New directions in retinal research

W. Rowland Taylor[1] and David I. Vaney[2]

[1]Neurological Sciences Institute, Oregon Health and Science University, 505 NW 185th Avenue, Beaverton, OR 97006, USA
[2]Vision, Touch and Hearing Research Centre, School of Biomedical Sciences, The University of Queensland, Brisbane, Queensland 4072, Australia

Direction-selective retinal ganglion cells (DSGCs) respond to image motion in a 'preferred' direction but not the opposite 'null' direction. Extracellular spike recordings from rabbit DSGCs suggested that the key mechanism underlying the directional responses is spatially offset inhibition projecting in the null direction. Recent patch-clamp recordings have shown that this inhibition, which acts directly on the DSGC, is already direction selective. Dual recordings established that the inhibition arises from starburst amacrine cells (SBACs) located on the null side of the DSGC but not from those on the preferred side. Thus, for each radially symmetric SBAC, processes pointing in different directions would provide the null-direction inhibition to subtypes of DSGCs with different preferred directions. Ca^{2+} imaging revealed that the SBAC terminal processes respond more strongly to image motion away from the soma than towards the soma, therefore accounting for the direction selectivity of the inhibitory input to the DSGCs.

Neurons that respond selectively to the direction of image motion are found in many parts of the visual system. In the retina, direction-selective responses are shown by several types of ganglion cells, the axons of which project along the optic nerve to the visual centres of the brain. The direction-selective ganglion cells (DSGCs) fire strongly when an image moves in a 'preferred' direction across the receptive field but they are silent for movement in the opposite 'null' direction. Numerous studies have been undertaken on DSGCs in the 40 years since they were discovered in the rabbit retina [1,2] and, in the past year, major progress has been made in elucidating the neuronal circuitry that underlies direction selectivity in the retina. Although these new studies are beginning to provide answers to one of the longest standing questions in visual neuroscience, they have also thrown up new puzzles that promise to have broad implications for neurobiology.

Most of the research has been focused on the On–Off DSGCs, which account for 10% of the ganglion cells in the rabbit retina (reviewed in Ref. [3]). The On–Off DSGCs are of four subtypes, which respond preferentially to image motion in one of the four cardinal ocular directions (upwards, downwards, forwards, backwards) [4]. It appears that each point on the retina is covered by four DSGCs of different subtypes, whereas DSGCs of the same subtype tile the retina in a territorial manner, with little overlap of their dendritic fields [5,6]. The On–Off DSGCs have a distinctive bistratified dendritic tree [7,8], with the proximal arborization in sublamina *b* of the inner plexiform layer activated by light objects (On responses) and the distal arborization in sublamina *a* activated by dark objects (Off responses).

In a classic extracellular recording study, Horace Barlow and Bill Levick [9] examined the receptive-field properties of DSGCs in detail and they proposed that the key mechanism underlying the generation of direction selectivity is spatially offset inhibition projecting in the null direction. Apparent-motion stimuli using two spots flashed sequentially revealed that the activation of any point in the receptive field suppresses the subsequent activation of other points located towards the null direction but not the preferred direction [9–12]. Thus, preferred-direction motion would activate excitation before inhibition, whereas null-direction motion would activate a long-lasting inhibition that cancels the subsequent excitation. The finding that antagonists of the inhibitory transmitter GABA abolish direction selectivity provided strong support for this inhibitory scheme [13,14]. Two of the prime objectives of recent studies have been to identify the source of the GABA-mediated inhibition and to determine its site of action, whether postsynaptically on the DSGC itself or presynaptically on the excitatory interneurons.

Excitatory and inhibitory synaptic inputs

Apparent-motion stimuli also revealed that facilitation of excitatory inputs occurs for preferred-direction sequences [9,15] but extracellular recordings of action potentials failed to disentangle the contributions of asymmetric inhibition and asymmetric facilitation to direction selectivity. However, patch-clamp recordings of synaptic currents in microscopically identified DSGCs have enabled the excitatory and inhibitory inputs to be examined directly, based on the assumptions that the excitation is mediated by non-selective cation channels and the inhibition is mediated by Cl^- channels. The excitatory and inhibitory components can be compared under various stimulus conditions, either by measuring the currents when the DSGC is clamped at the inhibitory and excitatory reversal potentials [16] or, more rigorously, by performing a conductance analysis of serial current–voltage relations [17,18].

The patch-clamp studies showed that the direction-selective responses of the ganglion cells are crucially dependent on inhibition acting directly on the cell [19]. As

Corresponding author: W. Rowland Taylor (taylorw@ohsu.edu).

http://tins.trends.com 0166-2236/03/$ - see front matter doi:10.1016/S0166-2236(03)00167-X

the Barlow–Levick model [9] would predict, the inhibitory receptive field is spatially offset from the excitatory receptive field [16,18]. The DSGC receives excitatory input over a field that is largely coincident with the spike-mapped receptive field and, correspondingly, with the dendritic tree [20,21]. By contrast, the DSGC receives inhibitory input over a wider field that covers both the dendritic tree and an area to one side that is first activated by null-direction motion. The area to the opposite side that is first activated by preferred-direction motion is virtually free of inhibitory input [16]. The spatial offset between the excitatory and inhibitory inputs provides a prerequisite for the postsynaptic generation of direction selectivity within the DSGC itself, because the excitation and inhibition tend to be coincident for image motion in the null direction but not in the preferred direction [17,22].

However a key finding of the patch-clamp studies, first made on turtle DSGCs by Lyle Borg-Graham [17], is that the synaptic currents recorded in the DSGCs are already direction selective and thus, by inference, the neurotransmitter inputs that activate these currents are also direction selective (see also Ref. [23]). Taken together, the recent studies indicate that direction selectivity is established presynaptically to the DSGC but is then sharpened by postsynaptic interactions between the excitation and inhibition. In rabbit On–Off DSGCs, the excitatory inputs tend to be larger in the preferred direction, whereas the inhibitory inputs tend to be larger in the null direction. This complementary 'push–pull' arrangement [18] means that the total synaptic conductance is largely independent of the direction of image motion [19], but the changing ratio of excitation to inhibition drives the synaptic reversal potential to positive values in the preferred direction and to negative values in the null direction.

Starburst amacrine cells

Excitatory glutamate inputs to retinal ganglion cells arise from ~10 types of cone bipolar cell, which provide vertical links with the photoreceptors, whereas inhibitory GABA or glycine inputs arise from 30–40 types of amacrine cell, which provide lateral links within the inner plexiform layer [24–26]. In addition, two types of amacrine cell provide excitatory ACh inputs to some types of ganglion cell, most notably the DSGCs [27–29]. The cholinergic amacrine cells have a distinctive radially symmetrical morphology, with the primary dendrites branching regularly and repeatedly to form numerous distal processes, which are studded with varicosities, thus giving the cells the appearance of 'starburst' fireworks [30–32]. Starburst amacrine cells (SBACs) are found throughout the vertebrate subphylum [33] and comprise two paramorphic types [34,35]: the Off-SBACs stratify within sublamina *a*, whereas the displaced On-SBACs stratify within sublamina *b* [36–38]. The On- and Off-SBACs stratify at precisely the same levels in the inner plexiform layer as the On–Off DSGCs [39,40] and, within each stratum, the processes of numerous overlapping SBACs co-fasciculate with those of the DSGCs [41–43].

The SBACs have been shown to contain and release GABA in addition to ACh [44–46], raising the intriguing possibility that the SBACs supply the null-direction inhibition to DSGCs. The SBACs receive bipolar and amacrine cell input over the whole dendritic tree but make synaptic output to ganglion cells from only the varicose distal zone [47]. Vaney *et al.* [42] proposed that this proximal–distal segregation of the input and output synapses could underlie the crucial spatial asymmetry necessary for generating direction selectivity, if the processes on different sides of SBACs provide selective output to DSGCs with different preferred directions. In principle, the SBACs could supply either asymmetric GABA inhibition or asymmetric nicotinic excitation. Both elements are combined in the push–pull starburst model (see figure 3 of Ref. [48]), in which an SBAC process pointing in one radial direction is hypothesized to excite selectively a DSGC with a matching preferred direction and to inhibit selectively an overlapping DSGC with the opposite preferred direction. Several related models of direction selectivity have been proposed in which a common radial amacrine cell generates the spatial asymmetries underlying the different preferred directions [24,49–52].

The evidence that the SBACs are the key players in the generation of direction selectivity in the retina has been contradictory. Although nicotinic-ACh-receptor antagonists reduce the responsiveness of DSGCs by about one half, they do not affect the direction selectivity under most conditions [28,53]. In the rabbit retina, laser ablation of small patches of On-SBACs on either side of DSGCs reduced the responsiveness of the DSGCs but did not affect the null-direction inhibition [54]. In the mouse retina, by contrast, immuno-ablation of most SBACs appeared to abolish direction selectivity [55], in that all recorded On–Off ganglion cells were directional in the control animals but non-directional in the experimental animals; moreover, the loss of retinal direction selectivity was reflected in loss of the optokinetic eye reflex. These conflicting results might reflect species differences but this view is challenged by the findings that another cholinergic toxin, AF64A, produces similar effects in birds and mammals [56] (G. Yang and I.G. Morgan, unpublished). This neurotoxin significantly affected the visual responses of morphologically identified DSGCs in the rabbit retina, both by increasing the null-direction responses and by decreasing the preferred-direction responses [56].

Direction-selective inhibition

Direct evidence that the SBACs provide an asymmetric inhibitory input to DSGCs has recently been obtained by Shelley Fried, Thomas Münch and Frank Werblin [16], who made simultaneous patch recordings from a DSGC and an overlapping On-SBAC. The soma of the SBAC was located on either the null side or the preferred side of the DSGC, which correspond to the flanks first encountered by null-direction or preferred-direction motion, respectively. Depolarization of SBAC somata located on the null side, within the inhibitory flank of the DSGC, produced inhibitory currents in the DSGC, whereas depolarization of SBAC somata located on the preferred side surprisingly had no effect. These experiments are technically very

difficult, and only three null-side pairs and three preferred-side pairs were recorded, but the demonstration of a spatially asymmetric inhibitory input appears robust. When this important result is combined with the earlier finding that the inhibitory input to DSGCs is direction selective [16,18], it suggests that the release of GABA from SBAC processes is direction selective.

Theoretical modelling studies [50,51] of the electrotonic properties of SBACs had predicted that the terminal processes of a SBAC would be activated more strongly by centrifugal image motion (away from the soma) than centripetal image motion (towards the soma). For example, a terminal on the right side of an SBAC would be activated more strongly by a visual stimulus moving from left to right than by one moving from right to left, and this could form the basis for directional transmitter release from individual terminals. However, passive electrotonic models also indicated that the soma should be activated more strongly by centripetal stimuli [57], but patch-clamp recordings from SBACs showed that the soma is actually activated more strongly by centrifugal stimuli [38,58]. Thus, it is unclear how the responses of the soma are related to the responses of the terminal processes, which are not accessible to recording electrodes. To circumvent this problem, Thomas Euler, Peter Detwiler and Winfried Denk [58] used two-photon laser-scanning microscopy to monitor the cytosolic Ca^{2+} concentration in the processes of SBACs filled with a Ca^{2+}-indicator dye. Because the infrared laser light is not absorbed by the photoreceptors and produces its visible excitation in a narrow band of the inner plexiform layer, well below the photoreceptors, the retina remained responsive to an independent visual stimulus projected onto the photoreceptors through the condenser of the microscope.

The Ca^{2+}-imaging study was a technical tour-de-force that produced two key findings [58]. First, visual stimuli elicited intracellular Ca^{2+} transients in segments of the SBAC dendritic tree that were not reflected in other segments; thus, individual processes or groups of processes can be considered as independent computational units, as originally proposed on electrotonic grounds [59,60]. Second, the Ca^{2+} transients produced in the terminal processes were direction selective, tending to be greater for centrifugal than centripetal image motion. If the direction-selective Ca^{2+} response produces direction-selective transmitter release from the SBAC terminals, this could account for the directional synaptic inputs to DSGCs, provided that the directional signals are preserved through selective contacts between the SBAC terminals and the DSGCs. However, this scenario is greatly complicated by the fact that the SBACs contain both ACh and GABA, which might be released by different mechanisms [46,61], perhaps operating at different sites on the SBAC processes.

The dendritic co-fasciculation of the SBACs and the DSGCs is a remarkable feature of their neuronal architecture but its functional significance has remained obscure. Both the early dye-injection studies [42,43] and a recent Golgi-staining study [62] concluded that the dendrites of each DSGC fasciculate with the processes of SBAC somata located on all sides of the DSGC. However, Fried *et al.* [16] reported that the amount of fasciculation between overlapping dendritic trees was about three-times greater if the SBAC soma was located on the null side rather than the preferred side. Such asymmetric fasciculation could provide a morphological substrate for the asymmetric inhibition revealed by paired cell recordings but this finding remains to be confirmed by a detailed study.

Although the recent studies have demonstrated that direction selectivity is generated presynaptically to the DSGC, they provide few insights into the cellular mechanisms responsible. The spatial organization of the radial processes of SBACs is no doubt important, but the finding that the Ca^{2+} responses of SBAC processes remain direction selective in the presence of $GABA_A$ receptor blockers [58] does not support the early hypothesis that the electrotonic generation of direction selectivity in SBACs is augmented by 'on-the-path' inhibition between the soma and the terminals [50]. However, inhibitory mechanisms might still be implicated in the generation of direction selectivity, given that it has recently been reported that manipulation of the Cl^- gradient within SBACs abolishes the direction selectivity of the somatic potential elicited by centrifugal and centripetal stimuli (K.E. Gavrikov, A.V. Dmitriev, K.T. Keyser and S.C. Mangel, unpublished). The direction selectivity of SBACs might also be generated by some sort of facilitatory mechanism, perhaps through active membrane conductances or intracellular signaling pathways (see also Ref. [63]).

Direction-selective excitation

Extracellular recording studies indicated that DSGCs receive about half their excitatory drive from cone bipolar cells, largely through the glutamate-mediated activation of NMDA receptors, and receive the other half from SBACs, through the activation of nicotinic receptors by ACh [28,53]. Although recent patch-clamp studies have revealed that the excitatory inputs to DSGCs are direction selective [16–18], the relative contributions of the glutamatergic and cholinergic inputs have not been examined. Fried *et al.* [16] used two-spot stimuli to test whether the direction selectivity of the excitatory inputs to DSGCs arises from preferred-direction facilitation or from null-direction inhibition acting presynaptically on the excitatory interneurons. Their data largely support a presynaptic inhibitory mechanism, which has the advantage that it can account for the actions of GABA receptor antagonists in abolishing direction selectivity.

Fried *et al.* [16] presumed that this inhibition acts on the bipolar cells but such a scheme faces several problems with its neuronal implementation [3]. Most importantly, there are insufficient cone bipolar cells to provide dedicated populations for each of the four preferred directions of image motion [62,64,65]. Thus, it would be necessary to suppose that separate terminal branches of an individual bipolar cell are dedicated to different preferred directions; the issue then arises as to how synapses on different branches could be capable of independent activity in response to common-sourced excitatory drive. It is probable that SBACs and DSGCs receive input from the same bipolar cells [62,66], raising

the circuitous possibility that the excitatory inputs to SBACs are already direction selective.

It is also possible that the null-direction inhibition acts presynaptically on the SBACs, but this was not considered in detail by Fried *et al.* [16], perhaps because the cholinergic input to DSGCs appears so enigmatic. Although nicotinic receptor agonists can drive the DSGCs to conduction block, apparently by acting directly on them [27], it is not possible to drive the DSGCs with visual stimuli designed to activate selectively the SBAC input. Bipolar cells are small-field neurons and, thus, DSGCs receive glutamatergic input over an area that is not much wider than the dendritic field of a ganglion cell; it appears that this sets the limit of both the excitatory input field and the resulting spike-mapped receptive field [16,18,20,21]. By contrast, SBACs are large-field neurons, and DSGCs potentially receive cholinergic input from many SBACs located beyond the dendritic field of the ganglion cell. A DSGC cannot be driven by visual stimulation of these overlapping SBACs, even on the preferred side of the DSGC where there is little inhibition to counteract the excitation. These results from extracellular recording studies are compatible with the findings of the double-patch recordings, which showed that a DSGC can not be driven by electrical stimulation of a preferred-side SBAC [16].

It is clear, however, that such stimulation outside the classical receptive field does facilitate the responses to subsequent stimulation within the receptive field. This facilitation can be readily demonstrated for preferred-direction stimuli [67] but it might in fact be spatially symmetrical [3,54,68], as discussed in the following paragraph. It seems possible, therefore, that depolarization of a preferred-side SBAC, although ineffective on its own, would facilitate the response of the DSGC to flashed illumination of the receptive-field centre. The characteristics of the preferred-direction facilitation led Vaney *et al.* [3] to propose that the cholinergic input from SBACs is gated by the glutamatergic input from bipolar cells. This could occur presynaptically, so that an SBAC varicosity would release ACh only when it receives direct input from an overlying bipolar cell, regardless of the bipolar-cell input to other parts of the SBAC. If the cholinergic inputs to a DSGC were asymmetrical but subject to gating by glutamate, then the excitatory inputs would appear directional. Moreover, the excitatory field would be limited by the spatial extent of the bipolar cell input and centred on the DSGC dendritic tree, in agreement with the experimental findings [16,18].

However, the idea that facilitation by ACh underlies the direction selectivity of the excitatory input is challenged by several studies indicating that the facilitation is symmetrical [3,54,68]. Richard Masland and colleagues tested the effects of nicotinic receptor antagonists after blocking the null-direction inhibition with GABA receptor antagonists, thus making the DSGCs responsive to all directions of image motion. The spike responses of DSGCs to apparent-motion stimuli were symmetrically reduced under these conditions [68], suggesting that the DSGC received feedforward ACh-mediated excitation from both null-side and preferred-side SBACs. By contrast, Fried *et al.* [16] were unable to elicit excitatory currents in DSGCs when they electrically stimulated single SBACs located on either the null side or the preferred side of the DSGC. How can these results be reconciled? Perhaps ACh diffuses extrasynaptically, setting the general excitability of the ganglion cells in the starburst strata and elsewhere in the inner plexiform layer. This hypothesis is consistent with the findings that the β2α3 nicotinic ACh receptor is distributed throughout the inner plexiform layer and that much of the labelling is not associated with recognizable synapses [69].

Notwithstanding the above scenario, is it possible to reconcile the symmetrical model of ACh-mediated facilitation with the asymmetrical push–pull model of direction selectivity? GABA receptor blockers are required to reveal the null-direction facilitation, which is normally masked by the null-direction inhibition [3,54,68]. Thus, it cannot be excluded that symmetrical ACh-mediated facilitation might be rendered directional through presynaptic inhibition by the same GABA that acts postsynaptically on the DSGC. However, the required circuitry becomes complex and lacks the elegant simplicity proposed for the inhibitory inputs to SBACs (Fig. 1). This open-ended discussion raises the possibility that the GABA and ACh in SBACs might have different targets depending on their modes of release and re-uptake, which in turn might be differentially affected by both the directional Ca^{2+} responses and the voltage responses of the SBAC terminals.

Postsynaptic mechanisms

Given that the excitatory and inhibitory inputs to DSGCs are already directional [16–18], what role is played by the postsynaptic interactions between the spatially offset inputs in generating the responses of DSGCs? A hallmark of direction selectivity in the retina is the finding that DSGCs respond directionally to small displacements covering a fraction (a 'subunit') of the receptive field [9,70]. Postsynaptic models of direction selectivity rely upon the localized action of shunting inhibition to generate subunits [17,22,71,72], but this places conflicting constraints on the electrical properties of the DSGC. In an electrically passive dendritic tree, an excitatory input at a distal location will effectively depolarize the somatic spike initiation zone only if the dendritic length constant is relatively long. Such a cell will be electrically compact, however, and a shunting inhibitory input would be effective over a physically more extensive dendritic region, owing to the stronger electrical coupling between dendritic regions. Therefore, if shunting inhibition is to act locally, the dendritic length constant should be relatively short, implying an electrically extensive cell.

The electrical properties of DSGCs have not been examined in detail and it is not known whether active dendritic conductances contribute to the direction-selective responses [73]. Visual stimulation of the distal dendrites effectively generates spikes at the soma [20,21], suggesting that the dendritic tree, if passive, is indeed electrically compact. If so, then the inhibition in one dendritic stratum (On or Off) should interact with the excitation in the other (Off or On), as shown by a recent extracellular recording study [12] (but see Ref. [11]).

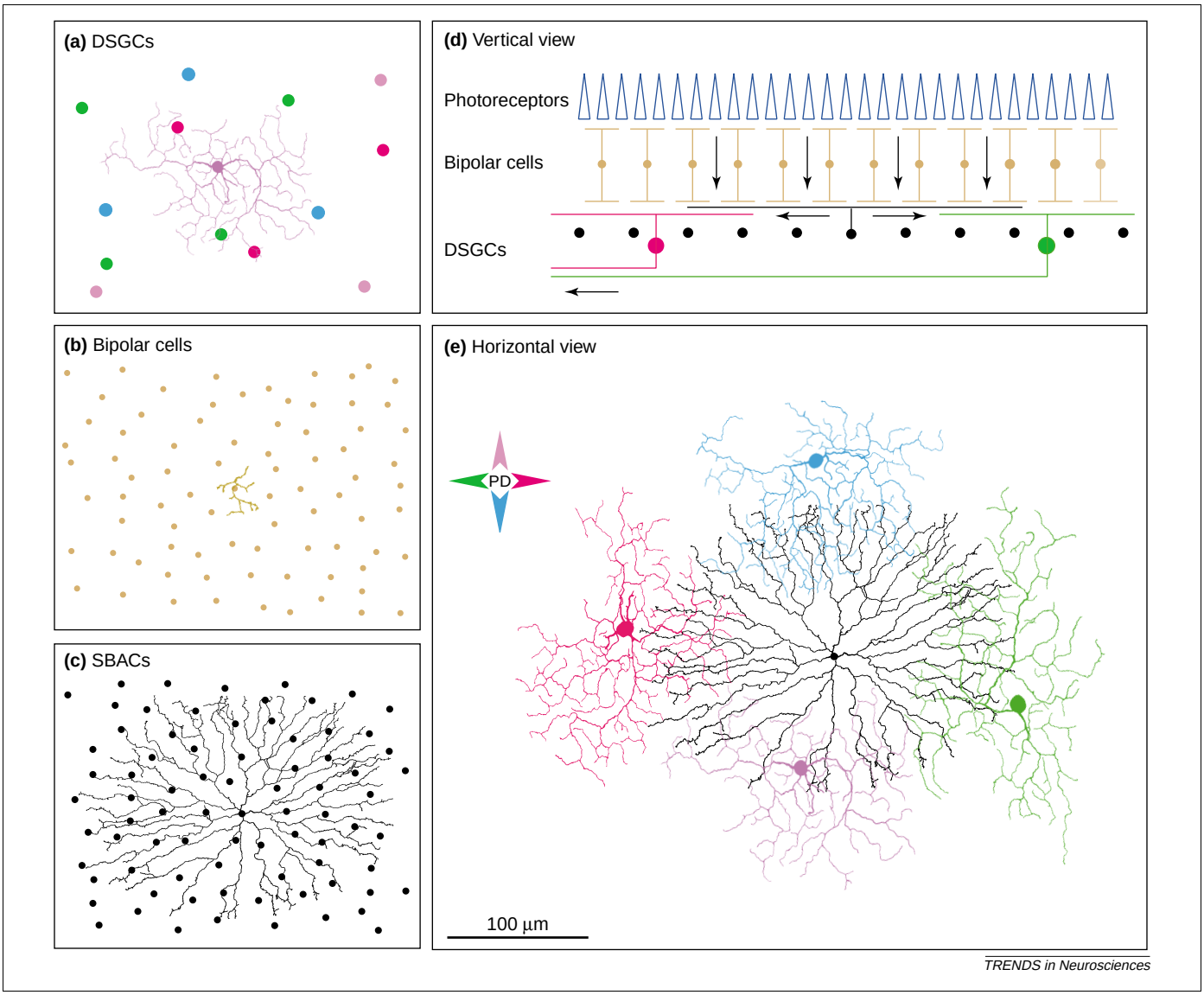

Fig. 1. Neuronal architecture of direction selectivity. In peripheral rabbit retina, there are ~100 On–Off direction-sensitive ganglion cells (DSGCs) mm^{-2}, of four subtypes with orthogonal preferred directions (PD), here coded in different colours (a). The DSGCs have a bistratified dendritic tree but, for simplicity, only the circuitry in the On sublamina is shown. The dendrites of DSGCs receive excitatory glutamatergic inputs from the axon terminal of cone bipolar cells (b) and both excitatory cholinergic and inhibitory GABAergic inputs from the processes of starburst amacrine cells (SBACs) (c). Both the bipolar cells and SBACs have a density of ~500 cells mm^{-2}, but the narrow-field bipolar cells tile the retina with little overlap whereas the wide-field SBACs show ~50-fold overlap of their dendritic fields. The SBACs receive bipolar-cell input over the whole dendritic tree but provide output to ganglion cells through the outer ring of terminal processes (d). Euler *et al.* [58] used two-photon laser-scanning microscopy to record the Ca^{2+} responses in the starburst terminals and showed that these are direction selective, responding more strongly to image motion away from the soma than to that towards the soma. Subsequently, Fried *et al.* [16] used paired recordings from an SBAC and a DSGC to show that the inhibitory input is spatially asymmetric, arising from SBACs located on the null side of the DSGC but not on the preferred side. Thus, a single SBAC can provide null-direction inhibition to four subtypes of DSGCs with different preferred directions (e). Taken together, these results account for the findings of Taylor and Vaney [18] and of Fried *et al.* [16], that the inhibitory input to DSGCs is direction selective and is offset towards the null side of the cell. The DSGCs also receive a direction-selective excitatory input, but it is not known whether this arises in the bipolar cells (perhaps through presynaptic inhibition by the SBACs) or whether the cholinergic input from the SBACs is directional (but of opposite polarity to the directional inhibition). Scale bar in (e) represents 120 μm in (a–c).

Moreover, some anatomical evidence also argues against local dendritic processing. Confocal microscopy indicates that the $GABA_A$ receptors are not confined to the side branches of DSGCs but are also found on the main branches [74], where they could shunt excitatory inputs over large portions of the dendritic tree [71,72].

The limited available evidence supports the hypothesis that the fine spatial resolution of direction selectivity and its robustness in response to widely varying stimuli depend on presynaptic mechanisms rather than on local dendritic processing within the DSGC (L. Borg-Graham, unpublished). However, postsynaptic processing might be particularly effective for global stimuli that fully engage the central excitatory field and the spatially offset inhibitory field. This notion could explain why direction-selective responses are strongest for grating stimuli whose spatial half-width matches the size of the receptive field, irrespective of the temporal frequency [75].

Concluding remarks

Recent studies have established that SBACs play the key role in the generation of direction selectivity in the retina. SBACs not only provide the direction-selective inhibitory inputs to DSGCs but also might account for the

direction-selective excitatory inputs, either directly or indirectly. However, several important issues remain to be resolved, including the cellular mechanisms that generate direction-selective responses in the SBAC processes, the neuronal circuitry that underlies the direction-selective excitatory inputs, and the developmental mechanisms that lead to the specific connections between SBAC processes and each subtype of DSGC. Hopefully the resolution of these issues will not take another 40 years.

Acknowledgements

Our research on direction selectivity in the retina is supported by project grants from the National Health and Medical Research Council of Australia.

References

1 Barlow, H.B. and Hill, R.M. (1963) Selective sensitivity to direction of motion in ganglion cells of the rabbit's retina. *Science* 139, 412–414
2 Barlow, H.B. *et al.* (1964) Retinal ganglion cells responding selectively to direction and speed of image motion in the rabbit. *J. Physiol.* 173, 377–407
3 Vaney, D.I. *et al.* (2001) Direction-selective ganglion cells in the retina. In *Motion Vision: Computational, Neural, and Ecological Constraints* (Zeil, J., ed.), pp. 13–55, Springer
4 Oyster, C.W. and Barlow, H.B. (1967) Direction-selective units in rabbit retina: distribution of preferred directions. *Science* 155, 841–842
5 Vaney, D.I. (1994) Territorial organization of direction-selective ganglion cells in rabbit retina. *J. Neurosci.* 14, 6301–6316
6 Amthor, F.R. and Oyster, C.W. (1995) Spatial organization of retinal information about the direction of image motion. *Proc. Natl. Acad. Sci. U. S. A.* 92, 4002–4005
7 Amthor, F.R. *et al.* (1984) Morphology of on–off direction-selective ganglion cells in the rabbit retina. *Brain Res.* 298, 187–190
8 Oyster, C.W. *et al.* (1993) Dendritic architecture of ON–OFF direction-selective ganglion cells in the rabbit retina. *Vision Res.* 33, 579–608
9 Barlow, H.B. and Levick, W.R. (1965) The mechanism of directionally selective units in rabbit's retina. *J. Physiol.* 178, 477–504
10 Wyatt, H.J. and Daw, N.W. (1975) Directionally sensitive ganglion cells in the rabbit retina: specificity for stimulus direction, size, and speed. *J. Neurophysiol.* 38, 613–626
11 Amthor, F.R. and Grzywacz, N.M. (1993) Inhibition in ON–OFF directionally selective ganglion cells of the rabbit retina. *J. Neurophysiol.* 69, 2174–2187
12 Stasheff, S.F. and Masland, R.H. (2002) Functional inhibition in direction-selective retinal ganglion cells: spatiotemporal extent and intralaminar interactions. *J. Neurophysiol.* 88, 1026–1039
13 Wyatt, H.J. and Daw, N.W. (1976) Specific effects of neurotransmitter antagonists on ganglion cells in rabbit retina. *Science* 191, 204–205
14 Caldwell, J.H. *et al.* (1978) Effects of picrotoxin and strychnine on rabbit retinal ganglion cells: lateral interactions for cells with more complex receptive fields. *J. Physiol.* 276, 277–298
15 Grzywacz, N.M. and Amthor, F.R. (1993) Facilitation in ON–OFF directionally selective ganglion cells of the rabbit retina. *J. Neurophysiol.* 69, 2188–2199
16 Fried, S.I. *et al.* (2002) Mechanisms and circuitry underlying directional selectivity in the retina. *Nature* 420, 411–414
17 Borg-Graham, L.J. (2001) The computation of directional selectivity in the retina occurs presynaptic to the ganglion cell. *Nat. Neurosci.* 4, 176–183
18 Taylor, W.R. and Vaney, D.I. (2002) Diverse synaptic mechanisms generate direction selectivity in the rabbit retina. *J. Neurosci.* 22, 7712–7720
19 Taylor, W.R. *et al.* (2000) Dendritic computation of direction selectivity by retinal ganglion cells. *Science* 289, 2347–2350
20 Yang, G. and Masland, R.H. (1992) Direct visualization of the dendritic and receptive fields of directionally selective retinal ganglion cells. *Science* 258, 1949–1952
21 Yang, G. and Masland, R.H. (1994) Receptive fields and dendritic structure of directionally selective retinal ganglion cells. *J. Neurosci.* 14, 5267–5280
22 Torre, V. and Poggio, T. (1978) A synaptic mechanism possibly underlying directional selectivity to motion. *Proc. R. Soc. Lond. B Biol. Sci.* 202, 409–416
23 DeVoe, R.D. *et al.* (1989) Not by ganglion cells alone: directional selectivity is widespread in identified cells of the turtle retina. In *Neurobiology of the Inner Retina* (Osborne, N.N., ed.), pp. 235–246, Springer
24 Vaney, D.I. (1990) The mosaic of amacrine cells in the mammalian retina. *Prog. Retinal Eye Res.* 9, 49–100
25 MacNeil, M.A. and Masland, R.H. (1998) Extreme diversity among amacrine cells: implications for function. *Neuron* 20, 971–982
26 Masland, R.H. (2001) Neuronal diversity in the retina. *Curr. Opin. Neurobiol.* 11, 431–436
27 Masland, R.H. and Ames, A. (1976) Responses to acetylcholine of ganglion cells in an isolated mammalian retina. *J. Neurophysiol.* 39, 1220–1235
28 Ariel, M. and Daw, N.W. (1982) Pharmacological analysis of directionally sensitive rabbit retinal ganglion cells. *J. Physiol.* 324, 161–185
29 Reed, B.T. *et al.* (2002) Rabbit retinal ganglion cell responses mediated by α-bungarotoxin-insensitive nicotinic acetylcholine receptors. *Vis. Neurosci.* 19, 427–438
30 Famiglietti, E.V. (1983) 'Starburst' amacrine cells and cholinergic neurons: mirror-symmetric on and off amacrine cells of rabbit retina. *Brain Res.* 261, 138–144
31 Vaney, D.I. (1984) 'Coronate' amacrine cells in the rabbit retina have the 'starburst' dendritic morphology. *Proc. R. Soc. Lond. B Biol. Sci.* 220, 501–508
32 Tauchi, M. and Masland, R.H. (1984) The shape and arrangement of the cholinergic neurons in the rabbit retina. *Proc. R. Soc. Lond. B Biol. Sci.* 223, 101–119
33 Perry, V.H. and Walker, M. (1980) Amacrine cells, displaced amacrine cells and interplexiform cells in the retina of the rat. *Proc. R. Soc. Lond. B Biol. Sci.* 208, 415–431
34 Vaney, D.I. *et al.* (1981) Matching populations of amacrine cells in the inner nuclear and ganglion cell layers of the rabbit retina. *J. Comp. Neurol.* 199, 373–391
35 Masland, R.H. and Mills, J.W. (1979) Autoradiographic identification of acetylcholine in the rabbit retina. *J. Cell Biol.* 83, 159–178
36 Bloomfield, S.A. and Miller, R.F. (1986) A functional organization of ON and OFF pathways in the rabbit retina. *J. Neurosci.* 6, 1–13
37 Taylor, W.R. and Wässle, H. (1995) Receptive field properties of starburst cholinergic amacrine cells in the rabbit retina. *Eur. J. Neurosci.* 7, 2308–2321
38 Peters, B.N. and Masland, R.H. (1996) Responses to light of starburst amacrine cells. *J. Neurophysiol.* 75, 469–480
39 Famiglietti, E.V. (1987) Starburst amacrine cells in cat retina are associated with bistratified, presumed directionally selective, ganglion cells. *Brain Res.* 413, 404–408
40 Famiglietti, E.V. (1992) Dendritic co-stratification of ON and ON–OFF directionally selective ganglion cells with starburst amacrine cells in rabbit retina. *J. Comp. Neurol.* 324, 322–335
41 Tauchi, M. and Masland, R.H. (1985) Local order among the dendrites of an amacrine cell population. *J. Neurosci.* 5, 2494–2501
42 Vaney, D.I. *et al.* (1989) Dendritic relationships between cholinergic amacrine cells and direction-selective retinal ganglion cells. In *Neurobiology of the Inner Retina* (Osborne, N.N., ed.), pp. 157–168, Springer
43 Vaney, D.I. and Pow, D.V. (2000) The dendritic architecture of the cholinergic plexus in the rabbit retina: selective labeling by glycine accumulation in the presence of sarcosine. *J. Comp. Neurol.* 421, 1–13
44 Vaney, D.I. and Young, H.M. (1988) GABA-like immunoreactivity in cholinergic amacrine cells of the rabbit retina. *Brain Res.* 438, 369–373
45 Brecha, N. *et al.* (1988) Cholinergic amacrine cells of the rabbit retina contain glutamate decarboxylase and γ-aminobutyrate immunoreactivity. *Proc. Natl. Acad. Sci. U. S. A.* 85, 6187–6191
46 O'Malley, D.M. and Masland, R.H. (1989) Co-release of acetylcholine and γ-aminobutyric acid by a retinal neuron. *Proc. Natl. Acad. Sci. U. S. A.* 86, 3414–3418
47 Famiglietti, E.V. (1991) Synaptic organization of starburst amacrine cells in rabbit retina: analysis of serial thin sections by electron microscopy and graphic reconstruction. *J. Comp. Neurol.* 309, 40–70

48 Vaney, D.I. and Taylor, W.R. (2002) Direction selectivity in the retina. *Curr. Opin. Neurobiol.* 12, 405–410
49 Werblin, F. (1991) Synaptic connections, receptive fields, and patterns of activity in the tiger salamander retina. A simulation of patterns of activity formed at each cellular level from photoreceptors to ganglion cells. *Invest. Ophthalmol. Vis. Sci.* 32, 459–483
50 Borg-Graham, L.J. and Grzywacz, N. (1992) A model of the direction selectivity circuit in retina: transformations by neurons singly and in concert. In *Single Neuron Computation* (Zornetzer, S.F., ed.), pp. 347–375, Academic Press
51 Poznanski, R.R. (1992) Modelling the electrotonic structure of starburst amacrine cells in the rabbit retina: a functional interpretation of dendritic morphology. *Bull. Math. Biol.* 54, 905–928
52 Grzywacz, N.M. *et al.* (1997) Is the input to a GABAergic or cholinergic synapse the sole asymmetry in rabbit's retinal directional selectivity? *Vis. Neurosci.* 14, 39–54
53 Kittila, C.A. and Massey, S.C. (1997) Pharmacology of directionally selective ganglion cells in the rabbit retina. *J. Neurophysiol.* 77, 675–689
54 He, S. and Masland, R.H. (1997) Retinal direction selectivity after targeted laser ablation of starburst amacrine cells. *Nature* 389, 378–382
55 Yoshida, K. *et al.* (2001) A key role of starburst amacrine cells in originating retinal directional selectivity and optokinetic eye movement. *Neuron* 30, 771–780
56 Amthor, F.R. *et al.* (2002) Effects of the destruction of starburst-cholinergic amacrine cells by a toxin AF64A on rabbit retinal directional selectivity. *Vis. Neurosci.* 19, 495–509
57 Rall, W. (1964) Theoretical significance of dendritic trees for neuronal input–output relations. In *Neural Theory and Modeling* (Reis, R.F., ed.), pp. 73–97, Stanford University Press
58 Euler, T. *et al.* (2002) Directionally selective calcium signals in dendrites of starburst amacrine cells. *Nature* 418, 845–852
59 Miller, R.F. and Bloomfield, S.A. (1983) Electroanatomy of a unique amacrine cell in the rabbit retina. *Proc. Natl. Acad. Sci. U. S. A.* 80, 3069–3073
60 Velte, T.J. and Miller, R.F. (1997) Spiking and nonspiking models of starburst amacrine cells in the rabbit retina. *Vis. Neurosci.* 14, 1073–1088
61 O'Malley, D.M. *et al.* (1992) Co-release of acetylcholine and GABA by the starburst amacrine cells. *J. Neurosci.* 12, 1394–1408
62 Famiglietti, E.V. (2002) A structural basis for omnidirectional connections between starburst amacrine cells and directionally selective ganglion cells in rabbit retina, with associated bipolar cells. *Vis. Neurosci.* 19, 145–162
63 Barlow, H. (1996) Intraneuronal information processing, directional selectivity and memory for spatio-temporal sequences. *Network Comput. Neural Syst.* 7, 251–259
64 Famiglietti, E.V. (1981) Functional architecture of cone bipolar cells in mammalian retina. *Vision Res.* 21, 1559–1563
65 Brown, S.P. and Masland, R.H. (1999) Costratification of a population of bipolar cells with the direction-selective circuitry of the rabbit retina. *J. Comp. Neurol.* 408, 97–106
66 Dacheux, R.F. *et al.* (2003) Synaptic input to the on–off directionally selective ganglion cell in the rabbit retina. *J. Comp. Neurol.* 456, 267–278
67 Amthor, F.R. *et al.* (1996) Extra-receptive-field motion facilitation in on–off directionally selective ganglion cells of the rabbit retina. *Vis. Neurosci.* 13, 303–309
68 Chiao, C.C. and Masland, R.H. (2002) Starburst cells nondirectionally facilitate the responses of direction-selective retinal ganglion cells. *J. Neurosci.* 22, 10509–10513
69 Dmitrieva, N.A. *et al.* (2003) Identification of cholinoceptive glycinergic neurons in the mammalian retina. *J. Comp. Neurol.* 456, 167–175
70 Grzywacz, N.M. *et al.* (1994) Directional hyperacuity in ganglion cells of the rabbit retina. *Vis. Neurosci.* 11, 1019–1025
71 Koch, C. *et al.* (1982) Retinal ganglion cells: a functional interpretation of dendritic morphology. *Philos. Trans. R. Soc. London Ser. B* 298, 227–263
72 Koch, C. *et al.* (1983) Nonlinear interactions in a dendritic tree: localization, timing, and role in information processing. *Proc. Natl. Acad. Sci. U. S. A.* 80, 2799–2802
73 Velte, T.J. and Masland, R.H. (1999) Action potentials in the dendrites of retinal ganglion cells. *J. Neurophysiol.* 81, 1412–1417
74 Jeon, C.J. *et al.* (2002) Pattern of synaptic excitation and inhibition upon direction-selective retinal ganglion cells. *J. Comp. Neurol.* 449, 195–205
75 He, S. and Levick, W.R. (2000) Spatial–temporal response characteristics of the ON–OFF direction selective ganglion cells in the rabbit retina. *Neurosci. Lett.* 285, 25–28