6

Dynamic Gating of Retinal Transmission to the Visual Cortex by the Lateral Geniculate Nucleus

S. M. SHERMAN

Department of Neurobiology, State Department of New York, Stony Brook, NY, USA

THE thalamus functions as a dynamically gated relay of peripheral information to the cerebral cortex (Singer, 1977; Burke and Cole, 1978; Sherman and Koch, 1986, 1990; Steriade and Deschênes, 1988; Steriade and Llinás, 1988). This means that data available to the cortex is filtered through the thalamus, and the nature of the information relayed by the thalamus varies according to many factors. These include behavioural state (e.g., alert or drowsy), focus of attention, and nature of sensory stimuli. The cellular mechanisms that control filtering by thalamic relay cells are of obvious importance, and these have been studied most thoroughly with regard to gating of retinogeniculate transmission in the cat's lateral geniculate nucleus. Although we need to have much more information about neuronal circuitry and functional properties involving the lateral geniculate nucleus, we can now begin to appreciate some of the mechanisms and implications of this dynamic gating.

Functional Circuitry Involving the Cat's Lateral Geniculate Nucleus

Lamination and retinal input

The cat's lateral geniculate nucleus can be divided into several different zones, all of which receive retinal input and project to the visual cortex (for review, see Sherman, 1985). The clearly laminated portion includes the A-laminae (lamina A and lamina A1) and C-laminae (lamina C, lamina C1, lamina C2, and lamina C3); lying medial to this is the medial interlaminar nucleus and geniculate wing, which are less clearly laminated. One well understood con-

Address for Correspondence: Department of Neurobiology, State Department of New York, Stony Brook, New York, NY 11794-5230, USA

comitant of the lamination is ocular input: laminae A, C, and C2 are innervated by the contralateral nasal retina; laminae A1 and C1 are innervated by the ipsilateral temporal retina; and neither retina directly innervates lamina C3. Even the medial interlaminar nucleus is divided into zones innervated by one or the other eye, but the geniculate wing, which extends mediodorsally from the medial interlaminar nucleus, seems to be innervated throughout by both eyes. Most attention has been focused on laminae A and A1, which appear to be a reasonably matched set differing chiefly in terms of ocular input. Since nearly all of our information concerning gating of retinogeniculate transmission derives from studies of the A-laminae, the following account is limited to these laminae.

It is worth pointing out that two different retinal ganglion cell types, called X and Y cells, innervate the A-laminae. Other types innervate the C-laminae, medial interlaminar nucleus, and geniculate wing (Sherman, 1985). It is beyond the scope of this review to describe these cell types in detail (for such detailed reviews, see Lennie, 1980; Stone, 1983; Rodieck and Brening, 1983; Sherman, 1985), but suffice to say that these represent the retinal starting points for several parallel and largely independent neuronal streams that pass through the lateral geniculate nucleus to visual cortex. They convey information about different aspects of the visual scene that are analyzed separately, in parallel, and are combined at some as yet unspecified cortical site. While subtle differences do exist between X and Y circuitry and intrinsic properties within the lateral geniculate nucleus (Sherman and Koch, 1986, 1990), these are overlooked below in view of more significant features of retinogeniculate gating that are shared by them.

Geniculate circuitry

Figure 1 schematically summarises circuitry related to the lateral geniculate nucleus. The retinal signal is transmitted to visual cortex via relay cells. These comprise roughly $\frac{3}{4}$ of the neurons in the main laminae. The remaining $\frac{1}{4}$ are interneurons, meaning that they do not project outside of the lateral geniculate nucleus. The neurotransmitter used for retinogeniculate transmission is an excitatory amino acid, such as glutamate or a similar compound, and this transmitter affects relay cells via a combination of postsynaptic receptors generally classified as NMDA (N-methyl-D-aspartate) or non-NMDA, the latter including several sub-types (Mayer and Westbrook, 1987; Scharfman *et al.*, 1990; Sillito *et al.*, 1990a, b; Esguerra *et al.*, 1992). The effectiveness of this retinogeniculate synapse in relaying retinal signals to cortex is strongly influenced by several nonretinal afferents (see below).

Local inhibitory cells. The interneurons, which use γ-aminobutyric acid (GABA) as a neurotransmitter, provide a powerful inhibitory input to relay cells. A separate, local source of inhibition to relay cells are the cells of the

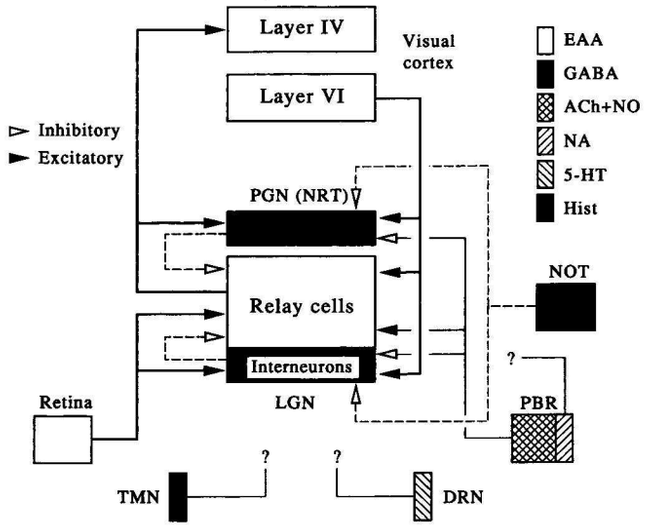

FIG. 1. Schematic view of functional circuits involving the lateral geniculate nucleus. **Abbreviations:** *PGN*, perigeniculate nucleus; *NRT*, thalamic reticular nucleus (PGN is part of the NRT); *LGN*, lateral geniculate nucleus; *TMN*, tuberomammillary nucleus of hypothalamus; *DRN*, dorsal raphé nucleus; *PBR*, parabrachial region; *NOT*, nucleus of the optic tract, which is part of the pretectum; *EAA*, excitatory amino acid, such as glutamate; *GABA*, γ-aminobutyric acid; *ACh*, acetylcholine; *NO*, nitric oxide; *NA*, noradrenaline (also norepinephrine); *5-HT*, serotonin; *Hist*, histamine. Where sufficiently detailed information is available, excitatory and inhibitory inputs are distinguished. Where insufficient information is available to assign specific postsynaptic effects for inputs, these are designated with question marks.

perigeniculate nucleus, a thin band of cells lying just dorsal to the A-laminae and thought to be a part of the thalamic reticular nucleus[1]. Like interneurons, all perigeniculate cells are GABAergic. Interneurons and perigeniculate cells influence relay cells via both $GABA_A$ and $GABA_B$ receptors (Bloomfield and Sherman, 1988; Crunelli *et al.*, 1988; Soltesz *et al.*, 1989). Clearly, these local inhibitory cells can powerfully influence the extent to which relay cells will transmit retinal information to cortex. At the extremes, high levels of activity amongst the local GABAergic cells would translate into maximum inhibition of relay cells, which would reduce or block retinogeniculate transmission; in con-

[1]The thalamic reticular nucleus is a thin band of GABAergic cells that borders the dorsal thalamus laterally, rostrally, ventrally, and dorsally. It can be divided into several subregions, each of which is intimately associated with a thalamic nucleus in a manner essentially like that of the perigeniculate nucleus with the lateral geniculate nucleus. The perigeniculate nucleus is thus a subregion of the thalamic reticular nucleus that is associated with the lateral geniculate nucleus.

trast, low activity levels amongst the GABAergic cells would leave the relay cells relatively excitable and promote efficient retinogeniculate transmission.

Thus pathways that influence these GABAergic cells will indirectly affect retinogeniculate transmission. Retinal axons innervate interneurons but not perigeniculate cells, and collaterals of geniculocortical axons innervate perigeniculate cells but not interneurons (see Figure 1). This is the main difference between the innervation patterns of perigeniculate cells and interneurons. Because retinal axons innervate interneurons and relay cells, this inhibitory circuit is called "feed-forward inhibition", and because perigeniculate cells receive input from relay cells they inhibit, this inhibitory circuit is called "feed-back inhibition". However, whether there is true feed-forward or feed-back inhibition depends on details of circuitry at the single cell level. Figure 2 illustrates this point.

True feed-forward inhibition involving retinogeniculate axons and interneurons is shown in Figure 2A, where the retinal axon innervates the interneuron and relay cell, and the interneuron innervates the *same* relay cell. In this schema, any excitation caused by the retinal axon would lead shortly thereafter to inhibition. Figure 2B illustrates a different form of inhibitory circuit, because the postsynaptic interneurons do not inhibit the same relay cell that is innervated by the retinal axon. The effect here is that the retinal axon directly excites a relay cell and indirectly inhibits its neighbours. There is some anatomical evidence to favour the scheme of Figure 2A. More specifically, many retinal terminals are involved in complex synaptic circuits known as "triads" in which the retinal terminal contacts both a terminal from an interneuron and a relay cell dendrite (Guillery, 1969a, b; Wilson *et al.*, 1984). It should be noted that this does not rule out the added presence of the circuit shown in Figure 2B.

A similar possibility exists for inhibitory circuits involving perigeniculate cells. Figure 2C shows a true feedback inhibitory circuit in which activity in a relay cell would lead to its own subsequent inhibition. Figure 2D shows a different circuit, analogous to that in Figure 2B, in which activity in a relay cell would serve to inhibit its neighbours. Present evidence is insufficient to determine whether one or both circuits outlined by Figure 2C, D is relevant.

Other extrinsic inputs to these local GABAergic circuits are considered in the following paragraphs.

Corticogeniculate input. The descending corticogeniculate input is often overlooked, but it has been estimated that there are roughly 10 corticogeniculate axons for every geniculocortical one (see Appendix in Sherman and Koch, 1986), and this pathway provides the plurality and perhaps the majority of synaptic inputs to relay cells (Guillery, 1969a,b; Wilson *et al.*, 1984; Sherman and Koch, 1986, 1990). This pathway is obviously of great importance to retinogeniculate transmission. Unfortunately, past studies have failed to indicate a function for this pathway commensurate with its size, although another chapter in this book does suggest at least one clear function (Sillito, 1993).

Corticogeniculate axons use an excitatory amino acid as a transmitter

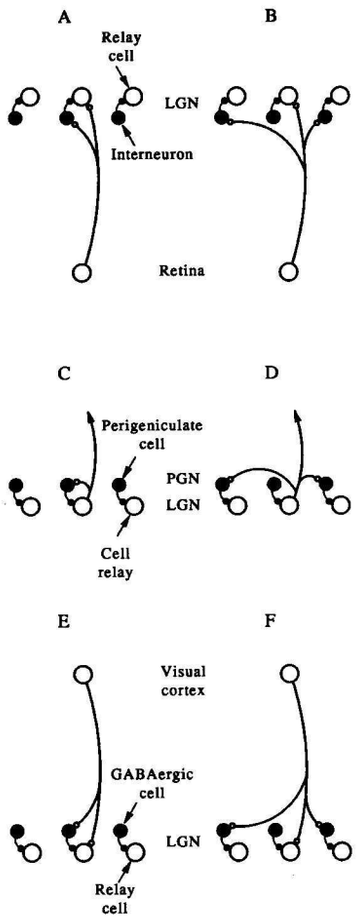

FIG. 2. Possibilities for organisation of local inhibitory, GABAergic inputs (see text for details). **A:** Retinogeniculate axon innervates interneuron and relay cell, and the interneuron innervates the same relay cell. This is true feed-forward inhibition. **B:** Retinogeniculate axon innervates interneurons and relay cell, but the innervated interneurons do not innervate the same relay cell. Instead, they innervate its neighbours. The effect of activity in the retinogeniculate axon would be to excite the relay cell while inhibiting its neighbours. **C:** Axon collateral from relay cell innervates perigeniculate cell that, in turn, innervates the same relay cell. This is true feed-back inhibition. **D:** Axon collateral from relay cell innervates perigeniculate cells that do not innervate the same relay cell. Instead, they innervate its neighbours. The effect of activity in the relay cell would be to inhibit its neighbours. **E:** Single corticogeniculate axon innervates local GABAergic cell (interneuron and/or perigeniculate cell) and relay cell, and the GABAergic cell innervates the same relay cell. In this schema, the corticogeniculate axon would directly excite and indirectly inhibit the relay cell, the end result being difficult to predict. **F:** Single corticogeniculate axon innervates GABAergic cells and relay cell, but the innervated GABAergic cells do not innervate the same relay cell. Instead, they innervate its neighbours. The effect of activity in the corticogeniculate axon would be to excite the relay cell while inhibiting its neighbours.

(Scharfman *et al.*, 1990; McCormick and Von Krosigk, 1992; McCormick, 1992) and provide an excitatory input to relay cells, interneurons, and perigeniculate cells (see Figure 1). Transmission onto relay cells seems to involve the same mixture of NMDA and non-NMDA receptors seen in retinogeniculate transmission (Scharfman *et al.*, 1990), but an additional receptor, a metabotropic receptor, also appears to be activated by corticogeniculate axons (McCormick, 1992; McCormick and Von Krosigk, 1992). The metabotropic receptor provides a slow but lengthy depolarisation due to inactivation of an outward K^+ conductance (McCormick and Von Krosigk, 1992).

Thus the corticogeniculate pathway can directly excite relay cells or indirectly inhibit them via interneurons and perigeniculate cells. The final balance of effects on retinogeniculate transmission depends on specific circuitry entered into by corticogeniculate axons. Figure 2E, F suggests two possibilities. In one (Figure 2E), the same corticogeniculate axon provides input to local GABAergic cells and the relay cells that these GABAergic cells innervate, thereby both exciting and inhibiting the relay cell. It is difficult to predict the outcome of this circuit on the excitability of the relay cell. In the other circuit (Figure 2F), there is a lateral offset between relay cells innervated by the GABAergic targets of the corticogeniculate axons and the relay cells directly innervated by these axons. This allows the visual cortex to activate a specific locus of geniculate relay cells while simultaneously inhibiting its neighbours. Available evidence favours the latter circuitry (Tsumoto *et al.*, 1978).

Brainstem input. An assortment of ascending pathways derives from the brainstem, primarily from the region of the midbrain and upper pons. Activity in the brainstem inputs seems particularly involved in controlling retinogeniculate transmission during various behavioural states such as sleep and alert wakefulness. It may also be important to controlling the relay of retinal signals during eye movements.

Most of the brainstem input to the A-laminae of the cat's lateral geniculate nucleus derives from cholinergic cells of the parabrachial region (de Lima and Singer, 1987; Fitzpatrick *et al.*, 1989). We recently showed that most or all of these cholinergic parabrachial cells co-localise NADPH-diaphorase, implying that their axon terminals use both acetylcholine and nitric oxide as neurotransmitters (Bickford *et al.*, 1993). Like corticogeniculate axons, these axons directly innervate both relay cells and the local GABAergic cells (see Figure 1). However, there is an important functional difference: although the same transmitters are used (i.e., acetylcholine and, presumably, nitric oxide), these axons depolarise relay cells while they hyperpolarise interneurons and perigeniculate cells (McCormick and Prince, 1987; McCormick and Pape, 1988). This differential action seems to be due to different postsynaptic receptors associated with the different cell types. That is, relay cells are excited via a combination of a nicotinic receptor that gates a conductance increase for cations and an M2 muscarinic receptor that gates a conductance decrease for K^+; interneurons and perigeniculate cells are inhibited via an M1 muscarinic receptor that gates a

conductance increase for K^+. As a result, these cholinergic axons from the parabrachial region appear to excite the relay cells both directly and indirectly, the latter via disinhibition.

Also providing an input to the lateral geniculate nucleus are noradrenergic cells in the parabrachial region[2], serotonergic cells in the dorsal raphé nucleus, and GABAergic cells in the pretectum. Noradrenalin seems to increase excitability of both local GABAergic cells and relay cells in the lateral geniculate nucleus, although certain details of this effect have yet to be elucidated (see McCormick, 1992). Effects of serotonin are complex. Iontophoresis onto relay cells *in vivo* generally inhibits them, but *in vitro* studies suggest that this is the consequence of direct excitation that is stronger for local GABAergic cells than for relay cells (McCormick, 1992). Understanding of the function of the input from the pretectum, which arises exclusively or nearly so from the nucleus of the optic tract, derives as yet only from morphological evidence. Such evidence suggests that GABAergic axons from the pretectum innervate mainly interneurons and perigeniculate cells, but not relay cells (Cucchiaro *et al.*, 1993). It seems likely that these axons act to inhibit the local GABAergic circuits, thereby exciting relay cells via disinhibition.

Hypothalamic input. Finally, there is a poorly understood, recently appreciated input from the tuberomammillary nucleus of the hypothalamus (see Figure 1). These axons use histamine as a neurotransmitter (Airaksinen and Panula, 1988; Uhlrich *et al.*, 1993). Histamine application to relay cells generally excites them (McCormick, 1992).

Intrinsic Properties of Relay Cells

It is clear from Figure 1 that many nonretinal regions of the brain can affect retinogeniculate transmission, either directly by innervating relay cells or indirectly by innervating perigeniculate cells and interneurons. However, a relay cell does not act as a simple linear integrator of inhibitory and excitatory inputs, because these cells display a number of conductances that depend on membrane voltage. That is, how a relay cell responds to retinal and other inputs varies in a nonlinear fashion with membrane voltage. One way of looking at this is considering that nonretinal afferents can affect the membrane voltage of relay cells, and this will markedly affect retinogeniculate transmission beyond what one might expect from simple excitation or inhibition. An obvious example of this is the voltage-dependent Na^+ conductance underlying the action potential, but there are many others, too many to cover in detail here (Jahnsen and Llinás,

[2]The organisation of the cholinergic and noradrenergic cell groups in the cat is a bit less tidy than in other mammals, such as rodents. For instance, in rats, the equivalent cholinergic cell group is called the pedunculopontine tegmental nucleus, and the equivalent noradrenergic cell group is called the locus coeruleus; these well-defined nuclei do not overlap. In cats, these cell groups do overlap and thus fail to lie within well-defined nuclei. We thus refer to these cell groups as the parabrachial region.

1984a, b; Sherman and Koch, 1986, 1990; Steriade and Llinás, 1988; McCormick, 1991). As examples of this property, only two voltage-dependent conductances are considered below, a ligand-gated response involving the NMDA receptor and a purely voltage-gated response involving a Ca^{2+} conductance[3].

The NMDA receptor

As noted above, both retinogeniculate and corticogeniculate transmission are partially accomplished via the NMDA receptor. This receptor is unusual in that the membrane conductance it gates depends on membrane voltage (Mayer and Westbrook, 1987; Scharfman *et al.*, 1990). When relatively hyperpolarised, the channel can be blocked by Mg^{2+} so that the process beginning with ligand-receptor coupling leads to little or no flow of cations into the cell. Depolarisation tends to clear the Mg^{2+} block so that receptor activation now leads to cation entry into the cell, which depolarises it. Among these cations is Ca^{2+}, and entry of Ca^{2+} can lead to secondary effects of NMDA channel activation, including Ca^{2+}-dependent and second messenger events (Mayer and Westbrook, 1987). Also, recent evidence suggests that retinogeniculate transmission can exhibit a phenomenon like long-term potentiation and that this depends on the NMDA receptor (Scharfman *et al.*, 1991). Activation of the NMDA receptor can thus have multiple effects on retinogeniculate transmission, many of which remain poorly understood, and successful activation of this receptor depends strongly on membrane voltage.

The low threshold Ca^{2+} conductance

Figure 3 illustrates the main features of the low threshold Ca^{2+} conductance (Jahnsen and Llinás, 1984a, b). Here, the effects on a relay cell in the geniculate A-laminae to the *same* depolarising current pulse is shown at different initial levels of membrane voltage. If the cell starts at a relatively depolarised level, the current pulse leads to tonic depolarisation of the cell, which, if large enough, evokes conventional action potentials for as long as the depolarisation exceeds the action potential threshold (Figure 3, top). At a slightly more hyperpolarised starting level, a purely ohmic response is seen, because the resultant membrane depolarisation remains below threshold for conventional action potentials (Figure 3, middle). Surprisingly, at an even more hyperpolarised starting level, the

[3]Other voltage-dependent conductances include at least two inward and two outward currents (Jahnsen and Llinás, 1984a, b; Sherman and Koch, 1986, 1990; Steriade and Llinás, 1988; McCormick, 1991). These are: 1) a slow inward Na^+ conductance producing a plateau depolarisation; 2) a high threshold Ca^{2+} conductance that may be generated in the dendrites; 3) an outward K^+ conductance that repolarises the cell following the action potential; and 4) an outward K^+ conductance known as the A-current. There also exists an outward K^+ conductance that depends only on Ca^{2+} entry into the cell and not on membrane voltage *per se*.

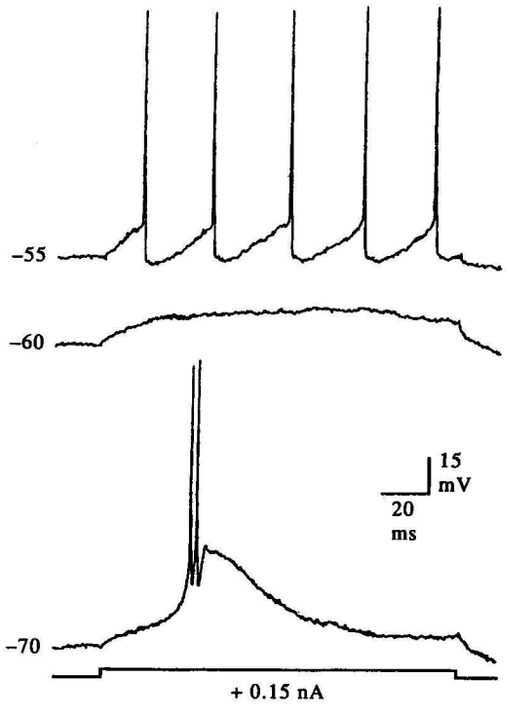

FIG. 3. Intracellular recording from a geniculate relay cell *in vitro* showing low threshold Ca^{2+} conductance. The *same* positive current (0.15 nA) is injected into the cell at 3 different values of membrane voltage. **Top:** Depolarised membrane voltage at which the low threshold Ca^{2+} conductance is inactivated. The injected current depolarises the cell, resulting in a tonic stream of action potentials for as long as the cell is sufficiently depolarised. **Middle:** Intermediate membrane voltage at which the low threshold Ca^{2+} conductance is still inactivated. The injected current depolarises the cell, but because the membrane voltage is initially further from threshold for activation of action potentials than in the top trace, this threshold is never reached, resulting in a purely ohmic response. **Bottom:** Hyperpolarised membrane potential at which the low threshold Ca^{2+} conductance is inactivated. Now, the injected current activates the low threshold Ca^{2+} conductance, and a brief, high frequency burst of action potentials rides its crest.

cell responds to the current pulse with a large, triangular depolarisation, large enough to evoke a burst of high frequency action potentials (Figure 3, bottom). One very important point made by Figure 3 is that there is a range of membrane voltage in which further hyperpolarisation can make the cell more responsive to depolarising input.

The triangular depolarisation of Figure 3, bottom, is caused by activation of a Ca^{2+} conductance, allowing Ca^{2+} to enter the cell and depolarise it. This conductance is rapidly inactivated by depolarisation. Thus at more depolarised membrane voltage, as in Figure 3, top, middle, this Ca^{2+} conductance is already inactivated and cannot be activated by depolarisation. However, sufficient

hyperpolarisation of the cell for roughly 50–200 msec or more de-inactivates the Ca^{2+} conductance, allowing any subsequent, sufficiently large depolarisation to activate it, as in Figure 3, bottom. It is important to note that very brief hyperpolarisation (i.e., < 50 msec or so) is insufficient to de-inactivate the Ca^{2+} conductance. This time dependency of de-activation means that the Ca^{2+} conductance cannot be evoked at a rate greater than about 20 Hz (Jahnsen and Llinás, 1984a, b). Thresholds for activation, inactivation, and de-inactivation are relatively sharp, and this causes the Ca^{2+} conductance and its resultant depolarisation to be nearly all-or-none or spike-like (Jahnsen and Llinás, 1984a, b). Because it has a lower activation threshold than a conventional action potential, it is called "low threshold", and is often simply called the "low threshold conductance" or "low threshold spike". These same phenomena regarding the low threshold spike that were first described *in vitro* are also seen *in vivo*, and low threshold spikes can be activated in suitably hyperpolarised relay cells by EPSPs and visual stimulation (Lo *et al.*, 1991; Lu *et al.*, 1992; Guido *et al.*, 1992a).

It must be remembered that the only signal to be conducted over the long geniculocortical axons is that carried by action potentials. Thus cortex cannot be aware of low threshold spiking directly. However, the continuous, tonic stream of action potentials evoked during prolonged depolarisation when the low threshold spike is inactivated (Figure 3, top) is qualitatively different from the high frequency intermittent bursts that ride the crests of low threshold spikes (Figure 3, bottom). As noted above, the time dependency of low threshold spikes ensures that the action potential bursts are well separated from one another. These two different modes of firing have been termed the *relay mode* or *tonic mode* during inactivation of the low threshold spike, because the firing pattern is tonic and more closely resembles that of retinal afferents, and the *burst mode* during low threshold spike activation (Jahnsen and Llinás, 1984a, b).

The low threshold spike and neuronal oscillations. Jahnsen and Llinás (1984a, b) pointed out that low threshold spiking could be made cyclic and rhythmical by the presence of several conductances intrinsic to relay cells in addition to and related to the Ca^{2+} conductance. They suggested that, following the evoked Ca^{2+} conductance, a series of K^+ conductances could be invoked to hyperpolarise the cell for 50–200 msec. While the Ca^{2+} entry depolarises the cell and thus inactivates the low threshold spike, the ensuing, long hyperpolarisation due to the outward flow of K^+ serves to de-inactivate the low threshold spike again. As the K^+ conductances become inactivated, the membrane then passively repolarises, which serves to activate the next low threshold spike, and this process continues cyclically. The low threshold spiking would continue to oscillate, the particular frequency depending on the precise conductances involved. Such oscillations associated with the low threshold spike are often seen during *in vitro* recording and under certain conditions of *in vivo* recording (Jahnsen and Llinás, 1984a, b; Deschênes *et al.*, 1985; Domich *et al.*, 1987; Steriade *et al.*, 1987; Steriade and Llinás, 1988; Curró Dossi *et al.*, 1992; Huguenard and McCormick, 1992; McCormick, 1992; Nuñez *et al.*, 1992). More recently, it has been argued that only lower frequency oscillations of bursting (0.5–4 Hz) can be maintained by intrinsic conductances, and that higher frequencies of oscillation reflect dynamic properties of the local GABAergic circuits (McCormick, 1992; Curró Dossi *et al.*, 1992).

These oscillations seem especially interesting, because this sort of cyclic activity may underlie EEG epochs associated with various behavioural states. For example, synchronised EEG patterns with frequencies of 6–10 Hz are associated with certain phases of sleep, and this may reflect a massive switching of many or most thalamic neurons into the burst mode of firing. While intrinsic conductances may suffice to promote oscillatory bursting in an individual neuron, they are insufficient by themselves to entrain all thalamic cells to the same rhythm and phase, which is necessary if low threshold spiking underlies various synchronised EEG phenomena. Steriade and his co-workers (Deschênes *et al.*, 1985; Steriade *et al.*, 1985, 1987; Curró Dossi *et al.*, 1992) provided evidence from *in vivo* recording that the thalamic reticular nucleus serves to synchronise bursting oscillations amongst relay cells of the dorsal thalamus.

The notion here is that such oscillatory bursting represents a functional disconnection of retinogeniculate transmission. Because the bursts represent the consequences of intrinsic conductances associated with the low threshold spike and/or activity in circuits of the thalamic reticular nucleus, they no longer reflect afferent activity of retinal axons. The actual signal reaching cortex is a pattern of brief epochs of high frequency (> 250 Hz) action potentials separated from one another by 50–200 msec, and the cortex can unambiguously distinguished this from tonic activity representing the relay mode. The low threshold bursting may represent a state of inattention in the visual system that occurs during sleep or other behavioural states. If so, it seems significant that this state is signalled to cortex positively via the bursting rather than by no signal at all, because no signal could be confused between functional disconnection during visual inattention or no visual stimulation during visual attention. Thus one hypothetical function of the low threshold spike is that it represents a type of switch between faithful relay of retinal information and functional disconnection associated with oscillatory bursting, and this switch is controlled simply via membrane voltage.

The low threshold spike as a nonlinear amplifier for retinogeniculate transmission. There is, however, one other function that can be attributed to the low threshold spike. If the oscillations seen during certain *in vitro* and *in vivo* conditions invariably appeared with low threshold spikes and represented functional blockade of retinogeniculate transmission, then hyperpolarised cells could not respond to visual stimuli. That is, during an epoch of hyperpolarised membrane voltage and de-inactivation of the low threshold spike, visual stimuli, if sufficiently large to activate the relay cell, would activate a low threshold spike leading unerringly to oscillatory bursting that no longer reflected the visual

stimulus. However, recent evidence from *in vivo* recording makes clear that visual stimuli can reliably activate low threshold spikes without oscillations and that the pattern of bursting reflects the visual stimulation (Guido *et al.*, 1992a; Lu *et al.*, 1992). Figure 4 shows examples of low threshold spikes evoked by visual stimulation as a function of membrane voltage.

Thus low threshold spiking does not always imply functional blockade of retinogeniculate transmission, but the pattern of action potentials relayed to cortex is clearly different between the burst and relay modes. Figure 5 shows a typical example of a relay cell responding to a drifting sinusoidal grating at two different levels of membrane voltage, a depolarised level (Figure 5A) during which the cell responded in the relay mode because the low threshold spike was inactivated, and a hyperpolarised level (Figure 5B) during which the cell responded in the burst mode because the low threshold spike was activated. Two features distinguish these responses.

First, the signal-to-noise ratio (where the spontaneous activity represents the noise) is much greater during the burst mode of firing than during the relay mode (Guido *et al.*, 1992b). This is due to the fact that, during the burst mode, although the overall response is less, there is proportionately even less spontaneous activity because of the hyperpolarised membrane voltage. Simple detection of a visual stimulus is thus enhanced during the burst mode of firing. Such an enhancement has been formally demonstrated with receiver operating characteristic (ROC) analysis (Guido *et al.*, 1992b).

Second, responses are much more linear during relay mode responses than during those of the burst mode. The drifting sinusoidal grating presents a sinusoidal modulation of contrast to the receptive field, and linearity of response can readily be determined for such stimuli by performing a Fourier analysis of the response profile (Shapley and Lennie, 1985): a linear response is dominated by the first Fourier component (F1), which would have the same sinusoidal shape as does the contrast variation of the stimulus, while a nonlinear response is reflected by additional higher harmonics (e.g., F2, F3, ..., Fn) that distort the shape of the response profile from a sinusoidal form. Responses during the relay mode indeed have a relatively sinusoidal profile and are dominated by the F1 Fourier component (Figure 5A). During low threshold spiking (Figure 5B), the response shows only an early peak where the bursts of action potentials are evoked, and significant higher harmonics (F2, etc.) are seen in the response profile. In other words, the low threshold spike provides an amplification that permits a hyperpolarised relay cell to respond to a retinal input, but the amplification is achieved at the expense of linearity.

These differences between the response profiles illustrated in Figure 5A, B can be predicted from the nature of the relay and burst modes. The relay mode involves graded responses to a prolonged depolarising input during which the response can mimic the stimulus in both time and amplitude. In contrast, the burst mode involves a nearly all-or-none response followed by an obligatory silent period (see Figure 3), which in turn implies a nearly stereotypical response

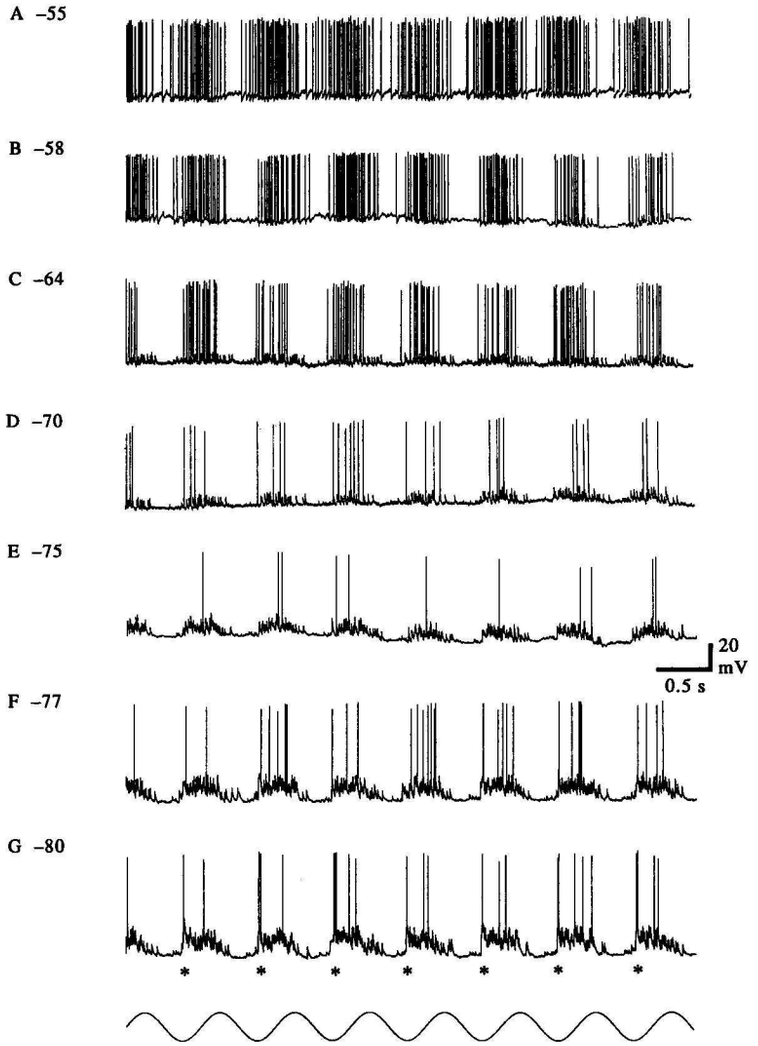

FIG. 4. Intracellular records showing responses of a geniculate relay cell to a drifting sinewave grating at different membrane potentials (from Lu *et al.*, 1992). The bottom trace represents the sinusoidal contrast changes presented by the drifting grating. Each LT spike is depicted by an asterisk below the trace. **A:** Responses at the resting membrane potential, which was − 65 mV. **B:** Responses at a membrane potential of − 67 mV. **C:** Responses at a membrane potential of − 75 mV. **D:** Responses at a membrane potential of − 78 mV. **E:** Responses at the most hyperpolarised membrane potential. Here, the cell was sufficiently hyperpolarised that responses of any type were rare. In **A** and **B**, no LT spikes were seen and the response was purely relay mode. LT spikes were often activated at more hyperpolarised potentials (**C** and **D**). Note that, when they occur, they are always the first response evoked, and tonic responses may occur later. More than one LT spike may rarely be evoked during a stimulus cycle (e.g., the 4th cycle of **D**).

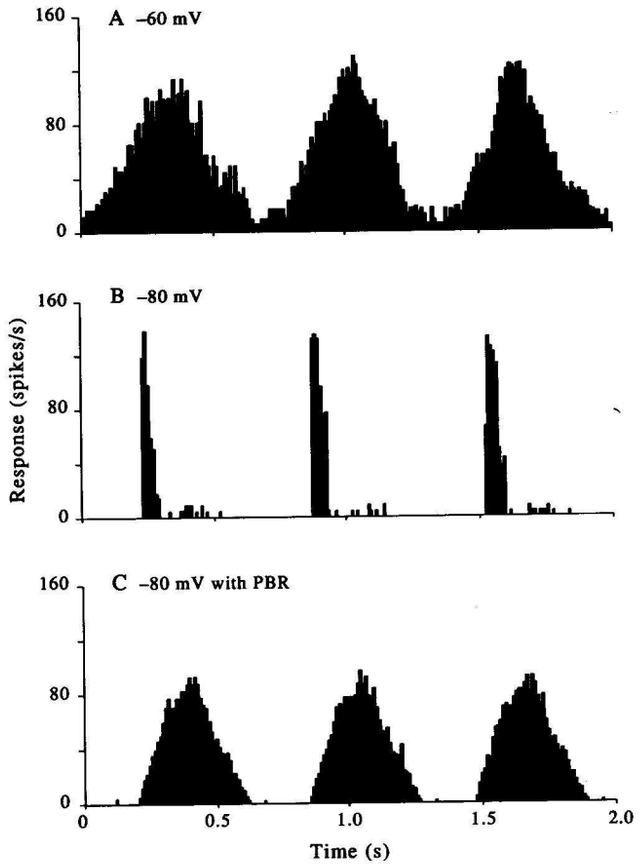

FIG. 5. Typical response histograms to 3 successive stimulus cycles of a drifting grating for a geniculate relay cell (from Lu *et al.*, 1993). **A:** Responses at −60 mV without parabrachial activation. There is no evidence of LT spiking, and the cell thus responded in the relay mode. Note the fairly sinusoidal response profile, matching the contrast changes in the stimulus, thereby indicating considerable linear response summation. **B:** Responses at −80 mV before parabrachial activation. LT spiking was evident, and the cell thus responded in the burst mode. Note that compared to **A**, the response profile here is less sinusoidal, indication more nonlinear distortion in the response. **C:** Responses during parabrachial activation beginning at the same membrane potential (−80 mV) as in **B**. Soon after parabrachial activation, the cell switched from the burst to the relay mode, and the membrane gradually depolarised by 5–10 mV. As the LT bursts were eliminated, and the response shows much more linear summation. Note the similarity between histograms in **A** and **C**.

to any suprathreshold stimulus. Also, the higher level of spontaneous activity seen during relay mode responses enhances linearity by minimising half-wave rectification in the response. This simply means that inhibitory responses to the visual stimulus can be expressed faithfully by a reduction in the spontaneous activity without which a nonlinear distortion due to a basement effect would ensue. Lack of spontaneous activity during the burst mode thus enhances nonlinear distortion in the stimulus/response relationship. For the visual cortex to faithfully reconstruct the visual stimulus, it is important that signals relayed to it via retinogeniculate transmission are as linear as possible. In other words, linear responses represented in the relay mode are needed for the visual system to analyze the details of a stimulus; the nonlinear distortion represented in the burst mode would enable the visual system to determine the presence of a stimulus, but detailed analysis of the stimulus would be compromised.

From the above observations, it is possible to offer a hypothesis for function of low threshold spikes in addition to oscillatory activity that interferes with retinogeniculate transmission. When attention is fully directed at a visual target, those geniculate relay cells mapping the corresponding region of visual space are kept relatively depolarised via influence of corticogeniculate and/or brainstem inputs. The depolarisation inactivates the low threshold spike and raises spontaneous activity, both of which help to preserve response linearity so important to detailed analysis of the target. Since attention is already directed at the target, its detection is not an issue, and thus the raised spontaneous activity and subsequently lowered signal-to-noise ratio do not pose an obstacle for visual processing. Those relay cells mapping other, unattended regions of visual space are kept sufficiently hyperpolarised to de-inactivate the low threshold spike. This serves not only to keep spurious spontaneous noise down in regions mapped to no targets of interest, but it also keeps the cells in their most sensitive state for detecting a novel stimulus. That is, a novel and potentially important stimulus would evoke a low threshold spike in one of these hyperpolarised relay cells, and the signal transmitted to cortex would be readily detected. If the cortex then wanted to shift attention to this novel target for further detailed analysis, it could bring into play new levels of activity via appropriate corticogeniculate and/or brainstem pathways to depolarise the relay cells in question.

Summary and Conclusions

The transmission of retinal signals to cortex is clearly affected by the membrane voltage of the relay cell. Both cortical and brainstem inputs to the lateral geniculate nucleus can regulate membrane voltage, either by direct effects on relay cells or indirectly through effects on local GABAergic circuits. A relatively depolarised relay cell would exhibit enhanced responsiveness to retinal input partly because its initial membrane voltage is closer to action potential threshold and partly because depolarisation permits the NMDA receptor component of the retinal EPSP to develop. Not only would a

depolarised membrane voltage mean a greater synaptic transfer in retinogeniculate transmission, it would also promote more linear transmission by preventing retinal activation of the highly nonlinear low threshold spike. A hyperpolarised membrane voltage helps to eliminate spurious signals in retinogeniculate transmission by reducing spontaneous activity, but the resulting de-inactivation of the low threshold spike means that the relay cell can efficiently signal the presence of new, potentially salient visual targets.

It is hard to predict the precise role of corticogeniculate axons in controlling membrane voltage, because details of circuitry as suggested by Figure 2E, F have yet to be clarified. However, the direct input of cortical inputs to relay cells seems well designed to control membrane voltage. There is considerable convergence in this pathway, so that each relay cell on average is innervated by roughly 100 cortical axons (see Appendix to Sherman and Koch, 1986). Such convergence implies that, during periods of activity in the corticogeniculate pathway, a constant bombardment of asynchronous EPSPs will temporally summate to shift membrane voltage fairly smoothly. Cortical terminals innervate distal dendrites (Guillery, 1969a, b; Wilson *et al.*, 1984), and this would create further temporal dispersion of EPSPs, resulting in smooth changes in membrane voltage. Finally, the corticogeniculate pathway seems to use the metabotropic glutamate receptor, which acts to produce slow, long-standing depolarisations (see above). It seems likely that one key role of the corticogeniculate pathway is to modulate membrane voltage of the relay cells, but this hypothesis has yet to be rigorously tested.

A similar role can be suggested for the parabrachial region, since *in vivo* activation of this pathway or *in vitro* application of its chief neurotransmitter, ACh, produces prolonged depolarisation. Indeed, Figure 5C shows that activation of the parabrachial region produces the expected result on responses of a relay cell to a visual stimulus (Lu *et al.*, 1993). Before parabrachial activation (Figure 5B), the hyperpolarised cell produced a nonlinear response characterised by low threshold spiking, but during such activation (Figure 5C), the responses were much more linear and devoid of low threshold spikes, just as they are when the cell is depolarised (Figure 5A).

While corticogeniculate and brainstem inputs may share an important final mode of operation, the control of membrane voltage, there are clear and important functional differences between them. Corticogeniculate input is unimodal in the sensory domain, being limited to vision, and has a precise retinotopic organisation (Updyke, 1975; Robson, 1983, 1984). This suggests that its role may be to control retinogeniculate transmission within precisely defined regions of visual field. Brainstem inputs, on the other hand, are more globally organised, and probably some are multimodal, involving relative attention amongst several sensory systems. They likely act to control retinogeniculate transmission in a more sweeping, state-dependent manner.

Finally, it should be clear that our understanding of nonretinal control of retinogeniculate transmission is at best rudimentary. At one level, the above

hypotheses of the possible functions of various nonretinal inputs need to be much more extensively tested. Both the brainstem and corticogeniculate inputs are heterogeneous: at least several subtypes of corticogeniculate axon have been identified (Tsumoto and Suda, 1980), and brainstem inputs include cholinergic, serotonergic, noradrenergic, GABAergic, and histaminergic axons that almost certainly subserve different functions. How these different cortical and brainstem inputs interact with one another, which must certainly occur during normal visual behaviour, is an important issue that has not yet been approached experimentally. At another level, we are just beginning to appreciate how membrane voltage may affect retinogeniculate transmission of visual signals, and most of this effort has been limited to the low threshold spike. Many other voltage-dependent processes exist, and how they interact and affect retinogeniculate transmission is virtually unknown.

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