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The Anatomy and Physiology of Gating Retinal Signals in the Mammalian Lateral Geniculate Nucleus

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In the mammalian visual system, the lateral geniculate nucleus is commonly thought to act merely as a relay for the transmission of visual information from the retina to the visual cortex, a relay without significant elaboration in receptive field properties or signal strength. However, many morphological and electrophysiological observations are at odds with this view. In this paper, we will review the different anatomical pathways and biophysical mechanisms possibly implementing a selective gating of visual information flow from the retina to the visual cortex. We will argue that the lateral geniculate nucleus in mammals is one of the earliest sites where selective, visual attention operates and where general changes in neuronal excitability as a function of the behavioral states of the animal, for instance sleep, paradoxical sleep, arousal etc., occur.

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Abstract

In the mammalian visual system, the lateral geniculate nucleus is commonly thought to act merely as a relay for the transmission of visual information from the retina to the visual cortex, a relay without significant elaboration in receptive field properties or signal strength. However, many morphological and electrophysiological observations are at odds with this view. Only $10-20\%$ of the synapses found in geniculate relay neurons are retinal in origin. Roughly half of all synapses derive from cells in layer VI of visual cortex; roughly one third are inhibitory and GABAergic, derived either from interneurons or from cells of the nearby perigeniculate nucleus. Most of the remaining synapses probably derive from cholinergic, noradrenergic and serotonergic sites within the brainstem reticular formation. Moreover, recent biophysical studies have revealed several ionic conductances present in all thalamic neurons. One is a voltage- and time-dependent Ca^{2+} conductance that produces a low threshold spike. Activation of this conductance transforms a geniculate neuron from a state of faithful relay of information to one of bursting behavior that bears little relationship to the activity of its retinal afferents. Another is a Ca^{2+} dependent K^{+} conductance underlying the long-lasting afterhyperpolarization following an action potential. Activation of this current leads to spike frequency adaptation in response to sustained, suprathreshold input. Intracellular recordings from pyramidal cells in slices of mammalian hippocampus have shown that one of these currents (I_{AHP}) can be blocked by noradrenalin or acetylcholine, leading to an increased cellular excitability. Thus, gating of geniculate relay cells can be effected through at least three different mechanisms: (1) conventional GABAergic inhibition (through interneurons and perigeniculate cells), which is controlled via brainstem and cortical afferents; (2) the low threshold spike, initiating the bursting behavior, controlled by either GABAergic inhibition or the corticogeniculate input; and (3) inhibition of I_{AHP} via noradrenergic and cholinergic afferents from the brainstem reticular formation. It is now abundantly clear that geniculate circuitry and the intrinsic electrophysiological properties of geniculate neurons are no longer compatible with the notion that the lateral geniculate nucleus serves as simple relay. Instead, we suggest that it serves to modulate the transmission of retina-to-cortex signals as a function of inputs from nonretinal sources. This state-dependent gating of visual processing may be the neuronal substrate involved in certain forms of selective visual attention.

1. Introduction

The mammalian visual system, and particularly the retino-geniculo-cortical component, has been a popular and fruitful subject of neurobiological enquiry. As a result, a great deal is known about its functional organization. In the retina, the organization of neuronal interconnections results in changes in receptive field properties of single neurons at each synaptic level (Dowling, 1970) and the same principle seems to apply to the visual cortex (Hubel and Wiesel, 1977; Gilbert, 1983). That is, the main functional significance of neural circuitry within these structures seems to be the elaboration of receptive field properties that allow the visual system to extract information about the visual stimulus. The lateral geniculate nucleus does not satisfy this generalization, because receptive fields of geniculate neurons are virtually identical to those of their retinal inputs, although some subtle differences have been noted (Hubel and Wiesel, 1961; Cleland, Dubin and Levick, 1971; Hoffmann, Stone and Sherman, 1972; Bullier and Norton, 1979; So and Shapley, 1981; Shapley and Lennie, 1985).

As a result, considerable confusion and speculation has surrounded the discussion of geniculate function. Indeed, on page 562 of their recent review, Shapley and Lennie (1985) state:

> "The visual function of the lateral geniculate nucleus has remained somewhat mysterious. Is the LGN simply a relay nucleus, or is substantial visual information processing done there?"

We argue that the answer to the above question is "No" on both counts. As noted above, the similarity of retinal and geniculate receptive fields argues in favor of the notion that geniculate neurons act as mere relays of information from retina to visual cortex. However, numerous morphological and physiological observations, the summary of which forms a large portion of this paper, indicate that, in fact, the lateral geniculate nucleus has a more subtle and important function than to serve as a mere relay station. We suggest that one function of this thalamic nucleus is to gate or control the gain of signal transmission being relayed from retina to cortex (see also Singer, 1977; Yingling and Skinner, 1977; Burke and Cole, 1978; Crick, 1984; Ahlsen, Lindstrom and Lo, 1985).

This paper explores some of the types of gating or gain control carried out by geniculate circuitry and suggests some specific biophysical mechanisms underlying them. This gain control, in the sense that we are using the term, reflects the ability of retinal axons to drive geniculate relay cells. It can be operationally defined in terms of the number or frequency of action potentials seen in the geniculate neuron relative to that in its retinal afferents. This concept is what we mean when we refer below to the efficacy of retino-geniculate transmission.

Unless otherwise explicitly noted, we shall confine ourselves in the present manuscript to anatomical and physiological data relevant to the cat. Several recent reviews can be consulted for details of the functional organization of the cat's central visual pathways (Stone, Dreher and Leventhal, 1979; Lennie, 1980; Sherman and Spear, 1982; Sherman, 1985). Our reference to the lateral geniculate nucleus includes only the dorsal division, which projects to cortex; we are not concerned with the ventral division of the lateral geniculate nucleus, which has a different embryological origin and does not project to visual cortex. We shall concentrate in particular on laminae A and A1, which form the dorsal laminae of the lateral geniculate nucleus, because these have been the most intensively studied. They form a reasonably matched pair receiving ocular input from either the contralateral nasal (lamina A) or ipsilateral temporal (lamina A1) retina. Much less is known about the physiology and intrinsic circuitry of other geniculate laminae. Intimately related to the layers A and A1 is the perigeniculate nucleus, which lies just dorsal to lamina A above the lateral geniculate nucleus. The perigeniculate nucleus is often considered to be part of the reticular nucleus of the thalamus (see Singer, 1977; Montero and Singer, 1984), although some consider it to be a separate thalamic nucleus (e.g. Ahlsen, Lindstrom and Lo, 1982). In any case, the perigeniculate nucleus represents an important contributor to geniculate circuitry (see below).

2. X and Y Pathways

As illustrated in figure 1a, a prominent feature of laminae A and A1 is their participation in two parallel, independent neuronal pathways from retina to cortex. These are the X and Y pathways, and each is thought to perform functionally distinct operations in the processing of visual information. It is beyond the scope of this paper to consider in detail the functional significance of these pathways, but one of us (Sherman, 1979, 1985) has suggested that the Y pathway is involved in the primary analysis of basic form vision and the X pathway is secondarily used to raise spatial resolution; other hypotheses have also been suggested (Ikeda and Wright, 1972; Stone *et al.*, 1979; Lennie, 1980).

The X and Y retinal ganglion cells form two physiologically distinct neuronal classes, corresponding in the cat to two morphological classes respectively termed β and α cells (Boycott and Wassle, 1974; Stanford and Sherman, 1984). Every X and Y cell from the retina innervates lamina A or A1 of the lateral geniculate nucleus. Each geniculate cell receives all of its retinal input from one or very few retinal ganglion cells of the same type (X or Y). *Thus, the receptive field of each geniculate cell is virtually identical to that of its retinal input* (Hubel and Wiesel, 1961; Cleland *et al.*, 1971; Hoffmann *et al.*, 1972; Bullier and Norton, 1979; So and Shapley, 1981; Shapley and Lennie, 1985). There is no significant

receptive field transformation in the relay of retinal information to the cortex. This implies that we can refer to geniculate cells as X or Y in the same sense as we use these terms for the retina.

Differences between the X and Y pathways are not limited to the retina and passively transmitted by the central pathways, because geniculate X and Y cells differ in morphology (Friedlander, Lin, Stanford and Sherman, 1981), synaptic inputs (Wilson, Friedlander and Sherman, 1984; Hamos, van Horn, Raczkowski, Uhlrich and Sherman, 1985) and intrinsic response properties (Bloomfield and Sherman, 1984). Essentially all geniculate Y cells and most X cells are relay cells, which means that their axons project to the visual cortex; the remaining X cells, which are also monosynaptically innervated by retinal X axons, seem to be local inhibitory interneurons. The question as to whether retinal Y axons, as well as X axons, innervate a subset of interneurons remains a point of controversy. Dubin and Cleland (1977) argued that interneurons could be distinguished from relay cells because the former could be *transsynaptically* activated from cortex, while the latter could only be *antidromically* activated from cortex (see also Lindstrom, 1982; Ahlsen, Grant and Lindstrom, 1982). By their criteria, Dubin and Cleland (1977) found geniculate cells of both X and Y classes that were identified as interneurons. However, Friedlander *et al.*, (1981) demonstrated that these criteria did not always distinguish interneurons from relay cells, and, further, that no Y cell was sufficiently small to be an interneuron (Fitzpatrick, Penny and Schmechel, 1984). By other morphological criteria as well, including dendritic structure and the presence and nature of dendritic appendages, only a subset of X cells so far have displayed morphological properties generally associated with interneurons (Friedlander *et al.*, 1981; Hamos *et al.*, 1985). An unambiguous physiological demonstration of interneurons remains to be seen, and until then, we shall adopt the assumption that interneurons are mostly, if not exclusively, retinally innervated by X axons.

Differences are also evident in the geniculocortical termination patterns of X and Y cells from laminae A and A1 (Stone and Dreher, 1973; Ferster and LeVay, 1978; Geisert, 1980; Humphrey, Sur, Uhlrich and Sherman, 1985a,b). Axons of both types innervate striate cortex (area 17) more densely in layer IV and less densely in layer VI. However, the terminal fields of Y axons are much more extensive than are those of X axons. Also, whereas the X axons only innervate area 17, many Y axons innervate area 18, and many bifurcate to innervate both areas.

3. Synaptic Inputs to Geniculate Relay Cells

It is remarkable that, for both X and Y cells, retinal input represents a small minority (10 – 20%) of afferent synapses (see below for details; Guillery, 1969a,b; Wilson *et al.*, 1984).

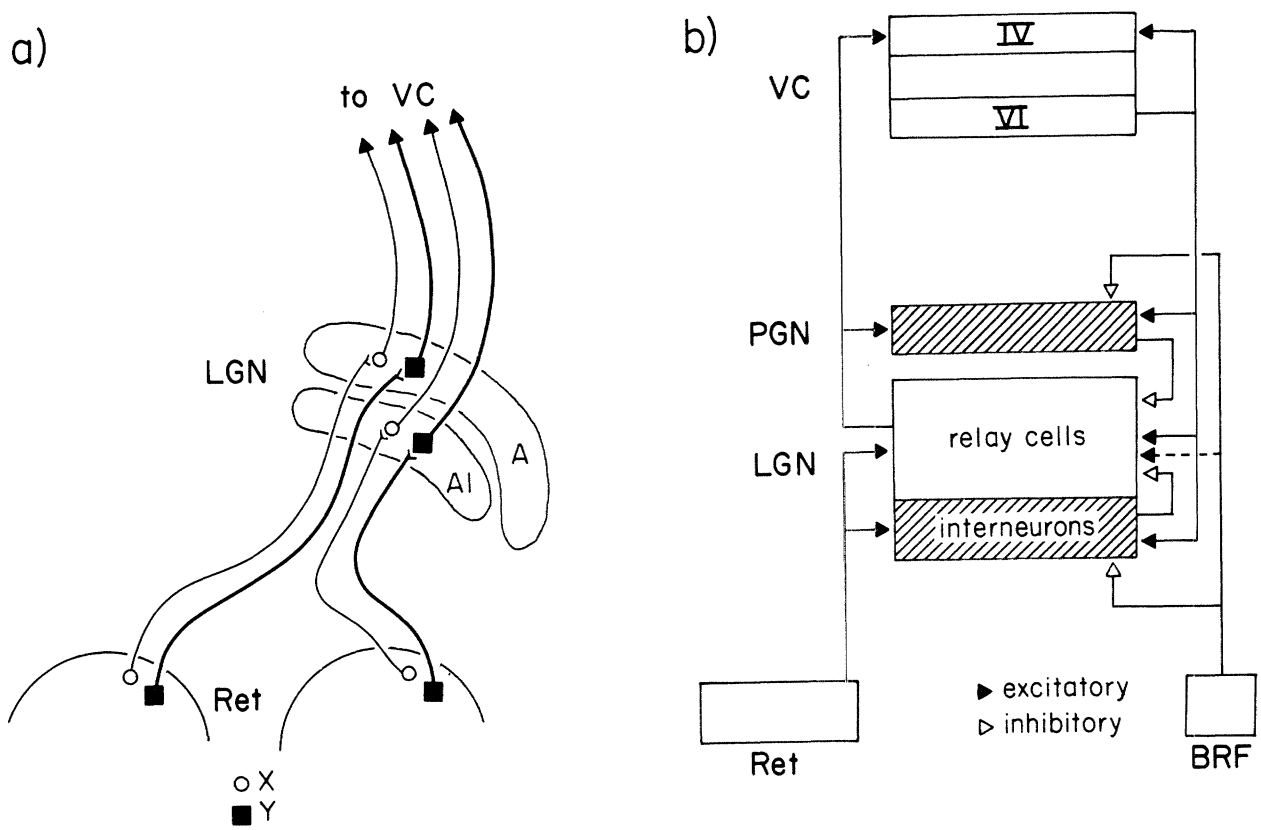

Figure 1. Schematic diagrams of the cat's retino-geniculo-cortical pathways. *Abbreviations: X*, X cell; *Y*, Y cell; *Ret*, retina; *LGN*, lateral geniculate nucleus; *A and A1*, geniculate laminae A and A1; *VC*, visual cortex; *BRF*, brainstem reticular formation (which includes midbrain and pontine components); *PGN*, perigeniculate nucleus (which is probably a subnucleus of the reticular nucleus of the thalamus); *IV and VI*, cortical layers IV and VI. (a) Diagram illustrating the X and Y pathways from retina through the lateral geniculate nucleus to the visual cortex. (b) Schematic diagram illustrating the functional relationships between the various inputs to geniculate relay cells. The hatching highlights the inhibitory, GABAergic inputs to relay cells. Excitatory and inhibitory pathways are separately shown. The dashed line refers to the putative, long-lasting excitatory action of cholinergic and/or noradrenergic fibers from the brainstem reticular formation. See text for details.

As noted above, these geniculate cells do not substantially alter the receptive fields of their retinal inputs in their relay to cortex. This implies that the nonretinal synapses on these cells, which represent $80-90\%$ of all synapses, are used for another purpose. One likely function of this massive nonretinal input is to gate or modify the retina-to-cortex relay. As the first central station in the processing of visual information en route to cortex, the lateral

geniculate nucleus is strategically sited to control the flow of this input to cortex. Before any understanding of this function can be realized, it is first necessary to understand the sources of extraretinal inputs to geniculate relay cells as well as the synaptic environment of these cells.

3.1 Cortico-Geniculate Pathway

Figure 1b schematically illustrates the known nonretinal afferents to relay cells of laminae A and A1. A pronounced pathway originates among layer VI pyramidal cells of cortical areas 17, 18 and 19 (Guillery, 1967; Jones and Powell, 1969; Gilbert and Kelly, 1975; Updyke, 1975). This projection involves roughly half of the pyramidal cells in layer VI (Gilbert and Kelly, 1975). From knowledge of the size of areas 17, 18 and 19 (Tusa, Palmer and Rosenquist, 1978; Orban, 1984), the density of layer VI cells (Beaulieu and Colonnier, 1983) and the number of geniculate relay cells (Bishop, Jeremy and McLeod, 1953; Sanderson, 1971), we estimate that each geniculate relay cell roughly receives convergent input from at least 10 cortical axons (see appendix). Cross-correlation analysis between a visual cortex cell and a geniculate neuron reveals an excitatory pathway if the receptive field centers of both neurons are separated by less than 1.7° (Tsumoto, Creutzfeldt and Legendy, 1978; see also Ahlsen, Grant and Lindstrom, 1982). Larger separations produce inhibitory cortico-geniculate interactions. Conduction velocities of cortico-geniculate fibers seem to be especially heterogeneous and include some quite slowly conducting axons (Tsumoto *et al.*, 1978).

3.2 The Perigeniculate Pathway

The perigeniculate nucleus is functionally organized quite like the reticular nucleus of the thalamus, a sheet-like structure enveloping much of the dorsal thalamus (Scheibel and Scheibel, 1966; Jones, 1975; Steriade and Deschenes, 1984). Indeed, the perigeniculate nucleus may well be a substructure of the thalamic reticular nucleus. All axons from the thalamus to the cerebral cortex pass through the thalamic reticular nucleus, as do all the reverse projections from the cortex to the thalamus. It is believed that most, if not all, of these axons passing in both directions through the reticular nucleus of the thalamus emit collaterals that make excitatory synaptic contacts (Ide, 1982). In particular, the perigeniculate nucleus receives collaterals from geniculate X and Y relay cells (Dubin and Cleland, 1977; Ahlsen, Lindstrom and Sybirska, 1978; Friedlander *et al.*, 1981; Ahlsen and Lindstrom, 1982). The neurons in the perigeniculate nucleus (and in the thalamic reticular nucleus) appear to be GABAergic and thus inhibitory (Lindstrom, 1982; O'Hara, Lieberman, Hunt and Wu, 1983; Oertel, Graybiel, Mugnaibi, Elde, Schmechel and Kopin, 1983; Fitzpatrick *et*

al., 1984; Montero and Singer, 1984). Axons of the perigeniculate neurons enter laminae A and A1 to innervate geniculate cells there (Jones, 1975; Cucchiaro, Uhlrich, Hamos and Sherman, 1985). The connections involving geniculate relay cells, perigeniculate cells, and descending inputs from the visual cortex are retinotopically organized (Minderhoud, 1971). Furthermore, the reciprocal pathway between geniculate and perigeniculate cells (figure 1b) represents the morphological substrate for feedback inhibition described for geniculate relay cells (Dubin and Cleland, 1977). It is not yet clear whether perigeniculate cells innervate X and Y cells indiscriminantly (Lindstrom, 1982; Ahlsen and Lindstrom, 1982) or whether, as morphological data described below suggest, they focus their input onto Y cells.

3.3 Pathways from the Brainstem Reticular Formation

Morphological and electrophysiological studies indicate that both the lateral geniculate and the perigeniculate nuclei receive input from the brainstem reticular formation, mostly from the caudal midbrain and rostral pons (Singer, 1973; Foote, Maciewicz and Mordes, 1974; Leger, Sakai, Salvert, Touret and Jouvet, 1975; McBride and Sutin, 1976; Hoover and Jacobowitz, 1979; Moore and Bloom, 1979; Sakai, 1980; Kimura, McGeer, Peng and McGeer, 1981; Wiklund, Leger and Persson, 1981; Fibiger, 1982; Ahlsen and Lo, 1982; Ahlsen, 1984; Hughes and Mullikin, 1984). There is a corresponding plethora of effects on geniculate cells attributed to activation of brainstem neurons. These effects differ in their time-courses, post-synaptic actions and sites of origin.

Stimulating the brainstem reticular formation by brief electrical shocks typically eliminates hyperpolarizing potentials in cat geniculate relay cells (Fukuda and Iwama, 1971; Singer, 1973; Fukuda and Stone, 1976). It had previously been suggested that this disinhibition is due to brainstem-induced inhibition of the GABAergic interneurons (see, for instance, Singer, 1973 and 1977). Ahlsen, Lindstrom and Lo (1984) showed recently that, indeed, electrical stimulation of various brainstem sites causes large hyperpolarizing potentials in both perigeniculate neurons and geniculate interneurons. This inhibition has a latency of about $10-12msec$ and a duration of about $100msec$. However, stimulation of some brainstem sites inhibits geniculate relay cells (Foote *et al.*, 1974).

At least three components of the projection from the brainstem reticular formation to the lateral geniculate nucleus have been recognized. The best understood one consists of noradrenalin (or norepinephrine) containing fibers that originate in the locus coeruleus and that provide a dense, uniform innervation of the lateral geniculate nucleus (Moore and Bloom, 1979; Kromer and Moore, 1980; Sakai, 1980; Wiklund *et al.*, 1981). In rats, electrical stimulation of the locus coeruleus, local application onto cell bodies in the locus coeruleus of the excitatory amino acid glutamate, and direct iontophoretic application of noradrenalin onto geniculate cells all lead to a delayed but dramatic increase in the firing

rate of most spontaneously active geniculate neurons (Nakai and Takaori, 1974; Rogawski and Aghajanian, 1980; Kayama, Negi, Sugitani and Iwama, 1982; Kayama, 1985). This facilitation usually occurs 0.2 to a few seconds after the onset of the electrical stimulation and subsids gradually within several seconds after cessation of the stimulation (Kayama, 1985). If the optic nerve is sectioned to prevent visually mediated synaptic input, neither direct application of noradrenalin nor electrical stimulation of the locus coeruleus activates geniculate neurons, although the same cells can easily be excited by iontophoresis of glutamate (Rogawski and Aghajanian, 1980). In other words, the action of the pathway from the locus coeruleus onto geniculate relay cells is contingent upon prior or simultaneous excitation of the relay cells, a characteristic property of neuromodulatory substances.[1] There is some evidence that the facilitation seen after local noradrenalin application or after electrical stimulation of the brainstem can be blocked in rats by α adrenoceptor antagonists (Rogawski and Aghajanian, 1980; Kayama *et al.*, 1982). This mechanism appears to affect directly the relay cells since application of picrotoxin, which blocks the action of GABA, does not produce a facilitation of the relay cell response, excluding the possibility that noradrenalin inhibits the inhibitory interneurons and perigeniculate cells which in turn inhibit the relay cells.

The other two brainstem pathways to the lateral geniculate nucleus are less well understood. One is serotonergic and derives largely, but not completely, from the dorsal raphe nucleus (Pasquier and Villar, 1982). Application of serotonin seems to have a depressant effect on geniculate neurons (Kemp, Roberts and Sillito, 1982). The third pathway is cholinergic and, in the cat, seems to originate in the parabrachial nucleus (Sakai, 1980; Kimura *et al.*, 1981).[2] Iontophoretic application of acetylcholine produces increased activity among geniculate neurons (Kemp and Sillito, 1982; Sillito, Kemp and Berardi, 1983).

In summary, neurons of the brainstem reticular formation can act in a variety of fashions to affect geniculate relay cells and thus retino-geniculate transmission. Two distinct actions exist. One is a short-latency, short-lasting effect inducing hyperpolarizing postsynaptic potentials in geniculate interneurons and perigeniculate cells. This seems to involve conventional synaptic processes. The other is a long-latency, long-lasting effect that directly increases the excitability of geniculate relay cells. This may result from unconventional

[1]Neuromodulators evoke no direct, independent change in the postsynaptic membrane potential but will alter the efficacy or the time course of neurotransmitter actions (Barker, 1978).

[2]There has been some confusion about the source of cholinergic inputs to the lateral geniculate nucleus from the brainstem. In the rat, where these inputs were first described, they arise from a nucleus known as the cuneiform nucleus (Hoover and Jacobowitz, 1979; Fibinger, 1982). However, the area identified in the cat as the cuneiform nucleus contains cells that are neither cholinergic nor afferent to the lateral geniculate nucleus; only the parabrachial region of the cat fits this description, and it may be that the terminology has obscured a genuine homology between the rat's cuneiform nucleus and the cat's parabrachial nucleus (for a discussion of this, see Kimura *et al.*, 1981).

synaptic processes involving neuromodulators that alter certain membrane conductances, such as a Ca^{2+} dependent K^+ current (see below).

3.4 Microcircuitry in the Lateral Geniculate Nucleus

The microcircuitry of geniculate X and Y cells has recently been described with reasonable clarity (Wilson *et al.*, 1984; Hamos *et al.*, 1985). Four major synaptic profiles exist (Guillery, 1969a), and for the most part their origins are reasonably well established. These synaptic terminals have been called RLP (for round vesicles, large profile, and pale mitochondria), RSD (for round vesicles, small profile, and dark mitochondria) and F1 and F2 (for flattened vesicles). Together, they comprise $> 95\%$ of the synaptic profiles present in laminae A and A1 (Guillery, 1969b). RLP terminals derive from retinal axons and asymmetrical synapses. They are excitatory and comprise $10-20\%$ of all synaptic profiles. RSD terminals derive mostly or completely from areas 17, 18 and 19 of cortex. Synapses from these terminals are also asymmetrical and excitatory, and they make up roughly $40-45\%$ of all terminals present.[3] F1 terminals seem to derive mostly or exclusively from perigeniculate cells (O'Hara, Sefton and Lieberman, 1980; Montero and Scott, 1981; Cucchiaro *et al.*, 1985) and contribute roughly $20-25\%$ of the synaptic terminals present. Their symmetrical synapses are inhibitory and use GABA as their neurotransmitter (Lindstrom, 1982; O'Hara *et al.*, 1983; Oertel *et al.*, 1983; Fitzpatrick *et al.*, 1984; Montero and Singer, 1984). Finally, F2 terminals, which are also thought to be GABAergic and inhibitory, derive from dendrites of X innervated interneurons (Fitzpatrick *et al.*, 1984; Hamos *et al.*, 1985), form symmetrical synapses and contribute roughly $20-25\%$ of the synapses present. Other rare terminal types also have been described, and some of the terminals not accounted for by this classification ($< 5\%$) might derive from the brainstem reticular formation (see, for instance, Lima, Montero and Singer, 1984).

The specific patterns of these synapses differ markedly for X and Y cells. For both cell types, cortical synapses present slightly less than half of the total synaptic input and terminate on the distal dendritic shafts. The retinal input and both types of inhibitory synapses terminate on proximal dendrites. However, here the similarities between X and Y cells end. On X cells, retinal and F2 terminals end in *triadic* synaptic arrangements on dendritic spines — the RLP terminal contacts the F2 terminal and both contact the same dendritic appendage or spine — and few F1 profiles are seen. On Y cells, retinal and F1 profiles terminate near one another without triadic circuitry, and few spines or F2 terminals are found. Thus, X cells receive *feedforward* inhibition from local geniculate interneurons and Y cells receive *feedback* inhibition from perigeniculate cells. This distinction may be an oversimplification,

[3]We shall often refer to RLP and RSD terminals as retinal and cortical terminals, respectively.

since Lindstrom (1982) argues on physiological grounds that both types of inhibition are found in both X and Y cells.

4. Signal Transmission through X and Y Cells

Cleland and colleagues (1971), by recording simultaneously from pairs consisting of a geniculate cell and its retinal afferent in the anesthetized cat, were able to account for every spike in the geniculate cell by an appropriately timed spike in the retinal afferent. Thus each action potential in a retinal afferent produced no more than one spike in the postsynaptic geniculate X or Y cell. However, not every afferent spike led to one in the postsynaptic cell. The gain of the retinogeniculate synapse is thus less than one. For a given geniculate neuron, this gain is state-dependent and can vary with the animal's level of arousal (Godfraind and Meulders, 1969; Meulders and Godfraind, 1969; Coenen and Vendrik, 1972). Based on known synaptic circuits and membrane conductaces, there are at least three ways by which the gain can be changed, and these represent three different means of controlling gating in the lateral geniculate nucleus. One relies on conventional, GABAergic postsynaptic inhibition; the second involves the action of a Ca^{2+} dependent K^+ conductance; and the third is based on a time- and voltage-dependent Ca^{2+} conductance.

4.1 Postsynaptic Inhibition

Since X and Y relay cells exhibit large numbers of inhibitory terminals on their proximal dendrites, classic postsynaptic inhibition of these neurons can obviously reduce the gain of retino-geniculate transmission. As noted above, these inhibitory synapses appear to be GABAergic. GABAergic synapses are generally thought to operate via the classical, bicuculline-sensitive, $GABA_A$ postsynaptic receptors by increasing a chloride conductance (Curtis and Johnston, 1974; Dingledine and Langmoen, 1980; Dunlap, 1981; Segal and Barker, 1984). The resultant inhibitory postsynaptic potential (IPSP) does not markedly hyperpolarize the cell, since the equilibrium potential for Cl^- is generally close to the resting membrane potential of the cell (between -60 and $-75mV$). In other words, activation of the $GABA_A$ receptor mediates a *silent* or *shunting* inhibition, increasing the membrane conductance at that location and thus reducing the cell's input resistance. This shunts or short-circuits the excitatory input that arrives during the increased Cl^- conductance. Computer simulation of synaptic inputs in branched dendritic trees have shown that this type of inhibition can be very effective in reducing excitatory postsynaptic potentials (EPSPs), if the inhibition is on the direct path between excitation and the soma (Koch, Poggio and Torre, 1982, 1983). The proximal location of most inhibitory synapses on geniculate relay

cells is consistent with such a process.

A different GABAergic effect has been described that acts via a distinctly different type of postsynaptic receptor, the $GABA_B$ receptor (Bowery, Doble, Hill, Hudson, Shaw, Turnbull and Warrington, 1981; Bowery, Hill and Hudson, 1983; Simmonds, 1983; Newberry and Nicoll, 1984a,b, 1985). This receptor binds the GABA agonist baclofen but is bicuculline-resistant. Newberry and Nicoll (1984a,b, 1985) describe such a receptor on hippocampal cells, arguing that the receptors control K^+ channels. Since the equilibrium potential for K^+ (roughly $-90mV$) is much more negative than the cell's resting potential, activation of $GABA_B$ receptors results in significant hyperpolarization. Furthermore, little change in the cell's input resistance is seen during the GABAergic response. Thus, compared to the action of the $GABA_A$ receptor, activation of the $GABA_B$ receptor leads to a significant postsynaptic hyperpolarization *below* the level of the membrane resting potential. Computer simulations show that this type of inhibition reduces EPSPs, with little regard for the position of the inhibitory synapse with respect to the excitatory one (Koch *et al.*, 1982; O'Donnell, Koch and Poggio, 1985). Whereas the $GABA_A$ activated inhibition can be quite strong and nonlinear, $GABA_B$-mediated responses act much more linearly, inhibiting the electrical activity of the neuron by offsetting EPSPs with an hyperpolarization.

Our understanding of the action and distribution of the $GABA_B$ receptor is just beginning. Present notions suggest that the $GABA_B$ receptor may occur less frequently in the mammalian brain than does the $GABA_A$ receptor. Therefore, until we have evidence to the contrary, it is probably wise to view the bulk of the GABAergic inhibition in the cat's lateral geniculate nucleus as acting via the $GABA_A$ receptor, or in other words, as silent or shunting inhibition. This is supported by evidence that IPSPs mediated by geniculate interneurons can easily be reversed by an injection of Cl^- ions into the cell (Lindstrom, 1982; see also McIlwain and Creutzfeldt, 1967) and that local application of bicuculline leads to a loss of inhibitory mechanisms in geniculate neurons (Sillito and Kemp, 1983; Berardi and Morrone, 1984). However, it is intriguing that two types of inhibitory synapses are observed: one from the F1 terminal, which derives from perigeniculate neurons, and one from the F2 terminal, which derives from geniculate interneurons. Perhaps one operates via a $GABA_A$ receptor and the other via a $GABA_B$ receptor.

Our final point regarding postsynaptic inhibition involves an interesting difference between X and Y cells. As noted above, the inhibitory input to Y cells — predominantly of the F1 type — occurs on proximal dendritic shafts, while inhibitory input to X cells — predominantly of the F2 type — occurs primarily on dendritic spines in triadic arrangements with retinal synapses. One of us (Koch, 1985) has recently modeled the significance of this morphological difference. Due to the proximal location of F1 terminals on Y cells, inhibition from these terminals will tend to reduce both retinal and cortical inputs more or less equally. For X

cells, the morphology of the spine effectively isolates the inhibitory effect to the spine, limiting its inhibitory action to the retinal input and isolating its action from the dendritic shaft and the soma (Koch and Poggio, 1983). Moreover, increased activity in the retinal afferent (e.g. from appropriate visual stimuli) will lead to increased amounts of inhibition at the geniculate relay cell. The local nature of inhibition is only conserved in the model, however, if the reversal potential of the inhibitory synapses is equal or near to the resting potential of the cell. If the interneuron is not itself inhibited, the firing of the retinal afferent will not only give rise to an EPSP but also — via the interneuron — to a delayed inhibition, effectively vetoing subsequent retinal input. Since cortical input to geniculate relay cells is predominately restricted to peripheral dendritic shafts, the electrotonic propagation of EPSPs to the soma induced by cortico-geniculate fibers will be little affected by silent inhibition on spines. The local circuit — comprising the spine and an inhibitory synapse with a reversal potential close or equal to the resting potential of the cell — is functionally equivalent to *presynaptic inhibition*, although the locus of inhibition is postsynaptic (Koch, 1985).

In summary, activation of the GABAergic mediated inhibition will lead to a general reduction in cellular excitability in geniculate Y cells and to a selective disabling of specific retinal inputs in geniculate X cells, as long as the geniculate interneuron is not itself inactivated.

4.2 Voltage- and Time-Dependent Conductances in Thalamic Neurons

Recent biophysical studies emphasize that the integrative properties of thalamic neurons can be very nonlinear. Jahnsen and Llinas (1984a,b; Llinas and Jahnsen, 1982) used an *in vitro* thalamic slice preparation to show that nearly all thalamic (including geniculate) neurons of the guinea pig exhibit a rich variety of time- and voltage-dependent conductances. Altogether, Jahnsen and Llinas (1984a,b) identified 6 voltage-and time-dependent conductances plus one dependent solely on Ca^{2+}. Four of the conductances lead to inward current: a fast Na^{+} conductance underlying the action potential, a slow Na^{+} conductance, a low threshold Ca^{2+} conductance underlying the low threshold (LT) spike, and a high threshold Ca^{2+} conductance. Three K^{+} conductances lead to outward current: one is voltage-dependent and repolarizes the cell following the action potential, and two are responsible for the afterhyperpolarization. The components of the afterhyperpolarization are a transient voltage-dependent K^{+} conductance (I_A) and a slower K^{+} conductance that depends only on Ca^{2+} and not explicitly on the membrane potential (I_{AHP}). Evidence exists that most or all of these conductances exist for neurons of the cat's thalamus, at least for the ventroanterior and ventrolateral thalamic nuclei (Deschenes, Paradis, Roy and Steriade, 1984; Roy, Clercq, Steriade and Deschenes, 1984). While all of these conductances may

contribute to the gating properties of thalamic neurons, we shall examine in somewhat more detail only the conductances subserving the spike afterhyperpolarization and the LT spike because these are the best understood and seem to be the most important for altering retino-geniculate transmission.

4.2.1 Properties of the Spike Afterhyperpolarization

The hyperpolarization following a spike discharge is important for the integrative properties of a neuron, since the strength and duration of this afterhyperpolarization controls the extent to which the neuron adapts to long-lasting excitatory inputs. Results from the guinea pig thalamic slice preparation (Jahnsen and Llinas, 1984b) and the cat's *in vivo* lateral thalamic nuclei (Deschenes *et al.*, 1984) indicate that action potentials are followed by a prolonged afterhyperpolarization with an overall duration of $25-45msec$ or longer, the basis of which is an increased K^+ conductance. Removing the Ca^{2+} from the bathing solution or intracellular injection of EGTA, a Ca^{2+} chelator, abolishes the afterhyperpolarization, strongly implicating a Ca^{2+} dependent K^+ conductance.

Elegant work done on bullfrog sympathetic ganglion cells (Pennefather, Lancaster, Adams and Nicoll, 1985) and in rodent hippocampal neurons (Lancaster and Adams, 1985; Adams and Lancaster, 1985) has established two distinct Ca^{2+} dependent K^+ conductances underlying the spike afterhyperpolarization. One conductance, termed I_C, depends on both intracellular free calcium Ca^{2+} and membrane voltage while the second conductance, I_{AHP} depends only on Ca^{2+}. The time-course of I_C is at least an order of magnitude faster than I_{AHP}. Moreover, I_{AHP} can be blocked by acetylcholine in bullfrog neurons and by both noradrenalin and acetylcholine in rodent neurons, while I_C is blocked by neither substance.[4]

This last property of I_{AHP} gives rise to a physiological mechanism by which the gain of thalamic neurons can be altered. When a prolonged depolarizing current pulse is injected into a hippocampal pyramidal cell, the cell responds with an initial burst of spikes after which time it remains silent for the duration of the pulse. This spike frequency adaptation or accommodation is markedly attenuated by local application of noradrenalin, which causes the cell to fire throughout the depolarizing current pulse (Madison and Nicoll, 1982, 1984). The basis of this striking modification of spike frequency adaptation involves the blockage of I_{AHP} via a cyclic AMP mechanism subsequent to Ca^{2+} entry into the cell. We propose that the activation of noradrenalin containing fibers from the locus coeruleus increases the

[4] It should be noted that recent evidence from mammalian hippocampal neurons (Madison and Nicoll, 1985) suggests both that this excitatory blockage of I_{AHP} by noradrenalin operates via a β receptor and that a noradrenergic α receptor mediates an *increase* in an K^+ conductance. This may prove significant in light of the above mentioned data suggesting that noradrenalin excites rat geniculate cells via an α receptor (Rogawski amd Aghajanian, 1980; Kayama *et al.*, 1982; see also Aghajanian, 1985).

excitability of geniculate relay cells by a similar mechanism. That is, noradrenalin inhibits a long-lasting Ca^{2+} dependent K^+ current, similar to I_{AHP}, and this modifies the response of the cell to long-lasting depolarizing inputs. The noradrenalin action is most likely mediated by a second messenger, such as cAMP. Furthermore, a slow EPSP can be elicited in hippocampal pyramidal cells by activation of the cholinergic synaptic input, which acts via muscarinic receptors. The basis of this slow EPSP may be again a severe reduction in I_{AHP} (Nicoll, Madison, Lancaster and Adams, 1985). It is possible that cholinergic inputs from the parabrachial nucleus of the brainstem reticular formation produce such effects on geniculate neurons.

4.2.2 Properties of the LT Spike

The Ca^{2+} conductance that underlies the LT spike becomes *inactive* when the cell's membrane is more depolarized than about $-60mV$. At normal resting levels (-55 to $-60mV$), the LT spike is thus blocked, and the cell responds to depolarization fairly linearly with a tonic stream of fast, conventional Na^+ action potentials. When the membrane potential is hyperpolarized beyond about $-60mV$ to $-65mV$ for at least $100mscc$ (the actual voltage- and time-dependencies may vary somewhat from cell to cell), the Ca^{2+} conductance is **de-inactivated** and the LT spike can be initiated by a small depolarization (e.g. from an EPSP). The overall LT response is composed of two distinct parts. First is the LT spike proper, which is a slowly rising and falling triangle-like potential. The LT spike has a rather low threshold firing level and results from movement of Ca^{2+} into the cell. Second is a rapid succession of 1 to 4 fast spikes ($> 300Hz$). These spikes occur most generally at the crest of the slower LT spike and reach firing level at approximately $-40mV$. The fast spikes are generated by a voltage-dependent Na^+ conductance. The upward stroke of the LT spike is followed by the afterhyperpolarization, which roughly lasts for about $100-200mscc$. Subsequently, another LT spike can start a new cycle, and this process can be repeated many times. Thalamic cells therefore exhibit two distinct response modes to afferent input: a tonic, faithful "relay" mode at resting levels, and a bursting, nonlinear mode if hyperpolarized. The latter blocks the normal relay of information to the cortex and thus may be an important cellular mechanism in the overall gating by geniculate neurons of the retina-to-cortex signals.

This dual transmission mode not only exists *in vitro* for the guinea pig thalamus, but similar behavior has also been documented *in vivo* for the cat's ventroanterior and ventrolateral thalamic nuclei (Deschenes *et al.*, 1984; Roy *et al.*, 1984), and preliminary evidence extends this to cells of the cat's lateral geniculate nucleus recorded *in vivo* (Bloomfield and Sherman, unpublished observations). Also many geniculate cells in unanesthetized cats exhibit bursty periods of behavior reminiscent of LT spikes, and burst periods correlate with various phases of alertness (Bizzi, 1966; Nelson, McCarley and Hobson, 1983; McCarley, Benoit and

Barrionuevo, 1983). This pattern has also been associated with stimulation of the brainstem reticular formation (Singer, 1973). Responses consistent with LT spikes thus appear to be ubiquitous for mammalian thalamic neurons. The importance of such responses for gating of thalamocortical transmission with regards to selective visual attention has recently been explored (Crick, 1984).

4.2.3 Physiological Mechanisms for Controlling LT Spikes

Clearly, the LT spike can be an important means of regulating the state of a geniculate relay cell. It thus becomes crucial to understand how the brain controls LT spike activation (i.e. depolarizing the cell once the Ca^{2+} conductance is de-inactivated), inactivation (i.e. establishing membrane levels more depolarized than about $-55mV$), and de-inactivation (i.e. establishing membrane levels more hyperpolarized than about $-60mV$ for $100-200msec$).

Activation of LT Spikes: As Jahnsen and Llinas (1984b) have shown, synaptic activation is sufficient to trigger LT spikes, if the underlying Ca^{2+} conductance is de-inactivated. Since retinal input is a potent source of EPSPs in geniculate cells, retinal activity, whether spontaneous or visually elicited, is a plausible candidate for triggering LT spikes and the subsequent depression of retino-geniculate-cortical transmission. EPSPs from corticogeniculate axons are another possible source of LT spike activation. However, since any form of depolarization is a plausible candidate for triggering an LT spike once the cell is in a de-inactivated state, it may be that dis-inhibition can also activate an LT spike. That is, release from an hyperpolarizing input, which in itself might de-inactivate the LT spike, could discharge this spike. It has been shown in rats, for example, that the cessation of an excitatory visual stimulus applied to the centre of the receptive field of the geniculate neuron leads to a burst of spikes (French, Sefton and Mackay-Sim, 1985). The late burst of spikes may reflect an underlying LT spike that follows the release of inhibition.

Inactivation of LT Spikes: To inactivate the Ca^{2+} conductance underlying LT spikes, it is sufficient to prevent the cell from becoming hyperpolarized more than about $5-10mV$ from its "normal" resting level,[5] normal being operationally defined as that level most often seen with good intracellular impalements. For thalamic neurons, this is typically between -55 and $-65mV$. It may be that the cell's true resting membrane potential (i.e. in the absence of all synaptic input) is sufficiently depolarized to inactivate the Ca^{2+} conductance mediating the LT spike. Conversely, it may be that the cell normally is tonically depolarized by synaptic input so that this conductance is inactivated and that without this tonic synaptic input the cell would be sufficiently hyperpolarized to de-inactivate the Ca^{2+} spike. The distinction between these possibilities is reconsidered below.

[5]The LT spike can also be inactivated if the membrane potential becomes more hyperpolarized than about -80 to $-85mV$ (Jahnsen and Llinas, 1984a,b). However, since such hyperpolarization is rarely if ever seen during physiological conditions, we shall disregard this possible means of LT spike de-inactivation for the remainder of this paper.

De-inactivation of LT spikes: While physiological inactivation and activation of the Ca^{2+} conductances underlying the LT spike can be readily explained, de-inactivation is more complex. Both Jahnsen and Llinas (1984a,b) and Deschenes *et al.* (1984) used only hyperpolarizing current injection from the intracellular recording electrode to control this de-inactivation. We may now ask, "How does the neural circuitry of the lateral geniculate nucleus *physiologically* hyperpolarize geniculate relay cells to accomplish de-inactivation of the Ca^{2+} conductances and LT spike?" Three quite different mechanisms for the hyperpolarizing de-inactivation are considered here.

First, inhibitory inputs may sufficiently hyperpolarize the relay cell to de-inactivate the Ca^{2+} conductance. This straightforward explanation suggests that perigeniculate or geniculate interneurons control the inactivation and de-inactivation of the LT spikes, and thus gating. Crick (1984) has proposed that such a scheme, with the requisite hyperpolarization controlled from the reticular nucleus of the thalamus, is the biophysical mechanism underlying certain forms of visual attention.

Unfortunately, there are several problems with this hypothesis. If the inhibition is GABAergic and acts via $GABA_A$ receptors, and thus via a Cl^- conductance increase, then inhibition will not sufficiently hyperpolarize the cell to de-inactivate the Ca^{2+} conductance underlying the LT spike. Also, effective shunting of the excitatory synaptic input (Koch, Poggio and Torre, 1983) during de-inactivation might prevent any EPSPs from triggering the LT spike. While GABAergic inhibition via $GABA_B$ receptors and a K^+ conductance increase might be compatible with needs for hyperpolarization and maintained neuronal input resistance, this does not account for the time dependency of LT spike de-inactivation. The hyperpolarization must be maintained for $100msec$ or more and there is no evidence that the IPSPs generated in geniculate cells of the cat are sufficiently long-lasting to accomplish this (Eysel, 1976; Lindstrom, 1982). For these reasons, we feel it is unlikely that GABAergic inhibition by itself is sufficient to control de-inactivation of the LT spikes.

Second, some of the inputs onto geniculate cells may act in an unconventional manner. This may include some of the inhibitory (F1 or F2) terminals or, perhaps, the few (5%) synapses that cannot be classified and that may derive from the brainstem reticular formation. These terminals may discharge neurotransmitters or co-factors that hyperpolarize the cell for $> 100msec$ through some as yet undetermined receptor/conductance mechanism.[6] Unconventional transmitter-induced conductance changes have been explored only recently and in other neuronal systems (Belcher and Ryall, 1977; Jan and Jan, 1983; Jones,

[6]It is interesting in this regard that all synaptic terminals found within the cerebral cortex to contain neuropeptides also contain GABA (Hendry, Jones, DeFelipe, Schmechel, Brandon and Emson, 1984). Neuropeptides are thought to act frequently as neuromodulators rather than as conventional neurotransmitters. Perhaps some of the GABAergic terminals in the lateral geniculate nucleus also contain neuropeptides or analogous substances that function as neuromodulators to produce long-lasting hyperpolarization.

1985). Given our general ignorance about the cellular electrophysiology and biophysics of mammalian geniculate neurons, it is difficult to propose anything more specific about such a speculative suggestion.

Third, LT spike de-inactivation may be effected by disfacilitation of a tonic excitatory input. The cortico-geniculate pathway seems an ideal candidate for this. As noted above, the majority of excitatory inputs onto geniculate relay cells derive from cortex. We estimate (see appendix) that each geniculate relay cell receives convergent input from at least 10, and most likely many more, cortico-geniculate neurons. Furthermore, the cortico-geniculate input is heterogeneous with respect to conduction velocity and therefore heterogeneous with respect to latency as well (Tsumoto *et al.*, 1978). Unlike the retinal input to geniculate cells that derives from a few axons of equal conduction velocity and thus excites the geniculate cell synchronously (Cleland *et al.*, 1971; Hoffmann *et al.*, 1972), the cortical input almost certainly arrives asynchronously. This, plus the distal dendritic location of cortico-geniculate synapses, a location that tends to spread out the cortically induced EPSPs in time, suggests that activity in cortico-geniculate fibers can maintain a steady depolarization in geniculate relay cells. Perhaps when one records a $-60mV$ "resting" potential, this actually indicates a true resting potential of, say, $-75mV$ that is tonically depolarized to $-60mV$ by activity among cortico-geniculate fibers. Phrased differently, prolonged inactivity ($> 100msec$) in the cortico-geniculate fibers can de-inactivate the Ca^{2+} conductance and permit the next retinal — or even cortical — EPSP to trigger the LT spike.

The functional significance of the massive cortical input to the thalamus is unknown. Despite many experimental attempts to elucidate some important function for this pathway, only subtle changes in receptive field properties of lateral geniculate neurons have been described following manipulation of the cortico-geniculate projection (for instance, by cooling; Kalil and Chase, 1970; Richard, Gioanni, Kitsikis and Buser, 1975; Schmielau and Singer, 1977; Geisert, Langsetmo and Spear, 1981). Such minor and ephemeral functions as suggested belie the anatomically massive extent of this projection. Note, however, that the majority of these experiments have been performed on anesthetized animals. Our suggestion that this pathway may play a key role in gating of the retina-to-cortex relay is, in our opinion, much more at harmony with the anatomy than any of the prior suggestions. Nonetheless, while perhaps an attractive notion, there is as yet no direct evidence to support it. For example, one requirement of this hypothesis is a reasonable level of maintained activity among the cortico-geniculate neurons. Unfortunately, published data suggest that only a subset of these cells has any detectable spontaneous activity (Gilbert, 1977; Harvey, 1980). Of course, one would like to know the response properties of these neurons in cats during different physiological states of attention, and it is not clear how large a subset of these cells must be active to control LT spikes in the manner suggested. It is possible that one or several of the proposed mechanisms, such as hyperpolarizing synaptic input from

perigeniculate cells and lack of excitatory input from cortico-geniculate fibers, must act in conjunction in order for LT spike de-inactivation to occur.

5. Conclusion and Summary: The Lateral Geniculate Nucleus as a Gate to the Visual Cortex

The main purpose of this paper is to focus attention on the function of the cat's lateral geniculate nucleus (and, in a more general sense, the mammalian thalamus). Although the receptive field approach has suggested no major function for geniculate circuitry beyond a fairly simple relay of retinal signals to cortex, three lines of enquiry paint a different picture. First, retinal synapses form a small minority of inputs to geniculate relay cells. Second, activation of inputs to the general region of the lateral geniculate nucleus from as yet poorly defined regions in the brainstem reticular formation can alter the gain of the retino-geniculate synapse. Third, biophysical studies of thalamic neurons reveal a rich array of voltage- and time-dependent conductances that can significantly alter the transmission of retino-geniculate synapses. This paper has focussed on biophysical mechanisms possibly subserving gating and the different anatomical pathways over which these mechanisms may be controlled. In this last section, we shall reconsider some of these schemes from the point of view of their possible functional role.

5.1 GABAergic Inhibition

One mechanism is based on conventional inhibition of geniculate relay cells via GABAergic interneurons and perigeniculate cells. Recent evidence suggests that GABAergic synapses can lead to an increase in either a Cl^- or a K^+ conductance, depending on whether the postsynaptic receptor is $GABA_A$ or $GABA_B$. Furthermore, we have pointed out that the two classes of geniculate relay cell, X and Y, seem to have different circuits involving different types of GABAergic terminals. For Y cells these are F1 terminals from perigeniculate cells to dendritic shafts; for X cells these are F2 terminals from interneurons to dendritic appendages in triadic arrangements with retinal terminals. Computer modeling of these different circuits suggests different forms of gating in X and Y relay cells (Koch, 1985). In the case of silent or shunting inhibition (i.e. an increase in a Cl^- conductance), inhibition shunts the excitatory synaptic input on the same spine or dendrite as the inhibitory synapse while leaving the electrical activity in the rest of the cell little changed. Thus, GABAergic IPSPs in geniculate relay cells will selectively reduce or abolish the contribution of specific retinal afferents to the output of the geniculate relay cell. A hyperpolarizing synapse (i.e. an increase in a K^+ conductance) acts by subtracting from the existing intracellular potential

with far less regard to the relative spatial positioning of the synapses than occurs in the case of the silent inhibition. Thus, the output of the entire relay cell can be partially or even completely blocked by hyperpolarizing inhibition to dendrites.

5.2 Low Threshold Spikes

The second gating mechanism involves activation of the LT spike, which can virtually shut down retino-geniculate transmission for $150msec$ or more. Physiological control of the LT spike is mostly a matter of speculation. This control may involve inhibitory synaptic input (e.g., from the perigeniculate nucleus), the action of which hyperpolarizes the cell and thus de-inactivates the Ca^{2+} conductance (Crick, 1984). Alternatively, the hyperpolarization needed to de-inactivate the LT spike may require disfacilitation via lowered activity in the excitatory cortico-geniculate afferents. Once these fibers are inactivated, geniculate cells are in a potential "burst" mode, while activity among the cortico-geniculate fibers switches the geniculate neurons into a linear, tonically firing mode. Furthermore, since the cells of origin of the cortico-geniculate pathway lie in visual cortex (i.e. areas 17, 18 and 19), gating decisions are the direct result of visual cortical processing.

What, if any, is the physiological significance of the bursting response? The simplest hypothesis we can advance is that the LT spike and the accompanying long-lasting hyperpolarization shuts down geniculate input to visual cortex. Thus, if the LT spike is inactivated, the lateral geniculate nucleus will transmit information from the retina more or less faithfully, subject to the modulation by cortical or brainstem afferents. Once an LT spike has been initiated, it will block retino-geniculate transmission for at least 100 to $150msec$. A more complex proposition (Crick, 1984) holds that the bursting response (i.e., the action potentials riding the crest of an LT spike), in a particular subset of geniculate relay cells temporarily enhances certain related synaptic circuits, thereby expressing the fact that the observer, whether cat or primate, currently *attends* to an object at that particular receptive field position (for an overview of some of the relevant psychophysical literature, see Treisman 1983 and Julesz, 1984). Our first hypothesis, which emphasizes the reduction of retino-geniculate transmission following the burst of action potentials, is so different from Crick's (1984) that the contrast between them serves as an effective reminder of our present uncertainty about the specific functional role of the LT spike. We are confident only that it must play a most important role in retino-geniculate transmission that has yet to be elucidated.

In any case, our hypothesis that the cortico-geniculate pathway serves to control the LT spike is inexplicable if single cortical axons monosynaptically excite geniculate neurons and disynaptically inhibit them through the action of perigeniculate neurons. This would prevent

the cortico-geniculate pathway from exerting a pronounced and prolonged depolarization of geniculate cells. However, the data of Tsumoto *et al.* (1978) described above suggest a more complex wiring consistent with our hypothesis. These authors report an excitatory action of cortico-geniculate fibers onto geniculate cells if the receptive field centers of the geniculate and cortical cells were separated by less than 1.7^o and an inhibitory action if the centers were more than 1.7^o apart. Thus, the retinotopic arrangement of connections between the visual cortex, the perigeniculate nucleus and the lateral geniculate nucleus is somewhat eccentric. Activity in a cortico-geniculate axon will excite a geniculate cell and inhibit its neighbors, a process that helps to implement *lateral inhibition* in the relay cells.

5.3 Afterhyperpolarization

A third mechanism mediating increased excitability in geniculate relay cells involves blockage of the cell's accommodation in response to a maintained excitatory input. While under normal conditions many cells will respond to such an input with a few action potentials at the start of the excitatory input, abolishing accomodation leads to a maintained output of action potentials throughout the duration of the input. It has been shown in mammalian hippocampal cells that the removal of accomodation is due to a reduction in a voltage-insensitive, Ca^{2+} dependent K^+ current, I_{AHP} (Madison and Nicoll, 1984), due to the direct application of noradrenalin and acetylcholine. Since it seems likely that a Ca^{2+} dependent K^+ current is present in cat geniculate cells, we propose that the excitatory action of noradrenergic fibers and cholinergic fibers from the brainstem reticular formation is due to the blockage of I_{AHP}. This type of excitation is effected by using noradrenalin and acetylcholine as neuromodulators rather than as conventional neurotransmitters.

We must emphasize a potentially important proviso to this specific hypothesis. Our suggestion derives partly from observations that noradrenalin can excite both geniculate and hippocampal neurons in mammals, and that in hippocampal cells the excitation involves blockage of I_{AHP}. However, some evidence, which has already been discussed, suggests that the noradrenergic excitation of these two neuronal populations operates via different receptors (an α receptor for geniculate cells in the rat and a β receptor for rodent hippocampal cells). This may mean that the underlying ionic bases differ for the two modes of noradrenergic excitation.

5.4 Summary

We have proposed three different biophysical mechanisms by which retino-geniculate

transmission can be altered or gated. These involve conventional GABAergic inhibition, the LT spike, and I_{AHP}. The GABAergic inhibition in geniculate relay cells is induced from either geniculate interneurons or perigeniculate cells. If it acts via a $GABA_A$ receptor to shunt postsynaptic potentials, it can selectively reduce or abolish the contribution of specific afferents to the output of the relay cell. That is, all excitatory synaptic input located more distally to the inhibition becomes cancelled (see above). Similarly, by inhibiting a specific set of geniculate interneurons or perigeniculate cells, it may be possible to promote high levels of retino-geniculate transmission through specific patterns of input lines from the retina. Conversely, the LT spike and reduction of I_{AHP} affect the postsynaptic geniculate cell's responsiveness to all excitatory inputs, including all retinal afferents, independent of their anatomical position in the dendritic tree. Moreover, the changes in cellular excitability appear to be long-lasting (up to several minutes). Thus, GABAergic inhibition may affect retino-geniculate gating transiently by focusing on patterns of retinal afferents, whereas the gating mechanisms of the LT spike and removal of accomodation via the reduction of I_{AHP} may operate through a different set of afferents and on a longer time-scale. The significance of the two anatomical sources of gating control may be that cortical areas 17, 18 and 19, being exclusively concerned with vision, control transfer of attention within the visual sense, whereas the brainstem reticular formation, most of the cells of which respond to all sensory modalities, controls the efficacy of geniculo-cortical activity for the other sensory modalities.

The cortico-geniculate pathway may be further subdivided into pathways from different cortical areas (i.e., areas 17, 18 and 19) and possibly also into separate X- and Y-dominated pathways. These pathways affect GABAergic inhibition of geniculate relay cells in a conventional synaptic manner and, as we have suggested above, may also control LT spikes. Control of retino-geniculate gating via cortico-geniculate fibers, which implies gating within the visual system, offers an interesting set of possibilities. The retinotopic arrangement of cortico-geniculate connections, even with the above caveat of slightly offset connections to emphasize lateral inhibition, implies that such gating could vary across the visual field to permit changes in fixation or attention to different visual objects. Also, if populations of cortico-geniculate fibers differentially innervate X and Y cells, a plausible possibility yet to be tested experimentally, the cortex would be able to gate differentially geniculate X and Y cells. This would allow the input lines to cortex to be dominated by one or the other pathway. During fast-paced activity when high acuity is not essential, such as playing basketball, it might be beneficial to open the gates of the general-purpose Y pathway and close those of the X pathway; conversely, during reading, the high-acuity X pathway might be favored, and the gates would be set accordingly.

Finally, such gating within the visual system might be important to such perceptual phenomena as the elevated visual threshold during saccadic eye movements (Helmholtz,

1866; Burr, Holt, Johnstone and Ross, 1982). This saccadic suppression is thought to prevent an unstable percept of the world during rapid eye movements. Interestingly, geniculate X and Y cells of the cat may be differentially affected during saccadic eye movements (Noda, 1975; for further details see Koch, 1985).

The brainstem pathways to the lateral genculate nucleus include, among others, cholinergic inputs from the parabrachial nucleus, noradrenergic inputs from the locus coeruleus, and serotonergic inputs from the dorsal raphe nucleus. Fibers from these brainstem regions affect GABAergic inhibition of geniculate relay cells in a conventional — if indirect — manner and also control the excitability of geniculate relay cells, possibly with control of I_{AHP}. These brainstem inputs may be used to direct attention to a specific sensory modality as for instance occurs when we block out extraneous and irrelevant sounds while reading. These inputs may also be important in the overall changes of geniculate cell responsiveness during sleep and arousal (Singer, 1977). Livingstone and Hubel (1981) report increased spontaneous firing rates and enhanced responses to optimal stimuli upon arousal (see also Coenen and Vendrik, 1972; Nelson *et al.*, 1983; McCarley *et al.*, 1983). Furthermore, neurons in both the dorsal raphe nucleus and the locus coeruleus fire more rapidly during periods of increased alertness, such as paradoxical sleep and arousal (Chu and Bloom, 1973; Foote, Aston-Jones and Bloom, 1980). These brainstem afferents may thus modify retino-geniculate transmission during arousal by increasing the excitability of geniculate relay cells.

While plausible hypotheses may be advanced, much more research needs to be directed at the putative mechanisms underlying gating of retina-to-cortex transmission. We do not even have a clear idea as to what specific visual function is subserved by this gating, beyond the general and rather hazy notion that it is related to visual attention (see also Singer, 1977; Yingling and Skinner, 1977; Burke and Cole, 1978; Crick, 1984; Ahlsen, Lindstrom and Lo, 1985). We also can only guess as to what might be the functional significance of the three different forms of gating involving conventional GABAergic inhibition, LT spikes, and I_{AHP}). Only with much more research directed at these questions can we truly begin to appreciate the functional significances of the lateral geniculate nucleus and other thalamic nuclei.

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Appendix

The number of cortico-geniculate neurons can be estimated as follows. Virtually all of these cells derive from layer VI of cortical areas 17, 18 and 19, and roughly half of these layer VI cells innervate lamina A and A1 (Gilbert and Kelly, 1975). For area 17, Beaulieu and Colonnier (1983) have estimated the density of cells in layer VI to be roughly 17000 cells per mm^2 of surface area. The surface area for area 17 is $380mm^2$ (Tusa *et al.*, 1978). Thus layer VI of area 17 contains roughly $6.5 \cdot 10^6$ cells, of which about $3.2 \cdot 10^6$ innervate laminae A and A1. Areas 18 and 19 are each about $1/6$ as large in surface area as is area 17 (Orban, 1984). If we assume a similar layer VI density for these areas (no published data on layer VI density exist for these areas, but the assumption seems reasonable), this implies roughly an additional $1.1 \cdot 10^6$ cortico-geniculate cells to innervate laminae A and A1. Overall, roughly $4.0 - 4.5 \cdot 10^6$ cortical cells innervate laminae A and A1 (for each hemisphere). Sanderson (1971) points out that the total number of cells in the lateral geniculate nucleus is roughly $4.5 \cdot 10^5$ (see also Bishop *et al.*, 1953). Laminae A and A1 may contribute roughly $1/2$ to $1/3$ of this number. Taken together, this implies that the cortico-geniculate cells innervating laminae A and A1 outnumber these geniculate cells by $10 - 20$ to 1. However, since Robson (1983) points out that cortico-geniculate axons have widespread arbors that cross laminar borders, each axon must consequently diverge to innervate several geniculate cells. As the divergence factor (i.e. the number of geniculate cells innervated by each cortico-geniculate axon) increases, so must the convergence factor (i.e. the number of cortico-geniculate axons that innervate each geniculate cell). In fact, the convergence factor is the product of the divergence factor and the ratio of cortico-geniculate axons to postsynaptic geniculate cells. As noted, this latter ratio is $10 - 20$ and if the divergence ratio is, say $5 - 10$, then the convergence ratio would be roughly 100. That is, on the average, each geniculate cell receives some input from about 100 cortical cells.

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