8

THALAMUS

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

As we shall see in this chapter, however, the thalamus does much more than act merely as a passive and machinelike relay of information to the cortex. Instead, the ability to pass through this gateway is determined by specialized neuronal circuitry. The gate can be: (1) completely open, which results in the relay of all information to cortex; (2) completely closed, which cuts off cortex from the outside world; or (3) partially open, which permits certain information to reach cortical levels. Thus the thalamus filters 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).

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 the neocortex. This includes somatosensory information from the muscles, deep tissues, and skin; visual information from the eyes; auditory information from the ears; gustatory information from the taste buds; and olfactory information from the nose, after relaying through the olfactory cortex (which is the paleocortex, rather than neocortex). Each part of the thalamus, in turn, receives fibers from the area of the cortex to which it projects (E. G. Jones, 1985).

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. Authors 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, one of which is the reticular nucleus of the thalamus (RNT; also known as the nucleus reticularis thalami or the thalamic reticular nucleus), have reciprocal connections with specific nuclei in the dorsal thalamus (E. G. Jones, 1985; Ohara and Lieberman, 1985). The epithalamus lacks direct afferent or efferent connections with the cortex and is actually more closely associated with the hypothalamus; it will not be considered further here.

The dorsal thalamus can be divided into a number of discrete nuclei (Fig. 8.1). We now recognize that many, and perhaps all, of these nuclei have unique functional correlates, with specific input and output routes. These routes are limited to the same hemisphere, since no contralateral connections involving any thalamic nucleus have been found. An exhaustive survey of all dorsal thalamic nuclei is beyond the scope of this chapter (see E. G. Jones, 1985, for a more thorough account), but examples of the best studied nuclei follow. The *lateral geniculate nucleus* (LGN) relays input from the retina to visual cortex. There are actually 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"; the ventral division, which is part of the ventral thalamus, 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)

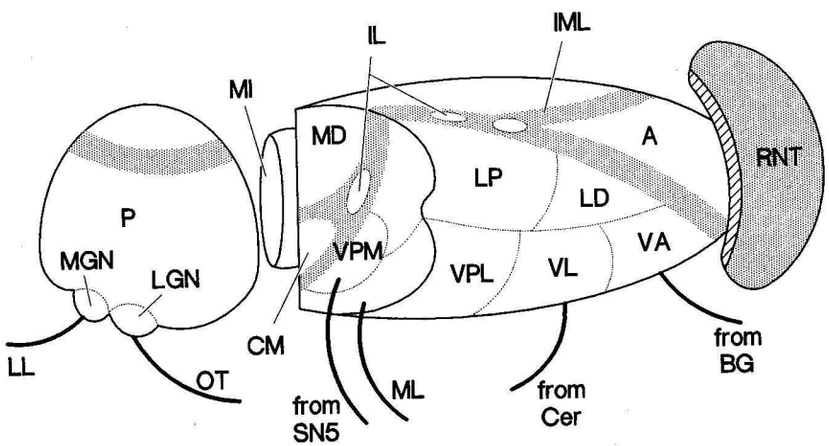

FIG. 8.1. Schematic three-dimensional view of right thalamus with many of its major nuclei. A cut is placed in the posterior part to reveal a representative cross section. Some of the important ascending afferents are also shown. To prevent obscuring of the dorsal thalamus, only the rostral tip of the reticular nucleus of the thalamus (RNT) is shown. Other abbreviations: A, anterior; BG, basal ganglia; Cer, cerebellum; CM, centromedian; IL, intralaminar nuclei; IML, internal medullary lamina; LD, lateral dorsal; LGN, lateral geniculate nucleus; LL, lateral lemniscus; LP, lateral posterior; MD, mediodorsal; MGN, medial geniculate nucleus; 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; VPL, ventral posterolateral; VPM, ventral posteromedial. See E. G. Jones (1985) for details of connectivity of these nuclei. (Redrawn from Brodal, 1981.)

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 posteromedial 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, whereas 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 from the parabrachial nucleus of the pons and projects to the primary somatosensory cortex. The pulvinar is innervated by the superior colliculus and the pretectum. The *ventral lateral nucleus* receives the majority of its input from the deep cerebellar nuclei and projects to the primary motor cortex. The *ventral anterior nucleus* is innervated by the basal ganglia and projects to both the motor cortex and the basal ganglia.

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 to be truly 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.

Figures 8.2 and 8.3 illustrate 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 this 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 exist within other thalamic nuclei, such as the VPL, VPM, and MGN (E. G. 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 the medial interlaminar nucleus which, despite its name, is really just a part of the LGN.

NEURONAL ELEMENTS

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 8.4 schematically illustrates the major afferents for a typical dorsal thalamic nucleus. Seen in this perspective, the retinal or lemniscal afferents to

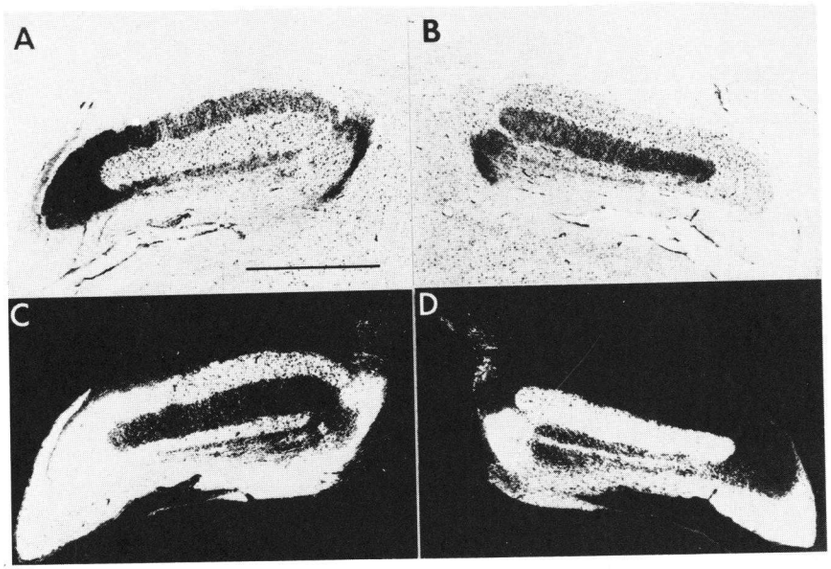

FIG. 8.2. Photomicrographs of the cat's LGN, showing its lamination as seen in coronal view near the middle of the nucleus. The sections were treated for autoradiography after retinogeniculate terminals from the right eye were labeled by injection of that eye with tritiated proline. The labeled terminals are dark in the bright-field views and bright in the dark-field views. Although not labeled, the perigeniculate nucleus is the thin band of neurons lying just above lamina A. See Fig. 8.3a for labeling plus an interpretation of these photomicrographs. **A.** Bright-field view of left LGN. **B.** Bright-field view of right LGN. **C.** Dark-field view of left LGN. **D.** Dark-field view of right LGN. (From Sherman, 1985.)

relay cells are one class among several and thereby are a minority. The other afferents include long pathways from the cortex and brainstem reticular formation plus local inputs from RNT cells and interneurons.

Retinal or lemniscal afferents. The best characterized input to a dorsal thalamic nucleus is that which conveys the main sensory message to be relayed to cortex. 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. For simplicity, we shall refer to these afferents as the retinal (or retinogeniculate) and lemniscal (or lemniscothalamic) afferents; generic terms for other afferents are thus nonretinal and nonlemniscal.

In cats, retinal ganglion cells can be divided into at least three physiologically and morphologically distinct classes: X cells, Y cells, and the remainder, which we shall refer here to as W cells. Their main features are summarized in Table 8.1 (see also Sherman and Spear, 1982; Sherman, 1985; and Chap. 6). Other

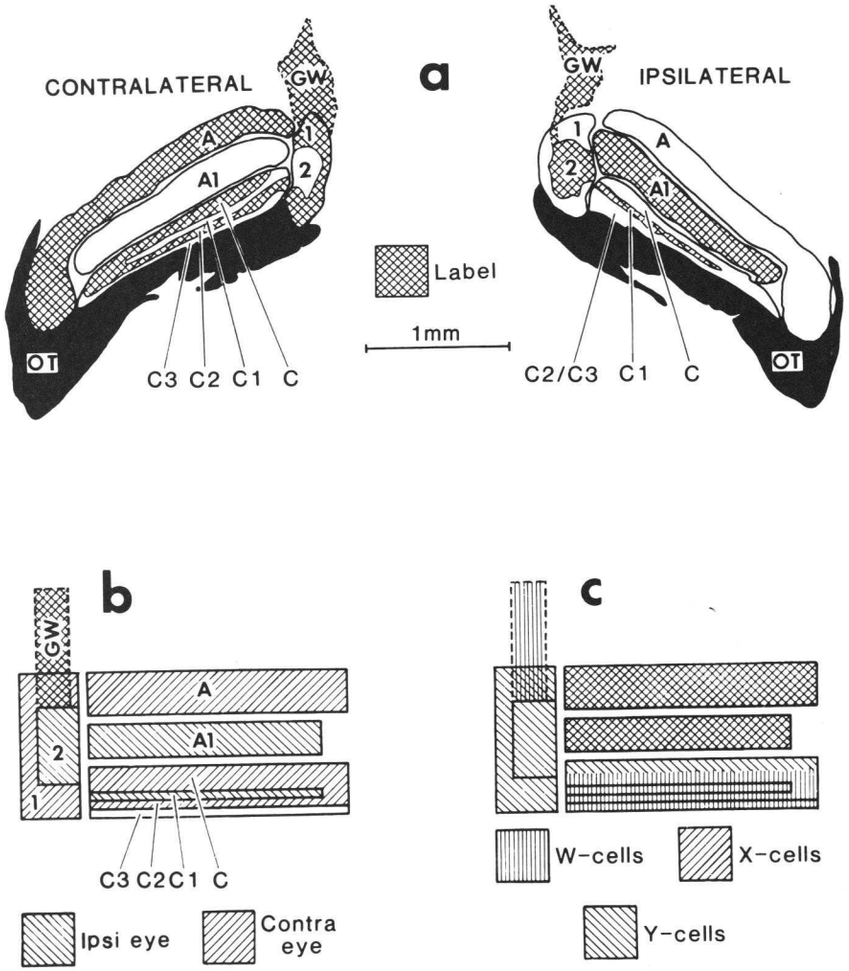

FIG. 8.3. Lamination of the cat's LGN. **a.** Interpretation of the photomicrographs in Fig. 8.2. For the left (*contralateral*) LGN, the right nasal retina projects to laminae A, C, and C2, lamina 1 of the medial interlaminar nucleus (MIN), and the geniculate wing (GW); for the right (*ipsilateral*) LGN, the right temporal retina innervates laminae A1 and C1, lamina 2 of the MIN, and the GW. Not shown is MIN lamina 3, which would appear more rostrally in the LGN; this lamina is innervated by axons from the contralateral temporal retina. Neither retina innervates lamina C3 (which is innervated by the midbrain), and both retinas innervate the GW, which is the only geniculate region binocularly innervated. **b.** Schematic view of ocular input to geniculate laminae shown in *a*. **c.** Schematic view of distribution of W, X, and Y cells by lamina. W cells are limited nearly exclusively to the C-laminae and GW. X cells are limited nearly exclusively to the A-laminae. Y cells are found in the A-laminae, the MIN, and the top tier of lamina C. OT, optic tract. (From Sherman, 1985.)

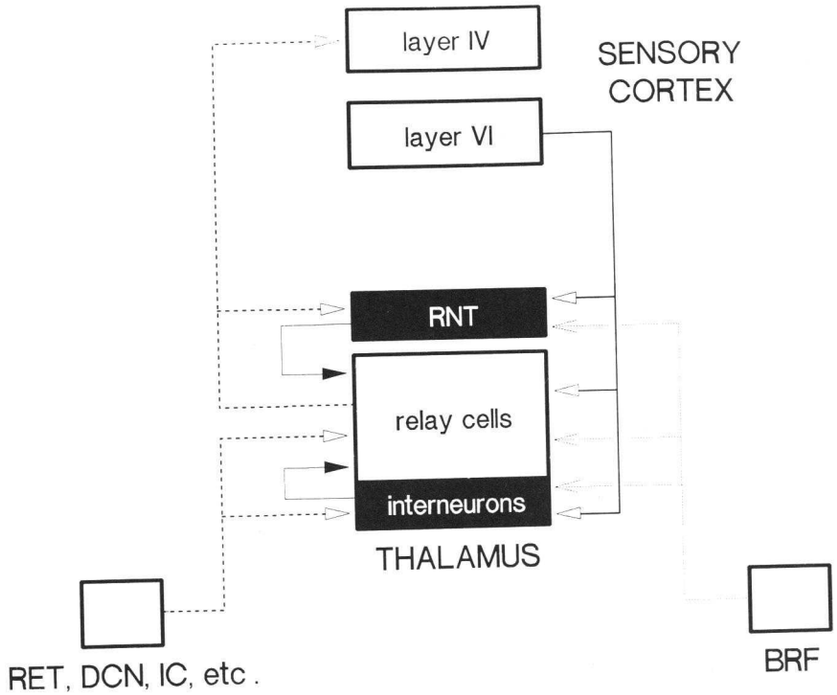

FIG. 8.4. Schematic summary of main inputs to thalamic relay cells. The main sensory input arrives from retina (RET) via the optic tract, the dorsal column nuclei (DCN) via the medial lemniscus, and the inferior colliculus (IC) via the lateral lemniscus. Local GABAergic inhibitory input is provided by interneurons and cells of the reticular nucleus of the thalamus (RNT). Other main inputs include axons from layer 6 of sensory cortex and cholinergic, noradrenergic, or serotonergic axons from the brainstem reticular formation (BRF). (Redrawn from Sherman and Koch, 1986.)

Table 8.1. Main Features of W, X, and Y in Retina and LGN Cells

Property	W cells[a]	X cells	Y cells
Receptive field size	Large	Small	Medium
Contrast sensitivity	Poor	Fair	Good
Spatial resolution	Poor	Good	Fair
Temporal resolution	Poor	Fair	Good
Axonal conduction velocity	Slow	Medium	Fast
Retinal ratio	10–20%	75–80%	5–7%
LGN relay cell ratio	10%	40–50%	40–50%

[a]Here we refer only to the subset of W cells that seem to be involved in retinogeniculate innervation; see Sherman (1985) for details.

mammals, including primates, have comparable retinal ganglion cell classes (Stone, 1983; Rodieck and Brening, 1973; Sherman, 1985). Every X and Y cell, but only a minority of W cells, innervates the LGN. The A-laminae in the cat's LGN include only X and Y cells (Fig. 8.3c). We know most about X and Y cells there, but, unfortunately, very little is yet known about W cells. Thus most of our comments are restricted to the X and Y pathways through the geniculate A-laminae. Each of these retinal cell types innervates a unique geniculate cell type, thereby establishing W, X, and Y classes of geniculate cell and parallel, functionally distinct W, X, and Y pathways. This organization of W, X, and Y pathways has led to the important concept of *parallel processing*, whereby each of the pathways analyzes somewhat different aspects of the visual scene (for details, see Sherman and Spear, 1982; Stone, 1983; Shapley and Lennie, 1985; Sherman, 1985). Parallel processing seems to be a feature of all sensory systems (Dykes, 1983; E. G. Jones, 1985).

Retinogeniculate axons appear to be excitatory and glutamatergic, which means they use the amino acid glutamate or a similar compound as a neurotransmitter (Kemp and Sillito, 1982). Recent evidence suggests that part of this excitatory input is mediated via receptors for *N*-methyl-D-aspartate (NMDA; Moody and Sillito, 1988; Lo and Sherman, 1989). Likewise, at least some of the lemniscal input to VPL uses a glutamate-like substance and NMDA receptors (Salt, 1988).

Within the appropriate geniculate lamina, each retinal axon arborizes repeatedly to form many short branches, each of which ends in a knoblike terminal (Bowling and Michael, 1984; Sur et al., 1987). It is at these terminals that synapses are formed. The terminal arborizations are relatively restricted, of the order of 100–300 μm in diameter, although X arbors are consistently smaller than are Y arbors. The restriction of these terminal arbors is necessary for maintaining the retinotopic map. Retinal X axons outnumber Y axons by roughly 10 to 1, but the ratio of X to Y geniculate cells postsynaptic to these retinal axons is only about 2 to 1 (Sherman, 1985; see also below). This change in X/Y ratios between retina and LGN seems to result largely from the fact that retinogeniculate Y arbors are more extensive than are the X arbors. Most geniculate cells receive their retinal input from a single axon, or a very small number. There is thus little convergence in retinogeniculate circuitry, although considerable divergence exists, because each retinal axon innervates roughly 5–10 (for X axons) or 30–50 (for Y axons) geniculate neurons. The limited convergence maintains small receptive fields among geniculate neurons and helps to preserve spatial acuity in the visual system.

The nature of lemniscal input to other thalamic nuclei is not known to the same detail as is the case for retinogeniculate axons. However, the basic features seem similar for all thalamic nuclei (E. G. Jones, 1985). Thus lemniscal afferents to the VPL and MGN exhibit the same general morphology as do retinogeniculate axons, and there seems to be little convergence among lemniscothalamic connections.

Cortical afferents. The most numerous inputs to thalamus originate among layer six pyramidal cells of the cortex (see Fig. 8.4). Like retinal or lemniscal axons, these cortical axons are excitatory and appear to be glutamatergic (Giuffrida and Rustioni, 1988). Strong reciprocity exists in thalamocortical connections, because the cortical input for each thalamic nucleus generally 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 projects back, respectively, to the VPL and MGN.

The anatomically dominant input to thalamus arises from cortex. In fact, there seems to be at least an order of magnitude more corticothalamic axons than thalamocortical ones. Thus roughly four million 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. Nonetheless, 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. Corticogeniculate neurons seem to be heterogeneous and probably represent several functional classes (Tsumoto and Suda, 1980), 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, and these have not yet been thoroughly studied. Afferents from the brainstem reticular formation in the pons and midbrain (see Fig. 8.4) include cholinergic neurons (i.e., using acetylcholine as a neurotransmitter) of the pedunculopontine tegmental nucleus, noradrenergic neurons (i.e., using norepinephrine) of the locus coeruleus, and serotonergic neurons (i.e., using serotonin) of the raphe nucleus. These inputs can either excite or inhibit thalamic neurons (see Chap. 2 and below).

The LGN receives additional although sparse brainstem inputs that may be unique to the visual pathways, and these are thus omitted from Fig. 8.4. 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, but the neurotransmitters for the collicular and pretectal inputs are not known. They will not be further considered in this chapter, and the reader is instead referred to the discussion of this in several recent papers (Harting et al., 1986; Fitzpatrick et al., 1988).

Inputs from the RNT. A final extrinsic source of innervation to each dorsal thalamic nucleus derives from the RNT (Jones, 1985; Ohara and Lieberman, 1985; Sherman and Koch, 1986). The RNT should not be confused with the brainstem reticular formation. The RNT 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 RNT associated with it, and reciprocal connections are formed between them (E. G. Jones, 1985; Ohara and Lieberman, 1985; Sherman and Koch, 1986). That is, relay cell axons

en route to cortex pass through the appropriate RNT zone, where they emit collateral terminals, and the RNT cells in turn project axons back into the dorsal thalamic nucleus. It is worth noting that corticothalamic axons also pass through the appropriate RNT zone en route to their thalamic destination, and they also provide collateral innervation to these RNT cells. Finally, the RNT is also innervated by the same regions of brainstem that innervate the dorsal thalamus. The RNT cells are GABAergic (i.e., they use gamma-aminobutyric acid, or GABA, as a neurotransmitter) and inhibit their dorsal thalamic targets.

For the cat's LGN, the related RNT zone is known as the perigeniculate nucleus, and it lies just dorsal to lamina A. Among purists, there is some controversy as to whether or not the cat's perigeniculate nucleus is a part of the RNT or whether it is a special GABAergic cell group unique to the LGN. Because all of its connections seem completely analogous to other RNT regions, and because no other RNT zone for the LGN has yet been defined, we shall consider it to be a part of the RNT.

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 RNT en route. Roughly 300,000 relay cells reside in each of the A-laminae of the cat's LGN (Sanderson, 1971), and Fig. 8.5A,B illustrates relay X and Y cells there. These are fairly representative of thalamic relay cells in other nuclei.

Interesting morphological differences between these geniculate relay cell types have been documented (Sherman, 1985). Compared to the Y cells, the X cells are slightly smaller with thinner dendrites and thinner axons; the dendritic arbors of Y cells tend to be spherical, whereas those of X cells tend to be oriented perpendicularly to laminar borders and thus along projection lines; and the Y cells tend to have smooth dendrites, whereas many appendages (i.e., collections of knobs, thorns, or spines) exist on X cell dendrites, particularly near proximal branch points. These appendages mark the postsynaptic sites of retinal input and synaptic glomeruli (see below).

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 project to both striate cortex (area 17 or V1) and extrastriate cortex (mostly area 18, but also area 19 and the lateral suprasylvian cortex). The X cells project exclusively to area 17, whereas the Y and W cells project to striate and extrastriate cortices. However, in primates, nearly all geniculate neurons 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.

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 : 1 relay cell to interneuron ratio, but the rat's VPL has practically no interneurons

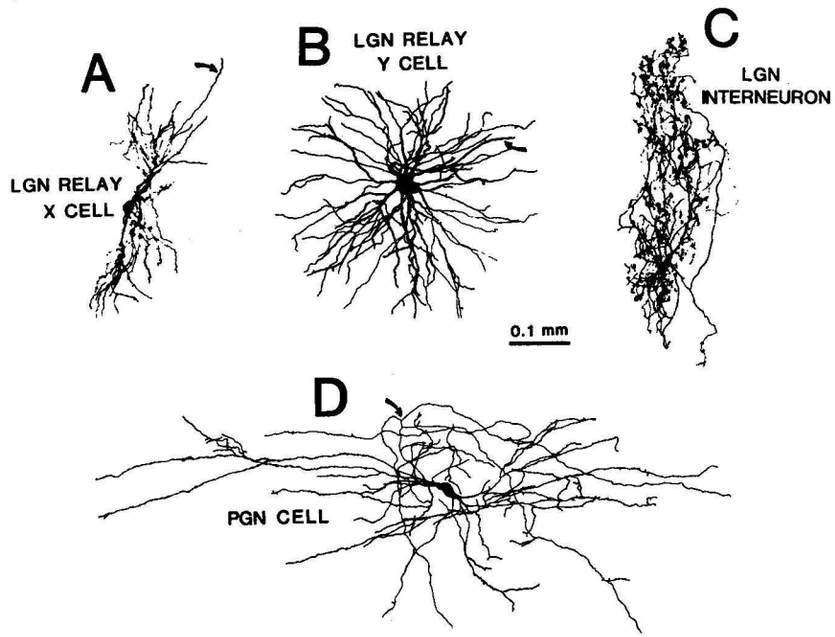

FIG. 8.5. Tracing of four representative neurons from the cat's LGN and perigeniculate nucleus, which is the equivalent of the RNT for the A-laminae of the LGN. Each of the cells was first studied physiologically and then labeled intracellularly with horseradish peroxidase. Where obvious, the axon is indicated by an arrow. **A.** Relay X cell. **B.** Relay Y cell. **C.** Interneuron. **D.** Perigeniculate neuron. (Redrawn from Sherman and Koch, 1986.)

(Ohara et al., 1983; Ralston, 1983; Spreafico et al., 1983; Fitzpatrick et al., 1984). 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).

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, sinuous dendrites (Fig. 8.5C). 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 (Ralston, 1971; Famiglietti and Peters, 1972; Hamos et al., 1985; Ralston et al., 1988). Many of the synapses from interneurons are thus dendritic in origin.

Most or all of these interneurons also have a conventional axon that arborizes

locally, typically within the dendritic arbor (Hamos et al., 1985; Montero, 1987). However, recent evidence suggests that at least some interneurons in the cat's VPL nucleus may lack an axon (Ralston et al., 1988). In the cat's LGN, interneurons seem to be associated mostly with the X pathway, since they receive retinal input only from X axons and contact mostly only relay X cells (Sherman and Friedlander, 1988). All interneurons are GABAergic, and both their dendritic and axonal outputs inhibit their postsynaptic targets.

We have previously described RNT cells as a source of nonretinal or nonlemniscal afferents to the dorsal thalamus. Although this is correct, RNT cells do not project beyond the thalamus, instead providing 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. For this reason, we illustrate the morphology of a perigeniculate neuron (Fig. 8.5D) along with a relay X and Y cell and an interneuron in Fig. 8.5. It is not yet clear what, if any, fundamentally different role in retinogeniculate and lemniscothalamic transmission is played by the RNT 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, 1971; Wilson et al., 1984; Hamos et al., 1985; E. G. Jones, 1985; Montero, 1987; Ralston et al., 1988). The following description derives from the LGN.

Four major types of synaptic terminal exist in the LGN (Guillery, 1971), and their origins are largely defined. RLP terminals (*r*ound vesicles, *l*arge profiles, and *p*ale mitochondria) form asymmetrical synapses and comprise 10–20% of all synaptic profiles. They derive from retina. 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. Most RSD terminals derive from cortex, although some derive from brainstem sources. *F* terminals (*f*lattened vesicles) form symmetrical synapses and represent a little more than one quarter of the terminals in the LGN. 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 mostly arise from axons of RNT cells and interneurons, although some brainstem axons may also form F1 terminals; 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 8.6 schematically

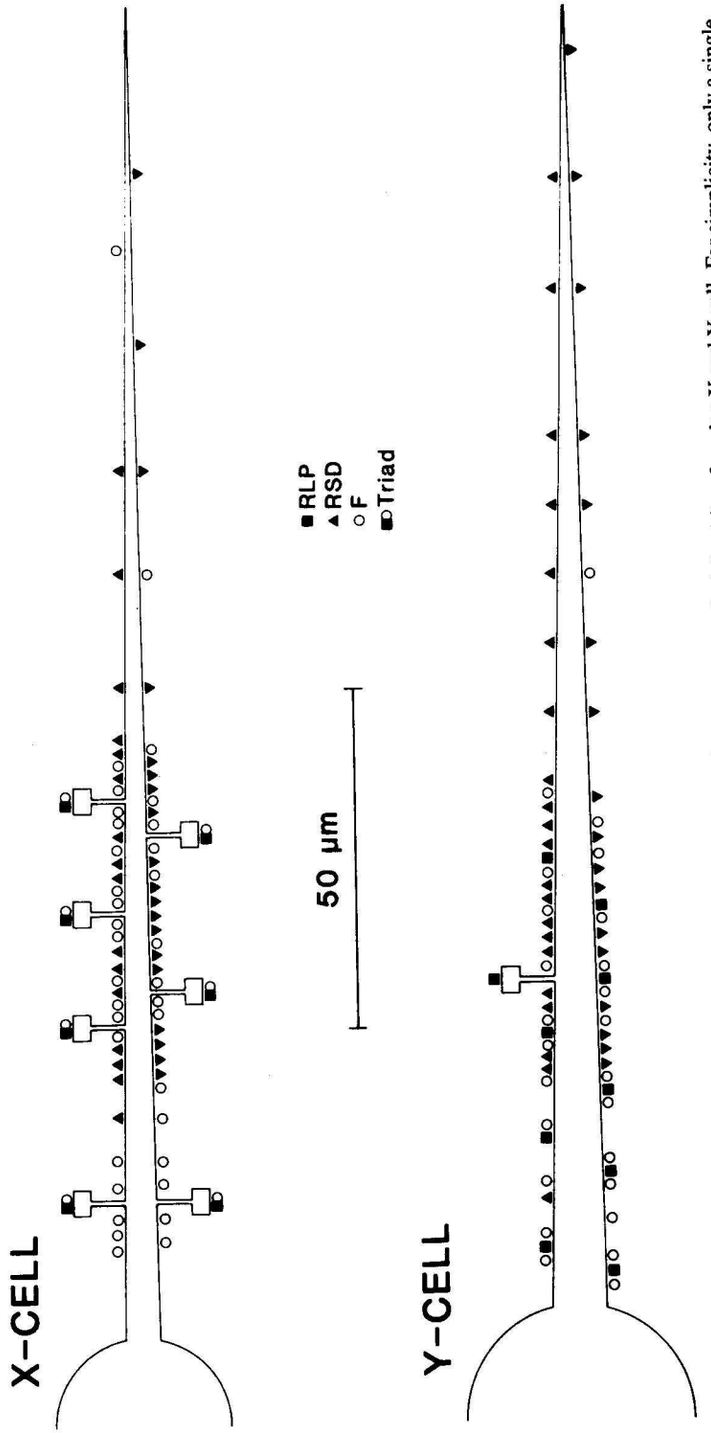

FIG. 8.6. Schematic representation of the distribution of synaptic terminals onto a typical dendrite of a relay X and Y cell. For simplicity, only a single, unbranched dendrite is shown for each neuron. Each type of synaptic terminal (RLP, RSD, and F), and also synaptic triads are indicated by separate symbols. The density (synapses per micrometer 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. Although all of the small squares represent F terminals, these can be divided into F1 and F2 types. F2 terminals, which derive from interneuronal dendrites, are largely limited to X cells as parts of the triadic synaptic arrangements located in glomeruli; F1 terminals, which derive from axons of interneurons, RNT cells, and brainstem cells, are found on both X and Y cells and do not participate in triads. The RSD terminals on the more peripheral dendrites derive nearly exclusively from corticogeniculate axons, whereas those more proximally located include many from brainstem axons. See text for details. (From Wilson et al., 1984.)

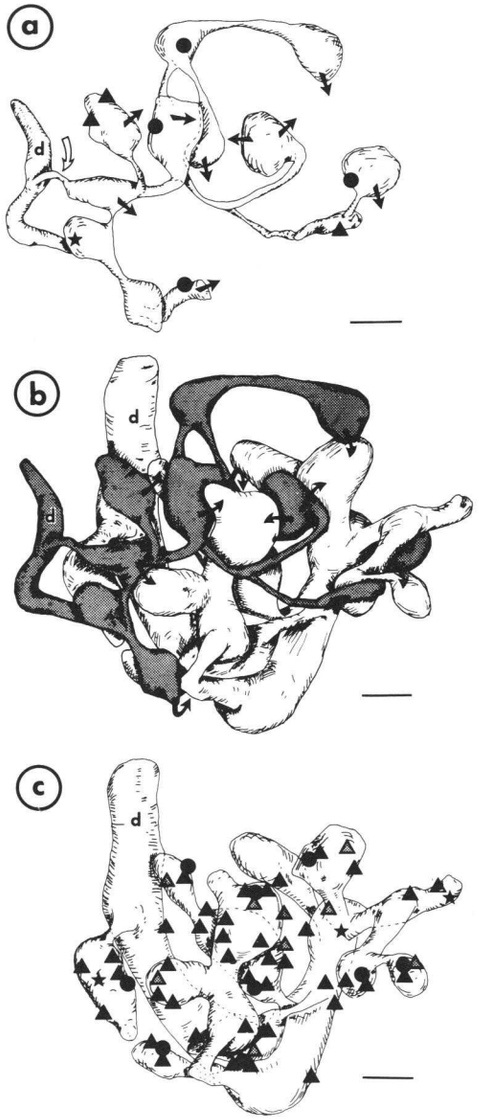

FIG. 8.7. Reconstruction of a glomerular zone in the geniculate A-laminae of the cat's LGN, showing the F2 terminals from an intracellularly labeled interneuron, the postsynaptic cluster of appendages from a relay X cell, and the location of synaptic contacts; each scale bar represents 1.0 μm. **a.** 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* (clear area). The synapses from the F2 terminals onto the relay X cell's appendages are illustrated (solid arrows; these represent

summarizes the 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 RSD input (i.e., mostly of cortical origin) dominates distal dendrites. However, major differences between 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 requires a description of the glomerulus and the synaptic triad.

A *glomerulus* is a complex synaptic structure (Fig. 8.7). 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 do not seem to be associated to any degree with the Y pathway (Sherman, 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 complexly interrelate with each other. A retinal terminal is typically located at or near the glomerular center and is surrounded by a number of other terminals. This retinal terminal contacts two different postsynaptic elements: an F2 terminal that derives from dendritic appendages of interneurons; and a dendritic appendage, or less frequently a dendritic shaft, 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.

Because three terminal types are involved, this special neuronal circuit within the glomerulus is known as a triad (see Koch, 1985, for a detailed hypothesis concerning the role of these triadic circuits). Figure 8.8 illustrates a triad involving RLP and F2 terminals and a dendritic appendage of a relay X cell. F1 and RSD terminals are also present in the glomerulus, and these may contact both F2 terminals and the relay X cell in triadic arrangements. 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 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 Y cells is simpler and

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the same solid arrows as in *a*). **c.** Unlabeled postsynaptic dendrite (d) from a relay X cell with eight appendages that receive all of the neuron's synaptic input in the reconstructed zone. These include nine synapses from RSD or retinal terminals (circles), nine 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 three 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.)

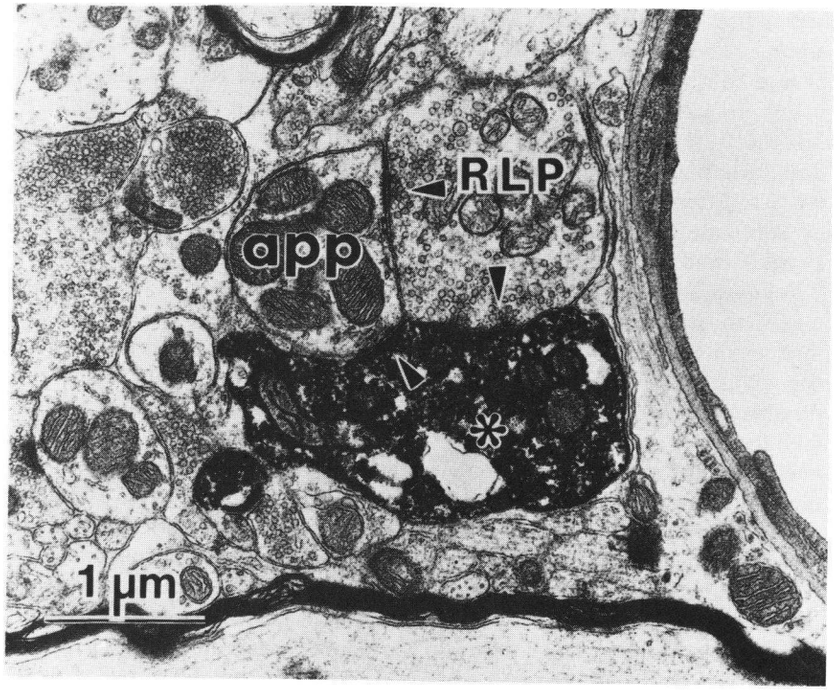

FIG. 8.8. Electron micrograph of a triadic synaptic relationship from the A-laminae of the cat's LGN. An interneuron was labeled with horseradish peroxidase, which created an electron-dense reaction product; its labeled F2 terminal is dark in this micrograph. A retinal terminal (RLP) contacts both the 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.

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 Y cells. More than 90% of the F input to these cells is of the F1 variety, whereas roughly two thirds of F input onto X cells is of the F2 variety.

INPUTS TO INTERNEURONS

Input to interneurons has been worked out in less detail (Hamos et al., 1985). 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. 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.

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. 8.9). The values of neuronal input resistance for these cells are 15–25 MΩ (megohms), and their passive membrane time-constants are 8–11 msec.

One of the reasons for the electrotonically restricted dendritic arbors of X and Y relay cells is the nature of their dendritic branches. These branches closely adhere to Rall's "3/2 branching rule" (Bloomfield et al., 1987), whereby the diameters of the daughter dendrites raised to the 3/2 power and summed equals the diameter of the parent dendrite raised to the 3/2 power (Rall, 1977). Such branching matches impedance on both sides of the branch point and permits efficient current flow across these branches in *both* directions (see Appendix). This 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 dendritic 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 electrotonically compact (Bloomfield and Sherman, 1989), 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 leads to poor current flow across these branch points. As a result, much of the synaptic circuitry in distal dendrites, including that involving the F2 terminals, is functionally isolated from the soma and axon (Fig. 8.9). 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.

Recent computational modeling based on these observations suggests an interesting mode of operation for these interneurons (Sherman, 1988; Bloomfield and Sherman, 1989), which is schematically depicted by Fig. 8.10. Clusters of dendritic appendages, which are major sites of input and output, represent local circuits whose computations are largely independent of activity in other clusters and in the soma; the axonal output is controlled instead 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

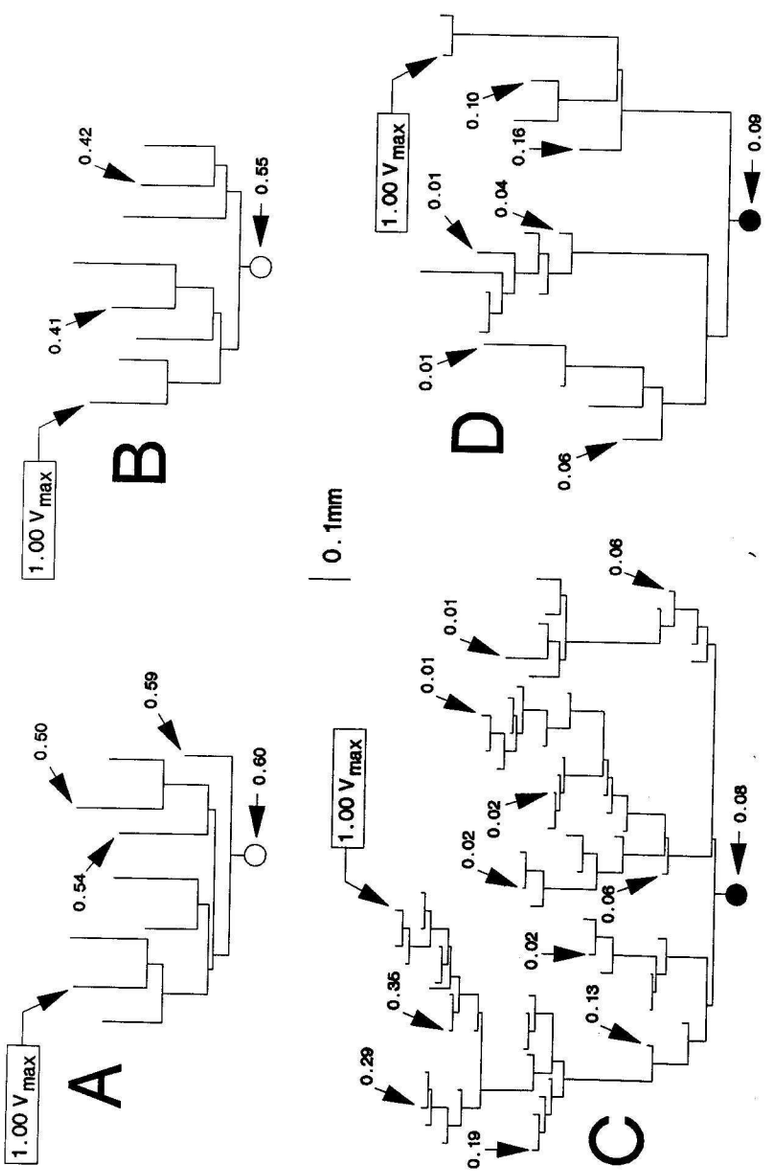

FIG. 8.9. **A–D.** Cable modeling of attenuation of a single voltage injection (i.e., the activation of a single synapse) within the dendritic arbors of the two relay X cells (A,B) and two interneurons (C,D) from the A-laminae of the cat's LGN. The site of voltage injection is indicated by the boxed 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.)

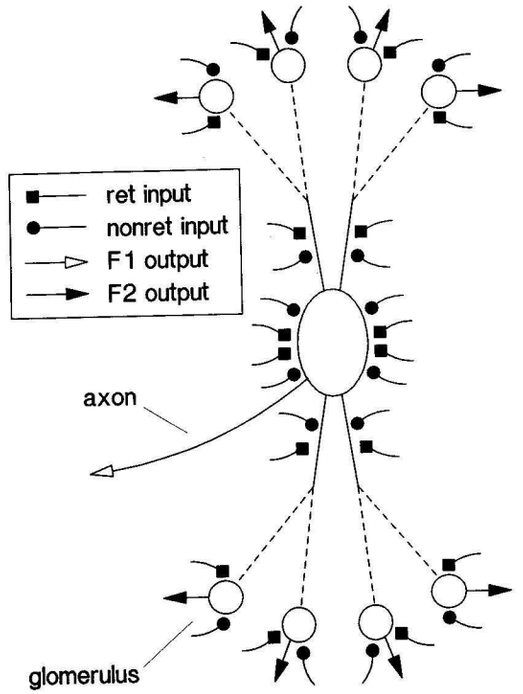

FIG. 8.10. Schematic view of hypothesis for functioning of interneurons in the cat's LGN. Retinal and nonretinal inputs are shown to the glomeruli as well as to the proximal dendrites and soma. The glomerular inputs are acted upon and lead to F2 outputs from the dendrites, whereas the inputs to the proximal dendrites and soma led 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 each other. Most glomeruli are also functionally isolated from one another.

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, 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, whereas integration of the dendritic F2 outputs depends on local inputs and involves a different postsynaptic target.

BASIC 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 still depend on a certain amount of

guesswork, 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 contains roughly 400,000 neurons (Sanderson, 1971). Of these, perhaps 300,000 are relay cells and 100,000 are interneurons. The interneurons seem exclusively part of the X pathway. 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 slightly fewer than 100,000 retinogeniculate axons; however, the X : Y ratio among these axons is much higher—at roughly 10 : 1—than is the case for geniculate relay cells (Sherman, 1985). The reason is that retinogeniculate Y axons innervate many more geniculate neurons than do X axons. The geniculate cells in the A-laminae are also innervated by more than four million corticogeniculate axons (Sherman and Koch, 1986), although the details of how these 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 RNT and brainstem reticular formation.

INTRINSIC CIRCUITRY

The basic organization of the cat's LGN is summarized schematically in Fig. 8.11. 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 reticular formation. Major inhibitory input derives from local GABAergic cells, which are the interneurons and RNT cells. Both of these GABAergic cells are innerated by cortex and by the brainstem reticular formation. In addition, RNT cells are innervated by axon collaterals from the relay cells, and interneurons receive input from retinal X axons.

Although much of the circuitry outlined in Fig. 8.11 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 or lemniscal input onto proximal dendrites in close association with GABAergic input. The GABAergic input derives from RNT cells and interneurons. Also innervating proximal dendrites are inputs from the brainstem reticular formation. Distal dendrites are dominated by cortical input, but the electrotonic compactness of relay cells implies that even these distal inputs are quite important functionally.

Figure 8.11 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 or lemniscal 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, because 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, interneurons also seem to be intimately related to X but not Y circuitry. They are innervated by retinal X axons, and their dendritic outputs nearly exclusively innervate relay X cells. 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.

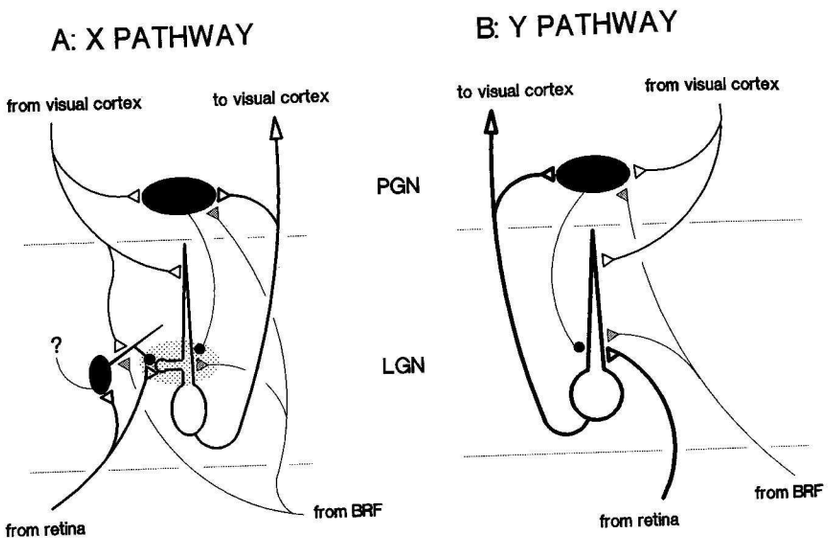

FIG. 8.11. Schematic view of X and Y circuits for the A-laminae of the cat's LGN. **A.** X pathway. Much of the input to X relay cells (open), including inputs from retina, from dendrites of interneurons (filled), from the perigeniculate nucleus (PGN, a part of the RNT), and from the brainstem reticular formation (BRF), is filtered through glomeruli (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 BRF; the target of the interneuron's axon remains unknown, except that it is extraglomerular. The PGN cell is innervated from geniculocortical axons, corticogeniculate axons, and BRF axons. **B.** Y pathway. This diagram is much simpler, because interneurons do not appear to be present. The retinal axon contacts the relay cell (open) on proximal dendritic shafts among axon terminals, from cortex, PGN, and brainstem. Cortical and brainstem inputs to the relay and PGN cells are similar to that shown in A. Although not illustrated, it seems that at least some PGN axons can innervate both relay X and Y cells.

It should be emphasized that the circuit schematically represented by Fig. 8.11 is preliminary and greatly simplified. Many questions still remain. For one example, what is the interrelated pattern of innervation involving single cortical axons, RNT cells (or interneurons), and relay cells? The implication of this last question is illustrated in Fig. 8.12 which shows two very different functional circuits that adhere to our superficial knowledge of interconnections among these cell populations. Figure 8.12A shows a true feedback inhibitory circuit in which

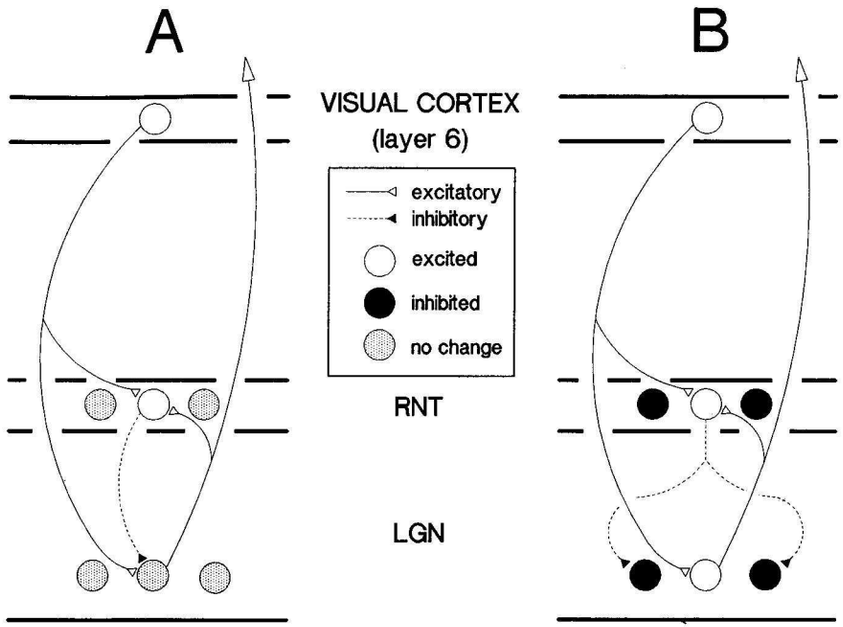

FIG. 8.12. Different circuits involving the RNT. **A.** Simple feedback inhibition for which thalamic relay cells and RNT cells are reciprocally connected. Activity of relay cell leads to its own inhibition after two synaptic delays. Likewise, activation of a corticothalamic axon leads to monosynaptic activation of the relay cell followed by disynaptic inhibition. These circuits thus act through negative feedback to keep the firing rates of thalamic relay cells from changing very much. **B.** A more complex circuit for which relay cells and RNT cells are connected with a lateral displacement. Activity of a relay cell now will disynaptically inhibit its neighbors. Because these neighbors normally activate RNT cells that inhibit the relay cell in question (not shown), this leads to disinhibition of that relay cell. Furthermore, a similar displacement of corticothalamic connections will both excite the relay cell and disinhibit it.

a relay cell's axon collateral excites an RNT cell that, in turn, inhibits this same relay cell; also, the cortical axon that monosynaptically excites the relay cell disynaptically inhibits it through the RNT cell. Figure 8.12B depicts a very different picture: RNT cells excited by the relay cell inhibit only its neighbors, which would have the effect of *disinhibiting* that relay cell by preventing its neighbors from inhibiting it through the RNT. Also in Fig. 8.12B, the cortical axon excites the relay cell directly and disinhibits it indirectly by disynaptically inhibiting that relay cell's neighbors. Indirect evidence for the cat's LGN favors the circuit shown in Fig. 8.12B (see Sherman and Koch, 1986). However, this conclusion is tenuous, and our main point here is that, even though we can draw detailed circuit diagrams such as that shown by Fig. 8.11, we still cannot answer many functional questions about this circuit until we know more about single cell connections.

MEMBRANE PROPERTIES

SYNAPTIC RESPONSES

Figure 8.13A,B illustrates the responses of a geniculate relay cell to a synchronous volley of impulses arriving via its retinal afferents. Such responses typically consist of a monosynaptic EPSP followed by a disynaptic or multisynaptic IPSP. The IPSP is generated from interneurons and/or RNT cells (cf. Figs. 8.6, 8.8, 8.11, and 8.12). This excitatory/inhibitory sequence is exhibited by most thalamic cells in response to a lemniscal volley. Because of the monosynaptic nature of the retinal or lemniscal input, a relay cell responds to such input with a relatively fixed latency (Fig. 8.13C).

The responses shown in Fig. 8.13 were obtained under artificial experimental conditions from a preparation physiologically distorted by various drugs and anesthetics. During natural activity, these thalamic responses would be heavily modulated by nonretinal or nonlemniscal inputs. In order to comprehend how nonretinal pathways can control responses of thalamic neurons to retinal inputs, and similarly how nonlemniscal pathways control responses of VPL and MGN neurons to their lemniscal inputs, we must first understand the intrinsic electrophysiological properties of these thalamic neurons.

INTRINSIC CONDUCTANCES

The intrinsic electrophysiological properties of neurons play a great role in determining their integrative characteristics (see Chap. 2 of this book). 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. Instead, these cells have a variety of active membrane conductances, many controlled in a conventional manner by ligand binding of neurotransmitters, but some controlled by membrane voltage and others 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 and within RNT neurons (McCormick and Prince, 1988; Steriade and Llinás, 1988). These conductances all lead to currents that alter the membrane potential. The number of active conductances described for thalamic neurons continues to grow, and the present number is at least six. 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, and for the most part these have been described in detail in Chap. 2.

Na^+ conductances. Two voltage-dependent Na^+ conductances have been described. The fast, inactivating Na^+ conductance described by Hodgkin and Huxley is voltage dependent and subserves the conventional action potentials. The other Na^+ conductance is persistent and noninactivating. This creates a

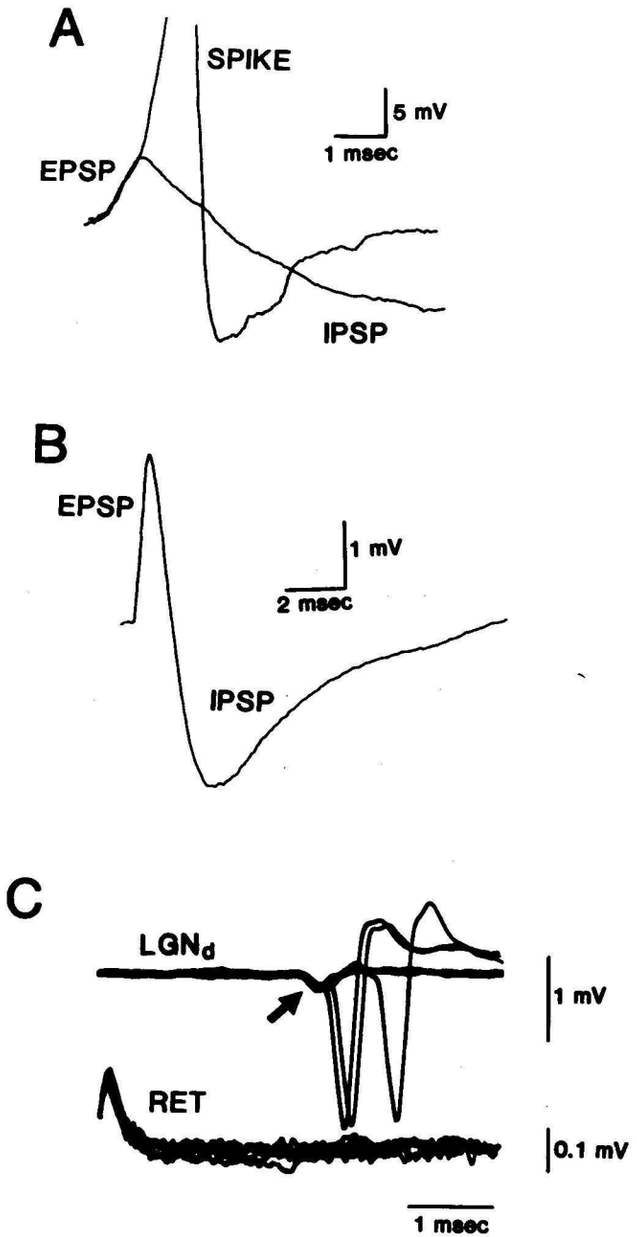

FIG. 8.13. Examples of retinogeniculate transmission in cats. **A.** Intracellular records from a geniculate relay cell showing response to electrical stimulation of the optic chiasm. Responses to two different levels of stimulation are superimposed. At the lower level, a monosynaptic EPSP is followed by a disynaptic IPSP. At the higher level, threshold is reached for an action potential (SPIKE). **B.** Computer average of 100 responses at the lower level of stimulation for the same cell as in **A.** This shows the EPSP and IPSP more clearly. **C.** Extracellular records from a geniculate neuron (LGN) and its simultaneously recorded retinal input (RET). The trace showing the geniculate cell's responses is triggered from the preceding action potential of the retinal afferent. For the geniculate trace, at a fixed delay after each retinal spike, a brief potential occurs which is known as the *s-potential* (arrow). The s-potential is thought to represent the extracellularly recorded EPSP. In many, but not all, traces, the s-potential is followed soon after by an action potential. Thus each geniculate spike is preceded at a fairly fixed time by a retinal spike, although not every retinal spike evokes one in the postsynaptic cell. (A,B redrawn from Bloomfield and Sherman, 1988; C redrawn from Cleland et al., 1971.)

plateau depolarization and partially regulates the generation of rhythmic firing in thalamic neurons.

Ca^{2+} conductances. Likewise, 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 and lemniscothalamic transmission described more fully below; it is often known as the *low-threshold Ca^{2+} spike* or *conductance*. The currents associated with these Ca^{2+} conductances have been called, respectively, I_L for the high-threshold one and I_T for the low-threshold one (see Chap. 2). The low-threshold spike occurs both in RNT cells and in thalamic relay neurons, but preliminary evidence suggests that, at least for the LGN, this conductance plays little role in interneurons (McCormiock and Pape, 1988).

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.

IMPORTANCE OF THE LOW-THRESHOLD SPIKE

The low-threshold spike is especially important for the control of retinogeniculate and lemniscothalamic transmission (see Chap. 2). It is activated by a small depolarization from rest (thus the low threshold) that opens membrane channels permeable to Ca^{2+}, thereby increasing a Ca^{2+} conductance (Steriade and Llinás, 1988). The ensuing, all-or-nothing Ca^{2+} spike is relatively slow and has a triangular wave form (Fig. 2.4D). Superimposed onto this spike are 2–7 fast, conventional Na^+ action potentials. This entry of Ca^{2+} into the cell activates one or more voltage- and Ca^{2+}-dependent K^+ conductances that hyperpolarize the neuron for 50–200 msec. This hyperpolarization is sufficiently strong to create a relative refractory period during which the cell is fairly inexcitable and can thus no longer relay retinal or lemniscal information to cortex. Interestingly, if the membrane potential is always held more positive than approximately −60 mV, the low-threshold Ca^{2+} conductance is *inactivated*. This inactivation can be

reversed, or *deinactivated,* if the membrane potential is held below approximately −65 mV for at least 50–100 msec. When deinactivated, the low-threshold spike can be triggered by a small depolarization.

Any change in activity that hyperpolarizes the cell sufficiently long to deinactivate this Ca^{2+} conductance primes the cell for the initiation of the low-threshold spike. Physiologically, such deinactivation can result either from active hyperpolarization through GABAergic or other inputs, or from reduction of a tonic depolarizing input, such as the corticothalamic pathway. Any sufficiently large depolarization can then *activate* the low-threshold spike. This can be done either via an EPSP (e.g., from a retinal or lemniscal input) or via the relative depolarization that ensues from removing the deinactivating source (e.g., cessation of the hyperpolarizing input or restoration of the tonic depolarizing one). In fact, often the hyperpolarization due to the series of K^+ conductances following the low-threshold spike is sufficient in time and amplitude to deinactivate this spike, and the passive repolarization following these K^+ conductances activates it (Steriade and Llinás, 1988). This can be repeated for many cycles until some other input to the cell breaks through. The result is a neuron that enters a phase of cyclic, rhythmic activity at 6–10 Hz.

THALAMIC GATING FUNCTIONS

RELAY VERSUS BURST RESPONSE MODES

Thalamic relay cells therefore exhibit two distinct response modes: a *relay* mode and a non-relay *burst* mode (Sherman and Koch, 1986). If the cell is at rest or slightly depolarized so that its membrane is above roughly −60 mV, it is in the relay mode. Now a suprathreshold EPSP will induce a train of normal action potentials (see Fig. 2.5D). Within physiological limits, the frequency of action potentials monotonically rises with increasing EPSP amplitude. Under these conditions, transmission through the thalamic relay neuron to the cortex will lead to a pattern of input to the cortex that faithfully reflects the pattern of retinal or lemniscal input to the thalamus. However, once a thalamic neuron becomes hyperpolarized sufficiently long to deinactivate a low-threshold spike, it enters the burst mode (Fig. 2.5E). Now a suprathreshold EPSP will trigger a low-threshold spike, and many such spikes may ensue as the cell bursts rhythmically. Until this bursting cycle is broken, the neuron no longer relays sensory input to the cortex because its firing pattern bears no resemblance to the pattern of its retinal or lemniscal inputs.

RNT CONTROL OF RESPONSE MODES

Although thalamic neurons may switch between relay and burst modes at any time, the relay mode appears to be the state of most thalamic neurons in the awake, alert animal, whereas the burst mode dominates during less alert periods, including drowsiness and quiet or non-REM sleep (Steriade and Llinás, 1988). 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 RNT cells can spontaneously generate rhythmic discharges at a rate of approximately 10 Hz. The low-threshold spike appears to be the underlying cause of this endogenous bursting behavior, and the oscillations can be generated within individual RNT cells. Dendrodendritic synapses exist among RNT neurons, and these could serve to synchronize entire RNT regions. Recent studies have demonstrated that groups of deafferented RNT neurons can generate such synchronized oscillatory activity in the absence of external input (Steriade and Llinás, 1988).

Because RNT neurons provide an inhibitory, GABAergic input to thalamic relay cells, the RNT entrains its oscillatory activity onto these relay cells. That is, the synchronized bursts of RNT activity would lead to waves of hyperpolarization among relay cells; this would deinactivate 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 RNT via surgical or chemical means abolishes the oscillations (Steriade and Llinás, 1988).

ROLES OF OTHER INTRINSIC CONDUCTANCES

The low-threshold spike is the best studied and most dramatic membrane conductance relating to thalamic cell function, but other conductances are present that play more subtle roles in gating of the transmission of retinal or lemniscal input to cortex. Because these are not yet well established or studied for thalamic neurons, only several will be briefly noted below.

Afterhyperpolarization. The afterhyperpolarization (AHP) following action potentials is important for the integrative properties of the neuron. That is, the AHP is a hyperpolarization that establishes a relative refractory period for the neuron, and thus the strength and duration of the AHP controls the extent to which the neuron adapts to long-lasting excitatory inputs. This is known as spike frequency *adaptation* or *accommodation,* and is reflected by the inability of the neuron to respond at high frequencies to a prolonged afferent input. Results from both the guinea pig and cat indicate that action potentials in thalamocortical cells are followed by a prolonged AHP with an overall duration of up to 70 msec, whereas their duration in RNT cells is much shorter (8–10 msec). The different duration of the AHP is reflected in much higher firing rates for reticular than for thalamocortical cells. The basis of the AHP is an increase in one or possibly two Ca^{2+}-dependent K^+ conductances, since removal of extracellular Ca^{2+} or intracellular injection of Ca^{2+} buffers prevents these long-lasting AHPs.

Studies of bullfrog sympathetic ganglion cells (see Chap. 3) and rodent hippocampal neurons (see Chap. 11) have shown that most of the AHP and its consequent spike frequency accommodation can be essentially suppressed by local

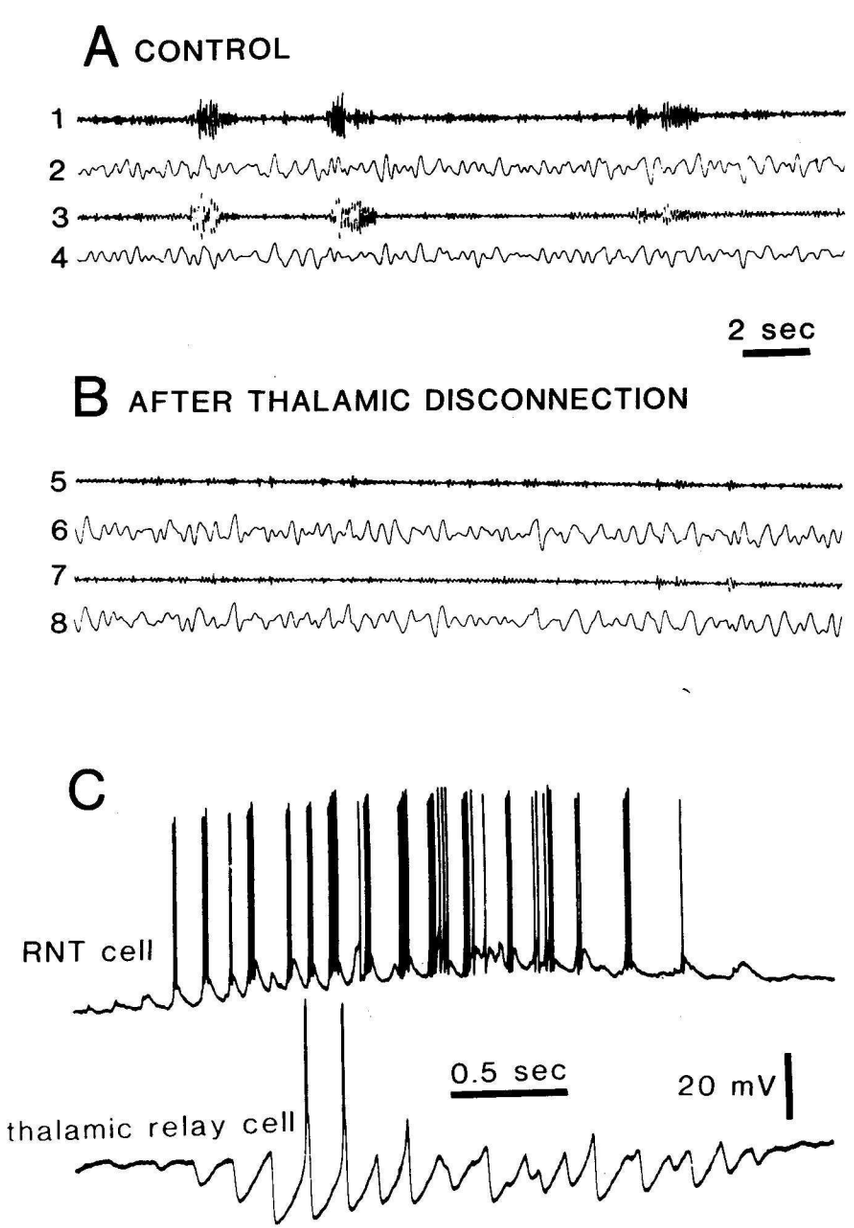

FIG. 8.14. Relationship of thalamus to spindle activity in the cortical electroencephalogram (EEG) of cats. **A,B.** Effect on the EEG of rostral thalamic transections that disconnect the thalamus from the cortex. The numbering of traces is as follows: 1 and 5, higher-frequency EEG (7–14 Hz) for right hemisphere; 2 and 6, lower-frequency EEG (0.5–4.0 Hz) for right hemisphere; 3 and 7, higher-frequency EEG (7–14 Hz) for left hemisphere; 4 and 8, lower-frequency EEG (0.5–4.0 Hz) for left hemisphere. **A.** Normally (before transection), each hemisphere shows activity in both the higher (7–14 Hz) and the lower (0.5–4.0 Hz) filtered traces. **B.** After transection, the higher frequencies are selectively eliminated from the EEG. **C.** Activity of thalamic neurons during an EEG spindle. During the spindle, the RNT 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 RNT 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.)

application of norepinephrine and/or acetylcholine (Sherman and Koch, 1986; Steriade and Llinás, 1988). This suppression involves the blockade of a slow, Ca^{2+}-dependent K^+ current known as the I_{AHP} (see Chap. 2). Because thalamic relay cells display an AHP and receive cholinergic and noradrenergic input from the brainstem, a similar mechanism may work in the thalamus to vary the gain of lemniscothalamic transmission.

Plateau potential. Thalamic neurons show a voltage-dependent Na^+ conductance, which shows very little if any inactivation. This leads to a persistent, inward current known as $I_{Na,p}$ (see Chap. 2), and it generates plateaulike potentials that can outlast the duration of the initial stimulus. It serves as a sort of counterweight to I_{AHP}; that is, it tends to counterbalance the Ca^{2+}-dependent K^+ conductance by generating a slow rebound depolarization. The $I_{Na,p}$ thus has a definite role in controlling the gain of lemniscothalamic transmission.

High-threshold Ca^{2+} spikes. Presumed intradendritic recordings in thalamic relay cells have also revealed a voltage-dependent, high-threshold Ca^{2+} conductance, similar to that observed in Purkinje cells (Steriade and Llinás, 1988; see also Chap. 7). This conductance triggers all-or-none depolarizing responses in the dendrites and soma that are followed by the activation of Ca^{2+}-dependent K^+ conductances (Steriade and Llinás, 1988). It is likely that dendritic spikes play a crucial role in relaying to the cell body postsynaptic potentials that are generated on dendrites.

SYNAPTIC TRANSMITTERS

GLUTAMATERGIC INPUTS

The major inputs to relay cells are the retinal or lemniscal inputs and the cortical inputs, and these all appear to be glutamatergic (see above). Of particular interest here is the nature of the postsynaptic receptors to glutamate-like substances. These basically fall into two major classes (for a review, see Mayer and Westbrook, 1987; see also Chap. 2).

The first class is what we shall refer to as the *non-NMDA* receptors. Based on the pharmacology of agonists and antagonists, many authors recognize two or three classes of non-NMDA receptor, but for the purposes of our treatment, we can lump them together. The non-NMDA receptor acts in a fairly straightforward way, and its activation increases the conductance to Na^+ and perhaps other cations, thereby depolarizing the cell.

The second class is the *NMDA* receptor. All cells responsive to glutamate-like substances seem to have non-NMDA receptors, and only a subset of these also have NMDA receptors. The NMDA receptor has the interesting property of being both voltage and transmitter dependent. At relatively depolarized levels of the membrane, 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: these Mg^{2+} ions are permitted to approach the channel by a hyperpolarized membrane but are driven away by a depolarized membrane. The range over which membrane depolarization can increase conductance of the channel associated with the NMDA receptor seems to vary across cells, but can extend from −140 mV to −40 mV. 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. In other words, the NMDA receptor complex can act as a sort of molecular AND gate.

The two receptors offer different means of gating synaptic transmission. With the conventional, non-NMDA receptor, EPSP amplitude decreases with membrane depolarization as the reversal potential for the EPSP is reached. However, with the NMDA receptor, EPSP amplitude actually increases with membrane depolarization over some physiological range, usually peaking near the resting potential, before further membrane depolarization toward the reversal potential reduces the EPSP amplitude. Evidence exists for the LGN and VPL that at least some of the relay cells use NMDA receptors for their retinal or lemniscal inputs (Moody and Sillito, 1988; Salt, 1988; Lo and Sherman, 1989). For these relay cells, any input that tonically modulates membrane potential (e.g., the cortical input) can determine the size of the retinal or lemniscal EPSP and thus offer a sensitive means of gating retinogeniculate or lemniscothalamic transmission (see Koch, 1987).

GABAERGIC INPUTS

Thalamic relay cells receive a large GABAergic input from RNT cells and interneurons. To a first approximation, these GABAergic inputs will inhibit the relay cells and thereby depress retinogeniculate and lemniscothalamic transmission. However, there are two provisos or complications to be added to this approximation.

First, two distinct GABAergic receptors, $GABA_A$ and $GABA_B$ receptors, are present in the thalamus, and both seem to exist on relay cells (Sherman and Koch, 1986; Bloomfield and Sherman, 1988). Activation of the $GABA_A$ receptor increases a Cl^- conductance, whereas activation of the $GABA_B$ receptor increases a K^+ conductance. Because the reversal potential for K^+ is much more negative (at roughly −100mV) 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, and $GABA_B$ inhibits more by hyperpolarizing the membrane. The $GABA_A$ response is thus much more nonlinear, acting more like a voltage multiplication, whereas the $GABA_B$ response is more linear, acting like simple voltage subtraction. Also, the $GABA_A$ response is somewhat faster than is the $GABA_B$ response.

Second, although both $GABA_A$ and $GABA_B$ activation counteract EPSPs and thus are inhibitory, they might also play an important role in controlling the relay versus burst response modes of relay cells. That is, both GABAergic responses may provide sufficient hyperpolarization to deinactivate the low-threshold spike. $GABA_B$ receptors would be more effective in this regard, because they provide more hyperpolarization and less shunting of an activating input.

BRAINSTEM INPUTS

As discussed above, various nuclei in the brainstem project in a diffuse manner to both the ventral and the dorsal thalamus. The best studied of these afferent inputs derive from the cholinergic, noradrenergic, and serotonergic neurons of the brainstem reticular formation, but the specific input patterns vary across species and thalamic nuclei (Singer, 1977; Sherman and Koch, 1986; Steriade and Llinás, 1988). For instance, in the cat, cholinergic inputs predominate to the LGN but not to the VPL (Fitzpatrick et al., 1989), and cholinergic inputs to the rat's LGN are relatively sparse (Levey et al., 1987). The effects on thalamic neurons of stimulating various sites in the brainstem reticular formation have proven complex and difficult to understand, although it seems clear that these brainstem sites are partially responsible for mediating arousal and alertness or drowsiness and sleep. The use of in vitro slice preparations as well as intracellular electrophysiology has permitted us to come to a much clearer understanding of the modulatory role of the brainstem reticular formation (Sherman and Koch, 1986), particularly for the cholinergic inputs.

Cholinergic inputs. The application of acetylcholine onto the mammalian thalamus leads to a complex constellation of effects. For RNT neurons, acetylcholine causes a small, slow, long-lasting *increase* in a K^+ conductance, and this is mediated by an M_2 muscarinic receptor. This increase in K^+ conductance leads to a long-lasting hyperpolarization, which in turn deinactivates the low-threshold spike and switches the RNT neuron into the burst mode (McCormick and Prince, 1987a,b). A similar slow and long-lasting *increase* in a K^+ conductance has been observed upon application of acetylcholine in GABAergic thalamic interneurons in the cat's LGN (McCormick and Pape, 1988). However, since the Ca^{2+} underlying the low-threshold spike appears to be absent in interneurons, this increase in K^+ conductance serves only to inhibit action potentials.

Application of acetylcholine to relay cells produces a more complex response (McCormick and Prince, 1987a,b). The most prominent response is a rapid depolarization due to an increased cation conductance that is subserved by a nicotinic receptor. This nicotinic response is often followed by a slower depolarization due to activation of a muscarinic receptor that decreases a K^+ conductance. These nicotinic and muscarinic depolarizations, by inactivating the

low-threshold Ca^{2+} spike, keep the neuron in its relay mode. Some relay cells may also respond with a slow increase in a K^+ conductance, which is subserved by an M_2 muscarinic receptor and is much like the muscarinic response of RNT cells and interneurons.

On balance, the final impact on thalamocortical processing of this ascending brainstem cholinergic input remains something of a mystery. On the one hand, this input reinforces retinogeniculate and lemniscothalamic transmission by depolarizing the relay cells and inhibiting the interneurons. This depolarization makes the relay cells more sensitive to retinal and lemniscal input and encourages them to remain in the relay mode. On the other hand, cholinergic input seems to switch RNT cells into the burst mode, and, as noted above, this could indirectly switch relay cells into this mode as well. Perhaps the final answer is to be found in more detailed studies of thalamic circuits, because, as suggested by Fig. 8.12B, connections between the RNT and its accompanying dorsal relay nucleus may represent a sort of indirect, positive feedback circuit at the single cell level rather than a negative feedback. It may be that cholinergic axons enhance the relay mode of some relay cells directly while indirectly promoting the burst mode of others through the RNT. When such details are better understood, the role of the ascending cholinergic input might become much clearer.

Noradrenergic inputs. The noradrenergic innervation of the thalamus arises largely, if not exclusively, from neurons in the locus coeruleus. The postsynaptic effects of norepinephrine seem more straightforward than are those of acetylcholine (McCormick and Prince, 1988). In the LGN, MGN, and RNT, norepinephrine produces a decrease in K^+ conductance that leads to a slow depolarization lasting for more than 1 min. The effective resting potential in all thalamic cells is thereby shifted to more positive values, promoting the relay mode and facilitating the ability of retinal or lemniscal EPSPs to trigger conventional action potentials.

Serotonergic inputs. A rather poorly understood innervation of thalamus originates with serotonergic neurons of the dorsal raphe nucleus in the brainstem. The function of this input has been studied sparsely in the LGN, and its overall action there seems to depress retinothalamic transmission (see Sherman and Koch, 1986). However, we must know more about both the responses of thalamic neurons to serotonin as well as the distribution of this serotonergic input to other thalamic nuclei.

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 or Y). Thus the 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, antagonistic 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; Sherman, 1985; Shapley and Lennie, 1985). Perhaps the most dramatic difference is the presence of a purely inhibitory receptive field for the nondominant eye having a homonymous position to that of the dominant eye's receptive field. Such details have yet to be established for other sensory pathways, but preliminary data suggest a resemblance in receptive field properties between MGN or VPL cells and their lemniscal inputs. For the purposes of the present discussion, we conclude that no significant receptive field transformation occurs 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 observed when progressing through the synaptic zones of retina or cortex and also 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

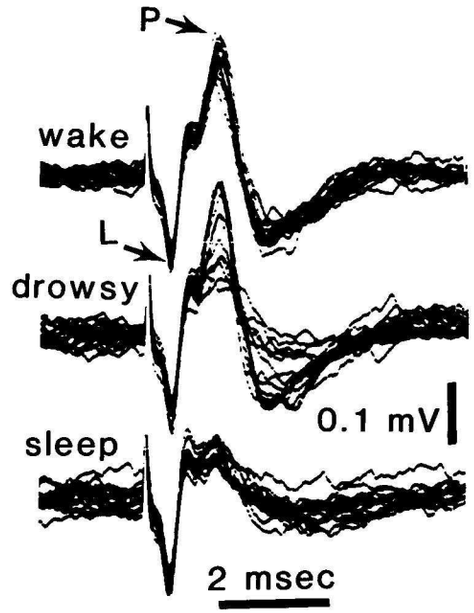

FIG. 8.15. Effects of different levels of consciousness on the ability of the thalamus to transmit synaptic information to cortex. Illustrated are field potentials recorded from the cat's ventral anterior thalamus in response to electrical stimulation of the brachium conjunctivum. Input from the brachium conjunctivum is analogous to lemniscal input for the ventral anterior nucleus. The response consists of a presynaptic afferent "lemniscal" component (L) plus a postsynaptic relayed component (P). The amplitude of the latter component is a measure of the gain of lemniscothalamic transmission. Note that, although the presynaptic component is unchanged, the postsynaptic component gets progressively smaller as the animal descends into sleep through drowsiness. (Revised from Steriade and Llinás, 1988.)

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 functional change in receptive fields across the retinogeniculate or lemniscothalamic synapse 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 (10–20%) present in the neuropil and onto relay cells is retinal in origin. 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 or control the gain of retinogeniculate transmission.

This provides a unique role for the thalamus: it is not merely a passive relay, but instead 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 (see Fig. 8.15). This active filtering has not been revealed by the usual receptive field studies, possibly because the anesthetics used in such studies block action of many of the nonretinal pathways, but recording in unanesthetized animals has revealed considerable state-dependent variation in responsiveness of geniculate neurons. While it seems clear what general role the LGN and other thalamic nuclei play, further work is needed to reveal how many different types of retinogeniculate and lemniscothalamic filtering exist and precisely how these filtering functions are achieved.

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 structures, 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 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 are 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. 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 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.

The connectional relationships between these structures are shown in the diagram in Fig. 9.2. In dealing with this complexity, it is helpful to distinguish between inputs and outputs. With regard to the caudate nucleus and the putamen,