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REVIEW ARTICLE

Dual response modes in lateral geniculate neurons: Mechanisms and functions

S. MURRAY SHERMAN

Department of Neurobiology, State University of New York, Stony Brook

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Abstract

Relay cells of the lateral geniculate nucleus, like those of other thalamic nuclei, manifest two distinct response modes, and these represent two very different forms of relay of information to cortex. When relatively hyperpolarized, these relay cells respond with a low threshold Ca^{2+} spike that triggers a brief burst of conventional action potentials. These cells switch to tonic mode when depolarized, since the low threshold Ca^{2+} spike, being voltage dependent, is inactivated at depolarized levels. In this mode they relay information with much more fidelity. This switch can occur under the influence of afferents from the visual cortex or parabrachial region of the brain stem. It has been previously suggested that the tonic mode is characteristic of the waking state while the burst mode signals an interruption of the geniculate relay during sleep. This review surveys the key properties of these two response modes and discusses the implications of new evidence that the burst mode may also occur in the waking animal.

Keywords: Lateral geniculate nucleus, Low threshold spike, Signal detection, Burst and tonic modes, Corticogeniculate pathway

Introduction

As the synaptic stages of the visual system are ascended, receptive fields became increasingly complex. This elaboration and increasing complexity, it is generally believed, continues through extrastriate visual areas and provides the visual system with the means of reconstructing the visual environment in some detail. However, the retinogeniculate synapse is the one major synaptic level across which little receptive-field elaboration occurs: the basic center/surround organization of the receptive fields of geniculate relay cells is, to a first approximation, the same as the center/surround organization seen in receptive fields of their retinal afferents (Hubel & Wiesel, 1961; Cleland et al., 1971; Hoffmann et al., 1972). Largely because of this, visual processing occurring at the level of the lateral geniculate nucleus has been neglected compared to other main synaptic levels along the visual pathways.

Although generally ignored in this context, morphological data were available early on to dispel the notion that the lateral geniculate nucleus is a mere relay. A simple relay function would imply that synaptic inputs to geniculate relay cells should be dominated by retinal afferents. In fact, retinogeniculate synapses constitute only 10-20% of synaptic input to these cells (reviewed in Guillery, 1969*a*,*b*, 1971; Sherman & Koch, 1986, 1990; Sherman, 1993). Local inhibitory, GABAergic cells (i.e. interneurons and cells of the nearby thalamic reticular nucleus) provide roughly one-fourth of these inputs; the plurality of synapses, nearly 50%, derive from corticogeniculate axons; and the rest reflect projections from other subcortical regions, such as brain stem and hypothalamus (see Fig. 1). In fact, among all the sources of major input to the lateral geniculate nucleus, the retina provides among the *smallest* inputs. Such complex circuitry dominated by nonretinal inputs hardly seems consistent with a simple relay.

Recent work suggests that the lateral geniculate nucleus provides a variable and dynamic gateway for the relay of retinal information to cortex (Sherman & Koch, 1986, 1990; Steriade & Llinás, 1988; Steriade et al., 1990, 1993; Sherman, 1993; McCormick & Bal, 1994). The gateway can be open or closed to varying degrees under the control of nonretinal inputs, and this determines what sort of information will be filtered out and what is actually relayed. By controlling the flow of visual information relayed to cortex, the lateral geniculate nucleus thus plays an essential role in various visual attentional mechanisms and state-dependent effects of visual information processing.

It has now been well established that geniculate relay cells, like those of all other thalamic nuclei, respond in one of two very distinct patterns known as *tonic* and *burst* modes.* Tonic

Reprint requests to: S. Murray Sherman, Department of Neurobiology, State University of New York, Stony Brook, NY 11794-5230, USA.

*"Tonic" used in this sense refers to a response mode of a geniculate relay cell, and here it is paired with "burst". Unfortunately, the term "tonic", when paired with "phasic", has also been used in a very different context for geniculate relay cells to refer to cell type: "tonic" for X and "phasic" for Y. X and Y cells, the relay cell types found in the A-laminae of the cat's lateral geniculate nucleus, display both response modes. Throughout this account, we shall use "tonic" only to refer to response mode and not to cell type.

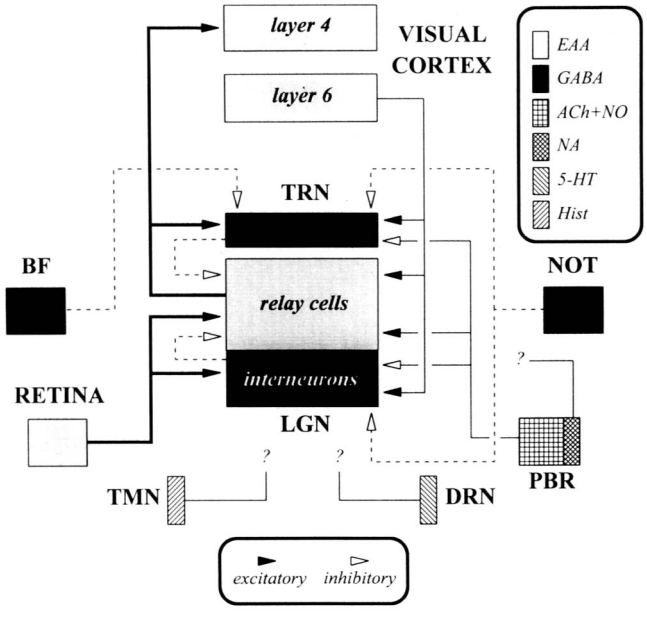

Fig. 1. Schematic diagram of functional circuitry related to the lateral geniculate nucleus and nearby thalamic reticular nucleus of the cat. Shown are the various inputs, the transmitters used by these inputs, and their postsynaptic mode of action. Most of the data upon which this diagram is based can be found in Sherman and Koch (1986, 1990), McCormick (1992), and Sherman (1993). More recent evidence is included for inputs from the nucleus of the optic tract (Cucchiaro et al., 1993), parabrachial region (Bickford et al., 1993), tuberomammillary nucleus (Uhlrich et al., 1993), and basal forebrain (Bickford et al., 1994). Question marks indicate uncertainty about excitatory or inhibitory effects of inputs. 5-HT: serotonin; ACH: acetylcholine; BF: basal forebrain; DRN: dorsal raphé nucleus of brain stem; EAA: excitatory amino acid (e.g. glutamate); GABA: γ-aminobutyric acid; Hist: histamine; LGN: lateral geniculate nucleus; NA: noradrenaline; NO: nitric oxide; NOT: nucleus of the optic tract of pretectum; PBR: parabrachial region of brain stem; TMN: tuberomammillary nucleus of hypothalamus; and TRN: thalamic reticular nucleus.

mode is characterized by a steady stream of unitary action potentials; burst mode is characterized by clusters of 2–10 action potentials with interspike intervals of ≤4 ms and with silent periods of ≥50–100 ms between bursts (for details, see Jahnsen & Llinás, 1984*a*,*b*; Lo et al., 1991; Huguenard & McCormick, 1992; McCormick & Huguenard, 1992; Guido et al., 1995). These response modes occur in relay cells of all thalamic regions of all mammalian species so far studied and are not seen in the main afferents (Jahnsen & Llinás, 1984*a*,*b*; Lo et al., 1991; Bal et al., 1995). The different patterns of firing they represent mean that tonic and burst response modes impart a different quality to the thalamic relay. Whether a geniculate relay cell happens to be responding in burst or tonic mode can be quite important to the nature of visual information reaching cortex for further processing. Most of the remainder of this article is devoted to these response modes and the effects they seem to have on the relay of information to cortex.

Cellular bases of tonic and burst firing: The low threshold spike

Thalamic relay cells in general, and those of the lateral geniculate nucleus more specifically, express a number of voltage-dependent membrane conductances.† This means that various ion channels open or close as membrane potential fluctuates, thereby permitting flow of various ions into or out of the cell. Such flow leads to further changes in membrane potential, and these changes affect the probability that action potentials arriving *via* retinal axons will be relayed to cortex.

The conventional Na^+/K^+ action potential is the best known example among the voltage-dependent conductances. The most intensely studied and probably the most important among the other voltage-dependent conductances is that underlying the low threshold Ca^{2+} spike. It is the activation state of this conductance that determines whether the relay cell responds in tonic or burst mode. The underlying conductance involves flow of Ca^{2+} into the cell via T-type Ca^{2+} channels. The resultant current is thus known as the *T-current* or I_T. The low threshold spike, low threshold conductance, and I_T all refer to different aspects of the same phenomenon.

Voltage dependency of the low threshold spike

Fig. 2 shows the voltage dependency of the low threshold spike for a typical geniculate cell. These recordings were made *in vitro* from a slice through the lateral geniculate nucleus of a cat. They illustrate a simple experiment during which the same depolarizing pulse is injected through the intracellular recording electrode into the geniculate cell; the variable here is the initial level of membrane polarization when the pulse is delivered. When the cell initially is relatively depolarized (Fig. 2A), it responds to the depolarizing pulse with a string of unitary action potentials that last as long as the injected pulse maintains sufficient depolarization to reach firing threshold. This is the tonic response mode. When the cell initially is moderately hyperpolarized (Fig. 2B), a purely ohmic response is seen without firing. This is because the starting membrane potential is further from firing threshold than is the case in Fig. 2A, and the same injected pulse is no longer able to reach threshold for firing. From Figs. 2A and 2B, one might predict that the same current injection starting from further initial depolarization would only continue to lead to ohmic responses without action potentials. However, Fig. 2C shows that this is not the case. Now from a more hyperpolarized level than is the case for Fig. 2B, the same depolarizing pulse leads to a large, spike-like, triangular depolarization; this is sufficiently large to reach firing threshold and thus to discharge a high-frequency burst of 2–10 action potentials riding the crest of the underlying depolarization. This firing pattern is the burst mode, and the spike-like depolarization underlying the burst of action potentials is the low threshold spike. Note that the burst of action potentials is very brief and, unlike the tonic response, does not last for the duration of the depolarizing pulse.

The phenomenon of Fig. 2 can be explained by the voltage dependence of the low threshold spike. This spike results from a voltage-dependent Ca^{2+} conductance, permitting Ca^{2+} to enter the cell and depolarize it. This conductance is *inactivated* by membrane depolarization more positive than about −60 mV (Figs. 2A and 2B) and is *de-inactivated* at more hyperpolarized levels (Fig. 2C). The low threshold conductance also has a time

†For details of the full range of voltage-dependent conductances known for thalamic neurons, see Jahnsen and Llinás (1984*a*,*b*), Huguenard and McCormick (1992), and McCormick and Huguenard (1992).

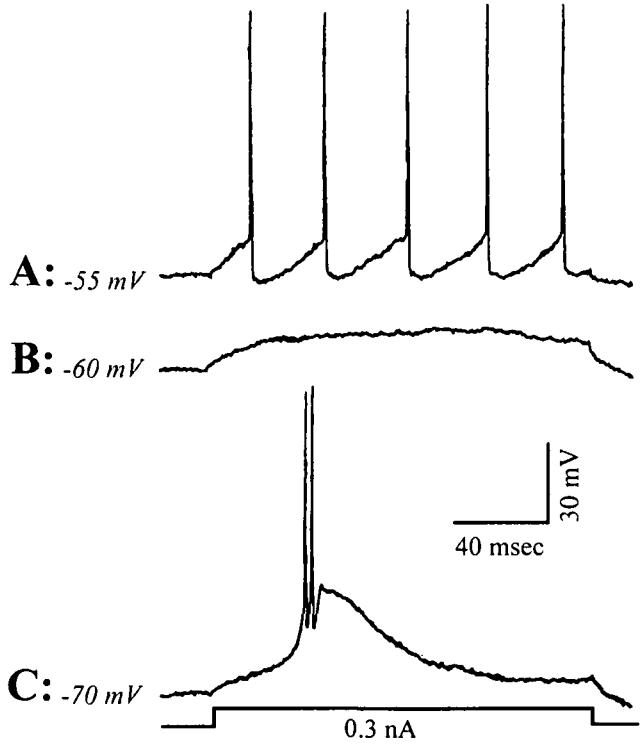

Fig. 2. Voltage dependency of low threshold spike. The example shows intracellular records from an *in vitro* slice preparation of a geniculate cell taken from a cat. The same 0.3 nA current pulse (bottom trace) is injected into the cell *via* the recording electrode at three different initial levels of membrane polarization. A: Tonic response at −55 mV. The conductance underlying the low threshold spike is inactivated at −55 mV. B: Purely ohmic response at −60 mV. The low threshold conductance is still inactivated at −60 mV, and the injected depolarizing pulse is insufficient to drive the cell to discharge action potentials. C: Burst response at −70 mV. The low threshold conductance is now de-inactivated at −70 mV, and the depolarizing pulse activates a low threshold spike, producing a burst of two action potentials riding its crest. Redrawn from Sherman (1993).

dependency for de-inactivation, requiring roughly 100 ms of hyperpolarization to fully de-inactivate. Once de-inactivated, this conductance can be *activated* by a suitably large depolarization (Fig. 2C), such as a depolarizing current injection or an EPSP. The activated conductance leads to the largely all-or-none depolarization of the low threshold spike. It is called "low threshold" because it is activated at a more hyperpolarized level than is the conventional action potential. The time dependency of de-inactivation means that the low threshold spike has something like a refractory period, since it cannot be activated at a frequency greater than about 10 Hz, and the cell is typically silent between the bursts of action potentials.

Nonlinear distortion associated with the low threshold spike

The low threshold spike provides an amplification that expedites the generation of action potentials in a hyperpolarized cell. However, because of the largely all-or-none, spike-like depolarization resulting from the Ca^{2+} conductance, the amplification is nonlinear. This nonlinearity is clear when burst firing is compared to tonic firing. As noted above, during the tonic firing of Fig. 2A the cell continues to respond as long as the injected pulse depolarizes the cell sufficiently to reach threshold for action potentials. Not shown in Fig. 2A is the fact that the amplitude of the current injection affects the frequency of action potentials: the greater the amplitude, the higher the frequency of firing. There is thus a close and fairly linear relationship between the stimulus parameters of duration and intensity and the response parameters of duration and frequency.

This relationship is absent during burst firing for two reasons. First, the time dependency of de-inactivation of the low threshold conductance means that the response is intermittent despite a continuous stimulus, so that the *same* single burst will result from a very brief stimulus as well as from one lasting up to about 100 ms. Second, the nearly all-or-none nature of the low threshold spike means that it is fairly stereotyped in size and shape, and its level of depolarization is what determines the pattern of action potentials in the burst. Thus a stimulus barely suprathreshold for activating a low threshold spike would produce nearly the same response as a much larger stimulus, and since action potentials are the only signal transmitted to cortex, this difference in stimulus strength is not encoded in the relay. Put another way, burst responses riding the low threshold spikes show a very compressed dynamic range in their ability to encode stimulus strength. The end result during burst mode is a signal relayed to cortex that does not faithfully represent the stimulus in either duration or amplitude. Thus, compared to tonic firing, burst firing introduces considerable nonlinear distortion in the relay of signals to cortex. The functional significance of this is considered below.

Rhythmic firing during burst mode

The low threshold spike has been most intensely studied with the *in vitro* slice preparation. Once activated in this preparation, it tends to occur spontaneously and rhythmically, although individual, arrhythmic bursts can also appear *in vitro*. Activation of the low threshold spike from the requisite hyperpolarized level is rapidly followed by repolarization of the membrane to the original hyperpolarized level. This is partly because the depolarization of the low threshold spike itself rapidly inactivates the I_T. Various other voltage-dependent conductances then become activated (for details, see Jahnsen & Llinás, 1984*a*,*b*; McCormick & Pape, 1990; Huguenard & McCormick, 1992; McCormick & Huguenard, 1992): a series of K^+ conductances keeps the membrane hyperpolarized long enough to de-inactivate I_T, and these are followed by a depolarizing current (known as I_h, because it is activated by hyperpolarization) that activates the next low threshold spike, and the process is repeated. This results in lengthy epochs during which the cell fires with fairly evenly spaced bursts separated by ≥100 ms, and usually ≥250 ms. The actual interburst interval, and thus burst frequency, depends on a variety of factors that need not concern us here (for details, see Jahnsen & Llinás, 1984*a*,*b*; Huguenard & McCormick, 1992; McCormick & Huguenard, 1992). The result is rhythmic bursting that occurs spontaneously in the sense that, once started, no further extrinsic stimulus is needed to maintain it. To stop this firing pattern, it is necessary to depolarize the cell strongly enough and for a sufficient duration to inactivate the low threshold spike and promoting tonic firing. Rhythmic bursting is typically seen *in vitro*, but some cells respond in burst mode arrhythmically with random, single bursts.

As we shall see below, both rhythmic and arrhythmic bursting occur *in vivo*.

Because tonic firing of the depolarized relay cell represents a fairly linear transformation between stimulus and response, this response mode provides a faithful relay of afferent signals. However, when a cell bursts rhythmically, the discharge pattern is minimally, if at all, influenced by external stimulation, and the signal reaching cortex bears little or no relationship to any (e.g. retinal) input patterns. One interpretation of this behavior is that burst mode, at least during rhythmic bursting, represents a functional disconnection of the relay from the inputs. In fact, tonic mode has sometimes been called "relay" mode, implying that burst mode is used for something other than a relay function.

It is important to remember that most of the data underlying these notions about the functional significance of tonic and burst firing modes derives from *in vitro* preparations. One would like to know how relevant they are to the *in vivo*, whole animal preparation, which does not involve the massive denervation of the thalamic relay cells resulting from preparing brain slices or dissociated cells. Ideally, one would like to test this hypothesis in awake, behaving animals.

The first *in vivo* studies of the response modes in cats demonstrated that, when the animal entered certain phases of sleep, thalamic relay cells began to burst rhythmically, and such rhythmic bursting was not seen during awake, alert states (Livingstone & Hubel, 1981; McCarley et al., 1983; Steriade & McCarley, 1990; Steriade et al., 1993; Steriade & Contreras, 1995). This seems consistent with the *in vitro* data reviewed above and with the hypothesis that awake animals have depolarized thalamocortical cells that operate in tonic mode and thus faithfully relay information to cortex. During certain sleep phases, the cells become hyperpolarized and thus burst rhythmically, which prevents relay of information to cortex. On this view, bursting relay cells would not be a feature of an awake, alert animal. It has also been suggested that rhythmic bursting could be associated with epileptic seizures that would also interrupt the thalamic relay (Steriade & Llinás, 1988; McCormick & Feeser, 1990; Huguenard & McCormick, 1992; Steriade, 1992; Steriade et al., 1993; Huguenard & Prince, 1994; Steriade & Contreras, 1995). Recent studies of visual response properties of relay cells in the lateral geniculate nucleus of cats suggest that this view is incomplete.

Visual responses of geniculate relay cells

If the burst mode represents a complete failure of the relay through thalamus, it follows that, *in vivo*, a geniculate relay cell sufficiently hyperpolarized to de-inactivate its low threshold spike should either remain silent or begin bursting, and the pattern of bursting, whether rhythmic or arrhythmic, should bear no relation to the presence of visual stimuli that would activate the same cell were it depolarized and firing in tonic mode. This is clearly not the case. Recordings from lightly anesthetized cats *in vivo* show that cells in burst mode only occasionally fire rhythmically during spontaneous activity; more commonly, they fire arrhythmically with randomly occurring bursts separated by $\geq$ 100 ms. More importantly, such bursting cells respond quite reliably to visual stimuli, except that the response is in the form of bursts riding the crests of low threshold spikes rather than streams of unitary action potentials that occur during depolarization and in the tonic mode (Guido et al., 1992, 1995). Typically, the cell responds reliably to each occurrence of the visual stimulus (e.g. each cycle of a flashing or drifting sinusoidal grating or each flash of a spot in the receptive-field center) with a single low threshold spike and a burst of action potentials. These bursts follow repeated visual stimulation up to about 10 Hz and are not entrained by an intrinsic pacemaker. These same properties of bursting responses have been reported for geniculate cells in awake, behaving cats (Guido & Weyand, 1995), so they are not artifacts of the lightly anesthetized preparation.

Since geniculate cells do, in fact, respond to visual stimuli while in either tonic *or* burst mode, and since these modes represent very different types of stimulus/response transformation (see above and Fig. 2), the two response modes appear to subserve different forms of information transfer to the visual cortex. What, then, is the difference in the nature of the relay during these response modes? One way to answer this question is to determine how a given cell responds to the same set of visual stimuli when in each response mode. This can be accomplished by recording responses to visual stimuli and using intracellular current injection to hold the cell at different membrane potentials. Depolarizing currents inactivate the low threshold spike and establish the tonic mode, and hyperpolarizing currents deinactivate the low threshold spike and enable the burst mode. The average response histograms in Fig. 3 show spontaneous activity as well as responses to 4 cycles of a sinusoidal grating drifting through the receptive field of the cell. When the cell is depolarized and in tonic mode (Fig. 3A), the spontaneous activity is relatively high, and the visually evoked discharge essentially reproduces the sinusoidal profile of the drifting grating. However, when the cell is hyperpolarized and in burst mode (Fig. 3B), the spontaneous activity is relatively low, and the response to the grating is no longer sinusoidal, but *the cell does respond quite vigorously to the visual stimulus while in burst mode.*

The responses illustrated in Fig. 3 illustrate two interesting differences between tonic and burst mode.

1. Transmission exhibits a much greater degree of linearity during tonic mode than during burst mode, and Fourier analysis of the responses confirm this impression (Guido et al., 1992, 1995). That is, Fourier analysis shows that the response during tonic mode is dominated by the fundamental Fourier component, while the response during burst mode contains considerably more harmonic distortion. Furthermore, this difference in linearity was found for every geniculate cell tested (Guido et al., 1995). The nonlinear distortion of the response to the sinusoidal stimulus during burst mode presumably reflects the nonlinear amplification of the low threshold spike, which provides a similar response regardless of the amplitude or duration of any suprathreshold stimulus (see above). The difference in spontaneous activity also contributes to the difference in linearity, because the full range of excitation and inhibition caused by the visual stimuli can only be signaled by a modulation of the ongoing spontaneous activity. To put this another way, in the extreme case of zero spontaneous activity, an on-center relay cell could only respond to an excitatory stimulus (e.g. a spot brighter than background); it could not respond to an inhibitory one (e.g. a dark spot), and the presence of such an inhibitory stimulus could not be transmitted to cortex. The higher spontaneous level during tonic mode helps to prevent nonlinearities due to half-wave rectification in the response.

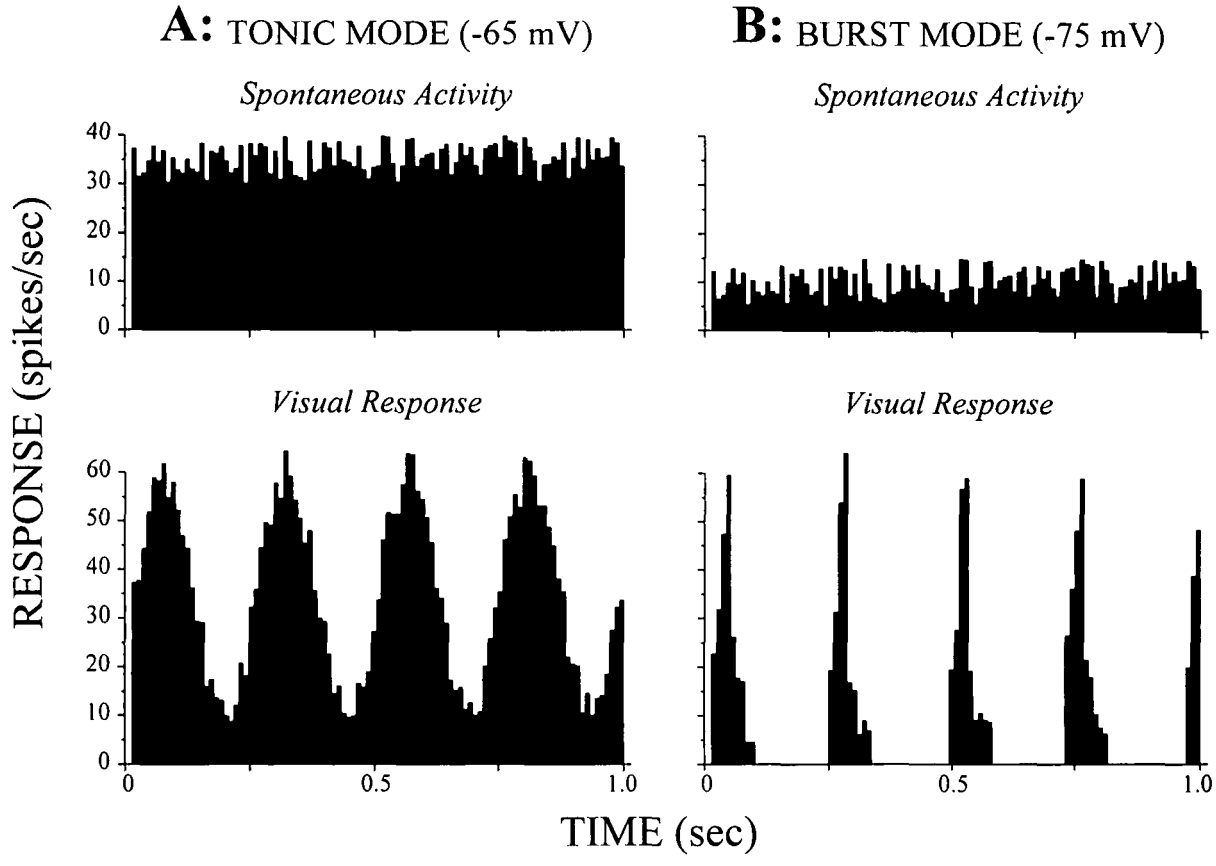

Fig. 3. Average response histograms from the same geniculate cell showing features typical of tonic and burst response modes. The cell was recorded intracellularly from a cat *in vivo*, and current injection was used to promote either tonic firing by depolarization or burst firing by hyperpolarization. The top histograms show spontaneous activity, while the bottom ones show the evoked response to 4 cycles of a sinusoidal grating drifted through the cell's receptive field. A: Tonic mode. B: Burst mode. Note that the tonic mode is associated with a higher level of spontaneous activity and a visual response that more faithfully represents the sinusoidal pattern of the stimulus. Note also that the visual response during burst mode, while distorted in shape with respect to the visual stimulus, is nonetheless robust. For other examples, see Guido et al. (1995).

2. The observation that responses to visual stimulation are robust in both modes but that spontaneous activity is much lower in burst mode suggests that signal- (e.g. visual response) to-noise (e.g. spontaneous activity) ratios are actually improved during burst mode (Guido et al., 1995). This, in turn, would mean that cells in burst mode are better able to detect a stimulus than when in tonic mode. This hypothesis has been tested formally by using techniques of signal-detection theory to create receiver operating characteristic curves for responses during tonic and burst mode. These assess the ability of a cell to detect a visual stimulus against background noise (Green & Swets, 1966; Macmillan & Creelman, 1991). Such an analysis showed that *every* geniculate cell tested in both response modes was better able to detect the visual stimuli when in burst mode than when in tonic mode (Guido et al., 1995). Furthermore, the more difficult a stimulus was to detect (e.g. due to lower contrast), the greater was the detection advantage of the burst over the tonic mode. This is consistent with the nearly all-or-none properties of the low threshold spike, since any suprathreshold stimulus, even of low salience or contrast, would evoke nearly the same low threshold spike and thus the same burst of action potentials. This stands in contrast to the situation during tonic firing, when a less salient or lower contrast stimulus would produce a smaller response. Thus, signal-to-noise ratios are much less affected by stimulus salience during burst mode than during tonic mode.

Control of response mode

Recent evidence suggests that geniculate relay cells do indeed switch between these firing modes depending on the behavioral needs of the animal (Guido & Weyand, 1995). This means that at least some of the nonretinal inputs must be able to effect this switching and determine response mode. Because of the voltage dependency of the low threshold spike, this may be accomplished most simply through depolarization or hyperpolarization of relay cells, but other factors might also contribute (cf. Lo & Sherman, 1993). The two major sources of such control are the visual cortex and parabrachial region of the brain stem (see Fig. 1).

Parabrachial control

The parabrachial region provides an excitatory (i.e. depolarizing) input to geniculate relay cells (see Fig. 1). Fig. 4 summarizes the synaptic mechanisms underlying this effect (McCormick &

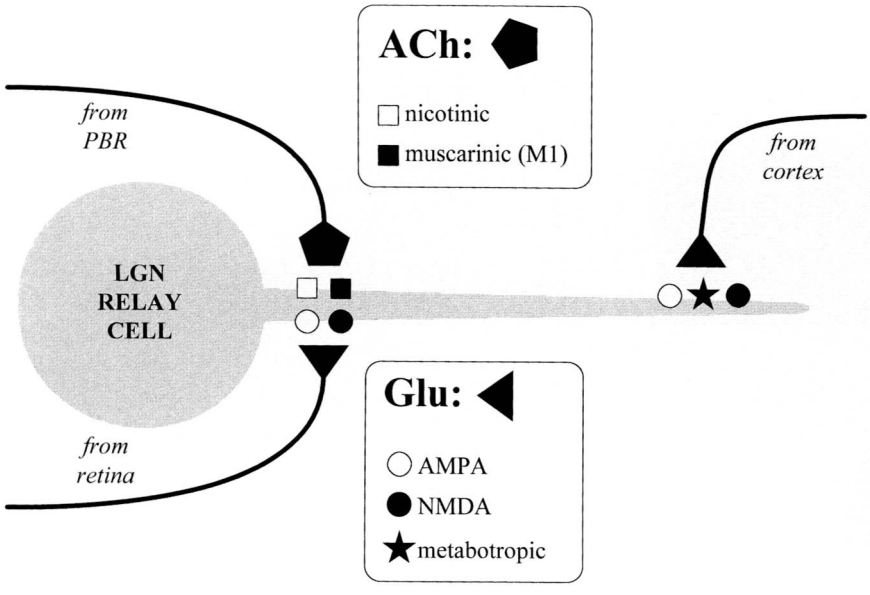

Fig. 4. Schematic diagram of glutamatergic and cholinergic inputs to geniculate relay cell (LGN RELAY CELL) plus associated postsynaptic receptors. The glutamatergic inputs derive from both retina and cortex. Note that retinal inputs innervate proximal dendrites, while cortical inputs innervate distal dendrites (reviewed in Guillery, 1969*a*,*b*, 1971; Sherman & Koch, 1986, 1990; Sherman, 1993), so these inputs are not likely to share many postsynaptic receptors. Also, while both make use of ionotropic AMPA and NMDA receptors, the cortical input in addition activates a metabotropic glutamate receptor. The cholinergic inputs derive from the parabrachial region, and they activate both nicotinic and M1 muscarinic receptors, the former being ionotropic and the latter, metabotropic. While not shown, the parabrachial axons also contain NO (see Fig. 1), but little is known at the cellular level of associated postsynaptic receptors or modes of action of NO.

Prince, 1986, 1987; Hu et al., 1989*a*,*b*; McCormick, 1989). Most of the parabrachial input is cholinergic (see Fig. 1). Relay cells possess a nicotinic receptor, the activation of which leads to a fast EPSP due to increase in cation conductance. This receptor is *ionotropic*, meaning that it has a direct link with the affected ion channels controlling the cation conductance. In addition, an M1 type muscarinic receptor mediates a much slower and prolonged EPSP due to a decrease in K^+ conductance. This receptor is *metabotropic*, meaning that it is indirectly linked to the affected K^+ channels via a second-messenger pathway. Since activation of either receptor depolarizes the cell, any depolarization sufficiently strong and long-lasting would tend to inactivate I_T and thus promote tonic firing in the targeted relay cells.

One can activate the parabrachial input to test this prediction simply by electrically stimulating the cells of origin in the brain stem. Such activation *in vivo* does indeed cause dramatic switching of geniculate relay cells from burst to tonic mode (Lu et al., 1993). Also, *in vitro* application of ACh in the lateral geniculate nucleus, which can be viewed as a way to mimic *in vivo* activation of the parabrachial region, eliminates low threshold spiking and causes bursting cells to fire in tonic mode (McCormick, 1989, 1992).

Visual cortex control

The visual cortex, like the parabrachial region, also provides direct excitatory inputs to relay cells (see Fig. 1), and by the same reasoning as above, one would predict its activation to promote tonic firing. This prediction has been more difficult to test *in vivo*, because electrical activation of this pathway will also activate geniculocortical axons antidromically. However, a consideration of the pharmacological properties of the geniculocortical pathway summarized in Fig. 4 suggested another, less direct approach. Both retinal and cortical axons are glutamatergic, and both inputs depolarize relay cells by activating ionotropic glutamate receptors, including AMPA and NMDA types (Kemp & Sillito, 1982; Moody & Sillito, 1988; Sillito et al., 1990; Scharfman et al., 1990; Hartveit & Heggelund, 1990; Heggelund & Hartveit, 1990; Kwon et al., 1991). An important difference, though, is that corticogeniculate but not retinogeniculate inputs activate a metabotropic glutamate receptor that, like the muscarinic receptor described above for the parabrachial pathway, triggers a second-messenger pathway that shuts off a K^+ "leak" conductance (McCormick & Von Krosigk, 1992). Therefore, it is possible to mimic activation of the corticogeniculate input fairly specifically by applying agonists for the metabotropic glutamate receptor onto geniculate relay cells. When this is done *in vivo*, geniculate cells switch from burst to tonic firing mode (Godwin et al., 1994; Vaughan et al., 1994).

As noted above, the corticogeniculate projection has long been recognized as providing the largest single input to the lateral geniculate nucleus. Yet an understanding of its function has proven elusive despite the considerable attention it has received (reviewed in Singer, 1977; Sherman & Koch, 1986, 1990; Koch, 1987; Sherman, 1993). Earlier studies have provided somewhat contradictory and confusing results, some suggesting that the pathway facilitates relay cell responses, and others, that it inhibits them (Kalil & Chase, 1970; Richard et al., 1975; Schmielau & Singer, 1977; Baker & Malpeli, 1977; Geisert et al., 1981; McClurkin & Marrocco, 1984; McClurkin et al., 1994). Schmielau and Singer (1977) have proposed that corticogeniculate input is important to binocular functions, such as stereopsis. More recent studies have suggested that the pathway affects temporal properties of relay cell discharges (McClurkin et al., 1994), and indeed, controlling response mode would alter such temporal properties. Another recent study suggests that this pathway promotes correlated firing among nearby relay cells with similar receptive-field properties (Sillito et al., 1994). Earlier work indicates that the corticogeniculate pathway is composed of different cell types (Tsumoto & Suda, 1980; Katz, 1987), so it may well be that its large size is actually a reflection of several distinct functions that different constituents of the pathway perform. Controlling response mode would be a critical role for some component of the cortical input to play.

In any case, activation of either of these major inputs to the lateral geniculate nucleus, that from cortex or that from the parabrachial region, clearly causes geniculate cells firing in burst mode to switch to tonic mode. Whether inactivation of these

pathways can switch cells from tonic to burst mode has yet to be tested explicitly.

Possible functions of the tonic and burst response modes

Previous speculation about the functional significance of these response modes in thalamic relay cells has assumed that bursting occurs only rhythmically and only during certain phases of sleep and that these cells fire exclusively in tonic mode when the animal is awake and alert (Steriade & Llinás, 1988; McCormick & Feeser, 1990; Huguenard & McCormick, 1992; Steriade, 1992; Steriade et al., 1993; Huguenard & Prince, 1994; Steriade & Contreras, 1995). Clearly, thalamic relay cells, including those of the lateral geniculate nucleus, do burst rhythmically during certain phases of sleep (McCarley et al., 1983; Steriade & Llinás, 1988; Steriade et al., 1990, 1993; Steriade & Contreras, 1995), implying a functional disconnection of these cells from their main afferents and an interruption of the thalamic relay. However, it now seems clear that these relay cells can also fire arrhythmically in burst mode, when the animal is alert (Guido & Weyand, 1995). This new finding suggests that burst firing can subserve more than one function, depending on the animal's behavioral state.

In the sleeping animal, the rhythmic form of bursting may effectively disable the geniculate relay, as has been suggested by others. Such rhythmic bursting may provide a positive signal to cortex that nothing is being relayed despite the possible presence of sensory stimuli, and this is less ambiguous than no activity, which could either mean no relay or no stimulus. However, the new suggestion of this article is that geniculate relay cells in awake animals can respond either in tonic mode or in an *arrhythmic* burst mode. The latter, by virtue of its low spontaneous activity and nonlinear response characteristics, may enable the relay to respond emphatically, if coarsely, to subtle but potentially significant changes in afferent activity. Therefore, because the tonic mode appears suited to passing high-fidelity information about specific stimuli, the arrhythmic burst mode could predominate when a cell is not engaged in the detailed analysis of a particular stimulus. This could occur when the animal is searching for a stimulus, attending to a part of the visual field not mapped by the cell in question, attending to signals *via* another sensory modality, or, if in a drowsy state, not attending to anything at all. In all of these conditions, the particular properties of the arrhythmic burst mode enhance the probability that an unexpected and possibly interesting or dangerous visual object will be detected. Once this occurs, perhaps upon the signal reaching cortex, it could trigger events by increasing activity in the corticogeniculate inputs (and perhaps also the parabrachial inputs) that would switch the relay to tonic mode, allowing a more detailed and accurate analysis of afferent signals.

Two additional observations are worth making about this hypothesis. First, the parabrachial and other brain-stem inputs are organized more diffusely than is the corticogeniculate input and are likely to have more global effects on the geniculate relay. These brain-stem inputs seem best suited to controlling response mode based on more global behavioral states, such as overall level of attentiveness, drowsiness, or sleep. They are also probably multimodal in nature and could thus be involved in switching response mode through the lateral geniculate nucleus depending on which sensory modality has captured the animal's attention. Finally, the effects of eye movements on the geniculate relay (Büttner & Fuchs, 1973; Noda, 1975; Lal & Friedlander, 1989), which include effects on response mode (Guido & Weyand, 1995), are probably controlled by parabrachial inputs and other brain-stem inputs. In contrast, the corticogeniculate projection conveys strictly visual information and is organized in a precise retinotopic fashion. This enables it, in principle, to allow some geniculate cells to operate in tonic mode while others respond in burst mode. This notion of the burst mode bears some resemblance to Crick's (1984) "searchlight hypothesis". Second, by exercising control over response mode at the thalamic level, the brain takes advantage of the fact that the behavior of a relatively small number of relay cells can be efficiently governed in this manner. To achieve the same result once the signals reach cortex would require control of a vastly larger number of neurons.

In summary, relay cells of the lateral geniculate nucleus, like those of other thalamic nuclei, manifest two distinct response modes: burst and tonic. The burst mode is dependent on the activation state of a low threshold Ca^{2+} spike that triggers a short burst of conventional action potentials and can only recur after a variable but significant latency. The Ca^{2+} spike is voltage-dependent, and only when cells are relatively hyperpolarized do they respond in burst mode. Cells switch to tonic mode when depolarized. Excitatory input from either cortical or brain-stem parabrachial inputs predisposes geniculate cells to fire in tonic mode. It has been suggested previously that the tonic mode is characteristic of the waking state while the burst mode signals an interruption of the geniculate relay during sleep. It is argued here that the burst mode actually takes two forms, a rhythmic form in sleep and an arrhythmic form during waking states. The signal relayed during the arrhythmic burst mode has a higher signal-to-noise ratio, so it is easier to detect, but this mode distorts the signal. Relay cells in tonic mode are able to transmit information with higher fidelity but with a lower signal-to-noise ratio. The arrhythmic burst mode may permit more robust transmission of potentially important changes in retinal signals. This, in turn, could trigger a switch to tonic mode *via* increased activity in cortical, parabrachial, or other afferents, so that the newly detected stimulus can be more accurately analyzed.

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