SYMPOSIUM REPORT

Synaptic physiology of direction selectivity in the retina

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Detection of the direction of image movement is accomplished first in the retina by an elegant neuronal circuit, which integrates multiple levels of spatially asymmetric synaptic interactions among subsets of bipolar, amacrine and ganglion cells. Central to these interactions is the asymmetric GABAergic inhibition exerted by the starburst amacrine cell (SAC), a cholinergic and GABAergic interneuron with a radially symmetric dendritic tree. SACs make reciprocal GABAergic synapses on each other to create a direct inhibitory receptive field surround, which suppresses the response of each SAC to centripetal image movement. Each radially projecting branch of a SAC responds to image movement with a centrifugal bias and, through directionally asymmetric synaptic connections with the dendrites of direction-selective ganglion cells (DSGCs), exerts a spatially offset inhibition that vetoes the response of DSGCs to image movement in a specific (null) direction. Recent physiological studies have greatly advanced our understanding of the mechanism of direction selectivity and also revealed a new level of complexity that remains to be understood.

The ability of the retina to detect the direction of image movement was discovered in the early 1960s by Barlow, Hill and Levick in a series of classic studies that showed that certain types of retinal output neurons respond vigorously to an image moving across their receptive fields in a particular (preferred) direction, but give little or no response to the same image moving in the reverse (null) direction (Barlow & Hill, 1963; Barlow *et al.* 1964; Barlow & Levick, 1965). The main synaptic circuit that performs this fundamental computation is now believed to reside in the inner plexiform layer (IPL) of the retina and consist of only a handful of cell types. This circuit is functionally well defined and experimentally approachable, making it an ideal model system for understanding neuronal inter-action and network computation. Indeed, the mechanism underlying direction selectivity has been under intense investigation for the past four decades (Taylor & Vaney, 2003; Demb, 2007; Fried & Masland, 2007). However, even in this seemingly simple system (as compared to many other brain areas), the nature of cellular and synaptic interactions is far from simple. The wiring diagrams and signalling codes embedded in the direction-selective circuit have been enigmatic and have only recently begun to reveal some key mechanistic details.

Two types of DSGCs have been found in the rabbit retina (Barlow *et al.* 1964), the On and On–Off types, which can be further classified into three and four subtypes, respectively, based on their preferred directions in the retina (Oyster & Barlow, 1967; Oyster *et al.* 1972). DSGCs project to both the midbrain and the dorsal lateral geniculate nucleus of the thalamus (Buhl & Peichl, 1986; Pu & Amthor, 1990*a,b*; Dacey *et al.* 2003) and are believed to be involved in multiple functions, including the control of extraocular muscles for eye movement and optokinetic nystagmus (Oyster & Barlow, 1967; Oyster *et al.* 1972). Because most of the mechanistic properties of DSGCs are derived from On–Off DSGCs, which are more numerous than On DSGCs, the synaptic physiology discussed below is based mainly on studies of On-Off DSGCs, which will be referred to simply as DSGCs henceforth.

Synaptic physiology of direction-selective ganglion cells

Barlow & Levick (1965) suggested that the direction selectivity of ganglion cells is built from sequence-discriminating subunits. The primary mechanism for this discrimination was thought to result from a spatially offset lateral inhibition, which vetoes responses to sequences corresponding to stimulus movement in the null direction. Pharmacological experiments subsequently found that GABA receptor antagonists block direction selectivity by bringing out strong responses of DSGCs to stimulus

movement in the null direction, suggesting that the spatially offset inhibition is mediated by GABA (Wyatt & Day, 1976; Caldwell *et al.* 1978); however, the site of this critical GABAergic inhibition had remained unclear for a long time. Direct measurement of the inhibitory input to DSGCs became possible when patch-clamp recordings were successfully applied to DSGCs in the whole-mount retina in the early 2000s (Taylor *et al.* 2000; Borg-Graham, 2001). Fried *et al.* (2002) subsequently concluded that (1) the direct inhibitory current input to a DSGS is larger for stimulus movement in the null direction than that in the preferred direction; (2) the inhibitory input precedes the excitatory input when the stimulus moves in the null, but not in the preferred direction; (3) the spatial extent of the inhibitory current input is offset from the DSGC dendritic field toward the null direction. The excitatory current input to a DSGC is also directionally asymmetric: larger for preferred direction movement than for null direction movement; however, the spatial extent of the excitatory input roughly coincides with the DSGC dendritic field (Fried *et al.* 2002; Taylor & Vaney, 2002). These findings establish that the synaptic inputs to a DSGC are already directionally asymmetric.

GABAergic inputs from starburst amacrine cells to direction selective ganglion cells

The dendrites of DSGCs costratify with those of cholinergic (starburst) amacrine cells, which exist as two mirror-symmetric populations across the IPL (Masland & Mills, 1979; Vaney *et al.* 1981; Famiglietti, 1992). SACs have four to five primary dendrites, each branching out regularly into secondary and tertiary processes, with numerous varicosities imbedded in the distal dendritic zone (Famiglietti, 1983; Tauchi & Masland, 1984; Vaney, 1984). The dendritic tree emanates from the soma with a nearly perfect radial symmetry, rendering the cell a 'starburst' appearance and, hence, its popular name (Famiglietti, 1983). The dendrites of DSGCs also cofasciculate with starburst dendrites (Famiglietti, 1992; Vaney & Pow, 2000; Dong *et al.* 2004), suggesting intimate synaptic interactions between the two cell types, as evidenced by the electron-microscopic findings of direct synapses between them (Dacheux *et al.* 2003). Because SACs contain and release not only ACh, but also GABA (Brecha *et al.* 1988; Vaney & Young, 1988; O'Malley & Masland, 1989), they have long been proposed as a likely source of the critical lateral inhibition to DSGCs (Vaney, 1990; Borg-Graham & Grzywacz, 1992).

Functional evidence for a key role of SACs in direction selectivity came first from the findings that immunotoxin and neurotoxin ablation of SACs resulted in an apparent elimination of direction-selective responses in the retina, as well as a loss of optokinetic nystagmus (Yoshida *et al.* 2001; Amthor *et al.* 2002). Direct detection of a GABAergic
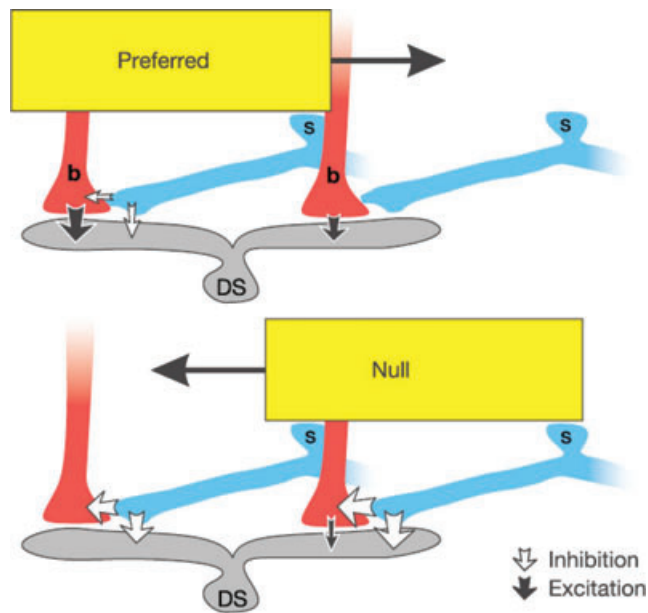
input from SACs to DSGCs was accomplished first by Fried *et al.* (2002), who recorded simultaneously from pairs of SACs and DSGCs in the whole-mount rabbit retina and showed that DSGCs receive inhibitory synaptic inputs from SACs located on their null, but not their preferred, side. This important result, which was initially derived from a small number of paired recordings, was subsequently confirmed by many paired recordings (Lee *et al.* 2006), and it establishes that SACs exert a spatially offset GABAergic inhibition directly on DSGCs via directionally asymmetric hardwiring between SACs and DSGCs. This landmark finding forms the basis of the current model of direction selectivity of DSGCs (Fried *et al.* 2002; Taylor & Vaney, 2003) (Fig. 1). However, for this asymmetric wiring model of direction selectivity to work, the release of GABA from each dendritic branch of a SAC must also be directionally selective, as implicated by the finding that the inhibitory input to a DSGC is greatly reduced during either preferred-direction motion or two-spot flashes that simulate preferred-direction motion (Fried *et al.* 2002, 2005; Taylor & Vaney, 2002) (Fig. 2). Otherwise, SAC dendrites that make GABAergic synapses onto a DSGC from the null side will still suppress the DSGC when a light stimulus moves in the preferred direction, even though such a GABAergic inhibition is not expected to lead the glutamatergic excitation. Thus, a key component of the direction selective mechanism must reside upstream from DSGCs in SACs.

Direction-selective GABA release from SACs

At the first glance, it may seem paradoxical that a morphologically symmetric cell like the starburst would produce the strong spatial asymmetry required for direction-selective GABA release. However, despite on the radial symmetry of starburst dendrites, there is a profound polar asymmetry in synaptic organization along each dendrite. Input synapses on starburst dendrites distribute roughly uniformly along the entire dendritic length, whereas output synapses are localized in the distal varicose zones, where synaptic vesicles are concentrated (Famiglietti, 1991). These distal varicose zones are believed to be electrotonically semi-isolated, due to the thin diameter of the dendrites and the heavy expression of KV3 voltage-gated potassium channels on the proximal dendrites (Miller & Bloomfield, 1983; Ozaita *et al.* 2004). This polar asymmetry in input–output relation, combined with the short electrotonic length of the dendrites, is thought to enable the distal dendrites to process directional signals independently. Computational models based on these properties predict that centrifugal stimulus movement activates the distal dendrites more strongly than does centripetal movement (Poznanski, 1992; Borg-Graham, 2001; Tukker *et al.* 2004). In a groundbreaking Ca^{2+}-imaging experiment, Euler *et al.*

(2002) used two-photon microscopy to show that distal starburst dendrites indeed respond to spot illumination with intracellular Ca^{2+} transients that are restricted to distal dendrites, and that these local Ca^{2+} responses tend to be directionally selective: stronger for centrifugal than for centripetal stimulus movement (Euler *et al.* 2002). Fourier analysis of somatic voltage responses of SACs and compartmental modelling further predict that non-linear interactions between voltage-gated Ca^{2+} channel activation and a voltage gradient along the dendrites can produce directional asymmetry in the distal dendrites without synaptic inhibition (Hausselt *et al.* 2007).
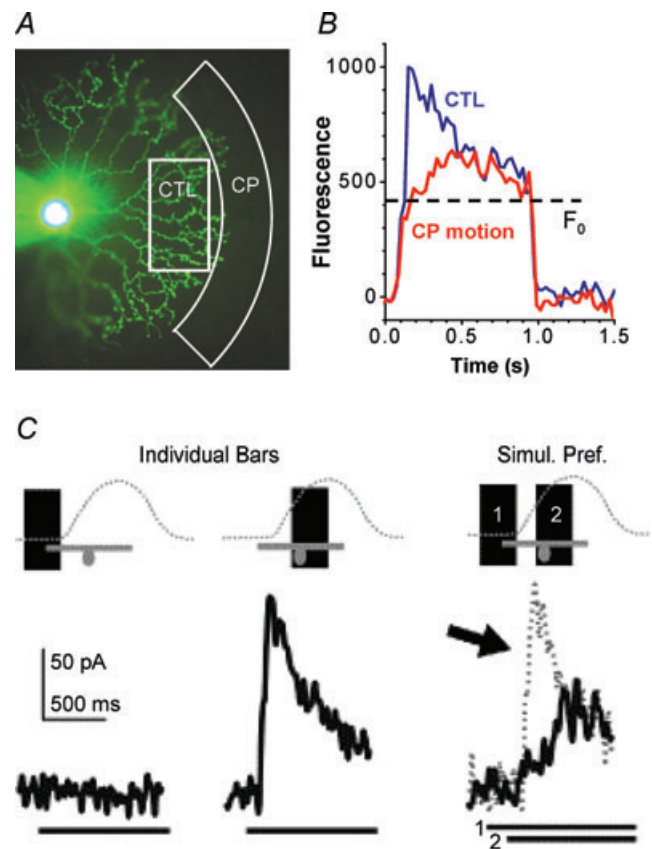
However, while intrinsic electric properties of SACs can produce a centrifugally biased response to image movement, they are not sufficient to account fully for the direction-selective responses observed in distal starburst dendrites, especially when the stimulus moves centripetally from outside the starburst dendritic field.

Two-spot apparent motion experiments show that direction selectivity in distal starburst dendrites involves both centrifugal excitation and centripetal inhibition (Lee & Zhou, 2006). It is important to note that stationary spot illumination, without centrifugal motion, already evokes a significant Ca^{2+} response at distal starburst dendrites (Euler *et al.* 2002; Lee & Zhou, 2006), which is suppressed by two-spot stimulation simulating centripetal motion (Lee & Zhou, 2006) (Fig. 2). Similarly, a stationary spot

Figure 1. A current model of direction selectivity in DSGCs based on asymmetric wiring between SACs and DSGCs
The processes of starburst cells ('s', blue) that point in the null direction provide inhibition to DS cell dendrites ('DS', grey). Starburst processes respond best to movement away from the cell body, which makes the inhibitory input delivered to DS cells larger for movement in the null direction (bottom panel) than for movement in the preferred direction (top panel). An additional inhibition acts presynaptically to reduce excitation for null direction movement. Although this presynaptic inhibition is depicted as coming from starburst cells, the existence of another type of cell cannot be ruled out. The excitatory input to DS cells probably comes from bipolar cells ('b', red) and may also have a cholinergic component from other starburst cells. For movement in the null direction, the inhibitory input reaches each subregion of the DS cell ahead of the stimulus edge and therefore before excitation. For movement in the preferred direction, inhibition lags behind excitation. Reproduced from Fried *et al.* 2002, *Nature* 420, 411–414; reprinted by permission from Macmillan Publishers Ltd.

Figure 2. Directional suppression of calcium responses in SAC distal dendrites and of inhibitory inputs to DSGCs by two-flash apparent motion
A, photomicrograph of a SAC under whole-cell current clamp with a pipette filled with Oregon Green 488 BAPTA-1. The rectangle (marked CTL) indicates the area in which a control light is flashed both to elicit a light response and to measure the Ca^{2+} response from the dendrites. Simulated centripetal motion is generated by flashing another light in the surround area (CP) 200 ms prior to the onset of the control (CTL) flash. Scale bar: 50 μm. *B*, the average fluorescence response of eight varicosities in area CTL to a CTL flash (blue trace) is strongly suppressed by a preceding CP flash that simulates a centripetal motion (red trace). F_O indicates the basal fluorescence intensity immediately prior to the light response. *C*, inhibitory synaptic inputs to a DSGC in response to flashed bars (100 × 300 μm). Simulated preferred-direction motion greatly suppresses the inhibitory input to the DSGC, showing a similarity to the suppression of the calcium response in SAC dendrites by CP motion. Adapted from from Lee & Zhou (2006), *Neuron* 51, 787–799 and from Fried *et al.* (2005), *Neuron* 46, 117–127, with permission from Elsevier.

illumination readily evokes a large GABAergic input to preferred direction motion (Fried *et al.* 2005), which can be suppressed by two-spot stimulation simulating preferred direction motion (Fried *et al.* 2005). These results suggest that a spatially offset lateral inhibition is critical and represents a common mechanism of direction selectivity in both DSGCs and SACs.

How does the asymmetric inhibition to a SAC come about? An important clue to the underlying synaptic circuitry comes from dual patch clamp recordings from neighbouring starburst cells (Zheng *et al.* 2004; Lee & Zhou, 2006). Overlapping SACs, including those that contact each other only by their distal dendrites, mutually inhibit each other via reciprocal, GABA$_A$ receptor-mediated synapses. The spatial extent of this lateral inhibition matches closely that of the direct inhibitory receptive field surround, which is also mediated mainly by GABA$_A$ receptors. The characteristically prolonged nature of the GABAergic transmission between SACs is also consistent with the kinetics of the surround inhibition to SACs. Together, these results indicate that the synaptic mechanism for direction selectivity in distal starburst dendrites is built primarily from a classic centre–surround receptive field, with the centre receiving glutamatergic inputs from bipolar cells, and the surround receiving a direct GABAergic input from neighbouring SACs (Fig. 3). Such a concentric receptive field structure would normally be directionally symmetric for a neuron that makes the output decision at the soma or axon hillock. However, because the output decisions in a SAC are made independently in individual distal dendrites, the concentric receptive field structure produces a profound directional asymmetry at distal dendrites, where synaptic inputs from the centre (centrifugal direction) are dominated by glutamatergic excitation from bipolar cells, but synaptic inputs from the surround (centripetal direction) are mediated predominantly by GABAergic inhibition. This synaptic mechanism, together with a centrifugal facilitation produced, in part, by intrinsic properties of SACs, would produce robust direction-selective GABA release from SACs (Lee & Zhou, 2006).

Summary and concluding remarks

The direction-selective circuit so far identified consists primarily of DSGCs, SACs and bipolar cells. At the DSGC level, direction selectivity is shaped largely by a spatially offset inhibition from SACs, whose distal dendrites both release GABA asymmetrically and synapse on DSGCs asymmetrically. Direction selectivity in DSGCs is further sharpened by directionally asymmetric excitatory inputs and by a postsynaptic mechanism, which involves local signal processing and spike generation in DSGC dendrites (Oesch *et al.* 2005). At the SAC level, direction selectivity is formed in the distal starburst dendrites by a profound polar asymmetry between centrifugal excitation and centripetal inhibition. GABAergic inhibition, mediated largely by reciprocal inhibition between SACs, plays a key role in suppressing SAC responses to centripetal stimulus motion. However, the nature of GABAergic and glycinergic inputs during centrifugal motion is currently unclear. A model based on a differential expression of two different chloride transporters proposes that the excitability of GABAergic input changes as the image moves centrifugally or centripetally along a SAC dendrite (Gavrikov *et al.* 2003, 2006). Further experiments are required to test directly the predictions of this model. In addition to synaptic interactions, intrinsic cellular properties also play an important role in shaping direction selectivity in SAC dendrites, predominantly by contributing to centrifugal facilitation (Hausselt *et al.* 2007). At the bipolar cell level, direction-selective release of glutamate is strongly implicated by the asymmetric excitatory inputs received by DSGCs, but the underlying mechanism is unclear. A key issue is whether local
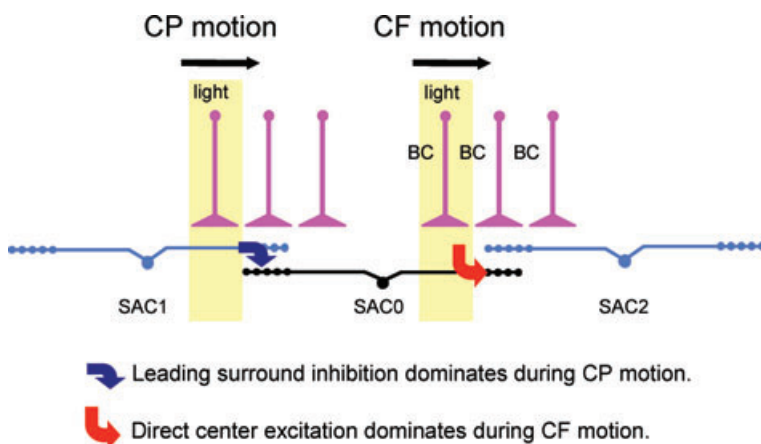
Figure 3. A synaptic model of direction selectivity at the distal processes of SACs
The concentric centre–surround receptive field of a SAC (SCA0) is shaped largely by a centre excitatory input from bipolar cells (BC) and a surround inhibitory input from neighbouring SACs. Centripetal (CP) light movement evokes a leading GABAergic input (blue arrow) to the distal zone from the surround SACs (represented by SAC1), whereas centrifugal (CF) light movement evokes predominantly an excitatory input (red arrow) to the distal zone from the centre. Adapted from Lee & Zhou (2006, *Neuron* 51, 787–799 with permission from Elsevier.

terminals of a bipolar cell axon can function independently to provide directionally biased glutamatergic inputs to several DSGCs. An intriguing possibility in this regard is that SACs asymmetrically inhibit bipolar cell axon terminals, which in turn synapse on DSGCs in a spatially selective manner.

While the critical GABAergic contribution of SACs to direction selectivity is well accepted, the cholinergic role of SACs remains mysterious. Various models of cholinergic contributions to direction selectivity and motion sensitivity have been proposed over the years (Masland *et al.* 1984; Vaney, 1990; Grzywacz *et al.* 1998; Chiao & Masland, 2002). However, the basic mode of nicotinic cholinergic action in the retina still remains obscured: does ACh mediate fast neurotransmission at precise synaptic sites between SACs and DSGCs, and/or does it play a diffuse, paracrine role in modulating the activity of many ganglion cells? This will be another interesting area of future study. A recent preliminary report indicates that detailed characterization of cholinergic synaptic physiology may help us gain new insights into the function of SACs (Lee *et al.* 2006).

Two revelations from the past four decades of studies of direction selectivity seem to stand out as particularly striking. First, from a functional point of view, direction selectivity illustrates an enormous amount of integration of multiple synergistic mechanisms even in a relatively simple system. Such integration may be important for network computation in general. Second, from an anatomical view point, the direction-selective circuit reveals a new level of synaptic selectivity and network specificity that was previously unappreciated. The developmental mechanisms underlying the establishment of the selective connectivity within this circuit will continue to intrigue neurobiologists, perhaps for another four decades.

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