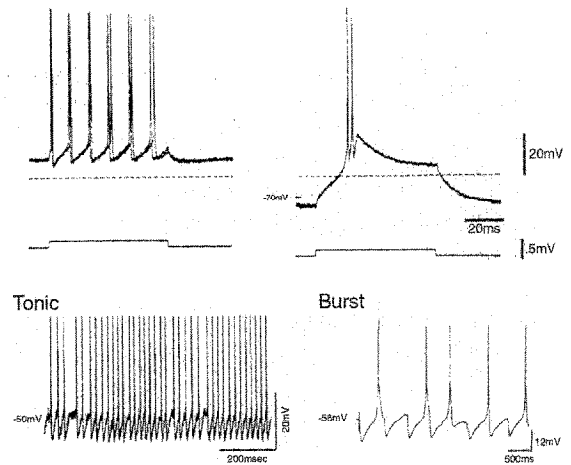

Fig. 8. Upper: Tonic (left) and burst (right) firing of a thalamic neuron depolarized by injection of current from relatively depolarized and hyperpolarized resting membrane potentials. Recorded *in vitro* slices of guinea pig thalamus. From Jahnsén and Llinás (1984). Lower: Tonic and burst firing from thalamic neurons recorded *in vivo*.

The cell is then said to be in burst firing mode. Burst firing mode is typical of relay neurons during states of drowsy inattentiveness and early slow wave sleep when input from the brainstem is suppressed. Then the cells typically display repetitive bursting behavior, each burst of action potentials being succeeded by a period of after-hyperpolarization during which the low threshold calcium conductance is again deinactivated, leading to a further burst and so on. The cell is now in an oscillatory state.

It would seem that, left to themselves, relay cells have a tendency to drift towards hyperpolarization as the consequence of their possession of an intrinsic K^+ leak current, I_{KL} (reviewed in McCormick et al., 1993). Hyperpolarization, however, leads to release of a hyperpolarization-activated cation current (I_H) which can lead to a slow depolarization and the discharge of action potentials at about 0.5–4 Hz, the so-called delta rhythm when recorded in the electroencephalogram and typical of deep sleep. The voltage dependent calcium current, I_t, when released from inactivation in cells recovering from hyperpolarization, causes them to fire in burst mode at about 7–14 Hz, the so-called spindle waves of the electroencephalogram recorded during early phases of sleep. During the awake state, when thalamic cells are relatively depolarized they can be driven to discharge tonically by externally or internally generated stimuli. Under these circumstances, higher frequency discharges

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in the 20–50 Hz ("40 Hz") range are embedded in the so-called desynchronized wave form of the awake electroencephalogram (Steriade and Amzica, 1996; Timofeev and Steriade, 1997; Steriade, 2001).

An effect of corticothalamic stimulation on relay cells is inhibition, leading to spindle oscillations

Despite the obvious glutamatergic nature of corticothalamic synapses, which is evidenced by the ability to record

NMDA-, AMPA- and metabotropic glutamate receptor-based EPSCs in relay cells under appropriate conditions (Figs. 9, 10) (McCormick and von Krosigk, 1992; Kao and Coulter, 1997; Golshani et al., 1998; Turner and Salt, 1998), another effect of corticothalamic stimulation on relay cells is the disynaptic, feed-forward inhibition resulting from coactivation of the reticular nucleus. A single weak electrical pulse applied to the corticothalamic fibers leads to a small, short latency EPSP in a relay cell, but this is quickly obliterated by a deep and prolonged IPSP lasting up to 100 ms and representing the input from the reticular nucleus
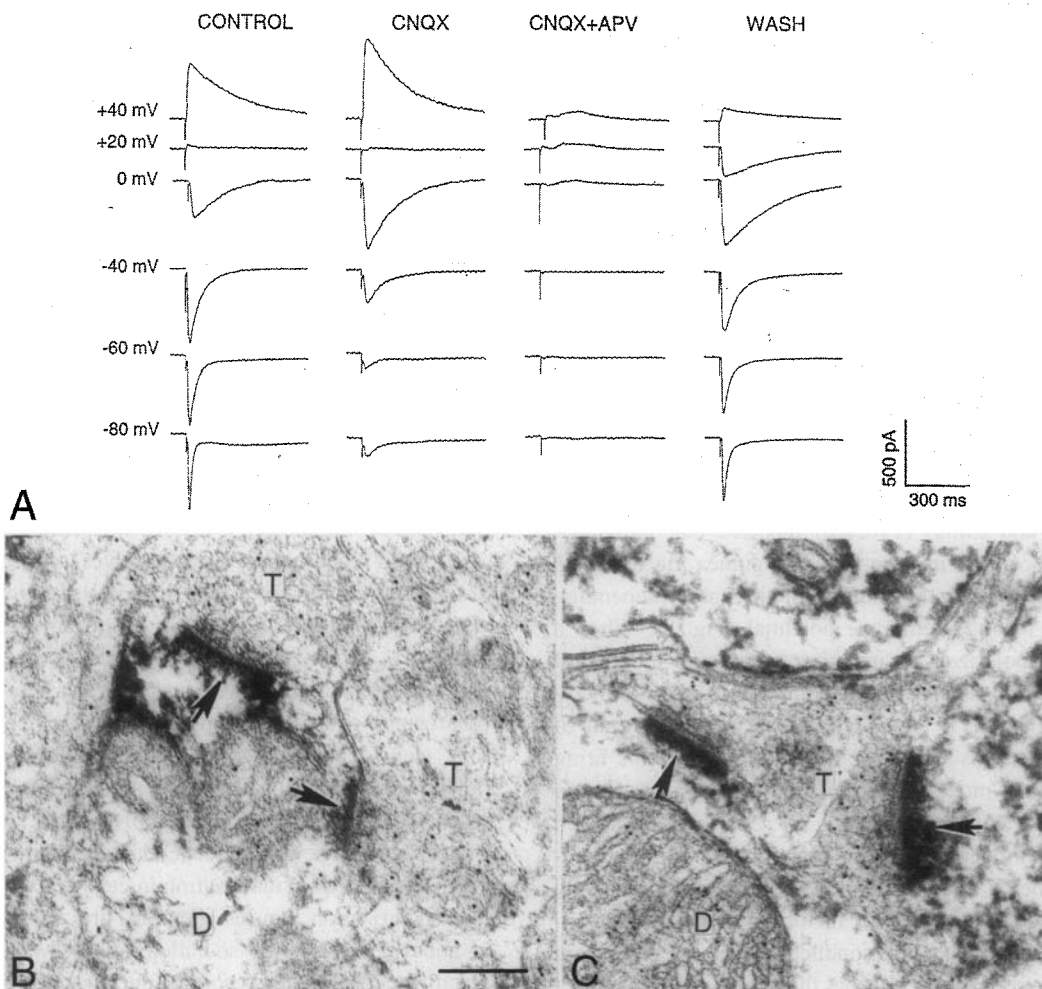

Fig. 9. **A.** Whole cell recordings from a relay neuron in the ventral posterior nucleus of a mouse thalamocortical slice *in vitro*, showing EPSCs recorded in response to stimulation of corticothalamic fibers, in the presence of AMPA (CNQX) and NMDA (APV) receptor antagonists. From Golshani et al. (1998). **B,C.** Electron micrographs of glutamate immunoreactive corticothalamic axon terminals (T) ending on dendrites at synapses in which the postsynaptic densities (arrows) are strongly immunoreactive for NMDA (A) and AMPA (B) receptors. Bar 0.5 μm.
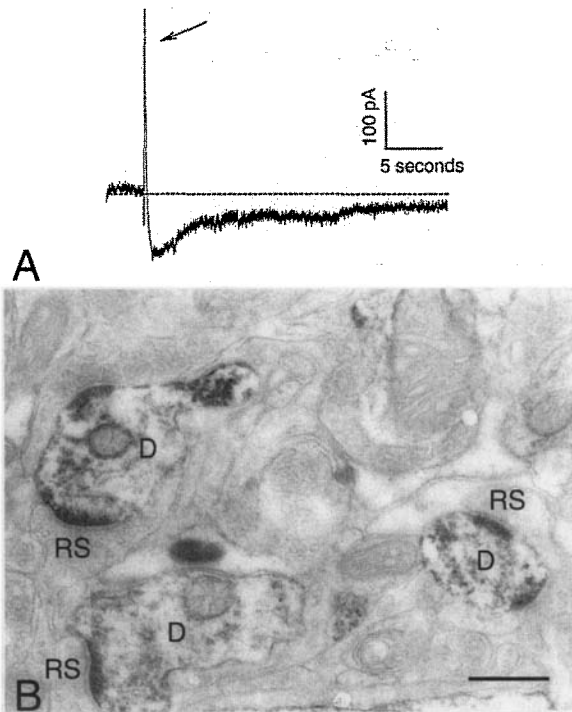
Fig. 10. **A.** Long lasting EPSC representing metabotropic glutamate receptor-based response of a relay cell to stimulation of cortico-thalamic fibers in the presence of NMDA, AMPA- and GABA$_A$-receptor antagonists. Arrow indicates preceding GABA$_B$-mediated IPSC. From Golshani et al. (1998). **B.** Corticothalamic terminals (RS) in the ventral posterior nucleus of a rat, ending on dendrites that are strongly immunoreactive for metabotropic glutamate receptor mGluR$_{1a}$. Bar 0.5 μm.

(Fig. 11A). This IPSP can be shown, as would be expected, to consist of both GABA$_A$ and GABA$_B$ receptor-mediated components. The importance of corticothalamic-induced inhibition of the relay cells is that it drives them towards the burst firing mode. As they recover from this inhibition, the low threshold calcium conductance is deinactivated and the cells fire a burst of action potentials (Fig. 11B). This has the effect of re-exciting, via the collaterals of thalamocortical fibers, the reticular nucleus cells which then fire a new burst of action potentials. These re-inhibit the relay cells which burst again on recovering, and so the cycle continues at 7–14 Hz, the spindle frequency. Recordings made simultaneously from reticular nucleus and relay cells in the underlying ventral posterior nucleus clearly demonstrate synchrony of their discharges at spindle frequencies, as well as

the synaptic interplay between the two sets of cells (Fig. 11C). The initial effect of corticothalamic activation upon the reticular nucleus cell is a steeply-rising EPSP, leading to a short train of action potentials (Fig. 11B). That on the relay cells is predominantly the disynaptic inhibition described above, succeeded by a burst of action potentials. Re-excitation of the reticular nucleus cell is evident in the second and subsequent trains of discharges, all of which are preceded by a step-wise EPSP in which each step increment in amplitude can be correlated with one of the action potentials of the burst in a connected relay cell. Each successive event in the oscillation of the relay cell is a facsimile of its predecessor: inhibition succeeded by burst firing (von Krosigk et al., 1993; Warren et al., 1994; Bal et al., 1995).

Apart from causing repetitive burst firing in relay cells, a reticular nucleus cell, by reason of the widespread terminations of its axon alone, has the effect of distributing the disynaptic inhibitory effects of corticothalamic stimulation across many relay cells, thus helping to promote synchrony throughout the whole thalamo-cortico-thalamic network. Spread of corticothalamic effects across many reticular nucleus cells and recruitment of others by collateral inputs from the thalamo-cortical axons of bursting relay cells will also serve to spread spindle oscillations across most of the thalamus and cortex. Studies *in vivo* indicate that spindle oscillations start more or less simultaneously throughout the thalamus, rather than spreading slowly across it (early reports of slowly spreading synchrony *in vitro* are thought to have been due to absence of intact corticothalamic connections in the preparation) (Kim et al., 1995; Steriade and Amzica, 1996). The simultaneous onset of spindles throughout cortex and thalamus implies rapid diffusion of reticular nucleus effects on relay cells and equally rapid collateral excitation of widespread sectors of the reticular nucleus by bursting relay cells. Although the corticothalamic system is particularly powerful in inducing spindle oscillations, it is the reticular nucleus that is the prime mover in synchronizing the oscillations of virtually all cells in the network. Its capacity to do this is enhanced when the weak inhibitory effects of one reticular nucleus cell on another are removed (Sohal et al., 2000).

The power of the corticothalamic projection to induce low frequency oscillations in the spindle range clearly depends upon the capacity of the disynaptic inhibitory effect of the reticular nucleus to overcome the direct,
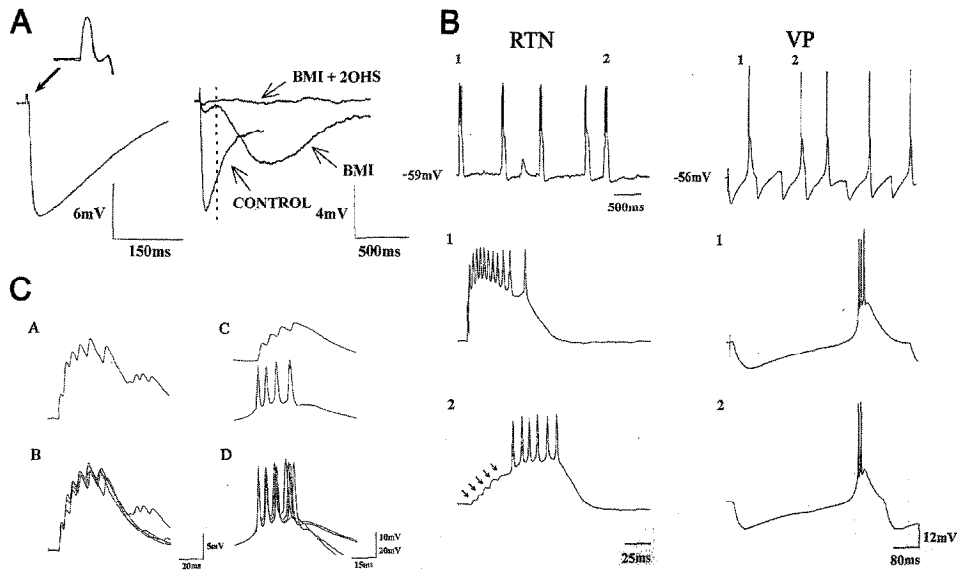
Fig. 11. **A.** Left panel: Whole cell recording from a relay neuron in the ventral posterior nucleus of a mouse thalamocortical slice *in vitro*, showing that a single weak electrical stimulus (arrow) applied to the corticothalamic fibers elicits a small monosynaptic EPSP that is quickly obliterated by the deep and long lasting disynaptic IPSP which reflects the collateral corticothalamic excitation of the reticular nucleus. Right panel shows that this IPSP consists of GABA$_A$ and GABA$_B$ components revealed by application of selective antagonists bicuculline (BMI) and 2-hydroxysaclofen (2OHS). **B.** Low frequency oscillations induced by a single, weak electrical stimulus to corticothalamic fibers in two neurons of the reticular (RTN) and ventral posterior (VP) nucleus of the mouse thalamocortical slice. First response on the part of the RTN cell is a steep EPSP surmounted by a burst of action potentials. First and all subsequent responses of the VP cell are characterized by the disynaptic inhibition from RTN cells, with burst firing as the cell recovers from the hyperpolarization. Second and subsequent responses of the RTN cell are characterized by step-wise pattern of increasing EPSP amplitude, reflecting collateral excitation from axons of the bursting VP cell, leading to renewed burst firing. **C.** Details of single (A, C) and superimposed repreated EPSCs in RTN cells and of bursts of action potentials (C, D) in a connected VP Cell. B,C from Warren et al. (1994).

monosynaptic excitatory effect of corticothalamic fibers upon the relay cells of the dorsal thalamus. To effect this, the strength of the corticothalamic input to the reticular nucleus should, of necessity, be stronger than that to the relay cells. Modeling studies in which the inputs to reticular nucleus relay cells are set at equal strengths result in a failure to elicit oscillatory activity in the network (Destexhe et al., 1998). How can synapses made by branches of the same axons on reticular nucleus cells and relay cells differ in strength or efficacy? Recent observations provide a resolution of this dilemma.

Using a minimal stimulation paradigm and low Ca^{2+} conditions in which the probability of vesicle release is reduced to close to zero, it is possible to record unitary EPSCs in relay cells and reticular nucleus cells in response to stimulation of a small number of corticothalamic fibers (Fig. 12). Under these conditions, and with GABA and NMDA receptor-based responses excluded, corticothalamic EPSCs in the reticular nucleus cells are nearly three times larger than in relay cells (Fig. 12B) (Golshani et al., 2001). A basis for this difference in AMPA-receptor based synaptic strength has been discovered in the presence of nearly three times as many GluR$_4$ receptor subunits at the corticothalamic synapses on the reticular nucleus cells than at corticothalamic synapses on relay cells (Fig. 12C, D). GluR$_3$ subunits are present in equal numbers and GluR$_1$ and GluR$_2$ subunits are not expressed in the thalamus (Liu et al., 2001). Hence, corticothalamic synapses on reticular nucleus cells are enriched with GluR$_4$ receptor subunits, and increases in channel opening time consequent upon this enrichment should account for the larger EPSCs in the reticular nucleus cells.

Collateral corticothalamic and thalamocortical inputs to reticular nucleus cells possess different properties

As mentioned above, in *in vitro* slices of rodent thalamus, it is possible to separate in reticular nucleus cells' EPSCs derived from orthodromic activation of corticothalamic fibers and EPSCs derived from collaterals of antidromically activated thalamocortical axons on the basis of latency (Fig. 13) (Liu et al., 2001). In the mouse thalamocortical slice, minimal EPSCs elicited in reticular nucleus cells by antidromic invasion of thalamocortical collaterals occur at latencies of less than 3 ms while those elicited by orthodromic activation of the thinner corticothalamic fibers occur with latencies longer than 6 ms. The amplitudes of minimal corticothalamic EPSCs are remarkably consistent, probably reflecting the presence of a single vesicle release site at the relatively small,

single synaptic contacts (Fig. 13). The rise times of these EPSCs are, however, quite variable, reflecting the scatter of corticothalamic terminals across the dendritic tree of the reticular nucleus cell. By contrast, minimal EPSCs resulting from activation of thalamocortical collateral synapses in reticular nucleus cells have variable amplitudes, reflecting the presence of multiple release sites at the large perforated synaptic contacts with their multiple synaptic segments (Fig. 13). Rise times are, however, very consistent, reflecting the localization of the thalamocortical synapses close to the cell soma. Unlike the corticothalamic synapses at which $GluR_4$ receptor subunits are enriched in comparison with $GluR_3$ subunits. $GluR_4$ and $GluR_3$ subunits appear in equal proportions at collateral thalamocortical synapses (Figs. 12, 13). At the larger collateral thalamocortical synapses, however, the overall number of AMPA receptor subunits is much higher than at the corticothalamic
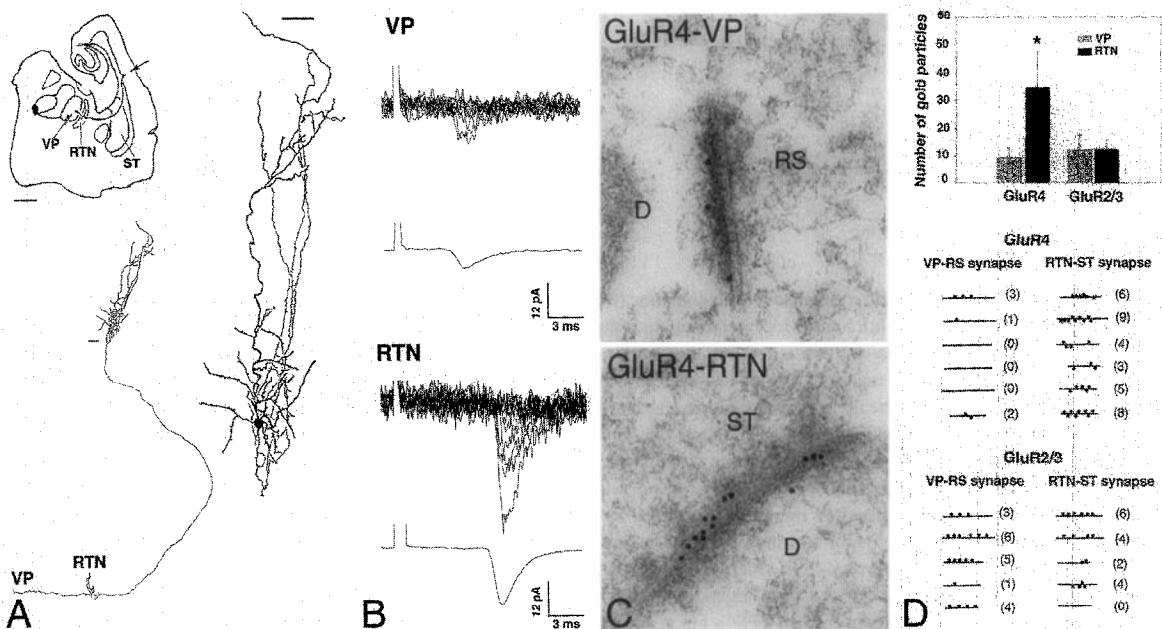

Fig. 12. **A.** Location and camera lucida drawings of a typical layer VI corticothalamic cell from a mouse thalamocortical slice preparation. The axon branches to innervate both the reticular nucleus (RTN) and the ventral posterior nucleus (VP). **B.** 10 superimposed consecutive traces and their mean, showing EPSCs recorded from a VP cell and an RTN cell in response to minimal stimulation of corticothalamic fibers. Minimal EPSCs in RTN cells have approximately three times greater amplitudes than those in VP cells. **C.** Immunogold labeling for GluR4 receptor subunits at corticothalamic (RS) synapses in VP and RTN showing larger number of particles in the RTN. **D.** Quantification of immunogold particles representing GluR4 and GluR 2/3 receptor subunits at postsynaptic densities of four serially sectioned corticothalamic synapses in VP and RTN. Number of GluR4 particles at corticothalamic synapses on RTN cells are approximately three times greater than at corticothalamic synapses on VP cells. From Golshani et al. (2000).
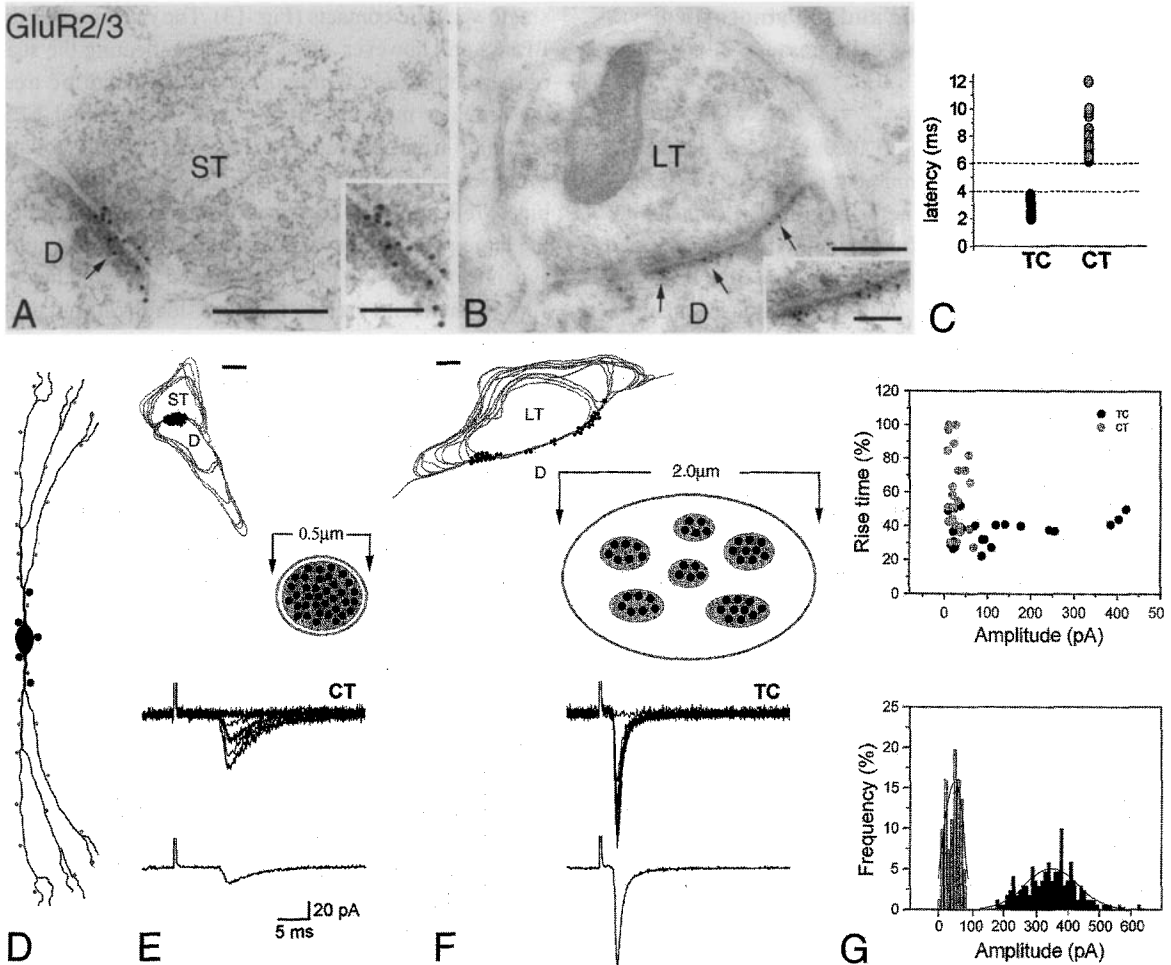
Fig. 13. **A,B.** Electron micrographs of terminals of corticothalamic (ST) and thalamocortical (LT) collaterals in the reticular nucleus of a mouse, showing immunogold labeling for GluR2 and 3 receptor subunits at their synapses. Corticothalamic terminals are characterized by a single vesicle release site, thalamocortical collateral terminals by multiple release sites (arrows). Bars 0.25 µm and 0.1 µm (insets). **C.** Bimodal latencies of EPSCs recorded from reticular nucleus cells in response to stimulation of subcortical white matter. Shorter latency responses reflect antidromic invasion of thalamocortical fibers (TC) and excitation of reticular cells via their collaterals. Longer latency EPSC's represent orthodromic activation of corticothalamic (CT) collaterals. **D.** Schematic view of a reticular nucleus cell showing proximal location of thalamocortical collateral synapses and more distributed distribution of corticothalamic collateral synapses. **E,F.** Upper: reconstructions from serial electron micrographs of corticothalamic (ST) and thalamocortical (LT) collateral synapses terminating on dendrites (D) of reticular nucleus cells, with the postsynaptic densities immunogold labeled for GluR 2/3 subunits. En face views of each synapse indicate single release sites at thalamocortical collateral synapse and multiple release sites at thalamocortical collateral synapse. Lower: overlay of 10 successive EPSCs and mean of these EPSCs recorded from reticular nucleus cells in response to minimal stimulation of corticothalamic or thalamocortical fibers. Minimal thalamocortical EPSCs have larger amplitudes and faster rise and decay times than minimal corticothalamic EPSCs. **G.** Upper: rise times of minimal thalamocortical EPSCs are relatively constant, reflecting proximal location of synapses, but amplitudes vary, probably reflecting wider variability in number of release sites. Minimal corticothalamic EPSCs have variable rise times reflecting more undespread distribution of the synapses, but constant amplitudes, reflecting the single release site. Based on Liu et al. (2001).

synapses. This may provide the capacity for the powerful re-entrant excitation of the reticular nucleus cells by bursts of action potentials in relay cells during the course of spindle oscillations. Some of the variance in the rise times of the EPSCs engendered in reticular nucleus cells by the thalamocortical collaterals may be attributable to the variable number of subunits located at each of the segments of the perforated synapse.

Interactions between cortex and thalamus during high frequency oscillatory activity

Although by no means universally accepted (Shadlen and Movshon, 1999), current thinking looks to coherent, higher frequency oscillations of large populations of cortical and thalamic neurons in the γ (20–50 Hz) range as concomitants of forebrain activities that underlie perception, cognition and directed attention (Llinás and Paré, 1991, 1997; Singer and Gray, 1995). In the sensory systems of the cerebral cortex, large scale synchrony of neurons in the areas that form links in the chain of corticocortical processing is thought necessary to ensure the binding of separate elements of sensory experience into a single cognitive event. It is inconceivable, however, that the thalamic nuclei with which these areas are reciprocally connected should not also oscillate in synchrony with these cortical areas. In seeking for thalamocortical connections that might serve to disperse thalamic activity across multiple cortical areas, attention in the past has tended to focus on the intralaminar nuclei which have traditionally been thought to possess axons that project diffusely to the cortex and to terminate there in layer I on the peripheral apical dendritic branches of pyramidal cells of all layers. Attractive as this hypothesis may seem, it rests upon evidence that is at best incomplete. It is now clear that the classical intralaminar nuclei project to relatively restricted regions of the cerebral cortex, that their axons are not excessively widely distributed and some appear to end in deeper layers rather than in layer I (reviewed in Steriade et al., 1997a). Moreover, a large number of intralaminar cells, perhaps the majority, project not to the cortex at all but to the striatum. This striatal projection of the intralaminar nuclei, unknown to Cajal, remains little investigated, even today. In circuit diagrams of the basal ganglia and thalamus used to "explain" the pathophysiology of movement disorders, it commonly goes unrepresented (Jones, 2001a).

Recent findings in monkeys reveal a hitherto unrecognized pattern of thalamic organization that provides a basis for the dispersion of thalamic activity across multiple cortical areas and for recruiting large constellations of thalamic and cortical neurons in synchronous activity that underlies discrete cognitive events (Jones, 1998a,b; 2001b). The data upon which this hypothesis rests are described in the following section.

The core and matrix of the primate thalamus

Immunocytochemical staining for the two major calcium binding proteins, parvalbumin and 28 kDa calbindin, reveals two distinct classes of relay neurons in the thalamus of monkeys and certain other primates (Jones and Hendry 1989; Diamond et al., 1993) (Fig. 14). Neurons immunoreactive for calbindin are distributed widely throughout the dorsal thalamus and can be found in every nucleus, however defined—relay, intralaminar, nonspecific, etc. Parvalbumin immunoreactive cells, by contrast, are found in certain nuclei only, typically in the principal sensory and motor relay nuclei, certain nuclei of the pulvinar and in some intralaminar nuclei. They are absent from all other dorsal thalamic nuclei. When present, they are typically found in large, dense clusters associated with densely terminating afferent fibers which are themselves parvalbumin immunoreactive. They appear as a core imposed on a diffuse background matrix of calbindin cells, hence the terminology used to describe the two cell classes. Calbindin cells tend to be slightly smaller than parvalbumin cells but are much larger than the intrinsic GABAergic neurons (Rausell et al., 1992). Unlike in some species such as cats, the intrinsic GABA cells do not express parvalbumin. The reticular nucleus cells do but these are not relay cells.

In some locations, there is a superficial impression of complementarity in the distributions of calbindin and parvalbumin cells and, where parvalbumin cells are absent, calbindin cells often appear in increased numbers. In the dorsal lateral geniculate nucleus, parvalbumin cells are found only in the magno- and parvocellular layers, while calbindin cells are concentrated in the S layers and interlaminar plexuses between these layers (Jones and Hendry, 1989; Hendry and Calkins, 1998) (Fig. 15). Closer inspection reveals, however, that the calbindin cells spread throughout the nucleus and are continuous with the larger population of calbindin cells in the adjoining inferior pulvinar nucleus (Jones, 1998a). In the ventral posterior nucleus zones of calbindin only cells are intercalated among the larger masses of parvalbumin cells and are especially concentrated in a parvalbumin absent zone along the posteromedial border of the ventral posterior medial (VPM) nucleus (Figs. 14, 15). Here, they are continuous with the larger population of calbindin cells in the posterior nucleus and anterior pulvinar nucleus. In the medial geniculate complex,
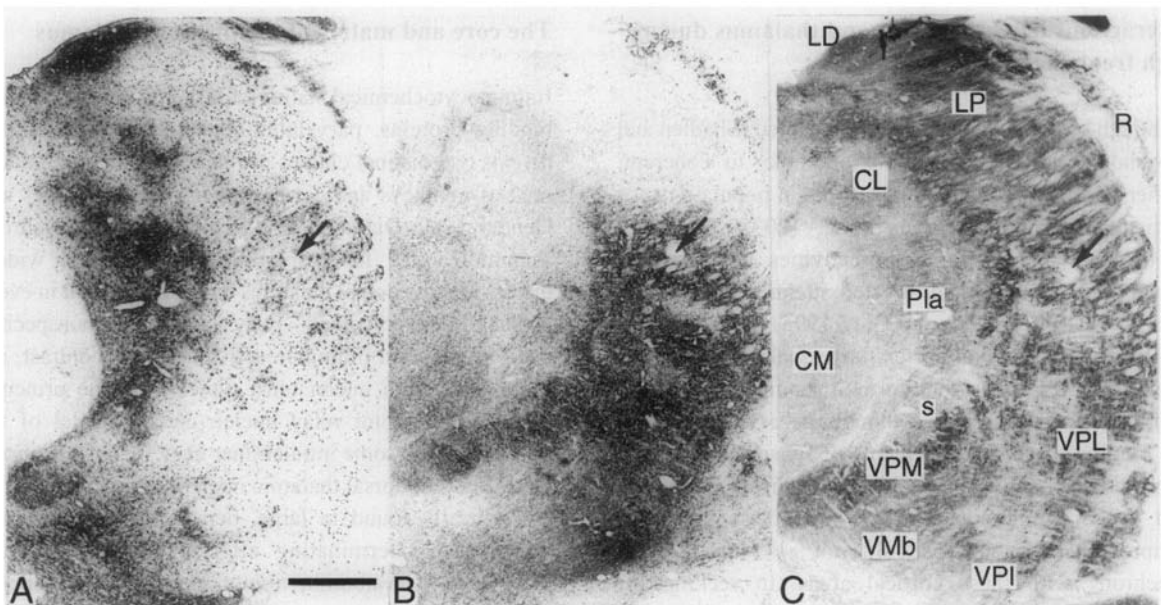
Fig. 14. Photomicrographs of adjacent frontal sections through the thalamus of a macaque monkey, showing the nuclei of the ventral complex stained immunocytochemically for calbindin (A), or parvalbumin (B), or histochemically for cytochrome oxidase (C). Note the restriction or concentration of parvalbumin core cells in certain nuclei, the widespread distribution of calbindin matrix cells, their increased concentration in nuclei from which core cells are absent, and the correlation of weak cytochrome oxidase activity with the concentration of matrix cells. Arrows indicate profiles of the same sectioned blood vessel. Bar 0.5 mm. From Jones (2001b).

the ventral nucleus is dominated by parvalbumin cells with only a few background calbindin cells of the matrix (Fig. 15). The more anterior of the dorsal nuclei has a mixed population of the two cell types, while the posterior dorsal nucleus possesses mainly calbindin cells, continuous with those of the inferior pulvinar nucleus. The magnocellular nucleus exhibits islands of calbindin cells alternating with islands of parvalbumin cells. In all nuclei where parvalbumin cells are concentrated, metabolic activity is high and histochemical staining for enzymes such as cytochrome oxidase (CO) is correspondingly high. Calbindin-rich zones, however, show weak CO staining (Fig. 14).

Parvalbumin cells and calbindin cells project differently upon the cerebral cortex. Parvalbumin cells show the well-known topographically organized projection in which adjacent groups of cells project to adjacent regions of one or at most two cytoarchitectronic areas of the cortex where they terminate in small (~600 µm), localized zones of terminals in the middle layers (deep III and IV) (Fig. 16). Calbindin cells, by contrast, project more diffusely. Adjacent cells can project to separated zones of cortex, including to different (though usually adjacent)

cortical areas (Rausell et al., 1991a, 1992). In these areas, their axons terminate in superficial layers (I, II and upper III). Every thalamic nucleus that contains both parvalbumin and calbindin cells, thus, has both focused, area-specific, middle-layer projections from parvalbumin cells of the core, and diffuse superficial-layer projections from calbindin cells of the matrix that are unconstrained by borders between functional areas in the cerebral cortex (Fig. 16). This dual projection can be found in both relay nuclei and the intralaminar nuclei. In nuclei in which only calbindin cells are found, diffuse superficial layer projections predominate. These may have a special significance, as outlined below.

The focused and diffuse characters of axonal projections to the cerebral cortex from core and matrix cells is reflected in their inputs from subcortical afferent pathways. Nuclei characterized by a high density of parvalbumin core cells, such as the ventral posterior nucleus, laminar dorsal lateral geniculate nucleus, and the ventral medial geniculate nucleus receive the terminations of ascending afferent pathways that are typically highly organized topographically and in which neurons at the various relay stations exhibit highly

localized receptive fields and specific stimulus-response properties. The fibers of these pathways, e.g. the medial lemniscus, P and M components of the optic tract, and the brachium of the inferior colliculus are themselves parvalbumin immunoreactive and terminate in localized, topographically ordered domains within the borders of the parvalbumin core.

Nuclei and portions of nuclei characterized by a high density of calbindin matrix cells, on the other hand, typically receive the terminations of ascending pathways such as the spinothalamic tract and brainstem tegmental auditory pathways that are more diffusely organized, less directly connected with their peripheral receptors, and whose fiber terminations characteristically spread quite diffusely through large regions of the thalamus unrestricted by borders between nuclei (Fig. 15). Neurons
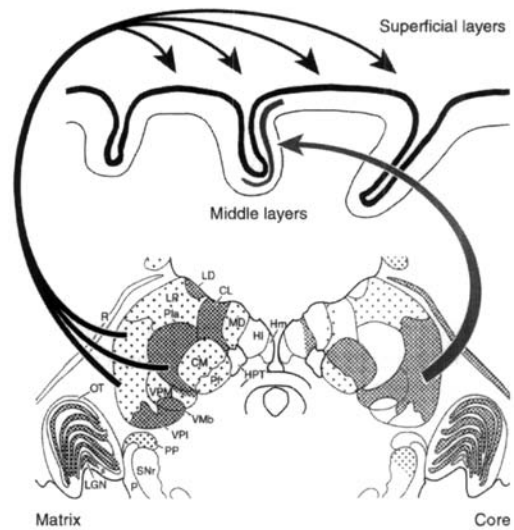
Fig. 16. Lower part of figure shows relative distributions and concentrations of calbindin matrix cells (left) and parvalbumin core cells (right) in a frontal section through the middle of a macaque monkey thalamus. Upper part of figure shows schematically the projection of the matrix to superficial layers of cortex over a relatively wide extent and unconstrained by borders between areas. Core cells restricted to individual nuclei, here exemplified by the ventral posterior nucleus, project in topographically ordered manner upon middle layers of single functional cortical fields. From Jones (2001b).
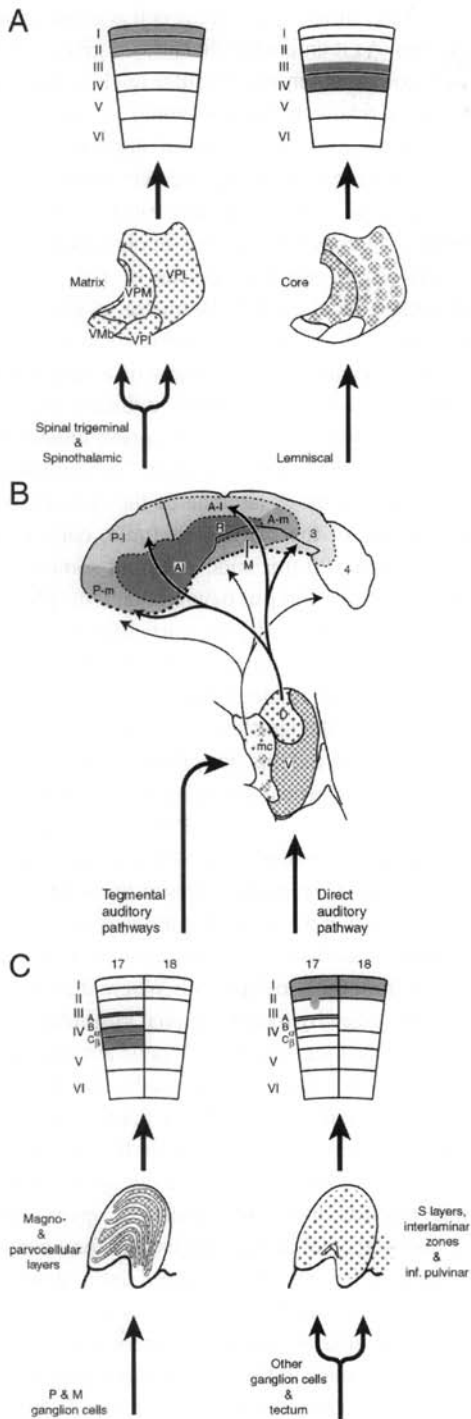
Fig. 15. Schematic views of diffuse and focused subcortical inputs to the matrix and core compartments of the ventral posterior (A), medial geniculate (B) and lateral geniculate (C) nuclei of the macaque monkey, their layer-specific and widespread and focused projections to the cerebral cortex. In A and C, cortical areas are indicated by schematic vertical sections with the layers indicated; in B the surface of the supratemporal plane with the auditory fields delineated by different intensities of parvalbumin immunoreactivity are indicated. Based on Jones (2001b).

receiving inputs from the less direct auditory pathways in the dorsal nuclei of the medial geniculate complex, for example, are not tonotopically organized, fatigue easily and tend to require novel stimuli to activate them. The spinothalamic tract, although containing a population of nociceptive-specific fibers is dominated by fibers with large receptive fields and multi-modal inputs. Patch-like terminations of these fibers are found wherever there are calbindin rich zones in and around the ventral posterior nucleus (Rausell et al., 1992). In the dorsal lateral geniculate nucleus, fibers ascending from the deeper layers of the superior colliculus and terminating in large numbers in the calbindin-rich inferior pulvinar nucleus, spill over into the dorsal lateral geniculate nucleus and terminate among the matrix cells of the S layers and interlaminar plexuses. These matrix regions are also innervated specifically by the least well characterized population of retinal ganglion cells which includes blue-on cells but apparently many other types as well (Martin et al., 1997).

Two kinds of corticothalamic fiber have different patterns of thalamic termination

Retrograde labeling studies have for many years shown that although the majority of cells projecting to a particular thalamic nucleus are found in layer VI of the cortical area related to that nucleus, a smaller but significant number is almost invariably found in layer V of the same area (Steriade et al., 1997a). Studies in rodents and carnivores have revealed not only that layer VI and layer V corticothalamic cells have very different morphologies but also that the terminations of their fibers adopt very different ramification and terminal patterns in the thalamus.

Corticothalamic neurons of layer VI typically are small, modified pyramidal cells with a narrow, ascending dendritic field centered on a short apical dendrite that ends in the middle layers of the cortex among the terminations of thalamocortical fibers (Fig. 4). Here, they receive monosynaptic inputs from the thalamocortical fibers. The axon of a layer VI corticothalamic cell, before leaving the cortex, gives off two or three recurrent collaterals which typically ascend within the confines of or closely adjacent to the vertical dendritic field of the cell (Ojima et al., 1992; Ojima, 1994). Each cell, therefore, influences a relatively narrow zone of the cortical area in

which it lies. The primary axon of the cell is directed only to the thalamus. As it enters the thalamus it gives off one or two short collaterals in the reticular nucleus and then terminates in a relatively narrow zone, in appropriate topographic order, only in the dorsal thalamic nucleus from which its parent cortical area receives input (Fig. 4). Some deep layer VI cells in rodents can have terminations extending across two related nuclei such as the ventral posterior and medial nucleus of the posterior group (Hoogland et al., 1987; Bourassa et al., 1995). Although ending in a relatively restricted zone of the related thalamic nucleus, the terminals of a single layer VI corticothalamic cell can apparently influence thalamic relay cells that project to regions of cortex outside the narrow cortical zone in which it resides. Corticothalamic axons terminating in the A laminae of the dorsal lateral geniculate nucleus of the cat, for example, concentrate their terminals in a 500 μm wide zone but some terminals extend for up to 1500 μm beyond that (Murphy and Sillito, 1996). In other words, the corticothalamic axon can influence an extent of the visual field representation in the lateral geniculate nucleus many times greater than that represented in the cortical column in which its parent cell resides. In rodents, too, fibers derived from a cell beneath a single cortical barrel in the somatosensory cortex may extend terminals into VP barreloids adjacent to the barreloid that provides input to that cortical barrel, and thus into thalamic regions representing other facial vibrissae (Hoogland et al., 1987; Bourassa et al., 1995).

Corticothalamic cells whose somata lie in layer V are quite different from those of layer VI. Where the layer VI cells are characterized by focused axonal ramifications in both cortex and thalamus, the layer V cells are characterized by diffuseness. The layer V cells are typically pyramidal in form with larger somata than the layer VI cells, and have a stout apical dendrite ending in a tuft of branches in layer I of the cortex. The axon is thick and as it descends towards the white matter it gives off a number of horizontal collaterals that extend for a considerable distance (Fig. 4). The primary axon descends towards the thalamus but this is only one of its targets for, depending on the area in which the parent cell lies, the axon will have branches to the tectum, other parts of the brainstem or spinal cord. Although the thalamic branch almost invariably traverses the reticular nucleus en route to the dorsal thalamus, it does not give off collaterals in the reticular nucleus. Within the dorsal thalamus, its terminations are not restricted to the nucleus from which

its parent cortical area receives inputs. Instead, branches extend across one or more adjacent nuclei. In the case of cells with somata located in the motor and somatosensory areas of the cortex, these additional nuclei commonly include those of the intralaminar system. In the case of cells in the primary visual cortex, nuclei of the pulvinar-lateral posterior complex are the targets, and in the case of cells in the primary auditory area of the cortex, the dorsal and magnocellular nuclei of the medial geniculate complex are the targets (Fig. 4). It is not without significance that many of the additional nuclei to which the layer V corticothalamic cells project, tend to be dominated by cells of the thalamic matrix. In them, the axons of the layer V corticothalamic cells terminate in small numbers of large boutons, quite unlike the numerous small boutons of layer VI corticothalamic cells. These larger boutons may enter into synaptic relationships with relay cells that are more like those of ascending afferent fibers than those of the terminals of the layer VI cells.

Widespread synchrony of the thalamus and cerebral cortex in cognition

During the alert, waking state, stimuli generated naturally in the external world or experimentally by artificial stimulation of a major subcortical afferent pathway, commonly lead to synchronous high frequency discharges in the 20–50 Hz ("40 Hz") range in discrete populations of thalamic relay neurons and in the cortical area or areas to which these project (Gray et al., 1989; Usrey and Reid, 1999). In the cortex, discrete populations of neurons in connected cortical areas can show similar synchrony which may serve to unite them temporarily as part of the process that ensures binding of distributed components of a sensory percept into a single experiential event (Gray et al., 1989; Singer and Gray, 1995). In magnetoencephalographic traces, 40 Hz activity can be seen moving across the cortex as new areas are recruited as part of what can be construed as a discrete conscious event (Ribary et al., 1991). Similarly, long range recruitment of parieto-temporal and frontal cortical areas into synchronous activity of this kind, may promote interactions that unite perception with the planning of strategies for action (Tononi et al., 1992).

The cells of the thalamic matrix clearly form a basis for dispersion of activity across larger areas of cortex

than those of the core with their focused projections to an individual area. Within an area, the terminations of matrix cell axons on distal dendrites in superficial layers and of core cell axons on more proximal dendrites in middle layers should serve as a coincidence detetection circuit leading to a high degree of temporal integration (Llinás and Paré, 1997) (Fig. 17). This in turn should promote synchronous activity in the cells of individual cortical columns and in a group of columns activated by the same stimulus. Oscillatory activity in these cortical columns should be fed back by layer VI corticothalamic cells to the thalamic nucleus from which they receive input, serving to reinforce the synchrony. Synchronous activity would be spread across other cortical columns in the same cortical area and in adjacent cortical areas by the diffuse projections of matrix cells in the thalamic nucleus. However, other thalamic nuclei and, through their matrix cells, other cortical areas should also be recruited into large scale coherent activity by the diffuse intracortical and corticothalamic projections of layer V corticothalamic neurons (Fig. 17). As an oscillation fades, these temporary links between discrete populations of cortical and thalamic cells with different relationships to a cognitive event would be broken. They would be reformed in new patterns as part of the process underlying new cognitive experiences.

Summing up

What Cajal would have thought of all the new data that have appeared on the thalamus in recent times can only be a subject of conjecture. He would no doubt have been gratified that his briefly-described observations on the reticular nucleus and on the thick and thin corticothalamic fibers should have proven to be so prescient. He would have related well to the remarkable two-way traffic that occurs between cortex and thalamus, since it provides a functional correlate of what he called the centrifugal and centripetal pathways, and he responded with renewed excitement whenever he revealed new two way connections of this kind associated with a brain or spinal center. As one who continually sought to perfect and apply new techniques that could reveal aspects of nerve cells hidden to the Golgi technique, he would have relished the wide variety of new methods that are now available for delineating neurons morphologically and chemically. What he would have made of the
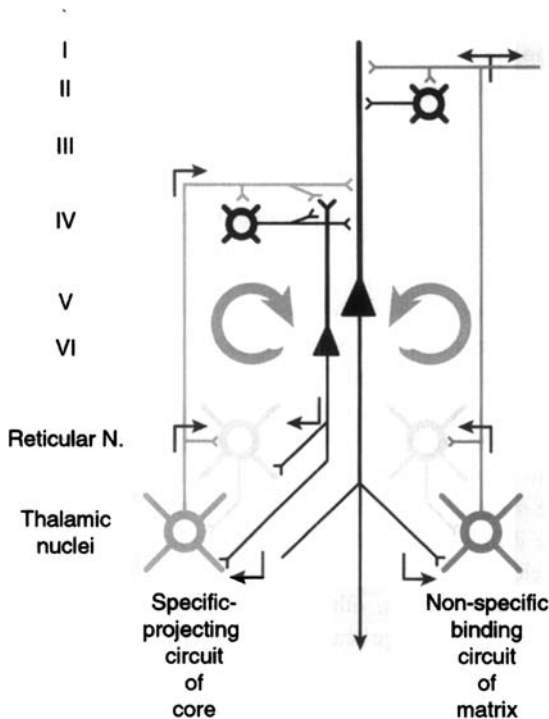
Fig. 17. Coincidence detection circuit formed by differential laminar terminations of matrix and core cells on cortical pyramidal cells. Inputs from core and matrix cells oscillating at high frequencies would be integrated over the dendritic tree and promote oscillatory activity in the cortical cells, activity that would be further promoted by feedback to the initiating thalamic nucleus by layer VI corticothalamic cells. Widespread extent of matrix cell terminations in cortex and of layer V corticothalamic axons in thalamus would promote synchrony of oscillations across wide regions of cortex and thalamic nuclei. From Jones (2001b). Based in part on Llinás and Paré (1997).

physiological discoveries on the dynamics of the system is open to question. For all his morphological insights and his remarkable capacity to derive fundamental biological principles from morphological observations, he was not, even by the standards of his time, particularly sophisticated physiologically. Early physiological observations pointing to the character of synaptic transmission, for example, did not enter into his thinking that led up to the formulation of the neuron doctrine. Where he did engage in physiological speculation, for example, about activity-dependent changes in the numbers and morphology of dendritic spines, he usually obtained it from others. While convinced of the active nature of connectivity between neurons, his contributions were primarily in mapping the static organization of connections within and between neurons in the different nuclei and cortices of the central nervous system, based on the principle of dynamic polarization, and how these defined the routes for the transmission of information through the brain and spinal centers.

It was a remarkable feat that the internal, cell-to-cell circuitry of virtually every nucleus and cortex as we know it today was built by Cajal's hands in the brief period between commencing work with the Golgi method in 1888 and the publication of the first volume of the *Textura del Sistema Nervioso* in 1899. The thalamus, despite all the new data outlined in this review, is no exception.

Acknowledgments

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