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# NEURAL ARCHITECTURE OF THE ELECTROSENSORY LATERAL LINE LOBE: ADAPTATIONS FOR COINCIDENCE DETECTION, A SENSORY SEARCHLIGHT AND FREQUENCY-DEPENDENT ADAPTIVE FILTERING

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**Summary**

**The electrosensory lateral line lobe (ELL) of weakly electric fish is the only nucleus that receives direct input from peripheral electroreceptor afferents. This review summarises the neurotransmitters, receptors and second messengers identified in the intrinsic circuitry of the ELL and the extrinsic descending direct and indirect feedback pathways, as revealed by recent *in vitro* and *in vivo* studies. Several hypotheses of circuitry function are examined on this basis and on the basis of recent functional evidence: (1) fast primary afferent excitatory postsynaptic potentials (EPSPs) and fast granule cell 2 $GABA_A$ inhibitory postsynaptic potentials (IPSPs) suggest the involvement of basilar pyramidal cells in coincidence detection; (2) voltage-dependent EPSPs and IPSPs, dendritic spike bursts and frequency-dependent synaptic facilitation support a sensory searchlight role for the direct feedback pathway; and (3) the contributions of distal and proximal inhibition, anti-Hebbian plasticity and beam *versus* isolated fiber activity patterns are discussed with reference to an adaptive spatio-temporal filtering role for the indirect descending pathway.**

Key words: coincidence detection, attention, descending feedback, signal filter, neural architecture, electrosensory lateral line lobe, adaptive filtering.

## Introduction

The electrosensory lateral line lobe (ELL) is the first and only site of termination of electrosensory afferents in teleost fish. The simple laminar structure of the gymnotiform ELL has led to a thorough analysis of its circuitry and *in vivo* and *in vitro* physiology. An earlier review (Carr and Maler, 1986) summarised the morphology of ELL cells and circuits in two species of gymnotiform fish, *Eigenmannia viriscens* and *Apteronotus leptorhynchus* (high-frequency wave species; see Bullock, 1969). Since then, these fish have continued to be the focus of numerous behavioral and electrophysiological studies. In this paper, we briefly update the ELL circuitry of these species and add information on the identification of the transmitters, receptors and second messengers of its neurons and afferents. We then focus on the physiology of an *in vitro* slice preparation of the ELL that has revealed important cellular adaptations for its sensory function.

## ELL: cells and circuitry

The ELL consists of four segments: the medial (MS), centromedial (CMS), centrolateral (CLS) and lateral (LS) segments. The MS receives input from ampullary electroreceptors; tuberous electroreceptor afferents trifurcate and project to the CMS, CLS and LS (Heiligenberg and Dye, 1982). There are numerous differences between the three tuberous segments related to their putative role as spatial and temporal filters (Metzner and Juranek, 1997; Shumway, 1989a,b; Turner et al., 1996), but segmental differentiation will not be emphasised in this review. Electrosensory afferents are fasciculated and travel in stereotyped trajectories to terminate topographically in each of the ELL segments (Lannoo et al., 1989). Thus, although the ELL segments are of different sizes, each receives a complete topographic map of electroreceptors; the rostro-caudal body axis is mapped rostral-to-caudal in the ELL, while the dorso-ventral axis is mapped along the medial-to-lateral ELL axis.

All ELL segments have an identical laminar organization consisting of the following layers (see Fig. 1). (1) A deep fiber layer (DFL) consisting of electroreceptor afferents and axons of commissural neurons. (2) A deep neuropil layer (DNL), the site of termination of electrosensory afferents on the basal dendrites of ELL projection cells and interneurons. This layer also contains ovoid cells and spherical cells; the spherical cells are involved in time coding and are not discussed further (see Carr and Maler, 1986). (3) A granular layer (GCL) containing granular interneurons and a recently described deep basilar

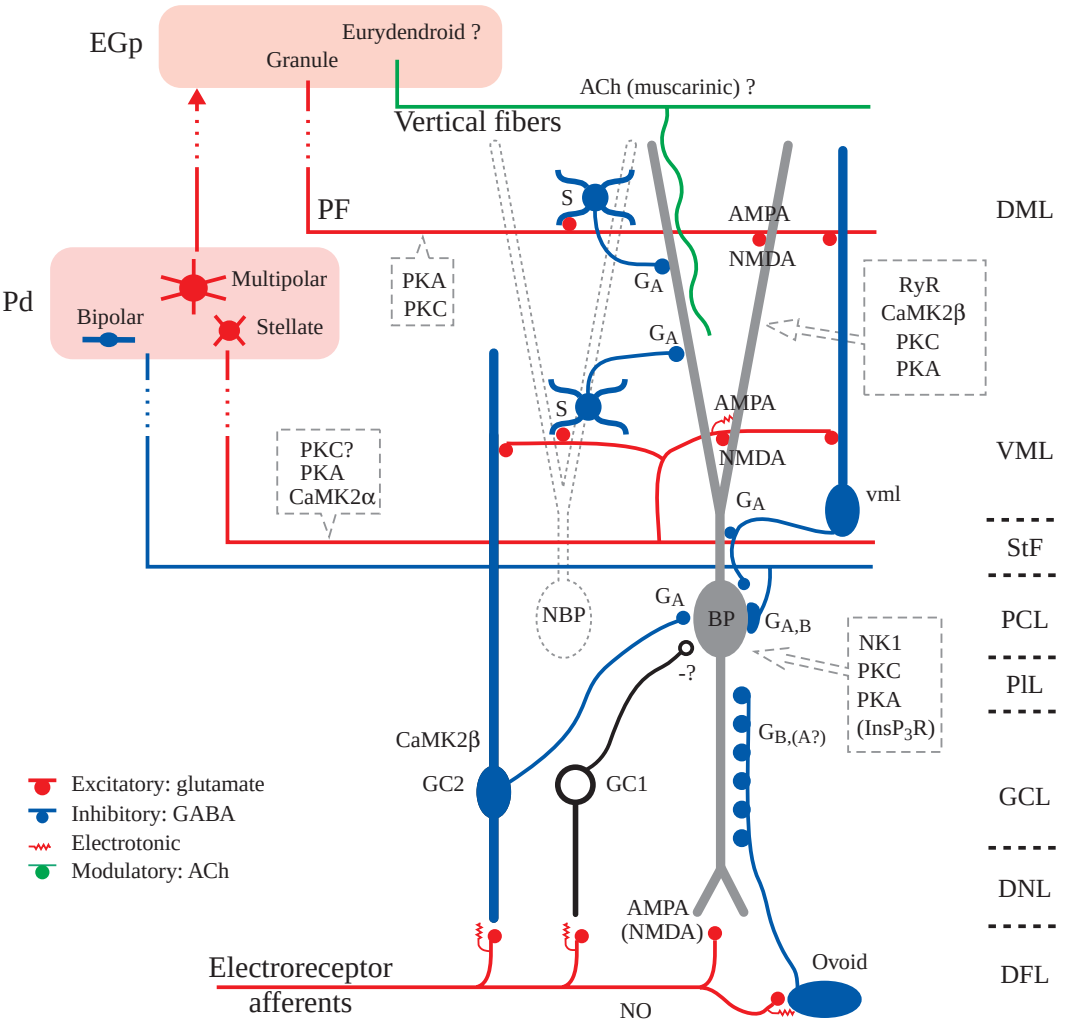


Fig. 1. Summary of the electrosensory lateral line lobe (ELL) intrinsic circuitry, efferent and afferent connections, transmitters and second messengers discussed in this paper. Because nonbasilar pyramidal cell (NBP) cell connectivity is identical to that of basilar pyramidal cell (BP) cells, with the exception of the absence of a basilar dendrite and associated electroreceptor afferent and ovoid cell inputs, only its position in the circuit is indicated. Grey dashed boxes indicate second messengers present in the soma and dendrites of pyramidal cells. EGp, eminentia granularis pars posterior; Pd, nucleus praeminentialis dorsalis. Cell types: GC1, granule cell type 1, GC2, granule cell type 2; NBP, nonbasilar pyramidal cell, BP, basilar pyramidal cell; vml, ventral molecular layer cell; S, stellate cell. Pathways: StF, stratum fibrosum (from Pd stellate and bipolar cells); PF, parallel fibers from EGp granule cells and vertical fibers probably from EGp eurydendroid cells. Colour code: blue, GABAergic cells and pathways; red, glutamatergic cells and pathways (glutamatergic pyramidal cells are shown in grey); green, cholinergic pathway. Receptors: $G_A$, $GABA_A$; $G_B$, $GABA_B$; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-aspartate; ACh, acetylcholine (muscarinic) second messengers: CaMK2α/β, $Ca^{2+}$/calmodulin-dependent kinase 2 (α or β subunit); RyR, ryanodine receptor; $InsP_3R$, inositol 1,4,5-trisphosphate receptor; PKC, protein kinase C; PKA, protein kinase; NO, nitrous oxide. Electrotonic (gap junction) synapses are indicated where they are formed by electroreceptor afferents on ovoid and granule cells and by StF excitatory fibers on pyramidal cells. Approximate laminae positions are shown on the right: DFL, deep fiber layer; DNL, deep neuropil layer; GCL, granule cell layer; PlL, plexiform layer; PCL, pyramidal cell layer; VML, ventral molecular layer; DML, dorsal molecular layer. Data are abstracted from Bastian (1993), Berman et al. (1995), Berman and Maler (1998a–c), Berman et al. (1997), Bottai et al. (1997, 1998), Maler (1979, 1999a,b), Maler and Hincke (1999), Maler and Mugnaini (1994), Maler et al. (1981a,b, 1982), Sas and Maler (1983, 1987), Turner and Moroz (1995), Wang and Maler (1994) and Zupanc et al. (1992). Polymorphic cells, somatostatin and substance P are not shown.

pyramidal cell (Bastian and Courtright, 1991). (4) The plexiform layer (PlL) containing mainly efferent axons of ELL pyramidal cells. (5) The pyramidal cell layer (PCL). (6) The stratum fibrosum (StF) containing axons of the direct feedback pathway (excitatory and inhibitory). (7) The ventral molecular layer (VML), the site of termination of StF excitatory fibers. (8) The dorsal molecular layer (DML), the site of termination of parallel fibers emanating from granule cells of the overlying cerebellum (eminentia granularis posterioris, EGp); this projection is described as the indirect feedback pathway. Vertical fibers in the DML, putatively emanating from EGp eurydendroid cells, are a second minor component of the indirect feedback pathway (Maler, 1979).

The most important features of ELL circuitry are summarised in Fig. 1. ELL pyramidal cells are of two basic types: basilar and non-basilar pyramidal cells, corresponding to the physiologically defined E and I cells (Saunders and Bastian, 1984). Basilar pyramidal cells have a thick basal dendrite ending in a dense arborization (see Fig. 2) that receives glutamatergic synaptic input from electrosensory afferents (Wang and Maler, 1994); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (and perhaps *N*-

methyl-D-aspartate, NMDA) receptors mediate the response. Non-basilar cells lack a basal dendrite (Maler, 1979), but receive disynaptic electrotonic (gap junction) and inhibitory input from two types of ELL interneuron (see below). Both types of pyramidal cell have apical dendrites that ramify in the molecular layer, where they receive electrosensory feedback (VML and DML) and proprioceptive input (DML only, Bastian, 1995; Sas and Maler, 1987). Pyramidal cells can also be classified with respect to their dorso-ventral position within the PCL (Bastian and Courtright, 1991) and this is correlated with their intracellular $Ca^{2+}$ stores (see below).

Electrosensory afferents also terminate on several types of interneuron including type 1 and type 2 granular interneurons (GC1, GC2), ovoid cells and polymorphic cells (they also terminate on multipolar cells, but this cell type has received little attention and will not be discussed further). Both GC1 and GC2 cells have basal dendrites in receipt of electrosensory input and axons terminating on the somata of pyramidal cells; the more numerous GC2 cell type also has an apical dendrite that ramifies in the molecular layer (Maler et al., 1981b; Maler and Mugnaini, 1994). The GC2 cell is γ-aminobutyric acid (GABA)-ergic and its synapses on pyramidal cells involve strictly $GABA_A$ receptors (Berman and Maler, 1998a). The GC1 cell is also believed to be inhibitory, but its transmitter is unknown; its inhibition of pyramidal cells appears to be linked to $K^+$ channels (Berman and Maler, 1998a). Earlier *in vivo* studies (Shumway and Maler, 1989) suggested that the GC2 cell is involved mainly in shaping the temporal response properties of pyramidal cells, while the GC1 cell generates the inhibitory surround of the pyramidal cell's receptive field. Polymorphic cells are also GABAergic, but their main site of termination appears to be GC1 cells (Maler and Mugnaini,

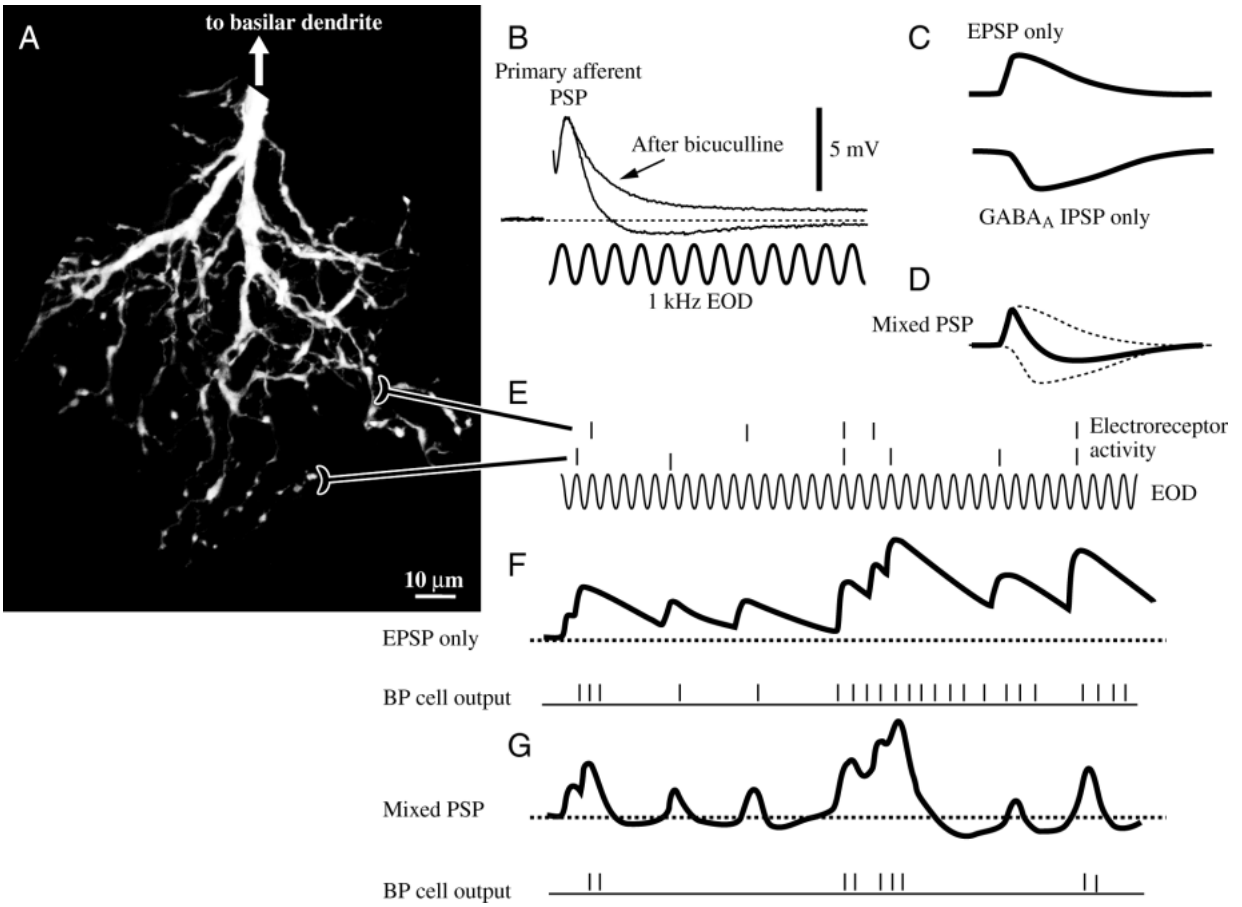


Fig. 2. Hypothesis for coincidence detection of electrosensory afferent activity. (A) A Lucifer-Yellow-filled basilar arborization of a pyramidal cell (see Berman and Maler, 1998a). The basilar dendrite is truncated in the image at the arrow. The positions of two imaginary primary afferent boutons are shown. (B) The response of a basilar pyramidal (BP) cell *in vitro* to stimulation of primary afferents (Berman and Maler, 1998a). The control response contains an excitatory postsynaptic potential (EPSP) and a small inhibitory postsynaptic potential (IPSP). After treatment with bicuculline, the EPSP peak was unchanged but the IPSP was blocked, revealing a slower EPSP decay. An idealised 1 kHz electric organ discharge (EOD) is shown below for timing comparisons. (C) Diagrams of the underlying EPSP and IPSP dynamics revealed in A. (D) These combine to form a mixed postsynaptic potential (PSP) (thick trace) that peaks at 1–2 ms and is truncated by the IPSP. (E) Idealised firing of two tuberous P units in response to a 1 kHz EOD. (F) The BP cell potential (solid line) that would be recorded at the soma if the EPSP in C acted alone. Note that the output of the BP cell is proportional to the combined firing rates of the two P units (lower trace). (G) The BP cell potential with mixed PSPs generated by the P units. The BP output now signals coincident P unit activity.

1994). It has been proposed that they permit electrosensory feedback to regulate spatial frequency filtering of pyramidal cells (Maler, 1989; Shumway and Maler, 1989).

The axons of GABAergic ovoid cells project bilaterally and climb the length of the basal dendrites of basilar pyramidal cells (Bastian et al., 1993; Maler and Mugnaini, 1994), where they form multiple synapses that generate slow inhibitory postsynaptic potentials (IPSPs) (mainly $GABA_B$ receptors: Berman and Maler, 1998a). Although these cells were hypothesised to be involved in the rejection of common-mode electrosensory inputs (Bastian et al., 1993), the role of slow inhibition in this function is unclear (Berman and Maler, 1998a).

ELL pyramidal cells project topographically to the midbrain (torus semicircularis) and the rhombencephalic nucleus praeminentialis dorsalis (Pd). The Pd is involved in two kinds of electrosensory feedback to the ELL: (1) direct feedback projection to the VML and (2) indirect feedback *via* the EGp projection to the DML.

### *Direct feedback*

Glutamatergic Pd stellate cells project *via* the StF, terminating in the VML on proximal apical dendrites of pyramidal cells and on GABAergic interneurons (Maler et al., 1981b, 1982); both AMPA and NMDA receptors are involved (Berman et al., 1997). The ELL–Pd connections are reciprocal and topographic (Maler et al., 1982). GABAergic Pd bipolar cells also project back to the ELL *via* the StF, but terminate on pyramidal cell somata where they act predominantly *via* $GABA_B$ receptors (Berman and Maler, 1998b). This pathway is spatially diffuse (Maler and Mugnaini, 1994).

### *Indirect feedback*

Several types of Pd cell project to the EGp (Sas and Maler, 1983), but with only a crude rostro-caudal topography. EGp granule cells project glutamatergic parallel fibers (Wang and Maler, 1994) in the medio-lateral axis across the DML of all ELL segments. These fibers terminate, using AMPA and NMDA receptors, on distal apical dendrites of pyramidal cells as well as on various interneurons. In addition, vertical fibers terminate in an orthogonal fashion to the parallel fibers; the vertical fibers probably emanate from EGp eurydendroid cells, are cholinergic and use muscarinic receptors in the ELL molecular layer (Maler, 1979; Maler et al., 1981a; Phan and Maler, 1983).

### *Second messengers*

Recent studies have begun to elucidate the second-messenger cascades within neurons of the ELL. Electroreceptor afferents contain nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d; Turner and Moroz, 1995), a marker for nitric oxide synthase; the location of the target of nitric oxide (i.e. soluble guanylate cyclase; Vincent, 1994) are not known, nor has the function of this second messenger been explored in the ELL. Both protein kinase A (PKA) and protein kinase C (PKC) are present in the ELL and are greatly enriched in its molecular layer (Maler, 1999a,b); it is likely that these second messengers are localised both in afferent fibers of the VML and DML and in pyramidal cells (see Fig. 1). A $Ca^{2+}$/calmodulin-dependent kinase (CaMK2) β-like subunit is found in ELL pyramidal cells and granular interneurons (Maler and Hincke, 1999). It has been proposed (Maler and Hincke, 1999) that PKA in feedback afferents and a CaMK2β-like subunit in pyramidal cells are together involved in the adaptive suppression of redundant input to the ELL (anti-Hebbian plasticity).

The CaMK2α subunit is present in the excitatory direct feedback pathway only (StF and VML); it has been proposed that this second messenger is important for non-linear facilitation of a sensory searchlight (Wang and Maler, 1998; Maler and Hincke, 1999; see below).

Ryanodine receptors are found in pyramidal cells (soma and dendrites) within the PCL but are lacking in deep basilar pyramidal cells (Zupanc et al., 1992). The inositol 1,4,5-trisphosphate ($InsP_3$) receptor is also found in the ELL, but is confined to the somata and proximal dendrites of only the most superficial pyramidal cells within the PCL (Berman et al., 1995). This correlates with the morphology and degree of 'phasicness' of pyramidal cells (Bastian and Courtright, 1991): superficial pyramidal cells ($InsP_3$ + ryanodine receptors) have extensive apical dendrites and are highly phasic; intermediate pyramidal cells (ryanodine receptors only) have modest apical dendrites and are phasic-tonic; deep basilar pyramidal cells (which have no intracellular $Ca^{2+}$ stores) have very small apical dendrites and give tonic responses. The exact connection between the $Ca^{2+}$ stores and temporal processing in pyramidal cells is unknown.

## Electrosensory input to basilar pyramidal cells: coincidence detection

On the basis of the response of electroreceptors to moving objects, Bastian (1981) predicted that convergence of primary afferent inputs and detection of coincident spikes by a higher-order neuron would be required to achieve the behavioral sensitivity of the electrosensory system. In apteronotids, the P type tuberous electroreceptor afferents (P units) fire in phase with the electric organ discharge (EOD) cycles (Hopkins, 1976); there is a range of probabilities of firing per EOD cycle that depends on the amplitude of the EOD (Nelson et al., 1997). This arrangement would permit coincidence detection with the resolution of the EOD (approximately 1 ms), which is consistent with the brief duration of electroreceptor-afferent-evoked excitatory postsynaptic potentials (EPSPs) (see below). Recent quantitative analysis has again suggested the need for coincidence detection in the active electrosense of *Apteronotus leptorhynchus* (Nelson et al., 1997). In recordings of EPSPs *in vitro* (Berman and Maler, 1998a–c), a striking feature of those generated in the basilar pyramidal cell dendrite arborization is their rapid dynamics compared with EPSPs generated by feedback pathways. Electroreceptor-afferent-evoked EPSPs peak at 1–2 ms and decay within 10 ms. In contrast, EPSPs

evoked from StF or parallel fibers peak at 4–6 ms and last more than 10 ms. Such rapid electroreceptor afferent postsynaptic potential (PSP) dynamics may be essential for the conservation of timing information for the detection of coincident electrosensory inputs; this may be similar to the role of fast EPSPs and coincidence detection in the auditory system (for a review, see Trussel, 1997).

The electrosensory afferent EPSPs are generated far from the cell body on the basal arborization (Fig. 2A). Theoretically, the cable properties of the basilar dendrite would temporally smear the EPSP and reduce its amplitude by the time it reached the soma, thus drastically low-pass-filtering the electrosensory signal and removing much of its high-frequency information. Two mechanisms may operate to alleviate this problem to allow fine-grained resolution of timing information in the afferent stream: inhibitory control of EPSP duration and voltage-gated dendritic channels. We have found evidence for the first mechanism (Berman and Maler, 1998a). Tuberous-afferent-evoked EPSPs in basal pyramidal cells are appreciably shortened by $GABA_A$ IPSPs, although they do not affect its amplitude; these IPSPs are due to the type 2 granular interneuron (Maler, 1979; Maler and Mugnaini, 1994) and prevent temporal smearing of the phase-locked P cell input.

Not only will the IPSP prevent the effects of a single presynaptic spike from lingering too long, but it will also depress the effects of a presynaptic spike that occurs within the IPSP window. For instance, if a presynaptic spike arrived 2–8 EOD cycles after the EPSP peak in Fig. 2B, its effect would be inhibited by the IPSP. The IPSP therefore acts as a high-pass filter or coincidence detector; spikes arriving on the same or the next EOD cycle will summate, whereas a spike arriving later will be inhibited. A stylised impression of this mechanism of coincidence detection is shown in Fig. 2. Without inhibition, the spike streams from two primary afferents summate and drive the cell (BP output) at a rate proportional to the rate of the incoming signal. With inhibition, only coincident spikes (within 1–2 EOD cycles) summate; IPSP inhibition and the faster EPSP relaxation prevent non-coincident spikes from summating. Interestingly, GABA-mediated inhibition has already been shown to enhance coincidence detection in this way in the auditory brainstem of the chick (Funabiki et al., 1998). Note that the cut-off frequency will be determined by the dynamics of the IPSP of the granule cell, which may itself be controlled (perhaps by GABAergic polymorphic cells, Maler and Mugnaini, 1994, see above).

In the ELL, this coincidence detection mechanism may be enhanced by the presence of active $Na^+$ channel activity on the dendrites that would amplify the larger EPSPs non-linearly and boost their rise time (Haag and Borst, 1996; Magee and Johnston, 1995). Voltage-dependent channels have been shown to boost the high-frequency component of synaptic inputs in the visual system of the fly (Haag and Borst, 1996) and in the electrosensory system of fish (midbrain: Fortune and Rose, 1997a,b). There is morphological evidence for $Na^+$ channels on basal dendrites (Turner et al., 1994), suggesting the possibility of active boosting of high-frequency components of the EPSP, although direct evidence for this mechanism is not yet available.

## The direct feedback pathway: adaptations for a sensory searchlight

As first suggested by Bratton and Bastian (1990), the direct feedback pathway to the ELL has many of the features initially proposed by Crick (1984) to underlie a cortico-thalamic sensory ‘searchlight’: (1) a subset of ELL–Pd connections is reciprocal, topographic and excitatory, thus forming a positive feedback loop (Sas and Maler, 1983, 1987); (2) the Pd stellate cells that project to the VML have receptive fields larger than those of ELL pyramidal cells, with a high gain appropriate to this role (Bratton and Bastian, 1990); (3) the inhibitory direct feedback projection emanating from Pd bipolar cells is topographically diffuse (Maler and Mugnaini, 1994), again consistent with Crick’s view of the role of the thalamic reticular nucleus. A searchlight mechanism may also require a non-linear element to amplify signals with respect to noise (Crick, 1984). We present below recent evidence for four types of non-linearity in the direct feedback pathway to the ELL: (1) voltage-dependent EPSPs; (2) dendritic spike bursts; (3) voltage-dependent inhibition (see Fig. 3); and (4) frequency-dependent synaptic facilitation (see Fig. 4).

### *Voltage-dependent EPSPs*

Stimulation of the StF in an ELL slice demonstrated that VML input to pyramidal cells has both AMPA and NMDA receptor components. The NMDA receptor contribution has a relatively fast onset so that it contributes to the peak of the EPSP. In comparison with primary-afferent-evoked EPSPs (see above), the StF-evoked EPSP has a slow time course (peak approximately 6 ms, duration more than 10 ms; Berman and Maler, 1998b; Berman et al., 1997). The StF-evoked EPSP is highly voltage-dependent both because of its NMDA component (Fig. 3C) and because of the activation of a prominent somatic persistent $Na^+$ current (Fig. 3D, $I_{NaP}$; Berman et al., 1997; Mathieson and Maler, 1988; Turner et al., 1994). This led Berman et al. (1997) to propose that temporal coincidence of electrosensory and direct excitatory feedback input to pyramidal cells would cause a voltage-dependent increase in feedback EPSP amplitude and thus non-linearly augment the response to the electrosensory input (Fig. 3E).

### *Dendritic spike bursts*

We have previously shown that $Na^+$ channels are found on the proximal apical dendrites of pyramidal cells and can support active propagation of action potentials (Fig. 3A; Turner et al., 1994). Dendritic spikes are passively propagated back to the soma, where they produce depolarising afterpotentials (DAPs); depending on the activity of $K^+$ channels, DAPs can trigger action potentials resulting in high-frequency spike bursts (Turner et al., 1994). Gabbiani et al.

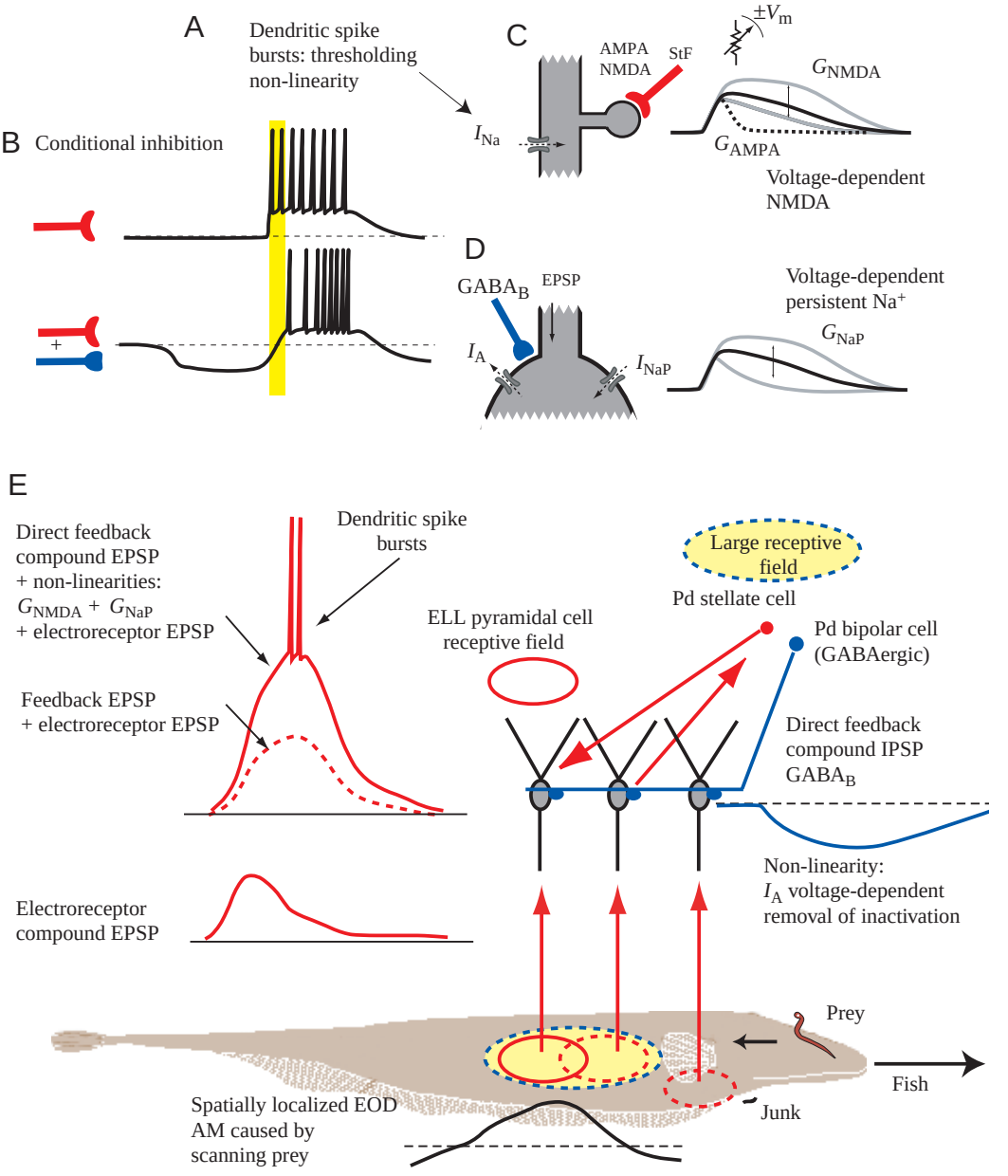


Fig. 3. Non-linearities in the direct descending pathway and the searchlight hypothesis. (A–D) Diagram of various non-linearities and their effects. (A) The $I_{Na}$ current on the apical dendrites of pyramidal cells produces dendritic spike bursts (Turner et al., 1994). These may be responsible for thresholding non-linearities implicated in feature detection (Gabbiani et al., 1996). (B) $GABA_B$ hyperpolarising inhibition at the soma acts as conditional inhibition by removing inactivation of $I_A$-like currents, thereby retarding spiking in the face of excitatory inputs (Berman and Maler, 1998b). (C) The voltage-dependence of *N*-methyl-D-aspartate (NMDA) receptor activation produces non-linear excitatory postsynaptic potential (EPSP) amplification. (D) The voltage-dependence of $G_{NaP}$ ($I_{NaP}$, persistent $Na^+$ current/conductance) non-linearly amplifies EPSPs. (E) The contribution of these non-linearities to the searchlight hypothesis. As a fish scans, a prey item will move over the small receptive fields (RFs) of pyramidal cells (dashed red circles). The first pyramidal cell to be excited drives a stellate cell in the nucleus praeminentialis dorsalis (Pd) (with a larger RF than that of the pyramidal cell), which in turn projects back to electrosensory lateral line lobe (ELL) pyramidal cells. Collateral activation of Pd γ-aminobutyric acid (GABA)-ergic bipolar cells provides diffuse inhibitory feedback to the ELL. Only cells that then receive coincident descending voltage-dependent excitation (NMDA, $I_{NaP}$ and $I_{Na}$) and stimulus-driven electroreceptor excitation will respond vigorously to the presence of the prey (cell with solid red circle RF) because of the non-linear increase in the feedback EPSPs. The red traces indicate the schematic impact of these non-linearities on the cell response. Lower trace: electroreceptor-generated compound EPSP alone. Dashed trace: electroreceptor EPSP combined with coincident excitatory feedback input. Trace with spikes: electroreceptor EPSPs combined with excitatory feedback and non-linearities (NMDA, $I_{NaP}$ and dendritic spike bursts). StF, stratum fibrosum; AM, amplitude modulation; IPSP, inhibitory postsynaptic potential; $V_m$, membrane potential; EOD, electric organ discharge.

(1996; see also Metzner et al., 1998) have suggested that these spike bursts are a thresholding mechanism that allows pyramidal cells to detect temporal features of electrosensory input (Fig. 3E). The voltage-dependence of the direct feedback EPSPs and the dendritic spike burst mechanism probably form a closely linked cascade, but a better understanding will require more rigorous computational and experimental analysis.

### *Voltage-dependent inhibition*

The direct feedback inhibitory input acts primarily *via* $GABA_B$ receptors (IPSP reversal potential −90 mV, duration more than 800 ms; Berman and Maler, 1998c). This inhibition is also highly voltage- and time-dependent: it is far more effective at suppressing the spike response to weak than to strong depolarisations. The underlying mechanism appears to be that the large hyperpolarisation produced by stimulating Pd

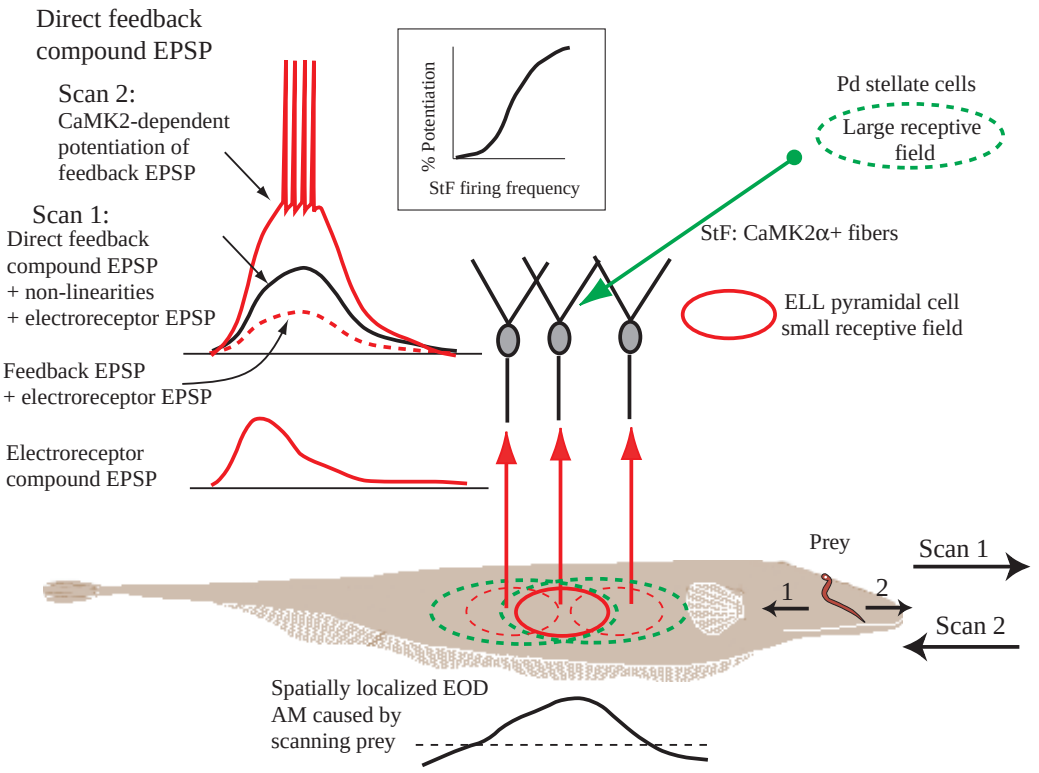


Fig. 4. Role of $Ca^{2+}$/calmodulin-dependent kinase (CaMK2) in the searchlight mechanism. Repeated scanning by a fish activates CaMK2-dependent potentiation (stratum fibrosum, StF, fibers contain CaMK2α). Repeated activation of the pathway by the stimulus (prey) recruits CaMK2 activity, which then potentiates that pathway. The traces show the schematic isolation of various inputs. Scan 1: bottom red trace, electroreceptor input alone; dashed red trace, feedback EPSP with electroreceptor input. Black trace: feedback excitatory postsynaptic potential (EPSP) with electroreceptor input and *N*-methyl-D-aspartate (NMDA) and $I_{NaP}$ non-linearities. Scan 2: all previous conditions plus CaMK2-dependent potentiation of feedback EPSPs. The inset shows that threshold-like behavior of CaMK2 autophosphorylation produces non-linear dependence of potentiation on presynaptic firing frequency. AM, amplitude modulation; Pd, nucleus praeminentialis dorsalis; ELL, electrosensory lateral line lobe; EOD, electric organ discharge.

bipolar cell axons in the StF removes inactivation from an $I_A$-like $K^+$ channel; the subsequent activation of this $K^+$ channel by depolarisation (EPSPs) slows the depolarisation, preventing or delaying spiking (conditional inhibition, Fig. 3B). Strong depolarisations rapidly inactivate the $I_A$ channel and permit spiking; steady-state depolarisation of the pyramidal cell also causes inactivation of $I_A$. This non-linearity will act in concert with those described above to filter out weak electrosensory inputs but allow strong inputs to be detected with high gain.

### *Frequency-dependent synaptic facilitation*

The direct excitatory feedback pathway is characterised by prominent post-tetanic potentiation (PTP; Bastian, 1996b; Wang and Maler, 1997, 1998) that can increase the evoked EPSP by more than 200 %. The VML is highly enriched in CaMK2α, and this kinase is essential for PTP at these synapses (but not in the DML; Wang and Maler, 1998). The ability of CaMK2α to enhance its activity by autophosphorylation (De Konnick and Schulman, 1998; Hanson et al., 1994; Hanson and Schulman, 1992) causes this kinase to show a non-linear dependence on frequency: a switch-like behavior (Hanson et al., 1994; Miller and Kennedy, 1986). We have shown that PTP of StF fibers is dependent on the frequency of stimulation (PTP occurs with 100 Hz, but not with 50 Hz stimulation; Wang and Maler, 1997), and this led to the hypothesis (Wang and Maler, 1998) that CaMK2α was responsible for a frequency-dependent switch that turned on potentiation of the direct feedback pathway. This switch might operate during the scanning movements used by these fish during foraging (Fig. 4): if the first pass across the food object (Fig. 4, scan 1) caused strong activation of StF fibers (>100 Hz), they would potentiate and therefore optimise the detection of the object on the second scan (Fig. 4, scan 2) *via* the first two non-linear mechanisms described above.

There has been a resurgence of interest in cortico-thalamic pathways, and several recent papers have proposed that this feedback also subserves stimulus-specific enhancement (Ergenzinger et al., 1998; Rauschecker, 1998; Sillito et al., 1994; Yan and Suga, 1996, 1998) in a manner similar to Crick's original searchlight formulation. It will be interesting to compare the underlying cellular mechanisms of the putative sensory searchlight in these very different neural systems.

## The indirect feedback pathway: adaptive spatio-temporal filtering

The crude topography and diffuse projection characteristics of the indirect feedback pathway (Sas and Maler, 1987), together with the poor response of Pd multipolar cells to moving electrosensory stimuli (they respond tonically to direct current EOD changes; Bastian and Bratton, 1990), have suggested an alternative role for this pathway compared with the direct projection's putative searchlight function. Bastian (1986a,b) and Shumway and Maler (1989) found that the pathway is likely to mediate an adaptive gain control phenomenon whereby ELL pyramidal cells respond with a

change in firing rate that is relatively insensitive to global changes in the EOD amplitude. Removal of the EGp input to the ELL (Bastian, 1986a,b) or antagonism of $GABA_A$ receptors in the ELL (Shumway and Maler, 1989) disrupted the response constancy, suggesting that control of molecular layer inhibition by the EGp input was responsible for gain control.

More recently, it has been shown that the PF pyramidal cell dendritic input displays anti-Hebbian plasticity; this provides an adaptive mechanism whereby pyramidal cell responses remain within an optimum range despite naturally recurring background changes in EOD amplitude (Bastian, 1996a,b, 1998).

The PF pyramidal cell EPSP consists of an AMPA and an NMDA receptor component. While both AMPA and NMDA components contribute to the peak of the EPSP (peaks at 4–6 ms), the NMDA component is longer-lasting and contributes to the slow decay of the EPSP (see Berman and Maler, 1998c; N. J. Berman and L. Maler, unpublished observations). There is also a substantial somatic/proximal dendrite $I_{NaP}$ contribution (approximately 50 %) to the EPSP. These inward currents are closely controlled by PF-activated inhibition.

### *Inhibitory control of indirect feedback*

The PF disynaptically inhibits pyramidal cells *via* stellate and vml cells. GABAergic IPSPs activated by the indirect feedback pathway differ in their temporal dynamics according to their target site (Fig. 5A,B). Selective application of $GABA_A$ antagonists (see Berman and Maler, 1998c) revealed that PF-recruited inhibition of distal dendrites (i.e. from nearby stellate cells) controlled mainly the peak amplitude of PF EPSPs (Fig. 5A–C), whereas inhibition that terminated on or near the soma (i.e. from vml cells) controlled mainly the slow

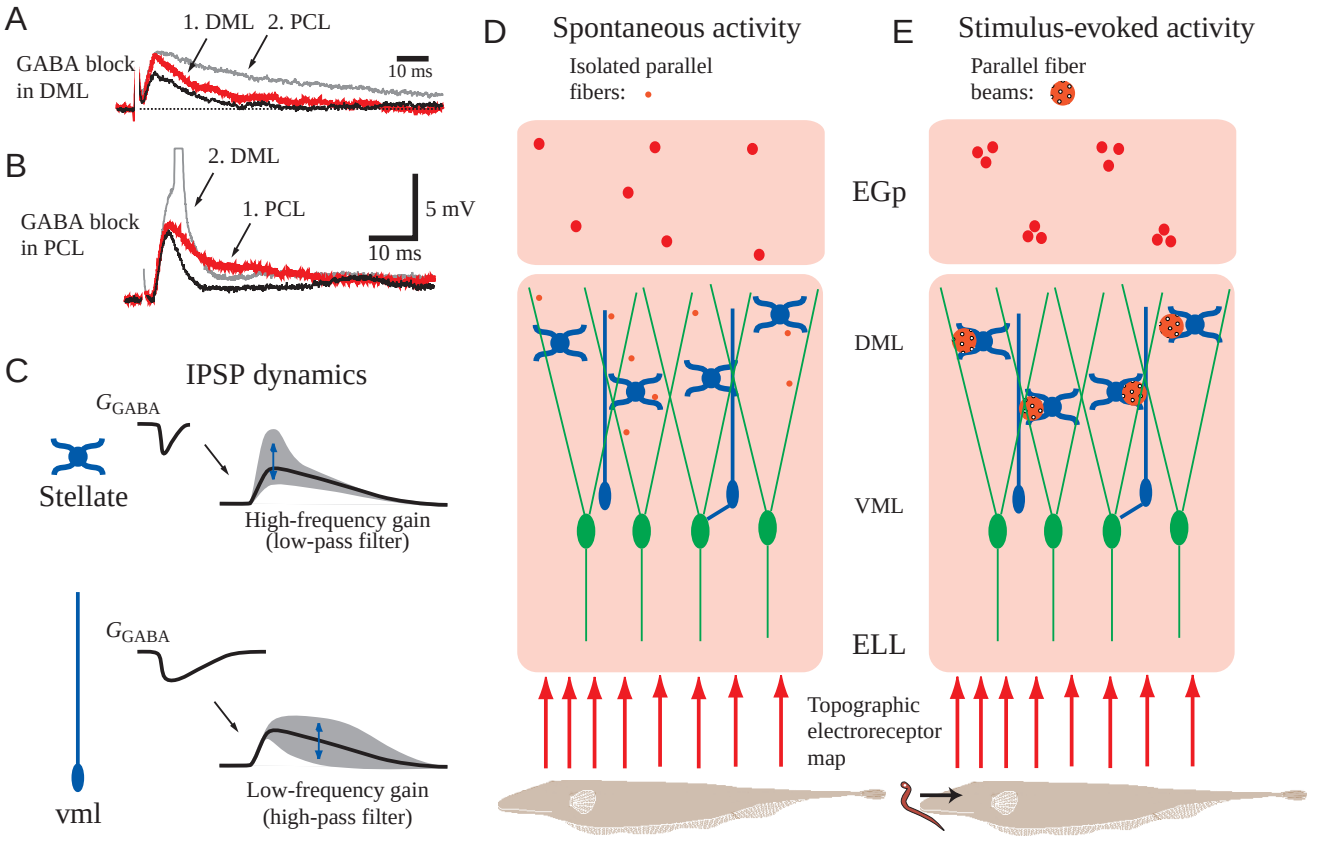


Fig. 5. Spatial and temporal features of the indirect feedback pathway (parallel fibers, PFs). (A) PF excitatory postsynaptic potentials (EPSPs) recorded *in vitro* (Berman and Maler, 1998c). The control EPSP (black trace) peak is increased by the application of a $GABA_A$ antagonist to the dorsal molecular layer (DML) region (1, DML, red trace). Subsequent pyramidal region applications (2, PCL, grey trace) increase the slow decay phase of the EPSP. (B) Reversed application of the $GABA_A$ antagonist (PCL first, then DML) similarly increases the slow decay phase (1, PCL) and then peak (2, DML) EPSP amplitude. (C) Diagram of stellate and ventral molecular layer (vml) cell inhibitory postsynaptic potential (IPSP) dynamics. Stellate cell γ-aminobutyric acid conductance ($G_{GABA}$) modulates EPSP peak amplitude causing low-pass filtering, whereas vml cell $G_{GABA}$ modulates EPSP decay causing high-pass filtering. (D,E) Hypothesis: beams *versus* diffuse activation of PFs. Diagrams show the fish body and its projection onto the electrosensory lateral line lobe (ELL) map and the overlying eminentia granularis pars posterior (EGp). (D) Spontaneous activity of EGp granule cells projects onto the ELL dorsal molecular layer (DML) from isolated fibers with low levels of activity. VML, ventral molecular layer. (E) Stimulus-evoked activity excites clusters of EGp granule cells, which then project beams of active fibers in the DML. These strongly activate stellate cells in their path.

decay phase of the EPSP. When PFs are stimulated at high rates (100 Hz activation of the PFs; Berman and Maler, 1998c), stellate cells modulate the amplitude of individual EPSPs, whereas vml cells modulate the low-frequency component of the inputs (the summating depolarising wave). We hypothesise that these timing differences determine the frequency-dependent gain control of these inhibitory pathways (Fig. 5C); stellate cells act as low-pass filters (control the gain of high-frequency inputs), while vml cells act as high-pass filters (control the gain of low-frequency inputs). Interestingly, these timing differences are the opposite of those seen in cortical cells, where distal inhibition lasts longer than proximal inhibition (Pearce, 1993). In ELL pyramidal cells, the longer proximal inhibition may be tuned to control slow inward currents activated by StF fibers, i.e. NMDA EPSPs and $I_{NaP}$ currents, or slower summed EPSPs from distal inputs. Not only will descending feedback exert complex controls on the tuning properties of pyramidal cells *via* these interneurons, but plasticity in the descending input to molecular layer interneurons (Bastian, 1998) may further influence the dynamics of feedback sensory filtering properties.

### Beams *versus* isolated activity

Stimulation of the PF pathway *in vitro* evoked inhibition even with very low stimulus intensities. The inhibition was revealed by an increase in EPSP amplitude following $GABA_A$ antagonism. This means that stellate cells can be driven past their firing threshold by the same intensity of stimulus that evokes a barely discernible EPSP in the pyramidal cell. While stellate cells may have a steeper activation function than pyramidal cells (as suggested by Maler and Mugnaini, 1994), another explanation based on morphological evidence considers the dendritic span of stellate and pyramidal cells. Stellate cells have small compact dendritic trees, whereas pyramidal cells have large apical dendritic trees that span the full extent of the molecular layer. The artificial nature of *in vitro* stimulation would tend to activate a beam of parallel fibers in the vicinity of the stimulating electrode. Any stellate cell that was encompassed by this beam would be strongly influenced by its activity. Conversely, a pyramidal cell in the field of termination would have only a fraction of its full dendritic tree sampling the beam's activity. Therefore, on purely morphological grounds, we would expect stellate cells to have a lower threshold of activation than pyramidal cells.

Although there is no evidence for beams of fiber activity *in vivo*, the hypothesis may be relevant to the studies of Bastian using natural stimuli. Bastian (1986a) found that removal of PF input (EGp lesions or anesthetic block) increased stimulus-driven responses, suggesting that inhibitory cells are strongly driven under natural conditions. However, he also found that the spontaneous activity of pyramidal cells decreased significantly after EGp lesions. These apparently contradictory results could be reconciled if stimulus-driven activity were spatially coherent (i.e. beams) but spontaneous activity were spatially diffuse. In the latter case, stellate cells would be largely unaffected by the experimental removal of this diffuse fiber activity, whereas the pyramidal cell apical dendritic tree, which integrates PF activity over a large area, would experience a substantial decrease in excitatory input (Fig. 5). This would lead to a net excitatory effect during non-stimulus-driven conditions, and a net inhibitory effect during stimulus-driven conditions.

## Conclusions

The intensive study of an *in vitro* preparation of the ELL has provided some cellular correlates of certain functions of this structure already suggested by *in vivo* experiments, notably the adaptations of synaptic transmission of electrosensory afferents to coincidence detection and temporal processing. These new discoveries have, however, also demonstrated unexpected subtleties in the cellular physiology of ELL neurons, the consequences of which will require both computational analyses and more refined *in vivo* studies. The ELL is the first and only target of electroreceptors but its major input is from massive feedback pathways. Further, these pathways are associated with multifunctional serine/threonine kinases and are capable of several forms of plasticity on time scales ranging from milliseconds to hours. Clearly, the computations of the ELL cannot be envisaged as static but rather as adapting so as to optimize, in real time, the extraction of electrosensory information from a continuously changing environment. Although the plasticity of ELL function will make it far more difficult to study, it is also likely to lead to insights into sensory processing that may be readily generalized to other sensory systems.

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