

Functional Organization of Thalamocortical Relays

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SUMMARY AND CONCLUSIONS

1. The thalamus has long been seen as responsible for relaying information on the way to the cerebral cortex, but it has not been until the last decade or so that the functional nature of this relay has attracted significant attention. Whereas earlier views tended to relegate thalamic function to a simple, machine-like relay process, recent research, reviewed in this article, demonstrates complicated circuitry and a rich array of membrane properties underlying the thalamic relay. It is now clear that the thalamic relay does not have merely a trivial function. Suggestions that the thalamic circuits and cell properties only come into play during certain phases of sleep to effectively disconnect the relay are correct as far as they go, but they are incomplete, because they fail to take into account interesting and variable properties of the relay that, we argue, occur during normal waking behavior. Although the specific function of the circuits and cellular properties of the thalamic relay for waking behavior is far from clear, we offer two related hypotheses based on recent experimental evidence. One is that the thalamus is not used just to relay peripheral information from, for example, visual, auditory, or cerebellar inputs, but that some thalamic nuclei are arranged instead to relay information from one cortical area to another. The second is that the thalamus is not a simple, passive relay of information to cortex but instead is involved in many dynamic processes that significantly alter the nature of the information relayed to cortex.

INTRODUCTION

Thalamic functions

The thalamus has not had good press in the recent past. After it had been recognized as the major source of inputs to the cerebral cortex (e.g., Elliot-Smith 1910; Nissl 1913), it had some years of relative glory. We learned that each of the major afferent pathways from the special senses and from other parts of the brain such as the globus pallidus, the cerebellum, or the mammillary bodies could only reach the neocortex by passing through one or another of the nuclei of the thalamus (summarized in Jones 1985). The thalamus was seen as serving the cerebral cortex, and all that the cerebral cortex could do necessarily depended on messages that passed through the thalamus. However, a close examination of what the thalamus might actually be doing as it passes messages to the cortex proved disappointing. More than 50 years ago, Glees and Le Gros Clark (1941) suggested that the lateral geniculate nucleus of the monkey simply represented a 1:1 relay of single retinogeniculate axons synapsing with single geniculate cells, so that messages might be passed faithfully from retina to cortex, and more recently Zeki (1993) wrote of this nucleus: "the . . . minutely studied lateral geniculate nucleus has told us very little that is of interest about vision as a process, beyond the vague state-

ment that it may act as a 'sharpeners' of the visual image, a surprisingly banal function for so large and complex a structure."

During the past 50 years, the complexity of local circuits within the thalamus was being defined, receptive fields of single cells in several thalamic nuclei were closely studied, rich two-way connections with the cerebral cortex and the thalamic reticular nucleus were revealed, a variety of transmitters used by the several thalamic circuits were identified, and a number of different postsynaptic receptors and voltage-sensitive membrane channels were demonstrated for thalamic cells. However, despite this wealth of new information, theories of what the thalamus might actually be doing in an active animal remained disappointing and generally surprisingly dull. The thalamic relay was seen as responsive to states of arousal, wakefulness, and sleep, modifying its outputs to the cerebral cortex in accordance with states of consciousness (Livingstone and Hubel 1981; McCarley et al. 1983; Steriade 1992; Steriade and Contreras 1995; Steriade and McCarley 1990; Steriade et al. 1993). In addition to this, the role that thalamic circuits might play in the production of epilepsy was defined (Huguenard and McCormick 1992; Huguenard and Prince 1994; McCormick and Feeseer 1990; Steriade 1992; Steriade and Contreras 1995; Steriade and Llinás 1988; Steriade et al. 1993). However, it generally has seemed that the complex circuitry of the thalamus might play no significant role in processing the information that is passed on to the cortex in a normal awake, behaving animal. One was left with the unpalatable conclusion that in the awake condition the cortex could perhaps have done as well with inputs received directly from the retina or the medial lemniscus as it achieves in reality with its thalamic inputs.

For some years now we (the two authors) have been exploring the extent to which our different views of the anatomic and functional organization of the thalamus might be brought together to produce a coherent view of the role of the thalamus. This exploration is far from complete, but we have reached an interim stage, where it may prove useful to summarize our current position, not so much to demonstrate what it is that the thalamus may be doing, but more to focus on important new questions that arise from recent advances in our knowledge.

In this review, we provide a background of basic current anatomic and physiological knowledge of the organization of the major thalamocortical pathways. We do not include the midline and intralaminar groups of thalamic nuclei, which are probably organized differently than the rest. We shall use the lateral geniculate nucleus and related visual relays of the cat as our main example. We do this because

knowledge of the cat's geniculate relay is more detailed than that of any other thalamic nucleus, and the analysis of sensory function in the visual pathways is more advanced and more readily quantifiable. We explore the extent to which observations on the visual relay may be generalizable to other thalamic nuclei, particularly the major relay nuclei, and we look closely at two recent developments in our knowledge of thalamic organization.

The first of these developments concerns the extent to which large parts of the thalamus are not parts of pathways over which sensory systems and subcortical cell groups can transmit information to the cerebral cortex. Instead, these "higher order" thalamic cell groups (see below and Guillery 1995) serve as pathways over which one area of cortex can be informed about what another cortical area is doing. The second development looks at the thalamic relay not so much as a system that either passes information to cortex or fails to pass information, depending on the state of consciousness of the animal, but rather as a system that can change the nature of the relay and thus the kind of information reaching cortex. One example among others that we emphasize later in this review is the recent finding that the thalamic relay can operate in two main modes: one transmits accurate information from a limited input in a form suitable for detailed analysis and the other passes a different pattern of stimuli to the cortex in a form that provides continuous, but not analytical, vigilance over a large part of the thalamic input, allowing the system to switch to detailed analysis when novel, interesting, or potentially dangerous stimuli are identified (see Guido et al. 1995).

At present, these two developments are independent of each other in terms of the evidence that supports either and also so far as their possible functional interactions may be concerned. However, we shall argue that if the model of geniculate function outlined in the second part of this review, which defines distinct modes of information transfer to cortex for the waking state, can be shown to have general applicability for all major thalamic nuclei, then we shall have a powerful clue to understanding how one cortical area may be able to influence the activity of another and how this influence may vary depending upon circumstances and in particular upon the novelty or importance of the output arising from the first cortical area.

Definitions

From a developmental and comparative point of view, the diencephalon can be divided into four distinct parts: the epithalamus, the dorsal thalamus, the ventral thalamus, and the hypothalamus (Jones 1985; Rose 1942). Here, we are concerned with only the dorsal and the ventral thalamus. The dorsal thalamus forms the main mass of the diencephalon in most mammals (Fig. 1), and this is the portion of the diencephalon from which the cerebral cortex receives most of its subcortical afferents (see Fig. 2). Generally, when people write about "the thalamus" they mean the dorsal thalamus, and we do this here. The ventral thalamus gives rise to the thalamic reticular nucleus (see Figs. 1 and 2) and to other structures that do not concern this review. The reticular nucleus lies on the pathways that link the thalamus and the cerebral cortex and receives its main afferents from

these pathways (Fig. 2). In turn, the reticular nucleus sends GABAergic, inhibitory axons back to the thalamus. In the cat and other carnivores, the reticular nucleus has at least two parts involved in visual relays. One is the visual sector of the reticular nucleus itself and the other is the perigeniculate nucleus (Mitrofanis 1994; Sanderson 1971a). Both share the same basic connections (Ahlsén et al. 1985; Friedlander et al. 1981; Jones 1985; Stanford et al. 1983; Uhlrich et al. 1991), and in the following, where we make no further identification, we shall include both when we speak of the reticular nucleus of the cat.

Figure 2 shows in a simplified schema that there are many distinct cell groups or nuclei in the thalamus. Each tends to receive afferents from one major functional source and to send efferents to one major cortical area, definable in terms of architecture and function as well as connections. Although modern methods have tended to reveal a multiplicity of afferent and efferent pathways for each thalamic nucleus, the one-to-one relationship illustrated in Fig. 2 still provides a good conceptual basis for understanding how each thalamic nucleus serves as a major relay from a particular afferent pathway to a corresponding cortical area. Figure 2 also shows that within the thalamic reticular nucleus it is possible to recognize separate sectors that have their major connections with one thalamocortical pathway, traversing one thalamic nucleus or group of nuclei. Finally, Fig. 2 shows there is a large component of axons that passes from the cerebral cortex back to the thalamus and reticular nucleus. The scheme shows these corticofugal axons going back to the parts of the diencephalon that correspond to the relevant afferent connections, but we shall see that this relationship only holds to a limited extent. There are some other corticofugal pathways, not shown in Fig. 2 but discussed in *Cortical afferents*, which pass back neither to the thalamic reticular nucleus nor to the thalamic nucleus innervating that cortical area. These provide opportunities for more complex and interesting interactions between cortical areas and thalamic nuclei.

MAJOR AFFERENTS TO GENICULATE RELAY CELLS

Understanding the functional relationships established by each of the afferent pathways in the thalamus is self-evidently a key to understanding the thalamus. The following overview of current knowledge of the afferent pathways cannot yet provide that key, but it should serve to focus on the many details that have yet to be defined before we really can expect to understand what happens in the thalamus.

For any one afferent system, one would like to know how its synaptic contacts relate to the thalamic relay neurons that pass information to the cortex, to the cells of the thalamic reticular nucleus, or to the interneurons concerned with intrathalamic circuitry. We need to know what parts of these neurons are contacted (cell bodies, proximal dendrites, distal dendrites, or spines), what transmitters are released, what receptors they activate, how they modify second messengers or currents in the postsynaptic cells, and how they influence voltage-sensitive conductances. We also would like to know what pattern of connections is made by single afferent axons and how this varies within an afferent population. That is, we need to know whether the relative distribution of terminal



FIG. 1. Photomicrograph of coronal section through thalamus of a cat. The section is stained with an antibody against parvalbumin, which is found in GABAergic cells of thalamic reticular nucleus and their terminals. The arrowheads indicate the midline, on the left are shown the dorsal thalamus (DT) and thalamic reticular nucleus (TRN).

branches to relay neurons, interneurons, or neurons of the thalamic reticular nucleus is relatively uniform for any one afferent population, or highly variable and how this distribution differs from one thalamic afferent system to another. However, not only are we ignorant about many of the details relating to any one afferent system, but we are not yet in a position to assert to what extent any of the relationships established for one thalamic nucleus must necessarily apply to all or most of the other nuclei. In the following, we will regard afferent axons that establish similar structural relationships in two nuclei as probably having similar functional roles, but we stress that speculations about function derived from this assumption are no stronger than the assumption itself.

In MAJOR AFFERENTS TO GENICULATE RELAY CELLS and OVERVIEW OF AFFERENTS TO OTHER THALAMIC NUCLEI, we start with a view of the lateral geniculate nucleus of the cat, and we especially focus on the two major laminae of this nucleus, the A laminae. We first identify each of the several distinct classes of afferent and then look at the morphological relationships of their terminals. The extent to which the features seen in this visual relay may be generalized for other thalamic nuclei is then examined briefly. In the subsequent sections (INTRINSIC CELL PROPERTIES, onward), we look at the functional properties, including synaptic mechanisms and intrinsic membrane properties, that determine the behavior of the neurons in the lateral geniculate nucleus, again considering the extent to which these may be generalizable to other thalamic nuclei.

Specific or primary ascending afferents

The first and most obviously important afferents to be considered in any discussion of the thalamus are those that are often thought of as the specific or primary afferent pathways. Historically, it was an analysis of these primary afferents that led to a first successful and functionally significant subdivision of the thalamocortical pathways (see Jones 1985; Le Gros Clark 1932; Rose and Mountcastle 1952;

Walker 1938). Although for any one nucleus these are not the only afferents, they can be regarded as the afferent pathways that give each nucleus its particular functional role, and we shall, in accordance with general usage, refer to them as primary afferents.

The primary afferents to the lateral geniculate nucleus come from the retina. We regard these as comparable with the auditory afferents that reach the medial geniculate nucleus from the inferior colliculus, or the somatosensory afferents going to the ventroposterolateral nucleus from the medial lemniscus and spinothalamic pathways (see Jones 1985). Afferents that go to the anterior thalamic nuclei from the mammillary bodies or to the ventrolateral and ventral anterior nuclei from the cerebellum and globus pallidus can reasonably be considered to be in the same category, although the functional properties of these systems relate to events in other parts of the nervous system, rather than events in the environment.

In the lateral geniculate nucleus, one can identify a number of particular features that characterize the primary afferents.

1) The retinal afferents are mapped topographically. That is, there is an accurate mapping of the retinal surface onto the lateral geniculate nucleus (Polyak 1957; Sanderson 1971a,b; Walls 1953). Where a group of afferents produces an orderly mapping of a sensory surface or of another part of the CNS, we shall refer to that afferent system as having "local sign", because activity in one part of the system necessarily will carry information about the locality of the origin of this activity.

2) Although we show in INPUTS FROM RETINAL AXONS that the temporal patterns of discharge in geniculate cells can differ markedly from those of the retinal afferents, the organization of receptive fields in terms of their spatial characteristics does not change significantly from the retinal afferents to the geniculate cells (Cleland et al. 1971; Hoffmann et al. 1972; Hubel and Wiesel 1961; Lennie 1980; Sherman 1985; So and Shapley 1979; Stone 1983; Troy 1983). In this, the geniculate synapse is probably characteristic for other thalamic relays, such as the somatosensory (Jones 1985;

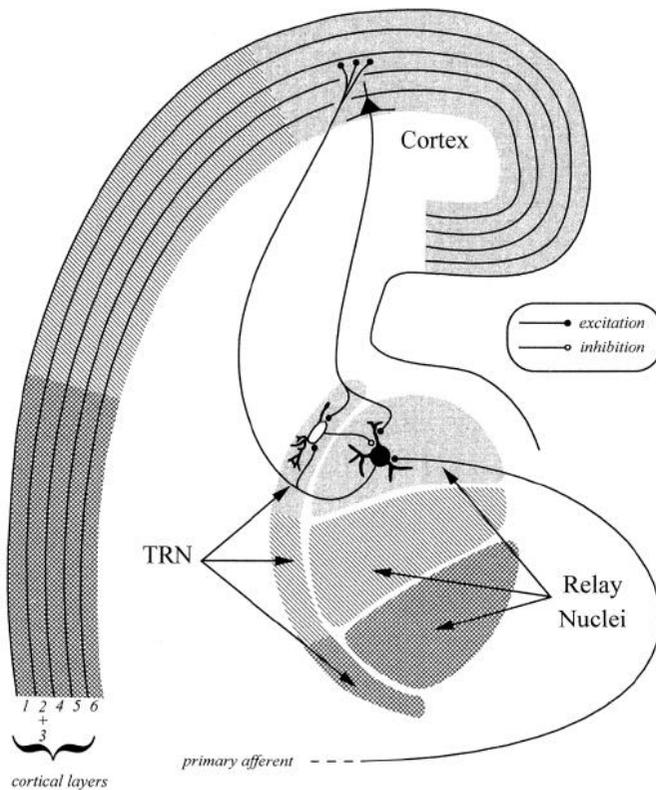


FIG. 2. Schematic view of major components involved in thalamocortical interactions. Three relay nuclei of DT (relay nuclei), three regions of the TRN, and three areas of cerebral cortex (cortex) are shown. Associated regions of DT, TRN, and cortex share the same shading pattern, and some of the interconnections are shown for the group with fine stippling. As shown, a primary afferent innervates relay cell on proximal dendrites, and relay the cell projects to layer 4 of cortex. As the axon of relay cell passes through TRN, it gives off a collateral that innervates reticular nucleus whose cells, in turn, project to relay cell. Axons from cortical cells in layer 6 innervate relay cells on their distal dendrites, and as these axons pass through TRN, they also provide collateral innervation of reticular cell. As indicated by key, all connections shown are excitatory except for the connection from the reticular cell to the relay cell, which is inhibitory.

Mountcastle 1980a; Poggio and Mountcastle 1963; Welker 1973) and auditory (Aitkin 1973; Aitkin and Webster 1972; Jones 1985; Mountcastle 1980b) relays. This is in contrast to the receptive field elaboration that is seen in retina, cortex, and other visual structures and on the basis of which the visual system eventually is able to reconstruct the visual scene. That is, there is an obvious function to these other visual structures. It is the failure of significant receptive field elaboration across the retinogeniculate synapse that suggests a unique function for geniculate circuitry.

3) Most but not all of the retinal afferents are composed of relatively thick axons. They have a characteristic branching pattern and relatively thick preterminal swellings (Bowling and Michael 1984; Mason and Robson 1979; Sur et al. 1987; Tamamaki et al. 1994). They all have a readily recognizable appearance in electron micrographs (Fig. 3) (see Famiglietti and Peters 1972; Guillery 1969a,b, 1971a; Guillery and Scott 1971; Hamos et al. 1987; Wilson et al. 1984; Wong-Riley 1972a,b)

4) The retinal afferents are glutamatergic, providing an excitatory input to the geniculate cells (Hartveit and Heggelund 1990; Heggelund and Hartveit 1990; Kwon et al. 1991;

Montero 1994; Moody and Sillito 1988; Scharfman et al. 1990; Sillito et al. 1990).

5) They are never postsynaptic to other neural processes, but where they make synaptic contacts with local interneurons, they may form triads (see above and Fig. 3C). They generally act upon parts of the dendrites that are close to the cell bodies of geniculate relay cells, either on the stem dendrites or on the grape-like appendages close to the primary dendritic branch points of these cells. They also act upon geniculate interneurons, which themselves are GABAergic, either simply on interneuronal stem dendrites (Hamos et al. 1985; Montero 1991) or, more commonly, in triadic arrangements where they contact dendritic output terminals of these interneurons, and both the retinal and interneuronal terminals contact the same relay cell dendrite (Fig. 3C) (Colonnier and Guillery 1964; Famiglietti and Peters 1972; Guillery 1969a; Hátori et al. 1974; Hamos et al. 1985, 1987; Montero 1986; Szentágothai et al. 1966; Wilson et al. 1984).

6) The triads commonly, but not invariably lie within "glomeruli", which are tightly packed groups of presynaptic and postsynaptic profiles partially or completely wrapped in thin sheets of astrocytic cytoplasm. Although the astrocytic wrapping has been stressed in most accounts as a possible diffusion barrier, there are some reasons for thinking that the extracellular spaces that lie adjacent to the astrocytic lamellae are likely to allow relatively free diffusion (Kuffler et al. 1984; Nicholson and Rice 1991). It seems plausible that the close packing of the synaptic profiles, and the complete absence of astrocytic processes from the interior of a glomerulus, may be of greater functional significance than the wrapping. The glomerular structure is such that astrocytic involvement in synaptic activity, which in other parts of the brain is known to include transmitter uptake and the clearance of extracellular potassium ions (Kuffler et al. 1984; Nicholls and Attwell 1990) is essentially excluded from the regions of the triads in the glomeruli, a point that may prove critical in understanding how the geniculate synapses can vary in their functional properties.

7) Several functionally distinct retinofugal axons reach the lateral geniculate nucleus. These are the W, X, and Y ganglion cell classes in the cat retina, which typically innervate different geniculate cells, so that the W/X/Y distinction remains among geniculate relay cells (Cleland et al. 1971; Friedlander et al. 1981; Hoffmann et al. 1972; Lennie 1980; Sherman 1985; So and Shapley 1979; Stone 1983; Troy 1983). Retinogeniculate X axons commonly relate to triads in glomeruli, whereas Y and W axons generally terminate outside glomeruli in simple arrangements not involving triads (Hamos et al. 1987; Raczkowski et al. 1987; Wilson et al. 1984).

8) There are other afferents, that can also be classified as visual afferents, coming from other cell groups (see Fig. 4 for those innervating the A laminae). For instance, those coming from the superior colliculus go to the C laminae and the pulvinar in the cat (Altman and Carpenter 1961; Graham 1977; Graybiel 1972; Harting et al. 1991a; Niimi et al. 1970), and axons from the pretectum innervate the A laminae (Cucchiari et al. 1991a; Graybiel and Berson 1980; Hughes and Mullikin 1984; Kubota et al. 1988; Wahle et al. 1994). The difficulty of providing a rigorous definition

of a primary afferent is illustrated by these axons. It can be argued that for afferents coming from the sensory periphery, like the retinal input to the geniculate relay, it is intuitively appealing to treat the input that reaches the thalamus after the fewest number of synapses as the primary afferent. However, collicular afferents to the C laminae share some of the features of retinal afferents enumerated above (Torrealba et al. 1981), and because it is possible to regard the tectothalamic afferents as a phylogenetically older visual afferent to the thalamus than the retinal input to the lateral geniculate nucleus, there is an alternative, equally appealing logic in treating these collicular afferents as primary afferents. In contrast, pretectal afferents to the lateral geniculate nucleus (see above) are probably best treated as a separate category, primarily because they are mostly GABAergic rather than glutamatergic (Cucchiario et al. 1991a; Wahle et al. 1994).

In summary, there are a number of characteristics that help to define the primary afferent axons. One that may prove critical for a definition has not yet been mentioned. This is the absence of any branches going to the thalamic reticular nucleus (see Figs. 4 and 6), a branch that is characteristic of most or all other geniculate afferents and is discussed in more detail below (*Reticular afferents*). The major defining features of primary afferents we have described are the size and the fine structural characteristics of the terminals, the nature of synaptic contacts established, and the formation of the contacts upon proximal dendrites. The transmitter (glutamate) and the postsynaptic receptors and currents also may prove critical in defining primary afferents in all parts of the thalamus.

Cortical afferents

Although the existence of corticothalamic axons was recognized early (Cajal 1911; von Flechsig 1896; Polyak 1957), clear experimental evidence about these axons could not be provided until first the axonal degeneration methods and later the autoradiographic tracing methods became available. For the visual pathways, corticogeniculate axons were described in the 1960s by axon degeneration methods and later by autoradiographic axon tracing (Beresford 1962; Guillery 1971b; Holländer 1974; Jones and Powell 1969b; Lin and Kaas 1977; Lund et al. 1975; Robson 1983; Szentágothai 1963). More recent studies in which a few individual axons are filled with biocytin (e.g., Bourassa and Deschênes 1995) have provided particularly striking images of these axons.

The following points have been established about the corticogeniculate axons.

1) They are organized topographically. That is, this projection shows local sign, and retinotopically the projection from the cortex corresponds to that from the retina. So far as is known, this is true for all of the cortical areas that send axons to the lateral geniculate nucleus (Updyke 1975), although it is likely that as retinotopy becomes lost in the far reaches of the multiplicity of visual cortical areas, so the local sign of the corticogeniculate pathway from certain extrastriate visual areas also might be lost.

2) The corticogeniculate axons are relatively fine axons that tend to run along the "lines of projection". These are lines that represent single points in the visual field, passing,

in the words of Walls (1953), through the geniculate layers like a toothpick through a club sandwich (see also Bishop et al. 1962). These axons give off small "drumstick-like" side branches along their intrageniculate course and often pass through more than one lamina. That is, as would be expected from point 1) above and the details given earlier about the arrangement of the retinal afferents, the individual axons relate to geniculate cells that receive from a single small area of the visual field.

3) In electron micrographs, these axons are seen to have small terminals (Fig. 3A) that tend to contact small profiles located peripherally on the dendritic arbors of relay cells or on slender, stem dendrites of interneurons. They rarely make synaptic contacts onto proximal dendrites of relay cells, nor do they commonly contribute to the triads or to the geniculate glomeruli (Cucchiario et al. 1991b; Guillery 1969a,b, 1971a; Montero 1991; Robson 1983; Vidnyánszky and Há-mori 1994; Weber and Kalil 1987; Wilson et al. 1984), and when they do, they relate to the peripheral rather than the central parts of the glomeruli (Vidnyánszky and Há-mori 1994). Weber et al. (1993) have suggested that the majority of their contacts are onto the dendritic shafts of interneurons, although Montero (1991) reports that relay cells receive more of these terminals than do interneurons.

4) The corticogeniculate axons, like the retinogeniculate axons, appear to be glutamatergic. Further details are given in INPUTS FROM CORTICAL AXONS.

5) In the lateral geniculate nucleus of the cat, the corticogeniculate axons form the plurality of synaptic contacts, probably 40–50% (Guillery 1969b; Wilson et al. 1984).

6) The corticogeniculate axons in the cat arise in several of the visual cortical areas, including areas 17, 18, and 19 (Updyke 1975, 1977). The connections from areas 17 and 18 go to all of the geniculate laminae, whereas those from area 19 go only to the small-celled C layers (which project to 19 but not 17 and 18). In the monkey, it is clear that striate as well as extrastriate cortical regions innervate the lateral geniculate nucleus, but the details of the extent and pattern of extrastriate input have yet to be elucidated (Lin and Kaas 1977; Maioli et al. 1984; Squatrito et al. 1988).

7) Some, and possibly all, corticogeniculate axons send collateral branches that innervate the cells of the thalamic reticular nucleus, and this projection, too, can have local sign, which for corticoreticular axons from area 17 of the rabbit can be as precise as the local sign in the corticogeniculate pathway (Crabtree and Killackey 1989; Montero et al. 1977) and in the cat shows good local sign in terms of receptive field localization (Sanderson 1971a,b; Uhlich et al. 1991).

8) All of the corticogeniculate axons that go to the lateral geniculate nucleus arise from pyramidal cells in layer 6 of the relevant cortical areas (Gilbert and Kelly 1975; Katz 1987). The contribution going to different geniculate layers appears to arise in different tiers of cortical layer 6 in the striate cortex of the monkey (Conley and Raczkowski 1990; Fitzpatrick et al. 1994; Lund et al. 1975).

Although it is known that there are layer 5 pyramids that also send axons to the thalamus (Bourassa et al. 1995; Deschênes et al. 1994; Rockland 1994), there is currently

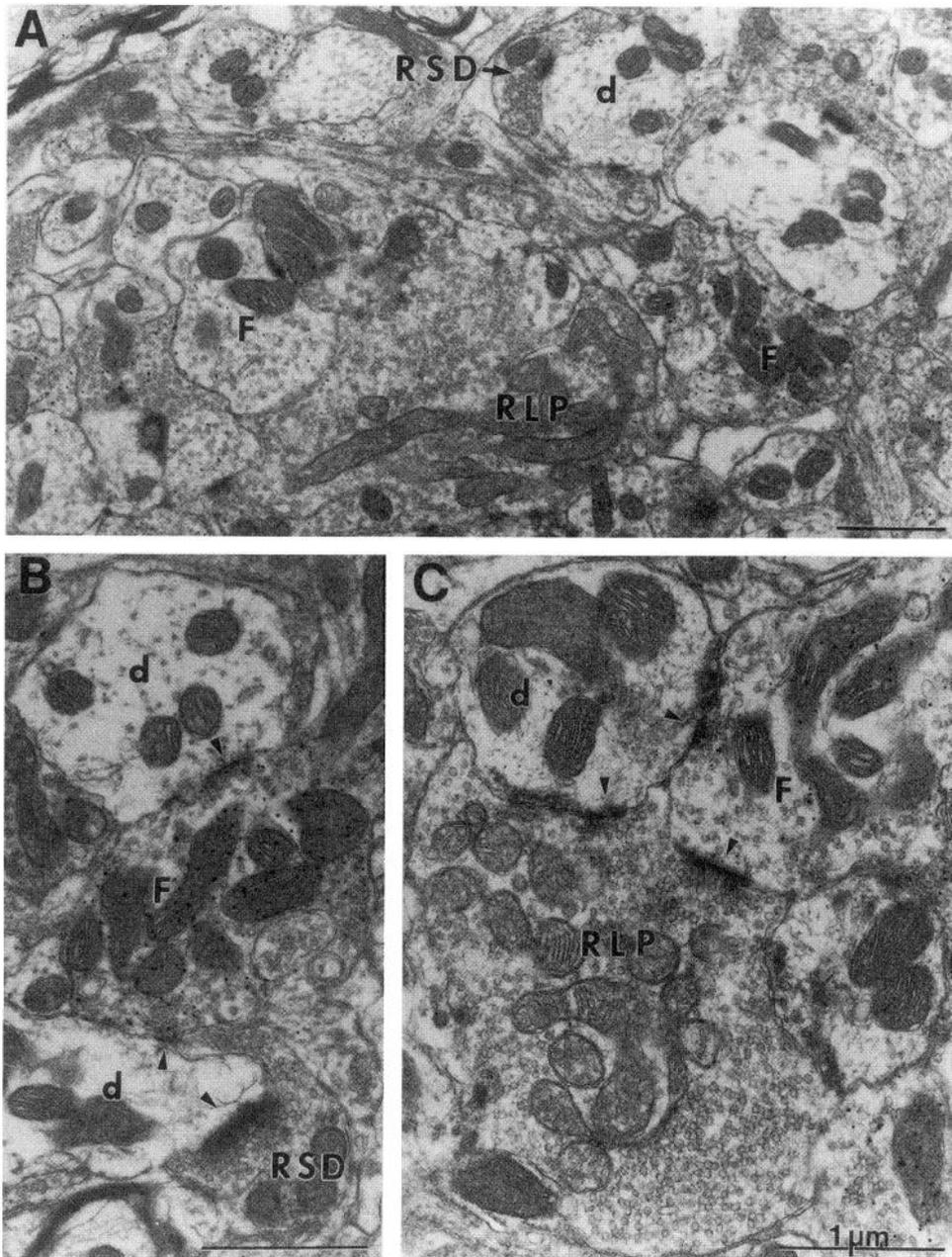


FIG. 3. Series of electron micrographs illustrating representative features of terminals in lateral geniculate nucleus of the cat. *A*: typical glomerulus with many interrelating terminals of different types, including F terminals (F), a RSD terminal (RSD), and a RLP (retinal) terminal (RLP). A dendritic profile (d) also is present in glomerulus. *B*: postembedding γ -aminobutyric acid (GABA) labeling of F terminal (F). Immunogold, seen as small black spots, was used to identify this profile as GABAergic. Note lack of GABA labeling in RSD and RLP terminals and in dendritic profile (d). The arrowheads point to synaptic contacts from postsynaptic side. *C*: triadic synaptic circuit. An F terminal (F) makes a contact onto a dendrite (d), and a RLP (retinal) terminal (RLP) contacts same dendrite and F terminal. Arrowheads point to these contacts. Scale bar in each panel is $1 \mu\text{m}$.

no evidence that any reach the lateral geniculate nucleus and the corticothalamic axons that arise in layer 5 are considered further below (*Cortical afferents*).

9) Gilbert (1977) has described the receptive fields of layer 6 cells as relatively large and as a mixture of ocular dominance categories. However, layer 6 gives rise to a claustral as well as a geniculate input (Katz 1987; LeVay and Sherk 1981). Recent evidence indicates that the cells projecting to claustrum have larger receptive fields than do those projecting to the lateral geniculate nucleus (Grieve and Sillito 1995), but exactly what sort of messages the lateral geniculate nucleus receives from layer 6 remains somewhat uncertain, and it is entirely possible that receptive field properties themselves are not the feature that is most relevant to the action of these axons; this

is considered in INPUTS FROM CORTICAL AXONS. An older report by Tsumoto and Suda (1980) makes two important points about the cortical axons innervating the lateral geniculate nucleus from area 17. First, they represent a heterogeneous population that seems likely to have multiple functions. When extrastriate inputs are included, the heterogeneity of inputs is likely to be greatly enlarged. Second, many of the cells they identified as corticogeniculate by antidromic activation from the lateral geniculate nucleus had no detectable responses to visual stimuli under the conditions of their preparation (i.e., anesthetized and paralyzed), suggesting that published receptive field studies of corticogeniculate cells may undersample significantly the sorts of receptive field properties represented in this pathway in awake, behaving animals.

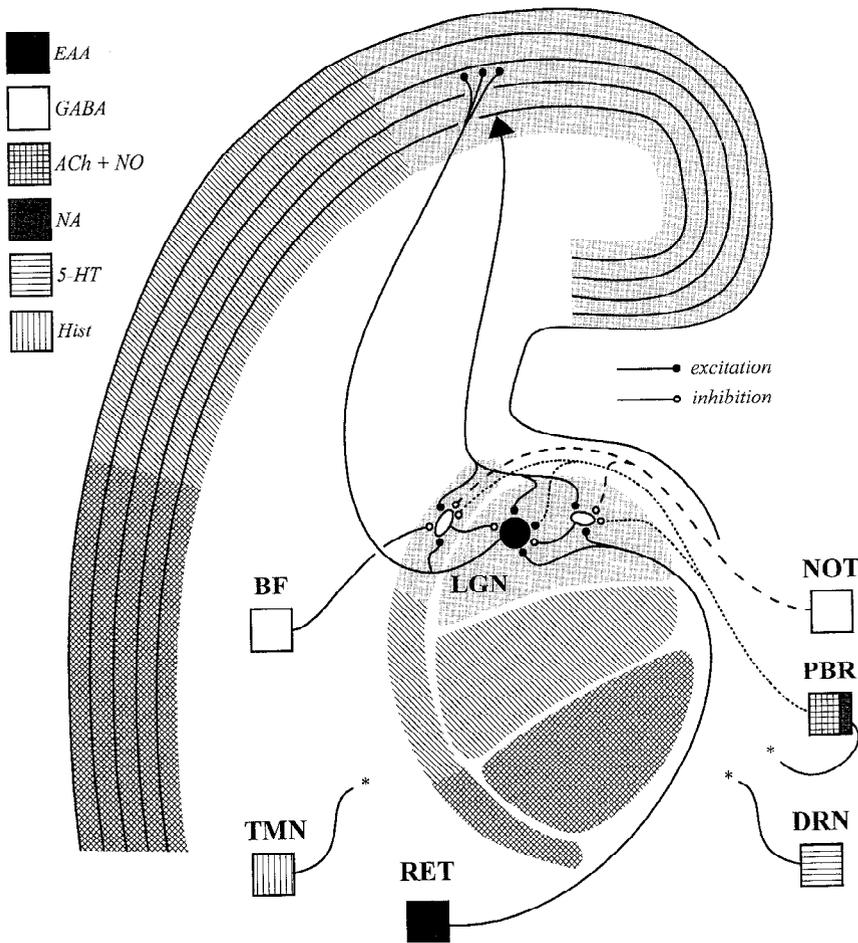


FIG. 4. Schematic view of major afferents to lateral geniculate nucleus of cat, following conventions of Fig. 2. Lateral geniculate nucleus contains both relay cells (filled circle) and interneurons (open oval). For simplicity, only the major and best studied inputs have been followed into the thalamus. Smaller and less well-studied inputs end in asterisks (*), and details of their connections within thalamus can be found in text. Neurotransmitters and inhibitory or excitatory effects of various inputs are indicated. Note that cholinergic axons from parabrachial region (axons that also colocalize nitric oxide) excite relay cells but tend to inhibit both GABAergic cell populations (i.e., reticular cells and interneurons). 5-HT, serotonin; ACh, acetylcholine; BF, basal forebrain; DRN, dorsal raphe nucleus (brain stem); EAA, excitatory amino acid (e.g., glutamate); Hist, histamine; LGN, lateral geniculate nucleus; NO, nitric oxide; NOT, nucleus of optic tract (pretectum); PBR, parabrachial region (brain stem); TMN, tuberomammillary nucleus (hypothalamus).

DIFFICULTIES IN STUDYING THE CORTICOGENICULATE PATHWAY. Despite the fact that corticofugal axons represent the largest single input to the thalamus (see *Cortical afferents*) and have been well documented for almost three decades, we know surprisingly little about their function. Considerable attention continues to be directed at this pathway (Koch 1987; Sherman 1993; Sherman and Koch 1986, 1990). Past studies have been somewhat confusing, some suggesting that the pathway facilitates relay cell firing, whereas others suggest the opposite (Baker and Malpeli 1977; Geisert et al. 1981; Kalil and Chase 1970; McClurkin and Marrocco 1984; McClurkin et al. 1994; Richard et al. 1975; Schmielau and Singer 1977). Schmielau and Singer (1977) have proposed that corticogeniculate input is important to binocular functions, such as stereopsis. More recent studies have suggested that the pathway affects temporal properties of relay cell discharges (Godwin et al. 1996; McClurkin et al. 1994) or establishes correlated firing among nearby relay cells with similar receptive field properties (Sillito et al. 1994). Despite these several hypotheses, we cannot yet assign any functions that would require the great size of the pathway, and the function of the corticothalamic axons remains one of the most important enigmas of thalamocortical relationships.

There are several interrelated problems that contribute to difficulties faced by studies of this pathway.

1) With few exceptions (e.g., Sillito et al. 1994; Tsumoto et al. 1978), virtually all studies of this pathway have involved

total inactivation of the entire area of relevant visual cortex by cooling or ablation, and the studies were performed in anesthetized cats. In such anesthetized cats, the pathway already may be subdued or inactive, so cortical inactivation might have little further effect. It thus might prove important to activate (as well as inactivate) the pathway. However, activation is technically difficult with the traditional means of electrical stimulation, because this also antidromically discharges geniculate relay cells, interfering with any effects sought.

2) The common approach of inactivation of all relevant cortex may be too crude. Because corticogeniculate axons, as a group, appear to excite relay cells directly and inhibit them indirectly (see Figs. 2 and 4), any global inactivation may simply sum these effects to near 0, leaving a weak, variable residue.

3) Related to the above, it is not clear that all corticogeniculate axons innervate their targets in the same pattern. In fact, as is indicated by Fig. 5, A and B, it is not even clear what the precise distribution of inputs to relay cells, reticular cells, and interneurons is, and this distribution is important to the eventual effects on relay cells. Each pattern illustrated in Fig. 5, A and B, may exist but for different populations of corticogeniculate axon. Some axons may innervate only relay cells and others only reticular cells and/or interneurons. As a result of these possible variations in connections, perhaps the final action upon the relay cells of some corticogeniculate axons mostly is to excite (or depolarize) these cells and of others mostly to inhibit (or hyperpolarize) them,

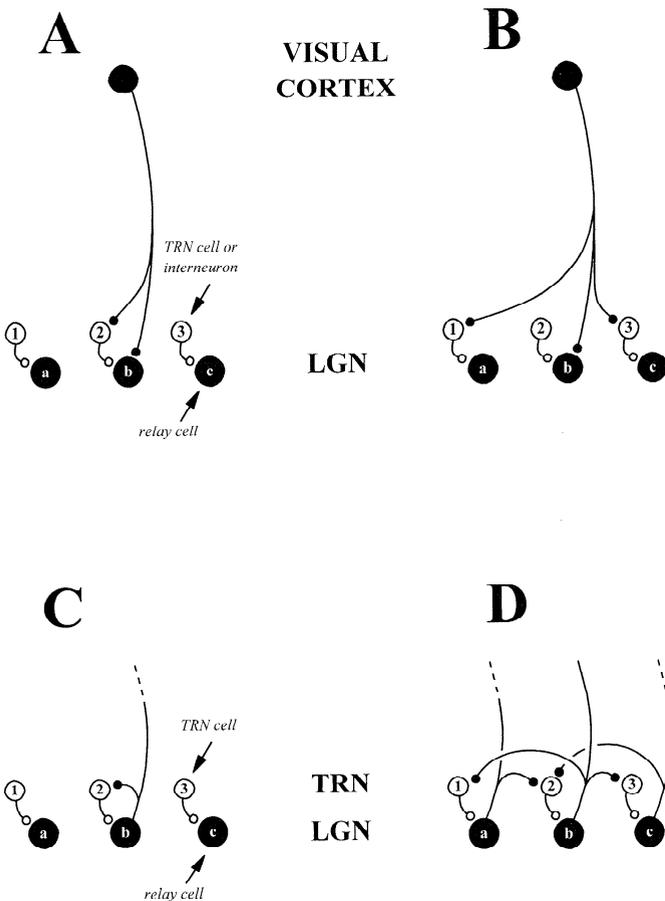


FIG. 5. Schema showing examples of different types of inhibitory circuits involving geniculate relay cells. See Fig. 4 legend for abbreviations. Excitatory cells and their synaptic outputs are shown as solid circles and inhibitory (GABAergic) cells and their outputs are shown as open circles. *A*: circuit beginning with cortical axon that represents feedforward inhibition. A cortical axon innervates relay cell *b* and directly excites it, but a collateral of this same axon excites reticular cell or interneuron 2 that then inhibits relay cell *b*. *B*: circuit beginning with cortical axon that does not represent feedforward inhibition. The main difference with *A* is that, although cortical axon still directly innervates and excites relay cell *b*, its collaterals excite reticular cells or interneurons 1 and 3, which then inhibit relay cells *a* and *c*. There would be no inhibitory effect on relay cell *b*. *C*: circuit beginning with relay cell axon that represents feedback inhibition. A collateral of axon from relay cell *b* excites reticular cell 2, which then inhibits cell *b*. *D*: circuit beginning with relay cell axon that does not represent feedback inhibition. Here, axon collaterals from relay cell *b* excite reticular cells 1 and 3, which then inhibit relay cells *a* and *c*, but do not directly influence relay cell *b*. There is thus no feedback inhibition. However, to follow the circuit further, the inhibition of relay cells *a* and *c* reduce their excitatory effect on reticular cell 2, resulting in less inhibition from this reticular cell onto relay cell *b*. Thus instead of feedback inhibition seen in *C*, this circuit represents opposite: feedback disinhibition.

so that specific patterns of activity are critical but are obscured with global activation or inactivation of cortex.

4) Most attempts to study the corticogeniculate pathway have focused on a single presumed function. It is more likely that there are multiple duties carried out in parallel by different cell types, analogous to the parallel W, X, and Y pathways emanating from the retina, and this would be consistent with the previous point. Despite of evidence for heterogeneity of corticifugal axons (see *Cortical afferents*), the possibility of more than one type of corticogeniculate axon since then largely has been ignored. There may well be several

different roles for this pathway, such as controlling binocular disparities for stereopsis (Schmielau and Singer 1977), enhancing correlated firing among related geniculate cells (Sillito et al. 1994), and switching geniculate cells between the qualitatively different response modes (discussed in *INTRINSIC CELL PROPERTIES* below) (see Godwin et al. 1996). We need a fuller understanding of how corticothalamic axons act upon geniculate and reticular cells and of the extent to which this action may be nonuniform for all of the corticogeniculate axons.

Afferents from diencephalic inhibitory neurons

RETICULAR AFFERENTS. Strictly speaking, the reticular nucleus is a part of the ventral thalamus, which receives afferents from the dorsal thalamus and cerebral cortex and sends axons back to the dorsal thalamus (Jones 1975, 1985). In addition, like the dorsal thalamus, it also receives afferents from the brain stem (Asanuma 1993; Berman 1977; Bickford et al. 1993; Cucchiario et al. 1991a, 1993; Edwards and de Olmos 1976; Hu et al. 1989a; Swanson and Hartman 1975; Uhrich et al. 1988) and from superior colliculus (Harting et al. 1980), but, unlike the dorsal thalamus, it receives innervation from basal forebrain (Bickford et al. 1994a; Chen and Bentivoglio 1993). The reticular nucleus sends no axons to the cortex and in this it is distinct from the dorsal thalamus (Jones 1985).

For many years, a detailed study of the axons that pass from the reticular nucleus to the thalamus proved difficult because the reticular cells lie among thalamocortical and corticothalamic axons. However, the axons now have been demonstrated clearly by anterograde and retrograde tracing methods with both light and electron microscopy (Crabtree and Killackey 1989; Cucchiario et al. 1990, 1991b; Harting et al. 1991a; Jones 1975; Liu et al. 1995b; Pinault et al. 1995; Uhrich et al. 1991). They pass in an ordered array from the thalamic reticular nucleus to each of the major thalamic nuclei, and they are thought to be crucial to the relationships established between cortical and thalamic activity for a number of reasons.

1) The reticular cells themselves receive afferents from collateral branches of thalamocortical and corticothalamic axons as these pass through the reticular nucleus (see Fig. 2 and 4) (see also Bourassa and Deschênes 1995; Conley and Diamond 1990; Conley et al. 1991; Crabtree 1992a,b; Crabtree and Killackey 1989; Friedlander et al. 1981; Harting et al. 1991a; Jones 1975, 1985; Stanford et al. 1983). It is not clear if only particular subpopulations of these axons send collaterals to the reticular nucleus or if all of them do. The issue merits study because cortical and thalamic influences on reticular activity will depend crucially on the particular population of cortical and thalamic cells that innervate reticular cells. Because there are relatively few reticular cells compared with the numbers of cortical and thalamic cells, it is possible that not all of the axons connecting thalamus and cortex give off branches to the reticular cells. There as yet have been no studies directed at the question of how many corticothalamic axons branch to innervate reticular cells, but this issue has been studied for geniculocortical axons. Most cells belonging to each of the major geniculate W, X, and Y cell classes innervate the thalamic reticular

nucleus (Friedlander et al. 1981; Stanford et al. 1981, 1983). The few that fail to show any branches among the reticular cells may be false negatives due to the difficulty of getting the intracellular label, horseradish peroxidase, into these fine collaterals.

2) Within the reticular nucleus there are separate sectors, each sector related primarily to one modality or to one group of thalamic nuclei and their cortical connections. That is, the cells within each reticular sector receive afferents from a specific thalamic cell group and from related cortical areas and in turn send their axons to cells in the same thalamic cell groups (Jones 1975, 1985).

3) In *Local interneuronal and reticular connections*, we show that each sector of the reticular nucleus (related to visual, auditory, somatosensory, etc., relays) can show a complex organization with different subregions having distinct connections. This is strikingly evident in the cat's visual relay, where the perigeniculate nucleus is linked primarily to the geniculate A laminae (Uhlrich et al. 1991), whereas the visual sector of the main body of the reticular nucleus connects to other parts of the lateral geniculate nucleus (Bickford et al. 1994b; Cucchiario et al. 1990). This draws attention to the fact, discussed further in *local interneuronal and reticular connections*, that each sector of the thalamic reticular nucleus (i.e., related to the visual, somatosensory, auditory, etc., relays) has a complex organization, with different subregions organized differently and relating to different portions of the thalamocortical pathways.

4) The interconnections among thalamus, reticular nucleus, and cortex show clear evidence for local sign. For the visual pathways, this means that a single point in the retina (or visual field) can be mapped onto a small part of the lateral geniculate nucleus, visual cortex (area 17), or the reticular nucleus through each of the systems of interconnecting pathways (Bourassa and Deschênes 1995; Conley and Diamond 1990; Crabtree and Killackey 1989; Liu et al. 1995b; Montero and Scott 1981; Montero et al. 1977; Shosaku et al. 1984; Uhlrich et al. 1991).

5) The reticular cells, like the thalamic interneurons, are GABAergic, and their geniculate terminals are not easy to distinguish from those of geniculate interneurons. Both form F terminals (see Fig. 3). Several recent studies (Cucchiario et al. 1991b; Harting et al. 1991a; Liu et al. 1995b; Uhlrich et al. 1991; see also Montero and Scott 1981) have successfully labeled axon terminals of reticular cells and have shown that the vast majority of them contact relay cells, both on their somata and their dendrites, and lie outside the glomeruli. Only a few of these reticular terminals (5–10%) contact interneurons or terminate in glomeruli.

6) With two known exceptions, all inputs to the lateral geniculate nucleus and the reticular nucleus send a branch to each of these two targets. One exception is the retinal input, which innervates the lateral geniculate nucleus only, and the other is the GABAergic projection from the basal forebrain, which targets the thalamic reticular nucleus but not the lateral geniculate nucleus. Inputs targeting both structures include that from cortex, brain stem (i.e., cholinergic, noradrenergic, and serotonergic axons from midbrain and pons), tectum (see above), pretectum, hypothalamus, and intrinsic axons from the reticular nucleus itself (Airaksinen and Panula 1988; Conley and Diamond 1990; Conley et

al. 1991; Crabtree 1992a,b; Crabtree and Killackey 1989; Cucchiario et al. 1991a; de Lima and Singer 1987a,b; de Lima et al. 1985; Liu et al. 1995b; Uhlrich et al. 1988, 1993). The C laminae of the lateral geniculate nucleus also receive afferents from the parabigeminal nucleus and the superior colliculus (Graham 1977; Graybiel 1972; Harting et al. 1991a,c; Niimi et al. 1970). A contribution to the reticular nucleus from these structures has not yet been documented.

Although the reticular neurons are sometimes treated as displaced interneurons, this is not acceptable as a developmental interpretation, because the reticular nucleus develops from the ventral thalamus, which is quite distinct from the dorsal thalamic origin of the main thalamic nuclei and their interneurons. The suggestion (Montero 1989) that the largest interneurons, the ones that lie between the main geniculate laminae, resemble the perigeniculate cells in terms of their synaptic inputs may point to functional similarities, but present evidence says nothing about developmental origins.

AFFERENTS FROM LOCAL GENICULATE INTERNEURONS. The local interneurons have many vesicle containing dendritic processes that are presynaptic to other geniculate dendrites and that are postsynaptic to other vesicle containing profiles, generally the retinal terminals that form one component of a triad (see Fig. 3C). The triads are a characteristic thalamic feature and presumably allow for a limited part of an interneuron to act on transmission along the retinogeniculocortical pathway. The suggestion that the triads, which involve the dendritic output terminals of interneurons, may operate using only a localized portion of the interneurons and not involve any axonal action potentials is considered more fully below in the discussion of cable properties of these cells (*Cable properties*).

The dendritic GABAergic terminals of the interneurons are commonly, but not invariably, seen as swellings at the end of thin stalks. Occasionally one can see that a stem dendrite of an interneuron contains a collection of synaptic vesicles and also makes a synaptic contact with another dendrite, generally of a relay cell. In addition, at least some interneurons have axons, which can be distinguished from the dendrites light microscopically (Guillery 1966; Tömböl 1969) and on fine structural grounds (Hamos et al. 1985; Montero 1987). These axons are presumably responsible for the action potentials that occasionally can be recorded from geniculate interneurons (Friedlander et al. 1981; McCormick and Pape 1988; Sherman and Friedlander 1988). However, it is difficult to determine whether all interneurons can generate action potentials or only some; those that have axons are most likely to have action potentials. Every interneuron from which recordings have been obtained by conventional techniques has had action potentials, and all geniculate interneurons that have been labeled for morphological analysis were first experimentally identified by physiological criteria. Because physiological identification of an interneuron requires that they exhibit action potentials, a population of axonless interneurons that have no action potentials may exist but would not be readily identified with conventional techniques. Action potentials may be required only for axonal outputs, but would not be necessary for dendritic outputs (see *Cable properties*). Montero (1987) has presented evidence that the

dendritic terminals end chiefly in glomeruli and are triadic, whereas the axonal terminals are extraglomerular and nontriadic. If it should prove that one is discharged with the action potential whereas the other is not, then the distinction becomes more important.

ROLE OF LOCAL AND RETICULAR INHIBITORY CIRCUITS IN THALAMIC FUNCTION. The action of any set of afferents on the geniculate relay cells and through them on the cortex will depend on several factors. Not only is the balance of the direct afferent action upon relay cells relative to interneurons important, but also the extent to which the further, indirect pathways through relay, reticular, and local inhibitory neurons in turn affect the membrane properties of the relay cells themselves will matter. The real difficulty is that we have no knowledge of how these local circuits operate during any particular visual episode, and all that we can do at present is to study the membrane changes of the geniculate cells and then use our knowledge of the local circuits, of the relevant transmitters, and of the receptors likely to be involved to devise pharmacological attacks that may reveal the workings of the circuits.

Furthermore, the detailed connectivity pattern of individual axons matters greatly (see Fig. 5). We already have explained above (*Cortical afferents*) why this is important for cortical afferents (Fig. 5, A and B). Figure 5, C and D, makes an analogous point for the feedback pathway between the lateral geniculate and thalamic reticular cells or interneurons. This is often thought of as "feedback inhibition" (Ahlsén et al. 1985; Lindström 1982). The circuit shown by Fig. 5C would result in feedback inhibition, because firing of a relay cell (*cell a*) would activate a local inhibitory cell that, by virtue of the circuit as drawn, inhibits *cell a*. However, the circuit of Fig. 5D is subtly different. Here, firing of a relay cell (*cell b*) leads to activation of local cells that inhibit not *cell b* but rather its neighbors. Furthermore, inhibition of these neighbors would reduce their excitation of the reticular cell that inhibits *cell b*, thereby implying a circuit for feedback disinhibition in Fig. 5D in contrast to the feedback inhibition shown on the left. Of course, the actual circuit may represent a combination of both connectivity patterns. Although there is some preliminary evidence that at least part of the circuit linking the reticular nucleus and the lateral geniculate nucleus involves feedback inhibition as shown by Fig. 5D (Lo and Sherman 1994), in general we have insufficient evidence to understand how these circuits work. This is true of most circuits involving relay cells. Because most afferent pathways, typically even their individual component axons, innervate both relay cells and local inhibitory cells (reticular cells or interneurons) and we do not know the details of the complete circuits, we generally cannot predict how these circuits will function under physiological conditions when specific subsets of afferents become active.

Brain stem afferents

Figure 4 summarizes what we know of the other afferent pathways to the geniculate A laminae and thalamic reticular nucleus from the pretectum, the parabrachial region, the basal forebrain, and the hypothalamus. The main subcortical, nonretinal input consists of cholinergic axons emanating from the parabrachial region (de Lima and Singer 1987b;

de Lima et al. 1985; Fitzpatrick et al. 1989; Raczkowski and Fitzpatrick 1989; Paré et al. 1988; Smith et al. 1988; Uhlrich et al. 1988); these axons also seem to colocalize nitric oxide (Bickford et al. 1993). Noradrenergic afferents exist that also emanate from the parabrachial region, lying amid the cholinergic cells, but this is a relatively small projection (de Lima and Singer 1987b; Fitzpatrick et al. 1989; Paré et al. 1988; Smith et al. 1988); these cells do not colocalize nitric oxide (Bickford et al. 1993). Also providing input are serotonergic cells in the dorsal raphe nucleus (de Lima and Singer 1978a), GABAergic cells in the pretectum (Cucchiaro et al. 1991a, 1993; Wahle et al. 1994), and histaminergic cells from the tuberomammillary nucleus of the hypothalamus (Airaksinen and Panula 1988; Uhlrich et al. 1992).

Although the afferents from the pretectal nuclei show a differential distribution to the X and Y pathways in the cat and to different geniculate laminae in Galago, (Cucchiaro et al. 1993; Funke and Eysel 1995; Harting et al. 1986), the major brain stem afferents are generally treated as though they have no evidence of local sign or functional localization and are often regarded as "diffuse" projections. When one considers the possible functions of any one of these afferent pathways in an awake behaving animal, the degree to which that pathway has local sign or lacks it will affect significantly the possible functional roles that can be assigned to that pathway, and for this reason, the precise functional meaning one can assign to a "diffuse brain stem projection" bears brief discussion.

Strictly speaking the term implies a lack of specificity of connections that is hard to prove. A truly diffuse projection would be one in which no component of the total projection shows any preference within the total terminal field of the projection for any particular cell group or part of a cell group. A diffuse projection is by its very nature one that must have generalized, nonlocalized actions on the highly localized thalamocortical pathways. However, evidence for "diffuse" connections is commonly based on relatively large lesions or tracer injections or on lesions or tracer injections that are not specific in terms of any localization of function known for the lesioned or labeled region. Where experiments involve just a few individual axons, it may be possible to define a degree of localization or a wide spread of terminal ramifications that cannot be shown by cruder methods involving larger axon populations. As such experiments involving rather few, well-localized axons become available, it may be possible to define some truly diffuse brain stem pathways, but at present, in the absence of clear evidence, it may be better to speak of these brain stem pathways as generalized, widespread, or poorly localized, leaving the precise patterning undefined.

OVERVIEW OF AFFERENTS TO OTHER THALAMIC NUCLEI

Primary afferents

In this section, we do not provide an analysis of each the afferent systems in the detail that we have given for the lateral geniculate nucleus. Many points still remain to be defined and may only become of interest as the functional capacities of each group of afferent pathways are understood.

Each of the major thalamic nuclei can be thought of as having its own primary afferents, and for the medial geniculate nucleus (Jones and Rockel 1971; Majorossy and Kiss 1976), the ventrobasal complex (Ralston 1969; Jones and Powell 1969a,b; Liu et al. 1995a), the ventrolateral and ventral anterior nuclei (Aumann et al. 1994; Grofová and Rinvik 1974; Harding 1973; Kultas-Ilinsky et al. 1980, 1991) and the anterior nuclei (Somogyi et al. 1978) the primary afferents can be readily defined and are seen to share many of the structural features of retinogeniculate afferents described above and illustrated in Fig. 3. That is, these afferent axons have much the same light and electron microscopical appearance as the retinal afferents, tend to terminate on large dendrites near cell bodies, commonly relate to glomerular structures, form triads, and, where the transmitter has been defined, are glutamatergic (Liu et al. 1995a; Ralston 1991; Salt 1987; Salt and Eaton 1989).

As a first approximation, one can anticipate that where receptive fields can be defined, there is not much change in receptive field properties when primary afferent axons are compared with the thalamic relay cells. This has held for those examples where receptive field properties have been defined, as in the ventrobasal complex (Iwamura and Inubushi 1974; Jones 1985; Mountcastle 1980a; Mountcastle et al. 1963; Poggio and Mountcastle 1963; Welker 1973) or medial geniculate nucleus (Aitkin 1973; Aitkin and Webster 1972; Calford and Webster 1981; Galambos 1952; Jones 1985; Mountcastle 1980b; Starr and Don 1972). Where a nucleus receives more than one functional type of afferent, details may differ as they do for X and Y cells in the lateral geniculate nucleus. For example, in the ventrobasal complex in primates, the synaptic relationships of spinothalamic axons tend to resemble those of the Y cell terminations, forming predominantly simple axodendritic extra-glomerular synapses, whereas the lemniscal axons are more like the X cell terminations, tending to synapse in glomeruli and commonly forming triadic junctions (Ma et al. 1987; Ralston and Ralston 1993). It appears that in the rat ventrobasal nucleus, where there are no interneurons and thus essentially no triads, any one dendritic segment can receive afferents from both ascending pathways, but in the monkey, there is, as yet, no good evidence that the two systems converge onto single neurons or single dendrites. This may prove to be an important problem for comparisons between the somatosensory and visual pathways. In the lateral geniculate nucleus of the cat, a single relay cell typically receives from either one or the other (X or Y) afferent pathway not both (Cleland et al. 1971; Hoffman et al. 1972; Sherman 1985; Stone 1983).

Cortical afferents

Each of the thalamic nuclei also appears to receive afferents from the cortex (Berson and Graybiel 1983; Jones and Powell 1968; Künzle 1976; Rinvik 1968; Updyke 1977) and these generally arise from layer 6 but may (see below) also come from layer 5 pyramidal cells. In general, the layer 6 corticothalamic terminals are, like those in the lateral geniculate nucleus, relatively small, have round synaptic vesicles, and are presynaptic to small, that is, peripheral, dendritic profiles (Jones and Powell 1969a,b; Liu et al. 1995a; Ma-

Majorossy and Kiss 1976; Morest 1975; Somogyi et al. 1978). Here, too, although we know rather little about the specific properties of these corticothalamic axons and generally have limited knowledge about the properties of the cortical cells from which they arise, it is reasonable to look for a closely comparable range of functions for all of these axons in each of the several major thalamic nuclei. For example, there is evidence that, like the axons that pass to the lateral geniculate nucleus, the cortical input to other thalamic nuclei is also glutamatergic (Bromberg et al. 1981; Deschênes and Hu 1990; Fonnum et al. 1981; Fosse and Fonnum 1987; Giuffrida and Rustioni 1988; Hámori et al. 1990; Ray et al. 1992; Young et al. 1983).

Although many corticothalamic axons are very like those seen in the lateral geniculate nucleus, there are others that do not fit this description and that, perhaps surprisingly, are more like the primary afferent axons. Such corticothalamic axons were first described on the basis of their electron microscopical appearance by Mathers (1972) in the lateralis posterior nucleus and the pulvinar of the squirrel monkey. They since also have been seen in the same nuclei in squirrels (Robson and Hall 1977), macaque monkeys (Ogren and Hendrickson 1979), and mice (Hoogland et al. 1991) and in the mediodorsal nucleus (Schwartz et al. 1991) of macaque monkeys. They have relatively large terminals that end in relation to large dendritic profiles, often in glomeruli and forming triads.

Light microscopical accounts have also shown two distinct types of cortical afferent terminating in the thalamus: coarser axons dominating in nuclei classically treated as association nuclei and finer ones in nuclei like the lateral geniculate nucleus or ventrobasal nucleus receiving the major ascending pathways (Bourassa et al. 1995; Guillery 1967; Hoogland et al. 1987; Ojima 1994; Rouiller and Welker 1991). One type is relatively thin, having small terminal boutons and also, apparently, giving collateral branches to the reticular nucleus, like the corticogeniculate axons described above. These originate in layer 6 and seem to innervate only dorsal thalamus and the thalamic reticular nucleus. The other is thicker, having large terminal boutons like the specific afferents and apparently giving no branches to the reticular nucleus. The latter type, described by Bourassa et al. (1995) for the rat, terminates with large endings in the LP nucleus, and these form as branches of corticotectal axons arising from layer 5 pyramidal cells of the somatosensory cortex. Rouiller and Welker (1991) described similar axons arising from the auditory cortex and ending in the dorsal division of the medial geniculate nucleus (see also Ojima 1994). It is interesting in this context that other primary afferents, such as retinal afferents to the lateral geniculate nucleus, also branch to innervate extrathalamic targets but do not innervate the thalamic reticular nucleus (Boivie 1978, 1979; Bowling and Michael 1984; Sur et al. 1987; Tamamaki et al. 1994).

These observations lead to conclusions that are briefly outlined here, not because we believe that they have been clearly established, but rather because they raise a number of important questions that readily now are accessible to current experimental techniques.

The group of thalamic nuclei that were classically regarded as "association" or secondary nuclei, because

they project to so-called association cortex of the frontal, parietal, and temporal lobes, have primary afferent pathways that have so far been poorly defined. Although it has been established that the tectum and pretectum send afferents to the LP/posterior group (Berman 1977; Graham 1977; Graybiel and Berson 1980; Harting et al. 1980; Uhlich et al. 1991), and although some other afferent pathways have been defined for the mediodorsal and the laterodorsal nuclei (Jones 1985), it is not clear that there are significant ascending afferent systems to these nuclei that are functionally comparable with the primary afferents of the major relay nuclei. At first sight, this afferent component seems to be absent for several of the classical thalamic association nuclei.

The morphological observations summarized above about corticothalamic axons that come from layer 5 pyramids suggest that these thicker axons may act as primary afferents for some of the thalamic nuclei that have few if any other primary afferent axons. Some indirect evidence in support of this view comes from a consideration of the effects that cortical lesions or inactivation have upon the receptive fields of cells in the thalamic nuclei we are considering. For a nucleus innervated by primary afferents such as the lateral geniculate or the ventrobasal nucleus, cortical inactivation has relatively little effect on the receptive fields of the thalamic cells (Baker and Malpeli 1977; Diamond et al. 1992; Geisert et al. 1981; Kalil and Chase 1970; McClurkin and Marrocco 1984; McClurkin et al. 1994; Richard et al. 1975; Schmielau and Singer 1977; Yuan et al. 1985). In contrast to this, in the nuclei that receive layer 5 afferents (pulvinar or the posterior group) from cortex, specific receptive field properties are lost after the cortical afferents are inactivated (Bender 1983; Diamond et al. 1992).

The possibility that significant cell groups in the thalamus receive their primary afferents from the cortex rather than from lower centers and pass a record of this cortical activity on to other cortical areas would give the thalamus a role in corticocortical communication far beyond anything recognized in the current literature on corticocortical interactions (e.g., DeYoe et al. 1994; Felleman and Van Essen 1991; Kaas 1978, 1987; Knierim et al. 1992; Nakamura et al. 1993; Preuss et al. 1993; Rockland and Pandya 1981; Salin and Bullier 1995; Van Essen 1985; Van Essen and Maunsell 1983; Van Essen et al. 1990, 1992; Young 1992; Zeki and Shipp 1988). We suggest that it is now necessary to recognize at least two functionally distinct corticothalamic systems. The first arises from layer 6 and plays an important role in transforming the firing properties of thalamic cells, whereas the other arises from layer 5 and provides a primary drive for thalamic cells in a select group of thalamic nuclei. These latter thalamic cells are probably under the influence of layer 6 cells as well in much the same way as are geniculate and other thalamic relay neurons, although in general, the evidence about the cortical areas from which any one thalamic region receives its layer 6 input still is defined poorly.

On the same basis, it is possible to recognize two types of thalamic nucleus, one receiving its primary afferents from noncortical sources and the second receiving its primary afferents from cortical sources. The former have been called *first order* relay nuclei and the latter, which receive their

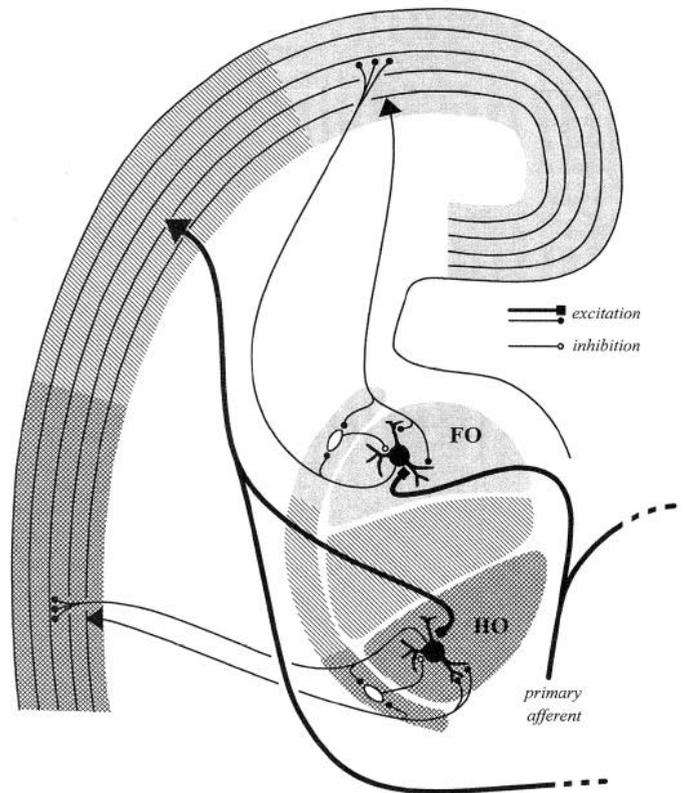


FIG. 6. Schematic representations of a first order (FO) and higher order (HO) thalamic relay, following conventions of Fig. 2. The first order circuit is virtually the same as that shown in Fig. 2, except that input from the primary afferent is shown as branching to innervate other subcortical regions. The higher order circuit here is quite similar to that of first order relay, with the chief difference relating to the cortical source of the afferent. This afferent arises from pyramidal cells in cortical layer 5. These corticothalamic axons share key features with the primary afferent shown for the first order relay: 1) many or all of them branch to innervate other subcortical targets; 2) they do not innervate the thalamic reticular nucleus; 3) and they innervate the relay cells with large terminals on proximal dendrites. See text for further details.

primary afferent stimuli after at least one passage through the thalamocortical pathways, have been called *higher order* relay nuclei (Guillery 1995). Figure 6 schematically illustrates this concept.

This view of corticothalamic afferents therefore recognizes not only that cortical areas can speak to each other through the thalamus, with one thalamocortical pathway reporting to its own cortical area the major (layer 5) output of another cortical area, it also recognizes that a variety of cortical areas might then, through their layer 6 corticothalamic connections, modify this report of a cortical output as this is passed through the thalamus.

The richness and complexity of such pathways, by means of which the cerebral cortex as a whole can be kept informed about its own activity, have been barely approached in what we know about corticothalamic and thalamocortical connections. Given the extent to which the primary afferent activity going to any known thalamic relay nucleus dominates the functional properties of the cortical area to which that nucleus has its primary projection, one can anticipate that cortical areas receiving thalamic afferents from higher order relay nuclei may well be dominated by that input rather than by the

many connections that come directly and without thalamic involvement from other cortical areas.

Local interneuronal and reticular connections

The local connections established by thalamic interneurons vary considerably from one nucleus to another. Whereas the interneurons form a prominent part of thalamic circuitry in the lateral geniculate nucleus of the cat, there appear to be no, or only very few, thalamic interneurons in the ventrobasal thalamic nucleus of the rat (Barbaresi et al. 1986; Harris and Hendrickson 1987). Spreafico et al. (1993) recently have explored the extent to which the distribution of interneurons varies from one species to another and from one nucleus to another. Further, although the dendritic F terminals of interneurons are a prominent part of the X cell pathway in cats or in the lemniscal pathway of monkeys, they are rare in the feline Y cell pathway or the macaque spinothalamic tract (Hamos et al. 1987; Ralston and Ralston 1993; Wilson et al. 1984). Thus the role of interneurons may vary greatly among various types of processing streams through thalamus. It follows that the extent to which the inhibitory influences that act upon the thalamocortical relay depend upon thalamic reticular cells only or upon a combination of thalamic reticular cells and local interneurons must at present be evaluated independently for each thalamic relay.

The reticular connections of the medial geniculate nucleus and the ventrobasal complex appear to be very like those of the lateral geniculate nucleus. Each of these thalamic cell groups relates to one sector of the reticular nucleus, and in each of these sectors, the reticulothalamic, thalamoreticular, and corticoreticular pathways show the same pattern of GABAergic inhibitory and glutamatergic excitatory interconnections as seen for the lateral geniculate nucleus (e.g., Peschanski et al. 1983). Within the reticular nucleus itself, these connections, like those in the visual sector, appear to be mapped, so that local sign, relating to the frequency map carried in the medial geniculate nucleus or to the map of the body surface in the ventrobasal complex (Conley et al. 1991; Crabtree 1992a,b; Hoogland et al. 1987), is readily recognizable within each of the relevant sectors. Similarly, there is evidence for local sign in the connections of the reticular nucleus with thalamocortical pathways to motor and cingulate cortex (Cicirata et al. 1990; Cornwall et al. 1990; Künzle 1976; Lozsádi 1994, 1995; Stepniewska et al. 1994).

There are some thalamocortical pathways, however, that connect to the reticular nucleus with little or no evidence of any local sign. Conley and Diamond (1990) compared the reticular connections of the pulvinar with those of the lateral geniculate nucleus and found that both connect to the visual sector of the reticular nucleus, the former to its medial third and the latter to its lateral two-thirds. They were able to define a topographic mapping for the geniculate connections of the reticular sector but were not able to do so for the pulvinar connections. For the auditory pathways, Conley et al. (1991) have described a comparable difference between the reticular connections of the first order auditory relay nucleus (the ventral part of the medial geniculate nucleus) on the one hand and the higher order auditory relays (the magnocellular and the posterior parts of the medial geniculate

nucleus) on the other. Both project to the auditory sector of the reticular nucleus but to different subdivisions of this sector, and whereas a topographical map could be demonstrated for the first order relay nucleus, no such map could be defined for the higher order nuclei. Crabtree (1996) has comparable data for the reticular connections of the somatosensory pathways. He describes reticular cells that have a mapped projection to the ventrobasal (first order) relay and that have a projection with no evidence of local sign to the higher order nucleus, the medial portion of the posterior complex (POM). In double label experiments, he finds many individual reticular cells with axons that participate in both of these strikingly different reticulothalamic pathways.

It is possible that there are maps in all of the pathways to and from the reticular nucleus, but from the examples cited above, it appears that for some of the higher order relay nuclei the maps are either very elusive or nonexistent. Recent evidence for the dorsomedial thalamic nucleus (Cornwall and Phillipson 1988) suggests that this higher order nucleus does have a definable map in the thalamic reticular nucleus. The higher order nuclei may be concerned with messages that bear no local sign or that have a completely different, currently undefined local sign.

The region of the ventral thalamus that forms the reticular nucleus has, throughout its major sectors, a characteristic latticework of criss-crossing axons that run through it, which gave rise to its original name (the Gitterkern, or lattice-nucleus) (see Berman and Jones 1977; Koelliker 1896). A consideration of the pattern of connections formed between the cerebral cortex and a thalamic nucleus, like the lateral geniculate nucleus or the ventrobasal nucleus, demonstrates that there has to be a quite complex system of crossing axons between the thalamus and the cortex. This is because each of these thalamic nuclei relates by thalamocortical and corticothalamic axons to several cortical areas and one cortical area can relate to several thalamic nuclei; both pathways show divergence and convergence of connections and these as well as the mirror reversals of cortical maps, like V1 and V2 relative to each other, necessarily must involve a considerable amount of crossing of axons (Nelson and LeVay 1985). It is reasonable to regard the latticework of the reticular nucleus as the site of at least some of this crossing. Nelson and LeVay (1985) showed that in cats there is a crossing of geniculocortical axons in the subcortical white matter. Lozsádi et al. (1996) have found a crossing of corticogeniculate axons in the region of the reticular nucleus. It is probable that early in development, both regions, the region of the cortical subplate (Shatz et al. 1991) and the region of the reticular and perireticular nuclei (Adams and Guillery 1994; Mitrofanis and Guillery 1993) involve some of these crossings. Perhaps corticothalamic axons cross in one place and thalamocortical axons in the other. The key to understanding how different corticothalamic circuits relate to each other within the reticular sectors of the adult may well be found in the crossings that occur during early development. The major point to be emphasized here is that within any one sector of the reticular nucleus, more than one cortical area is likely to be represented, and the reticular representation of any one small part of a cortical area is likely to be embedded within the complex latticework.

Within each functional sector of the reticular nucleus, then, there is an opportunity for the several cortical areas sharing a particular function, such as vision or hearing, to relate to each other, possibly allowing any one member of such a family of cortical areas to influence the way in which a related cortical area may be acting through the thalamic reticular nucleus upon either the first order thalamocortical relay or one of the higher order relays. The complexity of the connections that thus may be established within the reticular nucleus between the corticoreticular and thalamoreticular pathways merit detailed study. It is the outcome of such interactions that will be influencing the thalamic relays to which the reticular cells themselves are projecting.

The reticular nucleus, in addition to its cortical afferents, receives inputs from several other sources as well (e.g., cholinergic afferents from the parabrachial region and GABAergic ones from the pretectum and basal forebrain; see Fig. 4) (see also Asanuma and Porter 1990; Bickford et al. 1993, 1994a). As pointed out above, most of these afferents provide synaptic connections to the thalamus itself and also to the reticular nucleus so that an adequate knowledge about this nucleus may prove crucial to our understanding of how the several different afferent pathways discussed in earlier sections might act upon the thalamic relay cells.

Other afferent pathways

Other afferents to nongeniculate relays exist but will not be dealt with here because information about them is relatively limited or else what is known does not add significantly to the arguments being presented here. However, it is worth recording one point that may differentiate the visual relay from other sensory and ascending relays. This is the fact that for the visual relay, the lateral geniculate nucleus and the superior colliculus represent the first station at which cortical activity can act upon the retinofugal pathways. In contrast to this, descending axons from the cortex have access to earlier relays for the auditory, somatosensory, and other systems (Brodal 1981). That is, in these systems, the cortex can modulate information in structures more peripheral than the thalamus or even the brain stem, whereas in mammals the visual cortex cannot reach beyond the thalamus to the retina. All subcortical modulation of the visual inputs to cortex must occur at thalamic or collicular levels, and the extent to which this may affect comparisons between the geniculate and other thalamic relays is entirely unexplored.

INTRINSIC CELL PROPERTIES

Once we have a view of how synaptic contacts from various sources are distributed over the surface of a thalamic cell, we need to consider what transmitters are released and what receptors are activated by these afferent axon systems. We also need to understand how the transmitter actions modify the conductances and consequently the transmembrane currents of the postsynaptic cell and what part these may play in relation to the generation of the impulse that eventually passes to the cortex. These problems form the focus of this section, but a first step is to consider the extent to which postsynaptic potentials are attenuated between their sites of generation in the dendritic arbor and the site where they can influence the outputs of the cell.

Cable properties

In the case of relay cells and for interneurons that have axons, we need to understand how synaptic potentials generated in the dendrites affect the soma or axon hillock, the site where action potentials are generated. Also for interneurons, we must understand how these synaptic potentials propagate through the dendritic arbor to affect their dendritic, presynaptic outputs. To begin solving this problem, neurons may be modeled as passive cables (Bloomfield and Sherman 1989; Bloomfield et al. 1987; Jack et al. 1975; Rall 1977), and the postsynaptic potentials can be thought of as conducting electrotonically from dendritic sites toward the soma. More recent evidence of active processes in dendrite makes this assumption of simple electronic conduction more limited (see below), but such modeling remains the chief linking hypothesis between cell shape, the distribution of synaptic inputs, and the postsynaptic efficacy of these synapses.

When modeled as cables, geniculate relay cells appear to be electrotonically compact, suggesting that postsynaptic potentials even at the most distally located synaptic sites will attenuate by less than half en route to the soma (Bloomfield and Sherman 1989; Bloomfield et al. 1987). Interneurons appear to be much larger electrotonically so that distal synaptic inputs will not significantly affect the soma or the axon if there is one. These distal inputs may instead act locally only on the dendritic outputs formed there by the presynaptic dendrites of the interneurons (for details, see Bloomfield and Sherman 1989). The significance of this is considered more fully below (OTHER CONDUCTANCES).

While useful, cable modeling is severely limited because virtually all neurons, including thalamic neurons, do not simply sum inhibitory and excitatory inputs in a passive and linear fashion to produce an output (Llinás 1988; McCormick 1990; McCormick and Huguenard 1992; Sherman and Koch 1986, 1990; Steriade and Llinás 1988). Instead, the output of these cells depends upon a variety of active membrane conductances many of which are controlled by membrane voltage and others of which are controlled by other factors, such as concentration levels of Ca^{2+} ions. These conductances lead to transmembrane currents, which can have quite dramatic effects on how a cell responds to synaptic inputs.

Membrane conductances of relay cells

All relay cells have action potentials, which result from voltage-dependent Na^+ and K^+ conductances. Less well-known conductances also occur that affect the firing properties of the relay cells and thus alter the relay of information through thalamus. The major ones are considered below (for a more complete description, see Llinás 1988; McCormick 1990; McCormick and Huguenard 1992; Sherman and Koch 1986, 1990; Steriade and Llinás 1988)

LOW THRESHOLD Ca^{2+} AND RELATED CONDUCTANCES. Apart from those underlying action potentials, these are the most important conductances for relay cells. They control which of two distinct response modes, *tonic* or *burst*,¹ is

¹Tonic used in this sense refers to a response mode of a geniculate relay cell, and here it is paired with burst. X and Y cells, the relay cell types found in the A-laminae of the cat's lateral geniculate nucleus, display both response modes. This should not be confused with another, obsolete use of tonic when paired with phasic to refer to a cell type: tonic for X and phasic for Y. Throughout this account, tonic only will refer to response mode and not to cell type.

operative when a thalamic relay cell responds to afferent input (Crunelli et al. 1989; Jahnsen and Llinás 1984a,b; Lo et al. 1991; McCormick and Feeseer 1990). During the tonic mode of firing, the neuronal response to a depolarizing input is characterized by a steady stream of action potentials of a frequency and duration that correspond fairly linearly to stimulus strength and duration. During the burst mode, the neuronal response to such an input consists of brief bursts of action potentials separated by silent periods. It is worth emphasizing that this bears no resemblance to the known firing patterns of afferent inputs: for instance, retinogeniculate axons show no evidence of burst firing (Lo et al. 1991).

The activation state of the low threshold Ca^{2+} conductance, which is ubiquitous in relay cells in all dorsal thalamic nuclei of all mammals studied to date (Bal et al. 1995; Crunelli et al. 1989; Deschênes et al. 1984; Jahnsen and Llinás 1984a,b; Lo et al. 1991; McCormick and Feeseer 1990; Scharfman et al. 1990), is chiefly responsible for whether the cell responds in tonic or burst mode: when the low-threshold Ca^{2+} conductance is active, the cell responds in burst mode, and when it is inactive, the cell responds in tonic mode. The activation state itself is dependent on membrane voltage, and the conductance can be activated at a low threshold (i.e., from a more hyperpolarized level than the threshold for activation of conventional action potentials). When activated, it produces a low threshold spike (Bal et al. 1995; Jahnsen and Llinás 1984a,b; Lo et al. 1991; McCormick and Feeseer 1990; Scharfman et al. 1990). Figure 7, A–C, illustrates its voltage dependency. The underlying conductance is *inactivated* by membrane depolarizations more positive than about -60 mV (Fig. 7, A and B), but it is *deinactivated* at more hyperpolarized levels from which it can be *activated* by a suitably large depolarization (Fig. 7C), such as an excitatory postsynaptic potential (EPSP). The membrane current resulting from the low threshold Ca^{2+} conductance is known as the *T current*, because it represents an influx of Ca^{2+} ions via membrane pores known as T channels. This influx leads to a largely all-or-none, spike-like depolarization due to Ca^{2+} entry. This is the low-threshold spike. Thus the low-threshold Ca^{2+} conductance, low-threshold spike, and T current all refer to closely related phenomena.

The large depolarization associated with the low-threshold spike produces, at its peak, a high frequency burst of conventional (i.e., Na^+/K^+) action potentials. Between the low-threshold spikes, action potentials are rare, and thus the cell is relatively silent between the bursts of action potentials riding the crests of the low-threshold spikes. The low-threshold spike provides an amplification that permits a hyperpolarized cell to generate action potentials in response to a moderate EPSP. However, because of the largely all-or-none, spike-like depolarization resulting from the Ca^{2+} conductance, the amplification is nonlinear. As noted above, at depolarized levels during tonic mode firing, the neuronal response is characterized by a steady stream of action potentials of a frequency and duration that corresponds fairly linearly to stimulus strength and duration. In other words, tonic firing represents a relatively linear transformation between stimulus and response, whereas burst firing represents a more nonlinear transformation.

Activation of the low-threshold spike is rapidly followed

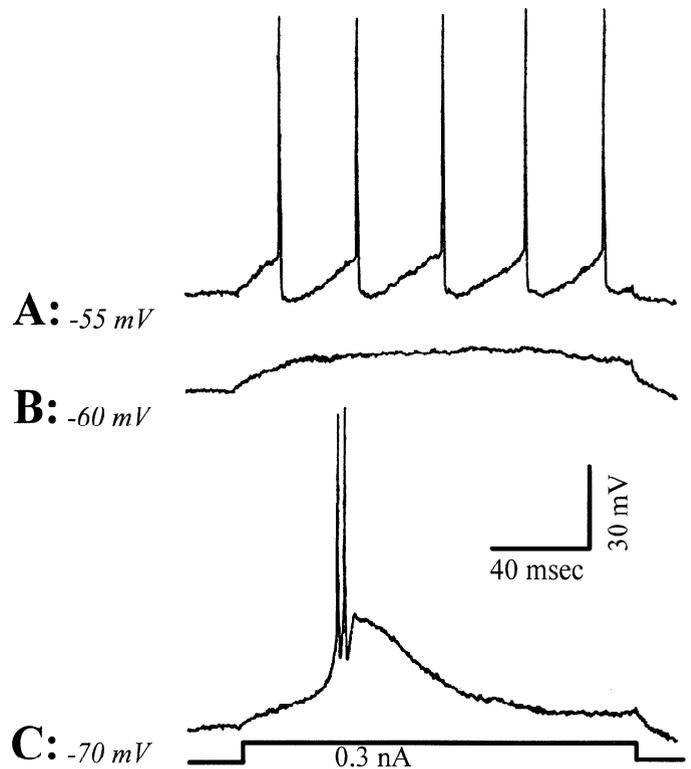


FIG. 7. Tonic and burst firing modes for lateral geniculate nucleus neuron from cat. Cell was recorded intracellularly in an in vitro slice preparation and was held at different initial membrane voltages as shown by adjusting current injected into the cell through recording electrode. Each of the three *top* traces shows response to same depolarizing 0.3 nA current pulse (*bottom*) injected into the cell, also via recording electrode. A: tonic response. When the cell is relatively depolarized (-55 mV), the current injection produces a membrane depolarization sufficient to evoke a stream of conventional action potentials. B: no response. At a middle level of polarization (-60 mV), the injected current pulse depolarizes the cell insufficiently to evoke action potentials, resulting in a purely ohmic response. C: burst response. When the cell is relatively hyperpolarized (-70 mV), the same depolarizing pulse now triggers a low-threshold Ca^{2+} spike. Riding the crest of this low-threshold Ca^{2+} spike is a burst of 2 conventional action potentials (number of action potentials in the burst can vary up to ~ 10). Low-threshold Ca^{2+} spike has a voltage dependency that prevents it from being activated from the more depolarized levels of A and B (see text for details).

by repolarization of the membrane to its former, hyperpolarized level by the rapid inactivation of the T current. In addition, there is an activation of various K^+ conductances, including one that is voltage dependent and one that is activated by the Ca^{2+} entry that occurs during the low-threshold spike. This repolarization serves partially to deinactivate the low-threshold spike, but there is also a time dependency for deinactivation: complete deinactivation requires that the hyperpolarization be maintained, generally for ≥ 100 ms. Under normal conditions, this limits the frequency with which low-threshold spikes can be evoked.

A conductance that is activated by membrane hyperpolarization and inactivated by depolarization often is associated with the low-threshold Ca^{2+} conductance. This *hyperpolarization-activated cation conductance*, leads, via influx of cations, to a depolarizing current, which is called the *h current* (McCormick and Pape 1990). Activation is slow, with a time constant of >200 ms. The combination of T current,

the above-mentioned K^+ conductances, and h current can lead to rhythmic bursting, which often is seen in recordings from in vitro slice preparations of thalamus. Hyperpolarizing a cell will activate the h current but so slowly that the T current fully deactivates. Once the h current is activated, it will depolarize the cell, thereby activating the T current. This, in turn, inactivates both the h and T currents while activating K^+ conductances, resulting in repolarization. The cycle then repeats. This leads to prolonged rhythmic bursting, typically at 3–10 Hz for the low-threshold spikes. This bursting can be interrupted only by a sufficiently strong and prolonged depolarization to produce tonic firing, and appropriate membrane voltage shifts can effectively switch the cell between rhythmic bursting and tonic firing.

These associated conductances have been most thoroughly studied in vitro, and the following relationships can be proposed on the basis of these studies. When the cell is depolarized, it fires in tonic mode. When hyperpolarized, it fires in burst mode, which is always characterized by *rhythmic* bursting. Random bursting is not possible according to this proposal. Switching between these two modes is effected by changing membrane potential. It has been suggested that the burst mode also is inevitably associated with rhythmic firing rather than random bursting in more physiological in vivo conditions (McCormick and Bal 1994; McCormick and Feeser 1990; Steriade and Llinás 1988; Steriade et al. 1993), but as we show below, this is not strictly correct.

A CURRENT. This current is present in most neurons of the central nervous system (Adams 1982; McCormick 1991; Rogawski 1985; Storm 1990). It is due to a voltage-dependent K^+ conductance, which has a similar voltage dependency to the T current, with similar activation and inactivation curves. Thus the A current is inactivated at depolarized membrane potentials and activated by a depolarization from a hyperpolarized membrane potential. Note one important distinction between the T and A currents: the T current is carried by Ca^{2+} , which flows *into* the cell and *depolarizes* it, whereas the A current is carried by K^+ , which flows *out* of the cell and thereby *hyperpolarizes* it. When the T current is activated by a small depolarization, it produces a large, depolarizing Ca^{2+} spike, which, as noted above, can be viewed as a nonlinear amplification of the activating depolarization. When the A current is activated, it hyperpolarizes the cell, which tends to offset the original, activating depolarization. The result is a slowing down of the initial depolarization with a delay and reduced frequency of action potentials.

It is not clear what function the A current serves. One suggestion (e.g., Adams 1982; Rogawski 1985; Storm 1990) is that it serves to extend the dynamic range of input/output relationships for neurons by limiting firing frequency. This would prevent the cell from reaching response saturation with low stimulus strength and allows it to signal the presence of stronger stimuli.

Whatever the purpose of the A current, which can be clearly demonstrated in thalamic relay cells under the controlled but artificial conditions of in vitro recording, it is rarely activated in these cells under more normal conditions. This is because of its interaction with the T current (Pape et al. 1994). Even though both conductances have similar voltage dependencies, they are not precisely the same. For

most relay cells, the activation and inactivation curves of the T current lie ≥ 10 mV hyperpolarized with respect to those of A current (Pape et al. 1994). This means that, when a cell is hyperpolarized sufficiently to deactivate both currents and is then depolarized, the T current will activate before the A current, and the resultant spike-like depolarization will rapidly inactivate the A current before it has a chance to develop. There is a narrow window of membrane voltage in which the T current is largely inactivated and the A current is largely deactivated, and depolarization that occurs within this limited membrane voltage range will activate the A current but not the T current.

OTHER CONDUCTANCES. Another Na^+ conductance, in addition to that responsible for the conventional action potential, exists for thalamic relay cells (Jahnsen and Llinás 1984a). This other Na^+ conductance, which is activated by a strong depolarization, is persistent and noninactivating, creating a plateau depolarization. When activated, it promotes sustained, tonic firing. Likewise, in addition to the Ca^{2+} conductance underlying the T current, there is one with a much higher threshold that is most likely located in the dendrites (Hernández-Cruz and Pape 1989; Jahnsen and Llinás 1984a); rather little is known about this Ca^{2+} conductance. A number of K^+ conductances (e.g., such as those leading to the spike afterhyperpolarization) exist in addition to those described above. These hyperpolarize the neuron for varying lengths of time following a conventional action potential. The amount of this hyperpolarization determines the relative refractory period of the cell, limiting its maximum firing rate.

Membrane conductances of interneurons

Interneurons, presumably because of their relatively small size, are much more difficult to record than are relay cells, and until recently, functional criteria to distinguish interneurons from relay cells during recording were lacking. Several such criteria now exist, especially for the in vitro preparation (Pape and McCormick 1988, 1995; Pape et al. 1994). However, except for these very recent experiments, few physiological data have been published regarding interneurons, and much less is known about their membrane properties.

ACTION POTENTIALS. The important issue as to whether all thalamic interneurons exhibit action potentials was discussed above (AFFERENTS FROM LOCAL GENICULATE INTERNEURONS). As we have noted earlier, it is possible that axonless interneurons exist and that these do not fire action potentials, but clearly some (if not all) possess axonal outputs and fire action potentials (Bloomfield and Sherman 1989; Hamos et al. 1985; Montero 1987). In any case, the massive output from presynaptic dendritic terminals could be discharged either with or without an action potential.

T AND A CURRENTS. Until recently, it was thought that, unlike relay cells, interneurons did not possess a T current. A recent analysis, however, shows that interneurons do indeed possess both T and A currents (Pape et al. 1994). However, subtle differences between cell types in their relative voltage dependencies causes the A current to obscure the T current in interneurons. This seems to be the opposite of the situation in relay cells, for which different voltage dependencies cause the T current to obscure the A current (see A CURRENT).

SYNAPTIC INTEGRATION IN INTERNEURONS. Not only is there a problem relating the membrane properties of interneurons to their morphological characteristics, but there is an even bigger problem understanding how the interneurons function in thalamic circuits. Unlike relay cells, which integrate synaptic inputs and membrane properties to produce a unified output via a single axon, interneurons may possess two quite distinct types of output. One is the axon, and the other is the dendritic terminal found distally on all parts of the dendritic arbor. As noted above, these dendritic outputs are both presynaptic, to dendrites of relay cells, and postsynaptic, mostly to axons from retina, brain stem, and other GABAergic neurons (e.g., other interneurons or reticular neurons). Cable modeling suggests that the dendritic terminals form clusters that are electrotonically isolated from each other and from the soma and axon (Bloomfield and Sherman 1989). This suggests that the interneuron integrates synaptic input via two different and independent routes: a conventional route involving proximal inputs playing out through the axon and a nonconventional route involving the dendritic terminals, which may involve many local, independent circuits.

Thus the dendritic terminals, which are the major output of the interneuron, may be effectively isolated from the soma. Because recordings of interneurons generally are made from the soma, it follows that such recordings will not reveal the integrative properties of this synaptic route through interneurons. Our limited knowledge of membrane properties of interneurons, derived from soma recordings only, therefore may relate only to the axonal output. This output may be minor and, as noted above, may not even exist on many interneurons. Clearly we need a way to investigate the synaptic and integrative properties as they relate to the dendritic terminals before we can begin to understand the role played by interneurons in thalamic functioning.

PROPERTIES OF SYNAPTIC INPUTS

Relay cells

As seen in Fig. 4, geniculate relay cells receive synaptic inputs from numerous sources. How these interact with one another and with the intrinsic properties of the relay cells largely determines how the cell responds to and thus relays retinal inputs. In recent years, a great deal has been learned about the pharmacology and physiology of the main inputs illustrated in Fig. 4. Of particular importance is the identification of neurotransmitters and postsynaptic receptors. Figure 8 illustrates these for the best understood inputs to relay cells of the lateral geniculate nucleus. Many postsynaptic receptors on relay cells are *ionotropic*, which means that the neurotransmitter binding to the receptor acts in a fairly direct fashion through a conformational change in the receptor to open a specific ion channel. Flow of ions into or out of the cell through these channels leads to the evoked postsynaptic potential. Some receptors are *metabotropic*, which means that they operate on the ion channels indirectly through second messenger pathways.

Ionotropic receptors usually are associated with faster postsynaptic responses than are metabotropic ones. Also, metabotropic receptor activation often produces other cellu-

lar effects through second messenger systems, and this can even lead to effects on more than one set of ion channels. However, ionotropic receptors also may produce second messenger effects that can be triggered by influx of certain ions (e.g., Ca^{2+}), even though the postsynaptic potential itself is evoked in a direct manner.

INPUTS FROM INTERNEURONS AND CELLS OF THE THALAMIC RETICULAR NUCLEUS. Both interneurons and reticular cells use γ -aminobutyric acid (GABA) as a neurotransmitter. They are thus said to be "GABAergic". Transmitters should no longer be classified as excitatory or inhibitory, because it is known that the same neurotransmitter can be both excitatory and inhibitory depending on the postsynaptic receptor (see below for examples). However, based on the available evidence, GABA seems to act in the thalamus in an inhibitory manner. Relay cells thus exhibit inhibitory postsynaptic potentials when inputs from either interneurons or reticular cells are activated. These potentials are generated through two different receptors, known as GABA_A , which is ionotropic, and GABA_B , which is metabotropic (Crunelli and Leresche 1991; Crunelli et al. 1988; Soltész and Crunelli 1992).

The GABA_A response involves opening a Cl^- channel, which inhibits the cell not so much by hyperpolarization (the reversal potential for Cl^- is only about -70 mV) as via a large decrease in neuronal input resistance that serves to shunt any excitatory postsynaptic potentials. The GABA_B response involves opening a K^+ channel, which more strongly hyperpolarizes the cell toward the K^+ reversal potential of roughly -100 mV with less effect on input resistance. The GABA_A response is typically faster than is the GABA_B response. Interneurons and reticular cells can provide three different types of input to the relay cell: axonal from the reticular cells, axonal from the interneurons, and dendritic from the interneurons. It is not clear how, if at all, GABA_A and GABA_B receptors correlate with these different sources of GABAergic input but the relationship could prove to be functionally significant.

INPUTS FROM RETINAL AXONS. Retinal afferents to the lateral geniculate nucleus use an excitatory amino acid (probably glutamate) as a neurotransmitter, and relay cells respond to this with a variety of ionotropic receptors (see Fig. 8). These can be divided into two main types (Hartveit and Heggelund 1990; Heggelund and Hartveit 1990; Kemp and Sillito 1982; Kwon et al. 1991; Moody and Sillito 1988; Scharfman et al. 1990; Sillito et al. 1990): *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA).

Activation of the AMPA receptors produces a prototypical, fast excitatory postsynaptic potential because of entry of Na^+ and perhaps other cations. The response associated with NMDA-receptor activation is unusual for three reasons. First, it has a voltage dependency so that the more hyperpolarized the cell, the less that receptor activation yields an EPSP. This is because the ion channel attached to the NMDA receptor becomes clogged with Mg^{2+} ions, preventing influx of cations to depolarize the cell (Kawajiri and Dingledine 1993; Mayer and Westbrook 1987). Prior depolarization of the cell prevents this Mg^{2+} block, and then activation of the NMDA receptor produces an EPSP. This EPSP is slower

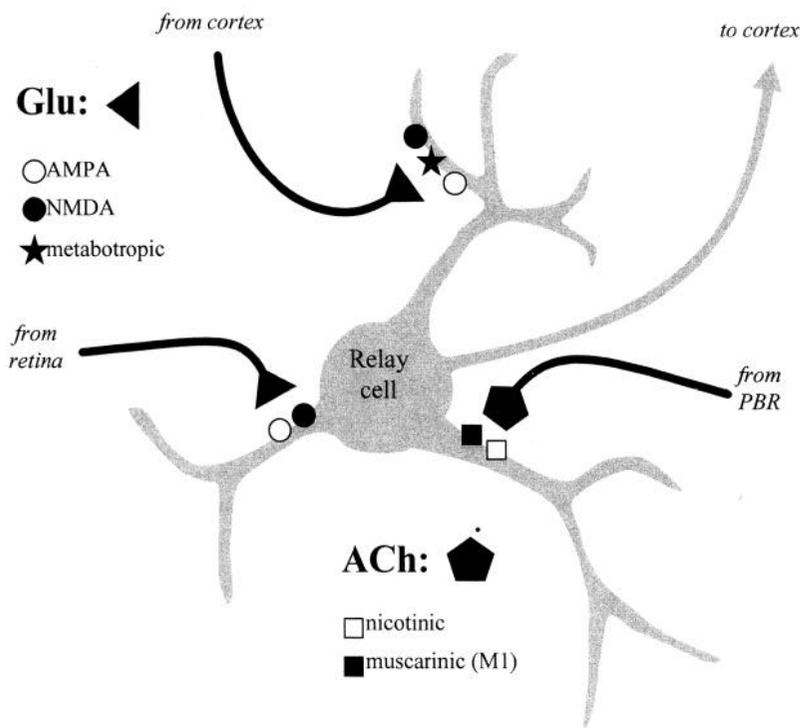


FIG. 8. Schematic diagram of postsynaptic receptors activated on relay cells of lateral geniculate nucleus from retinal, cortical, and parabrachial inputs.

than that produced by activation of the AMPA receptor. Second, although NMDA receptors are ionotropic, their activation involves considerable influx of Ca^{2+} , which can, in turn, activate certain second messenger pathways providing other postsynaptic effects. For instance, such a process is thought to play a role in long-term potentiation in hippocampal cells, a phenomenon shown to depend on NMDA receptors. It is not clear what role if any such a phenomenon might have in the geniculate relay. Third, activation of NMDA receptors requires the presence of glycine in addition to glutamate because of a strychnine-independent glycine site generally associated with the NMDA receptor (Johnson and Ascher 1987; Kleckner and Dingledine 1988; Mayer and Westbrook 1987; Mayer et al. 1989; Thomson et al. 1989). This is odd and remains a mystery, because no known source of glycinergic input to geniculate relay cells has yet been discovered. One could argue that metabolic levels of glycine present in the neuropil are sufficient to activate the glycine receptor, but how is this level modulated to affect the NMDA response, and if it is not modulated, why bother to evolve a receptor to an invariant substance?

Clearly, this arrangement of glutamatergic receptors on relay cells can strongly affect the nature of geniculate gating. If the relay cell is sufficiently hyperpolarized at the time of retinogeniculate input, the NMDA response is reduced, being more reduced with further initial hyperpolarization, and the AMPA response will dominate. This will not only influence the temporal properties of the relay, because the AMPA response is considerably faster than is that of the NMDA receptor, but NMDA activation also can lead to other effects due to activation of second messenger pathways. Any input that affects membrane potential of the relay cell can control the mix of NMDA and AMPA responses, and this could conceivably apply to any of the inputs to these cells illus-

trated in Fig. 4. This control can be exerted not only by nonretinal inputs, but also by the pattern of retinal inputs from visual stimulation, which also could be important, because a brief interlude of action potentials might be inadequate to depolarize the relay cell sufficiently to produce an NMDA response, but a more prolonged barrage might do so.

The postsynaptic receptors activated by retinal axons on interneurons have not yet been clearly documented.

INPUTS FROM CORTICAL AXONS. Corticogeniculate synapses appear to activate the same types of AMPA and NMDA ionotropic glutamate receptors as are activated by retinogeniculate synapses, but because of the very different locations of their synaptic inputs upon the dendritic arbor, these different synaptic populations presumably do not activate the same individual glutamate receptors. In addition to the ionotropic glutamate receptors, corticogeniculate synapses activate a metabotropic glutamate receptor on relay cells (see Fig. 8), a receptor type not activated via retinal inputs (McCormick and Von Krosigk 1992). Activation of this metabotropic receptor mobilizes a second messenger pathway that ultimately leads to reduction in a K^+ "leak" conductance. Reducing this conductance depolarizes the cell, and the resultant EPSP is quite slow and long lasting, much more so than is the EPSP associated with the ionotropic NMDA receptors, even the NMDA receptor.

The implications of the mix of AMPA and NMDA receptors activated from cortex are similar to those that apply to the receptors activated from the retina, and the metabotropic glutamate receptor adds another dimension to corticogeniculate function. Activation of the metabotropic receptor produces the slowest and longest lasting response, that of the AMPA receptor is the fastest and briefest, and that of the

NMDA receptor is intermediate. The slower responses, especially via the metabotropic receptor, would be better able to maintain more sustained changes in membrane voltage of relay cells. This could be quite important in allowing cortex to exert control over voltage-dependent conductances expressed by these relay cells. The slow response, however, would act like a low-pass temporal filter in transferring information across the synapse so that specific firing patterns in the cortical afferents would not be imposed on the relay cells. In contrast, EPSPs evoked via AMPA receptors would be faster and perhaps permit transfer of these firing patterns, but it would be less suitable for sustaining changes in membrane voltage.

These corticogeniculate axons also innervate both interneurons and reticular cells, but the postsynaptic receptors activated on these cells are not completely known, although recent evidence suggests a lack of metabotropic glutamate receptors on interneurons (Pape and McCormick 1995).

INPUT FROM PARABRACHIAL AXONS. In cats, most of the input to the lateral geniculate nucleus from the brain stem derives from cholinergic neurons in the midbrain and pontine tegmentum surrounding the brachium conjunctivum (Bickford et al. 1993; de Lima and Singer 1987b; Fitzpatrick et al. 1989; Paré et al. 1988; Raczkowski and Fitzpatrick 1989; Smith et al. 1988). This brain stem area thus is known as the parabrachial region. As is summarized by Figs. 4 and 8, activation of this input produces an excitatory postsynaptic potential due primarily to activation of two different receptors (McCormick 1989; McCormick and Prince 1987). The first is an ionotropic nicotinic receptor that produces a fast EPSP by permitting influx of cations. The second is a metabotropic muscarinic receptor, an M1 type, that triggers a second messenger pathway ultimately leading to a reduction in a K^+ conductance. This muscarinic response is a very slow, long-lasting EPSP. It seems remarkably similar to the metabotropic glutamate response seen from activation of corticogeniculate input (see above), and the possibility exists that both metabotropic receptors may be linked to the same second messenger pathway and K^+ channels.

In addition to acetylcholine (ACh), these axons appear to colocalize NO (Bickford et al. 1993), a neurotransmitter or neuromodulator with a widespread distribution in the brain (Bredt and Snyder 1992; Schuman and Madison 1991, 1994; Snyder 1992). Relatively little is known concerning the action of NO in the lateral geniculate nucleus, but recent studies suggest that its release from parabrachial terminals serves two possible roles: to switch response mode from burst to tonic (Pape and Mager, 1992), perhaps complementing the role of ACh in this regard, and to promote the generation of NMDA responses from retinal inputs (Cudeiro et al. 1994a,b, 1996).

OTHER INPUTS. Other sparse inputs to the lateral geniculate nucleus are shown in Fig. 4 and include noradrenergic axons from cells in the parabrachial region, serotonergic axons from cells in the dorsal raphé nucleus, GABAergic axons from cells from the pretectum, and histaminergic axons from cells in the tuberomammillary nucleus of the hypothalamus (see above for details). Noradrenalin seems to increase excitability of relay cells in the lateral geniculate nucleus and, like ACh, promote tonic firing (Funke et al. 1993; McCor-

mick 1992; Pape and McCormick 1989). Effects of serotonin are complex. Iontophoresis onto relay cells in vivo generally inhibits them, but in vitro studies suggest that this is the consequence of direct excitation that is stronger for local GABAergic cells than for relay cells (see below and McCormick 1992). Although pretectal axons innervate the lateral geniculate nucleus, morphological evidence from cats suggests that they might innervate mainly interneurons and not relay cells (Cucchiari et al. 1993). Interestingly, Feig and Harting (1994) provide analogous data from the Galago, from which they conclude pretectal afferents form inhibitory contacts in the lateral geniculate nucleus, and these frequently form onto interneurons, although relay cells also receive such innervation. Finally, histamine application to relay cells generally excites them (McCormick 1992).

Inputs to interneurons and reticular cells

Relatively few recordings have been made from interneurons and reticular cells. Retinal axons, which innervate the former but not the latter (see Fig. 4), produce EPSPs in interneurons (Ahlsén et al. 1985; Friedlander et al. 1981; Lindström 1982). The receptors underlying this have not been identified unambiguously but, based on shape of the evoked EPSPs, are likely to be ionotropic glutamate receptors. However, as noted above, recordings of interneurons may directly reveal inputs to the soma and proximal dendrites only, and we have indicated that many afferents primarily contact peripheral dendritic processes.

Activation of the cholinergic inputs from the parabrachial region generally inhibits interneurons and reticular cells (Ahlsén et al. 1984; McCormick 1992; McCormick and Pape 1988; McCormick and Prince 1986, 1987). This is interesting, because individual parabrachial axons branch to innervate these cells as well as relay cells, and, as noted above, these axons excite relay cells. This is accomplished by yet another type of muscarinic receptor, a type other than M1, that dominates on these GABAergic targets (Hu et al. 1989a,b; McCormick, 1989; McCormick and Prince 1986, 1987). Activation of this receptor increases a K^+ conductance, leading to hyperpolarization. However, cells of the thalamic reticular nucleus also respond to this cholinergic input with another, nicotinic receptor that leads to fast depolarization (Lee and McCormick 1995). Nonetheless, the main effect of cholinergic stimulation of these cells seems dominated by the muscarinic, inhibitory response (Dingle and Kelly 1977; Hu et al. 1989a,b; McCormick and Prince 1987). Because these interneurons and reticular cells inhibit relay cells, activation of this cholinergic pathway thus disinhibits relay cells. Nothing is as yet known about the action of NO on these local, GABAergic cells.

Noradrenalin depolarizes reticular cells by reducing a K^+ conductance (McCormick 1992; McCormick and Wang 1991), but has no clear effect on interneurons (Pape and McCormick 1995). Serotonin depolarizes reticular cells by blocking a K^+ conductance (McCormick 1992; McCormick and Wang 1991), and it produces a slight depolarization of some interneurons, not clearly affecting others (Pape and McCormick 1995). Histamine depolarizes interneurons but apparently through unknown presynaptic mechanisms and not through any direct effect on these cells (Pape and

McCormick 1995). It should be noted that these observations of effects on interneurons represent recording from the cell body and axon and thus may be limited to axonal output without reflecting effects on dendritic output (see above). We can assume the GABAergic input from pretectum inhibits its targets, which include reticular cells, interneurons, and probably relay cells (Cucchiari et al. 1993; Feig and Harting 1994). Finally, the GABAergic pathway from the basal forebrain to the thalamic reticular nucleus likely inhibits these cells, but we have noted above that this pathway does not directly innervate the lateral geniculate nucleus (Bickford et al. 1994a).

FUNCTION OF BURST AND TONIC RESPONSE MODES IN THE THALAMOCORTICAL RELAY

We have seen that thalamocortical relay cells display two response modes, burst and tonic, that depend upon the activation state of the low-threshold Ca^{2+} spike. Studies from in vitro slice preparations suggest that the burst mode implies rhythmic bursting that functionally disconnects the relay cell from its first order afferent input and interrupts the relay. This is because the rhythmic bursting is based on intrinsic cellular and local circuit properties and fails to reflect the pattern of retinal inputs impinging on the lateral geniculate relay cell. This view further suggests that faithful relay takes place only during the tonic firing mode. These modes thus appear to represent a state dependent switching on and off of the relay through the lateral geniculate nucleus. Inputs that affect membrane potential can readily switch relay cells between modes by inactivating or deinactivating the low-threshold spike.

The first in vivo studies of the response modes in cats demonstrated that, when the animal entered certain phases of sleep, thalamic relay cells began to burst rhythmically and that such rhythmic bursting was not seen during awake, alert states (Livingstone and Hubel 1981; McCarley et al. 1983; Steriade and Contreras 1995; Steriade and McCarley 1990; Steriade et al. 1993). This led to the hypothesis that awake animals have depolarized thalamocortical cells that operate strictly in tonic mode and thus faithfully relay information to cortex; during certain sleep phases, the cells become hyperpolarized and thus burst rhythmically, which prevents relay of information to cortex. Studies of visual response properties of relay cells in the lateral geniculate nucleus of cats suggest that this view, although correct as far as it goes, is incomplete. Recent data, reviewed in the following paragraphs, indicate that both tonic and burst response modes normally are used by geniculate relay cells to transmit visual information to cortex.

Visual responses of geniculate relay cells

If the burst mode represents a complete failure of the relay through thalamus, it follows that, in vivo, a geniculate relay cell sufficiently hyperpolarized to deinactivate its low-threshold spike should either remain silent or begin bursting rhythmically, whether in the presence of a visual stimulus or during spontaneous activity. Recording from lightly anesthetized cats in vivo shows that cells in burst mode rarely, but occasionally, fire rhythmically during spontaneous activity;

more commonly, they fire instead during spontaneous activity with randomly occurring bursts. Also, such cells respond quite reliably to visual stimuli, except that the response is in the form of bursts riding the crests of low-threshold spikes rather than streams of unitary action potentials that occur during depolarization and in the tonic mode (Guido et al. 1992, 1995; Mukherjee and Kaplan 1995). These bursts follow the temporal properties of the visual stimulation rather than any intrinsic pacemaker frequency. Recent but preliminary evidence suggests that the same response properties can be seen in awake, behaving cats (Guido and Weyand 1995).

Because geniculate cells respond to visual stimuli in either tonic or burst mode, and these modes represent different types of stimulus/response transformation (cf. Fig. 7), these response modes almost certainly represent different forms of relay of visual information to cortex. Figure 9 illustrates the key differences in how a cell responds to visual stimuli during tonic and burst response modes (see also Guido et al. 1995) and shows that the cell does respond quite vigorously to the visual stimulus while in burst mode. These response characteristics suggest two differences between tonic and burst mode.

First, tonic mode displays much greater linear summation than does burst mode. When applied to visually evoked responses such as those shown in Fig. 9, the response profile of a cell with good linear summation will correlate well with differing visual stimuli. Thus the sinusoidal response profile during tonic mode firing reflects a linear transformation between the visual stimulus, which is a drifting sinusoidal grating, and the response. In contrast, the response profile during burst mode firing reflects a nonlinear distortion of the sinusoidal stimulus. This very likely results from the nonlinear amplification of the low-threshold spike, which provides a similar response regardless of the amplitude or duration of any suprathreshold stimulus (see above). These impressions have been confirmed by Fourier analysis of the responses of the cells during the two response modes (Guido et al. 1992, 1995) and also by analysis of responses to flashing spots (Mukherjee and Kaplan 1995). It should be noted that the difference in spontaneous activity contributes to the difference of the responses, because the higher level during tonic mode helps to prevent nonlinearities due to half-wave rectification in the response.

Second, the lower spontaneous activity during burst mode coupled with vigorous visual responsiveness during either mode (Guido et al. 1995) suggests the possibility that the ratio between signal (visual response) and noise (spontaneous activity) actually is improved during burst mode. This, in turn, suggests that cells in burst mode might be more capable of detecting a stimulus than when in tonic mode. This possibility has been tested formally by using techniques of signal detection theory to create receiver operating characteristic curves for responses during tonic and burst mode; these curves test the ability of the cell to detect a visual stimulus against background noise (Green and Swets 1966; Macmillan and Creelman 1991). Every geniculate cell so tested displays considerably better detection of the visual stimuli when in burst mode than when in tonic mode (Guido et al. 1995). Furthermore the more difficult a stimulus is to detect (e.g., stimuli of lower contrast), the greater the detec-

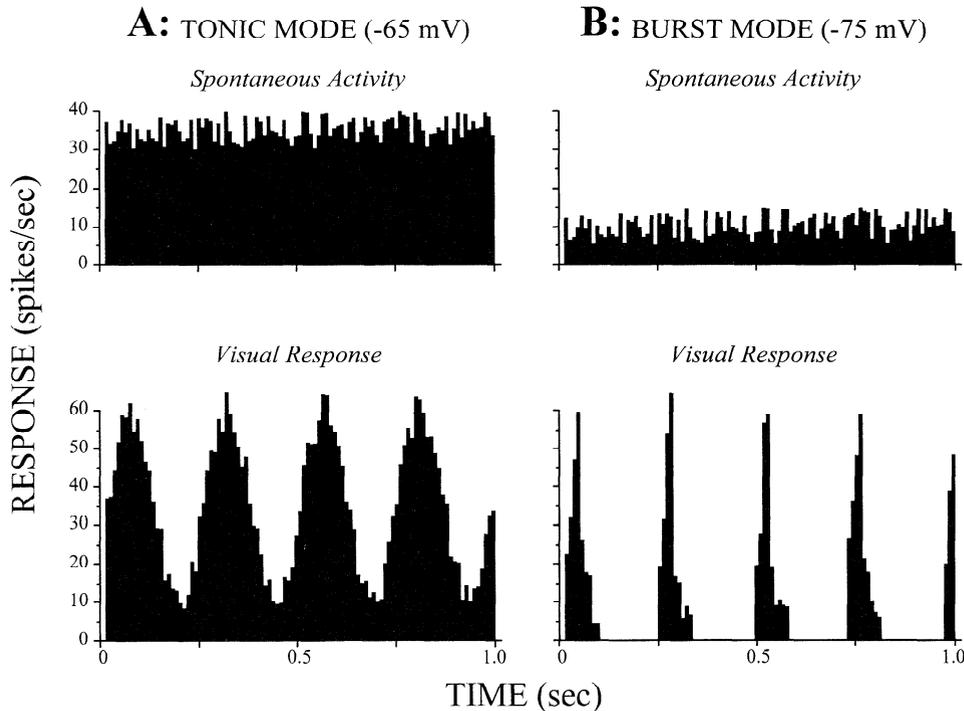


FIG. 9. Spontaneous activity and visually driven responses of geniculate cell recorded in a cat in vivo during tonic and burst modes. The cell was recorded intracellularly, and current injection was used to adjust mean membrane voltage to either -65 mV, which was sufficiently depolarized to inactivate T current and promote tonic responses, or -75 mV, which was sufficiently hyperpolarized to deinactivate T current, allowing it to be activated and promote burst responses. *Top*: histograms show spontaneous activity; *bottom*: responses shown to 4 cycles of a sinusoidal grating drifted through receptive field. *A*: tonic mode; *B*: burst mode.

tion advantage of the burst over the tonic mode. This is because a less salient stimulus would produce a smaller response during tonic mode, but such a stimulus, if detectable, would provide nearly the same response during burst mode as would a more salient stimulus.

Besides the differences in linear summation and signal detection, response mode has an effect on temporal tuning (Mukherjee and Kaplan 1995). Geniculate neurons firing in tonic mode respond to a broad range of temporal frequencies, whereas those in burst mode respond to a much narrower range. In engineering terms, cells in tonic mode behave as low-pass temporal filters, whereas those in burst mode act as band-pass filters. Differences are particularly striking at low temporal frequencies, to which cells in tonic mode respond much better.

It thus seems clear that both response modes efficiently relay visual information to cortex. Burst mode is better for initial detection of stimuli. This may be effective during visual search when the less accurate analysis permitted by the nonlinear responses is nonetheless sufficient for target acquisition. It also may be useful when attention is directed elsewhere (c.g., to another part of visual space or to another sensory modality) as a sort of "wake-up" call for novel and potentially interesting or dangerous stimuli. This notion is in many ways similar to the "searchlight" hypothesis for burst firing first advanced by Crick (1984) in relation to the possible function of the thalamic reticular nucleus in attention. However, the nonlinear distortion associated with burst mode suggests that, although the stimulus can be detected readily, it will not be as accurately analyzed while the relay is in this mode. Tonic mode, with its more linear relay of visual information, would permit more faithful signal analysis. The differences between these response modes in temporal tuning (Mukherjee and Kaplan 1995) are also

consistent with this hypothesis, because the low-pass tuning during tonic mode would respond well to lower temporal frequencies that result from stimuli being tracked and thus fixed fairly stably on the retina, which would be expected for stimuli analyzed in detail. Sudden changes in the visual world (e.g., the appearance of a novel stimulus) or visual search would not have much representation of low temporal frequencies, so if cells in burst mode are concerned with such tasks, they need not be sensitive to these lower frequencies.

Control of response mode

We can suggest from the above that geniculate relay cells switch between tonic and burst firing modes depending on the requirements of the visual system regarding signal detection or analysis. For this to be plausible, there must be a ready means for nonretinal inputs to control these response modes. This may be accomplished through effects on the membrane potential of relay cells, because the low-threshold Ca^{2+} conductance underlying the burst mode is voltage dependent, but other factors as noted below also could contribute to controlling response mode. Evidence does exist that both parabrachial and cortical inputs can do this.

Electrical activation of the parabrachial region in vivo causes dramatic switching of geniculate relay cells from burst to tonic mode (Lu et al. 1993). Likewise, in vitro application of ACh, the chief transmitter used by parabrachial inputs to the lateral geniculate nucleus, eliminates low-threshold spiking, causing bursting cells to fire in tonic mode (McCormick 1989, 1992). The role of corticogeniculate input in control of response mode has been more difficult to assess in vivo, because electrical activation of this pathway also usually activates geniculocortical axons antidromically, obscuring the interpretation of any effects. However, be-

cause corticogeniculate but not retinogeniculate inputs use a metabotropic glutamate receptor, it is possible to mimic activation of the corticogeniculate input fairly specifically by applying agonists for this receptor to geniculate relay cells. When this is done *in vivo*, geniculate cells switch firing mode from burst to tonic (Godwin et al. 1996).

It thus appears that both of these major inputs to the lateral geniculate nucleus, from cortex and from the parabrachial region, strongly influence response mode. Each of these pathways also connects to the thalamic reticular nucleus (Fig. 4), one with clear evidence of local sign corresponding to position in visual space and the other with no evidence for local sign and probable exerting global actions. Although the precise role of the reticular nucleus in controlling the switch between tonic and burst modes remains to be defined in the alert animal, it should be clear from its connections that the reticular nucleus is likely to be intimately involved in the switch. Because activation of parabrachial or cortical inputs switches firing mode from burst to tonic, it seems likely that inactivation of these pathways does the opposite, but this remains to be tested.

Suggested role of response mode for vision

From the above, we can speculate on the possible role of burst and tonic response modes for vision. When the animal is not attending to a particular visual stimulus, either because it is searching for a stimulus, attending visually to another stimulus, attending via another sensory modality, or not attending at all but in a drowsy state, the geniculate relay cells for that particular stimulus will be in burst mode. This suggests that the cortical or parabrachial inputs to these geniculate cells are relatively quiescent. Such firing in burst mode enhances the ability of the geniculate relay cells to detect the presence of a novel stimulus, one that is potentially interesting or threatening. Such enhanced detection, however, is associated with nonlinear distortion and is thus unsuitable for accurate stimulus processing. Once novel stimuli or major components of a visual scene are detected, if they are sufficiently significant, then relay cells can be switched via activation of the cortical or parabrachial inputs to tonic firing. Because the stimuli now are detected, burst firing is no longer so important. The tonic firing now enhances linear processing through the lateral geniculate nucleus and permits the visual system to analyze the scene more faithfully.

By definition, the corticogeniculate input conveys strictly visual information, and it is mapped with great retinotopic precision. Thus its control of response mode would be limited to attentional needs within the visual domain. For instance, if the animal were paying attention to one stimulus (e.g., likely with the fovea or area centralis, but conceivably with peripheral retina), geniculate cells mapped to the rest of the visual field would be maintained in burst mode, primed to detect any new stimulus of potential interest or danger. On the other hand, the parabrachial input, which probably lacks local sign (see above *Brain stem afferents*), is likely to be multimodal in nature and may be initiated by a specific sensory stimulus or by a general change in level of arousal or mood.

Thalamic relay cells, including those of the lateral geniculate nucleus, burst rhythmically during certain phases of

sleep (McCarley et al. 1983; Steriade and Contreras 1995; Steriade and Llinás 1988; Steriade et al. 1990, 1993), and this seems to imply a functional disconnection of these cells from their main afferents, interrupting the thalamic relay. Our suggested role for the burst mode of firing is not incompatible with this other role. Instead, we are suggesting that, depending on the animal's behavioral state (e.g., alert vs. sleeping), burst firing can subserve at least two quite different roles or perhaps two extremes of one role: either providing a computational mode in the awake animal that can record significant but possibly minor changes in specific afferent activity and use this to focus the tonic mode upon the cause of these changes for more accurate analysis, or else, in the sleeping animal produce the same switch from burst to tonic mode, but only in response to major stimuli that are seen as sufficiently threatening or significant to wake the animal. That is, sleeping may involve more complete functional shutting off of cortical and parabrachial inputs, more analogous to the *in vitro* situation where these inputs are physically removed. The low levels of activity present in these pathways during the waking state may permit single low-threshold spikes but prevent rhythmic bursting. Bursting, when rhythmic, may provide a positive signal to cortex that nothing is being relayed despite the possible presence of sensory stimuli, and this is less ambiguous than no activity, which could either mean no relay or no stimulus. When the bursting is arrhythmic, cortex can interpret this arrhythmicity as representing responses evoked by sensory stimuli.

FINAL OVERVIEW

The thalamus, through the nuclei we have here called first order nuclei, provides the main path to the cerebral cortex for information about what the outside world is doing or what the subcortical parts of the brain are doing. In addition, other nuclei of the thalamus, here called the higher order nuclei, receive primary afferents that come from layer 5 pyramidal cells of the cerebral cortex, and these provide information about what the cerebral cortex is doing, particularly about the output pathways of the cortex. These two types of thalamocortical pathway provide the major information channels through the thalamus.

Corticothalamic afferents from layer 6 pyramidal cells, the parabrachial afferents, and possibly some of the other afferents going to the thalamus, can be regarded as modulatory pathways. They appear to control response mode of the thalamocortical relay: promoting either burst mode, for close monitoring of changes in the relayed inputs, or tonic mode, to permit more accurate reconstruction of events being relayed. Burst mode would be preferred for enhanced vigilance, and tonic mode could be invoked by activity among afferents from layer 6 of cortex or from the parabrachial region when a relayed signal is detected that is of potential interest, danger, or pleasure to the animal. Not only would this apply to signals relayed from the periphery through first order thalamic relay nuclei, but in a comparable manner, one can anticipate that higher order thalamic nuclei can serve to monitor patterns of output from cortical areas, so that when particularly important output messages are sent out from layer 5 pyramidal cells, the higher order nuclei can be set from burst to tonic mode, thereby permitting information

about the novel cortical output to pass to another (higher) cortical area.

Whereas the primary afferent axons from subcortical and from layer 5 cortical origins send no terminals to the thalamic reticular nucleus, the cortical axons that come from layer 6 and the axons from the parabrachial nucleus, which can be regarded as modulatory axons, send branches to this nucleus. The reticular nucleus in turn also can produce a modification of the discharge properties of thalamic relay cells, so that it becomes important to define how the several inputs to any one sector of the reticular nucleus may relate to each other. Further, it is necessary to distinguish pathways that have local sign and that therefore can be expected to act upon a limited part of any active sensory or corticofugal pathway from pathways that lack local sign or have poorly defined local sign, which are more likely to have a global modulatory influence upon thalamic transmission. Furthermore, and perhaps of greatest interest, are the possibilities that arise within the thalamic reticular nucleus for higher order circuits to act upon first order circuits, and vice versa, providing opportunities for one cortical area to modify the discharge properties of thalamic relays to other cortical areas.

We have outlined a significant number of axon connections and synaptic relationships that reveal an extraordinary potential for complexity in thalamic transmission. We have shown that it is unrealistic to regard the thalamus as a simple relay conveying messages from the periphery to the cortex without significant modification. Some of the complexity of the thalamus is beginning to be resolved, but perhaps one of the most challenging features of this cell group is to resolve the detailed connections and functional significance of many synaptic relationships that we have presented in this review.

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