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HOW VOLTAGE-GATED ION CHANNELS ALTER THE FUNCTIONAL PROPERTIES OF GANGLION AND AMACRINE CELL DENDRITES

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Carolo Terzuolo and his colleague T. Araki pioneered the use of double barrel microelectrodes to study spinal cord motoneurons (1, 19). Based on simultaneous intracellular recordings and extracellular field potential analysis, they suggested that the dendrites of motoneurons supported impulse activity for retrograde action potentials initiated in the axon. Although this conclusion was later criticized by Rall (14) during a period when dendrites were generally regarded as passive structures, evidence in recent years (20, 6, 8, 7, 16, 17, 18) supports the idea that many dendritic structures which were once thought to be passive, in fact, contain voltage-gated ion channels, including those for sodium. It appears that the concepts advanced by Terzuolo and Araki may apply to many cells, including retinal ganglion cells. In this paper we will discuss the structure and function of retinal ganglion cells and compare their physiology with that of on-off amacrine cell dendrites, both of which appear to have active dendritic membrane. However, in these two contrasting cell types it appears that the physiological activation of dendritic impulse activity is different: on the one hand, the dendrites of amacrine cells generate dendritic impulses before a somatic spike is initiated (12), whereas in ganglion cells, the dendritic impulse appears to be generated as a retrograde impulse from an initiation site within the axon (8, 16) and conforms to the kind of idea promoted by Terzuolo and Araki (19).

Synaptic processing in the vertebrate retina is conveyed through two different neuropile layers, including the outer (OPL) and inner (IPL) plexiform layers. Processing in the OPL is largely done by graded slow potentials, generated by photoreceptors, bipolars and horizontal cells. In the IPL, where bipolar terminals feed into amacrine and ganglion cells, we begin to see evidence of impulse generation as part of the outcome of synaptic processing. Impulse generation in retinal ganglion cells is the well-established means by which these cells communicate with the brain. In addition however, impulse activity in the dendrites of some amacrine cells has raised interesting questions about synaptic processing in the IPL and what role impulses play in the dendrites of amacrine cells, which serve both post- and presynaptic functions. TTX-sensitive impulses in amacrine cell dendrites were first described by Miller and Dachuex (12) and more recently by Cook et al. (3, 4). Many if not all On-Off amacrine cells are inhibitory and release

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either GABA or glycine; a feedforward inhibition onto ganglion cells is a prominent outcome of their activity (13). Recent studies by Cook (3) have suggested that glycinergic amacrine cells require TTX-sensitive impulses in order to release glycine and that the surround inhibition mediated by these cells is eliminated in the presence of bath-applied TTX. In other words, it appears that, in the presence of TTX, the light-evoked EPSP of amacrine cells, which can be substantial in amplitude, is insufficient to release neurotransmitter to sustain inhibitory function. Because the retina is generally a tonic system, in which many cells release transmitter in the dark, a requirement for impulse activity as a means of releasing transmitter has not been fully explored as to the mechanism or advantages of such a system.

The role of dendritic impulse activity is not solely confined to a consideration of amacrine cell function, but may also include the properties of ganglion cell dendrites, where modeling studies have suggested that dendrites must have voltage-gated ion channels for proper activation and regulation of impulse activity. According to this model, which has also been advanced for pyramidal cells of the cerebral cortex (18), dendrites behave as passive, integrative structures for synaptic currents, but once the impulse is generated (perhaps in the axon hillock or thin axonal region), an active impulse propagates in a retrograde fashion to engage the dendrites. This retrograde impulse resets the charge on the membrane capacitance and prevents tonic polarization of the dendrites (from synaptic inputs or retrograde impulses) from providing continuous stimulation to the impulse generation site. If dendrites are modeled as passive structures, then tonic synaptic input generates a high frequency rate of firing that is difficult to regulate. Evidence for direct, spike initiation in dendrites has been observed in pyramidal cells (18) and ganglion cells (20) of the rabbit retina through simultaneous intradendritic and somatic recordings.

In addition to voltage-gated Na^+ channels, recent studies have raised the possibility that at least one type of voltage-gated Ca^{++} channel, the T-Type Ca^{++} channel, may be more densely represented in ganglion cell dendrites than in the soma (9). Because T-type Ca^{++} channels can be activated by synaptic currents, the presence of these channels in the dendrites raises new questions about the mechanisms of dendritic integration in these structures. Thus, non-linear behavior of amacrine and ganglion cell dendrites may play important roles in their functional organization. However, when comparing the dendrites of amacrine and ganglion cells, these non-linear properties must be interpreted differently, as amacrine cells have transmitter release functions, whereas, with one exception (15), ganglion cell dendrites appear to be exclusively postsynaptic.

The upper panel of Figure 1 illustrates flatmount views of a horse radish peroxidase stained On-Off amacrine and a sustained On ganglion cell. The ganglion cell has both a dendritic branching tree and an axon, whereas the amacrine cell has only dendritic branching and lacks a separate axonal structure. Superficially, it is difficult to distinguish the dendritic tree morphology of an amacrine cell when compared to that of a ganglion cell. However, at a more microscopic level, the branching characteristics of the two cell types are quite distinct.

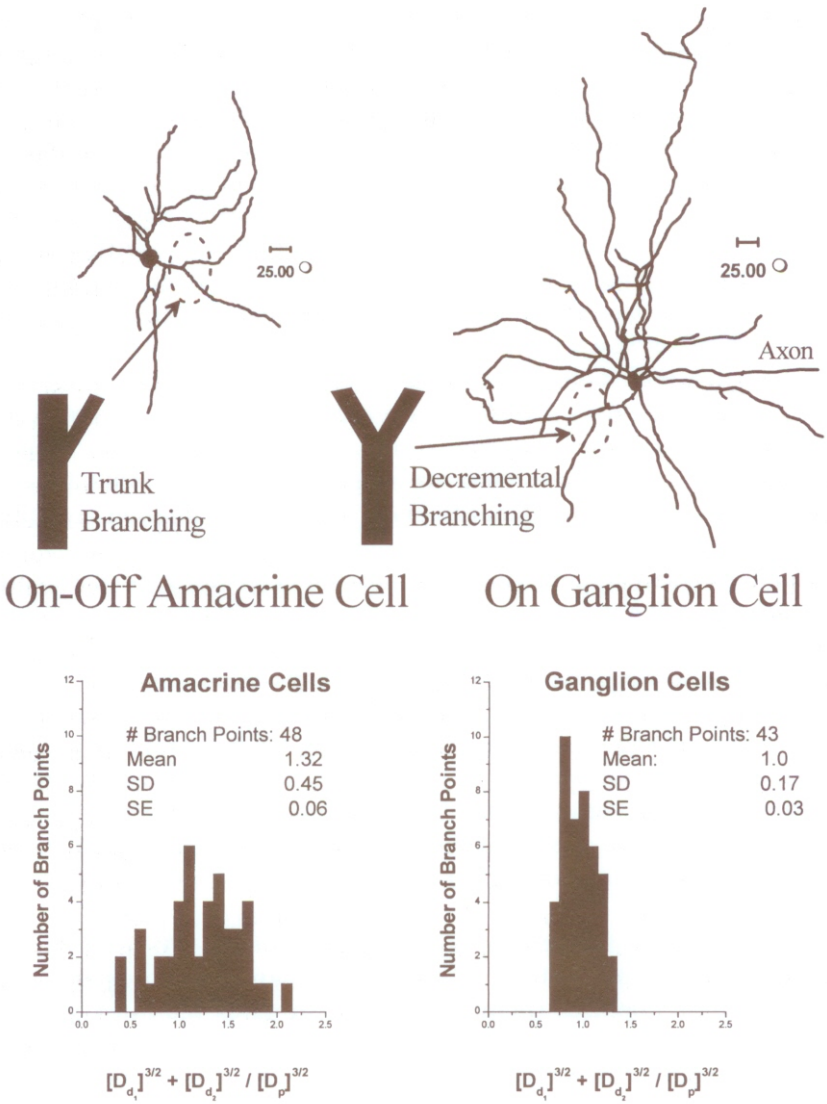

Fig. 1. - *Horseradish peroxidase stained On-Off amacrine and On ganglion cell of the mudpuppy (Necturus maculosus) retina viewed in flatmount at similar magnifications.*
The two histograms below show the branching relationships based on the 3/2 power rule of Rall, in which each of the two daughter branches raised to the 3/2 power are divided by the parent diameter raised to the 3/2 power. A value of 1 predicts a branch which has the same impedance as that of a non-branching structure. The ganglion cell branches conform to this relationship with a mean value of 1.0, whereas the amacrine cells have a value greater than 1.0 with a mean of 1.32. The drawing insets illustrate the differences between these two branching strategies in that amacrine cells often branch without a decrement in the parent branch, whereas ganglion cells branch with both daughters smaller than the parent.

The lower panel of Figure 1 illustrates histogram distributions of the branching relationships between a group of On-Off amacrine and ganglion cell dendrites

based on measurements of the diameter of the parent dendrite and the diameter of the two daughter branches, each raised to the 3/2 power. Rall has demonstrated that if the sum of the diameter of the two daughter branches, each raised to the 3/2 power, is equal to that of the parent (raised to the 3/2 Power) the impedance of the branching point is the same as if the parent did not branch at all. Figure 1 shows micrometer filar eyepiece measurements of daughter and parent from several different On-Off amacrine and several different ganglion cell dendrites. Note that the 3/2 power relationship for the ganglion cells is narrowly centered around a mean value of 1.0, whereas that of the amacrine cell branches is greater, with a mean value of 1.32. In other words, the amacrine cell branching pattern is one in which one or both of the daughter branches is larger than the prediction of Rall for conservation of branch impedance. A closer examination of the branching pattern of these amacrine cells suggests that the parent often gives rise to a smaller daughter branch, but continues without decrementing, as conceptually illustrated in the inset. This branching pattern is what we refer to as non-decremental or "trunk branching" in which the parent dendrite gives off smaller daughter branches without itself decrementing significantly. In general, this difference in the dendritic branching pattern between amacrine and ganglion cells suggests that charge generated in amacrine cell dendrites is more likely (in a comparative sense) to remain in the dendritic tree, whereas a greater fraction of the charge generated in ganglion cell dendrites will move towards the soma. Perhaps more importantly, the trunk branching pattern of amacrine cell dendrites may serve to distribute and control the dendritic impulse traffic in a centrifugal (away from soma) pathway, whereas the ganglion cell branching pattern is more likely to support centrifugal impulse traffic in which all of the daughter branches could be activated by dendritic impulse current, due to the conservation of impedance at the branching points. The advantages of 3/2 power branching for ganglion cell dendrites will become more evident below.

Figure 2 illustrates an intracellular recording from an On-Off amacrine cell. The light-evoked response (upper left) consists of a fluctuating EPSP, together with large and small amplitude impulses (duration of light stimulus indicated by bar below trace). We have previously suggested that the large amplitude impulses are generated by the soma and that the small amplitude spikes are generated in the dendrites, which fail and decay passively into the soma (12). Because the dendritic spike retains a relatively sharp rise time in presumed soma recordings, we have speculated that this spike must be generated or propagated close to the soma before decaying passively. Both dendritic and somatic impulses are blocked by TTX and presumably depend on sodium. These two impulses can be differentially activated by intracellular current injection (lower two traces on left and middle trace on right). A closer examination of the physiological record shows that dendritic impulses are generated before the larger somatic spike and often appear to bring the somatic spike to threshold (traces at upper right). Thus, in amacrine cells, the sequence of events appears to be a dendritic EPSP, which gives rise to an impulse of dendritic location, followed by a somatic spike. Although it is possible to adjust the stimulus intensity,

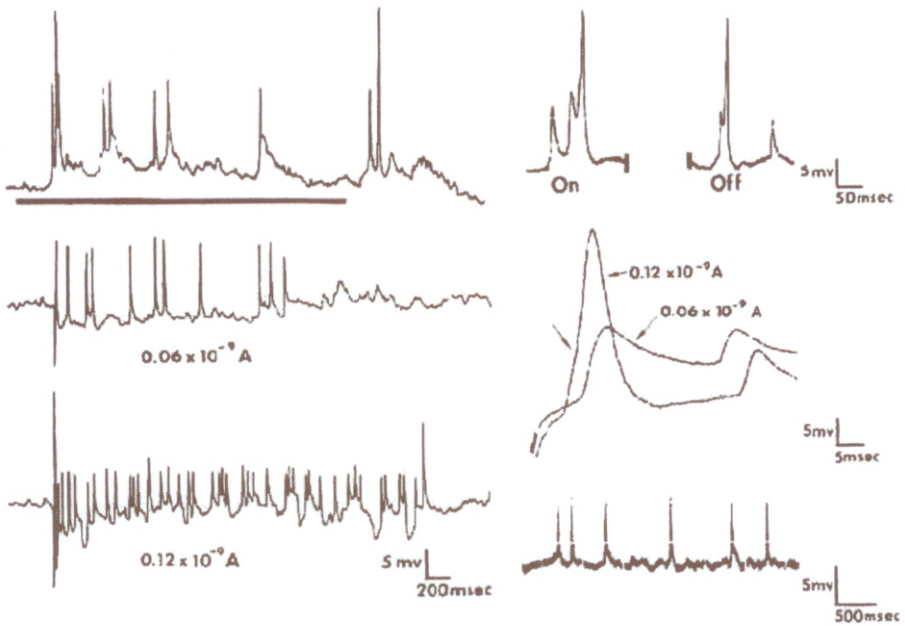

Fig. 2. - *Physiology of On-Off amacrine cells revealed by intracellular recordings. Light-evoked response illustrated in upper left trace, showing impulses of two different amplitudes.*
The upper right record shows an expanded time scale and illustrates that smaller amplitude impulses preceded the generation of a single, larger spike, at light on and off. Current injected into the cell evoked small amplitude impulses (middle left), whereas increased current evoked a single large amplitude impulse and a train of smaller spikes. Middle right traces show that increasing the current injection strength initiated a small amplitude impulse at first, which appeared to generate the large amplitude spike. Lower right record shows spontaneous, small amplitude impulses recorded from another cell in the absence of light stimulation. From Ref. 11, with permission.

or light stimulus position to evoke small amplitude EPSPs, it is more difficult to find stimulus conditions in which dendritic impulses are evoked, without evoking some somatic spikes as well. Nevertheless, in a few cases, we have observed tonic impulse activity in On-Off amacrine cells and these tonic spikes appear to be those attributed to dendritic activity without somatic impulses (lower right).

What role does impulse activity serve in the function of amacrine cells? Most amacrine cells serve an inhibitory function and appear to release either GABA or glycine (13). A prominent IPSP in ganglion cells is one signature of amacrine action and can be blocked with either picrotoxin or strychnine (or both), pointing to a pharmacologically dual mode of inhibitory action. Recordings from ganglion cells have revealed the appearance of both slow and fast inhibitory events and we suggested that the fast IPSPs had properties that were similar to the characteristics of dendritic impulse activity in amacrine cell dendrites (11). More recently, Cook et al. (3) have demonstrated that a glycinergic surround inhibitory response of ganglion cells in the salamander retina is blocked by TTX, suggesting that impulse activity in amacrine cells is essential for the release of neurotransmitter.

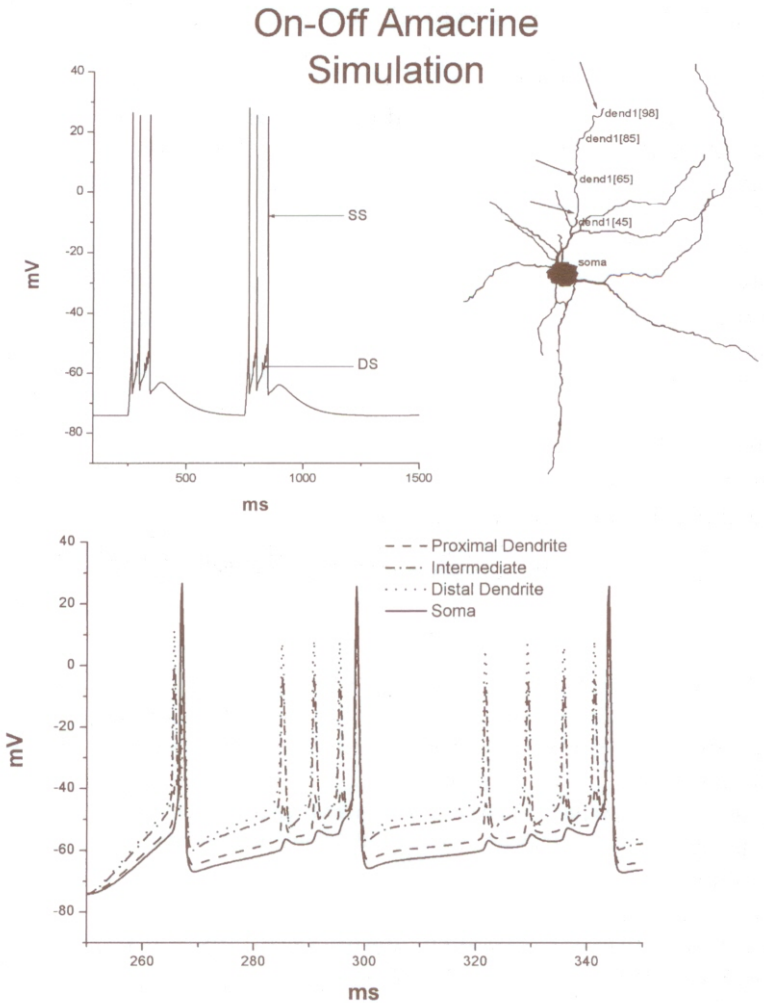

Fig. 3. - *With a channel density distribution in which the dendrites have a significant complement of voltage-gated ion channels, a simultaneous injection of alpha conductance changes were applied into each of thirteen input sites along two dendrites (200-1000pS with a peak delay of 100ms).*
These conductance changes were initiated at 250 and 750 ms delays to simulate the on-off character of on-off amacrine cell light responses. The upper left panel shows that the alpha conductance changes evoked both large and small amplitude impulses very similar to the kinds of activity observed physiologically. The lower panel illustrates a recording from three different dendritic sites, indicated by arrows in the flatmount view of the cell, as well as the soma. The somatic spike was modified by having a larger contribution from the $I_{K, Ca}$ current to make the spike more rapidly accommodating. When the impulse is initiated, it begins in the most distal compartment of the dendrite, based on a "sealed end" condition. It is actively conducted towards the soma, but decays passively near the proximal dendrite recording site, as the impedance mismatch becomes too great for active propagation to continue. As the passive dendritic impulse decays into the soma, the combination of the EPSP-like response and the attenuated dendritic impulse evokes a somatic spike which engages the cell in rapid order. The three somatic impulses illustrated in this simulation occur intermittently, while dendritic spike activity continues. However, once the somatic spike has invaded the dendritic tree, an additional delay is encountered before the next dendritic impulse takes place.

To better understand how amacrine cells generate dendritic impulse activity, we carried out a series of simulations using realistic morphologies of amacrine cells and the multichannel model of impulse generation developed by Fohlmeister and Miller (8, 7). By fixing the voltage-gated ion channels in the soma and then altering their density in the dendrites, using an even distribution of channel conductance (mS/cm), we determined that the dendrites must have about 1/2 or more of the channel density assigned to the soma in order to generate dendritic impulse activity which precedes that of the soma and thus conforms to the physiological observations.

Figure 3 illustrates the simulated events observed in different regions of the cell when synaptic currents are generated in the dendrites using a transient conductance change described by an alpha function with a peak conductance of 200-1000 pS and a peak delay of 100 ms in 13 different compartments along two dendrites. In order to restrain the somatic impulse from firing with the same frequency as the dendritic impulse, the $I_{K, Ca}$ current was enhanced to lengthen the interspike interval. In this example the synaptic current generates dendritic impulses which precede the generation of the somatic spike. Although a more detailed description of these simulations is beyond the scope of this paper, the presence of an active, impulse generating capability in the dendrites of On-Off amacrine cells could provide the means by which voltage-gated calcium channels are activated to facilitate the release of neurotransmitter. While we are accustomed to seeing transmitter release from retinal neurons controlled by graded slow potentials, the On-Off amacrine cells appear to be the first cell type in which a threshold for transmitter release has been observed. However, we do not know whether this threshold exists through a voltage threshold for activating voltage-gated calcium channels or whether a threshold exists for activation of the transmitter release machinery perhaps through the accumulation of internal calcium. Nevertheless, dendritic impulse activity appears to be necessary for the normal inhibitory functions of On-Off amacrine cells and the special branching patterns of their dendrites may serve to channel the impulse traffic for optimizing this function. Although localized dendritic spiking can be initiated from many different dendrites, when the somatic spike is initiated, it can actively propagate throughout the entire dendritic tree and thus provide a near simultaneous polarization of all transmitter release sites. This concept was developed a number of years ago based on intracellular recording experiments (11).

In contrast to our observations on amacrine cell dendrites, recordings from retinal ganglion cells do not reveal the presence of impulse activity in dendrites which precedes that observed in the soma. Nevertheless, impulse activity in the dendrites, generated as a retrograde impulse beginning in the soma, appears to be important for proper regulation of the rate of impulse activity. Figure 4 shows the frequency of impulse activity in a ganglion cell model with and without voltage-gated ion channels in the dendrites (8, 7). For passive dendrites, the impulse activity shows a very high frequency of firing and is difficult to regulate. In contrast, when voltage-gated ion channels are in the dendrites, at a density that is too low to support local spiking from synaptic inputs, an attenuated dendritic spike travels in the retrograde direction

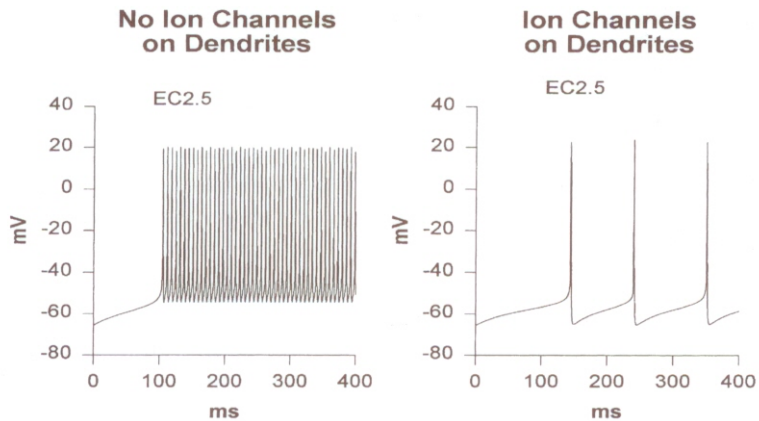

Fig. 4. - *In this example an equivalent cylinder model of a ganglion cell was simulated with (right) and without (left) voltage-gated ion channels in the equivalent cylinder.*
The passive conductance of the two models was adjusted so that the input resistance of the two cells (measured at the soma) was the same. Without voltage-gated ion channels in the dendritic compartments, current injected into the soma produces a high rate of impulse activity. In contrast, when ion channels are present in the dendrites (at lower density than the soma) impulse frequency evoked by the same level of current injection is markedly reduced. Modified from Figure 6 (Ref. 8) with permission.

throughout the dendritic tree. If voltage-gated ion channel density is uniform in the dendrites, then, because of the impedance conserving nature of the branching pattern of the dendrites, this impulse can, in principle, invade the entire dendritic tree. One of the main reasons for which retrograde spiking in ganglion cell dendrites is important is the requirement for resetting the membrane capacitance, to prevent the accumulation of synaptic and non-synaptic charge in the dendrites from providing continuous, suprathreshold stimulation to the impulse generating site in the axon hillock or thin segment region. When the dendrites are passive, the long time constant (~ 70 ms; Ref. 2) of the membrane allows the dendrites to hold synaptic charge that outlasts the synaptic conductance change; rapid resetting of the membrane potential by the retrograde impulse limits the duration of action of this effect. In addition, passive dendrites force the soma impulse to passively invade the dendritic tree, with a progressive slowing of the dendritic current and the preservation of charge which can also provide subsequent stimulation to the site of impulse initiation through a kind of echo effect. Here again, an active impulse in the dendrites prevents impulse slowing and charge storage in the dendrites. The retrograde impulse wipes the membrane clean of stored charge and permits impulse activity to be more closely determined by on-going synaptic events, rather than the preceding ones.

The model that emerges from the previous analysis suggests that the dendrites of ganglion cells have a relatively low level of voltage-gated ion channels and that, for synaptic currents, the dendrites behave as passive integrating structures, funneling synaptic currents into the soma. However, more recent evidence in our laboratory has suggested that ganglion cells have T-type calcium channels whose properties are such that, in principle, they could augment or modify synaptic currents generated in

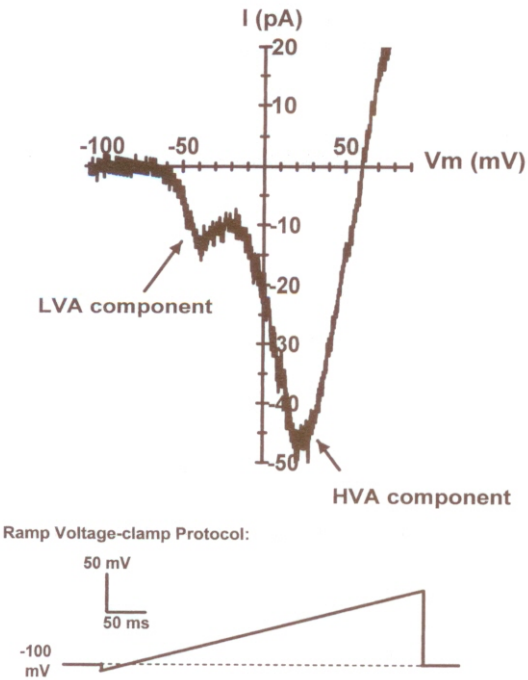

Fig. 5. - *A current-voltage relationship revealing two different inward currents, including a low voltage-activated (LVA) and high voltage-activated (HVA) calcium currents observed in a tiger salamander retinal ganglion cell.* The top trace shows the calcium currents under voltage-clamp conditions, while the bottom trace illustrates the voltage ramp used to vary the holding potential. Recording conditions favored the isolation and augmentation of calcium currents (e.g., the external bathing medium contained Cs, TEA, TTX, and elevated – 15 mM – calcium; the intracellular pipette was primarily composed of CsF).

the dendrites. Figure 5 shows the inward currents generated by a ramp voltage clamp in a dissociated ganglion cell from the tiger salamander retina. The inward current evoked at relatively low membrane potentials is characteristic of low voltage-activated (LVA) calcium channels. Further evidence that this current is generated by calcium channels will be provided in a forthcoming publication. An important finding in our studies of the LVA current in ganglion cells is that the current seems to be larger in the dendrites than in the soma. To our knowledge this is the first time that a voltage-gated ion channel has been found at higher levels in the dendrites than in the soma and this difference alone begs an interpretation.

Figure 6 illustrates an equivalent cylinder model (1λ) of a ganglion cell in which LVA currents are represented in both the dendrites and the soma at different levels (No channels, 5X, 10X and 20X). Consistent with the model of Coulter et al. (5), the LVA current was modeled as a permeability change with a soma value of $3.6X10^{-7}$ $cm^3/sec/cm^2$. In this simulation maximal activation of the LVA current was created by passing a current into the soma to hyperpolarize the cell, after which a simulated synaptic conductance change was introduced through an alpha function (peak conductance = 1 nS with a peak delay of 100 ms) applied to the mid region of the equivalent cylinder. Note that the transient synaptic responses are significantly augmented and shaped by the presence of the LVA channels in the dendrites.

The presence of LVA calcium currents has been observed in many retinal cell types, including ganglion cells (10). However, this current has previously been of

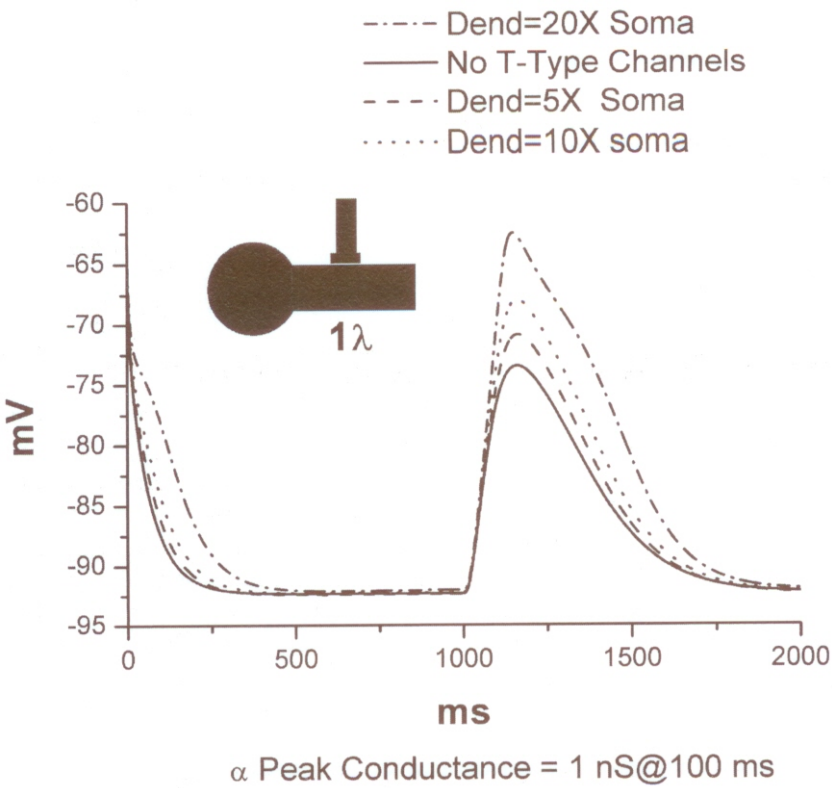

Fig. 6. - *A computer simulation was developed using an equivalent cylinder model of a ganglion cell, with a dendritic length equal to 1* λ.
Four different simulations were carried out in which the membrane was either entirely passive, while three simulations were done in which the dendritic membrane contained 5X, 10X and 20X the LVA channel density of the soma. To fully activate the LVA currents, a hyperpolarizing pulse was applied at the beginning of the simulation to bring the membrane potential to approximately the same amplitude, at close to -95 mV. This required different current levels for each of the simulations. For each level of T-type calcium channels, the charging curve is increasingly shaped by the activation of the LVA current. At 1000 ms, an alpha conductance was introduced at a spatial position of 0.5 λ (1 nS@100 ms) to simulate an EPSP-like response. It is readily apparent that the amplitude of the response is markedly influenced by the presence of T-type channels which serve to augment the response amplitude and modify its waveform. Thus, T-type calcium channels in the dendrites of ganglion cells can augment the amplitude and time course of synaptic responses.

little interest to most physiologists because of its relatively small size. Yet, the small size of this current observed in retinal ganglion cell soma recordings could reflect a much larger current if these channels are found in higher density in the dendrites. We are presently evaluating the LVA current with intradendritic whole-cell and outside-out patch recordings from dendrites to evaluate the range of functional possibilities which these channels might play in dendritic integration, regulation of internal calcium and the degree to which these currents can enhance or modify synaptic events.

SUMMARY

The present study compares the structure and function of retinal ganglion and amacrine cell dendrites. Although a superficial similarity exists between amacrine and ganglion cell dendrites, a comparison between the branching pattern of the two cell types reveals differences which can only be appreciated at the microscopic level. Whereas decremental branching is found in ganglion cells, a form of non-decremental or "trunk branching" is observed in amacrine cell dendrites. Physiological differences are also observed in amacrine vs ganglion cells in which many amacrine cells generate dendritic impulses which can be readily distinguished from those of the soma, while separate dendritic impulses in ganglion cell dendrites have not been reported. Despite these differences, both amacrine and ganglion cell dendrites appear to contain voltage-gated ion channels, including TTX-sensitive sodium channels. One way to account for separate dendritic impulses in amacrine cells is to have a higher density of sodium channels and we generally find in modeling studies that a dendritic sodium channel density that is more than about 50% of that in the soma is required for excitatory, synaptic currents to give rise to local dendritic spike activity. Under these conditions, impulses can be generated in the dendrites and propagate for some distance along the dendritic tree. When the soma generates impulse activity in amacrine cells, it can activate, antidromically, the entire dendritic tree. Although ganglion cell dendrites do not appear to generate independent impulses, the presence of voltage-gated ion channels in these structures appears to be important for their function.

Modeling studies demonstrate that when dendrites lack voltage-gated ion channels, impulse activity evoked by current applied to the cell body is generated at rates that are much higher than those observed physiologically. However, by placing ion channels in the dendrites at a reduced density compared to those of amacrine cells, the firing rate of ganglion cells becomes more physiological and the relationship between frequency and current (F/I relationship) can be precisely matched with physiological data.

Recent studies have demonstrated the presence of T- type calcium channels in ganglion cells and our analysis suggests that they are found in higher density in the dendrites compared to the soma. This is the first voltage-gated ion channel which appears more localized to the dendrites than other cell copartments and this difference alone cries for an interpretation. The presence of a significant T-type calcium channel density in the dendrites can influence their integrative properties in several important ways. First, excitatory synaptic currents can be augmented by the activation of T-type calcium channels, although this is more likely to occur for transient rather than sustained synaptic currents because T-type currents show strong inactivation properties. In addition, T-type calcium channels may serve to limit the electrical load which dendrites impose on the spike initiation process and thus enhance the speed with which impulses can be triggered by the impulse generation site. This role whill enhance the safety factor for impulses traveling in the orthograde direction.

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