British Journal of Pharmacology (2007) 150, 383–390

0007–1188/07 $30.00
www.brjpharmacol.org

REVIEW

Cellular mechanisms underlying the pharmacological induction of phosphenes

L Cervetto[1], GC Demontis[2] and C Gargini[2]

[1]*Dipartimento di Fisiologia e Biochimica 'G. Moruzzi', Università di Pisa, Pisa, Italy and* [2]*Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università di Pisa, Pisa, Italy*

Visual sensations evoked by stimuli other than luminance changes are called phosphenes. Phosphenes may be an early symptom in a variety of diseases of the retina or of the visual pathways, but healthy individuals may perceive them as well. Phosphene-like phenomena are perhaps the most common side effect reported in clinical pharmacology. Ivabradine, a novel anti-anginal drug that reduces heart-rate by inhibiting the hyperpolarization activated current expressed in cardiac sinoatrial node cells (I_f) induces phosphenes in some patients. One hypothesis is that ivabradine interacts with the visual system by inhibiting hyperpolarization-activated current in retinal cells (Ih). An I_h current with properties similar to cardiac I_f has been reported in retinal neurones. Under normal circumstances most of the random fluctuations generated within the retinal circuits do not reach the level of conscious perception because they are filtered out. Presumably, filtering occurs mostly within the retina and one serious candidate for this action is the ability of I_h to act as a negative-feedback mechanism. I_h activation in the membrane of visual cells causes dampening of responses to slow noisy inputs thus tuning the visual system to perceptually more relevant signals of higher frequency. I_h inhibition, by altering at the retinal synapses the filtering of signals generated by thermal breakdown of rhodopsin or other fluctuations, is expected to increase the probability of phosphene occurrence. It is the purpose of the present paper to outline and discuss the features of the visual system and the pharmacological conditions relevant to phosphene perception.
British Journal of Pharmacology (2007) **150,** 383–390. doi:10.1038/sj.bjp.0706998; published online 8 January 2007

Keywords: phosphene perception; phosphene induction; ivabradine; HCN channels; hyperpolarization activated currents (I_f, I_h); I_f and I_h inhibitors; heart rate-lowering drugs

Introduction

The visual sensations evoked by stimuli other than luminance changes are called phosphenes (from the Greek *phos*, light and *phainain*, to show). Phosphenes can be spontaneous or provoked in a number of ways including a gentle pressure on the eyelids, an electrical or magnetic stimulation of the eye or of the visual cortex (Brindley and Lewin, 1968; Tyler, 1978; Barker *et al*., 1985). von Helmholtz (1896) gave an early review of the effects of pressure stimulation of the eye; Pflügers (1865) showed that the visual threshold for electric stimuli follows his law of electrotonic stimulation. A more recent quantitative account on the threshold electrical stimulation of the eye and of the visual cortex can be found in Attwell (2003) and Tehovnik *et al*. (2006), respectively. Phosphene induction by electrical stimulation of the visual pathway with electrodes implanted on the retina or on the visual cortex is currently regarded as a very promising method for making the blind see again (Dobelle *et al*., 1974; Schmidt *et al*., 1996; Zrenner, 2002).

In general, phosphenes appear spontaneously when the viewer is subjected to prolonged visual deprivation and it has been argued that this occurrence may be related to an increased cortical excitability to the incoming visual input (see Boroojerdi *et al*., 2000). Phosphenes may appear with a variety of patterns: they often have a chaotic structure in the form of sparks, sometimes they appear as a glowing circle or part of it, or as a spiral moving in concentric circles (see Walker, 1981). In a substantial fraction of migraine sufferers, phosphenes may appear in more organized forms such as, for instance, the so-called fortification structure (Richards, 1971). More complex and picturesque spontaneous visual phenomena are often indicated as phosphenes, but when associated with emotional factors, drugs, alcohol, stress, fever or psychotic conditions, they should be referred to as visual hallucinations. In general, luminous phenomena such as phosphenes are largely geometric forms non-culturally biased, whereas hallucinations are more complex, iconic forms, culturally controlled (Siegel, 1977).

The perception of phosphenes is very common and often experienced in the absence of an identifiable pathological

Correspondence: Professor L Cervetto, Dipartimento di Fisiologia e Biochimica, Università di Pisa, Via S Zeno 31, Pisa I-56127, Italy.
E-mail: cervetto@farm.unipi.it
Received 7 August 2006; revised 17 October 2006; accepted 31 October 2006; published online 8 January 2007

condition of the retina or of the visual pathways: in a large number of these cases the causes underlying phosphene generation are difficult to assess (Rosenbaum *et al*., 1987). Phosphenes, mostly occurring upon eye movements may be associated with optic neuritis and in this case they may be caused by mechanical aggravation of a damaged or inflamed optic nerve (Davis *et al*., 1976). Visual symptoms that also include phosphenes constitute an early sign of optic nerve demyelination in patients that will later develop multiple sclerosis (see Wilkstrom *et al*., 1980; Levin and Lessel, 2003). Severe myopia, changes in eye pressure and vitreous retraction, which may be a prelude to retinal detachment, stimulate the visual cells mechanically thus generating phosphenes (Forzli el and Brasseur, 1999; Enoch *et al*., 2003). Spontaneous visual perceptions associated with retinal and optic nerve diseases may overlap with those resulting from retrochiasmal disorders (Murtha and Stasheff, 2003). In all these cases, a number of other subjective symptoms, and objective signs of damage as well, can be detected by conventional neurological and ophthalmic tests. Phosphenes are also a prominent symptom associated with the aura, the warning sensation that preludes the onset of migraine (see Queiroz *et al*., 1997). Finally, phosphenes and other visual hallucinations are often a collateral effect of a variety of pharmacological agents (see Fraunfelder and Fraunfelder, 2001). Attemping a comprehensive explanation of the mechanism underlying drug-induced phosphene seems impractical because of the variety of molecular and cellular actions that one may encounter. It is perhaps useful, however, examining some of the features of the visual system and the pharmacological conditions relevant to phosphene perception.

Spontaneous activity of the visual system in complete darkness

It is well established that the visual system, as well as other brain regions, is continually active and that, in the dark, retinal ganglion cells (RGC) generate a spike discharge whose rate may fluctuate randomly with frequent irregular bursts (dark discharge, see Levick, 1973). This notion supports the psychophysical theory of the visual threshold proposed by Barlow (1965) according to which the visual system operates in the presence of an intrinsic noise. The perceptual correlate of this noise may be identified with the fuzzy grey sensation experienced in darkness even when all after-images have faded (*Eigengrau* – subjective grey of Hering, 1878; *Eigenlicht* – subjective light of von Helmholtz, 1896). In the past, there has been considerable debate on the site of origin of the maintained discharge. It has been proposed, for instance, that the dark discharge is the expression of the autochthonous activity of the RGC (Hughes and Maffei, 1965). This explanation was suggested by the fact that the time course of changes in the discharge rate, upon switching off an adapting light, is much shorter than the change in threshold sensitivity of RGC. Other evidence, based on selectively damaging the photoreceptor cells argues against this conclusion (Rodieck, 1967) and together with indirect arguments (Barlow, 1965) seems to place the source of noise in the photoreceptors. On occasions the firing rate of a RGC is observed to undergo spontaneously a remarkable sequence of oscillations that may even drive the discharge frequency to levels above those achieved by illumination changes (Rodieck and Smith, 1966; Cavaggioni, 1968). The origins for this patterned activity have long been debated, and vascular reflexes (Granit, 1955) and changes of ocular pressure (Collins, 1967) have been charged with being the causes. Further analysis of this patterned activity by multineurone recordings in cat (Mastronarde, 1989) and salamander retinas (Brivanlou *et al*., 1998) have shown that the sources of noise responsible for spontaneous firing in RGC are distributed at different retinal levels. Fluctuations may be observed as early as in photoreceptors where they reflect features of the photo-transductive machinery. A prominent component of this noise is that caused by spontaneous breakdown of rhodopsin (Baylor *et al*., 1980, 1984; Rieke and Baylor, 1996; Jones, 1998), which has been shown to be effective in modulating the firing activity in ganglion cells (Brivanlou *et al*., 1998). Owing to the stability of the rhodopsin molecule, thermal breakdown occurs infrequently: an average life of several 100 years has been estimated for a rhodopsin molecule at 37 °C (see Baylor, 1996). One must consider, however, that because of the large number of molecules (up to 10^9) packed in the disks at the outer segment of a rod, spontaneous breakdown of rhodopsin may occur in a single rod as frequently as every few tens of seconds. Considering then that the retina contains approximately 10^6 rods with their uncorrelated spontaneous events, it turns out that the frequency at which these signals impinge on a ganglion cell can be very high and may explain some of the features of the spontaneous firing in the RGC. Patterns of sustained activity, however, have been demonstrated also when all chemical transmission is blocked, suggesting that RGC may produce spontaneous current fluctuations that depolarize their membrane above the firing threshold even in the absence of signals from the distal retina (Brivanlou *et al*., 1998).

The neuronal *trans*-membrane voltage needed to produce retinal phosphenes by an externally applied electric field has been recently estimated as 0.6–200 μV (Attwell, 2003). It should be noted that the amplitude of the spontaneous fluctuations in the retina usually exceeds this value (Baylor *et al*., 1984). Under normal circumstances, the fluctuations that spontaneously arise within the retinal circuits are not perceived because the retina possesses efficient mechanisms for filtering out noisy signals (Sampath and Rieke, 2004).

The functional connections between single RGCs and neurones of the visual cortex are very effective in driving simple cortical cells: because of the considerable divergence between retina and lateral geniculate nucleus (LGN) cortical neurones may be influenced by RGCs through multiple forward pathways (Kara and Reid, 2003). Spontaneous, light-independent, changes in the firing of visual cells have been reported in the LGN (Maffei *et al*., 1965) and inputs from the brainstem have been shown to modulate the transmission of retinal signals to the visual cortex through the LGN (Ozaki and Kaplan, 2006).

The occurrence or aggravation of spontaneous visual phenomena may therefore be expected in the presence of abnormal stimuli, as a consequence of an increased neuronal excitability or because of an impairment of the filtering properties at one or more stages of the visual pathway.

Abnormal visual excitation of retinal photoreceptors

A variety of pathological conditions of the eye and of the visual pathways may induce visual sensations in the absence of light stimuli. In addition to mechanical stimuli such as changes in the eye pressure, vitreous retraction, compression of the optic nerve, of particular interest is the activation of the phototransductive cascade by unliganded opsin. Inappropriate and constant activation of transduction by high levels of opsin occurs in Lebers congenital amaurosis causing photoreceptor degeneration (see Woodruff *et al*., 2003). A similar mechanism may also be responsible for the degeneration induced by vitamin A deprivation (Fain and Lisman, 1993). In affected patients continuous abnormal stimulation of visual cells that is caused by unliganded opsin is associated with a persistent luminous sensation and background desensitization (light adaptation), even in the absence of light. A similar condition, however, is hardly comparable with the dynamics of phosphene occurrence, generally referred to as transient flash-like events not entailing significant light desensitization.

Phosphenes of cortical origin

It has long been known that visual sensations may be evoked directly acting on the cortex without using low-level visual pathways. Electrical stimulation of the visual cortex in humans via implanted microelectrodes evokes phosphenes in both sighted and blind subjects (Brindley and Lewin, 1968; Dobelle *et al*., 1974). They are described as circular spots of white or coloured light (Dobelle and Mladejovsky, 1974; Schmidt *et al*., 1996) that conform to the receptive field characteristics of the non-human cortical neurones (Hubel and Wiesel, 1977; Hubel and Livingston, 1990). Similarly but less invasively, phosphenes may be elicited by transcranial magnetic stimulation (TMS) of the visual cortex (Barker *et al*., 1985). TMS is a technique whereby a rapidly changing magnetic field of appropriate strength, applied on the scalp surface, induces an electric current that stimulates the underlying cerebral cortex (see Cowey, 2005). TMS, when directed to excite the occipital cortex, induces phosphene perception in the visual field contralateral to the stimulated hemisphere (Meyer *et al*., 1991). Phosphene thresholds are a reliable parameter characterizing excitability of the occipital cortex (Stewart *et al*., 2001). An appropriate criterion for threshold determination is to present the subject with a set of TMS stimuli of randomly intermixed different intensities. The subject is asked to report the presence or absence of phosphenes after each stimulus and a sigmoidal function is then fitted to the measured responses. The stimulus intensity corresponding to 50% positive responses is taken as the phosphene threshold.

Although phosphenes may originate at different levels in the visual system, patient studies have demonstrated that they can be perceived only in the presence of an intact primary visual cortex (V1) (Cowey and Walsh, 2000). Furthermore, in normal observers the activation level of V1 determines whether phosphenes are detected (Silvanto *et al*., 2005).

Transient or persistent changes in the excitability of neurones, especially in the occipital region of the visual cortex, has received strong consideration and appear associated with brain susceptibility to migraine attacks (Welch *et al*., 1990). TMS threshold for phosphene generation in the visual cortex was reported to be significantly lower in migraine patients who experienced aura than in normal controls (Wray *et al*., 1995; Palmer *et al*., 2000; Aurora *et al*., 2003; Hall *et al*., 2004). The issue, however, is somewhat controversial and higher or normal phosphene thresholds have also been reported (see Afra *et al*., 1998; Bohotin *et al*., 2003; Antal *et al*., 2006). Other studies with different paradigms have added consistent data to support hyperexcitability of the visual cortex in migraineurs (Mulleners *et al*., 2001; Battelli *et al*., 2002; Young *et al*., 2004; Chronicle *et al*., 2006). Further corroboration comes from studies showing that drugs effective in preventing migraine all have the common property of diminishing neuronal excitability (see Buchanan *et al*., 2004; Linde, 2006). Excitability of the visual cortex may also be modulated by a variety of incoming signals: it has been recently shown that the neural activity giving rise to a phosphene is in competition with the cortical activity elicited by the presentation of a visual stimulus (Rauschecker *et al*., 2004). All these observations agree that any event apt to modify the excitability of the visual system is bound to enhance or reduce the incidence of phosphene perception. These events include a wide variety of conditions such as the occurrence of visual or non-visual stimuli, sensory deprivation, hypoglycaemia, fever, drug intoxication, psychotic episodes and epilepsy.

Drug-induced phosphenes: a possible consequence of I_h inhibition

Phosphene-like phenomena are perhaps the most common side effect reported in clinical pharmacology and a comprehensive list of the registered pharmacological agents that induce phosphenes is available (Fraunfelder and Fraunfelder, 2001). It is interesting to note that both stimulant and depressant agents can provoke phosphenes. This seemingly paradoxical observation may, in fact, be explained by the complexity of the neuronal circuits whereby the action of depressants differ in distinct brain regions: one should consider, for instance, the hyper-excitability phases that precedes narcotic-induced anaesthesia (see Sloan, 1998). Differences in form, colour and movement of phosphene-like events are associated with distinct inducing agents or, for the same agent, with different subjects. In general, the frequency of phosphene phenomena reported by informed subjects is four times higher than that reported by naïve individuals (Siegel, 1977). Despite all the differences it seems reasonable to assume that a wide variety of causal agents induce phosphene-like events either by a nonspecific direct stimulation of the visual system or by increasing the neuronal excitability or by both.

A newly developed class of heart rate-lowering compounds, whose common mechanism of action is the inhibition of a current responsible for the pacemaker activity of cardiac cells, induces visual symptoms in humans. Table 1 summarizes the present knowledge of the effects of these compounds. It should be noted, however, that these drugs were tested in different experimental conditions which do not allow a direct comparison in terms of affinity for I_f and I_h.

Table 1 I_f and I_h blocking properties of heart rate reducing molecules

	Alinidine	*Cilobradine*	*Ivabradine*	*Zatebradine*	*ZD7288*
IC_{50} for I_f (μM)	28[a]	0.021[b]–0.62[c]	1.5[d]	0.066[b]	0.3 μM[e]
IC_{50} for I_h in rods (μM)	NA	NA	2.7[f]	2.0[g]	5.9[h]
IC_{50} for HCN1 HE (μM)	NA	1.15[c]	2.05[c]–0.94[i]	1.83[c]	41[j]
Mechanism of block for I_f	Use-independent[a]	Use-dependent[b]	Use-dependent (current-dependent)[d]	Use-dependent[b]	Use-independent[e]
Mechanism of block for I_h in rods	NA	NA	Use-dependent[f]	Use-dependent[g]	Use-independent[h]
Mechanism of block for HCN1 HE	NA	Use-dependent[c] Use-dependent[c]	Closed channel block[i]	Use-dependent[c]	Open channel block[j]
HE HCN1 block reversal by hyperpolarization	NA	NA	NO[i]	Yes[c]	Yes[j]
Visual symptoms	Yes[k]	NA	Yes[l]	Yes[m]	NA
ERG studies	NO	Yes[n]	Yes[o]	Yes[p]	NO

Abbreviations: ERG, Electroretinogram; HCN, Hyperpolarization-activated, Cyclic Nucleotide sensitive; HE, Heterologously expressed; NA, Not available.
[a]Snyders and Van Bogaert (1987). Alinidine also blocks other currents.
[b]Van Bogaert and Pittors (2003). Zatebradine also blocks other currents.
[c]Stieber *et al.* (2006).
[d]Bucchi *et al.* (2002).
[e]BoSmith *et al.* (1993).
[f]Demontis *et al.* (2006).
[g]Satoh and Yamada (2002).
[h]Satoh and Yamada (2000).
[i]Bucchi *et al.* (2006).
[j]Shin *et al.* (2001).
[k]Ceremuzynski *et al.* (1987).
[l]Borer *et al.* (2003).
[m]Frishman *et al.* (1995).
[n]Maccarone *et al.* (2004).
[o]Gargini *et al.* (2006).
[p]Gargini *et al.* (1999).

The visual effects, especially those induced by ivabradine, have been extensively investigated in both animal models and humans. Ivabradine is a novel antianginal drug that reduces heart rate by inhibiting the hyperpolarization-activated current expressed in cardiac sino-atrial node cells (I_f) (Di Francesco, 1993, Di Francesco and Camm, 2004). During the non-clinical visual safety program, no toxic damage in any ocular structure has been reported in animal models upon administration of therapeutic doses for humans (EPAR Procoralan, 2005). The visual symptoms induced by ivabradine, reported by patients during the clinical programme, include most commonly phosphenes (14.5% of patients) and less frequently blurred vision. Visula effects appear generally within the first 2 months of treatment and their frequency increases with the dose of ivabradine. Most of these events were reported to occur in conditions of darkness or dim light, when the retinal sensitivity is high. Phosphenes are generally reported to be mild or moderate and to disappear even though treatment continued (77.5% of patients) or after treatment cessation (Borer *et al*., 2003; Tardiff, 2005, Savelieva and Camm, 2006). The host plausible hypothesis is that ivabradine interacts with the visual system by inhibiting hyperpolarization-activated current in retinal cells (I_h).

An I_h current with properties similar to cardiac (I_f) has been reported in retinal rods (Fain *et al*., 1978; Owen and Torre, 1983; Bader and Bertrand, 1984; Beech and Barnes, 1989; Demontis *et al*., 1999, 2002). I_h has also been found in cones (Yagi and MacLeish, 1994), bipolar neurones (Kim *et al*., 2003; Müller *et al*., 2003; Cervetto *et al*., 2005; Cangiano *et al*., 2006), amacrine (Kozuimi *et al*., 2004), RGC (Tabata and Ishida, 1996), and it is widely distributed in the cortex, hippocampus and thalamus as well as in peripheral nerves (see Robinson and Siegelbaum, 2003). I_h possesses unusual biophysical properties that allow it to play a multiple role in neuronal excitability. The I_h carrying channel is usually referred to as hyperpolarization-activated, cyclic nucleotide sensitive (HCN) and represents an evolutionary combination between the voltage-gated K^+ channel and the cyclic nucleotide-gated, non-voltage-gated K^+ channel. Thus I_h channel possesses a high permeability to K^+ ions, is voltage gated, but also modulated by intracellular cyclic adenosine monophosphate (cAMP) levels, allowing activity-dependent regulation. More important, the channel has substantial permeability to Na^+, such that on opening at typical neuronal resting potential, it generates an inward current, causing the cell to depolarize; yet the channel is activated not by depolarization (as with virtually all voltage-gated channels) but by hyperpolarization. Because hyperpolarization produces activation, which in turn leads to depolarization, the HCN channel possesses an inherent negative-feedback property. This negative-feedback principle is evident in the contribution of I_h to neuronal excitability. In a neurone recorded at rest with I_h inactive, a small depolarizing or hyperpolarizing input rapidly produces a steady-state change in voltage. With I_h active, however, a hyperpolarizing input causes slow I_h activation, producing a depolarizing current that returns the membrane potential toward rest. Conversely, a depolarizing input causes deactivation of the I_h that was active at rest; the loss of a tonic depolarizing current causes a hyperpolarization, again returning membrane potential towards rest. Thus I_h tends to stabilize membrane potential near the resting level against either depolarizing or hyperpolarizing inputs. More

precisely, I_h diminishes input resistance, thus minimizing the voltage change produced by a given synaptic current (Robinson and Siegelbaum, 2003). In physiological terms, I_h can be either excitatory or inhibitory with respect to its influence on action potential firing. Thus, the HCN embodies two opposing influences on neuronal excitability, preventing simple characterization as either inhibitory or excitatory.

Although all HCN channels possess the fundamental properties described earlier, I_h represents a family of currents with distinct kinetics and tissue distributions. The HCN family of genes, of which four subtypes have been identified (Santoro *et al*., 1998), encodes four isoforms (HCN1, 2, 3, 4) that when expressed in heterologous cells generate channels with distinct activation kinetics mirroring the properties of native I_h. The predominance of various HCN subtypes varies by location, with HCN1 and HCN2 most prevalent in the retina (Demontis *et al*., 2002; Cervetto *et al*., 2005; Gargini *et al*., 2006). Because the biophysical properties of HCN subtypes vary significantly, the contribution of I_h to neuronal behaviour also varies by both location and neurone type in each region, with individual neurones expressing varying amounts of different HCN isoforms. In addition, because I_h has the potential to affect excitability in a number of ways, modulation of I_h can significantly affect neuronal behaviour. The outcome of I_h activation will therefore depend on: (a) the functional properties of the specific channel subtype, (b) the electrophysiological milieu in which the channel operates (i.e. properties of the additional conductances present on the cell membrane) and (c) the spatial distribution and the nature of the synaptic inputs of the neurone. Recent evidence illustrates two opposite paradigms: in cortical pyramidal neurones I_h seems to take part in the generation of focal paroxysmal activities (Timofeev *et al*., 2002), by contrast a neurone-stabilizing effect of I_h has been suggested by a study in which I_h was enhanced pharmacologically (Poolos *et al*., 2002).

In the visual system I_h inhibition has been shown to modify the filtering properties of the retinal processing (Gargini *et al*., 1999; Mao *et al*., 2003; Gargini *et al*., 2006). In addition to the changes in the temporal properties of the light response, other effects that indicate an increased excitability were observed. I_h inhibition by zatebradine has been shown to increase the hyperpolarizing response to light in retinal rods and to induce oscillations during the recovery phase of the membrane potential (Satoh and Yamada, 2002). More recently it has been suggested that I_h inhibits generation of spontaneous action potential by human retinal receptors (Kewai *et al*., 2005). A current with the properties of I_h has been identified in the amacrine cells of the mouse where it contributes to stabilize the membrane potential (Kozuimi *et al*., 2004). Patch clamp measurements from retinal cells of mouse show that therapeutic levels of ivabradine are effective in blocking I_h at physiological ranges of membrane potential in rods and that this blockade is activity dependent (Demontis *et al*., 2006). Ivabradine reversibly reduces the ERG response to periodic stimuli of low temporal frequency, without alterations of morphology, channel distribution and pigment content (Gargini *et al*., 2006). Under normal circumstances, I_h activation in both the membrane of visual cells (Demontis *et al*., 1999) and in that of bipolar neurones (Cangiano *et al*., 2006) causes dampening of responses to slow noisy inputs thus tuning the visual system to perceptually more relevant signals of higher frequency. I_h inhibition, by altering at the rod synapse the filtering out of signals generated by thermal breakdown of rhodopsin or by other fluctuations in the phototransductive cascade and in the spontaneous firing of ganglion cells, is expected to increase the probability of phosphene occurrence. A possible explanation of how I_h inhibition may

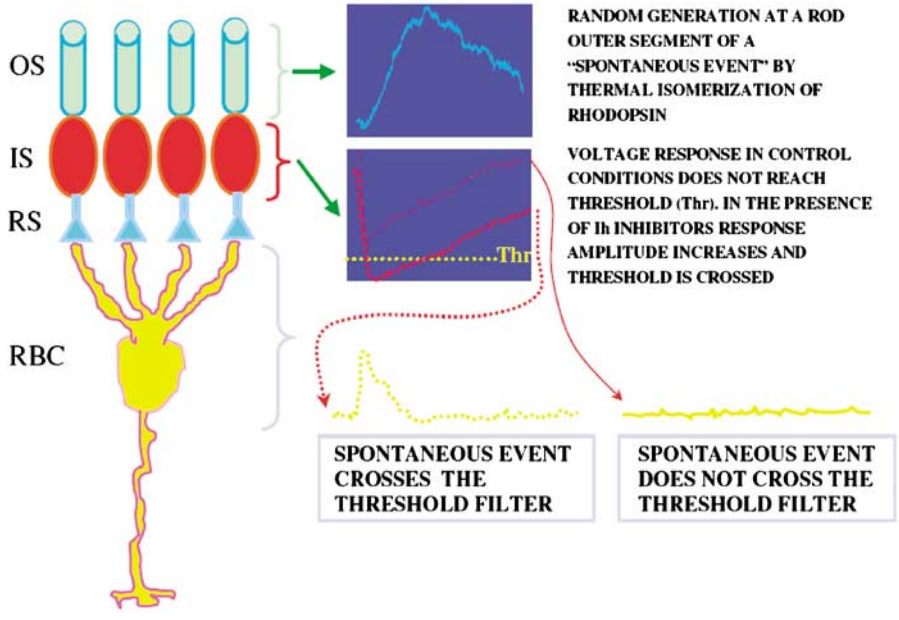

Figure 1 Example of a hypothetical retinal mechanism of phosphene induction by I_h inhibitors. Retinal rod outer segment (OS). Retinal rod inner segment (IS). Receptor synaptic ending (RS). Rod bipolar cell (RBC).

increase the probability of phosphene occurrence is illustrated in Figure 1. Random fluctuations occurring at the outer segment of visual cells are filtered out by the inner segment (Demontis *et al*., 1999) and transmitted to the synaptic endings. Further filtering was suggested to occur post-synaptically at the bipolar dendrites (Sampath and Rieke, 2004; Field *et al*., 2005) where HCN2 channels are in register with the synaptic ribbons and similarly disposed as the glutamate receptors, mGluR6 (Gargini *et al*., 2006). Suppression of filtering increases the probability of a noisy signal reaching the transmission threshold.

Impaired signal filtering by I_h inhibition need not be restricted somewhere in between retinal receptors and bipolar neuron dendrites as assumed in this scheme. In principle, there are several other locations within the retina and along the visual pathway that I_h inhibitors may target. Because I_h was also observed in thalamic relay neurons (McCormick and Pape, 1990; Nita *et al*., 2003), one may argue that phosphenes are possibly caused by I_h inhibition in central neurones. It must be pointed out, however that a central action of ivabradine seems unlikely because the blood–brain barrier is essentially impermeable to this molecule (see Savelieva and Camm, 2006).

Conclusions

It seems reasonable to conclude that a wide variety of causal agents may induce phosphene-like events either by a nonspecific direct stimulation of the visual system or by changing the neuronal excitability or by suppressing noise filtering processes. At variance with many other drugs for which the mechanisms of phosphene induction remain elusive, in the case of I_h inhibitors, experimental data are available to suggest an explanation for the occurrence of the visual phenomena. Recent evidence supports the idea that inhibition of I_h is the most probable cause for the visual symptoms experienced by both healthy volunteers and cardiac patients under ivabradine treatment. Under normal circumstances, most of the random fluctuations generated within the retinal circuits do not reach the level of conscious perception because they are filtered out. Presumably, filtering occurs within the retina at various levels and the ability of I_h to act as a negative-feedback mechanism makes HCN channels likely sites for such actions. It is, however, important to note that not all the findings from patients studies fit easily within the proposed framework. It is baffling to observe that while in nearly all patients ivabradine lowers the heart rate, only a relatively small fraction ($\sim$15%) experiences phosphenes. Somewhat confusing is also the fact that in the majority of cases phosphene occurrence resolve spontaneously during ivabradine treatment, at variance with the slowing of heart rate that seems to persist as long as the drug is given. It is not presently clear whether all this is due to a dose-threshold effect, to a drug target polymorphism or to some other cause. At therapeutic doses for humans ivabradine induces in animal models only small changes in the retinal activity (Gargini *et al*., 2006). The *in vivo* minor impact of the drug on the retinal HCN is consistent with the low passage of ivabradine across the blood retinal barrier.

Acknowledgements

We thank Dr M Bouly, Dr G Lerebours and Dr F Mahlberg-Gaudin for advice and encouragement.

Conflict of interest

The authors have been consultant/scientific advisors for the Institut De Recherches Internationales Servier (IRIS) the company that manifactures Procoralan (ivabradine).

References

Afra J, Mascia A, Gerard P, Maertensde Noordhout A, Schoenen J (1998). Interictal cortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. *Ann Neurol* **44**: 209–215.

Antal A, Artl S, Nitsche MA, Chadaide Z, Paulus W (2006). Higher variability of phosphene thresholds in migraineurs than in controls: a consecutive transcranial magnetic stimulation study. *Cephalgia* **26**: 865–870.

Attwell D (2003). Interaction of low frequency electric fields with the nervous system: the retina as a model system. *Radiat Prot Dosim* **106**: 341–348.

Aurora SK, Welch KMA, Al-Sayed F (2003). The threshold for phosphene is lower in migraine. *Cephalalgia* **23**: 258–263.

Bader CR, Bertrand D (1984). Effect of changes in intra- and extracellular sodium on the inward (anomalous) rectification in salamander photoreceptors. *J Physiol (London)* **347**: 611–631.

Barker AT, Jalinous R, Freeston IL (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet* **1**: 1106–1107.

Barlow HB (1965). Optic nerve impulses and Weber's law. *Cold Spring Harb Symp Quant Biol* **30**: 539–546.

Battelli L, Black KR, Wray SH (2002). Transcranial magnetic stimulation of the visual area V5 in migraine. *Neurology* **58**: 1066–1069.

Baylor DA (1996). How photons start vision. *Proc Natl Acad Sci USA* **93**: 560–565.

Baylor DA, Matthews G, Yau K-W (1980). Two components of electrical dark noise in toad retinal rod outer segments. *J Physiol (London)* **309**: 591–621.

Baylor DA, Nunn BJ, Schnapf JL (1984). The photocurrent, noise and spectral sensitivity of the monkey *Macaca fascicularis*. *J Physiol (London)* **357**: 575–607.

Beech DJ, Barnes S (1989). Characterisation of a voltage-gated K channel that accelerates the rod response to dim light. *Neuron* **3**: 573–581.

Bohotin V, Fumal A, Vandenheede M, Bohotin C, Schoenen J (2003). Excitability of visual V1-V-2 and motor cortices to single transcranial magnetic stimuli in migraine: a reappraisal using a figure-of-eight coil. *Cephalgia* **23**: 264–270.

Borer JS, Fox K, Jaillon P, Lerebours G (2003). Antianginal and antiischemic effects of ivabradine, an *I*(*f*) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* **107**: 817–823.

Boroojerdi B, Khalaf OB, Corwell B, Immisch I, Battaglia F, Muellbacher W *et al*. (2000). Enhanced excitability of the human visual cortex induced by short-term light deprivation. *Cereb Cortex* **10**: 529–534.

BoSmith RE, Briggs I, Sturgess NC (1993). Inhibitory actions of ZENECA ZD7288 on whole-cell hyperpolarization activated inward current (If) in guinea-pig dissociated sinoatrial node cells. *Br J Pharmacol* **110**: 329–343.

Brindley GS, Lewin WS (1968). The sensations produced by electrical stimulation of the visual cortex. *J Physiol (London)* **196**: 479–493.
Brivanlou IH, Warland DK, Meister M (1998). Mechanisms of concerted firing among retinal ganglion cells. *Neuron* **20**: 527–539.
Bucchi A, Baruscotti M, Di Francesco D (2002). Current-dependent block of rabbit sino-atrial node *I*(*f*) channels by ivabradine. *J Gen Physiol* **120**: 1–13.
Bucchi A, Tognati A, Milanesi R, Baruscotti M, DiFrancesco D (2006). Properties of ivabradine-induced block of HCN1 and HCN4 pacemaker channels. *J Physiol* **572**: 335–346.
Buchanan TM, Ramadan NM, Aurora S (2004). Future pharmacological targets for acute and preventive treatments of migraine. *Expert Rev Neurotherapeutics* **4**: 391–430.
Cavaggioni A (1968). The dark-discharge of the eye in the unrestrained cat. *Pflügers Arch Physiol* **304**: 75–80.
Cangiano L, Gargini C, Demontis GC, Della Santina L, Cervetto L (2006). Expression of hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels by rod bipolar cells endows them with a band-pass response to input signals. *Documenta Ophthalmol* **112**: 137 (*S2–S23*).
Ceremuzynski L, Nartowicz E, Dluzniewski M, Perkowicz J, Czarnecki W, Burduk P *et al.* (1987). ST 567 compared with propranolol in stable angina. *Eur Heart J* **8** Suppl): L159–L163.
Cervetto L, Della Santina L, Demontis GC, Gargini C, Paoli GT (2005). Distribution and properties of HCN-channels in the retina of mouse. *Invest Ophthalmol Vis Sci* **46**: B1014.
Chronicle EP, Pearson AJ, Mulleners WM (2006). Objective assessment of cortical excitability in migraine with and without aura. *Cephalgia* **26**: 801–808.
Collins CC (1967). Evoked pressure responses in the rabbit eye. *Science* **155**: 106–108.
Cowey A (2005). The Ferrier Lecture 2004. What can transcranial magnetic stimulation tell us about how the brain works? *Philos Trans R Soc B* **360**: 1185–1205.
Cowey A, Walsh V (2000). Magnetically induced phosphenes in sighted, blind and blindsighted observers. *Neuroreport* **11**: 3269–3273.
Davis FA, Bergen D, Scheuf C, McDonald I, Deutsch W (1976). Movement phosphenes in optic neuritis: a new clinical sign. *Neurology* **26**: 1100–1104.
Demontis GC, Longoni B, Barcaro U, Cervetto L (1999). Properties and functional roles of a hyperpolarisation-gated current in guinea-pig retinal rods. *J Physiol (London)* **515**: 813–828.
Demontis GC, Moroni A, Gravante B, Longoni B, Cervetto L, Di Francesco D (2002). Functional characterisation and subcellular localisation of HCN1 channels in rabbit retinal rod photoreceptors. *J Physiol (London)* **542**: 89–97.
Demontis GC, Gargini C, Paoli GT, Cervetto L (2006). Ivabradine inhibits the hyperpolarization-activated inward current (I_h) in mouse rod photoreceptors. *Documenta Ophthalmol* **112**: 102–103.
Di Francesco D (1993). Pacemaker mechanisms in cardiac tissue. *Ann Rev Physiol* **515**: 455–472.
Di Francesco D, Camm JA (2004). Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* **64**: 1757–1765.
Dobelle WH, Mladejovsky MG (1974). Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. *J Physiol (London)* **243**: 553–576.
Dobelle WH, Mladejovsky MG, Girvin JP (1974). Artificial vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis. *Science* **183**: 440–444.
Enoch JM, Choi SS, Kono M, Schwatz D, Bearse M (2003). Utilisation of eye movement phosphenes to help understand transient strains at optic disc and nerve in miopia. *Ophthalmic Physiol Opt* **23**: 377–381.
EPAR (European Public Assessment Report) Procoralan (2005) at: www.emea.eu.int.
Fain GL, Quanndt FN, Bastian BL, Gerschenfeld HM (1978). Contribution of caesium-sensitive conductance increase to rod response. *Nature* **272**: 467–469.
Fain GL, Lisman JE (1993). Photoreceptor degeneration in vitamin A deprivation and retinitis pigmentosa: the equivalent light hypothesis. *Exp Eye Res* **57**: 335–340.
Field GD, Sampath AP, Rieke R (2005). Retinal processing near absolute threshold: from behavior to mechanism. In: Hoffman JF (ed). *Ann Rev Physiol* **Vol. 67**. Annual Reviews: Palo Alto, CA, pp. 491–514.
Forzli el F, Brasseur G (1999). Signes fonctionelles annonciateurs d'un decollement de retine. *J Fr Ophthalmol* **22**: 869–871.
Fraunfelder FT, Fraunfelder FW (2001). In: Randall JA associates (eds). *Drug-Induced Ocular Side Effects,* 5th edn Butterworth Heinemann: Boston.
Frishman WH, Pepine CJ, Weiss RJ, Baiker WM (1995). Addition of zatebradine, a direct sinus node inhibitor, provides no greater exercise tolerance benefit in patients with angina taking extended-release nifedipine: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The Zatebradine Study Group. *J Am Coll Cardiol* **26**: 305–312.
Gargini C, Demontis GC, Bisti S, Cervetto L (1999). Effect, of blocking the hyperpolarisation-activated current (I_h) on the cat electroretinogram. *Vis Res* **39**: 1767–1774.
Gargini C, Demontis GC, Della Santina L, Cervetto L (2006). Effects of acute and chronic ivabradine administration on retinal function and morphology in pigmented rats. *Documenta Ophthalmol* **112**: 133 (S2–S16).
Granit R (1955). Receptors and sensory perception. *Yale University Press: New Haven*.
Hall SD, Barnes GR, Hillebrand A, Furlong PL, Sing KD, Holliday IE (2004). Spatio-temporal imaging of cortical desynchronization in migraine visual aura: a Magnetoencephalography Case Study. *Headache* **44**: 204–208.
von Helmholtz H (1896). Handbuch der Physiologischen Optik II. In: Southhall JCP (ed). Leopold Voss: Bd. Hamburg, Translation from the 3rd German edn., 1924. Republished: Dover: New York, 1962.
Hering E (1878). Zur lehre vom lichtsinne.. Translated by In: Hurvich LM and Jameson D (eds). *Outlines of the Theory of the Light Sense*. Carl Gerold's Sohn: Vienna;, Harvard University Press: Cambridge, MA, 1964.
Hubel DH, Livingston MS (1990). Color and contrast sensitivity in the lateral geniculate body and primary visual cortex of the macaque monkey. *J Neurosci* **10**: 2223–2237.
Hubel DH, Wiesel TN (1977). Functional architecture of macaque monkey visual cortex. *Proc R Soc Lond B Biol Sci* **198**: 1–59.
Hughes GW, Maffei L (1965). On the origin of the dark discharge of the retinal ganglion cells. *Arch Ital Biol* **103**: 45–59.
Jones GJ (1998). Membrane current noise in dark-adapted and light adapted isolated retinal rods of the larval tiger salamander. *J Physiol (London)* **511**: 903–913.
Kara P, Reid RC (2003). Efficacy of retinal spikes in driving cortical responses. *J Neurosci* **24**: 8547–8557.
Kewai F, Horiguchi M, Ichinose F, Ohkuma M, Isobe R, Miyachi E (2005). Suppression by an h current of spontaneous Na^+ action potentials in human cone and rod photoreceptors. *Invest Ophthalmol Vis Sci* **46**: 390–397.
Kim IB, Lee EJ, Kang TH, Chung JW, Chun MH (2003). Morphological analysis of the hyperpolarisation-activated cyclic nucleotide-gated cation channel (HCN1) immunoreactive bipolar cells in the rabbit retina. *J Comp Neurol* **467**: 389–402.
Kozuimi A, Jakobs TC, Masland RH (2004). Inward rectifying currents stabilise the membrane potential in dendrites of mouse amacrine cells: patch-clamp recordings and single-cell RT-PCR. *Mol Vis* **10**: 328–340.
Levick WR (1973). Maintained discharge in the visual system and its role in information processing. In: Yung R (ed). *Handbook of sensory Physiology. Vol VII/3* pp. 575–598.
Levin LA, Lessel S (2003). Risk of multiple sclerosis after optic neuritis. *JAMA* **290**: 403–404.
Linde M (2006). Migraine: a review and future directions for treatment. *Acta Neurol Scand* **114**: 71–83.
Maccarone R, Izzizzari G, Gargini C, Cervetto L, Bisti S (2004). The impact of organic inhibitors of the hyperpolarization activated current (I_h) on the electroretinogram (ERG) of rodents. *Arch Ital Biol* **142**: 95–103.
Maffei L, Moruzzi G, Rizzolatti G (1965). Geniculate unit responses to sine-wave photic stimulation during wakefulness and sleep. *Science* **149**: 563–564.
Mao BQ, Macleish PR, Victor JD (2003). Role of hyperpolarisation-activated currents for the intrinsic dynamics of isolated retinal neurons. *Biophys J* **84**: 2756–2767.

Mastronarde DN (1989). Correlated firing of retinal ganglion cells. *Trends Neurosci* **12**: 75–80.
McCormick DA, Pape HC (1990). Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J Physiol* **431**: 291–318.
Meyer BU, Diehl R, Steinmetz H, Britton TC, Benecke R (1991). Magnetic stimuli applied over motor and visual cortex: influence of coil position and field polarity on motor responses, phosphenes and eye movements. *Electroencephalogr Clin Neurophysiol Suppl* **43**: 121–134.
Mulleners WM, Chronicle EP, Palmer JE, Koehler Pj, Vredeveld JW (2001). Suppression of perception in migraine: evidence for reduced inhibition in the visual cortex. *Neurology* **56**: 178–183.
Müller F, Scholten A, Ivanova E, Haverkamp S, Kremmer E, Kaupp UB (2003). HCN channels are expressed differentially in retinal bipolar cells and concentrated at synaptic terminals. *Eur J Neurosci* **17**: 2084–2096.
Murtha T, Stasheff SF (2003). Visual dysfunction in retinal and optic nerve disease. *Neurol Clin* **21**: 445–481.
Nita DA, Steriade M, Amzica F (2003). Hyperpolarisation rectification in cat lateral geniculate neurons modulated by intact corticothalamic projections. *J Physiol (London)* **552**: 325–332.
Owen GW, Torre V (1983). High-pass filtering of small signals by retinal rods. Ionic studies. *Biophys J* **41**: 325–339.
Ozaki T, Kaplan E (2006). Brainstem input modulates globally the transmission through the lateral geniculate nucleus. *Int J Neurosci* **116**: 247–264.
Palmer JE, Chronicle EP, Rolan P, Mulleners WM (2000). Cortical hyper-excitability is cortical under-inhibition. Evidence from a novel functional test of migraine patients. *Cephalalgia* **20**: 525–532.
Pflügers EFW (1865). *Untersuchungen aus dem physiologischen Laboratorium zu Bonn*. Hirschwald: Berlin. S170–S171.
Poolos NP, Migliore M, Johnston D (2002). Pharmacological upregulation of h-channels reduces the excitability of pyramidal neuron dendrites. *Nat Neurosci* **5**: 767–774.
Queiroz LP, Rapoport AM, Weeks RE, Sheftel FD, Siegel SE, Baskin SM (1997). Characteristics of migraine visual aura. *Headache* **37**: 137–141.
Rauschecker AM, Bestman S, Walsh V, Thilo KV (2004). Phosphene threshold as a function of contrast of external visual stimuli. *Exp Brain Res* **157**: 124–127.
Richards W (1971). The fortification illusions of migraines. *Sci Am* **224**: 89–96.
Rieke F, Baylor DA (1996). Molecular origin of continuous dark noise in rod photoreceptors. *Biophys J* **71**: 2553–2572.
Rodieck RW (1967). Maintained activity of cat retinal ganglion cells. *J Neurophysiol* **30**: 1043–1071.
Rodieck RW, Smith PS (1966). Slow dark discharge rhythms of cat retinal ganglion cells. *J Neurophysiol* **29**: 942–953.
Robinson RB, Siegelbaum SA (2003). Hyperpolarisation-activated cation currents: from molecules to physiological function. *Annu Rev Physiol* **65**: 453–480.
Rosenbaum F, Harati YR, Friedman M (1987). Visual hallucinations in sane people: charles bonnet syndrome. *J Am Geriatr Soc* **35**: 66–68.
Sampath AP, Rieke F (2004). Selective transmission of single photon responses by saturation at the rod-to-rod bipolar synapse. *Neuron* **41**: 431–443.
Santoro B, Liu DT, Yao H, Bartsch D, Kandel ER (1998). Identification of a gene encoding a hyperpolarisation-activated pace-maker channel of brain. *Cell* **93**: 1–20.
Satoh TO, Yamada M (2000). A bradycardiac agent ZD7288 blocks the hyperpolarization-activated current (I_h) in retinal rod photoreceptors. *Neuropharmacology* **39**: 1284–1291.
Satoh TO, Yamada M (2002). Multiple inhibitory effects of zatebradine (UL-FS 49) on the electrophysiological properties of retinal rod photoreceptors. *Pflügers Arch* **443**: 532–540.
Savelieva I, Camm JA (2006). Novel I_f current inhibitor ivabradine: safety considerations. In: Camm J, Tendera M (eds). *Heart Rate Slowing by I_f Current Inhibition,*. Karger: Basel, vol. **43**: 79–96.
Shin SK, Rotheberg BS, Yellen G (2001). Blocker state dependence and trapping in hyperpolarization-activated cation channels: evidence for an intracellular activation gate. *J Gen Physiol* **117**: 91–101.
Siegel RK (1977). Hallucinations. *Sci Am* **237**: 132–140.
Silvanto J, Cowey A, Lavie N, Walsh V (2005). Striate cortex (V1) activity gates awareness of motion. *Nat Neurosci* **8**: 143–144.
Sloan TB (1998). Anaesthetic effects on electrophysiologic recordings. *J Clin Neurophysiol* **15**: 217–226.
Schmidt EM, Bak MJ, Hambrecht FT, Kufta CV, O'Rourzke DK, Vallobhanath P (1996). Feasibility of a visual prosthesis for blind based on intracranial microstimulation of the visual cortex. *Brain* **119**: 507–522.
Snyders DJ, Van Bogaert PP (1987). Alinidine modifies the pacemaker current in sheep Purkinje fibers. *Pflugers Arch* **410**: 83–91.
Stewart LM, Walsh V, Rothwell JC (2001). Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. *Neuropsychologia* **39**: 415–419.
Stieber J, Wieland K, Stöckl G, Ludwig A, Hofmann F (2006). Bradycardic and proarrhythmic properties of sinus node inhibitors. *Mol Pharmacol* **69**: 1328–1337.
Tabata T, Ishida AT (1996). Transient and sustained depolarization of retinal ganglion cells by I_h. *J Neurophysiol* **75**: 1932–1943.
Tardiff JC (2005). Ivabradine in clinical practice: benefits of I_f inhibition. *Eur Heart J Suppl* 7 (Suppl H): H29–H32.
Tehovnik EJ, Tolias AS, Sultan F, Slocum WM, Logothetis NK (2006). Direct and indirectactivation of cortical neurons by electrical microstimulation. *J Neurophysiol* **96**: 512–521.
Timofeev I, Bazhenov M, Sejnowski T, Steriade M (2002). Cortical hyperpolarization-activated depolarising current takes part in the generation of focal paroxysmal activities. *Proc Natl Acad Sci USA* **99**: 9533–9537.
Tyler CW (1978). Some new entoptic phenomena. *Vis Res* **18**: 1633–1639.
Van Bogaert PP, Pittors F (2003). Use-dependent blockade of cardiac pacemaker current (I_f) by cilobradine and zatebradine Eur. *Eur J Pharmacol* **478**: 161–171.
Walker J (1981). The amateur scientist: about phosphenes: patterns that appear when the eyes are closed. *Sci Am* **244**: 142–152.
Welch KMA, D'Andrea G, Tepley N, Barkley GL, Ramadan NM (1990). The concept of migraine as a state of central neuronal hyperexcitability. *Headache* **8**: 817–828.
Wilkstrom J, Poser S, Ritter G (1980). Optic neuritis as an initial symptom in multiple sclerosis. *Acta Neurol* **61**: 178–185.
Woodruff ML, Wang Z, Chung HY, Redmond TM, Fain GL, Lem J (2003). Spontaneous activity of opsin apoprotein is a cause of leber congental amaurosis. *Nat Genetic* **35**: 158–164.
Wray SH, Mijovic-Prelec D, Kosslyn SM (1995). Visual processing in migraineurs. *Brain* **118**: 25–35.
Yagi T, MacLeish PR (1994). Ionic conductances of monkey solitary cone inner segments. *J Neurophysiol* **71**: 656–665.
Young WB, Oshinsky ML, Shechter AL, Gebeline-Myers C, Bradley KC, Wassermann EM (2004). Consecutive transcranial magnetic stimulation: phosphene thresholds in migraineurs and controls. *Headache* **44**: 131–135.
Zrenner E (2002). Will retinal implants restore vision? *Science* **295**: 1022–1025.