parallel fiber system provides a continuous and very delicate regulation of the excitability of the cerebellar nuclei, brought about by the tonic activation of simple spikes in Purkinje cells, that ultimately generates the fine control of movement known as motor coordination. The fact that the mossy fibers inform the cerebellar cortex of both ascending and descending messages to and from the motor centers in the spinal cord and brainstem gives us an idea of the ultimate role of the mossy fiber system; it informs the cortex of the place and rate of movement of limbs and puts the motor intentions generated by the brain into the context of the status of the body at the time the movement is to be executed.

Because the Purkinje cell is an inhibitory neuron, the entire output of the elaborate cerebellar cortical neuronal network produces an organized, large-scale inhibition of neurons in the cerebellar nuclei. It should be recalled that of all the cells residing in the cortex only the granule cells are excitatory; all the rest are inhibitory. As illustrated in Figs. 7.15 and 7.16, an understanding of their membrane properties and synaptic interactions provides fundamental insight into the functioning of the cerebellar cortex.

8

THALAMUS

S. MURRAY SHERMAN AND CHRISTOF KOCH

The thalamus is the gateway to neocortex, and as such these two main components of the vertebrate telencephalon have evolved in close relation to each other. Virtually all routes to cortex are relayed via the thalamus, although inputs from other subcortical sites exist, such as brainstem, basal forebrain, and the claustrum. Our conscious perception of the world around us depends on information reaching cortex and being analyzed there, and thus the thalamus represents a key link in this process.

However, as well shall see in this chapter, the thalamus does much more than merely act as a passive and machine-like relay of information to cortex. Instead, the ability to pass through this gateway is determined by specialized neuronal circuitry: the gate can be completely open, which results in the relay of all information to cortex; completely closed, which cuts off cortex from the outside world; or partially open, which permits certain information to reach cortical levels. Also, the special properties of relay cells can strongly influence the nature of the thalamic relay. Thus the thalamus filters and transforms the flow of information to cortex and as such is an important neuronal substrate for many forms of attention (Singer, 1977; Sherman and Koch, 1986; Sherman, 1988, 1993; Steriade and Llinás, 1988; Steriade et al., 1993; Sherman and Guillery, 1996).

OVERALL ORGANIZATION

The thalamus is most highly developed in mammals and especially so in primates. All sensory systems pass through the thalamus on their way to neocortex. This includes somatosensory information from the muscles, deep tissues, and skin; visual information from the eyes; auditory information from the ears; and gustatory information from the taste buds. Each part of the thalamus, in turn, receives fibers from the area of cortex to which it projects (Jones, 1985).

The main exception to this pattern is the relay of olfactory information because the initial stages of olfactory processing represent phylogenetically very old circuitry that probably predates the evolution of thalamocortical pathways. Cells in the nasal epithelium project directly to the olfactory bulb (see Chap. 5), which then projects to the primary olfactory cortex (see Chap. 10). This cortex is paleocortex. It has three layers and evolved before neocortex (see Chap. 10), which has six layers. The olfactory path-

way can then be followed from olfactory paleocortex into the mediodorsal nucleus of the thalamus, from which it is relayed to the insular and orbital cortex, which is neocortex. Later in this chapter, we reconsider the olfactory pathway in the context of first- and higher-order thalamic relays.

The thalamus can be divided on the basis of connectivity and embryological origin into three main divisions: *dorsal thalamus*, *ventral thalamus*, and *epithalamus*. The dorsal thalamus, which is the largest division, has massive reciprocal connections with cerebral cortex and striatum; in fact, virtually the whole cortex receives a projection from the dorsal thalamus. People often mean "dorsal thalamus" when they refer simply to "thalamus." The ventral thalamus does not innervate cortex. However, it does receive innervation from cortex, and most of its subnuclei, collectively known as the *thalamic reticular nucleus* (TRN; also known as the *nucleus reticularis thalami* or the *reticular nucleus of the thalamus*), have reciprocal connections with specific nuclei in the dorsal thalamus (Jones, 1985; Ohara and Lieberman, 1985). The epithalamus lacks direct afferent or efferent connections with cortex and is actually more closely associated with hypothalamus; it will not be considered further here.

The dorsal thalamus can be divided into a number of discrete nuclei. Figure 8.1 and Table 8.1 illustrate the major thalamic nuclei that relay subcortical information to the cerebral cortex, and in some cases, to the basal ganglia as well. We now recognize that

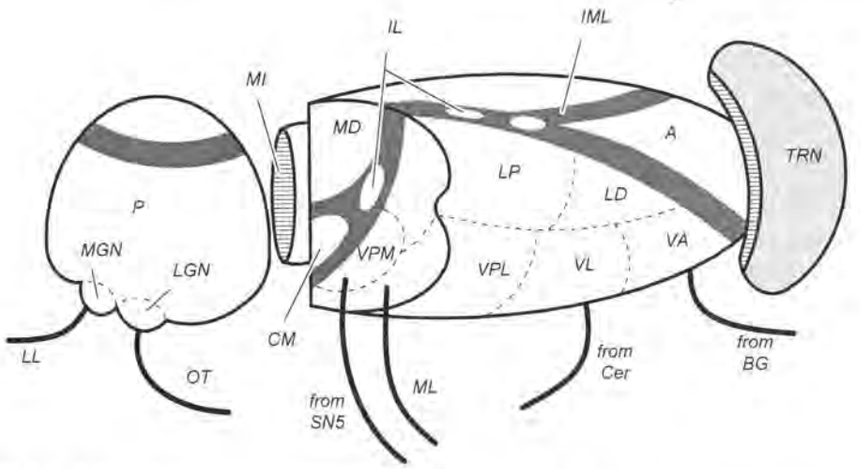

Fig. 8.1. Schematic three-dimensional view of right thalamus with many of its major nuclei. A cut is placed in the posterior part to reveal a representative cross section. Some of the important ascending afferents are also shown. To prevent obscuring the dorsal thalamus, only the rostral tip of the thalamic reticular nucleus (TRN) is shown. Other abbreviations: A, anterior; BG, basal ganglia; Cer, cerebellum; CM, centromedian; IL, intralaminar nuclei; IML, internal medullary lamina; LD, lateral dorsal; LL, lateral lemniscus; LP, lateral posterior; LGN, lateral geniculate nucleus; MGN, medial geniculate nucleus; MD, mediodorsal; MI, midline nuclei; ML, medial lemniscus; OT, optic tract; P, pulvinar; SN5, main sensory and spinal nuclei of the 5th nerve; ST, spinothalamic; VA, ventral anterior; VL, ventrolateral; VPL, ventral posterolateral; VPM, ventral posteromedial. See Jones (1985) for details of connectivity of these nuclei. [Redrawn from Brodal, 1981, with permission.]

Table 8.1. Thalamic Nuclei Relaying Subcortical Inputs

Nucleus	Major subcortical input	Projection
Pulvinar (Pu)*	Superior colliculus, pretectum	Visual cortex (dense)
Medial Geniculate Nucleus (MGN)	Lateral lemniscus	Auditory cortex (dense)
Lateral Geniculate Nucleus (LGN)	Optic tract	Visual cortex (dense)
Midline Nuclei (MI)	Spinal cord, cerebellum, basal ganglia	Cortex (diffuse) and basal ganglia
Central Medial Nucleus (CM)	Spinal cord, cerebellum, basal ganglia	Cortex (diffuse) and basal ganglia
Intralaminar Nuclei (IL)	Spinal cord, cerebellum, basal ganglia	Cortex (diffuse) and basal ganglia
Medial Dorsal Nucleus (MD)	Olfactory cortex, amygdala	Frontal cortex (diffuse)
Ventral Medial Nucleus (VM)	Substantia nigra	Cortex (diffuse)
Ventral Posteromedial Nucleus (VPM)	Trigeminal nerve	Somatosensory cortex (dense)
Ventral Posterolateral Nucleus (VPL)	Medial lemniscus	Somatosensory cortex (dense)
Posterior Nuclei (Po)	Superior colliculus, spinal cord	Insular cortex (dense)
Lateral Dorsal Nucleus (LD)	Fornix	Cingulate cortex (dense)
Ventral Lateral Nucleus (VL)	Cerebellum	Motor cortex (dense)
Ventral Anterior Nucleus (VA)	Cerebellum, basal ganglia	Cortex (diffuse)
Anterior Nuclei (A)	Subiculum, mammilary body	Olfactory cortex (dense)

Parenthetic abbreviations refer to locations of the nuclei in Fig. 8.1.

many, and perhaps all, of these nuclei have unique functional correlates, with specific input and output routes. Three generalizations can be made about these connections. First, all dorsal thalamic nuclei project to neocortex, but some tend to project *diffusely* to large, ill-defined cortical regions, terminating largely in layer 1 of cortex, while others project *densely* to more restricted, well-defined regions, terminating mostly in layer 4 (see Table 8.1). Second, these outputs of dorsal thalamic nuclei are limited to the same hemisphere, since no contralateral efferent connections involving any thalamic nucleus have been found. Third, no connections between dorsal thalamic nuclei have yet been described.

An exhaustive survey of all dorsal thalamic nuclei is beyond the scope of this chapter (for a more thorough account, see Jones, 1985), but examples of the best-studied nuclei follow. The *lateral geniculate nucleus* (LGN) relays input from the retina to visual cortex. There are two LGN divisions: the dorsal division, which is part of the dorsal thalamus, projects to cortex, and, unless otherwise specified, is what we mean by "LGN"; and the ventral division, which is part of the ventral thalamus and also receives retinal input but projects only subcortically, mostly to the midbrain. The *medial geniculate nucleus* (MGN) receives auditory input from the *inferior colliculus* and projects to auditory cortex. The *ventral posterolateral nucleus* (VPL) transmits somatosensory input from the body, providing the cortex with information about touch, pressure, joint position, temperature, and pain; its contiguous companion is the *ventral mediolateral nucleus* (VPM), which transmits somatosensory information from the head. The VPL receives ascending input from the spinal cord and dorsal column nuclei in the medulla, while the VPM receives input from the 5th cranial nerve via the main sensory and spinal nuclei of this nerve. The *basal ventral medial nucleus* receives gustatory input relayed from the pons and projects to primary somatosensory cortex. The *ventral lateral nucleus* receives most of its input from the deep cerebellar nuclei and projects to primary motor cortex. The *ventral anterior nucleus* is innervated by the basal ganglia and projects both to motor cortex and the basal ganglia. The *pulvinar* is a particularly interesting example. It has several divisions, and these are not yet completely understood or agreed upon. Much of its primary input that is related to cortex emanates from the superior colliculus and the pretectum, but another important source of such input derives from cortex itself. This relay of cortical information back to cortex exemplifies a newly appreciated type of thalamic nucleus; this is considered more fully near the end of this chapter.

THE LGN AS THE PROTOTYPICAL THALAMIC NUCLEUS

At the level of synaptic circuitry, more is known about the LGN than about any other thalamic structure, and this nucleus has been more thoroughly studied in the cat than in any other species. It seems likely that many of the organizational principles of the cat's LGN apply generally to other dorsal thalamic nuclei across mammals, although our present knowledge of most other such nuclei is too sparse for us to be completely comfortable with this generalization. Nonetheless, many of the specific examples for the functional organization of the thalamus derive from the cat's LGN, and most of the discussion of thalamus below refers to the LGN. It is thus worth briefly introducing this nucleus to the reader.

Figure 8.2 illustrates the laminar patterns of the cat's LGN (see Sherman and Spear, 1982; Sherman, 1985; Sherman and Koch, 1986). It is comprised of several laminae, most of which are innervated by one or the other retina. In addition to the segregation based on ocular origin, axons from neighboring retinal loci innervate neighboring geniculate zones, thereby setting up an orderly point-to-point map of visual space within the LGN. This is known as a *retinotopic map*, and analogous maps representing other sensory modalities exist within other thalamic nuclei, such as the VPL, VPM, and MGN (Jones, 1985). Most is known about the *A-laminae* (laminae A and A1) of the LGN, which form a reasonably matched pair, with lamina A innervated by the contralateral retina and lamina A1 innervated by the ipsilateral retina. The other main geniculate zones are the C-laminae and medial interlaminar nucleus, which, despite its name, is really just a part of the LGN. For details of these other LGN regions in the cat and how this relates to LGNs in other species, the reader can consult various reviews (Sherman and Spear, 1982; Stone, 1983; Sherman, 1985; Shapley and Perry, 1986; Hendry and Yoshioka, 1994; Casagrande and Norton, 1996); the remainder of our treatment will be limited to the A-laminae of the cat.

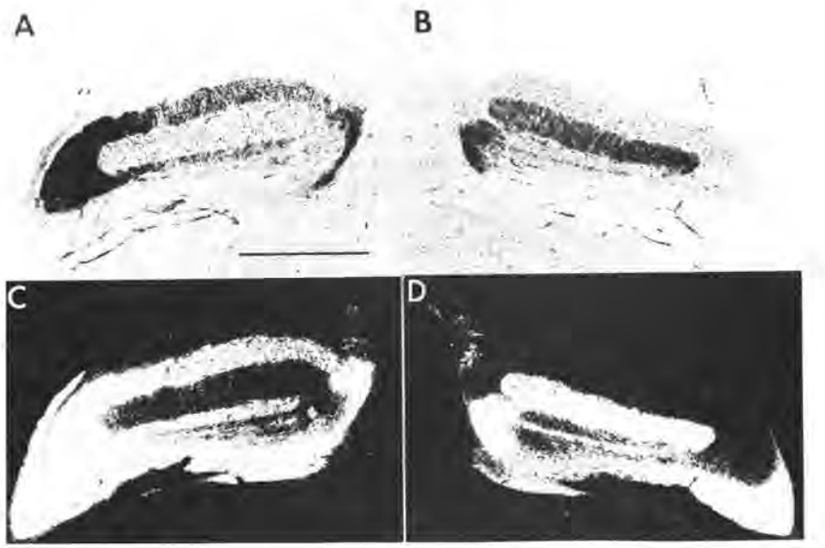

Fig. 8.2. Photomicrographs of left (**A,C**) and right (**B,D**) LGN of the cat as seen in coronal view near the middle of the nucleus. The sections were treated for autoradiography after retinogeniculate terminals from the right eye were labeled by injecting that eye with tritiated proline. The labeled terminals are dark, and this permits visualization of the various laminae innervated by one or the other eye. Lamina A is innervated by the contralateral eye, and lamina A1, by the ipsilateral eye. Lamina A is the most dorsal lamina, and lamina A1 is just beneath it. Thus the left lamina A and right lamina A1 are dark due to the autoradiographic labeling of terminals from the right eye. Other laminar zones below and medial to the A-laminae can also be seen, but these are not considered further here (see Sherman, 1985; for a fuller account of these laminae.) Although not labeled, the TRN lies just above lamina A. A,B, bright-field, C,D dark-field photomicrographs. [Revised from Sherman, 1985, with permission.]

NEURONAL ELEMENTS OF THE THALAMUS

The neuronal elements of the thalamus can be divided into three components: the *extrinsic afferent inputs* to the nucleus, the *relay cells* (or principal neurons) that project to cortex, and the *interneurons* (or intrinsic neurons).

INPUTS

Figure 8.3 schematically illustrates the major afferents for a typical dorsal thalamic nucleus. We can divide the inputs into two broad classes: *driving* and *modulatory* inputs. The driving input represents the primary information to be relayed to cortex, such as retinal input to the LGN. The modulatory input is all other input, and this serves to modulate or control the relay of information from the driving input to cortex. Modulatory input can be further subdivided into cortical modulatory inputs and brainstem modulatory inputs. Seen in this perspective, the retinal or driving afferents to LGN relay cells are one class among several and, at least in terms of number of synapses formed on these relay cells, are a minority input. The modulatory afferents include long pathways from the cortex and brainstem plus local inputs from TRN cells and interneurons. Figure 8.3 indicates both the inputs to thalamus and the neurotransmitters they use, but we shall return later to consider neurotransmitters and postsynaptic receptors in more detail.

Retinal or Driving Afferents. The driving input is the best characterized input to a dorsal thalamic nucleus. This input is glutamatergic, meaning it uses the amino acid glutamate or a similar compound as a neurotransmitter (Kemp and Sillito, 1982; Moody and Sillito, 1988; Salt, 1988; Scharfman et al., 1990; Kown et al., 1991; Salt and Eaton, 1996). For the LGN, this input arises from the ganglion cells of the retina, whose axons form the *optic nerve* and *tract*. The number of retinogeniculate axons from each retina varies with species; it is slightly under 100,000 in cats and is roughly 1 million in monkeys and humans (Rakic and Riley, 1983; Williams et al., 1983). Comparable input to the VPL and MGN derives, respectively, from the *medial lemniscus* and *lateral lemniscus*.

In cats, the retinal ganglion cells that innervate the A-laminae can be divided into two physiologically and morphologically distinct classes: *X cells* (also known as *β cells*) and *Y cells* (also known as *α cells*). See Chap. 6 for a fuller account of these and other retinal ganglion cell classes. Most details of the differences in morphology and receptive fields of X and Y cells do not concern us here (for details, see Sherman and Spear, 1982; Stone, 1983; Rodieck and Brening, 1983; Shapley and Lennie, 1985; Sherman, 1985, 1988), but subtle differences in the sort of visual information they carry do exist. This exemplifies an important principle for thalamic relays: the same nucleus can relay different sorts of signals to cortex in parallel. Other mammals, including primates, have comparable retinal ganglion cell classes (Stone, 1983; Rodieck and Brening, 1983; Shapley and Lennie, 1985; Sherman, 1985, 1988; Levey et al., 1987). Such parallel processing seems to be a feature of all sensory systems (Sherman and Spear, 1982; Stone, 1983; Dykes, 1983; Rodieck and Brening, 1983; Jones, 1985; Shapley and Lennie, 1985; Sherman, 1985, 1988). Every X and Y cell innervates the LGN and branches to innervate other targets in the midbrain (Bowling and Michael, 1984; Sur et al., 1987; Tamamaki et al., 1994). Furthermore, within the LGN, these retinal cell types each innervates a unique geniculate cell type, thereby establishing relay X and Y classes of geniculate cells and parallel, functionally distinct X and Y pathways.

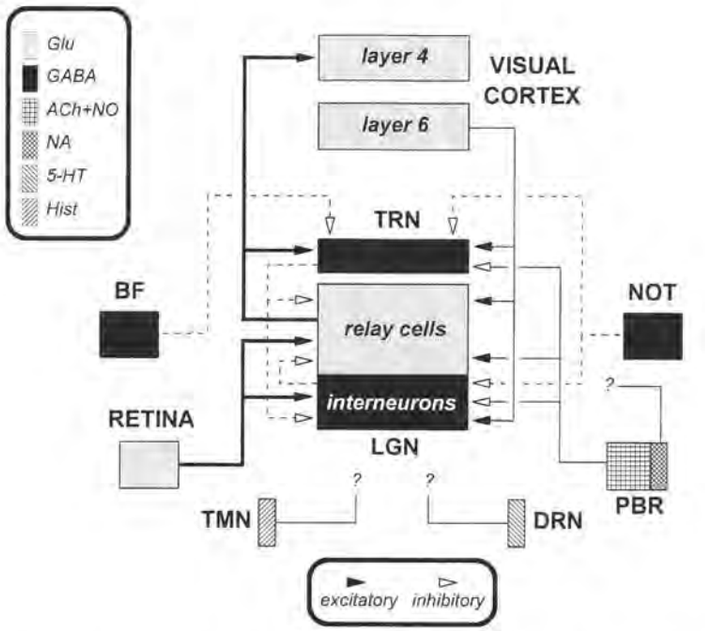

Fig. 8.3. Schematic summary of main inputs to thalamic relay cells, using the LGN as a prototypical example. The main sensory input arrives from retina via the optic tract. Local GABAergic inhibitory input is provided by interneurons and cells of the thalamic reticular nucleus (TRN). Other main inputs emanate from layer 6 of visual cortex, from the parabrachial region (PBR), from the dorsal raphé nucleus (DRN), from the tuberomamillary nucleus (TMN) of the hypothalamus, from the basal forebrain (BF), and from the nucleus of the optic tract (NOT). The key indicates the neurotransmitters used by the various inputs: Glu, glutamate; GABA, γ-aminobutyric acid; ACh, acetylcholine; NO, nitric oxide; NA, noradrenaline; 5-HT, serotonin; Hist, histamine. [Redrawn from Sherman and Koch, 1986, with permission.]

Cortical Afferents. A major input to thalamus originates among layer 6 pyramidal cells of the cortex (see Fig. 8.3). In fact, there seems to be at least an order of magnitude of more corticothalamic axons than thalamocortical ones. Thus in cats roughly 4,000,000 axons from visual cortex innervate the geniculate relay cells of the A-laminae (Sherman and Koch, 1986). Each cortical axon innervates many thalamic neurons, thereby establishing considerable divergence and convergence in the corticothalamic pathway. Like retinal (or driving) axons, these cortical axons are excitatory and appear to be glutamatergic (Giuffrida and Rustioni, 1988; McCormick and Von Krosigk, 1992; Montero, 1994). Strong reciprocity exists in thalamocortical connections, because the cortical input for each thalamic nucleus generally, but not always, originates from the same cortical area

that is innervated by the thalamic nucleus in question. Thus for the LGN, this cortical pathway emanates from visual cortex (mostly areas 17, 18, and 19), and roughly half of these layer 6 cells contribute to the corticogeniculate pathway. Likewise, somatosensory and auditory cortex project back, respectively, to the VPL and MGN.

The corticothalamic pathway faithfully adheres to the map established in the thalamic nucleus (see above). For instance, the corticogeniculate pathway conforms to the retinotopic map in the LGN. However, there is some question as to the precision of this map due to recent evidence that, in the cat, the spread of an individual corticogeniculate axon arbor can be quite extensive, having a maximal extent of 1.5 mm, although the central core is about 0.4–0.5 mm in diameter, which was taken to mean that each geniculate cell can be influenced by events far outside its classical receptive field (Murphy and Sillito, 1996). However, due to two other features of relay cells, it is also possible that individual corticogeniculate arbors even up to 1–2 mm across might still represent precise retinotopic connections. First, the dendritic arbor of a typical relay cell can have a diameter of roughly 0.4–0.5 mm. Since the corticogeniculate terminals contact peripheral dendrites, a single cortical axon contacting a single relay cell would have a terminal arbor of 0.4–0.5 mm across. However, it is likely that each corticogeniculate axon contacts many relay cells, and this raises the second point. Sanderson (1971) showed that relay cells representing the same receptive field location in visual space are not located along a single "projection" line through the LGN but rather scatter around that line with a spread of perhaps 1–2 mm, depending on the location of the receptive fields within the visual field. Thus a single corticogeniculate axon contacting many relay cells with closely matched receptive field locations might well spread up to 1–2 mm across, thereby adhering to an accurate and precise retinotopic map.

Another issue related to the corticogeniculate (and thus corticothalamic) feedback concerns the precision of these retinotopic patterns. Only a subset of pyramidal cells in layer 6 actually comprises the corticogeniculate pathway, the remainder innervating the claustrum, and these corticogeniculate cells tend to be located in the top half of layer 6 (Lund et al., 1975; Katz, 1987; Usrey and Fitzpatrick, 1996). These layer-6 corticogeniculate cells also project into that part of layer 4 that is supplied by geniculocortical input (Lund et al., 1975; Usrey and Fitzpatrick, 1996), implying that these layer 6 cells not only control the relay of information through LGN but may also modulate the flow of LGN input into cortex. It is interesting that, unlike some other intrinsic cortical circuits, the layer 6 projection to layer 4 is very limited in horizontal extent (Katz, 1987), thereby limiting the retinotopic spread of information. This allows for information to cycle between the visual cortex and the LGN in a precise retinotopic manner, allowing for the establishment of reverberatory loops.

Finally, corticogeniculate neurons seem to be heterogeneous and probably represent several functional classes (Tsumoto and Suda, 1980; Katz, 1987), although they have not yet been properly classified and it is not clear to what extent other corticothalamic pathways contain functional subsets of axons.

Brainstem Afferents. Other inputs to the thalamus emanate from various brainstem sources. The mix and relative strength of these brainstem inputs can vary both with species as well as with specific thalamic nuclei (Fitzpatrick et al. 1989). Afferents from the pons and midbrain (see Fig. 8.3) include cholinergic neurons (i.e., using acetylcholine as a neurotransmitter) of the *parabrachial region* (the cells of origin are located near the brachium conjuctivum; this is also known as the *pedunculopontine tegmental nucleus*), noradrenergic neurons (i.e., using noradrenalin; also known as *norepinephrine*) of the *locus coeruleus*, and serotonergic neurons (i.e., using serotonin) of the *dorsal raphé nucleus*. These inputs can either excite or inhibit thalamic neurons (see Chap. 2 and below). By far the most numerous of these inputs to the lateral geniculate nucleus of the cat is the cholinergic input, representing perhaps 90% of the brainstem input (Smith et al., 1988; Bickford et al., 1993). In many species, the cholinergic cells of the parabrachial region or pedunculopontine tegmental nucleus and noradrenergic cells of the locus coeruleus are distinct and separate. In others, such as the cat, they overlap extensively. Thus while the cells can be distinguished by their neurotransmitters, they may not always occupy distinct and separate nuclei.

Figure 8.3 also indicates other smaller and less well-studied brainstem inputs (Harting et al., 1986; Fitzpatrick et al., 1988; Cucchiaro et al., 1991, 1993; Uhlrich et al., 1993; Bickford et al., 1994). The *tuberomammilary nucleus* of the hypothalamus provides a histaminergic input. A GABAergic input (i.e., it uses γ-aminobutyric acid, or GABA, as a neurotransmitter) exists from the *basal forebrain* to the TRN, and while this input does not directly innervate dorsal thalamus, it can influence relay properties indirectly through the TRN. Finally, the LGN receives additional, although sparse brainstem inputs that may be unique to the visual pathways. These include afferents from the *superior colliculus* and *parabigeminal nucleus* of the midbrain and from the pretectal *nucleus of the optic tract* (NOT). The parabigeminal input is cholinergic, that for the pretectum is GABAergic, and that for the superior colliculus is thought to be glutamatergic. There is evidence that the GABAergic input from the NOT does not innervate relay cells directly but instead innervates TRN cells and interneurons, which would presumably disinhibit relay cells.

Inputs From the TRN. A final extrinsic source of innervation to each dorsal thalamic nucleus derives from the TRN (Jones, 1985; Ohara and Lieberman, 1985; Cox et al., 1996; Sherman and Guillery, 1996). The TRN forms a shell anteriorly and dorsally around the dorsal thalamus (see Fig. 8.1). Generally, each dorsal thalamic nucleus (e.g., the LGN, VPL, MGN, etc.) has a subnucleus of the TRN associated with it, and reciprocal connections are formed between them (Jones, 1985; Sherman and Guillery, 1996). That is, relay cell axons en route to cortex pass through the appropriate TRN zone, where they emit collateral terminals, and the TRN cells in turn project axons back into the dorsal thalamic nucleus. Figure 8.4D shows a representative TRN cell. It is worth noting that corticothalamic axons from layer 6 also pass through the appropriate TRN zone en route to their thalamic destination, and they also provide collateral innervation to these TRN cells. (However, see below for the pattern for layer 5 corticothalamic axons.) Finally, the TRN is also innervated by the same regions of brainstem that innervate the dorsal thalamus. The TRN cells are GABAergic and inhibit their dorsal thalamic targets.

RELAY NEURONS

Relay (or projection) neurons, which represent roughly 75% of the cells in most thalamic nuclei (but see below), are the only output of a dorsal thalamic nucleus. They

project to cortex with a collateral innervation of the TRN en route. Relay cells in intralaminar thalamic nuclei also project to the basal ganglia (see Fig. 8.1 and Table 8.1). An important feature of thalamic nuclei is that different classes of relay cell can exist within a nucleus to provide parallel streams of thalamocortical relay through each nucleus (Stone, 1983; Dykes, 1983; Rodieck and Brening, 1983; Jones, 1985; Sherman, 1985). This feature is best appreciated in the A-laminae of the cat's LGN and is considered in more detail below. However, other processing streams exist in other portions of the cat's LGN and in other thalamic nuclei and in other species.

X and Y Cells. Roughly 300,000 relay cells reside in each of the A-laminae of the cat's LGN (Sanderson, 1971); relay X and Y cells are illustrated in Fig. 8.4A,B. These are fairly representative of thalamic relay cells in other nuclei. The relay X cells receive retinal input nearly exclusively from β cells, and the relay Y cells, from α cells (see Chap. 6 for a description of these retinal ganglion cell types; see also Sherman and Spear, 1982; Stone, 1983; Rodieck and Brening, 1983; Shapley and Lennie, 1985; Sherman, 1985). It is likely that a similar relationship holds for other species as well, although knowledge of relay cell types and their retinal inputs is not as complete as for the cat. For example, in the monkey's (and human's) LGN, the main laminae are divided into a dorsal set of smaller cells known as the *parvocellular* laminae, and a ventral set of larger cells known as the *magnocellular* laminae. These laminae are innervated by distinct retinal cell types (see Chap. 6): $P\beta$ (for primate β; also known as P for parvocellular) innervate the parvocellular laminae, and $P\alpha$ (for primate α; also known as M for magnocellular) innervate the magnocellular laminae. Although there is still considerable debate on the subject, it seems likely that the parvocellular and magnocellular pathways are homologous, respectively, to the X and Y pathways in the cat. It also seems likely that comparable and perhaps homologous pathways exist for other species as well (Stone, 1983; Rodieck and Brening, 1983; Shapley and Lennie, 1985; Sherman, 1985; Irvin et al., 1993; Hendry and Yoshioka, 1994).

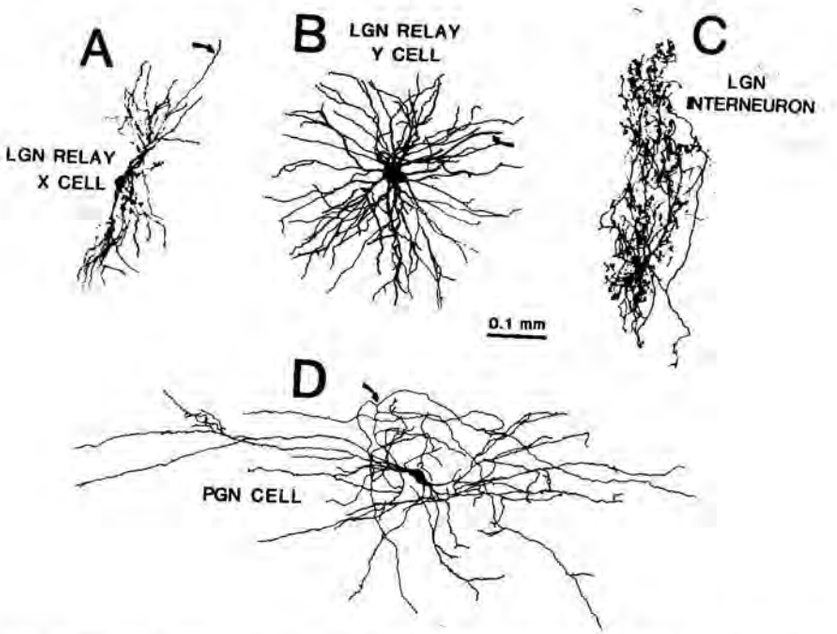

Fig. 8.4. Tracing of four representative neurons from the cat's LGN and TRN. Each of the cells was first studied physiologically and then labeled intracellularly with horseradish peroxidase. Where obvious, the axon is indicated by an arrow. **A:** Relay X cell. **B:** Relay Y cell. **C:** Interneuron. **D:** TRN neuron from the perigeniculate nucleus (PGN), a part of the TRN. [Redrawn from Sherman and Koch, 1986, with permission.]

The projection of relay cells concentrates in layer 4 of the cortical target area, with a smaller terminal zone in layer 6. In the cat, geniculate cells of the A-laminae project both to cortical areas 17 (striate cortex or V1) and 18 (V2). The relay X cells project exclusively to area 17, while the relay Y cells project to both areas. However, the homologous relay cells in primates project only to area 17. Similar relationships hold for other thalamic nuclei, since multiple projections from VPL to somatosensory cortex and MGN to auditory cortex have been described.

Lagged and Nonlagged Cells. Mastronarde (1987) described a new type of relay cell in the cat's LGN, which he termed *lagged*, and this is distinguished from the conventional type, called *nonlagged*. This new classification has received considerable attention (Humphrey and Weller, 1988; Saul and Humphrey, 1990, 1992; Heggelund and Hartveit, 1990; Lu et al., 1995). Essentially, nonlagged cells retain the same basic receptive field properties of the input retinal X or Y axons; they respond briskly and with short latency to visual stimuli. Lagged cells respond more sluggishly and with longer latency. One suggestion is that these represent two different temporal relay channels that can be used by cortex to create such features as directional selectivity for moving stimuli (Saul and Humphrey, 1990, 1992), but the specific significance of these cell types remains unclear (Lu et al., 1995). It is also not yet clear the extent to which lagged and nonlagged cell types are seen in other species or in other thalamic nuclei. Nonetheless, this observation of lagged and nonlagged relay cells holds promise to become a key feature of thalamic relays.

INTERNEURONS

Roughly 25% of the cells in most thalamic nuclei are local interneurons. However, as an example of the bewildering variation in relative numbers of relay cells and interneurons, the cat's LGN and VPL plus the rat's LGN have roughly a 3-to-1 relay cell-to-interneuron ratio, but the rat's VPL and other thalamic nuclei have practically no interneurons (Ohara et al., 1983; Ralston, 1983; Spreafico et al., 1983; Fitzpatrick et al., 1984; Jones, 1985). Thus analogous nuclei in the same animal (e.g., the rat's LGN and VPL) can vary in this regard, as can homologous nuclei across species (e.g., the VPL of cats and rats). Arcelli et al. (1997), in a recent study of the variation of GABAergic interneurons across nuclei and species, argued that this variation could be an index of "complexity" in the evolution of intrathalamic processing.

Interneurons have been best described for the LGN, but they seem basically similar in other thalamic nuclei. Geniculate interneurons have small cell bodies with long, thin, and sinuous dendrites (Fig. 8.4C). The dendrites are notable for giving rise to bulbous

appendages connected to the stem dendrite by long (10 μm or more), thin (usually less than 0.1 μm in diameter) processes; these appendages usually occur in clusters. Overall, the dendrites with their bulbous appendages look like the terminal arbor of an axon, and thus Guillery (1966) referred to these dendrites as *axoniform* in appearance. In fact, these bulbous appendages represent a major synaptic output of the cell, since they are synaptic terminals that are both presynaptic and postsynaptic to other elements in the geniculate neuropil (Guillery, 1969a,b; Ralston, 1971; Famiglietti and Peters, 1972; Hamos et al., 1985; Ralston et al., 1988). Most of the synapses from interneurons are thus dendritic in origin.

These interneurons usually have a conventional axon that arborizes locally, typically within the dendritic arbor (Hamos et al., 1985; Montero, 1987), although axonless interneurons may exist (Ralston et al., 1988). In the cat's LGN, interneurons seem to be mostly associated with the X pathway, since they receive retinal input only from X axons, and their dendritic outputs contact mostly only relay X cells (Sherman and Friedlander, 1988). Evidence for interneuronal influences on relay Y cells also exists (Lindström, 1982), and this may reflect the axonal output. All interneurons are GABAergic, and both their dendritic and axonal outputs inhibit their postsynaptic targets.

As noted above, the TRN is a source of nonretinal or modulatory afferents to the dorsal thalamus. TRN cells do not project beyond the thalamus and instead provide local, GABAergic, inhibitory input to thalamic relay cells. They are thus functionally in many ways similar to interneurons, and many investigators group them with interneurons as local inhibitory cells. It is not yet clear what, if any, fundamentally different role in the relay of driving inputs is played by the TRN cells and interneurons.

SYNAPTIC CONNECTIONS

TYPES OF SYNAPTIC TERMINAL

The synaptology of both relay cells and interneurons has been described on the basis of electron microscopic studies. Most of these studies have concentrated on the LGN and VPL with rather similar results (Guillery, 1969a,b; Wilson et al., 1984; Hamos et al., 1985; Jones, 1985; Montero, 1987; Ralston et al., 1988). The following description derives from the A-laminae of the LGN.

Four major types of synaptic terminal exist there (Guillery, 1969a,b), and their origins are for the most part known. *RLP* terminals (*r*ound vesicles, *l*arge profiles, and *p*ale mitochondria) form asymmetrical synapses. They derive from retina and are glutamatergic. While it had been thought that perhaps 10–20% of all terminals in the LGN are retinal in origin, newer evidence suggests that this percentage may be much smaller (Van Horn et al., 1997). *RSD* terminals (*r*ound vesicles, *s*mall profiles, and *d*ark mitochondria) also form asymmetrical synapses and are the most numerous, comprising roughly half of all terminals. Roughly half of the RSD terminals derive from cortex and are glutamatergic, and roughly half derive from brainstem sources (Erişir et al., 1997b). Most of these brainstem terminals are cholinergic, although some are noradrenergic or serotonergic. A few (probably less than 5%) of the terminals that otherwise resemble RSD terminals are relatively large and might be considered to be *RLD* terminals (*r*ound vesicles, *l*arge profiles, and *d*ark mitochondria). These mostly emanate from the parabrachial region of the midbrain and are cholinergic. *F* terminals

(*f*lattened vesicles) form symmetrical synapses and represent a little more than one quarter of the terminals in the LGN. These are GABAergic. Two subtypes, *F1* and *F2*, have been recognized. Although a constellation of features can distinguish them, the most salient are that F1 terminals derive from axons and are strictly presynaptic, whereas F2 terminals are dendritic in origin and are both presynaptic and postsynaptic. F1 terminals arise from axons of TRN cells, interneurons, and, in the case of LGN, from axons of NOT cells; F2 terminals derive from dendrites of interneurons.

INPUTS TO RELAY CELLS

Reconstructions at the electron microscopic level reveal that geniculate relay cells in the cat receive roughly 4000 synapses, nearly all onto their dendrites with rare contacts on their somata (Wilson et al., 1984). Figure 8.5 schematically summarizes the

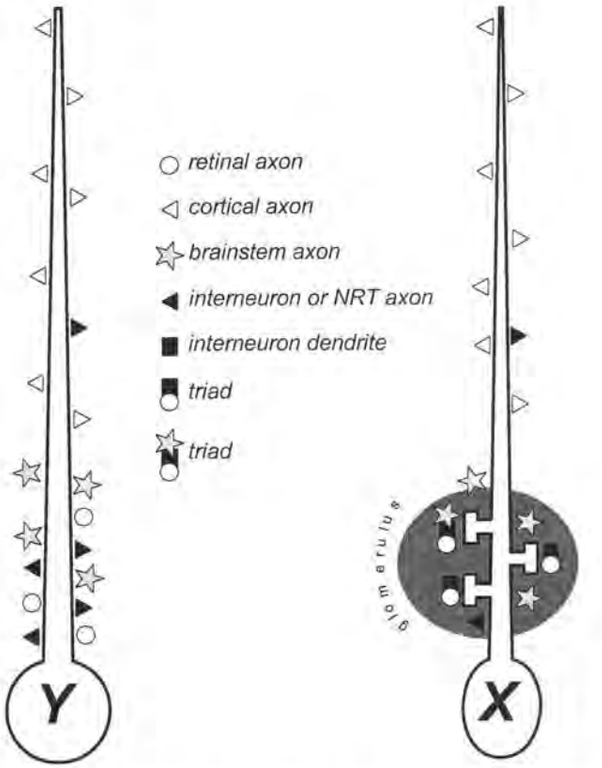

Fig. 8.5. Schematic representation of the distribution of synaptic terminals onto a typical dendrite of a relay X and Y cell. For simplicity, only a single, unbranched dendrite is shown for each neuron. Each type of synaptic terminal, as well as the synaptic triad, is indicated by a unique symbol. The density (synapses/μm of dendritic length) of each terminal type is also represented by the relative number of synaptic terminals. Dendritic appendages are denoted by the T-shaped attachments to dendrites, and the glomerulus related to the X cell is shown. See text for details. [Redrawn from Wilson et al., 1984, with permission.]

distribution of various types of synaptic input on the dendritic arbors of these relay X and Y cells. Relay cells in other thalamic nuclei probably have a comparable pattern of synaptic inputs. For both relay X and Y cells, inputs from retinal and F terminals concentrate in the proximal region of the dendritic arbor, whereas cortical RSD input dominates distal dendrites, and there is little or no overlap in these zones (Erişir et al., 1997a). Parabrachial RSD and RLD terminals are found proximally, among retinal terminals. However, major differences between relay X and Y cells exist in the types of F terminal present and in the detailed nature of the retinal input. To explain these differences, first a description of the *glomerulus* and the *synaptic triad* is required.

A glomerulus is a complex synaptic structure (Fig. 8.6). Glomeruli seem to be related to interneurons, and it is interesting that the rat's VPL, which lacks interneurons (see above), also lacks glomeruli (Ralston, 1983). For the A-laminae of the cat's LGN, glomeruli include a major set of inputs to proximal dendrites of relay X cells, but they associate rarely with the Y pathway (Wilson et al., 1984; Sherman, 1988; Sherman and Friedlander, 1988). Glomeruli are common in other thalamic nuclei, but the pattern of specificity for functional types outside of the LGN is presently unknown (Jones, 1985; Ralston et al., 1988). Glomeruli have terminals of all four types noted above, and these terminals interrelate with each other in a complex arrangement. Virtually all glomeruli in the LGN include a retinal terminal, which is typically located at or near the glomerular center and is surrounded by a number of other terminals. Thus the glomerulus represents an important morphological feature of retinogeniculate transmission. Other common terminals found in glomeruli are F terminals (both F1 and F2) and terminals from brainstem. Cortical terminals rarely if ever innervate glomeruli (Erişir et al., 1997a).

This retinal terminal in the glomerulus contacts two different postsynaptic elements: an F2 terminal that derives from dendritic appendages of interneurons, and a dendrite (or its appendage) of a relay X cell. The retinal terminal usually contacts several F2 terminals within a glomerulus, and all of the synapses formed by the retinal terminal are asymmetrical. The interneuron's F2 terminals, in turn, make symmetrical synaptic contacts onto the same postsynaptic element of the relay X cell, be it dendritic appendage or shaft, contacted by the retinal terminal. Since three terminal types are involved, this special neuronal circuit within the glomerulus is known as a *triad* (for a detailed hypothesis concerning the role of these triadic circuits, see Koch, 1985). Figure 8.7 illustrates a triad involving RLP and F2 terminals and a dendritic appendage of a relay X cell. A retinal terminal is usually the common presynaptic element in the triad, but occasionally other terminals, such as those from the brainstem, can serve this function. Both a retinal terminal and brainstem axon can

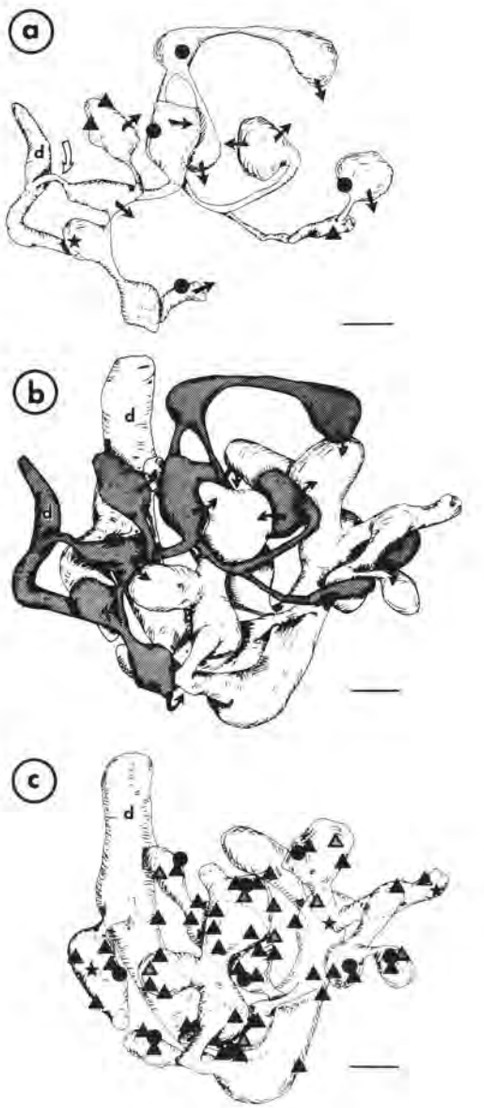

Fig. 8.6. Reconstruction of a glomerular zone in the geniculate A-laminae of the cat's LGN, showing the F2 terminals from an intracellularly labeled interneuron, the postsynaptic cluster of appendages from a relay X cell, and the location of synaptic contacts; each scale bar represents 1.0 μm. **a:** Labeled processes from the interneuron. A thin stem dendrite (d) emits an extremely fine process (open arrow) that arborizes into 12 F2 terminals connected by extremely fine processes. These terminals are postsynaptic to retinal or RLP terminals (circles), unlabeled F terminals (triangles; most or all of these may be F1 terminals, but they were not sufficiently reconstructed to be certain), and an RSD terminal (star). The labeled F2 terminals also form synaptic outputs (solid arrows). **b:** Combined reconstruction of the labeled interneuron's processes from a (stippled area) and unlabeled postsynaptic processes from c (open area). The synapses from the F2 terminals onto the relay X cell's appendages are illustrated (solid arrows; these represent the same solid arrows as in a). **c:** Unlabeled postsynaptic dendrite (d) from a relay X cell with 8 appendages that receive all of the neuron's synaptic input in the reconstructed zone. These include 9 synapses from RLP or retinal terminals (circles), 9 from F2 terminals of the labeled interneuron (stippled triangles; these correspond to the solid arrows in a and b), 40 from unlabeled F terminals (solid triangles), and 3 from RSD terminals (stars). The 16 triadic synaptic arrangements are illustrated by overlapping pairs of symbols for synapses from RLP and F terminals. [From Hamos et al., 1985, with permission.]

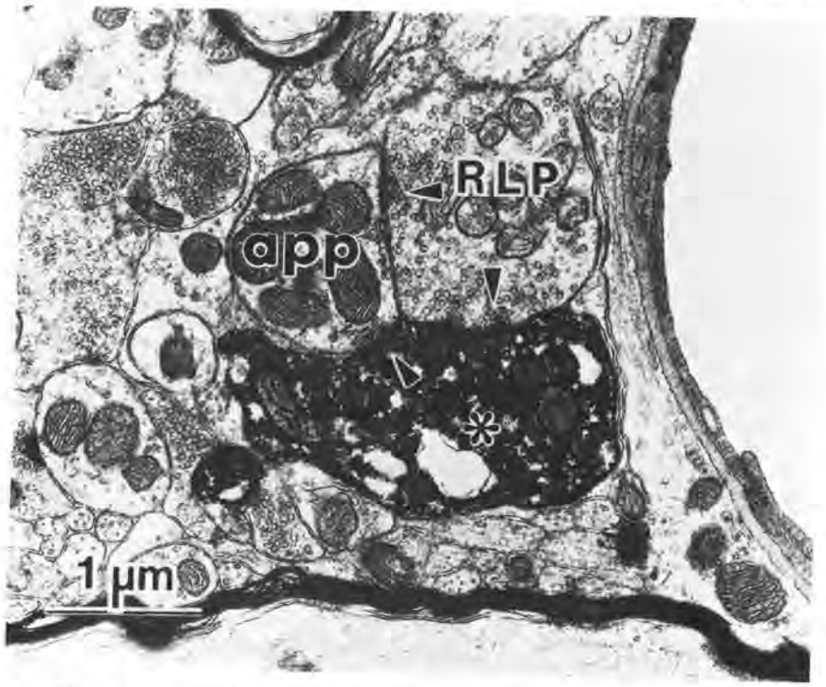

Fig. 8.7. Electron micrograph of a triadic synaptic relationship from the A-laminae of the cat's LGN. An interneuron was labeled with horseradish peroxidase, which creates an electron-dense reaction product, and its labeled F2 terminal is dark in this micrograph. A retinal terminal (RLP) contacts both the labeled F2 terminal and the dendritic appendage (app) of a relay X cell. The labeled F2 contacts the same appendage. Synaptic contacts are indicated by arrowheads. Scale: 1.0 μm.

share the same F2 terminal and postsynaptic relay X cell process in triadic circuitry within a glomerulus.

The vast majority of retinal input to relay X cells is filtered through this complicated circuitry of the glomerulus. Retinal input to relay Y cells is simpler and involves conventional asymmetrical synapses onto proximal dendritic shafts (Wilson et al., 1984; Sherman, 1988). F2 terminals are nearly always limited to glomeruli, and the lack of glomeruli associated with the Y pathway results in very few such terminals contacting relay Y cells. More than 90% of the F input to these cells is of the F1 variety, while roughly two-thirds of F input onto relay X cells is of the F2 variety.

INPUTS TO INTERNEURONS

As with our previous examples, most of our detailed knowledge of interneurons stems from studies of the LGN, but comparable studies in other thalamic nuclei, especially the VPL, reveal basically similar properties for thalamic interneurons (Ralston et al., 1988). In the LGN, many retinal, RSD, and F1 terminals contact interneurons (Hamos et al., 1985). Much of this input is focused onto their dendritic appendages, which are

the presynaptic F2 terminals. Input is also formed onto dendritic shafts and somata, and these are the only geniculate neurons that seem to receive significant retinal input onto their somata.

BASIC NEURONAL CIRCUIT

Enough is known about the cat's LGN to provide a schematic circuit diagram, including a fair estimate of the numbers of neuronal elements present. Of course, many of the specific features of this diagram remain somewhat uncertain, but the broad outlines seem clear. It seems likely that these broad outlines apply as well to other thalamic nuclei.

COMPONENT POPULATIONS

Each of the A-laminae of the cat's LGN contain roughly 400,000 neurons (Sanderson, 1971). Of these, perhaps 300,000 are relay cells and 100,000 are interneurons. The interneurons have two outputs, the major one being dendritic via F2 terminals and the minor one being axonal via F1 terminals. The dendritic output of interneurons seems to target relay X cells nearly exclusively, but the target nature of the axonal output is unclear. Slightly more relay X cells (150,000–200,000) than relay Y cells (100,000–150,000) seem to exist (Sherman, 1985). These geniculate neurons are innervated by a slightly fewer than 100,000 retinogeniculate axons and by more than 4,000,000 corticogeniculate axons (Sherman and Koch, 1986), although the details of how these latter axons innervate relay X and Y cells plus interneurons are not yet clear. We also still lack estimates for the number of afferent axons from the TRN and various brainstem sites, and such estimates are only partly available for other species.

INTRINSIC CIRCUITRY

The basic organization of major inputs to the cat's LGN is summarized schematically in Fig. 8.8. Many of the details of this circuit, including the differences between the X and Y pathways, have been described above. These relay cells also receive input from cortex and from the brainstem. Major inhibitory input derives from local GABAergic cells, which are the interneurons and TRN cells. Both of these GABAergic cells are innervated by cortex and by the brainstem parabrachial region. In addition, TRN cells are innervated by axon collaterals from the relay cells, and interneurons receive input from retinal X axons. TRN cells also receive a GABAergic input from the basal forebrain. Not included for simplicity are lesser known and probably smaller inputs described above from the hypothalamus (histaminergic), pretectum (GABAergic), the parabrachial region or locus coeruleus (noradrenergic), and the dorsal raphé nucleus (serotonergic).

Although much of the circuitry outlined in Fig. 8.8 is sketchy, the following conclusions can be tentatively drawn. Much of this repeats earlier points, but it is offered here as a concise summary. Relay cells receive retinal input onto proximal dendrites in close association with GABAergic and parabrachial input. The GABAergic input derives from TRN cells and interneurons. Distal dendrites are dominated by cortical input, and, at least for LGN relay cells, these inputs are limited to dendritic locations more distal than those of retinal inputs (Guillery, 1969a,b; Wilson et al., 1984; Erişir

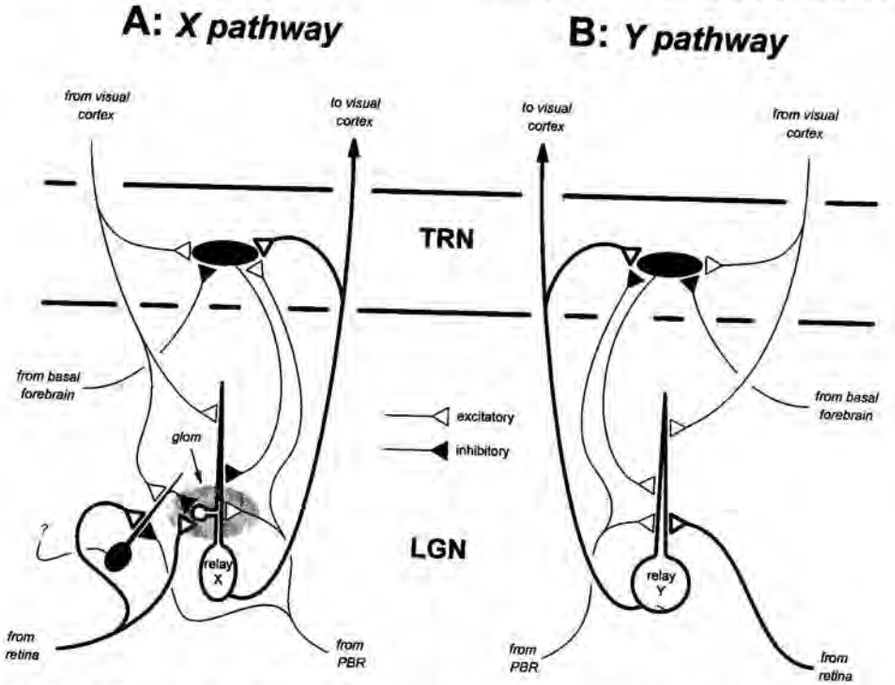

Fig. 8.8. Schematic view of X and Y circuits for the A-laminae of the cat's LGN. **A:** X pathway. Much of the input to relay X cells (open profile), including inputs from retina, from dendrites of interneurons (filled profile), from the thalamic reticular nucleus (TRN; filled profiles), and from the parabrachial region (PBR) is filtered through glomeruli (glom; stippled region). Retinal terminals engage in triadic relationships with terminals from the interneuron's dendrites and dendritic appendages on the relay cell. Cortical input dominates the peripheral dendrites of the relay cell. The interneuron is also innervated from retina, cortex, and the PBR; the target of the interneuron's axon remains unknown, except that it is extraglomerular. The TRN cell is innervated from geniculocortical axons, corticogeniculate axons, PBR axons, and axons from the basal forebrain. **B:** Y pathway. This pathway is much simpler, because interneurons do not appear to provide many inputs from their dendrites. The retinal axon contacts the relay cell (open profile) on proximal dendritic shafts among terminals from PBR axons. Other inputs to the relay and TRN cells are similar to that shown in A.

et al., 1997a). Some GABAergic inputs can also be seen on distal dendrites, although most are found proximally. However, the electrotonic compactness of relay cells implies that even the distal inputs can be quite important functionally.

Figure 8.8 also summarizes some differences between the X and Y pathways, and perhaps this can be taken as a reflection of the kinds of variation present throughout thalamic circuitry. Three main differences exist: the nature of retinal input, the presence of glomeruli, and the role of interneurons. Retinal input to relay Y cells is fairly straightforward, innervating proximal dendritic shafts in simple contact zones. Retinal input to relay X cells is much more elaborate, since it involves complicated triadic relationships that include dendritic terminals of interneurons. Glomeruli are also a major feature of X but not Y circuitry, and the glomerulus may be viewed as a major filter of retinogeniculate transmission (see above). Finally, interneuronal dendritic outputs also seem to be intimately related to X but not Y circuitry. The axonal targets of interneurons largely remain a mystery; however, the axons use F1 terminals and contact extraglomerular dendritic shafts, whereas the dendritic outputs use F2 terminals and contact dendritic appendages in glomeruli.

It should be emphasized that the circuit schematically represented by Fig. 8.8 is preliminary and greatly simplified. Many questions still remain. For example, what is the interrelated pattern of innervation involving single cortical axons, TRN cells (or interneurons), and relay cells? The implication of this last question is illustrated in Fig. 8.9 by showing two extremes of possible functional circuits involving inputs to relay cells and the local, GABAergic inhibitory cells. This adheres to our superficial knowledge of interconnections among these cell populations and makes the point that in many cases we still cannot even determine if activation of these circuits excites or inhibits relay cells. For instance, Fig. 8.9A shows a true feedback inhibitory circuit in which an axon collateral from a relay cell (cell b) excites a TRN cell (cell 2) that in turn inhibits this same relay cell. Figure 8.9B depicts a very different picture: now relay cell b excites TRN cells 1 and 3, but not 2, and TRN cells 1 and 3 do not inhibit relay cell b, but rather inhibit its neighbors (cells a and c). Since cells a and c excite the TRN cell (cell 2) that inhibits relay cell b, the net result of the circuit depicted in Fig. 8.9B is that activity in relay cell b results in its further *disinhibition*, which is precisely the opposite of the feedback inhibition resulting from Fig. 8.9A. Likewise, the circuits shown in Fig. 8.9C,D have opposite effects when the corticogeniculate axon is activated: that in Fig. 8.9C results in feedforward inhibition of relay cell b, while that in Fig. 8.9D results in feedforward disinhibition of this same cell. The message here is that the details count, particularly for connections of individual neurons, and we are not yet sufficiently certain of many of the details that enable us even to determine the final effect on relay cells of activating certain inputs or local circuits. It should be noted that the circuits depicted here are probably extreme examples, and combinations of each type probably exist.

DENDRITIC CABLE PROPERTIES

RELAY CELLS

Both X and Y classes of relay cell are electrically rather compact, with dendritic arbors extending for roughly one length constant (Bloomfield et al., 1987; Bloomfield and Sherman, 1989). In practice, this means that even the most distally located synaptic input can have significant effects on the soma and axon, with attenuation of postsynaptic potentials never exceeding one-third to one-half (see Fig. 8.10). One of the reasons for the electrotonically restricted dendritic arbors of relay X and Y cells is the nature of their dendritic branches. These branches closely adhere to Rall's *3/2 branching rule* (Bloomfield et al., 1987). This states that the diameters of the daughter dendrites each raised to the 3/2 power and summed equals the diameter of the parent dendrite raised to the 3/2 power (Rall, 1977; discussed in Johnston and Wu, 1995; Segev, 1995; Shepherd, 1998). Such branching matches impedance on both sides of the branch point and permits efficient current flow across these branches in *both* directions. This

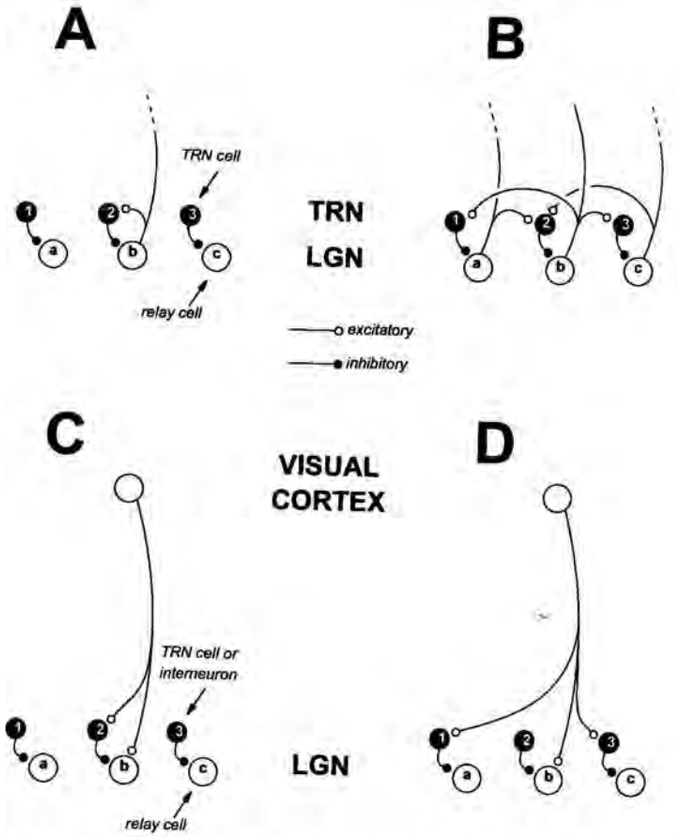

Fig. 8.9. Schema showing examples of different types of inhibitory circuits involving geniculate relay cells. Excitatory cells and their synaptic outputs are shown as open circles, and inhibitory (GABAergic) cells and their outputs are shown as solid circles. **A:** Circuit beginning with relay cell axon that represents feedback inhibition. A collateral of the axon from relay cell b excites TRN cell 2 that then inhibits cell b. **B:** Circuit beginning with relay cell axon that does not represent feedback inhibition. Here, axon collaterals from relay cell b excite TRN cells 1 and 3. These TRN cells then inhibit relay cells a and c, but do not directly influence relay cell b. There is thus no feedback inhibition. However, note that the inhibition of relay cells a and c reduce their excitatory effect on TRN cell 2, resulting in less inhibition from this TRN cell onto cell b. Thus, instead of feedback inhibition seen in A, this circuit represents feedback disinhibition, which is the opposite. **C:** 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 a TRN cell or interneuron 2 that then inhibits relay cell b. **D:** Circuit beginning with cortical axon that does not represent feedforward inhibition. The main difference in D is that, while the cortical axon still directly innervates and excites relay cell b, its collaterals excite TRN cells or interneurons 1 and 3, which then inhibit relay cells a and c. There would be no inhibitory effect on relay cell b.

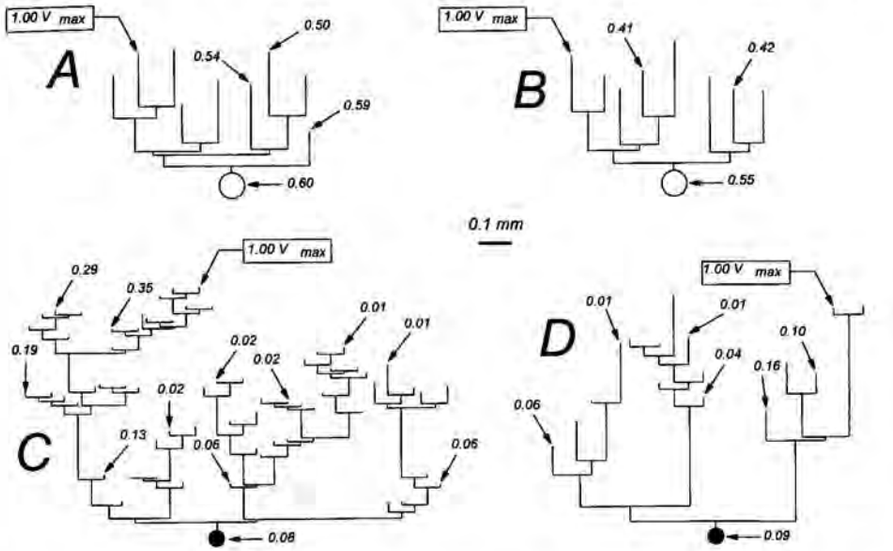

Fig. 8.10. **A–D:** Cable modeling of attenuation of single voltage injection (i.e., the activation of a single synapse) within the dendritic arbors of the two relay X cells and two interneurons from the A-laminae of the cat's LGN. The site of voltage injection is indicated by the boxed value labeled 1.00 V_{max} (maximum voltage). Voltage attenuation at various terminal endings within the arbor and soma is indicated by arrows and given as fractions of V_{max}. Note that voltage never falls below 0.5 of its maximum value anywhere within the dendritic arbor or soma for either relay cell. However, considerable voltage attenuation is evident for the interneurons so that very little of the synaptic current will reach the soma. [From Bloomfield and Sherman, 1989, with permission.]

maximizes the transmission of distal postsynaptic potentials to the soma. This also implies that a potential generated anywhere in the dendritic arbor or at the soma will be efficiently transmitted throughout the dendritic arbor. Among other things, this means that the discharge of an action potential will depolarize the entire dendrite arbor by tens of millivolts, and this could have significant effects on voltage-dependent processes in the dendrites (see below).

INTERNEURONS

Unlike relay cells, interneurons are not electrically compact (Bloomfield and Sherman, 1989). This is partly because their dendrites are thinner and longer than those of relay cells. More importantly, the dendritic branch points of interneurons violate the 3/2 branching rule, because daughter branches tend to be too thin. This limits the current flowing across these branch points. As a result, *providing that there are no major active conductances in the dendritic arbor of interneurons*, much of the synaptic circuitry in distal dendrites, including that involving the F2 terminals, would be functionally isolated from the soma and axon (Fig. 8.10). We emphasize the proviso here concerning the assumption of no significant Ca^{2+} and Na^{+} conductances in the dendrites, and this

attribute remains unknown. Ralston (1971) proposed some time ago that synaptic input onto the F2 terminals of interneurons in the cat's VPL would also be isolated from the soma. Other examples of this property are found in the olfactory bulb (see Chap. 5) and retina (see Chap. 6).

Computational modeling based on these observations with the assumption of passive cable properties suggests an interesting mode of operation for these interneurons (Sherman, 1988; Bloomfield and Sherman, 1989), which is schematically depicted by Fig. 8.11. Clusters of dendritic appendages, which are major sites of input

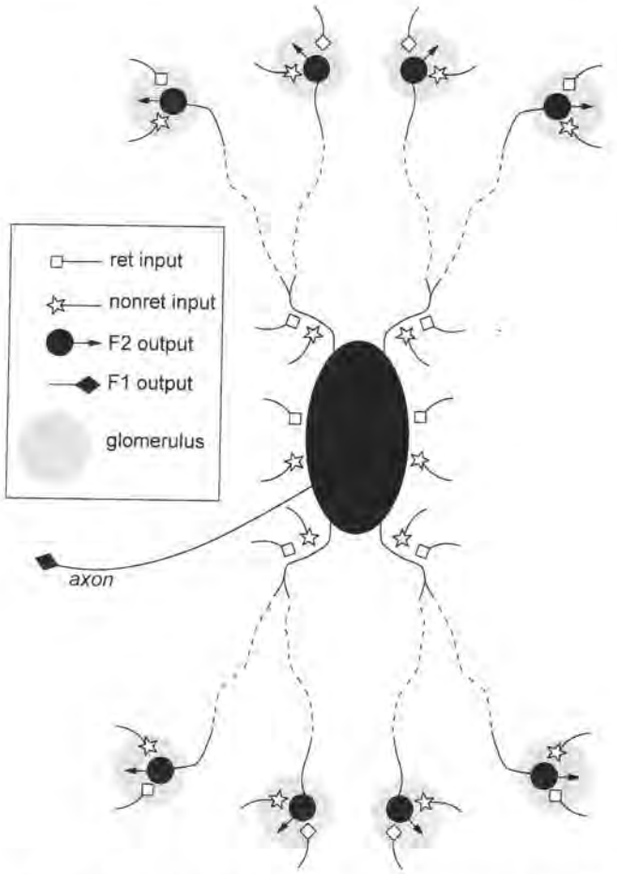

Fig. 8.11. Schematic view of hypothesis for functioning of interneurons in the cat's LGN. Retinal and nonretinal inputs are shown both to the glomeruli as well as to the proximal dendrites and soma. The glomerular inputs are acted upon and lead to F2 outputs from the dendrites, whereas the inputs to the proximal dendrites and soma lead to F1 outputs from the axon. The dashed lines indicate the electrotonic isolation between glomeruli and the proximal dendrites plus soma. This isolation suggests that the two sets of synaptic computations, peripheral for the glomerular F2 outputs and proximal for the axonal F1 outputs, transpire in parallel and independently of one another. Most glomeruli are also functionally isolated from one other.

and output, represent local circuits whose computations are largely independent of activity in other clusters and in the soma. In contrast, the axonal output is controlled in a more orthodox manner by input to the soma and proximal dendrites. This output appears to be mediated by conventional action potentials (Sherman and Friedlander, 1988). Also, while the dendritic F2 outputs innervate relay X cells through glomeruli, the axon forms F1 terminals that innervate dendritic shafts of unknown origin outside of glomeruli (Hamos et al., 1985; Montero, 1987; Sherman and Friedlander, 1988). This suggests that the interneuron simultaneously does double duty: integration of the axonal F1 outputs via action potentials depends on one set of proximal inputs and involves one type of postsynaptic target, while integration of the dendritic F2 outputs depends on local inputs and involves a different postsynaptic target. Examples of electrotonic properties governing similar operational modes are discussed in other chapters.

MEMBRANE PROPERTIES

INTRINSIC CONDUCTANCES

The intrinsic electrophysiological properties of neurons play a great role in determining their integrative characteristics (see Chap. 2). We can no longer view a thalamic cell as being a simple response element that linearly sums its synaptic inputs to determine its axonal output. Thus cable modeling as described above is only a beginning toward explaining how a neuron responds to various synaptic inputs. In reality, these cells have a variety of active membrane conductances. Many of these are controlled in a conventional manner by ligand-binding of neurotransmitters, including effects of second-messenger pathways activated by metabotropic receptors, but some are controlled by membrane voltage, and others are controlled by concentration levels of certain ions, such as Ca^{2+}.

Both in vitro and in vivo experiments directed at different thalamic nuclei across several mammalian species have revealed a surprising plethora of intrinsic membrane conductances present in all thalamic neurons, both in the dorsal thalamus nuclei as well as within TRN neurons (Steriade et al., 1987; Steriade and Llinás, 1988; Huguenard and McCormick, 1992; McCormick and Huguenard, 1992). These conductances all lead to currents that alter the membrane potential. The number of active conductances described for thalamic neurons continues to grow. Which conductances are active can greatly affect the nature of the thalamic neuron's relay of its input to cortex. Conductances found in thalamic neurons are generally found in many other brain cells as well; for the most part, these have been described in detail in Chap. 2. The major and best-understood ones operating in thalamic neurons are listed below (see also Chap. 2).

Na^+ Conductances. Two voltage-dependent Na^+ conductances have been described. The fast, inactivating Na^+ conductance, similar to the one described by Hodgkin and Huxley for the squid giant axon, is voltage dependent and subserves the conventional action potential. The other Na^+ conductance is persistent and non-inactivating. This creates a plateau depolarization that serves to inactivate certain currents, such as I_A and I_T (see below).

Ca^{2+} Conductances. There are at least two voltage-dependent Ca^{2+} conductances. One has a high threshold and is most likely located in the dendrites; rather little is known about this conductance. The other has a lower threshold and plays a dramatic role in retinogeniculate transmission (and the transmission of other driving inputs in other nuclei). It is often known as the *low-threshold Ca^{2+} conductance* and is described more fully below. This leads to Ca^{2+} entry into the cell, thereby depolarizing it and producing the *low-threshold spike*. The low-threshold spike occurs both in TRN cells and thalamic relay neurons, but preliminary evidence suggests that, at least for the LGN, this conductance normally plays little role in interneurons (see below).

Apart from those underlying the generation of conventional action potentials, the low-threshold Ca^{2+} conductance is probably the most important conductance for relay cells. The activation state of this conductance controls which of two distinct response modes, *tonic* or *burst*, is operative when a thalamic relay cell responds to afferent input (Jahnsen and Llinás, 1984a,b; Crunelli et al., 1989; McCormick and Feeser, 1990; Lo et al., 1991; Guido et al., 1992; Guido and Weyand, 1995; Mukherjee and Kaplan, 1995). "Tonic" 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 (Sherman, 1985). Throughout this account, we shall use "tonic" only to refer to response mode and not to cell type.

During the tonic mode of firing, this Ca^{2+} conductance is inactive, and the neuronal response to a depolarizing input is characterized by a steady stream of action potentials of a frequency and duration that increase monotonically with increases in the strength and duration of the depolarizing stimulus (see below). During the burst mode, when this Ca^{2+} conductance is activated, 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 this Ca^{2+} conductance is dependent on membrane voltage, and when activated, this conductance produces the low-threshold spike (Jahnsen and Llinás, 1984a,b; McCormick and Feeser, 1990; Lo et al., 1991; Huguenard and McCormick, 1992; McCormick and Huguenard, 1992). Figure 8.12A–C illustrates its voltage dependency. This actually depicts a simple experiment during which a standard depolarizing current pulse (bottom trace) was injected into the cell through the intracellular recording electrode, and the variable is the initial V_m, which differs among the three examples of Fig. 8.12A–C. When the cell starts off relatively depolarized (Fig. 8.12A), the current pulse depolarizes the cell beyond its action potential threshold, and a stream of unitary, conventional action potentials is discharged for as long as the cell is sufficiently depolarized. When the cell is hyperpolarized slightly from this level (Fig. 8.12B), the same depolarizing pulse is no longer sufficient to drive the cell to threshold, and a purely ohmic response occurs. However, when the cell is further hyperpolarized (Fig. 8.12C), the depolarizing pulse now activates a large triangular depolarization (the low-threshold spike) that is sufficient to drive the cell briefly above its threshold, thereby producing a high-frequency burst typically of 2–10 conventional action potentials. This burst has briefer interspike intervals (≤4 msec) than is seen during tonic firing (≥4 msec).

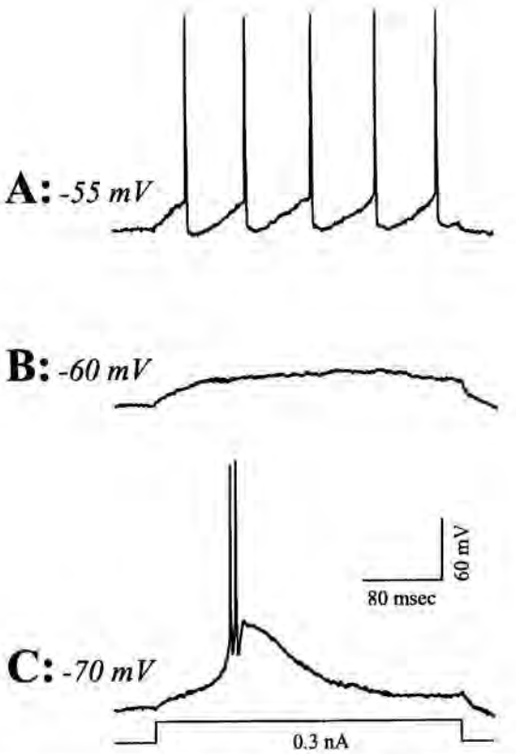

Fig. 8.12. Tonic and burst firing modes for the LGN neuron from cat. The cell was recorded intracellularly in an in vitro slice preparation and was held at different initial membrane voltages as shown by adjusting current injected into the cell through the recording electrode. Each of the three upper, recording traces shows the response to the same depolarizing 0.3 nA current pulse (bottom trace) injected into the cell, also via the 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 two conventional action potentials (the number of action potentials in the burst can vary up to about 10). The low-threshold Ca^{2+} has a voltage dependency that prevents it from being activated from the more depolarized levels of A and B (see text for details).

The behavior illustrated in Fig. 8.12 is explained by the voltage dependency of the Ca^{2+} conductance underlying the low-threshold spike: it is *inactivated* by membrane depolarizations more positive than about −60 mV (Fig. 8.12 A,B), but it is *de-inactivated* at more hyperpolarized levels from which it can be *activated* by a suitably large

depolarization (Fig. 8.12C), such as an EPSP. The membrane current resulting from the low-threshold Ca^{2+} conductance is known as I_T, because it represents an influx of Ca^{2+} ions via membrane pores known as *T channels*. This influx leads to a spike-like depolarization due to Ca^{2+} entry, and this produces the low-threshold spike. Thus the low-threshold Ca^{2+} conductance, low-threshold spike, and I_T all refer to closely related phenomena.

Activation of the low-threshold spike is quickly followed by repolarization of the membrane to its former, hyperpolarized level by the rapid inactivation of the T current (for a detailed account of I_T and related currents in thalamic neurons, see Jahnsen and Llinás, 1984a,b; Huguenard and McCormick, 1992; McCormick and Huguenard, 1992). In addition, there is an activation of various K^+ conductances (see below), 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 de-inactivate the low-threshold spike, but there is also a time dependency for de-inactivation: complete de-inactivation requires that the hyperpolarization be maintained, generally for $\geq$100 msec. This can be thought of as a sort of refractory period for the low-threshold spike. Thus a very brief hyperpolarization followed by depolarization will not produce a low-threshold spike, and the frequency of low-threshold spiking rarely exceeds 10 Hz. Between the low-threshold spikes and associated bursts of conventional action potentials, the cell is relatively silent.

The low-threshold spike provides an amplification that permits a hyperpolarized cell to generate action potentials in response to a moderate EPSP. The spike-like depolarization resulting from the Ca^{2+} conductance has an activation threshold. In many ways, this spike behaves like a conventional Na^+/K^+ action potential: both have an activation threshold and lead to voltage spikes. However, compared with the Na^+/K^+ spike, the threshold for the Ca^{2+} spike is less sharp and its amplitude is more graded. Nonetheless, its threshold and spike-like behavior mean that the amplification represented by the low-threshold spike is nonlinear. That is, the limited time course of the low-threshold spike limits the firing of action potentials to a brief burst typically lasting <20 msec even when an activating depolarization is sustained for much longer periods. Since these action potentials are the only response relayed to cortex, the time course of this response does not faithfully represent that of the input: both a very brief depolarization and one that lasted much longer would elicit similar responses relayed to cortex. Another feature of this nonlinearity is the representation of amplitude. The spike-like depolarization resulting from the activated Ca^{2+} conductance means that the low-threshold spike has a very compressed dynamic range. This means that, as an activating stimulus increases in amplitude, it will rapidly evoke the maximum low-threshold spike (and thus maximum burst of action potentials) so that further increases in stimulus amplitude cannot be represented. Indeed, it is not clear that the actual number of conventional action potentials in the burst riding the low-threshold spike codes for any stimulus variable. In contrast, the tonic response mode is much more linear in its stimulus/response relationship. Temporally, the duration of elevated firing during tonic mode lasts as long as the activating depolarization (see Fig. 8.12A), so time is well represented. Although not shown in Fig. 8.12A, during tonic firing there is also a relatively linear transformation between

stimulus amplitude and response frequency. Thus tonic firing represents a much more linear transformation than does burst firing.

K^+ Conductances. A number of voltage and/or Ca^{2+} dependent K^+ conductances exist that give rise to various membrane currents (see Chap. 2). The best known is the *delayed rectifier* (I_K), which is part of the action potential and repolarizes the neuron following the Na^+ conductance. Several others (I_A, I_C, and possibly I_{AHP}) hyperpolarize the neuron for varying lengths of time following a conventional action potential. The amount of this hyperpolarization determines the cell's relative refractory period, which limits its maximum firing rate. Finally, thalamic cells exhibit a variable K^+ "leak" current.

I_A and its relationship with I_T is particularly interesting. The voltage dependencies of these two currents are generally similar in that both are inactive at depolarized V_m and can be activated by depolarization from relatively hyperpolarized V_m. However, while I_T leads to depolarization due to Ca^{2+} entry, I_A leads to hyperpolarization due to K^+ leaving the cell. Since I_A is activated by depolarization, this means that it will oppose that depolarization, making it smaller and slowing it down. However, for most relay cells, the activation and inactivation curves of I_T are offset by at least 10 mV in the hyperpolarized direction with respect to those of I_A (Pape et al. 1994). This means that when a relay cell is hyeprpolarized sufficiently to de-inactivate both currents and is then depolarized, I_T will activate before I_A, and the resultant spike-like depolarization will rapidly inactivate I_A before it has a chance to develop. It may thus be uncommon to activate I_A in relay cells under most conditions. However, there is a narrow window of V_m in which I_T is largely inactivated and I_A is largely de-inactivated, and depolarization that occurs within this limited membrane voltage range will activate I_A but not I_T.

This pattern is different in interneurons (Pape et al., 1994), because the voltage dependencies of I_T and I_A largely overlap. Thus I_A and I_T will tend to be activated together, but the effect of I_A in offsetting and slowing the depolarization will prevent full expression of I_T. The result is that interneurons rarely express I_T (Pape et al. 1994).

Hyperpolarization Activated Conductance. A conductance that is activated by membrane hyperpolarization and inactivated by depolarization is often 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 I_h (McCormick and Pape, 1990). Activation is slow, with a time constant of >200 msec. The combination of I_T, the above-mentioned K^+ conductances, and I_h helps to support rhythmic bursting, typically at 3–10 Hz for the low-threshold spikes, which is often seen in recordings from in vitro slice preparations of thalamus (see also below). Hyperpolarizing a cell will activate I_h, but so slowly that I_T fully de-inactivates. Once I_h is activated, it will depolarize the cell, thereby activating I_T. This in turn inactivates both I_h and I_T while activating K^+ conductances, resulting in repolarization. The cycle then repeats. This leads to prolonged rhythmic bursting. 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. The significance of these different response modes in thalamic function is considered more fully below.

SYNAPTIC TRANSMISSION

GLUTAMATERGIC INPUTS

The retinal and cortical inputs to thalamus are both glutamatergic (see above).

Retinogeniculate (and Other Driving) Inputs. Retinogeniculate axons innervating relay cells (and driving inputs innervating relay cells in other nuclei) activate *ionotropic* receptors, meaning that there is a fairly direct and simple link between the postsynaptic receptor and the gated ion channel (see Chap. 2). The ionotropic glutamate receptors involved in retinogeniculate transmission include *NMDA* (*N*-methyl-D-aspartate) and *non-NMDA* types, the latter represented by *kainate* and *AMPA* ([±]-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) types (Kemp and Sillito, 1982; Moody and Sillito, 1988; Salt, 1988; Scharfman et al., 1990; Kwon et al., 1991; Salt and Eaton, 1996). The EPSP from NMDA activation is slower than that from AMPA/kainate activation and faster than that from metabotropic activation. Also, the NMDA receptor has the interesting property of being both voltage- and transmitter-dependent (Mayer and Westbrook, 1987). At relatively depolarized V_m levels, activation of the receptor increases the conductance of Na^+ and other cations (mostly Ca^{2+} and some K^+). However, at increasing membrane hyperpolarization, Mg^{2+} ions can clog the ion channel and reduce the conductance. The range over which membrane depolarization can increase conductance of the channel associated with the NMDA receptor seems to vary across cells, but it can extend from −140mV to −40mV. Thus, in order for an EPSP to be generated via an NMDA receptor, two events must occur simultaneously: the presynaptic presence of a glutamate-like neurotransmitter coupled with a postsynaptic depolarization sufficient to unblock the channel. As pointed out in Chap. 1, this enables the NMDA receptor complex to act as a sort of molecular *AND* gate (Koch, 1987).

Less is known about the pharmacology of retinal or driving input onto interneurons. Studies of the LGN in vitro suggest that the retinogeniculate EPSP controlling action potentials in interneurons involves only ionotropic glutamate receptors (Pape and McCormick, 1995). However, the retinal input onto dendritic terminals of interneurons, an input that may not greatly affect action potential generation (see above), may activate a metabotropic receptor (Zhou et al., 1994; Godwin et al., 1996b).

Corticogeniculate Inputs. Corticogeniculate axons onto relay cells appear to activate the same types of ionotropic receptors as do retinogeniculate axons. However, in addition to these, the axons from cortex also activate a *metabotropic* glutamate receptor on relay cells, and such a receptor is not activated by retinogeniculate axons (McCormick and Von Krosigk, 1992). Metabotropic receptors as a class are interesting, because they act indirectly on ion channels via second-messenger pathways, and activation of these pathways can lead to other cellular responses in addition to any effects on ion channels. The metabotropic receptor activated by corticogeniculate axons produces a very slow and long-lasting EPSP due to reduction of a K^+ "leak" current (McCormick and Von Krosigk, 1992). This longer time course of the metabotropic compared with

ionotropic response is ideal for switching relay cells from burst to tonic response mode, and observations from both in vitro and in vivo indicate that such switching does readily occur as a result of activation of the metabotropic glutamate receptors (Godwin et al., 1996a).

Cortical axons appear not to activate metabotropic glutamate receptors on interneurons (Pape and McCormick, 1995), but virtually nothing is known of the nature of glutamate receptors activated by these axons on TRN cells.

GABAERGIC INPUTS

Thalamic relay cells receive an inhibitory, GABAergic input from TRN cells and interneurons. The postsynaptic response to these inputs involve both $GABA_A$ and $GABA_B$ receptors (see Chap. 2). The former is ionotropic, and the latter, metabotropic. Activation of the $GABA_A$ receptor increases a Cl^- conductance, whereas activation of the $GABA_B$ receptor increases a K^+ conductance. Since the reversal potential for K^+ is much more negative (at roughly −100 mV) than that for Cl^+ (at roughly −70 mV), $GABA_B$ activation results in more hyperpolarization than does $GABA_A$ activation. However, the neuronal conductance increase and thus the decrease in neuronal input resistance is much greater with $GABA_A$ than with $GABA_B$. As a result, $GABA_A$ inhibits more by clamping the membrane at a subthreshold level and thus *shunting* EPSPs, while $GABA_B$ inhibits more by hyperpolarizing the membrane. The $GABA_A$ response is thus much more nonlinear, acting more like a voltage multiplication, while the $GABA_B$ response is more linear, acting like simple voltage subtraction (see Chap. 1). Also, the $GABA_A$ response is faster than is the $GABA_B$ response.

BRAINSTEM INPUTS

Parabrachial Inputs. In cats, most of the input to the lateral geniculate nucleus from the brainstem derives from the parabrachial region (de Lima et al., 1985; de Lima and Singer, 1987; Fitzpatrick et al., 1988; Smith et al., 1988; Raczkowski and Fitzpatrick, 1989; Fitzpatrick et al., 1989; Bickford et al., 1993). Activation of this input in relay cells produces an excitatory postsynaptic potential due primarily to activation of two different receptors (McCormick and Prince, 1987a; McCormick, 1989a, 1992). The first is an ionotropic nicotinic receptor that produces a fast excitatory postsynaptic potential 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 excitatory postsynaptic potential. 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. As is the case for cortical input, both in vitro and in vivo studies suggest that activating this cholinergic input switches the response mode of thalamic relay cells from burst to tonic (McCormick and Prince, 1987a; McCormick, 1989a, 1992; Lu et al., 1993).

Activation of the cholinergic inputs from the parabrachial region generally inhibits interneurons and reticular cells (Dingledine and Kelly, 1977; Ahlsén et al., 1984; McCormick and Prince, 1987a; McCormick and Pape, 1988). 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 (McCormick and Prince, 1987a; Hu et al., 1989a,b; McCormick, 1989a, 1992). 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 (Dingledine and Kelly, 1977; McCormick and Prince, 1987a; McCormick and Pape, 1988; Hu et al., 1989a,b; McCormick, 1989a, 1992). Since these interneurons and reticular cells inhibit relay cells, activation of this cholinergic pathway thus disinhibits relay cells (see Fig. 8.9).

In addition to ACh, these axons appear to colocalize *nitric oxide* (NO; Erişir et al., 1997a; Bickford et al., 1993), a neurotransmitter or neuromodulator with a widespread distribution in the brain (Schuman and Madison, 1991, 1994; Bredt and Snyder, 1992; Snyder, 1992). Relatively little is known concerning the action of NO in the thalamus, but recent studies suggest that its release from parabrachial terminals serves two possible roles in the lateral geniculate nucleus: to switch response mode from burst to tonic (Pape and Mager, 1992), perhaps complementing the role of acetylcholine (ACh) in this regard; and to promote the generation of NMDA responses from retinal inputs (Cudeiro et al., 1994a,b, 1996). A recent study suggests that NO may also serve to enhance NMDA receptor activation in TRN cells, although the source of inputs to activate these receptors has not been identified (Rivadulla et al., 1996). Nothing is as yet known about the action of NO on interneurons.

Other Brainstem Inputs. Other less well understood brainstem inputs to thalamus include noradrenergic axons from cells in the parabrachial region, serotonergic axons from cells in the dorsal raphé nucleus, and histaminergic axons from cells in the tuberomammilary nucleus of the hypothalamus; other inputs unique to specific thalamic nuclei may also occur, such as the GABAergic input to the LGN from cells from the pretectum (see above for details).

Noradrenalin seems to increase excitability of relay cells in the lateral geniculate nucleus. Like ACh, noradrenalin promotes tonic firing (McCormick, 1989a, 1992; Pape and McCormick, 1989; Funke et al., 1993). This neurotransmitter depolarizes TRN cells by reducing a K^+ conductance (McCormick and Wang, 1991), but has no clear effect on interneurons (Pape and McCormick, 1995). Effects of serotonin are complex. Ionophoresis 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 (McCormick, 1989a, 1992). Serotonin depolarizes TRN cells by blocking a K^+ conductance (McCormick and Wang, 1991), and it produces a slight depolarization of some interneurons, not clearly affecting others (Pape and McCormick, 1995). Finally, histamine application to relay cells generally excites them (McCormick, 1992). Histamine also 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).

GATING AND OTHER TRANSFORMATIONS IN THE THALAMIC RELAY

The rich array of membrane properties of thalamic relay cells plus their complex ensemble of inputs from various sources suggest that the relay of peripheral information to cortex is not a simple, trivial affair. Instead, it is a complex process that we are just beginning to understand. This is a marked change from earlier views of, for instance, the LGN, which was thought to provide a simple, machine-like relay of retinal information to cortex with minor processing added. This will be considered in more depth here, both in terms of the different burst and tonic response modes introduced above and the role they play in the thalamic relay, and in terms of what we are just beginning to learn about the role of cortical and brainstem inputs in this relay.

BURST AND TONIC RELAY RESPONSE MODES

Signal Transmission During Burst and Tonic Firing. Burst and tonic modes clearly represent two very different types of response to afferent input and thus two very different forms of thalamic relay. In fact, earlier studies suggested that tonic firing represented the only true relay mode and that burst firing, when it occurred, was always characterized by *rhythmic* bursting that was synchronized across large regions of thalamus. This functionally disconnected the relay cell from its primary afferent input, thereby interrupting the relay (McCarley et al., 1983; Steriade and Llinás, 1988; McCormick and Feeser, 1990; Steriade and McCarley, 1990; Steriade et al., 1990a,b, 1993; McCormick and Bal, 1994; Steriade and Contreras, 1995). The idea was that switching between these modes was accomplished by inputs that changed V_m. Rhythmic bursting was often seen in vitro, and the first in vivo studies of the response modes in cats demonstrated that, when the animal entered quiet or non-REM 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 Llinás, 1988; Steriade et al., 1990a,b, 1993; Steriade and McCarley, 1990; Steriade and Contreras, 1995).

However, more recent data in anesthetized and awake, behaving cats makes clear that cells can burst arrhythmically and asynchronously, and they can still respond well to visual stimulation (Lo et al., 1991; Guido et al., 1992, 1995; Guido and Weyand, 1995; Mukherjee and Kaplan, 1995; Sherman, 1995; Godwin et al., 1996a). That is, during spontaneous activity, the cells may often discharge a low-threshold spike with a burst response, but these burst discharges occur irregularly. When the cell is then stimulated visually, the cell may produce a burst in response to each presentation of the stimulus, and the bursting under these conditions clearly reflects the external stimulus rather than any intrinsic pacemaker (Guido et al., 1992, 1995; Guido and Weyand, 1995; Mukherjee and Kaplan, 1995; Sherman, 1995; Godwin et al., 1996a). There thus seem to be three different response modes: rhythmic bursting, arrhythmic bursting, and tonic firing. The first occurs during quiet or non-REM sleep, perhaps during drowsiness, and might also occur during epileptic episodes (McCarley et al., 1983; Steriade and Llinás, 1988; McCormick and Feeser, 1990; Steriade et al., 1990a,b, 1993; Steriade and McCarley, 1990; McCormick and Bal, 1994; Steriade and Contreras, 1995); this seems to be associated with an interruption of the relay through thalamus. The last two occur during active vision, meaning that both burst and tonic modes can be effective relay modes.

What, then, are the differences in the relay between burst and tonic firing modes? Figure 8.13 shows a representative example of an LGN relay cell in a lightly anesthetized cat responding to a visual stimulus, which is a sinusoidal luminance grating drifting through its receptive field. The same cell responds in tonic mode when depolarized (Fig. 8.13A) and in burst mode when hyperpolarized (Fig. 8.13B); both spontaneous activity (upper histograms) and visually evoked responses (lower histograms) are shown. Two main differences are evident. First, note that the response to the sinusoidal visual stimulus appears to be much more sinusoidal during tonic firing than during burst firing. This is because tonic mode displays greater linear summation than does burst mode (Guido et al., 1992, 1995; Mukherjee and Kaplan, 1995; Sherman, 1995). This is probably due to 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). The signal relayed to cortex is thus less distorted when the relay is in tonic mode, and this mode would thus be superior for accurate analysis by cortex of sensory stimuli. Second, note that while the visual response during both modes is robust, the spontaneous activity is much higher during tonic firing. The latter is actually an important feature of the linear summation during tonic firing,

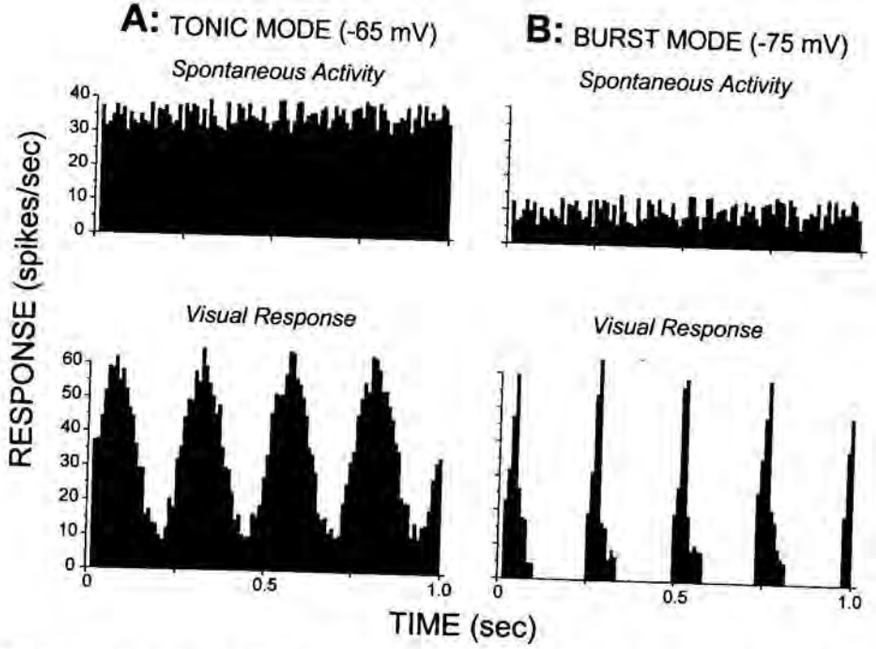

Fig. 8.13. Spontaneous activity and visually driven responses of geniculate cell recorded in a cat in vivo during tonic and burst modes. The cell was recorded intracellularly, and current injection was used to adjust mean membrane voltage to either −65 mV, which was sufficiently depolarized to inactivate I_T and promote tonic responses, or −75 mV, which was sufficiently hyperpolarized to de-inactivate I_T, allowing it to be activated and promote burst responses. The upper row of histograms shows spontaneous activity, and the lower row shows responses to four cycles of a sinusoidal grating drifted through the receptive field. **A:** Tonic mode. **B:** Burst mode.

because the higher background discharge minimizes nonlinearities due to half-wave rectification. Furthermore, burst firing provides a much higher signal (visual response)-to-noise (spontaneous activity) ratio than does tonic firing, implying that burst mode may be superior for detecting the presence of a stimulus (Guido et al., 1995). In fact, relay cells in burst mode are able to detect stimuli far better than when these same cells are in tonic mode (Guido et al., 1995; Sherman, 1995).

Perhaps burst mode is used during visual search or maybe during periods when attention is directed elsewhere (e.g., to another sensory modality or to another part of visual space) as a sort of "wake-up" call for novel and potentially interesting or dangerous stimuli. This idea is in some ways similar to the "searchlight" hypothesis for burst firing (Crick, 1984). However, while burst firing may be ideal for signal detection, the nonlinear distortion during this relay mode means that the stimulus will not be accurately analyzed. Tonic mode, with its more linear relay, would permit more faithful signal analysis.

Control of Response Mode. From the preceding discussion, one can imagine that relay cells can be switched via nonretinal inputs between modes. This may occur in a state-dependent fashion based on the requirements of the visual system regarding signal detection or analysis. For this to work, there must be a ready means for nonretinal inputs to control these response modes. This may be accomplished chiefly through effects on the membrane potential of relay cells, since the low-threshold Ca^{2+} conductance underlying the burst mode is voltage-dependent. Both parabrachial and cortical inputs appear to be able to 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, 1989a, 1992). NO, which is colocalized with ACh in the parabrachial terminals may also promote tonic firing (Pape and Mager, 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. Also, as can be appreciated from Fig. 8.3, any global activation or inactivation of cortex will both excite relay cells directly and inhibit them indirectly (via interneuron and TRN activation), and thus these cruder attempts to modulate corticothalamic inputs may produce weak or inconsistent results. However, because corticogeniculate but not retinogeniculate inputs use a metabotropic glutamate receptor (see above), it is possible to mimic activation of the corticogeniculate input onto relay cells 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. 1996a). Also, in vitro application of agonists to this metabotropic receptor switches firing from burst mode to tonic mode (McCormick and Von Krosigk, 1992).

OTHER EFFECTS OF NONRETINAL OR MODULATORY INPUTS ON THE THALAMIC RELAY

Although we have focused so far on the role of brainstem and cortical afferents to thalamus in terms of their ability to affect response mode, other roles may be played by these and other inputs regarding thalamic relay properties.

TRN Inputs. Although thalamic neurons may switch between relay and burst modes at any time during awake, alert behavioral states, the burst mode dominates during less alert periods, including drowsiness and quiet or non-REM sleep (McCarley et al., 1983; Steriade and Llinás, 1988; Steriade et al., 1990a,b, 1993; Steriade and McCarley, 1990; Steriade and Contreras, 1995). During such inattentive periods, the EEG in all mammals, including humans, becomes highly synchronized, and fast, rhythmic spike-like electrical phenomena known as *spindles* can be seen (see Fig. 8.14). These spindles have a frequency of 7–14 Hz.

This dominant feature of the synchronized EEG is generated in the thalamus (Steriade and Llinás, 1988). Studies of thalamic neurons have shown that all TRN cells can spontaneously generate rhythmic discharges at a rate of approximately 10 Hz. The

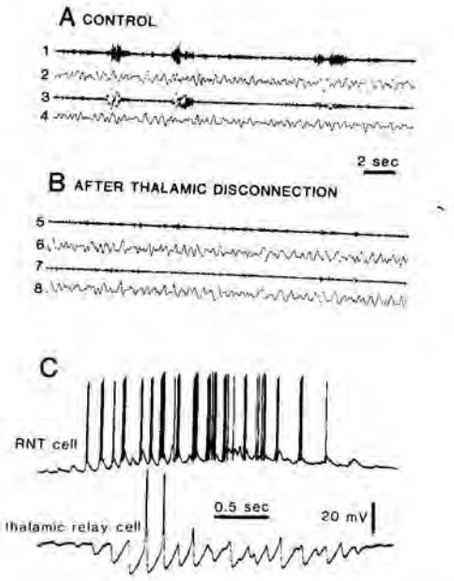

Fig. 8.14. Relationship of thalamus to spindle activity in the cortical electroencephalogram (EEG) of cats. **A,B:** Effect on the EEG of rostral thalamic transections that disconnect the thalamus from the cortex. The numbering of traces is as follows: 1 and 5, higher-frequency EEG (7–14 Hz) for right hemisphere; 2 and 6, lower-frequency EEG (0.5–4 Hz) for right hemisphere; 3 and 7, higher-frequency EEG (7–14 Hz) for left hemisphere; 4 and 8, lower-frequency EEG (0.5–4 Hz) for left hemisphere. Normally (**A**, before transection), each hemisphere shows activity in both the higher (7–14 Hz) and lower (0.5–4 Hz) filtered traces. After transection (**B**), the higher frequencies are selectively eliminated from the EEG. **C:** Activity of thalamic neurons during an EEG spindle. During the spindle, the TRN neuron (top) undergoes a long-lasting, slow depolarization that elevates its firing rate. In contrast, a thalamic relay cell (bottom) is hyperpolarized rhythmically, and the rebound from these hyperpolarizations often leads to low-threshold Ca^{2+} spikes. The elevated firing in the TRN cell seems to cause the rhythmic hyperpolarizations in the relay cell. [A,B revised from Steriade et al. 1987; C revised from Steriade and Llinás, 1988, with permission.]

low-threshold spike appears to be a key feature of this endogenous bursting behavior, and the oscillations can be generated within individual TRN cells. Also, groups of deafferented TRN neurons can generate such synchronized oscillatory activity in the absence of external input (Steriade et al., 1987; Steriade and Llinás, 1988). TRN neurons are extensively connected to other TRN cells via collaterals of the axon that innervates dorsal thalamus, and these connections could serve to synchronize entire TRN regions; dendrodendritic synapses may also exist among TRN neurons to further synchronize these cells.

Since TRN neurons provide an inhibitory, GABAergic input to thalamic relay cells, the TRN entrains its oscillatory activity onto these relay cells. That is, the synchronized bursts of TRN activity would lead to waves of hyperpolarization among relay cells; this would de-inactivate low threshold spikes in the relay cells, and they would synchronously enter the burst mode. By themselves, neurons in the LGN or VPL do not spontaneously generate spindle rhythmicity, since disconnecting the projection cells from the TRN via surgical or chemical means abolishes the oscillations (Steriade et al., 1987; Steriade and Llinás, 1988). Thus this feature of synchronized, rhythmic bursting among relay cells, which is associated with inattentive and unconscious states and interruption of the thalamic relay, depends critically on the TRN.

Brainstem Inputs. Non-REM sleep and spindle activity is associated with quiescence among many of the cholinergic inputs to the thalamus from the parabrachial region (Steriade and Contreras, 1995). It thus seems plausible that increasing activity among these inputs will serve to terminate the synchronized, rhythmic activity and restore relay cell responses to tonic or arrhythmic burst firing. This has yet to be demonstrated empirically, but it is consistent with other evidence presented above. While the effects of the various brainstem inputs is complex, many strongly inhibit TRN cells, and such inhibition may well serve to break up the functional network that synchronizes these cells. In any case, there is ample evidence that activity in brainstem afferents is associated with more alert behavioral states.

There is also evidence that eye movements can affect the geniculate relay (Büttner and Fuchs, 1973; Noda, 1975; Bartlett et al., 1976; Lal and Friedlander, 1989; Guido and Weyand, 1995). Both saccades and passive movement of the eye can have such effects. While the details for this have yet to be worked out, it seems likely that these effects are accomplished via brainstem afferents to thalamus.

Cortical Inputs. As noted above, the corticogeniculate input is both massive and heterogeneous. It is thus plausible that it subserves several distinct functions. Perhaps this is why earlier attempts to identify any *single* function for this "feedback" pathway have led to confusing and conflicting conclusions. For instance, some studies suggest that the corticogeniculate pathway facilitates relay cell firing, whereas other suggest the opposite (Kalil and Chase, 1970; Baker and Malpeli, 1977; Schmielau and Singer, 1977; Geisert et al., 1981; McClurkin and Marrocco, 1984; McClurkin et al., 1994). The large number of layer 6 inputs suggests that this feedback could be highly specific to receptive field location, orientation, direction of motion, and ocularity. Mumford (1994) has developed a detailed framework, based on ideas from machine vision, in which the

detection of weak or incomplete stimuli under noisy conditions (think of a gray mouse at dusk) would be enhanced via such feedback. In this context, it should be pointed out that the vast majority of experiments carried out in the LGN have involved anesthetized animals stimulated with single bars or gratings on a blank background, not a situation that might be expected to activate the type of feedback function suggested by Mumford (1994). Schmielau and Singer (1977) have proposed that corticogeniculate input is important to binocular functions, such as stereopsis. Several studies have identified a role for the corticogeniculate input in controlling inhibitory surrounds of geniculate relay cells (Sillito et al., 1993; Cudeiro and Sillito, 1996). More recent studies have suggested that the pathway affects temporal properties of relay cell discharges (McClurkin et al., 1994) or establishes correlated firing among nearby relay cells with similar receptive field properties (Sillito et al., 1994). Above we suggest that this input serves to control response mode, tonic or burst, of the relay cells. Given the likelihood that the corticogeniculate pathway is heterogeneous, these different suggestions for its function are not incompatible, and more functions may yet emerge.

FIRST- AND HIGHER-ORDER THALAMIC RELAYS

Every thalamic nucleus appears to receive afferents from layer 6 of the relevant cortical region or regions, such as visual cortex for LGN (Jones and Powell, 1968; Rinvik, 1972; Kunzle, 1976; Updyke, 1977; Berson and Graybiel, 1983). These layer 6 corticothalamic terminals have RSD morphology, are located on distal dendrites, and are rarely if every found in glomeruli (Jones and Powell, 1969a,b; Morest, 1975; Majorossy and Kiss, 1976a,b; Somogyi et al., 1978; Liu et al., 1995).

However, some thalamic nuclei also receive an input emanating from pyramidal cells of layer 5 (Mathers, 1972; Robson and Hall, 1977; Ogren and Hendrickson, 1979; Hoogland et al., 1991; Schwartz et al., 1991; Bourassa et al., 1995; Guillery, 1995; Sherman and Guillery, 1996). Examples of nuclei receiving layer 5 input are pulvinar, the mediodorsal nucleus, and the dorsal division of the medial geniculate nucleus, but a complete survey of nuclei receiving such input remains to be done. Interestingly, the pattern of innervation of these layer 5 inputs is more like that of primary afferents. That is, the innervation pattern of these layer 5 axons is more like that of retinal axons in the LGN than of layer 6 axons there. These layer 5 axons are relatively coarse and terminate in richly branched arbors, like retinal axons. This is unlike the finer layer 6 axons that terminate more simply. Like retinal axons, these layer 5 axons branch to innervate other brainstem targets, whereas the layer 6 axons terminate exclusively in thalamus. These layer 5 axons also end with large terminals, much like RLP terminals in the LGN, that contact proximal dendrites, often in triadic arrangements in glomeruli, whereas the layer 6 axons end with RSD terminals distally outside of glomeruli and without triadic arrangements. Finally, although both layer 5 and 6 axons pass through TRN en route to their dorsal thalamic target, the layer 5 axons do not seem to innervate TRN with a collateral, whereas layer 6 ones do. This, too, is like the primary input, since, for example, driving or retinal inputs do not innervate TRN.

These morphological observations suggest that corticothalamic axons from layer 5 may act as primary afferents for some of the thalamic nuclei that have few if any other primary afferent axons. It is noteworthy in this context that these thalamic nuclei known

to receive a layer 5 input lack a clearly defined or major subcortical input that could be regarded as primary. A consideration of the effects that cortical lesions or inactivation have upon the receptive fields of cells in the thalamic nuclei we are considering provides indirect evidence in support of this view that the primary input for these thalamic nuclei derives from layer 5 of cortex. For a nucleus innervated by primary subcortical afferents, such as LGN or VPL, cortical inactivation has relatively little effect on the receptive fields of the thalamic cells (Kalil and Chase, 1970; Baker and Malpeli, 1977; Schmielau and Singer, 1977; Geisert et al., 1981; McClurkin and Marrocco, 1984; Yuan et al., 1986; Diamond et al., 1992; McClurkin et al., 1994). In stark contrast to this, receptive field properties of cells in nuclei that receive layer 5 afferents from cortex are greatly affected after cortical inactivation (Bender, 1983; Diamond et al., 1992).

The layer 5 innervation pattern suggests that certain thalamic nuclei receive their primary afferents from the cortex rather than subcortically and they relay this afferent cortical activity to other cortical areas. This provides the thalamus with a much more extensive role in corticortical communication than previously considered (Kaas, 1978; Van Essen and Maunsell, 1983; Van Essen, 1985; Zeki and Shipp, 1988; Van Essen et al., 1990; Felleman and Van Essen, 1991; Knierim and Van Essen, 1992; Young, 1992; Nakamura et al., 1993; Preuss et al., 1993; DeYoe et al., 1994; Salin and Bullier, 1995). There are thus at least two functionally distinct corticothalamic systems. One derives from layer 6 and serves to modulate the relay properties of its thalamic target. The other derives from layer 5 and represents the primary information to be relayed by its target thalamic cells. Note that these latter thalamic relay cells are also under the modulatory influence of layer 6 input, which is ubiquitous for all thalamic nuclei.

By the same sort of logic, we can now recognize two types of thalamic nucleus—one receiving its primary afferents from subcortical sources and the other, from cortical sources. The former have been called *first-order* relay nuclei, and the second, *higher-order* relay nuclei because they receive their primary inputs from cortex that has already received and acted on information from its first-order thalamic relays (Guillery, 1995; Sherman and Guillery, 1996). This organization is summarized schematically in Fig. 8.15.

The first-order relay may be viewed as the initial transfer of peripheral information to cortex for further processing, and the higher-order relay may be viewed as the relay of information already processed somewhat by cortex. It is interesting in this context to reconsider the olfactory pathway, which has always stood out among sensory pathways as not having a primary thalamocortical component. In a sense, we can view the projection from the olfactory bulb to olfactory paleocortex as analogous to a first-order relay without a thalamic component, perhaps because it evolved before thalamus and neocortex. Then the projection from olfactory paleocortex through the mediodorsal thalamic nucleus to insular and orbital neocortex looks very much like a higher-order relay. Such a consideration of the olfactory pathway may provide some insights into evolution of thalamus and neocortex.

While we know very little about detailed properties of these higher-order thalamic nuclei, it seems parsimonious to suggest for now that they are similar to those we have described above, including the same sorts of cellular properties (including burst and

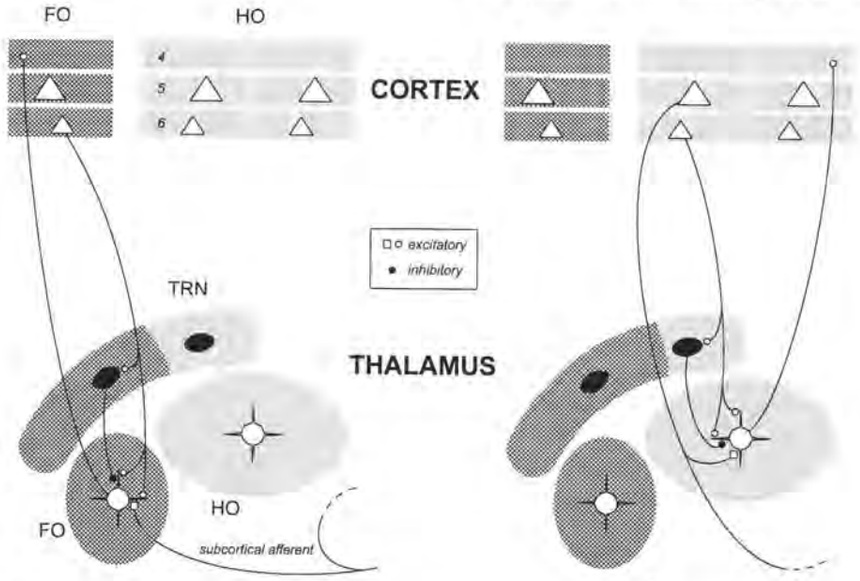

Fig. 8.15. Schematic representation of first-order (FO) and higher-order (HO) thalamic relays. Both types of relay receive a modulatory cortical input from layer 6 (only cortical layers 4, 5, and 6 are shown) that contacts distal dendrites of the relay cells with small terminals. These cortical axons also branch to innervate TRN. The first-order relay (left) receives its primary input from a subcortical afferent that contacts proximal dendrites with large terminals, often in glomeruli (not shown). This information is relayed to layer 4 of cortex. Note that the subcortical input branches to innervate other subcortical structures, but does not innervate TRN. The higher-order relay (right) receives its primary input from layer 5 of cortex, and this contacts proximal dendrites with large terminals, often in glomeruli (not shown). This information is relayed mainly to another area of cortex, terminating chiefly in layer 4. Note that the layer 5 input branches to innervate other subcortical structures, but does not innervate TRN. Thus in many ways the layer 5 input is like the subcortical input of a first order relay, but unlike the modulatory input from layer 6 of cortex. See text for details.

tonic firing), intrinsic circuits, and cortical and brainstem inputs. That is, both first- and higher-order thalamic relay nuclei have a "dominant" or "driving" input, which, for instance, derives from retina for the lateral geniculate nucleus and from cortical layer 5 for higher-order relays. This driving input is always modulated by a massive layer 6 cortical input as well as by various brainstem inputs.

An important implication of this view of thalamocortical interactions is that it permits a much richer avenue of communication among cortical areas. These areas can communicate through the thalamus, with some thalamocortical inputs relaying to their target cortical areas the output, via layer 5, of another cortical area. Furthermore, other cortical areas, via their layer 6 outputs, can modify this thalamic route of corticocortical communication.

FUNCTIONAL SIGNIFICANCE OF THALAMIC CIRCUITS

Noted above is the observation that each geniculate cell receives the vast majority of its retinal input from one or very few retinal ganglion cells of the same type (left or right retina, on or off center, X and Y). Thus the spatial receptive field of each geniculate cell is nearly identical to that of its retinal input: geniculate cells display circular receptive fields organized into concentrically arranged, antagonist centers and surrounds. Subtle differences have been described between receptive fields of geniculate cells and those of their retinal inputs, and these mostly involve greater inhibition seen postsynaptically (reviewed in Sherman and Spear, 1982; Shapley and Lennie, 1985; Sherman, 1985). Preliminary data suggest a similar resemblance in spatial receptive field properties between MGN or VPL cells and their driving inputs. For the purposes of the present discussion, we conclude that significant receptive field transformation occurs rarely if at all at the level of thalamus.

This absence of a major receptive field transformation across the retinogeniculate synapse stands in stark contrast to the obvious transformations seen when progressing through the synaptic zones of retina or cortex or across the geniculocortical synapse. Comparable transformations exist as well in other parts of the visual system, such as the superior colliculus and extrastriate visual cortex. Similar transformations also exist outside the thalamus in other sensory systems, such as the spinal cord and cortex for the somatosensory system, and the inferior colliculus and cortex for the auditory system. These other, extrathalamic transformations represent obvious, functional roles for these other regions of sensory systems: synaptic zones there clearly form more complex receptive field properties as the hierarchy is ascended, and this provides a basis for these sensory systems to extract information about stimuli in the world outside.

It is this absence of any clear spatial change in receptive fields across the retinogeniculate synapse (or across the synapse from driving inputs elsewhere) that has prompted many investigators to think of specific sensory thalamic nuclei as merely passive relay stations for signals from the periphery to cortex. However, such a trivial function belies morphological data presented above for the LGN that only a minority of the synapses present in the neuropil and onto relay cells is retinal in origin. This minority of synaptic terminals is only 10–20% by most accounts (Guillery, 1969a,b; Sherman and Koch, 1986; Sherman and Guillery, 1996), although newer data suggest that the value may be much less (Van Horn et al., 1997). The function of the vast majority of synaptic input seems invisible to conventional receptive field approaches. In fact, evidence accumulated over the past decade strongly suggests that this nonretinal input serves to gate retinogeniculate transmission or transform it in ways, such as the control of burst or tonic response modes, that will serve different behavioral needs of sensory processing.

This provides a unique role for the thalamus: it is not merely a passive relay nor is it primarily involved in receptive field elaboration; instead, it actively filters the flow of information to cortex, and the nature of the filtering is dependent on the animal's state of consciousness and alertness. This active filtering has not been revealed by the usual receptive field studies, but recording in unanesthetized animals has revealed considerable state-dependent variation in responsiveness of geniculate neurons. We are now beginning to gain insights into how certain nonretinal or modulatory inputs to

thalamus, such as from cortex or brainstem, control this filtering process. While it seems clear what general role the LGN and other thalamic nuclei play, it is neither clear how many different types of filtering exist for retinal and other driving inputs nor precisely how these filtering functions are achieved. Finally, there is new evidence that the relay function served by thalamus is not limited to transferring peripheral information (e.g., from retinal or spinal cord) to cortex, but that certain thalamic nuclei serve chiefly to relay information from cortex to cortex, and this role of thalamus may prove crucial to cortico-cortical interactions.

9

BASAL GANGLIA

CHARLES J. WILSON

The basal ganglia are a richly interconnected set of brain nuclei found in the forebrain and midbrain of mammals, birds, and reptiles. In many species, including most mammals, the forebrain nuclei of the basal ganglia are the most prominent subcortical telencephalic structures. The large size of these nuclei, and their similarity in structure in such a wide range of species, make it likely that they contribute some very essential function to the basic organizational plan of the brain of the terrestrial vertebrates. However, the assignment of a specific functional role for the basal ganglia has been difficult, as it has been for other brain structures that have no direct connections with either the sensory or motor organs.

The most widely accepted views of basal ganglia function are based on observations of humans afflicted with degenerative diseases that attack these structures. In all cases these diseases produce severe deficits of movement. None of the movement deficits is simple, however, or easily described. In some, such as Parkinson's disease, movements are more difficult to make, as if the body were somehow made rigid and resistive to changes in position. In others, such as Huntington's disease, useless and unintended movements interfere with the execution of useful and intended ones. In general, these symptoms affect only voluntary, purposive movements, with reflexive movements being relatively unaffected. These clinical observations have led most investigators to view the basal ganglia as components of a widespread system that is somehow involved in the generation of goal-directed voluntary movement, but in complex and subtle aspects of that process.

The anatomical connections of the basal ganglia link it to elements of the sensory, motor, cognitive, and motivational apparatus of the brain. These connections are best appreciated within the context of the arrangement of the several nuclei that make up the basal ganglia. A diagram showing the arrangement of the most prominent of these nuclei as they appear in a frontal section of the human brain is shown in Fig. 9.1. The major structures are the caudate nucleus, putamen, globus pallidus, substantia nigra, and subthalamic nucleus. Also seen in the diagram are the two largest sources of input to the basal ganglia, the cerebral cortex and the thalamus.

Several of the major connections between these structures are shown in Fig. 9.1. In dealing with this complexity, it is helpful to focus on the overall direction of information flow. Most of the input to the basal ganglia from other brain structures arrives