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Dorsal raphe nucleus projecting retinal ganglion cells: Why Y cells?

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Abstract

Retinal ganglion Y (alpha) cells are found in retinas ranging from frogs to mice to primates. The highly conserved nature of the large, fast conducting retinal Y cell is a testament to its fundamental task, although precisely what this task is remained ill-defined. The recent discovery that Y-alpha retinal ganglion cells send axon collaterals to the serotonergic dorsal raphe nucleus (DRN) in addition to the lateral geniculate nucleus (LGN), medial interlaminar nucleus (MIN), pretectum and the superior colliculus (SC) has offered new insights into the important survival tasks performed by these cells with highly branched axons. We propose that in addition to its role in visual perception, the Y-alpha retinal ganglion cell provides concurrent signals via axon collaterals to the DRN, the major source of serotonergic afferents to the forebrain, to dramatically inhibit 5-HT activity during orientation or alerting/escape responses, which dis-facilitates ongoing tonic motor activity while dis-inhibiting sensory information processing throughout the visual system. The new data provide a fresh view of these evolutionarily old retinal ganglion cells.

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Keywords

Retinal ganglion cells; Alpha cells; Y cells; Dorsal raphe nucleus

1. Introduction

Evidence for a direct retinoraphe pathway in the mammalian central nervous system was first provided by Warren E. Foote and his colleagues in 1978; ganglion cells in the cat retina were shown to send afferent fibers to the serotonergic dorsal raphe nucleus (DRN) located in the midbrain/rostral pons (Foote et al., 1978). The pathway was initially demonstrated following the injection of tritiated amino acids into the vitreous chamber of the eye, which after being incorporated into proteins in retinal ganglion cells, were transported via ganglion cell axons in the optic nerve to retinorecipient sites in the brain including the DRN. Labeled ganglion cell terminals were observed throughout the DRN with a heavier input to the lateral aspects of the nucleus. To confirm this novel direct retinal pathway to the DRN that was identified using the autoradiographic anterograde tracing technique, the neuroanatomical tracer horseradish peroxidase (HRP) was injected into the DRN of additional animals. Following uptake into retinal ganglion cell terminals and retrograde axonal transport to the eye, HRP was observed in neurons with large somata in the ganglion cell layer of the retina. Based on ganglion cell soma size, it was hypothesized that the DRN-projecting retinal ganglion cells might belong to a specific morphological type of retinal ganglion cell in the cat retina which had been described just a few years earlier, the alpha retinal ganglion cell (Boycott and Wässle, 1974).

Since the original description of a direct retinoraphe pathway in the cat, a retinal projection to the DRN has been described in several mammalian species including primates (see below) and the alpha retinal ganglion cell has been found to be a consistent morphological cell type in the mammalian retina (Peichl, 1991). The functional significance of a retinal projection to a brainstem structure not previously considered to be part of the classic subcortical visual system had remained virtually unexplored until very recently (Ren et al., 2013). Herein we provide an overview of the retinoraphe pathway in mammals and highlight new data supporting the suggestion by Foote et al. (1978) that the retinal ganglion cells (RGCs) projecting to the DRN are similar to the classic alpha cells of the cat retina that also display the associated Y-like physiological properties of transient responses and non-linear spatial summation. Recent work demonstrating that retinoraphe signals are capable of modulating serotonergic tone in the DRN and affective behavior is also discussed. We conclude by offering a hypothesis suggesting why, among the myriad types of retinal ganglion cells that populate the mammalian retina, it is the alpha-Y type RGC that provides signals to the DRN, the major source of serotonergic afferents to the forebrain.

2. The visual system: parallel streams of signals from the retina to the brain

The perception of shapes, color and objects moving in the natural world begins when light is absorbed by photopigments in rod and cone photoreceptors located in the outer retina. The signaling cascade initiated by photon capture is then converted into an electrical signal. The simplest common pathway these signals take from the eye to the brain is from

photoreceptors to bipolar cells to ganglion cells (Fig. 1). RGCs convey the signals centrally as action potentials, transmitted via their axons in the optic nerve. It is now widely accepted as a basic organizational principle of the vertebrate retina that different types of ganglion cell transmit different aspects of the visual input to the brain via multiple parallel informational streams (Stone, 1983; Dacey, 2004; Wässle, 2004; Masland and Martin, 2007). Because RGCs project to a diverse set of brain structures that use different regions of the spatiotemporal frequency spectrum, the types of ganglion cell appear to be equally diverse in morphology and physiology, perhaps as suggested by Sterling (2004), to match the message to the specific ‘end user’; thus RGCs appear to comprise some 10–20 morphological types with the exact number depending on species and the parameters used for classification (see Masland, 2012a and references therein). While great advances have been made in recent years describing ganglion cell types based on morphology and/or molecular phenotype, a detailed understanding of how different morphological types of ganglion cell relate to different aspects of the visual image remains far from complete (Masland, 2012b).

2.1. Retinal ganglion cell axon collateralization

As mentioned above, it seemed reasonable to postulate that specific types of ganglion cell send their axons to specific targets in the brainstem with these parallel informational streams ultimately converging in the neocortex to give the unified coherent conscious experience of the visual world. But abundant data indicate that this is not the case since the great majority of individual ganglion cells project, via branching axons, to multiple targets such as the lateral geniculate nucleus (LGN), the thalamic nucleus relaying visual signals to the primary visual cortex, and the superior colliculus (SC), a midbrain multi-modal sensorimotor integration center (Dhande and Huberman, 2014). For example, in the rabbit almost all RGCs project to the SC (Vaney et al., 1981). In the cat, 50% of all RGCs project to the SC and 80% project to the LGN; at least 30% of all RGCs must therefore project to both the SC and LGN via axon collaterals (Kelly and Gilbert, 1975; Illing, 1980; Illing and Wässle, 1981; Wässle, 1982; Farid Ahmed et al., 1984; Kondo et al., 1993,1994). Intrinsically photosensitive retinal ganglion cells (ipRGCs) that innervate the hypothalamic suprachiasmatic nucleus (SCN), a circadian clock, send collateral branches to the intergeniculate leaflet (IGL), the SC and the olivary pretectal nucleus (OPN) (Pickard, 1985; Morin et al., 2003; Baver et al., 2008). A subpopulation of these ipRGCs also has axons that bifurcate within the eye *en route* to the optic disk, forming intra-retinal axon collaterals that terminate in the inner plexiform layer (IPL) of the retina (Joo et al., 2013), apparently to convey irradiance information to dopaminergic amacrine cells (Zhang et al., 2008, 2012). In the macaque monkey retina, approximately 90% of the RGCs project to the LGN (Perry et al., 1984). Thus in the primate retina, most if not all RGC types project to the LGN and/or SC (Dacey, 2004). Bowling and Michael (1980) impaled single optic tract fibers in the cat and after physiological characterization and intracellular filling with HRP they reported that individual Y (alpha) ganglion cell axons branched repeatedly, sending collaterals to the SC, the medial interlaminar nucleus (MIN), and to one or more laminae within the dorsal LGN (Fig. 2). A later study using the smaller tracer molecule biocytin to fill individual Y-cell axons, consistently revealed additional collaterals to the pretectum (Tamamaki et al., 1995).

The RGCs that innervate the DRN also have branching axons that terminate in multiple targets. DRN-projecting RGCs send axon collaterals to both the LGN and SC (Fite et al., 2003; Luan et al., 2011). RGC axon collateralization is thus a prominent feature of the mammalian visual system and an important way in which RGCs convey the same information simultaneously to diverse end users in parallel streams (Giolli and Towns, 1980) (Fig. 3). In the discussion that follows we assume that the same information reaches all terminal branches of DRN-projecting RGC axons. However, we acknowledge that there are data showing that in some systems, action potentials carried by axon collaterals can be blocked or altered under certain conditions (Debanne et al., 1997).

3. Retinal afferents to the dorsal raphe nucleus

In addition to the retinoraphe pathway described in the cat (Foote et al., 1978), retinal afferent fibers have been reported to innervate the DRN in several mammalian species including the rat (Sprague Dawley and Wistar), Mongolian gerbil (*Meriones unguiculatus*), Chilean degus (*Octodon degus*), tree shrew (*Tupaia belangeri*) and a new world monkey (*Cebus apella*) (Shen and Semba, 1994; Kawano et al., 1996; Fite et al., 1999; Reuss and Fuchs, 2000; Fite and Janušonis, 2001; Frazão et al., 2008; Luan et al., 2011). A retinoraphe projection has not been observed following intraocular tracer injections in the golden hamster (*Mesocricetus auratus*), the California ground squirrel (*Spermophilus beecheyi*) or the Nile grass rat (*Arvicanthis niloticus*) (Major et al., 2003; Morin and Allen, 2006; Gaillard et al., 2013). In the mouse, only a very weak retinal projection to the region of the DRN (Hattar et al., 2006) or no retinoraphe projection has been observed (Morin and Studholme, 2014).

It remains to be determined whether these reported differences in the retinoraphe projection arise from adaptive-phylogenetic differences or from technical issues. There is evidence that at least some of the reported differences might be technique related. For example, as mentioned above, Foote et al. (1978) described the retinoraphe pathway in the cat using intraocular ³H-amino acid injections and the autoradiographic procedure whereas others more recently did not report retinal afferent fibers to the cat DRN following intraocular injections of the anterograde tracer cholera toxin B (CTB) visualized using anti-CTB and the avidin–biotin method (Matteua et al., 2003). In the negative report of a retinoraphe projection in the ground squirrel, a similar CTB tracing method was used (Major et al., 2003). Shen and Semba (1994) compared retinal afferent fiber labeling in the rat DRN using different tracers. Differences in DRN fiber density were reported with CTB-HRP being the most sensitive (i.e., CTB-HRP > CTB ≫ HRP). They also examined survival times after intraocular injections ranging from 3 to 21 days and indicated that at least 7 days was required for optimal labeling; most of the negative reports described above used shorter survival times. However, intraocular CTB-Alexa Fluor injections do label retinoraphe projections in the rat and gerbil (Zhang, Li, Lu, Pickard, Pu, So and Ren, unpublished observations). It is also possible that the thin axonal branches of the ganglion cells innervating the midbrain present a barrier limiting effective transport of some tracer molecules in particular species (Tamamaki et al., 1995). Thus it seems that the inability to visualize a retinoraphe projection in at least some instances may be due to technical issues arising from anterograde tracing methods. Tracer injections into the DRN to retrogradely

label RGCs may prove to be a more effective way to consistently demonstrate a retinoreciprocal projection (Foote et al., 1978; Shen and Semba, 1994; Fite et al., 1999; Luan et al., 2011). Recent advances in defining monosynaptic inputs onto serotonergic neurons in the DRN may also be especially useful in resolving some of these questions (Dorocic et al., 2014; Ogawa et al., 2014).

Among the species in which a retinal projection to the DRN has been described to date, the terminal field appears to be most robust and well defined in the Mongolian gerbil and therefore this rodent has emerged as the ‘model system’ for investigating the retinoreciprocal projection in mammals. In general, the pattern of innervation of the DRN is similar among animals; retinal afferent fibers emerge from the optic tract at the level of the pretectum/anterior SC and descend into the periaqueductal gray (PAG) to form a plexus in the DRN. Retinal fibers are distributed from each eye bilaterally throughout the rostrocaudal extent of the gerbil DRN with the lateral aspects of the nucleus slightly more heavily innervated, similar to the cat (Fite et al., 1999). The subgroup of serotonin (5-HT) neurons in the lateral component of the mid-caudal DRN (i.e., lateral wings) is termed the ventrolateral part of the dorsal raphe nucleus/ventrolateral periaqueductal gray, DRVL/VLPGA (Hale and Lowry, 2011). Many neurons in the DRN synthesize 5-HT and these neurons give rise to ascending serotonergic pathways that innervate widespread areas of neocortex, striatum and forebrain limbic regions (see below). There is also a large population of GABAergic interneurons in the DRN. At present there are no anatomical data available that demonstrate which DRN neurons are postsynaptic to retinal afferents. Although ultrastructural examination has long been considered the gold standard for identifying synaptic interactions in the CNS, the relatively low density of retinal afferent fibers in the DRN renders electron microscopic analyses of optic synapses in the DRN a significant challenge. Recent advances using pre- and postsynaptic markers with triple-label confocal fluorescence microscopy and high-resolution immunofluorescence (array tomography) could be applied to determine the neurotransmitter signature of DRN neurons receiving retinal synaptic contacts (Wouterlood et al., 2002; Henny and Jones, 2006; Soiza-Reilly and Commons, 2014). Such detailed morphological information regarding the target neurons of retinal afferents in the DRN is necessary to further our understanding of the functional organization of this sensory pathway that modulates serotonergic neurotransmission.

Retrograde tracers injected into the DRN have been used to define the specific morphologic type of retinal ganglion cell that project to it. As mentioned above, DRN-projecting ganglion cells in the cat retina have large somata consistent with the morphology of the alpha retinal ganglion cell type (Boycott and Wässle, 1974; Foote et al., 1978). DRN-projecting ganglion cells were also described in the gerbil retina using similar techniques (Fite et al., 1999). Labeled DRN-projecting ganglion cells were distributed over the entire retina with significant regularity (non-randomness) in their distribution (a property of the alpha ganglion cell type, Peichl, 1991) although two populations of ganglion cell were suggested based on soma diameter (Fite et al., 1999). However, because retrograde tracer filling of the dendritic arbors of the labeled DRN-projecting ganglion cells was incomplete, information regarding dendritic field size, shape, or stratification pattern in the IPL was not available. The number of DRN-projecting ganglion cells was small; DRN-projecting ganglion cells in the gerbil retina were estimated to represent about 1% of all ganglion cells (Fite et al., 1999).

DRN-projecting RGCs in the gerbil retina have been analyzed in much greater detail more recently by intracellular filling of ganglion cells in retinas maintained *in vitro* following tracer injections into the DRN *in vivo*. In these experiments light-evoked responses were first recorded in DRN-projecting RGCs and then the cells were filled with dye to determine their morphology (Luan et al., 2011). Because intracellular dye filling labels the dendritic arbor in its entirety, several morphological characteristics of these cells were determined. Of 104 DRN-projecting retinal ganglion cells that were filled completely, approximately 85% of the cells exhibited morphological characteristics similar to the classic alpha cell morphology described in the cat retina: large somata, a large dendritic field, and dendritic processes that were straight and radially oriented with little overlap (Fig. 4) (Luan et al., 2011). In addition to the alpha-like cells, a small minority of DRN-projecting ganglion cells exhibited a completely different morphology with small but dense dendritic fields (Luan et al., 2011) consistent with the two types of ganglion cell afferent to the DRN suggested earlier by Fite et al. (1999). In summary, the morphology of the vast majority (85%) of DRN-projecting ganglion cells in the gerbil retina resembles that of alpha ganglion cells, supporting the suggestion made by Foote et al. (1978) that DRN-projecting cat retinal ganglion cells belong to the alpha retinal ganglion cell type.

4. DRN-projecting ganglion cells are alpha-Y retinal ganglion cells

Shortly after the identification of alpha cells as a morphological type of ganglion cell in the cat retina, it was determined by intracellular dye filling of ganglion cells after physiological recordings, that cat alpha cells were the anatomical substrate of the physiological brisk-transient Y cell in the cat retina (Cleland et al., 1975; Peichl and Wässle, 1981). Y cells were distinguished from the other major physiological type of cat ganglion cell described at the time, the X cell (which corresponded to the morphological beta cell), by their large concentrically organized receptive fields, brisk-transient responses to stimuli, enhanced sensitivity to moving stimuli, fast axonal conduction velocity, and non-linear spatial summation of stimuli presented over the receptive field.

X (β) cells have a linear receptive field computational mechanism, whereby they compute local temporal contrast by combining excitatory and inhibitory signals over both the receptive field center and antagonistic surround (Enroth-Cugell and Robson, 1966). The non-linear Y (α) cells have a receptive field computational mechanism which computes broad changes in contrast magnitude by summing signals from independent regions of the receptive field that combine at the ganglion cell to generate the response (Demb et al., 1999). Both Y (α) and X (β) ganglion cells were divided further based by their response polarity to spots of light presented to their receptive field centers; 'ON' cells increase firing in response to light increments and 'OFF' cells increase their firing in response to light decrements. These physiological responses correlate with the stratum in the IPL in which their dendrites ramify (Famiglietti and Kolb, 1976). Alpha-Y ON and OFF ganglion cells occur at about equal densities across the retina and form independent mosaics (Peichl, 1991). The physiological properties of retinal ganglion cells with large somata and large dendritic fields are similar across species ranging from frogs to primates suggesting that the alpha-Y cell may be a highly conserved retinal ganglion cell type (Table 1).

If the large alpha-like DRN-projecting retinal ganglion cells in the gerbil retina belong to the alpha-Y retinal ganglion cell type, then they should also exhibit the classic Y-like physiological properties associated with alpha cells including large receptive fields, transient responses and non-linear spatial summation. The physiological properties of DRN-projecting alpha ganglion cells were examined in the gerbil retina and indeed they have large receptive fields, transient responses and the characteristic pattern of non-linear spatial summation (Fig. 5) (Luan et al., 2011). The gerbil DRN-projecting alpha-Y ganglion cells were further classified physiologically as 'ON' or 'OFF' depending on where their dendrites ramified in the IPL; 80% ramified in the ON region of the IPL and the remaining 20% sent their dendrites into the distal OFF sublamina of the IPL (Luan et al., 2011). It is not clear at this time why there is the strong bias for ON DRN-projecting RGCs. Importantly, DRN-projecting alpha-Y RGCs were shown to also send collateral axons to innervate both the SC and LGN; different retrograde tracers were injected into the DRN and SC or DRN and LGN producing double-labeled ganglion cells (Fite et al., 2003; Luan et al., 2011). Triple-labeling experiments have not yet been performed but it seems very likely that individual alpha-Y RGCs may send axons to the DRN, SC, and LGN (see Bowling and Michael, 1980; Tamamaki et al., 1995) and that these different end users use these signals for both visual perception and for additional non-image-forming functions.

4.1. DRN-projecting alpha-Y ganglion cells do not appear to be ipRGCs

In 2002 a new photoreceptor was discovered in the mammalian retina in addition to rods and cones (Berson et al., 2002; Hattar et al., 2002). Ganglion cells projecting to the SCN were shown to express an invertebrate-like opsin, melanopsin that renders these retinal ganglion cells intrinsically photosensitive (ipRGCs) (see Pickard and Sollars, 2012 for review). Using immunocytochemical techniques and electrophysiological recording three different subtypes of ipRGCs were subsequently identified that varied in their dendritic stratification pattern in the IPL, their intrinsic photosensitivity and their targets in the brain (Baver et al., 2008; Schmidt and Kofuji, 2009, 2010). More recently, cre-lox mouse lines have been developed that identify ipRGCs with greater sensitivity than was previously possible. In these mice, two additional morphological types of ipRGC have been identified that express EGFP driven from the melanopsin promoter and ipRGC sub-types are now termed M1-M5 (Ecker et al., 2010). It has been reported that the M4 sub-type corresponds to the ON-alpha retinal ganglion cell with alpha-like morphology and the characteristic Y-like nonlinear pattern of spatial summation (Estevez et al., 2012). However, M4 ipRGCs express such low levels of melanopsin that immunocytochemical amplification procedures are necessary to detect the protein and even then not all M4 cells expressing EGFP are positive for melanopsin protein although they all show a weak intrinsic response to light; these ipRGCs project to the LGN and play a functional role contributing to visual contrast sensitivity (Estevez et al., 2012; Schmidt et al., 2014).

The mouse M4 ganglion cell differs however, from other alpha-Y ganglion cells described to date including the DRN-projecting alpha-Y ganglion cells in the gerbil retina. M4 ganglion cells show a strong sustained response to light stimulation of their receptive fields unlike the transient responses described in all other alpha-Y ganglion cells (Table 1). Classic alpha-Y ganglion cells are designed to detect movement and a sustained response to stimuli

would not seem optimal for the detection of moving stimuli. In addition, all the M4 ipRGCs in the mouse retina are 'ON' retinal ganglion cells (Estevez et al., 2012; Schmidt et al., 2014), not showing the typical ON and OFF pairing characteristic of alpha-Y retinal ganglion cells (Peichl, 1991). Thus the mouse M4 ipRGC does not appear to be a classic alpha-Y type RGC and there are no reports that M4 ipRGCs send afferent fibers beyond the thalamus. Consistent with this interpretation, Luan et al. (2011) were unable to detect melanopsin in gerbil DRN-projecting alpha-Y ganglion cells using standard immunocytochemical procedures. The DRN-projecting alpha-Y cells also showed no intrinsic response to light when rod/cone signals were blocked pharmacologically. Moreover, both ON and OFF alpha-Y retinal ganglion cells send axons to the DRN (Luan et al., 2011). It should be noted however, that immunocytochemical amplification procedures for the detection of melanopsin were not used when DRN-projecting ganglion cells were examined and that extracellular recordings were conducted when gerbil DRN-projecting ganglion cells were analyzed physiologically (Luan et al., 2011). Therefore if DRN-projecting ganglion cells in the gerbil retina do exhibit a small intrinsic melanopsin-mediated light-evoked membrane depolarization, it most likely would have been missed. Even with these caveats considered, it seems unlikely that the M4 ipRGC innervates the DRN or that M4 melanopsin-expressing ipRGCs are the classic alpha-Y retinal ganglion cell.

5. The DRN and serotonergic modulation of the visual system

The DRN is situated in the mesencephalon/rostral pons and from one- to two-thirds of the neurons in the DRN utilize 5-HT as a neurotransmitter (Kirby et al., 2003 and references therein). The large majority of DRN projection neurons are serotonergic and they are the major source of serotonergic input to the forebrain where 5-HT regulates the activity of local networks (Steinbusch, 1981; Jacobs and Azmitia, 1992; Abrams et al., 2004). As implied by their widespread projections, DRN 5-HT neurons are involved in a broad repertoire of physiological processes including the modulation of sensory processing and motivational states (Jacobs and Azmitia, 1992; Lucki, 1998).

DRN 5-HT neurons project in a topographic manner to many targets throughout the forebrain and lower brainstem via several ascending and descending pathways. The topographic organization of the subpopulations of DRN serotonergic neurons is complex with 5-HT subgroups organized in both rostrocaudal and dorsoventral planes. Serotonergic neurons located more rostrally project to fore-brain structures such as the caudate putamen, substantia nigra and to virtually all neocortical regions. Serotonergic neurons located more caudally project to other forebrain sites such as the septum, hippocampus and entorhinal cortex, suggesting that subpopulations of DRN serotonergic neurons may modulate specific forebrain systems (Abrams et al., 2004; Clark et al., 2006; Calizo et al., 2011; Vasudeva et al., 2011). Serotonergic neurons in the DRVL/VLPGA, the DRN region that receives the strongest input from the retina (Shen and Semba, 1994; Kawano et al., 1996; Fite et al., 1999), project to several structures of the central visual system, including the LGN, SC, IGL and primary visual cortex (Villar et al., 1988; Jacobs and Azmitia, 1992; Waterhouse et al., 1993; Janušonis et al., 1999, 2003) where 5-HT functions as a neuromodulator, actively shaping the response properties of visual system networks (Jacobs and Fornal, 1999a;

Hurley et al., 2004). Individual DRVL/VLPGA serotonergic neurons give rise to collateral projections to visual system targets such as LGN and SC (Pasquier and Villar, 1982; Villar et al., 1988) which allows for temporally coordinated modulation of these functionally related visual system circuits. In addition to having axons that exit the DRN, 5-HT neurons in the DRVL/VLPGA appear to exert inhibitory control over serotonergic projection neurons in the dorsal (DRD) and ventral (DRV) DRN subgroups, thus acting as serotonergic raphe–raphe interneurons (Ljubic-Thibal et al., 1999; Hale and Lowry, 2011; Janiska et al., 2012). Although it appears that DRN-projecting RGCs may have a slight preference to innervate neurons in the DRVL/VLPGA, DRN-projecting RGCs may modulate the activity of neurons in several DRN 5-HT subgroups either by direct retinal input or indirectly via 5-HT neuron interconnections within the DRN complex thereby contributing to the serotonergic modulation of diverse processes.

Serotonin mediates its effects through the activation of at least 14 different receptor subtypes. Adding to this complexity, 5-HT receptors are located presynaptically and postsynaptically, or both and they can undergo extensive post-translational modification (see Hannon and Hoyer, 2008 for review). Within visual areas of the brain (e.g., LGN, SC and SCN) 5-HT afferents generate a potent inhibition of visual responses via 5-HT_{1B} receptor-mediated presynaptic inhibition of glutamate release from retinal terminals (Mooney et al., 1994; Pickard et al., 1999; Belenky and Pickard, 2001; Smith et al., 2001; Chen and Regehr, 2003). 5-HT receptor-mediated postsynaptic mechanisms also inhibit visual processing (5-HT_{1A}, 5-HT_{2A}, 5-HT₃, and 5-HT₇) (Rogawski and Aghajanian, 1980; Kayama et al., 1989; Smith et al., 2001; Xiang and Prince, 2002) although the effect of 5-HT on neurons in the primary visual cortex may be dependent on the firing rate of retinogeniculate transmission (Seeburg et al., 2004; Watakabe et al., 2009). 5-HT_{2A} receptor expression is abundant in layer IV of the primary visual cortex in primates (Shukla et al., 2014) but not in rodents (Watakabe et al., 2009). In addition to its role in sensorimotor processing and perception, DRN 5-HT afferents play an important role in the modulation of other physiological processes including motivational states, stress, appetite, sleep, and aggression among others. A complete overview of the functional topography of the 5-HT DRN subgroups and behaviors they modulate is beyond the scope of this review (see Lucki, 1998; Abrams et al., 2004; Hale and Lowry, 2011; Paul and Lowry, 2013; Cohen et al., 2015).

Although the majority of DRN projection neurons utilize 5-HT as a neurotransmitter, the DRN is a heterogenous structure and many DRN neurons (i.e., 40–60%) are non-serotonergic. Other transmitters localized to DRN neurons include GABA, glutamate, dopamine, and several neuropeptides (Fu et al., 2010; Hioki et al., 2010). GABAergic interneurons within the DRN appear to play a particularly important role in shaping the response and/or tonic activity of DRN 5-HT neurons. DRN GABAergic interneuron terminals contact serotonergic DRN neurons which express GABA_A receptors and GABA application to the DRN strongly inhibits DRN serotonergic neurons (Michelsen et al., 2007). Glutamatergic afferents from the medial prefrontal cortex and lateral habenula nucleus converge on DRN GABAergic interneurons which in turn inhibit 5-HT neurons (Celada et al., 2001; Varga et al., 2003; Jankowski and Sesack, 2004) although recent work has also suggested a direct excitatory input to DRN 5-HT neurons from the lateral habenula (Dorocic et al., 2014) further illustrating the complexity of the DRN. Very recently Challis et al.

(2013) reported that experience-driven sensitization of DRN GABAergic neurons strengthened monosynaptic inhibition of DRN 5-HT neurons. Moreover, many GABAergic axons in the DRN are arranged in a synaptic triad with a glutamatergic axon and a common postsynaptic target. GABA can presynaptically gate glutamate release at this synaptic triad through a combination of a rapid/transient GABA_A-mediated facilitation and a more delayed and sustained GABA_B-mediated inhibition of serotonergic neuron activity (Soiza-Reilly et al., 2013). Although this synaptic arrangement is a common feature in the DRN, the source of the GABA axons shown to regulate excitation at the synaptic triad remains to be determined and it is unknown if this synaptic arrangement is shared equally among all DRN subgroups.

When activity driven c-Fos expression has been examined in the DRN, c-Fos levels increase almost exclusively in GABAergic DRN neurons (see below). These data provide additional support for the notion that inputs to the DRN may preferentially target local circuit DRN GABAergic neurons which suppress DRN 5-HT activity and that this reduction in 5-HT activity plays a prominent role in the ability of serotonergic neurons to influence sensory information processing. It should also be noted that GABAergic innervation of the DRN arises from multiple distant sources including the lateral and rostral hypothalamic preoptic areas, substantia nigra and ventral tegmental area as well as from local GABAergic interneurons (Gervasoni et al., 2000; Kirouac et al., 2004; Dorocic et al., 2014; Taylor et al., 2014).

6. Regulation of DRN serotonergic activity

The modulation of DRN neuron activity results from the complex interaction of glutamatergic excitatory and GABAergic inhibitory neurotransmission arising from extra-raphe regions as well as from local sources that also include serotonergic interneurons (McDevitt and Neumaier, 2011; Janiska et al., 2012; Soiza-Reilly and Commons, 2014; Dorocic et al., 2014; Ogawa et al., 2014). DRN 5-HT neurons vary their tonic activity across the sleep/wake cycle. During the quiet waking state DRN serotonergic neuron firing activity is slow and highly regular ($\approx 1-3$ Hz), upon entering slow-wave sleep the activity decreases and during rapid-eye-movement (REM) sleep activity falls virtually silent. However, as outlined below, Jacobs and Fornal (1999b) provide evidence that the involvement of DRN 5-HT activity in behavioral state control maybe a by-product of its more fundamental role in motor control and regulation of sensory information processing.

In their attempt to define specific stimuli that altered the activity of DRN 5-HT neurons in the freely behaving cat, Jacobs and colleagues recorded the response of DRN neurons to a variety of intense conditions, especially those that are biologically and ecologically relevant: thermoregulatory, cardiovascular and glucoregulatory challenges, tonic mildly painful stimuli, loud noise, physical restraint and a natural enemy (a dog). Despite that fact that these stimuli evoked strong behavioral responses, none of them significantly altered DRN 5-HT tonic neural activity beyond the level normally seen during an undisturbed active waking state (Veasey et al., 1997; Jacobs and Fornal, 1999b). These studies primarily interrogated DRN neurons on longer time-scale modulation, consistent with the view at the time that neuromodulatory systems were acting tonically. Transient responses of serotonergic neurons

have been less frequently studied but might be more revealing when attempting to define the role of the DRN in the modulation of specific behaviors (Nakamura et al., 2008). In freely moving rats, transient firing of DRN neurons has been shown to encode diverse and specific sensory, motor and reward events. The results were consistent with serotonergic neurons being able to suppress sensory responses at the earliest stages of cortical processing, perhaps via 5-HT₃ ionotropic receptors (Ranade and Mainen, 2009). Very recent work using optogenetic activation of DRN 5-HT neurons has shown that these cells signal information about reward and punishment on multiple timescales revealing the rich and diverse types of 5-HT signaling in the DRN (Cohen et al., 2015). It is now widely acknowledged that stressful events alter DRN 5-HT activity (Kirby et al., 2007) and stress-induced changes in 5-HT neuronal firing may happen on several timescales.

Bright light flashes (0.25–0.5 Hz) were also reported to evoke no clear change in the spontaneous firing rate of the recorded DRN units (Mosko and Jacobs, 1974; Shima et al., 1986). Auditory and light stimuli were reported to excite cat 5-HT DRN neurons but the responses in this study suggested that these effects were not from direct sensory afferents (Trulson and Trulson, 1982). Using a slightly greater stimulation rate of 2 Hz (to more closely match the spontaneous firing rate of DRN neurons) and for a longer duration, Fite et al. (2005) established that *in vivo* photostimulation could alter the activity of gerbil DRN neurons using c-Fos expression as an indirect measure of neural activity.

The light pulses used by Fite et al. (2005) may have more closely approximated moving stimuli, the preferred stimuli of alpha-Y retinal ganglion cells. These investigators reported that c-Fos expression in the gerbil DRN was altered by the light flashes but in a complex time of day dependent manner with increases in c-Fos expression during the late night but with decreases in c-Fos expression during the day and early night (Fite et al., 2005); it is not clear that the c-Fos expression observed was a result of direct retinorecipient stimulation. The neurotransmitter content of the DRN neurons expressing c-Fos was not determined in this study. However, in several other studies examining FOS expression in the DRN after diverse methods were used to stimulate the DRN (carbachol injections into the nucleus pontis to induce REM sleep, Torterolo et al., 2000; swim stress, Roche et al., 2003; two models of depression, Berton et al., 2007; high frequency stimulation of the subthalamic nucleus, Tan et al., 2011), increases in FOS immunoreactivity were noted almost exclusively in DRN GABAergic interneurons which, as indicated above, synapse with and inhibit DRN 5-HT neurons. Activation of orexinergic signals to the DRN that originate in the lateral hypothalamus has also been reported to increase DRN c-Fos expression but only in non-serotonergic, presumably GABAergic, interneurons (Adidhama et al., 2012).

It seems reasonable to conclude that the type of photic stimulus, the duration of the stimulus, the intensity and perhaps even the time of day the stimulus is applied may affect how the DRN responds to light. Ren and colleagues recently investigated the role of retinal input to the DRN by creating a model in which a subset of DRN-projecting retinal ganglion cells were continually active with at least a sixfold increase in their spontaneous firing rate (Ren et al., 2013). In doing so, these investigators circumvented the specific light stimulation parameters required to alter DRN activity. In their model, rod and cone photoreceptors were selectively eliminated in gerbils using *N*-methyl-*N*-nitrosourea (MNU), a direct acting

alkylating agent that targets photoreceptors. The elimination of photoreceptors produced an increase in the firing rate of the OFF DRN-projecting alpha-Y ganglion cells in animals maintained in constant darkness. In this model only OFF ganglion cells show increased spontaneous activity since ON ganglion cells appear to depend on tonic excitatory input to drive resting activity whereas OFF ganglion cells continue to fire in the absence of synaptic input (Margolis and Detwiler, 2007,2011). It is worth noting that a similar change in the spontaneous firing rate of OFF retinal ganglion cells is also observed in other animal models of photoreceptor degeneration (Royal College of Surgeons dystrophic rat, Pu et al., 2006; P23H transgenic rat, Sekirnjak et al., 2011) indicating that the increased activity in OFF DRN-projecting ganglion cells in the MNU-treated animals was due to photoreceptor loss rather than to an effect of MNU on retinal ganglion cells.

It is known that maintaining rodents, including gerbils, in constant dark conditions produces a depressive-like behavioral state (Gonzalez and Aston-Jones, 2008; Lau et al., 2011; Monje et al., 2011). This depressive-like condition induced by constant darkness was reversed in MNU-treated animals with increased spontaneous activity of DRN-projecting OFF alpha-Y retinal ganglion cells; DRN serotonin levels were also changed in these animals (Ren et al., 2013). The effect of increased spontaneous activity in the subset of OFF retinal ganglion cells afferent to the DRN on depressive-like behavior was equivalent to treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine and the anti-depressant imipramine. Moreover, silencing retinal ganglion cell firing or specific immunotoxin ablation of DRN-projecting retinal ganglion cells increased depressive-like behaviors (Ren et al., 2013). The findings demonstrate for the first time, that retinoraphe signals modulate DRN serotonergic levels and affective behavior. These findings raise the possibility that the well documented photic effects on mood (Stephenson et al., 2012), may be mediated at least in part via the direct retinoraphe projection.

7. Why Y cells?

In the preceding discussion we have provided an overview of the data establishing that retinal ganglion cells with alpha-like morphologic and Y-like physiologic characteristics provide the dominant retinal input to the DRN and that serotonergic neurons of the DRN dynamically sculpt ongoing sensory processing in the visual system by inhibiting visual input via several 5-HT receptor mechanisms. In addition, we briefly reviewed the relationship between DRN 5-HT neuron activity and behavioral state suggesting that this relationship may be a by-product of its more fundamental role in motor control and regulation of sensory information processing and that both transient modulation of 5-HT neuron activity may be a short timescale modulation in addition to the tonic change in activity associated with behavioral state. Now we address the question of why alpha-Y retinal ganglion cells send afferent fibers to the DRN in the context of the role DRN 5-HT neurons play in modulating motor and sensory systems.

DRN 5-HT activity is almost totally suppressed during REM sleep which is characterized by an inhibition of the motor neurons controlling anti-gravity muscle tone. This led Jacobs and colleagues to examine the relationship between DRN 5-HT activity and muscle tone and a strong positive association was observed. More specifically, a subset of DRN-5-HT neurons

increase their activity during oral-buccal activities such as chewing/biting, licking or grooming and the increased activity terminates with the end of the behavior. On the other hand, during attentional shifts in response to novel stimuli, DRN serotonergic neurons may fall silent (Jacobs and Fornal, 1999b). Thus, an increase in the activity of serotonergic DRN cells over baseline waking levels is strongly related to the level of tonic motor output; an increase in serotonergic neurotransmission facilitates motor output (Jacobs and Fornal, 1993). At the same time, this increased activity of serotonergic DRN cells inhibits information processing in sensory afferent systems; serotonin inhibits information processing in the visual system at both thalamic (Rogawski and Aghajanian, 1980; Kayama et al., 1989; Monckton and McCormick, 2002) and cortical levels (Waterhouse et al., 1990). In rats performing an odor-guided spatial decision task, transient activation of DRN neurons was observed during port entry and exit (motor facilitation) and inhibition of DRN neurons during odor sampling (sensory disinhibition and motor inhibition (Ranade and Mainen, 2009). A decrease in serotonergic DRN cell baseline waking activity levels occurs when animals respond to a strong or novel visual stimulus. This typically occurs in association with large eye movements, turning of the head or orienting toward the stimulus with concurrent suppression of ongoing movements, when 5-HT DRN activity falls completely silent for many seconds. Thus, during orientation responses ongoing tonic motor activity is dis-facilitated and sensory information processing is disinhibited by the dramatic reduction in DRN 5-HT activity (Fornal et al., 1996).

We offer the possibility that signals arising in the retina itself may alter processing in the visual system via the serotonergic DRN in a feed-forward manner. This hypothesis suggests why, among the 10–20 types of retinal ganglion cells that have been described to date, it is the alpha-Y ganglion cell that provides the majority of retinal signals to the DRN. The alpha-Y ganglion cell responds with the shortest latency and the fastest conduction velocity amongst all retinal ganglion cells (30–40 m/s), about twice as fast as that of the cat X (β) ganglion cell (17–23 m/s) (Cleland et al., 1971). We propose that retinal alpha-Y ganglion cell input to the DRN facilitates orienting/escape responses and/or responses to novel moving stimuli and that the optic fibers synapse primarily on DRN GABAergic interneurons. These local GABAergic neurons then inhibit DRN 5-HT neurons thereby reducing 5-HT activity which dis-facilitates tonic motor activity and dis-inhibits processing of retinal signals in the LGN, SC, and visual cortex and in carnivores also the MIN.

The alpha/Y retinal ganglion cell has a large receptive field with an antagonistic center-surround organization and uses a complex computational mechanism to sum stimuli over the dendritic field (non-linear summation) (Demb et al., 1999). The wide dendritic field allows alpha-Y cells to collect and sum information from many photoreceptors via many bipolar cells improving the signal-to-noise ratio and thus allowing greater contrast sensitivity; threshold for a spot stimulus over the dendritic field can be as low as 0.8% contrast (Dhingra et al., 2003). Wide spatial summation reduces sensitivity to high spatial frequencies thus allowing these cells to encode higher temporal frequencies. Lastly, a consequence of wide-field summation is a vigorous response to a fine stimulus that reverses contrast or moves within the dendritic field (Sterling, 2004). These non-linear response properties of alpha-Y ganglion cells serve two of its end users well, the cortical area MT that receives alpha-Y signals via the LGN and detects motion as an attribute of visual perception and the SC that

responds to movement by generating orienting responses, eye movements or defensive movements such as escape or avoidance behavior (Comoli et al., 2012). The thick axons and high conduction velocity of alpha-Y ganglion cells are additional design features necessary for responding optimally to movement. If the third end user, the DRN uses retinal input to indirectly inhibit serotonergic neurons that modulate the activity of functionally related neuronal systems including retinal input to the SC, LGN and visual cortex, perhaps the DRN end user is concerned primarily with the speed at which the signals arrive from the retina and therefore uses collateral branches from the fastest conducting retinal ganglion cells, the alpha-Y cell to modulate visual input.

Alpha-Y retinal ganglion cells with collateral axonal projections to the LGN, SC, MIN and DRN appear perfect to mediate these responses. A novel stimulus such as a sudden movement in the alpha-Y cell receptive field: (1) is perceived rapidly via the LGN/cortical stream but with low resolution as the alpha-Y cell extracts as fast as possible the minimum amount of information necessary for a quick response (Li, 1992); (2) initiates an alerting/escape response via input to the SC, a multi-modal visuomotor integration and coordination center with considerable efferent projections to the brainstem and spinal cord (Dean et al., 1989; Schenberget al., 2005; Liu et al., 2011; Comoli et al., 2012); (3) is better perceived in dim light conditions since Y-cell input to the MIN in carnivores arises from the region of the retina coincident with the tapetum (Lee et al., 1984); and (4) rapidly suppresses DRN serotonergic neuron tonic activity which dis-facilitates ongoing motor activity and removes inhibition of visual system information processing, especially the high resolution ganglion cell afferents in the LGN. Retinal afferent fibers terminating in the LGN contain presynaptic 5-HT_{1B} receptors that when activated inhibit retinal ganglion cell glutamate neurotransmission and thus a reduction in DRN 5-HT activity dis-inhibits retinal input to the LGN (Chen and Regehr, 2003). Similarly, during attentive fixation the response of visually driven neurons in the posterior parietal cortex is enhanced, most likely due to a decrease in DRN 5-HT activity (Mountcastle et al., 1981).

It is interesting to note that the behavior of amphibians provides an appealing phylogenic comparison to the Y-cell hypothesis put forth herein for mammals. Frogs jump away when a predator approaches. The stimulus on the retina that elicits this escape behavior, a looming or expanding dark object, is conveyed to the colliculus exclusively via OFF alpha-Y RGCs, the 'dimming detectors' (Arai et al., 2004; Ishikane et al., 2005). In the case of the frog, this response does not require cortical evaluation of the nature of the pending danger or additional modulation of the Y-cell input via serotonergic systems. Since these animals are equally at home in water and on land, the specific direction of their leap is of little consequence, they simply tend to leap toward where it is darker (Lettvin et al., 1959). Recently, an 'approach-sensitive' OFF retinal ganglion cell with alpha-like morphological characteristics has been identified in the mouse. It is suggested that these cells fulfill an 'alert function' by signaling approaching motion such as that of a bird of prey (Münch et al., 2009). An alpha Y-like cell mediating an alerting signal would be well suited for the rapid initial analysis of the gross features of the approaching object; it is of little consequence whether the bird of prey is an eagle or a hawk. In freely behaving rats, eye movements keep the visual fields of the two eyes continuously overlapping above the animal at the expense of binocular alignment. Overhead looming objects were shown to initiate an immediate escape

response (Wallace et al., 2013). The maintenance of constant overhead surveillance by a retinal system that counteracts rapid head movements may be an evolutionary old system mediated by the highly conserved alpha-Y cell.

As described above, Ren and co-workers reported that increasing the spontaneous activity of the OFF DRN-projecting alpha-Y cells produced a profound decrease in depressive-like behavior and an increase in the number of DRN 5-HT neurons in the lateral DRN expressing 5-HT detected using immunocytochemical procedures (Ren et al., 2013). These data suggest that in this model the Y-cell retinorecipient projection stimulates DRN neuron 5-HT production and/or neurotransmission. At first glance these data appear to be at odds with the proposed hypothesis: Y-cell input to the DRN, evoked by moving/looming stimuli facilitates orientation/escape responses via a reduction in 5-HT neuronal activity. However, in the model of Ren et al. (2013) in which all rod and cone photoreceptors were eliminated, only DRN-projecting OFF alpha Y-cells increased spontaneous firing and OFF alpha-Y cells comprise only 20% of the alpha-Y cell input to the DRN (Luan et al., 2011). Thus in the intact animal the great majority of alpha Y-cell input to the DRN is from ON alpha Y-cells. At present, nothing is known regarding the neuron targets within the DRN that receive ON Y-cell and OFF Y-cell inputs. It is possible that within the heterogeneous DRN 5-HT and GABA neurons might be targeted by different Y-cell types and this could explain the apparent inconsistency in the hypothesis. If OFF DRN-projecting alpha-Y retinal ganglion cells, representing 20% of the Y-cell cell input (Luan et al., 2011), target DRN 5-HT neurons then DRN 5-HT neuronal activity would have been increased in the MNU-treated animals described by Ren et al. (2013) (DRN-projecting ON Y-cells were silent). If on the other hand, ON DRN-projecting alpha-Y retinal ganglion cells, which represent 80% of the Y-cell input to the DRN (Luan et al., 2011), synapse on DRN GABA interneurons that inhibit DRN 5-HT neurons, then in the intact animal natural stimuli activating both ON and OFF DRN-projecting Y-cells would collectively result in a reduction of DRN 5-HT neuron tonic activity (Fig. 6). Fortunately, this prediction of ON Y-cell input to DRN GABA neurons and OFF Y-cell input to 5-HT neurons can be tested functionally by comparing c-fos expression in GABA and 5-HT neurons in control and MNU-treated animals. If OFF Y-cells selectively innervate 5-HT cells then these cells should selectively increase Fos expression in MNU-treated animals in which ON Y-cells are silent. Preliminary results indicate that Fos expression in the gerbil DRN is significantly increased in DRN 5-HT cells in animals treated with MNU (Zhang, Li, Lu, Pickard, Pu, So and Ren, unpublished observations) data consistent with the model presented in Fig. 6. Determination of the neurotransmitter phenotype of all DRN neurons receiving ON and OFF Y-cell input will provide further insight into the functional role of the highly conserved retinal Y-cell and its projections to visual nuclei and the DRN.

The discussion has been focused on the alpha Y-cell input to the DRN and its potential role in escape/orientation responses to moving or looming stimuli. However, in addition to the DRN-projecting Y-cells, another morphological type of retinal ganglion cell also sends axons to the DRN, although these cells represent only about 15% of the ganglion cell population afferent to the DRN (Luan et al., 2011). In the study of Ren and colleagues in which DRN-projecting ganglion cells were eliminated and depressive-like behavior was increased, all DRN-projecting ganglion cells would have been ablated including the non-Y

cell population (Ren et al., 2013). The role of non Y-cell DRN-projecting ganglion cells in regulating DRN 5-HT signaling is unknown. The input from retinal ganglion cells may play a role in mediating photic effects on DRN serotonergic tonic activity contributing to baseline activity during waking hours. Overall reduction of retinal activity including DRN-projecting RGCs (i.e., constant dark conditions) induces a depressive-like behavioral state and an increase in spontaneous firing of OFF Y-cell input to the DRN reverses this state and increases serotonergic tone (Ren et al., 2013). Thus, the retinoraphe pathway may contribute to the well documented effects of light on mood.

8. Summary

Retinal ganglion cells with large somata, large dendritic fields, and a complex spatial summation mechanism, the classic alpha-Y retinal ganglion cell, described initially in the cat retina, send axons into the optic nerve that branch repeatedly and terminate in at least four sites that perform very diverse functions, the LGN, MIN, SC and DRN. The same signals are apparently used quite differently by each end user. The alpha-Y retinal axons terminating in the LGN are used for rapid visual discrimination of potentially threatening movements but with fewer feature details, while those synapsing in the SC stimulate orienting/escape responses for quick action. The Y-cell branches innervating the MIN in carnivores assist in these process under dim light conditions and the retinal collateral branches terminating in the DRN may dynamically alter the activity of the serotonergic neurons, enhancing sensory processing in the LGN and SC while concurrently dis-facilitating tonic motor activity. Our hypothesis offers a new view on the complex role of the alpha-Y cell found in retinas from amphibians to primates. The current model is a first step toward unraveling the role of retinal input to the DRN and will certainly require modification as new data are generated. The complexity of the DRN cell types, afferents and efferents is daunting but recent technological advances offer the possibility that new insights into serotonin's many functions are not far away (Dayan and Huys, 2015).

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Fig. 1.

The layers of the mouse retina. The simplest common pathway for information flow in the retina is from photoreceptors to bipolar cells to ganglion cells. Ganglion cells send signals to the brain via the optic nerve

Figure adapted with permission from Masland (2012b).

Fig. 2.

A single ON-center Y-type retinal ganglion cell axon in the cat. After physiological recording and characterization as a Y-type cell, the ganglion cell axon was filled with horseradish peroxidase (arrow indicates site of injection into the axon). Axon filling allowed for re-construction of the entire axonal arborization showing its terminations in the dorsal lateral geniculate nucleus (LGNd), the medial inter-laminar nucleus (MIN), and the superior colliculus (SC). Only a small percentage of cat Y-type cells send additional axon collaterals to the DRN. Scale bar= 1 mm.

Figure adapted with permission from Bowling and Michael (1980).

Y (alpha)-cells project to visual nuclei and the DRN which in turn sends serotonergic afferents to the same visual structures

Fig. 3. Y-cells project to visual structures and the DRN. The DRN in turn regulates activity in visual nuclei. Brain schematic of serotonin system adapted with permission from Ranade et al. (2014) *Curr Biol* 24:R803-R805.

Fig. 4. Dendritic morphology of DRN-projecting RGC in the gerbil. The morphology of intracellularly injected DRN-projecting RGCs resembles the classic alpha RGC: large perikaryon, three to four trunk-like primary dendrites, and large dendritic field consisting of straight and radially oriented dendritic processes. Arrow depicts axon; scale bar= 100 μ m. Adapted from Luan et al. (2011).

Fig. 5.

Y-like physiological response properties of DRN-projecting RGCs in the gerbil. (A) Spatial frequency tuning characteristic of a Y-cell. Note the cell's response reached a peak at 0.07 c/°. (B) The peri-stimulus-time histograms of the cell's responses to contrast reversal sinusoidal gratings (spatial frequency: 0.07 c/°, temporal frequency: 2 Hz, contrast: 100%). The numbers to the left of the histograms depict spatial phases. Characteristic of Y-like cells, this cell had frequency doubling at two spatial phases, 0° and 180°, respectively. (C) Y-like fast Fourier transformation, the fundamental component (F1) is represented by

triangular symbols (Δ), while the second harmonic (F2) is shown with open circular symbols (o).

Adapted from Luan et al. (2011).

Fig. 6.
Model of ON and OFF Y-cell RGC input to the DRN. In animals with a normal retina (Intact) both ON and OFF Y-cells innervate the DRN with the vast majority (80%) showing an increase in firing rate with light increments and dendrites in the inner stratum of the IPL (ON-cells). It is hypothesized that ON Y-cells project predominately to GABA neurons in the DRN whereas the smaller population of OFF Y-cells afferent to the DRN (20%) synapse on 5-HT neurons. In MNU-treated animals all rod and cone photoreceptors die and OFF retinal ganglion cells (RGCs) show an increase in spontaneous activity resulting in a tonic increase in 5-HT neuron activity.

Table 1

Cross-species comparison of alpha-Y ganglion cells.

Species	Central projections	Discharge pattern	Conduction vel. (m/s)	Axon size	Dendritic field size range (μm)	Soma size range (μm)	Percent of all RGCs	Coverage factor	Range of acell density/ mm^2
Goldfish	Tectum ¹	Transient and non-linear ²							
Frog	Tectum and pretectum ^{3,4}	Transient and non-linear ³	2.4 ³		400–1000 ^{3,4}				
Killer Whale ⁵						80–100	3.1%		6–8
Rats	LGN, SC ^{6,7}	Transient and nonlinear ⁸	6.8–25 ⁹	19–22 ¹⁰ 20.4 ¹¹	α_o 550–780 α_i 350–550 ON>OFF45% ¹⁰ peripheral retina	α_o 19–22 ¹⁰ α_i 21–24 ¹⁰ α_o 22–28 ¹² α_i 22 $\pm$ 32 ¹²	3–4% ¹⁰ 1–5% ¹³	α_o 2.1 @ 5.2 mm ¹⁰ α_i 1.4 @ 5.2 mm ¹⁰	40–110 ¹⁰ 50–150 ¹³
Gerbil	LGN, SC ^{14,15}	Transient and nonlinear ¹³			255–541 ¹⁵	14–30 ¹⁵			
Rabbit	LGN, SC ^{16,17}	Transient and nonlinear ¹⁸	OFF 28.3 $\pm$ 8.23 ¹⁹ ON 20.6 $\pm$ 7.84 ¹⁹	15–31 ²⁰	180–1100 ²⁰	15–31 ¹⁶	1–1.4% ¹⁶	α_o 1.85 @ 2–7 mm ¹⁶ α_i 1.45 @ 2–7 mm ¹⁶	3–50 ¹⁶
Cat	LGN SC ^{21,22–25}	Transient and nonlinear ^{26–28}	Intraretinal 4.927 Extraretinal 51.9 $\pm$ 18.4 ²⁶	4–5.6 ²⁹	α_o 321–433 ³⁰ α_i 313–409 200–1200 ^{20,30}	α_o 19–22 ¹⁰ α_i 21–24 ¹⁰ 17–35 ^{21–30}	2–4% ^{20,30}	α_o 1.7 @ 3–4 mm ³⁰ α_i 1.35 @ 3–4 mm ³⁰	8–180 ^{20,30}
Macaque Monkey	LGN, SC ^{31–34}	Parasol ³² SM ³¹	Intraretinal 1.335 extraretinal 22.1 $\pm$ 8.6 ³⁵	Parasol 1.61–2.27 ³¹ SM 0.84–1.28 ³¹	Parasol 209 $\pm$ 70 @8mm ³⁶ SM 419 $\pm$ 110 P> SM 200% ³¹ SMi 318–528 SMo 278–532 ³¹	Parasol P_i 32.6 $\pm$ 4.9 ³⁷ P_o 30.2 $\pm$ 5.3 ⁵ 14–20 ³¹ SMi 14–18 SMo 13–17 ³¹	Parasol P_i 8% ³¹ P_o 8% ³¹ SM 3% ⁵	Parasol SM 1.7 @ 7–8 mm ³¹	
Human				Parasol 0.7–2 @ 8 mm ³⁸ 1.97 ³⁷	Parasol 225–375 @ 8 mm ³⁶ 170–210 @ 8 mm ³⁸	21.6 $\pm$ 3.55 ³⁷ 20–26 ³⁸	10% ³⁶		

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