9

THE THALAMIC INTERNEURON

S. Murray Sherman*

1. INTRODUCTION

In the thalamus, local, GABAergic interneurons play a crucial role in controlling the flow of information relayed to the cortex. Throughout the thalamus, with occasional variations with relay nucleus or species, these interneurons comprise roughly 20-25% of the cells present, the remainder being relay cells (see Arcelli et al., 1997; reviewed in Jones, 1985; Sherman and Guillery, 2001). As is the case with relay cells (see also below), there is probably more than one type of interneuron (Sanchez-Vives et al., 1996; Carden and Bickford, 2002), but this account will focus on the best known and prime exemplar, namely, the interneuron found in the cat's lateral geniculate nucleus, which appears to be widespread throughout the thalamus. Two particularly interesting features of this cell are the nature of its synaptic outputs, which are both axonal and dendritic, and the type of synaptic circuits that are entered into by the dendritic outputs. These two features form the focus of the rest of this narrative.

2. OUTPUTS OF THE INTERNEURON

Figure 1 shows an example each of the typical interneuron found in the cat's lateral geniculate nucleus plus the two relay cell types, X and Y, that the interneuron innervates (Friedlander et al., 1981; Sherman and Friedlander, 1988). The X and Y cells represent the thalamic links in two parallel, largely independent retino-geniculo-cortical streams, an arrangement common to mammals (reviewed in Sherman, 1985). A particularly interesting feature of the interneuron is that it has two different avenues for synaptic output. One is a conventional axon that arborizes within the dendritic arbor, and the other are clusters of terminals that emanate from distal dendrites (Guillery, 1969; Ralston, 1971; Famiglietti and Peters, 1972; Wilson et al., 1984; Hamos et al., 1985). These presynaptic dendritic terminals are shown more clearly in the inset for the interneuron in Figure 1. Electron microscopy reveals that both the axonal and dendritic terminals appear

*Department of Neurobiology, State University of New York, Stony Brook, NY 11794-5230

Dendritic Neurotransmitter Release, edited by M. Ludwig
Springer Science+Business Media, Inc., 2005

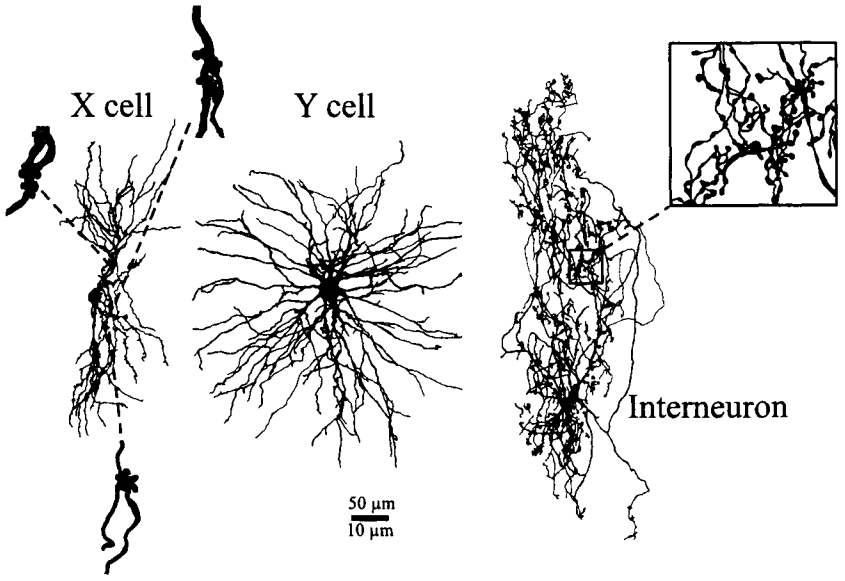

Figure 1. Representative cells of the cat's lateral geniculate nucleus. The cells were labeled intracellularly with horseradish peroxidase (from Friedlander et al., 1981; Sherman and Friedlander, 1988). Shown are relay X and Y cells and an interneuron. The scale bar is 50μm for the main drawings and 10μm for the insets.

to be inhibitory, because they have flattened or pleomorphic vesicles and form symmetric synaptic contacts, but they differ in other respects. One is that the axonal terminal, called *F1* ("F" for flattened vesicle), forms a simple, conventional synaptic contact onto the dendrites of both X and Y cells; whereas the dendritic terminal, called *F2*, is both postsynaptic to various terminals (see below) and presynaptic to X but rarely to Y cells. There are many more F2 outputs per interneuron than F1 outputs. Other differences between F1 and F2 outputs are noted below.

There is also a relationship between the structure of the relay cells and the different interneuron outputs. The Y cell, which receives predominantly F1 (axonal) inputs from the interneuron, has a fairly simple, radiate dendritic arbor with few appendages. The F1 terminals contact proximal dendritic shafts with simple, conventional synapses. The X cell has a bipolar dendritic tree, oriented perpendicular to laminar borders, but more interesting are the clusters of grape-like appendages near primary branch points (see higher power insets in Figure 1). These are not spines, lacking the apparatus found in true spines in cortex and hippocampus, but seem to be simple appendages. What is especially interesting about them is that they mark the postsynaptic target of both F2 (dendritic) terminals of interneurons as well as retinal terminals. F1 terminals onto X cells may contact these same appendages but also frequently contact dendritic shafts in the vicinity. Thus the vast majority of interneuron synapses onto both X and Y cells are onto proximal dendrites.

3. TRIADS AND GLOMERULI

As mentioned, the F2 terminals are both presynaptic and postsynaptic, and they commonly enter into complex synaptic arrangements known as *triads* (see Figure 2). Here, a single retinal terminal contacts both an F2 terminal and the appendage of a relay X cell, and the F2 terminal contacts the same appendage[†]. Thus, three synapses are involved: from the retinal terminal to the relay cell dendritic appendage, from the retinal terminal to the F2 terminal, and from the F2 terminal to the same appendage. Less commonly, an F2 terminal can be postsynaptic to a cholinergic terminal from the brainstem parabrachial region, and the same parabrachial axon (but not the same terminal) contacts the same relay cell (see Figure 2). While not as tightly organized as the common triad, this forms another sort of triadic arrangement, since three synapses are involved. Although not illustrated, occasionally F1 terminals are found presynaptic to F2 terminals (Guillery, 1969; Ralston, 1971; Famiglietti and Peters, 1972; Wilson et al., 1984; Hamos et al., 1985). As shown in Figure 2, F1 terminals from interneuron axons commonly contact dendritic shafts both within and outside of complex synaptic zones known as *glomeruli* (Szentágothai, 1963).

A simplified schema of a glomerulus is shown in Figure 2. Individual synaptic zones in the glomerulus are not juxtaposed to glial processes, but instead the entire synaptic complex is enclosed in a glial sheath. The function of this arrangement is not known, but since glial processes have been implicated in the uptake and regulation of neurotransmitters and other neuroactive substances (Pfrieger et al., 1992; Guatteo et al., 1996), their lack within a glomerulus might affect the extent to which neurotransmitters and other substances remain active.

Glomeruli occur in a range of complexities, from little more than a triad to a mass of tens of synapses. Every triad so far seen in the lateral geniculate nucleus of the cat contains at least one retinal terminal and one triad (and thus one F2 terminal). F1 terminals and parabrachial terminals are also commonly present in glomeruli, but terminals from layer 6 of cortex are virtually never there (EriÕir et al., 1997; but see Vidnyanszky and Hamori, 1994). It is worth noting that F1 terminals commonly derive from axons of GABAergic cells, and the other main source of GABAergic innervation to relay cells besides interneurons are cells of the nearby thalamic reticular nucleus. However, while reticular axons focus their contacts onto relay cells rather than interneurons, they contact mostly distal dendrites and are rarely found in glomeruli (Cucchiaro et al., 1991; Wang et al., 2001). It is thus from a process of elimination that we conclude that most F1 terminals in glomeruli and onto proximal dendrites outside of glomeruli emanate from interneurons.

4. CELLULAR PROPERTIES OF THE INTERNEURON

Given that there are two output routes for this thalamic interneuron - axonal and dendritic - the obvious questions arise as to how these are controlled and how they might

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[†]. Recently, Datskovskaia et al. (2001) have argued that there may be more Y retinal axon innervation of interneurons than previously thought, although Y cell involvement in triads was rarely seen, so this issue of the extent of the limitation to X cells of F2 and triadic innervation needs further resolution.

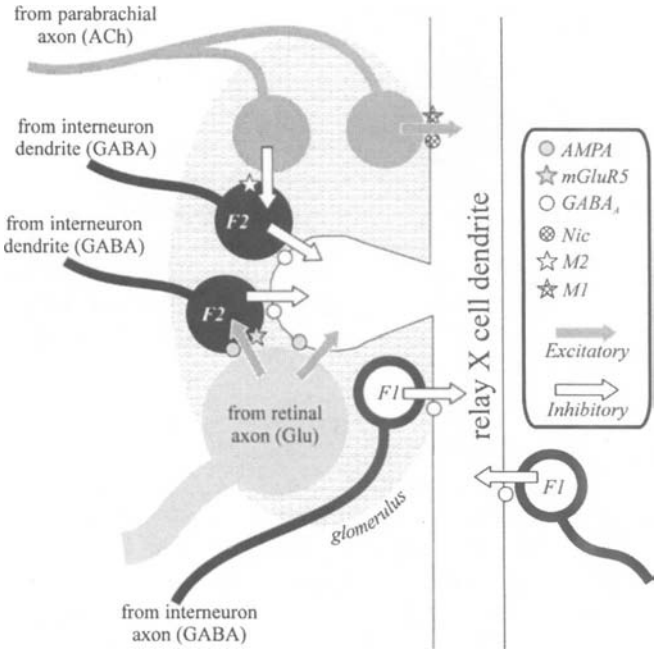

Figure 2. Schematic view of triad and glomerulus in cat lateral geniculate nucleus. Shown are the various synaptic contacts (arrows), whether they are inhibitory or excitatory, and the related postsynaptic receptors. For simplicity, the NMDA receptor on the relay cell postsynaptic to the retinal input has been left off. Abbreviations: *ACh*; acetylcholine; *AMPAR*, (RS)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; *F1* and *F2*; two types of synaptic terminal; *GABA*, γ-aminobutyric acid; *GABA$_A$R*, type A receptor for GABA; *Glu*; glutamate; *M1R* and *M2R*, two types of muscarinic receptor; *mGluR5*, type 5 metabotropic glutamate receptor; *Nicotinic*; nicotinic receptor;

relate to one another. The cable properties of the dendritic arbor offer an initial clue. These properties determine, among other things, how current flows through the dendrites and thus how effective synaptic inputs at one site affect membrane voltage at others, including the axon hillock or spike generating region. For practical purposes, we can consider the cell body and axon hillock as isopotential, so part of the problem reduces to a consideration of how synapses at various sites affect membrane voltage at the cell body.

An analysis of cable properties of interneurons compared to relay cells in the cat's lateral geniculate nucleus showed a striking difference (Bloomfield et al., 1987, 1989). Relay cells were found to be fairly compact electrotonically, largely because of their dendritic branching pattern that supports impedance matching across the branches. This minimizes current leakage across the membrane and thus reduces the extent of voltage attenuation as current flows from a distal dendritic location, across several branch points, to the cell body. The conclusion is that even postsynaptic potentials (PSPs; excitatory and inhibitory postsynaptic potentials are, respectively, EPSPs and IPSPs) generated at distal synaptic locations will attenuate by at most ~50% upon arriving at the cell body. In contrast, the branching pattern of interneurons is different: there are more branches, and they seem to create an impedance mismatch, leading to current leakage across branch

points. The result is that a PSP generated at a distal dendritic site will be attenuated by more than 90% at the cell body. The F2 terminals themselves are usually appended to the distal sites by long (10μm or more), thin (~0.1μm in diameter) processes (Hamos et al., 1985), which implies that inputs to these F2 terminals are even more isolated from the cell body and also from other F2 terminals on other dendritic branches (see also below).

Before considering further the implications of this cable modeling, there are several important provisos to be considered. Cable modeling requires many assumptions, including the value of certain parameters, such as membrane capacitance, that are basically guesses. Cables themselves act like low pass temporal filters, meaning that slow or sustained voltage changes will attenuate less than faster changes, and faster PSPs will attenuate more than the above modeling suggests. Perhaps most serious is the fact that cable modeling assumes a passive membrane, and in fact, interneurons, like all neurons, possess many ion channels that are dynamically gated (see also below); these will certainly affect cable properties. Thus, for example, the presence of voltage gated Na^+ or Ca^{2+} channels can greatly affect how PSPs are conducted to the cell body. Furthermore, the possibility of back-propagation of action potentials supported by dendritic Na^+ channels could mean that cell spiking will affect F2 terminal transmitter release.

Given these qualifications, cable modeling provides a useful if limited approach to understanding how inputs affect the postsynaptic cell. The picture that emerges for the interneuron is schematically shown in Figure 3, and there are two interesting conclusions drawn. First, because the branched dendritic arbor strongly attenuates PSPs from distal inputs, the main control of the axonal (F1) output is mostly limited to relatively proximal inputs. It is interesting in this context that these interneurons receive many synaptic inputs onto their cell bodies, whereas relay cells rarely have synapses (Hamos et al., 1985). Second, the strong electrotonic isolation of the dendritic (F2) terminals is such that PSPs generated in them will affect their release of GABA but will have little influence on the axonal output; also local clusters of F2 terminals will be functionally isolated from others. Below is offered some indirect evidence for this. In summary, cable modeling suggests that the interneuron multiplexes, with proximal synaptic inputs controlling the axonal output in a conventional manner and inputs onto the F2 terminals controlling them more or less independently, leaving one computational input/output route for the F1 terminals and many other independent ones for the F2 terminals.

However, modeling the dendritic arbor of the interneuron as a passive cable is clearly an oversimplification, since a number of voltage gated channels exist for the cell body and dendrites. Unfortunately, the interneuron has not been thoroughly studied in this regard, and some of the different observations are in conflict and require resolution (for details, see Sherman and Guillery, 2001). For instance, relay cells clearly possess many voltage gated T-type Ca^{2+} channels that, when activated, lead to an inward, depolarizing current, I_T; this results in an all-or-none, low threshold Ca^{2+} spike that propagates through the dendrites and cell body (Deschênes et al., 1984; Jahnsen and Llinás, 1984a,b; Hernández-Cruz and Pape, 1989; McCormick and Feeser, 1990; Scharfman et al., 1990; Bal et al., 1995). However, the situation in interneurons is less clear. Several studies claim that such a low threshold Ca^{2+} spike is rarely, if ever seen in these interneurons (Pape et al., 1994; Pape and McCormick, 1995; Cox et al., 2003; Govindaiah and Cox, 2004), while others conclude that they commonly occur (Zhu et al., 1999a,b). One explanation is that T type channels do exist in interneurons but that the generation of I_T is offset by I_A, which is created by a voltage gated K^+ conductance that hyperpolarizes the cell and has a similar voltage dependency for activation (Pape et al.,

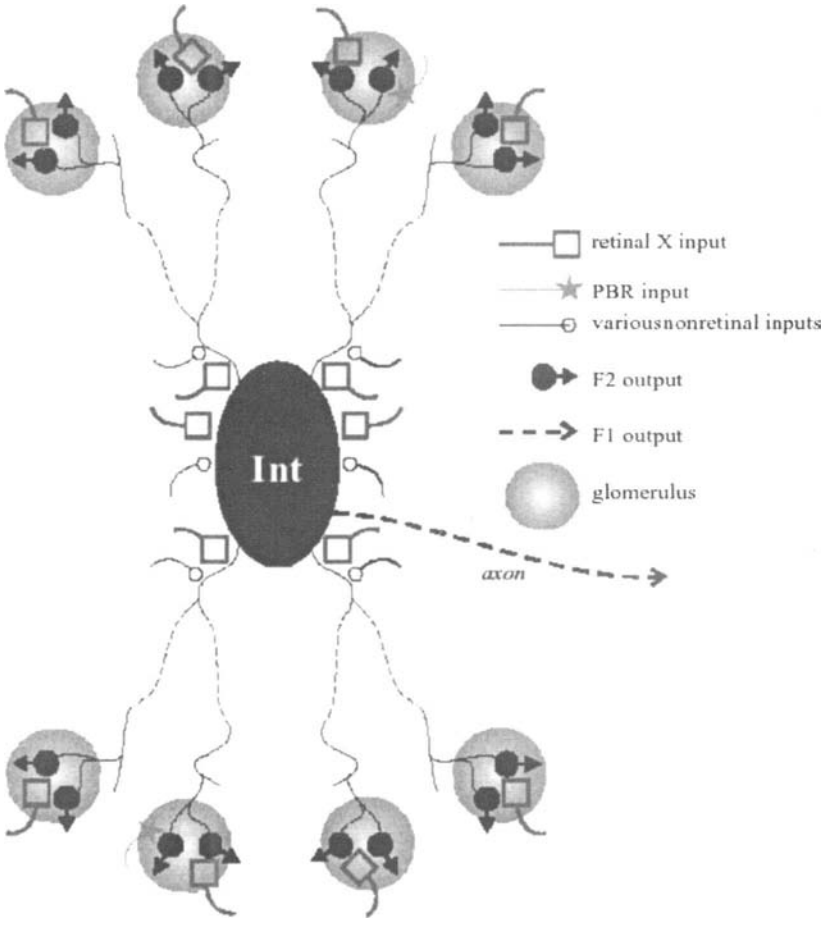

Figure 3. Schematic model for functioning of the interneuron (*Int*). The axon outputs (*F1*) are controlled by inputs onto the cell body and proximal dendrites. The peripheral dendritic outputs (*F2*) are controlled locally by direct inputs, mostly either retinal or from the parabrachial region (*PBR*), and these F2 circuits are within glomeruli. The dashed lines connecting proximal dendrites to the F2 circuits represent 5-10 levels of dendritic branching.

1994). This issue of whether or not a low threshold Ca^{2+} spike commonly exists in interneurons needs to be resolved, because such a spike could affect the dendritic F2 terminal, thereby limiting its isolation. Nonetheless, with this proviso, none of the voltage gated properties of the interneuron described to date, including no evidence for back-propagation of the action potential, require a major revision of the functional model illustrated by Figure 3.

There are several important implications of this model. One is that, if accurate, recordings from the interneuron, which to date have all been from the cell body, reveal properties of synaptic integration involving the axonal output but tell us nothing about integration that involves dendritic output, and this is the cell's major output. Likewise,

information about firing rate of the interneuron relates to activity of the axonal but not the dendritic output. Related to this, all of the interneurons recorded *in vivo* from the cat's lateral geniculate nucleus have receptive fields of X cells (Sherman and Friedlander, 1988), but since this analysis depends on judging firing rate of the cell, this tells us about the nature of the retinal inputs to proximal dendrites and the cell body being from retinal X but not Y cells, but reveals nothing about retinal inputs to the F2 terminals involved in triads. However, since these are effectively limited to X and not Y relay cells, these are also from X and not Y retinal axons (but see footnote 1). What is not clear is whether the same individual retinal axon(s) innervate both F2 terminals and proximal dendritic locations on the interneuron.

5. CONTROL OF THE F2 TERMINALS AND FUNCTIONING OF THE TRIAD

Given the importance of the dendritic F2 output of the interneuron, it is of obvious importance to understand how it is controlled and how it functions, particularly with regard to the triad. Part of the answer comes from recent *in vitro* experiments using a combination of agonists and antagonists and from immunocytochemical studies with the electron microscope that together elucidate the postsynaptic receptors found on the F2 terminals (Godwin et al., 1996; Cox and Sherman, 2000; Govindaiah and Cox, 2004). Figure 2 summarizes these data. For the retinal input to the F2 terminal, metabotropic glutamate receptors type 5 (mGluR5s) dominate, and there are also probably ionotropic glutamate receptors (AMPARs and perhaps NMDARs) as well (Godwin et al., 1996; Cox and Sherman, 2000). Activation of either glutamate receptor *increases* release of GABA from the F2 terminal (Cox and Sherman, 2000; Govindaiah and Cox, 2004). For the parabrachial input to the F2 terminal, type 2 muscarinic receptors (M2Rs) exist (Plummer et al., 1999; Carden and Bickford, 1999), and activation of these receptors *decreases* release of GABA from the F2 terminal (Cox and Sherman, 2000). Regarding the inputs of retinal or parabrachial axons onto the relay cell, the retinal input activates ionotropic glutamate receptors (AMPARs and NMDARs) only, and the parabrachial input activates both ionotropic nicotinic and type 1 muscarinic receptors (nicotinic receptors and M1Rs); activation of these various receptors on the relay cell produces EPSPs (reviewed in McCormick, 1992; Sherman and Guillery, 2001). Note that the dominant receptors on the F2 terminal, mGluR5s and M2Rs, are both metabotropic.

The observation that activation of mGluR5s on the F2 terminal increases GABA release is interesting because recordings from the cell body of interneurons has consistently reported no discernable direct affects of application of mGluR agonists (Pape and McCormick, 1995; Cox and Sherman, 2000; Govindaiah and Cox, 2004). If we assume that F2 release is increased from F2 terminals because of their depolarization by mGluR5 activation, then this depolarization is effectively attenuated before reaching the cell body. This provides some indirect evidence for the electrotonic isolation of the F2 terminals from the cell body and axon.

Unfortunately, we have no direct evidence as to how activation of the mGluR5s and M2Rs control the output of the F2 terminal. Nonetheless, we can make several plausible assumptions based on the functioning of these and other metabotropic receptors elsewhere (Nicoll et al., 1990; Mott and Lewis, 1994; Recasens and Vignes, 1995; Pin and Duvoisin, 1995; Conn and Pin, 1997; Brown et al., 1997).

These are:

- They operate by opening or closing a "leak" K^+ channel. Activation of the mGluR5s closes the leak channel and thus depolarizes the terminal, which in turn increases GABA release, whereas activation of the M2R opens the leak channel, thus hyperpolarizing the terminal and decreasing GABA release.
- Compared to ionotropic equivalents such as the AMPA and nicotinic receptors, higher rates of firing in the afferent input are required to activate the metabotropic mGluR5s and M2Rs. This has recently been confirmed for the mGluR5s on the F2 terminal (Govindaiah and Cox, 2004).
- While the ionotropic receptors involved produce PSPs with a latency of only about a msec or so and a duration of 10 msec or somewhat longer, the time course for the mGluR5 and M2R is much longer, with a latency of 10 msec or more and a duration of hundreds of msec or longer. Again, this has recently been confirmed for the mGluR5 on the F2 terminal (Govindaiah and Cox, 2004).

Given these assumptions, we can suggest the following consequences of activation of the various inputs to the F2 terminal. We assume that release of GABA by the F2 terminal has some background rate that the retinal or parabrachial afferents can up- or down-regulate.

5.1. Activation of the Parabrachial Input

These brainstem inputs display levels of activity that seem to correspond to overall levels of arousal and alertness: when the animal is in slow wave sleep, they are mainly silent, when the animal is drowsy, they are moderately active, and when the animal is fully aroused and alert, they are highly active (Steriade and McCarley, 1990; Steriade and Contreras, 1995). It thus follows that, when asleep, the direct excitatory cholinergic input to the relay cell is absent, and this is exacerbated by the absence of inhibition of the F2 terminal's output, which translates to an absence of disinhibition. Together this leads to a depression of the relay. When the animal is drowsy, the moderate level of activity in the parabrachial afferents would activate the nicotinic receptors on the relay cell, producing some excitation, and the activity may be sufficient to further enhance the relay by activating the M1Rs on the relay cell (producing a prolonged depolarization) and the M2Rs on the F2 terminal (producing a prolonged disinhibition). The relay would be more enhanced as the animal becomes more awake and aroused, because the higher activity in the parabrachial afferents will produce more direct nicotinic receptor and M1R excitation of the relay cell and more disinhibition via activation of the M2Rs on the F2 terminal. Thus activity levels among the parabrachial afferents, which correlates to levels of arousal, also correlates to enhancement in the ability of the relay cell to pass on information to cortex from retina, and the circuitry represented by the F2 terminal of the interneuron plays a significant role here.

5.2. Activation of the Retinal Input

The result here is a bit more complicated, because the triadic circuit provides a basis for direct excitation (retinal-to-relay cell) and indirect inhibition (retinal-F2 terminal-relay cell). With the above assumptions for relative activation of ionotropic and

metabotropic receptors that have been partially confirmed (Govindaiah and Cox, 2004), the following predictions follow. With low levels of retinal activity, only ionotropic receptors will be active, so EPSPs will be generated in the relay cell. If there is an AMPAR on the F2 terminal, the EPSPs will be abbreviated by disynaptic IPSPs. Unless there is a major difference between sensitivity of the AMPARs on the relay cell versus the F2 terminal, the only role of those on the F2 terminal will be to oppose the EPSP in the relay cell in a fairly linear fashion, but this will not change appreciably with firing level in the retinal afferent. However, as this firing level becomes sufficiently large to activate the mGluR5s on the F2 terminal, an extra dose of GABAergic inhibition will be apparent in the relay cell. There are two interesting features of this latter inhibition based on activating the mGluR5s: first, it appears and grows only after retinal firing exceeds some threshold that appears to be roughly 10Hz, growing with increasing afferent activity to roughly 200Hz (Govindaiah and Cox, 2004); and second, once activated, it will outlast the retinal activity by several seconds, because this is the duration of a mGluR-activated EPSP (Govindaiah and Cox, 2004). Also note that the interesting part of this process does not depend on the possible presence of an AMPAR on the F2 terminal: its presence and level would serve only to add a constant extra amount of disynaptic inhibition in the relay cell that would partly offset the monosynaptic EPSP there. It is the presence of the mGluR5 that adds an interesting extra inhibition that depends on the firing level of the retinal afferent and outlasts it, and several consequences may be contemplated as outlined below.

5.3. Effects on Contrast Gain Control or Adaptation

In general, the firing level of the the retinal axon is monotonically related to contrast in the visual stimulus, and thus the greater the contrast, the higher the firing level. This means that, once contrast exceeds a certain level, the retinal afferent fires sufficiently to activate the mGluR5s on the F2 terminal and thereby increases inhibition in the relay cell. This will reduce the responsiveness, or the gain, of the relay cell to retinal inputs, and, because of the temporal properties of the mGluR5s, this reduced contrast gain will last for several seconds or so even after the retinal afferent firing returns to normal or prior levels. This is a form of contrast gain control or adaption whereby the contrast response of the relay cell adjusts to overall contrast: as contrast increases enough to activate the triad circuit via the mGluR5s, gain or responsiveness in the relay cell reduces, and vice-versa.

There are many examples of such processes operating in the visual system. However, these effects on receptive field properties to date have been found mostly in visual cortex and perhaps in retina, but there has been no evidence of clear effects on the representation of contrast at the level of the lateral geniculate nucleus as suggested here (for recent statements of these issues, see Soloman et al., 2004; Carandini, 2004). This is an issue that seems worth pursuing, especially with regard to an effect that should be seen primarily in X and not Y cells.

5.4. Effects on Voltage Sensitive Properties

The above discussion considers how triadic circuitry might influence the balance of excitation and inhibition in the relay cell, the key being that higher rates of retinal input brings in extra inhibition via recruitment of mGluR5s on the relay cells, and higher rates

of parabrachial input does the opposite via recruitment of M2Rs. It also follows that this can have a net, long lasting effect on membrane potential of the relay cell, and this, in turn, can affect the play of the cell's voltage sensitive properties. Many voltage gated conductances exist that can be so affected, but a detailed accounting of these is beyond the scope of the present account (for reviews, see McCormick and Huguenard, 1992; Sherman and Guillery, 2001). As an example, consider the role of the voltage-gated T-type Ca^{2+} channels, which when activated, lead to an inward current, I_T, and an all-or-none, low threshold Ca^{2+} spike propagating through the dendritic tree and producing a burst of action potentials. When the cell is relatively depolarized, I_T is inactivated, no low threshold spike is produced, and the cell responds to suprathreshold inputs with a steady stream of unitary action potentials: this is *tonic* firing. When the cell is relatively hyperpolarized, inactivation of I_T is removed, and now an excitatory input will produce a low threshold spike and *burst* firing. The firing mode of the relay cell has important implications for functioning of the relay (Sherman, 2001). The point here is that triadic function may affect I_T and other such voltage sensitive properties in interesting ways. This clearly needs more study.

6. CONCLUSIONS

The thalamic interneuron exemplified by that found in the cat's lateral geniculate nucleus provides a potent GABAergic and thus inhibitory input to relay cells. It thus plays a key role in controlling the flow of information to cortex. The synaptic inputs from these interneurons to relay cells are particularly interesting for two reasons. First, the interneuron appears to employ two independent input/output routes: a conventional axonal one that integrates inputs onto the cell body and proximal dendrites; and an unconventional one involving dendritic outputs that are both presynaptic and postsynaptic. Cable modeling suggests that the dendritic output route is organized into numerous, functionally independent streams that are also independent of the cell body and thus action potential generation. Second, the dendritic outputs in addition to being presynaptic to relay cell dendrites, are postsynaptic chiefly to either retinal or parabrachial inputs. Details of these output synapses, which involve complex circuits known as triads found widely throughout thalamus, lead to rather speculative but testable ideas regarding how interneurons help modulate relay cell activity. It is hoped that following through some of these ideas will provide genuine insights into the functioning of this circuitry that appears key to thalamic relays.

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