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General features of inhibition in the inner retina

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Abstract

Visual processing starts in the retina. Within only two synaptic layers, a large number of parallel information channels emerge, each encoding a highly processed feature like edges or the direction of motion. Much of this functional diversity arises in the inner plexiform layer, where inhibitory amacrine cells modulate the excitatory signal of bipolar and ganglion cells. Studies investigating individual amacrine cell circuits like the starburst or A17 circuit have demonstrated that single types can possess specific morphological and functional adaptations to convey a particular function in one or a small number of inner retinal circuits. However, the interconnected and often stereotypical network formed by different types of amacrine cells across the inner plexiform layer prompts that they should be also involved in more general computations. In line with this notion, different recent studies systematically analysing inner retinal signalling at a population level provide evidence that general functions of the ensemble of amacrine cells across types are critical for establishing universal principles of retinal computation like parallel processing or motion anticipation. Combining recent advances in the development of indicators for imaging inhibition with large-scale morphological and genetic classifications will help to further our understanding of how single AC circuits act together to help decomposing the visual scene into parallel information channels. In this review, we aim to summarise the current state-of-the-art in our understanding of how general features of amacrine cell inhibition lead to general features of computation.

Author profiles

Katrin Franke did her PhD with Thomas Euler and Tom Baden at the Centre for Integrative Neuroscience at the University of Tübingen. Since January 2017 she is a Junior Research Group Leader at the Bernstein Centre for Computational Neuroscience at the University of Tübingen. Tom Baden did his PhD with Berthold Hedwig (Zoology, Cambridge, UK) and his postdocs with Leon Lagnado (LMB-MRC, Cambridge, UK) and Thomas Euler (CIN, Tübingen, Germany) before returning to the UK to take up his current group leader position at the University of Sussex. We share a common interest in understanding circuit computations in neuronal networks with particular focus on the early visual system of vertebrates.

Inhibitory amacrine cells shape visual information processing in the inner retina

The vertebrate retina is an established model system in neuroscience for sensory information processing. It decomposes the visual input into parallel channels, each selective for a specific feature like motion, contrast or edges (Wässle, 2004; Masland, 2012a). Already at the first synapse, signals from single photoreceptors (PRs) are split into more than a dozen bipolar cell (BC) types (Euler et al., 2014), which relay the information to more than 30 output channels formed by the retinal ganglion cells (RGC) (Robles et al., 2014; Sanes and Masland, 2015; Baden et al., 2016). Most computations towards retinal feature extraction are implemented in the second synaptic layer – the inner plexiform layer (IPL) (Gollisch and Meister, 2010). Here, at least 30 types of inhibitory amacrine cell (AC) form intricate connections with BCs and RGCs (Vaney, 1990) to shape and gate the excitatory pathways of the inner retina. The modulatory role of ACs is key for generating the functional diversity present in the retinal output (Masland, 2012b). While a handful of individual AC circuits have been studied at great detail, it is not clear how representative their functions are for the great majority of ACs and surprisingly little is known about more general computational principles that ACs as a whole impart on the retinal network. Here, we summarise current knowledge about how ACs contribute to information processing in the retina and speculate about more universal roles of AC function.

Alongside RGCs, ACs are the most diverse class of retinal neurons and they differ even more greatly in size and morphology than RGCs (Vaney, 1990; MacNeil and Masland, 1998; Masland, 2012b). Two major groups can be distinguished: “Small-field” types mainly signal vertically across synaptic layers of the IPL and are classically thought to modulate visual signalling locally over a small region of the visual field. In contrast, “wide-field” ACs predominantly transfer information laterally within single IPL strata and can span up to several millimetres of the retinal surface (Fig. 1a), thereby shaping visual information processing at a larger spatial scale. Although some wide-field ACs possess axons for fast signal transmission across large distances, most types use their dendrites as both input and output structures (Euler and Denk, 2001). In mammals, small-field ACs mainly release glycine as neurotransmitter (Menger et al., 1998), whereas wide-field types release GABA (Fig. 1b) (Pourcho and Goebel, 1983). Additionally, many ACs co-release a second neurotransmitter (e.g. glutamate (Lee et al., 2014)) or neuromodulator (e.g. nitric oxide (Vielma et al., 2011)). ACs provide type-specific inhibitory inputs to BC axon terminals (“presynaptic inhibitory inputs”) and RGC dendrites (“postsynaptic inhibitory inputs”) as well as to other ACs (“serial inhibitory inputs”) (Fig. 1c) (Eggers and Lukasiewicz, 2011; Zhang and McCall, 2012).

Individual amacrine cell microcircuits

A small number of specific AC circuits have been studied at great detail. One prominent example is the starburst AC, which provides the critical inhibition underlying direction-selective responses of rodent and lagomorph RGCs (Vaney et al., 2012). Several mechanisms have been suggested to contribute to the computation of direction selectivity in starburst ACs, including different intrinsic mechanisms, such as active membrane conductances (Hausselt et al., 2007), and network interactions like reciprocal inhibition between neighbouring starburst ACs (Lee and Zhou, 2006; Münch and Werblin, 2006; Enciso et al., 2010; Ding et al., 2016)). Likely by combining these mechanisms, each main dendritic branch of a single starburst AC is differentially tuned to stimuli moving centrifugally from the soma (Euler et al., 2002). As such, individual starburst AC dendrites are a central computational unit within inner retinal circuits that extract the direction of object motion.

Similarly, the A17 AC joins a morphological “setup” (the regular ~20 μm spacing of varicosities (Grimes et al., 2010)) with biophysical features, like the complement of expressed receptor types (Chávez et al., 2006; Grimes et al., 2009, 2015), such that each individual varicosity contains an independent “microcircuit” that provides highly local feedback. Hereby the cell provides synapse-specific gain control to individual rod BC axon terminals to modulate the sensitivity of the rod pathway. Further examples of well-studied AC types and circuits include the AII (Demb and Singer, 2012), A8 (Kolb and Nelson, 1981; Lee et al., 2015) and the glutamatergic AC (Lee et al., 2014; Tien et al., 2016) (for discussion of the role of glutamatergic outputs of ACs see (Baden and Euler, 2016)) as well as types of polyaxonal ACs (Baccus et al., 2008; Greschner et al., 2014; Murphy-Baum and Taylor, 2015). One key feature that all of these AC types have in common is that they use highly specific morphological and functional adaptations to carry out specific computations in a single or at most a small number of inner retinal circuits.

General amacrine cell functions

The population of ACs across types forms a dense network connecting all strata of the IPL, suggesting that the activity in any one cell – at least in principle – might affect the activity in any other cell of the network. One striking example in support of this notion is that altering the activity in a single salamander BC in the absence of visual stimulation changes firing rates in RGCs of different types and across large distances via polysynaptic pathways involving ACs (Asari and Meister, 2014). Because of this across-type interconnectivity, ACs might interact beyond their individual microcircuits, possibly contributing in addition to general features of inner retinal computation. Indeed, the complex synaptic arrangements the population of ACs forms in the IPL include stereotypic and repeating connectivity motifs. For example, likely all BCs receive independent reciprocal and lateral inhibition from different AC types at the same specialised output structure (Vigh et al., 2011; Grimes, 2012; Tanaka and Tachibana, 2013), the dyad synapse (Dowling and Boycott, 1966; Raviola and Dacheux, 1987). Similarly, RGCs consistently show an excess of inhibitory inputs compared to excitatory inputs across types and species and these inputs appear to be randomly distributed across the dendritic tree of individual RGCs (Freed and Sterling, 1988; Hitchcock, 1989; Kolb and Nelson, 1993). In addition, ACs form repeating and spatially extensive circuits via serial synaptic connections (Dowling and Boycott, 1966; Zhang et al., 2004) which shape the magnitude and timing of inhibition in the inner retina (Zhang et al., 1997; Roska et al., 1998; Eggers et al., 2007). One connectivity motif that is shared across all classes of inner retinal neurons – BCs (Molnar and Werblin, 2007; Rosa et al., 2016), ACs (Hsueh et al., 2008) and RGCs (Manookin et al., 2008; Cafaro and Rieke, 2013) – is crossover inhibition which connects the On and Off pathway via small-field ACs. Therefore, while type-specific morphological adaptations give rise to highly specific functions (see above), it seems reasonable to suggest that general characteristics of inner retinal connectivity shared across the ensemble of AC types will lead to general features of computation.

One “classical” example of such a general computation is the establishment of the antagonistic centre-surround organisation of BC and RGC receptive fields (e.g. (Kuffler, 1953)). The inhibitory surround of individual cells is largely generated in the inner retina by lateral inhibition provided by wide-field ACs (Flores-Herr et al., 2001; Ichinose and Lukasiewicz, 2005; Buldyrev and Taylor, 2013; Protti et al., 2014) (but see e.g. (Naka and Nye, 1971; Marchiafava, 1978)). However, numbers alone dictate that the surround of each of the ~14 BC and >30 RGC types cannot be created by an exclusive “partner AC” – there simply are not enough AC types in the retina. Instead, the inhibitory surround is likely at least

partially independent from each cell's individual micro-circuitry and instead emerges from general principles of inner retinal organisation.

Investigating general functional features of amacrine cells

Understanding how these general AC functions arise within the retinal network requires the systematic recording of light-evoked activity in many different retinal neurons under the same experimental condition (e.g. adaptational state, visual stimulation protocol) in the intact tissue preparation (i.e. the whole-mounted retina or, if possible, *in vivo*), where long-range inhibitory connections are preserved. For example, Johnston and Lagnado (Johnston and Lagnado, 2015) performed electrical single cell recordings of different RGC types in the whole-mounted goldfish retina to study the underlying mechanism of motion anticipation. Here, the visual system compensates for the temporal delay in phototransduction cascade and downstream signal transmission to accurately estimate the position of a moving object. This fundamental property of the retinal output occurs in the majority of RGC types and across species (Berry et al., 1999; Schwartz et al., 2007). In this study, they found that feedforward inhibition from ACs is critical for anticipating moving stimuli and locate this computation to the dendritic tree of individual RGCs. Since this mechanism applies to different RGC types which receive inhibitory inputs from different AC types, this study reveals a general function of the population of ACs. Similarly, Asari and Meister (Asari and Meister, 2012) investigated global principles of signal transmission in the inner retina by intracellularly manipulating single BCs in the whole-mounted salamander retina and simultaneously recording the spiking activity of many surrounding RGCs. They showed that AC function is critical for diversifying the signal properties (e.g. kinetic, adaptation) of different types of BC and RGC – another universal role of ACs.

To further investigate how inhibition from ACs shapes the visual signal in the inner retina in a general manner, one would ideally get closer to the critical site of AC interactions and monitor the activity in the cellular compartments that directly receive the inhibitory inputs. These include the axon terminals of BCs as well as dendritic processes of both ACs and RGCs. Here, optical population imaging of neuronal activity comes to shine. In contrast to electrical somatic recordings, which typically give only a limited representation of what happens in individual neuronal compartments distal to the recording site like axon terminals (Oltedal et al., 2006) or dendrites (Poleg-Polsky and Diamond, 2011), an optical imaging approach permits to record the activity of many sub-cellular structures in parallel at micrometer-resolution. Moreover, genetic targeting in combination with the spatial resolution provided by the imaging system allows unambiguous identification of the origin of the recorded signals (e.g. (Duebel et al., 2006; Odermatt et al., 2012; Yonehara et al., 2013)). Several recent studies drew on the opportunities provided by an optical approach to address general features of inner retinal function (e.g. characterisation of BC and RGC function in mouse and zebrafish (Dreosti et al., 2009; Odermatt et al., 2012; Baden et al., 2013, 2016; Borghuis et al., 2013a; Nikolaev et al., 2013; Rosa et al., 2016)). Importantly, the diversity of available indicators (Lin and Schnitzer, 2016) selective for different neuronal events allows to not only record neuronal activity per se but a specific biological process. For example, since the development of the glutamate indicator iGluSnFR (Marvin et al., 2013), it is now possible to record light-evoked glutamate release from BC axon terminals throughout the IPL (Borghuis et al., 2013b). Unlike presynaptic calcium, glutamate release directly corresponds to the output of BCs, not only accounting for presynaptic inhibition (e.g. (Borghuis et al., 2014)) but also any release dynamics of BC ribbon synapses (Burrone and Lagnado, 2000; Cho and von Gersdorff, 2012; Nikolaev et al., 2013). Another example relevant for studying

ACs are chloride indicators. They allow monitoring changes in the intracellular chloride concentration (e.g. (Duebel et al., 2006)) which can be directly linked to inhibitory inputs and therefore represent a promising tool for unravelling AC function in BC axon terminals and AC and RGC dendrites.

Evidence for a universal role of amacrine cells

A recent study (Rosa et al., 2016) used *in vivo* population imaging of calcium signals in zebrafish BC axon terminals to investigate the role of crossover inhibition on temporal signalling in the inner retina. Electrophysiological studies had shown before that crossover inhibition is involved in a variety of functions (Werblin, 2010), such as the compensation of synaptic rectification (Molnar et al., 2009). The large dataset of calcium responses across different strata of the IPL in combination with pharmacological manipulations allowed the authors to identify a novel, systematic effect of crossover inhibition on frequency tuning of BCs: While crossover inhibition shifts band-pass synapses into low-pass and therefore generates the sustained Off channel in the inner retina, it suppresses contrast responses in On BC terminals.

Recently, Franke and co-workers (Franke et al., 2016) systematically recorded glutamate release of >13,000 BC axon terminals across the whole IPL to investigate how AC circuits help to decompose the visual scene into the parallel channels carried by the BCs in mouse. By applying light stimuli of different spatial scales, they compared centre (“local”) responses – dominated by the excitatory input from photoreceptors – with centre-surround (“full-field”) responses – additionally including the inhibitory inputs from ACs. The authors found that the functional diversity among BCs critically relies on inhibitory inputs from ACs: While local responses are highly similar across BC types of the same response polarity (Fig. 2a), additional surround stimulation significantly increases the functional differences (decorrelates) between BCs (Fig. 2b). Already before, several studies demonstrated the effect of axonal inhibition provided by ACs for modulating temporal and spatial properties of BCs (Eggers et al., 2007; Purgert and Lukasiewicz, 2015). However, so far the importance of these axonal inputs for diversifying BC responses was underestimated compared to dendritic mechanisms like the expression of specific glutamate receptors (DeVries et al., 2006; Lindstrom et al., 2014). By using pharmacological manipulations they showed that GABAergic wide-field ACs provide the decorrelating inhibition to BC axon terminals. In contrast, glycinergic small-field ACs mainly shape BC function indirectly by gating the spatially extensive GABAergic network, challenging the classical view that small-field ACs are predominantly involved in local signal processing. Together these findings suggest that the two major groups of AC of the mouse retina act together to set the ratio of excitation and inhibition. This cooperative action increases functional diversity in the inner retina. The study also demonstrates a general and AC group-specific effect of GABAergic and glycinergic ACs across different BC types and IPL strata. Since ACs also provide inhibition to RGCs, there might be an additional step of signal decorrelation at the level of RGC dendrites (see (Asari and Meister, 2012)).

Amacrine cell function – specific or general?

What is the functional significance of the diverse population of ACs? Does every AC type have an isolated and specific function in one distinct circuit? Conversely, does every AC circuit contribute to more general effects of inner retinal computation? The truth probably lies somewhere in the middle. Clearly, at least some AC types have developed highly specific morphological and functional adaptations to perform particular computations (e.g. starburst

or A17 AC, see above). Despite these selective adaptations, the functions of individual AC types may still combine to serve a common goal. There is a rapidly growing body of literature (e.g. (Asari and Meister, 2012; Johnston and Lagnado, 2015; Franke et al., 2016; Rosa et al., 2016) arguing that general functions of ACs across types are critical for establishing universal principles of retinal signalling like parallel processing or motion anticipation.

Future directions

To get a better understanding how individual and general AC functions are organised will require a comprehensive characterisation of morphological and functional aspects of ACs, both at high resolution as well as the population level. In particular, for verifying the concept of a general mode of action of ACs it will be important to explore to what extent general computations performed by the population of ACs are independent of individual AC types. This might for example be achieved by deactivating single genetically defined AC populations. Here, transcriptional analysis (Macosko et al., 2015) in combination with large-scale electron microscopy (EM) datasets (e.g. (Helmstaedter et al., 2013)) will serve to identify the number of AC types and make them more accessible for targeted genetic manipulations. In parallel, advances in the development of sensors for imaging inhibition (e.g. (Paredes et al., 2016)) promise to provide a more direct approach for studying the role and integration of inhibitory inputs in inner retinal circuits at sub-cellular resolution in the near future. However, doing these types of experiments in a single species (like the mouse) may prove to be insufficient. After all, the degree of generality of AC function might vary for different species. To therefore truly probe to what extent general AC actions are a universal feature of inner retinal signalling it will be critical to compare results across species. Taken together, combining these different approaches will provide new insights into how the single AC circuits act together to shape information processing in the early visual system in a general manner.

Figure legends

Figure 1 | Organisation of the amacrine cell network in the inner retina. **a**, In the retina, photoreceptors (PRs, *purple*) transduce the visual input into an electrical signal and feed into bipolar cells (BCs, *green*) which provide input to the retina's output neurons, the retinal ganglion cells (RGCs, *blue*). This vertical excitatory pathway is extensively modulated by inhibitory amacrine cells (ACs) in the inner retina. Here, wide-field ACs (*red*) mainly transfer information laterally within individual synaptic layers, while small-field ACs (*orange*) predominantly mediate vertical signalling across synaptic layers. Arrows indicate main signal flow. HC: Horizontal cells (*yellow*). **b**, ACs form a complex and dense synaptic network in the inner plexiform layer. In mammals, wide-field ACs use GABA as neurotransmitter (brown vesicles), while small-field ACs use glycine (yellow vesicles). Bipolar cells use glutamate (grey vesicles). **c**, ACs provide inhibitory inputs to BC axon terminals (presynaptic inhibitory inputs), RGC dendrites (postsynaptic inhibitory inputs) as well as to other ACs (serial inhibitory inputs).

Figure 2 | Example of a general function of amacrine cells. **a**, A local stimulus (100 μm diameter, *yellow*) mainly activates retinal pathways directly beneath the stimulus including PRs and BCs as well as small-field ACs. The glutamatergic output of individual BCs in response to such a local light step (*left*) and contrast flicker (*right*), is nearly independent of the specific BC type recorded from (of the same polarity) – here exemplarily shown for two On (CBC9 and CBC6) and Off (CBC1 and CBC3a) BC types, (Franke et al., 2016). The last

row of traces represents an overlay of the previous two rows. Colour intensity used to indicate expected stimulus-driven activity level of individual neurons. **b**, Full-field stimulation (600 μm diameter) additionally recruits wide-field ACs which provide inhibitory GABAergic inputs to BC axon terminals and AC dendrites. This lateral inhibition decorrelates the BC responses, thereby increasing the functional diversity across BC types (Franke et al., 2016). Because the response diversification is observed for all BC types, which receive inputs from different AC types, this effect illustrates an example of a general role of AC in inner retinal signalling.

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