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REVIEW ARTICLE

Efferent influences on the bioelectrical activity of the retina in primates

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Abstract
Purpose The existence of retinopetal (sometimes referred to as "efferent" or "centrifugal") axons in the mammalian optic nerve is a topic of long-standing debate. Opposition is fading as efferent innervation of the retina has now been widely documented in rodents and other animals. The existence and function of an efferent system in humans and non-human primates has not, though, been definitively established. Such a feedback pathway could have important functional, clinical, and experimental significance to the field of vision science and ophthalmology.
Methods Following a comprehensive literature review (PubMed and Google Scholar, until July 2016), we present evidence regarding a system that can influence the bioelectrical activity of the retina in primates.
Results Anatomical and physiological evidences are presented separately. Improvements in histological staining and the advent of retrograde nerve fiber tracers have allowed for more confidence in the identification of efferent optic nerve fibers, including back to their point of origin.
Conclusion Even with the accumulation of more modern anatomical and physiological evidence, some limitations and uncertainties about crucial details regarding the origins and role of a top–down, efferent system still exist. However, the summary of the evidence from earlier and more modern studies makes a compelling case in support of such a system in humans and non-human primates.

Keywords Centrifugal fibers · Efferent fibers · Retinopetal fibers · Retina · Electroretinogram

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Introduction

The existence of retinopetal (sometimes referred to as "efferent" or centrifugal") axons in the optic nerve and retina in humans and non-human primates is a topic of long-standing debate. Efferent innervation of the retina in birds was theorized in the late 1800s, subsequently confirmed, and is now widely accepted [1]. The discovery of such fibers in birds prompted the discovery of similar systems in other vertebrates:

amphibians, reptiles, and some mammals. However, despite mounting evidence, the existence and function of an efferent system influencing the retinal function in mammals, especially in primates, was considered controversial until recently (for a detailed review, see Reperant et al. [2, 3]).

Anatomical evidence for the existence of an efferent retinal pathway in mammals was extensively debated in the 1960s and 1970s, but with improvements in technique and retrograde tracers, the evidence is now difficult to argue against. Currently, the debate has shifted to the exact location of cellular origin of efferent fibers, the neurochemicals involved, and their exact purpose in the visual system. Additionally, a new possibility for the origin of some of the efferent fibers emerged recently: direct retino-retinal connections [4–6].

It is generally believed that retinopetal axons have an inhibitory effect on the retina, but its functional role in mammals is still unknown and only hypothesized. It is possible that such an inhibition has implications for a more complete understanding of mechanisms behind several already established phenomena where interocular dependence is implied. Examples of such phenomena include the influence of contralateral light and dark adaptation upon vision (sometimes referred as "tonic interocular suppression") [7–13], interocular transfer of motion aftereffects [14–16], and the "binocular capture" effect [17, 18]. Furthermore, interocular dependence has been demonstrated for effects of acute intraocular pressure-induced unilateral changes [19, 20] and unilateral scleral depression [21] on the electroretinogram (ERG) in both eyes. A better understanding of these phenomena would also go beyond physiological mechanisms and could reveal a potential role in a number of clinical conditions (e.g., traumatic optic neuropathy and amblyopia).

The following review is a succinct summary of the anatomical and physiological evidence for efferent influence on the retinal activity with an emphasis on non-human primates and humans, along with some hypotheses about its functional, clinical, and experimental significance to the field.

Anatomical evidence for centrifugal connections to the retina of non-human primates

In 1941, Polyak [22] described fibers of unknown origin within the retina of chimpanzee. He charted their course and described the features of these fibers, coming to the conclusion that they are of extraretinal origin. At the time, only a few studies had been done on efferent innervation of mammalian retinas, but the existence of such unclassified fibers lent itself to the idea that centrifugal fibers are a part of the primate retina just as they were a part of previously reported avian retinas. Centrifugal fibers are now differentiated based on their axonal diameter, argyrophilia, successive bifurcations as they proceed peripherally in the retina resulting in attenuation of the fibers, and by their descending trajectory from the nerve fiber layer into the inner nuclear layer [23] (Table 1). The course of centrifugal fibers in non-human primates was described by Brooke et al. [24] and later agreed upon by Noback and Mettler [25]. They concluded that retinopetal axons originate in the tectal region and pass through the midbrain, optic tract, chiasm, and nerve before terminating in the retina [25].

In rats, horseradish peroxidase (HRP)-labeled neuronal somas were consistently found in the medial pretectal area after intraocular injection of HRP [26]. A later study observed labeled tracer in the contralateral periaqueductal gray matter as well, indicating that the pretectum and the mesencephalon are sources of centrifugal innervation to the rat retina [27]. Similar results were subsequently found in monkeys using HRP; retrogradely labeled neurons were detected in the brain after HRP injection in the optic nerve [28]. The dorsal raphe nucleus has also been shown to house retinopetal nerve fibers in monkeys [29], as well as the periventricular nucleus of the hypothalamus, lateral hypothalamic area, and midline nuclei of the thalamus on both sides and in the most rostral portion of the lateral geniculate nucleus [30]. Reperant et al. [3] published a comprehensive comparative analysis of the functional and anatomical organization of centrifugal visual system in vertebrate, further confirming that the centrifugal visual system constitutes a universal component of the vertebrate CNS, but has a high degree of variation between species.

All pertinent studies that explicitly address the question of the existence of retinopetal axons in non-human primates are summarized chronologically in Table 1. It is worth noting that 13 of the 16 studies published to date are supportive and that only three studies report negative findings. It should be also pointed out that 7 of the 13 positive studies used silver impregnating technique without tracing the course of

Table 1 Anatomical evidence for efferent (centrifugal) fibers in the optic nerve of non-human primates

References	Primate species	# of animals	Findings	Positive
(A) Using non-tracing methods				
Polyak [22]	Chimpanzee	1+	Described fibers of unknown origin with morphological characteristics of efferent fibers; Golgi preparation[a]	√
Brooke et al. [24]	?	1+	Confirmed the existence of fibers with EM	√
Dowling and Boycott [36]	*Macaca mulatta*	1+	No EM evidence in Golgi preparations	
Dowling and Boycott [37]	*Macaca mulatta*	1+	No EM evidence in Golgi preparations	
Honrubia and Elliott [38]	*Macaca mulatta*	28	Histological evidence; silver impregnation and wholemounts; detailed tracing of the course	√
Anderson [39]	*Saimiri sciureus*	26	Was not able to identify efferent fibers in standard light microscopy (paraffin embedding; paraphenylenediamine) and EM	
Noback and Metler [25]	*Macaca mulatta*	14	Silver nitrate and crystal violet staining; four groups with different lesions; differentiate between retinofugal and retinopetal degeneration; fibers originate in SC	√
Khosla et al. [40]	?	6	Thick argyrophilic fiber-like structures; no intraretinal neuronal origin could be identified	√
Silveira and Perry [41]	*Macaca mulatta*	1+	Modified reduced silver stain for neurofilaments; extensively branched axons originating from the ONH—presumably centrifugal fibers	√
Usai et al. [42]	*Macaca fascicularis*	1+	Reduced silver technique and wholemounts; population of very thick (2.1 μm) fibers originating in ONH; running between RNFL and GCL	√
(B) Using tracer methods or immunohistochemistry				
Perry et al. [43]	*Macaca mulatta*	11	Few HPR-traced fibers emerging from the ONH and branching in IPL; most evident near the ONH and the perifovea; large area of influence	√
Labandeira-Garcia et al. [28]	*Macaca nemestrina*	3	HRP retrograde tracing in the optic nerve identified neurons in the hypothalamus (premammilary area and posterior hypothalamic area)	√
Gastinger et al. [31]	*Macaca mulatta*	1+	H-IR axons from ONH to periphery, branched extensively and terminated in IPL, occasionally along blood vessels. Other axons circled the fovea and returned to ONH	√
Gastinger et al. [32]	*Papio anubis* and *Macaca mulatta*	1+	5-HT-immunoreactive axons emerged from the optic disk; most ran to the peripheral retina where they branched; most terminated in GCL, few in INL	√
Frazao et al. [29]	*Cebus paella*	5	Retrograde tracing with CTb identified neurons in dorsal raphe nucleus in the brain	√
Abudureheman and Nakagawa [30]	*Macaca fuscata*	3	Retrograde tracing with CTb identified neurons in the hypothalamus, lateral hypothalamic area, and midline nuclei of the thalamus	√

EM electron microscopy, *SC* superior colliculus, *H-IR* histamine immunoreacted, *ONH* optic nerve head, *RNFL* retina nerve fiber layer, *GCL* ganglion cell layer, *INL* inner nuclear layer, *IPL* inner plexiform layer, *HRP* horseradish peroxidase, *5-HT* 5-hydroxytryptamine, *CTb* cholera toxin B

[a] Presented also in The Vertebrate Visual System, Ed: H. Kluver, University of Chicago Press, 1957, pp. 250–252 [44]

the fibers to their origin and, therefore, can only be of suggestive nature (part A of Table 1). On the other hand, the 6 remaining studies used either retrograde tracing of nerve fibers or immunohistochemical methods and therefore, can be considered much more specific and conclusive (part B of Table 1). Of

particular interest may be the finding of histamine-immunoreactive and serotonin centrifugal axons in the monkey retina [31, 32]. The presence of histamine-immunoreactive axons likely has physiological significance. Histamine can selectively enhance the voltage-gated potassium currents of on-bipolar cells in the macaque retina [33]. This would be expected to have a direct effect on the ERG b-wave, and this hypothesis could be tested directly with selective antagonists of the receptor. Recently, histamine receptors have also been shown in horizontal cells, amacrine cells, and in cone pedicels in macaque retina [34], expanding the number of possible influences on retinal function. Similarly, a variety of possible influences can be predicted for the serotonin centrifugal axons, as six out of the eight serotonin receptors have been identified in human retina [35].

Despite the more specific and conclusive nature of recent findings, some uncertainty about the quantitative and functional importance of the pathways involved due to the uncertainty of the number of existing fibers and their exact origin still exists.

Anatomical evidence for centrifugal connections to the retina of humans

All anatomical evidence in humans was generated from autopsy cases or eyes removed during surgery. The first clear suggestion of the existence of efferent (centrifugal) fibers in the human optic nerve in the scientific literature published in English appeared in 1900 when Warrington and Dutton from University College Liverpool (UK) suggested that a few small-diameter fibers in the optic nerve of a patient who underwent unilateral optic nerve atrophy six months after surgical removal of the right eye were of centrifugal origin [45]. The work of Warrington and Dutton went largely unnoticed for more than 50 years, until Liss and Wolter [46] examined histologically the optic nerves from two patients, whose eyes had been surgically removed 11 and 16 years prior. Numerous relatively small-diameter nerve fibers were found in both optic nerves, in essence confirming the original observation from 1900.

The presence of undegenerated axons in the optic nerve can be considered proof of the existence of retinopetal axons, as long as enough time had passed so that all of the *afferent* fibers (originating from the retina and ending up in the brain) had degenerated by the time of examination. The time course of retrograde neural degeneration has been established in afferent nerves of the retinal system. It typically begins within hours after the injury and usually is fully developed within a few weeks [47]. Centrifugal fibers can also undergo anterograde degeneration, but it is much slower, which allows for *efferent* fiber visualization based on time (for discussion of anterograde vs. retrograde degeneration, see Vanburen [48]). Morphological studies of an enucleated eye 10 days after complete occlusion of the central retinal artery showed that all ganglion cells and centripetal (afferent) neurites had degenerated, whereas all of the presumed centrifugal (efferent) nerves with their cell bodies in the brain were still present in the optic disk. This allowed for a quantitative estimate of the remaining presumed centrifugal fibers, which was determined at around 10% of all fibers in the human optic nerve [49]. However, this number likely overestimates the real number of fibers (see "Discussion" section). Centrifugal fibers in the human retina and other mammals (dogs, cat, and guinea pig) were found to emerge from the optic disk and run toward the periphery before ending in the inner plexiform layer [50]. All relevant studies addressing the existence of efferent fibers in humans are summarized chronologically in Table 2.

Anatomical evidence for direct retino-retinal connections in non-human primates and humans

A direct retino-retinal connection through optic nerve fibers is a well-established phenomenon in birds, although it significance is unclear [61]. In contrast, direct retino-retinal connections were not established in mammals until 1981, when Bunt and Lund described the existence of ganglion cells projecting to the contralateral eye in rats during embryonic and early postnatal development [62]. Their observation was that such fibers disappear at postnatal day 5 (P5), and, therefore, they do to have any relevance to visual function. However, in 1988 Muller and Hollander [63] with a refined technique found retino-retinal fibers and stained contralateral ganglion cells surviving in adult rats (and rabbits) post-P5, thus raising the possibility for their visual function significance. These findings were confirmed and expanded recently in mice and adult rats [4, 5], and it was demonstrated that they likely affect the bioelectrical activity of the retina in rats [6].

Table 2 Anatomical evidence of efferent fibers in optic nerves and retina in humans documented with modern methods (since the 50s)

Reference	# of patients	Findings/Comments
Liss and Wolter [46]	1	Histological evidence, intact fibers found in optic nerve years after surgical removal of the eye
Wolter [51]	2+	Silver impregnation technique; potential efferent fibers found in both normal eyes and pathologically altered eyes
Ventura and Mathieu [50]	1+?	Silver impregnation technique (Gros–Bielschowski); Exogenous centrifugal fibers emerging through the disk rim slightly above RNFL toward the periphery
Wolter [52]	8	Silver impregnation technique of Hortega; patients had advanced diabetes, which resulted in degeneration of the centripetal nerve fibers, but preservation and proliferation of the centrifugal fibers
Pfister and Wolter [53]	1	Silver carbonate technique of Hortega; examination of the intraorbital part of optic nerve 5 days after enucleation; different staining of centripetal versus centrifugal fibers
Wolter and Knoblich [54]	1	Centrifugal fibers found 50 years after bilateral enucleation. Pathway of fibers described through chiasm and optic tract; silver carbonate technique of Hortega
Wolter [49]	2[a]	Centrifugal fibers present at and near the optic nerve head 10 days after complete occlusion of the central retinal artery; Hortega technique
Wolter and Moorman [55]	1	Inconclusive suggestive evidence. Axon stumps resembling centrifugal fibers observed; Hortega technique
Wolter and Lund [56]	1	Identified fibers showing characteristics resembling centrifugal fibers following photocoagulation of the retina; Hortega technique
Honrubia and Elliott [23]	20	Silver impregnation (Gallego method) and flat mounts; parallel studies of vertical retinal sections confirmed the descending trajectory of efferent fibers charted
Sacks and Lindenberg [57]	1	Case report of atrophic eyes (the absence of retinal tissue), but preserved axons within the left optic nerve (right optic nerve absent). Hematoxylin and eosin stain.
Reperant and Gallego [58]	16	The presence of centrifugal optic fibers found via Gallego method. Fibers may extend over one-quarter of the total retinal surface and terminate in the internal plexiform layer
Wolter [59]	1	Survival of nerve fibers 16 days after removal whose terminal swellings pointed in a distal direction, indicating axoplasmic flow toward the removed eye. Pyridine silver stain and electron microscopy
Wolter [60]	1	Nerve fiber stumps of centrifugal fibers were observed histologically as cytoid bodies (H&E stain) near a cut in the retina

[a] One of the two cases reported is described also in a separate article—see [54]

Although modern evidence for such connection is not available in humans or non-human primates, early studies in non-human primates suggest that they could exist in humans too. Dean and Usher [64] described degenerating axons in the contralateral optic nerve of a monkey eye that underwent a lesion in the retina. They expanded and confirmed their observation in 12 other monkeys in a subsequent report [65]. Similar observations in monkeys were reported at about the same time by Parsons [66] on six monkeys. Parsons also quotes Pick [67] of making similar observations in rabbits. The only observation supporting similar arrangement in humans was reported in 1904 by Meyer [68] in a boy with traumatic injury involving the left eye, which was enucleated and degeneration was noted in both optic nerves.

Physiological evidence for centrifugal feedback to the retina of non-human primates

Direct support: modulation of the ERG response after optic nerve transection

In lower mammals, the existence of retinopetal axons has been studied and elucidated by changes in retina electrophysiology in response to optic nerve blockade

or section (rabbits and cats) [69–71], cortical inactivation, and sleep (in rats) [72, 73]. Retinopetal axons are thought to have an inhibitory effect on retinal function; thus, by recording light-induced bioelectrical activity in the retina by the ERG and observing for specific changes, one can further confirm the existence of centrifugal fibers. The relevant findings are summarized chronologically in Table 3.

Jacobson [74] used central nervous system (CNS) depressants in cats and monkeys to show an increase in the ERG amplitude of an intact eye, whereas no change was noted on the side of the severed nerve. By sectioning one of the nerves, efferent inhibition was interrupted, abolishing the action on the ERG by the drugs. Furthermore, sectioning the optic nerve caused an immediate increase in the ERG. Overall, the ERG was found to increase in amplitude following optic nerve section, the administration of CNS depressants, or electrical reticular stimulation. Evidence of this central inhibition was later shown in cats when light stimulus presented to one eye inhibited a chiasmic response to light stimulus applied to the other eye [75, 76]. In addition, Abe [77] showed an increase in the amplitude of the b-wave of the ERG in rabbits as a direct result of optic nerve sectioning, in line with reports by Jacobson and Suzuki in the monkey. Similar effects in monkey's full-field ERG were observed by three other investigators: Mirsky et al. [78], Khosla et al. [40], and Maffei et al. [79] (Table 3A).

The study by Mirsky et al. is particularly interesting, as it addresses possible confounding issues from the effect of optic nerve transection on retinal circulation. The authors conducted an experiment on monkeys studying the impact of optic nerve transection on the change in full-field ERG caused by paroxysmal spike and wave EEG activity. They conducted it in two different ways: by an infraorbital optic nerve transection (which damages the central retinal artery; $n = 2$) and by an intracranial optic nerve transection (which spares the artery; $n = 2$). They clearly demonstrated that when the transection spares the artery and does not influence the ERG waveform, the ipsilateral ERG is unchanged during paroxysmal spike and wave EEG activity in monkeys, while the contralateral ERG (recorded from eye with an intact optic nerve) is decreased in amplitude. Thus, combined body of evidence from the five studies summarized in Table 3a directly supports the notion of an inhibitory effect of an intact optic nerve (presumably through retinopetal fibers) on the biotectural activity of the retina. However, a detailed investigation of the quantitative and retinal topographic aspects of this suppression has not been pursued and awaits further study.

Indirect support: the P-wave

The P-wave is a slow intraretinal potential that reflects a postsynaptic retinal response to electrical stimulation of the optic nerve. It was first recorded in monkeys by Ogden and Brown in mid-1960s, who suggested that the signal results from efferent feedback to the monkey retina [81, 82] (Table 3B). The maximal P-wave amplitude was localized to the inner plexiform layer, and the fibers that initiated it were confined to the dorsal half of the optic tract and lateral geniculate. Further confirmation of the P-wave was shown by stimulation of the optic tract which elicited several graded intraretinal potentials, which were negative in the optic nerve fiber layer and positive in the inner plexiform layer [83]. Since its initial discovery, this potential has been confirmed in later studies that measured intraretinal conduction velocities and signals by direct stimulation of the LGN [86, 87] (Table 3). However, later interpretations of the P-wave signal changed, and Fukuda et al. [86] assumed that the signal is likely propagated retrogradely predominantly by afferent axons. Furthermore, the antidromic effects can also be explained by gap junctions between retinal ganglion cells and amacrine cells [88, 89].

Indirect support: effects on mfERG

A regular multifocal ERG (mfERG) response is generated by complex interactions between the photoreceptors, on- and off-bipolar cells with minimal (if any) contribution from retinal ganglion cells in the initial part of the response (N1/P1/N2 complex) [90]. In a study focused on the changes in the multifocal VEP responses in macaques and cynomolgus monkeys, the authors recorded also a mfERG after optic nerve transection. An increase in the N1/P1/N2 mfERG complex after optic nerve transection was detected in the ipsilateral eye compared to the contralateral eye in a rhesus and in a cynomolgus monkey 3 years after the transection and the induction of elevated intraocular pressure in the same eye. This

Table 3 Physiological direct evidence of influence efferent influence on the bioelectrical activity of the retina in non-human primates

References	# of animals	Species	Findings/comments
(A) Effects on ERG amplitude after optic nerve transection			
Jacobson and Gerstling [74]	1+	*Macaca fascicullaris*	Immediate increase in the ERG amplitude followed section of the optic nerve when the animal was under light anesthesia
Mirsky et al. [78]	16	*Maccaca mullatta*	Decrease or loss of ERG components during spike-wave activity in EEG compared to periods without activity; in four animals, a unilateral optic nerve transection confirmed the efferent nature of the effect
Khosla et al. [40]	6	?	ERG b-wave decreased in both eyes after unilateral optic nerve transection for 2 days; 4th–6th day, it became supernormal in the operated eye; recovered to normal in the unoperated (fellow) eye
Maffei et al. [79]	3	*Macaca nemestrina*	Right optic nerve sectioned; full-field ERG from the right eye larger compared to the left eye, even when pattern ERG was extinguished in right eye at 5 weeks post-surgery
Maertz et al. [80]	1 + 1	*Macaca mullata* and *Macaca fascicularis*	A side result of a larger study: N1 and P1 peaks of the first-order kernel of mfERG increase in the ipsilateral eye after optic nerve transection[a]
(B) Intraretinal potentials from antidromic stimulation of the optic nerve (P-wave)			
Ogden and Brown [81]	20	*Macacca fascicularis*	First recording of the P-wave (an intraretinal parafoveal potential of short latency) as a result of antidromal stimulation of the optic nerve
Ogden [82]	20	*Maccaca mullatta*	Further studies on the P-wave, generated by stimulation of the optic tract and LGN; max amplitude of P-wave at the IPL; P-wave is likely postsynaptic in origin
Gouras [83]	1+	*Maccaca mullatta*	Stimulation of the optic tract elicits several graded intraretinal potentials, negative in RNFL and positive in IPL; one of them resembles the P-wave
Ogden [84]	1+ and 1+	*Macaca mullata* and *Saimiri sciureus*	Further characterization of the P-wave
Ogden [85]	4 and 3	*Cercocebus torquatus atys* and *Aotus triuirgatus*	Further characterization of the P-wave
Fukuda et al. [86]	5	*Macaca fuscata*	Further characterization of the P-wave. Assumed that the artificial antidromic stimulation is conducted by afferent optic nerve fibers
Fukuda et al. [87]	11	*Macaca fuscata*	Further characterization of the P-wave

[a] The main purpose of the study was the evaluation of the multifocal VEP; therefore, this finding was not explored in detail

uniform increase in the mfERG amplitude (bottom panels in Fig. 1, [80]) indicates an influence beyond a simple removal of retinal ganglion cell input to the mfERG signal. The amplitude increase is consistent, though, with the removal of putative centrifugal inhibitory influences on the mfERG. It is possible that such influences may be generated by retinopetal fibers with terminals in the outer plexiform layer, as described in monkeys before by Gastinger et al. [91].

Supernormal mfERG response of the first-order kernel was observed in the experimental eyes versus the contralateral (control) eyes after induction of experimental glaucoma in rhesus monkeys [92, 93]. This effect was more pronounced in the fovea. Similar results were obtained by other investigators after intravitreal administration of TTX, a substance that suppresses spiking activity of the retinal ganglion cells [90, 94–96]. Furthermore, intravitreal injection of TTX essentially eliminated the nasotemporal variation seen in the control records [94]. The nasotemporal variation of the mfERG was believed to be mostly due to the existence of the optic nerve head component of the mfERG [97, 98]. However, anatomical nasotemporal anisotropy in the retina has been demonstrated

for both cone photoreceptors [99–101] and retinal ganglion cells [99, 102, 103] in primates and corresponding anisotropy in contrast sensitivity has been demonstrated in humans [104, 105]. Therefore, there may be other contributions to this anisotropy, and it is possible that some of this influence could be of centrifugal origin.

Physiological evidence for centrifugal feedback to the retina of humans

Direct support: modulation of the ERG by non-visual and contralateral eye stimulation

A difference in the amplitude of ERG recorded monocularly and binocularly, when a binocularly recorded ERG would be smaller in amplitude compared to a monocularly recorded ERG, would imply an efferent influence on the ERG response, either directly from the opposite eye or through a feedback involving brain structures. To test this possibility, studies were conducted starting in the early 1950s (Table 4A). Although most studies supported such possibility [106–109], some studies were negative [110, 111], an indication that the effect may not be very pronounced and could be dependent on the recording conditions.

The rest of the studies (Table 4B) can be grouped into three sub-categories. In the first sub-category, early investigators recorded an ERG signal from the non-illuminated eye [112–114]. These findings have not been replicated and remain controversial to this day. Due to the slow time course of the signal recorded, they could be also of a non-retinal origin (e.g., a bioelectrical pupillary response).

The second sub-category is represented by a study demonstrating a non-visual sensory influence on the ERG response. In this experiment, Nikitooplou-Maratou et al. [116] found that a sound paired with a flash caused an increased b-wave of the ERG. This effect was observed only when sound and flash were presented simultaneously, which suggests that the effect of the sound on the retina should be mediated via a neural pathway, rather than by a humoral factor and likely through efferent fibers from the CNS to the human retina.

The third sub-category involves studies demonstrating the dependence of the ERG response in one eye on manipulation (either sensory of physical) of the contralateral eye. Thus, in 1964 Hellner [115] demonstrated a decrease in the ERG amplitude in one eye depending upon the frequency of a simultaneous flicker stimulation of the contralateral eye. More recently, Lovasik et al. [20] showed a decrease in pattern ERG in both eyes after unilateral decrease in ocular perfusion pressure in healthy volunteers. Similarly, Francis et al. [21] showed decrease in full-field ERG amplitude of both eyes after scleral depression in one eye. One possible explanation for these results is an efferent influence on ERG.

It is generally assumed that contralateral ERG effects come from cortical or subcortical neurons in the brain which are activated by information from the illuminated eye. Recent physiological findings in rat by Tang et al. [6] indicate that direct retino-retinal communication could be involved. They showed that electrical stimulation of one optic nerve can evoke a compound action potential in the contralateral optic nerve and that visual stimulation of one eye can induce an ERG-like signal in the contralateral eye. Moreover, experimental treatments that eliminated this signal in the non-stimulated eye also altered the ERG of the flashed eye, decreasing b-wave amplitude and lengthening b-wave duration.

Indirect support: attentional effects on the ERG

The presence of centrifugal pathways in the CNS and especially retinopetal fibers has led several authors to suggest that they may be important in the control of attention by filtering or gating sensory information [117–120]. While it is generally recognized that centrifugal processes do modulate sensation and are important in some circumstances in the modulation of attention, the role of retinopetal axons remains uncertain [121]. Critiques of early studies of early attentional evoked potentials emphasized the need to control for peripheral sensory factors (e.g., pupil size and eyelids), and to differentiate general state changes (arousal level) from specific effects of selective attention [122].

Demonstrating attentional modulation of retinal function in humans requires the use of the ERG. The ERG response is dominated by photoreceptor and bipolar cell retinal activity that may obscure or overwhelm attentional effects, which should be reflected more in inner retinal activity (amacrine and ganglion cells) [123–125]. Moreover, pupillary

Table 4 Physiological experimental evidence of efferent influence on the bioelectrical activity of the retina in humans

Reference	# of subjects	Evidence	Findings/comments
(A) Amplitude of monocularly versus binocularly recorded ERG			
Wirth [106]	1?	Positive	Monocular ERG larger in amplitude compared to binocular ERG
Dodt [107]	26	Positive	Monocular ERG larger in amplitude compared to binocular ERG
Uchermann [110]	10	Negative[a]	No difference between binocular and monocular ERG
Motokawa et al. [108]	3	Positive	Definite difference between ERGs recorded under monocular and binocular condition: deepening of the descending shoulder of the b-wave binocularly
Bagolini [111]	7	Negative[b]	No statistically significant difference in ERG amplitude between monocular and binocular stimulation
Steindler et al. [109]	20	Positive	Basically, a repeat of Ucherman/Bagolini study, but with positive results
(B) Other studies			
Monnier [112]	1?	Positive?	A slow potential, resembling the ERG c-wave recorded in the non-illuminated eye
Monnier [113]	1?	Inconclusive	Confirmed previous results, but changed interpretation, emphasizing similarity of time course with pupillary response
Marg [114]	2	Positive[c]	A slow potential, resembling the ERG c-wave recorded in the non-illuminated eye
Hellner [115]	10	Positive	A decrease in the ERG amplitude in one eye was observed depending upon the frequency of a simultaneous flicker stimulation of the contralateral eye
Nikitopoulou-Maratou et al. [116]	1+	Positive	A sound paired with a flash caused an increased b-wave of the ERG
Lovasik et al. [20]	10	Positive	Unilateral decrease in ocular perfusion pressure changed the pattern ERG in the manipulated and in the contralateral eye
Francis et al. [21]	42	Positive[d]	After scleral depression of diseased eye, ERG response decreased in that eye and in the fellow healthy eye; following scleral depression of the healthy eye, ERG decreased in the diseased eye

[a] However, an increase under monocular conditions was observed in 8 out of the 10 right eyes (see also main text)

[b] However, the intensity–response function of the b-wave amplitude showed a positive trend at lower light levels

[c] However, the effect was observed only in one of the two subjects

[d] The possibility for efferent influence was not considered by the authors

[126, 127] and eyelid responses [128] are affected by attention as well. Consequently, Hackley et al. [129] observed ERG changes with attention but attributed these to electromyographic changes in the eyelids.

Eason and colleagues performed a series of spatial, selective attention experiments to determine whether attentional modulation of retinal function could be detected [123, 130, 131]. Possible effects of pupillary and eyelid variations were eliminated as subjects were unaware of when and where the stimulus would be presented. Following pilot studies to determine the optimal stimulus conditions for eliciting a retinal response from skin electrodes [130], Eason et al. [131] employed a spatial selective attention task and demonstrated a difference in the ERGs elicited by attended versus non-attended patterned flashes. ERG b-waves and "after potentials" were larger for the attended field than for the unattended field. The b-waves tended to peak earlier for attended than for unattended stimuli. Eason [123] replicated the results of both experiments and expanded on the findings in a subsequent study. Mangun et al. [132] failed to replicate Eason's results in a slightly different experimental paradigm. No attentional effect was observed in the ERG b-waves, but effects were observed in the "after potential" portions of the ERG response and attributed to volume-conducted VEPs; however, no rigorous check of this hypothesis was pursued. Mangun et al. noted numerous disparities in the experimental conditions between their and Eason et al. experiments, including difference luminance levels, shorter interstimulus intervals, and different types of electrodes. No subsequent studies have explored this avenue of research in further detail and with more modern equipment. Thus, although some evidence about central influence on the bioelectrical activity of

the retina in humans exists, its exact mechanism and ramifications remain largely unexplored.

Indirect support: clinical case studies

The majority of physiological evidence for humans is clinical in nature. Both Karpe [133] and Diterle and Babel [134] reported supernormal ERGs in the contralateral eyes of patients with unilateral optic neuritis. However, little experimental detail was provided to evaluate the results. A more thorough clinical account appeared in 1959 when Suzuki reported that the dark-adapted ERG of a patient with traumatic injury of the left optic nerve (no light perception, pallor of the optic disk) was larger in the left eye compared to the right eye 66 days after an injury [135].

The reports presented in Table 5 summarize the findings in patients with (mostly) unilateral optic nerve diseases leading to decreased or abolished function of the optic nerve. When the effect of unilateral optic nerve trauma is evaluated, most of the studies are clearly positive, showing increased amplitude in the full-field ERG in the ipsilateral eye after unilateral optic nerve injury or damage [135–140] (Table 5A). On the other hand, when the effects on ERG were evaluated based on mixed etiology (Table 5B), an equal number of studies showed positive [109, 141, 142, 144] and negative [143, 145–147].

In the context of such disparate findings, it may be useful to discuss two points. First, some of the negative studies contain a non-uniform set of pathologies including cases of multiple sclerosis (MS) [147]. The authors presumed that the mechanism of damage from MS is similar to the mechanism of damage in cases of severe optic nerve injury. However, recent insight into the mechanisms underlying MS changes in brain tissue and optic nerve shows a rather complex and variable pathology, including active and inactive lesions, focal inflammation, demyelination, and remyelination and, in the case of optic nerve lesions, a significant overlap with similar pathologies with different etiology, like neuromyelitis optica [148, 149]. Thus, the variability of this type of pathology and the diversity in its presentation makes it unsuitable, in our opinion, for use as clinical proof for the existence of efferent influences on the retinal function at present time. Second, even within the more narrowly defined pathology, like severe traumatic unilateral optic nerve injury, the course of optic nerve degeneration can be quite variable, and as indicated by animal studies (e.g., [40]), changes in ERG amplitude can be dependent on the time elapsed since injury. Therefore, it is entirely possible that a temporary increase in ERG amplitude at certain point in time after injury can be missed.

Discussion

Initial studies on the efferent (centrifugal) fibers in the optic nerves of animals (including mammals) at the late nineteenth century and the beginning of the twentieth century were supportive, and the notion that such fibers exist even in higher mammals was quickly adopted to the point of acceptance as a standard knowledge and appearance in human physiology textbooks [150–152]. After the ensuing period of serious doubts, lasting about a century, is it time to re-introduce the presence of efferent fibers in the textbooks? The accumulated combined anatomical and physiological evidence presented in this review is largely positive and suggestive that, even in the case of non-human primates and humans, some fibers in the optic nerve conduct top–down information (from the brain to the eye), which can influence the bioelectrical activity of the retina. It is also likely, although much less certain, that few optic nerve fibers could provide a direct retino-retinal connection.

Nevertheless, questions and reservations remain. The reservations start with the uncertainty related to the estimate of the number of fibers present in the optic nerve, which varies from $\sim$10%, or $\sim$100,000 fibers [60] to about 25–35 fibers [28] or even as few as ten fibers [58]. As the first estimate was based on fibers surviving degeneration and there are considerable uncertainties related to both the speed and nature of degeneration (anterograde vs. retrograde), it seems likely that the true number of fibers per optic nerve is closer to the lower estimates. A study applying a combination of modern immunohistochemical and imaging methods is needed to establish a more definitive answer. Another reservation is related to the ambiguity related to the functions of the fibers. The clear majority of studies presented in this review suggest a suppressive influence on the retina, but the details related to the nature and of the physiological

Table 5 Physiological evidence of efferent influence on the bioelectrical activity of the retina in humans based on clinical reports

References	# of patients	Evidence	Findings/Comments
(A) ERG amplitude changes after unilateral optic nerve trauma			
Suzuki [135]	1	Positive	Dark-adapted ERG of the left eye (damaged optic nerve, NLP?, pallor of the optic disk) was larger than the right eye 66 days after an injury and until at least 293 days
Gills [136]	2	Positive	Two cases of old optic nerve transection in man and obtained higher ERG responses than in the intact fellow eyes
Feinsod and Auerbach [137]	1	Positive	Enhanced dark-adapted ERG in the right eye 4 days after a traumatic injury; absent right VEP
Hillman et al. [138]	1	Negative	ERG recorded on the 17th day after unilateral eye trauma of the left eye with no light perception showed decreased b-wave amplitude in the left eye and normal amplitude in the right eye[a]
Muller and Schmoger [139]	12	Positive	In 3 out of the 12 patients, supernormal ERGs were recorded after surgery for removal of a pituitary adenoma
Dawson et al. [140]	1	Positive	ERG recorded 15 months after traumatic unilateral right optic nerve section: OD–NLP, but dark-adapted ERG amplitude was larger compared to the one in the left eye and the peak was delayed
(B) ERG amplitude changes after optic nerve damage (mixed etiology)			
Feinsod et al. [141]	69	Positive	42% of the cases with optic atrophy displayed enhanced ERGs together with reduced or absent visual-evoked potentials
Feinsod et al. [142]	7	Positive	Patients with low visual acuity displaying enhanced ERG responses and reduced or extinct VEPs; none of these cases exhibited any sign of optic nerve affection and visual field defects
Ikeda et al. [143]	83	Negative	No supernormal ERG responses were observed in cases of optic nerve lesions; however, all cases were with very advanced pathology
Steindler et al. [109]	17	Positive	Consensual ERG responses are drastically reduced in unilateral optic atrophy; support the hypothesis that the transfer from one eye to the other is via efferent fibers in the optic nerve
Kaitz et al. [144]	11	Positive	Six out of the eight patients with unilateral intraocular foreign bodies who had been tested with a series of ERG intensities (5 log units) showed decreased signal in the unaffected eye
Wachtmeister and Azasi [145]	26	Negative	No significant difference between ERG amplitudes in the eyes of patients with unilateral optic atrophy
Vaegan et al. [146]	64	Negative	Claims diminished ERG responses after optic nerve atrophy; however, some of the examples show larger amplitudes
Frazer and Holder [147]	46	Negative	Optic neuritis patients: no significant difference in any ERG parameter between affected and fellow eyes; no patient with an interocular asymmetry of 30% or more; no supernormal ERG

[a] The authors admit the possibility that they could have missed an early transient supernormal response or that the retina may have been damaged by transient vascular disturbance

role of this suppression are scarce. Much more work is needed to reveal the pertinent mechanisms behind this phenomenon.

At least some of the efferent influences are transient and subject to adaptive phenomena, like habituation [116], which would attenuate their effect on the averaged ERG response and this may explain to some extent the negative results in some studies. Furthermore, the efferent influence can likely manifest itself as an "order effect" when ERG is recorded in a monocular but consecutive fashion from both eyes. Such effects were reported with the mfERG [153], but have not been explored further.

Apart from a direct effect on the ERG responses, a broader physiological (functional) significance for the visual system in general should be considered for the efferent influences. Currently, three major functions are considered. The first functional hypothesis links the efferent fibers to eye movements. Under this hypothesis, the efferent signal would act to

compensate for the effects produced by eye movement, like a transient elevation of the visual threshold which could reduce (or eliminate) blur during eye movement [2]. The second hypothesis assumes a role for the system in dynamic local adaptation or modulation of retinal sensitivity. Under this hypothesis, a constant scanning across the visual environment requires a rapid process of adaption of retinal sensitivity (as opposed to the relatively slow process of visual adaption limited by the speed of biochemical regeneration of visual pigments). Finally, the more recent identification of serotonin and histamine receptors on the retinopetal axons in monkeys [91] could suggest some role in optimizing retinal function at the ambient light intensity during the animal's waking period.

Similarly, the clinical significance of the efferent influences could be important in several areas, especially when trying to determine the functional status of the optic nerve in various clinical conditions when its function is thought to be compromised, like in traumatic optic neuropathy or other unilateral cases of optic neuritis or optic nerve atrophy. Furthermore, the existence of these phenomena would indicate that a caution should be exercised when interpreting an increase in ERG amplitude related to unilateral optic nerve trauma, etc. Another potential consideration is supernormal ERG amplitudes seen in cases of diabetic retinopathy [154], which may be due to problems with the efferent optic nerve fibers as suggested by certain rat data [155]. It is also possible that retino-retinal connections may play a role in spreading involvement to the initially unaffected eye in cases of unilateral trauma or inflammation of the contralateral eye or optic nerve, as suggested by some studies in rats where unilateral injury was administrated to the optic nerve [156, 157].

Conclusion

The preponderance of the existing evidence points to the existence of efferent (centrifugal or retinopetal) fibers in the optic nerve and retina in non-human primates and humans. Although their number may not be large, their branches cover extensive retinal areas, which indicates the possibility of exerting significant influences on the retinal function. Indeed, experiments in monkeys and humans indicate that measurable central effects on the ERG can be recorded under a variety of physiological conditions. Still, many aspects of the physiological role of these fibers remain unclear and await further experimental study.

Literature research

We searched the PubMed and Google Scholar databases to identify articles published up to July 27, 2016, using the following key terms: "efferent," "centrifugal," "retinopetal," "fibers," "retina," and "optic nerve" and combinations of thereof. The search was limited to articles that explored the subject matter in non-human primates or humans. Some articles revealed secondary bibliographical sources which were not present in the original searches and these leads were followed. Two limitations should be acknowledged in the literature search. Firstly, articles that contained pertinent data to this review may have been missed if the study was indirectly related to the retinal efferent system. And secondly, a concerted effort was made to identify and translate relevant publications in languages other than English, but some may have been missed.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Statement of human rights This article does not contain any studies with human participants performed directly by any of the authors.

Statement on the welfare of animals This article does not contain any studies with animals performed directly by any of the authors.

Informed consent As this article does not contain any studies with human participants performed directly by any of the authors, the concept of informed consent is not applicable.

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