Oral Proton Pump Inhibitors Disrupt Horizontal Cell-Cone Feedback and Enhance Visual Hallucinations in Macular Degeneration Patients

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Purpose. Visual hallucinations (VHs) occur in macular degeneration patients with poor vision but normal cognitive function. The underlying mechanisms are poorly understood. We report the identification of pharmaceutical agents that enhance VH and use these agents to examine the contribution of retinal neurons to this syndrome.

Methods. We detail clinical observations on VH in five macular degeneration patients treated with proton pump inhibitors having the core structure, 2-pyridyl-methylsulfinyl-benzimidazole. We tested possible retinal mechanisms using paired whole cell recordings to examine effects of these compounds on feedback interactions between horizontal cells and cones in amphibian retina.

Results. Five patients with advanced wet macular degeneration described patterned VHs that were induced or enhanced by oral proton pump inhibitors. The abnormal images increased with light, disappeared in the dark, and originated in the retina, based on ophthalmodynamometry. Simultaneous paired whole cell recordings from amphibian cones and horizontal cells showed that 2-pyridyl-methylsulfinyl-benzimidazoles blocked the negative shift in voltage dependence and increase in amplitude of the calcium current (I_{Ca}) in cones that is induced by changes in horizontal cell membrane potential. These effects disrupt the negative feedback from horizontal cells to cones that is important for the formation of center-surround receptive fields in bipolar and ganglion cells, and thus for normal spatial and chromatic perception.

Conclusions. Our study suggests that changes in the output of retinal neurons caused by disturbances in outer retinal feedback mechanisms can enhance patterned visual hallucinations. (*Invest Ophthalmol Vis Sci.* 2013;54:1485–1489) DOI: 10.1167/iovs.12-11091

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The Charles Bonnet Syndrome (CBS) is named after the Swiss philosopher Charles Bonnet who described visual hallucinations in his blind 89-year-old grandfather.[1–3] No psychiatric or cognitive disturbances are present in patients with CBS and, in most cases, there is no gross or microscopic brain pathology.[4] The neurophysiological basis of these phenomena has been attributed to the spontaneous discharge of nerve cells from the visual association cortex when blindness leads to reduced sensory input.[5,6] This hypothesis is known as the deafferentation theory and has become a widely accepted medical paradigm for explaining the neural basis of CBS.[5,7,8] However, this idea has never been validated.

In the current study, we report clinical and experimental observations that suggest altered retinal processing induces or enhances visual hallucinations in macular degeneration patients. We describe a group of five patients that reported the onset or enhancement of patterned visual hallucinations following the use of lansoprazole, omeprazole, and pantoprazole, three proton pump inhibitors (PPIs) sharing the core structure, 2-pyridyl-methylsulfinyl-benzimidazole. Although these drugs do not normally penetrate the blood-brain barrier, patients with exudative macular degeneration have a breakdown in the blood-retinal barrier in the outer retina, a region where proton pumps play important roles in visual processing.

Protons can influence negative feedback interactions between horizontal cells and cone photoreceptors.[9–11] This feedback loop is fundamental to the formation of center surround receptive fields in bipolar and ganglion cells.[12–14] Center-surround receptive fields improve the detection of edges, a process that is highly conserved from invertebrates to higher vertebrates.[15,16] Horizontal cell to cone feedback also appears to be critically important for color perception.[14,17–20]

We hypothesized that proton pump inhibitors may disrupt normal horizontal cell-photoreceptor cell feedback interactions and thereby alter spatial and chromatic perception. Complementing our clinical observations, we examined the effects of these drugs on horizontal cell to cone feedback interactions directly by recording simultaneously from cones and horizontal cells using an amphibian retina model system.

Methods

We identified five patients with advanced wet macular degeneration and poor vision who reported the onset or enhancement of visual hallucinations with the use of proton pump inhibitors for heartburn management. The diagnosis of wet ARMD was based on the presence of subretinal blood, intraretinal thickening, and exudate. Fluorescein angiography and spectral domain OCT imaging studies demonstrated subretinal neovascularization, retinal edema, and outer retinal disorganization. Each patient was cognitively intact, lived independently, and had no history of dementia, psychosis, or Parkinson's disease. Each patient was aware that the images were not real. IRB approval was obtained from Scripps Memorial Hospital.

Electrophysiology: Whole-Cell Recordings

Normal horizontal cell-photoreceptor cell feedback interactions were measured in retinal slices from the aquatic tiger salamander (*Ambystoma tigrinum*), a species whose large retinal cells allow one to record simultaneously from both horizontal cells and cones and thereby test the effect of proton pump-mediated feedback interactions directly. Horizontal cell feedback has been shown to operate by similar mechanisms in both amphibian and mammalian retina.[21] Experimental procedures were approved by the University of Nebraska Medical Center Institutional Animal Care and Use Committee and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Male and female adult aquatic tiger salamanders (*Ambystoma tigrinum*, 18–25 cm in length; Kons Scientific, Germantown, WI, and Charles Sullivan Co., Nashville, TN) were maintained on a 12-hour day/night cycle. Because maintained illumination can promote disassembly of synaptic ribbons in rods,[22–24] animals were sacrificed 1 to 2 hours after the beginning of subjective night. Retinal slices were prepared and whole cell voltage clamp recordings were obtained from synaptically connected cone and horizontal cell pairs as described in detail previously.[9,21] Briefly, I_{Ca} was measured in the cone by applying a ramp voltage protocol (–90 to +60 mV, 0.5 mV/ms, applied from a steady holding potential of –70 mV). The strength of horizontal cell–cone feedback was altered by changing the membrane potential of the horizontal cell between 0; –40 (approximating the dark resting membrane potential); –70 (approximating the membrane potential in light); and –90 mV. Changing the horizontal cell–membrane potential produced changes in both the amplitude and the voltage dependence of the cone I_{Ca}.[9] The changes in I_{Ca} caused by horizontal-cone negative feedback interactions were compared in the presence and absence of lansoprazole (Prevacid 100 μM; Sigma-Aldrich, St. Louis, MO) and omeprazole (Prilosec 100 μM; Sigma-Aldrich), two compounds that are representative of the structurally-related class of PPIs.

Results

The Table summarizes the clinical features of five patients who developed patterned visual hallucinations after treatment with a proton pump inhibitor for gastroesophageal reflux disease. Concurrently, all patients had wet macular degeneration with active subretinal neovascularization, a condition that causes breakdown in the blood-retinal barrier and leakage of blood products into the subretinal space. Three patients had no prior history of hallucinations. Two patients had a prior history of patterned hallucinations that increased with the use of omeprazole. All hallucinations were induced by bright light and disappeared after 20 to 30 minutes of darkness, indicating a dependence on the initiation of visual transduction and visual processing pathways. Retinal function was required since the hallucinations ceased after applying external pressure to the globe to raise intraocular pressure and reduce retinal circulation, a technique known as ophthalmodynamometry. The hallucinations returned consistently when external pressure was released. With timely discontinuation of the proton pump inhibitors, the hallucinations stopped or returned to baseline.

Electrophysiological studies using simultaneous paired whole cell recordings from cone photoreceptor cells and horizontal cells in the amphibian retina were used to evaluate the effects of lansoprazole (Sigma-Aldrich) and omeprazole (Sigma-Aldrich) on negative feedback from horizontal cells to cones. Figure 1A shows an example of a cone and postsynaptic horizontal cell used for simultaneous whole cell recording. Figure 1B shows the current/voltage relationship for cone I_{Ca} recorded while voltage clamping the postsynaptic horizontal cell at different membrane potentials. To mimic light-evoked hyperpolarization, we directly hyperpolarized the voltage-clamped horizontal cell, which caused the cone I_{Ca} to activate at more negative potentials and slightly increased I_{Ca} amplitude. We compared the cone I_{Ca} recorded when the horizontal cell membrane potential was clamped at –40 mV (approximating the resting potential in darkness; purple trace) with the

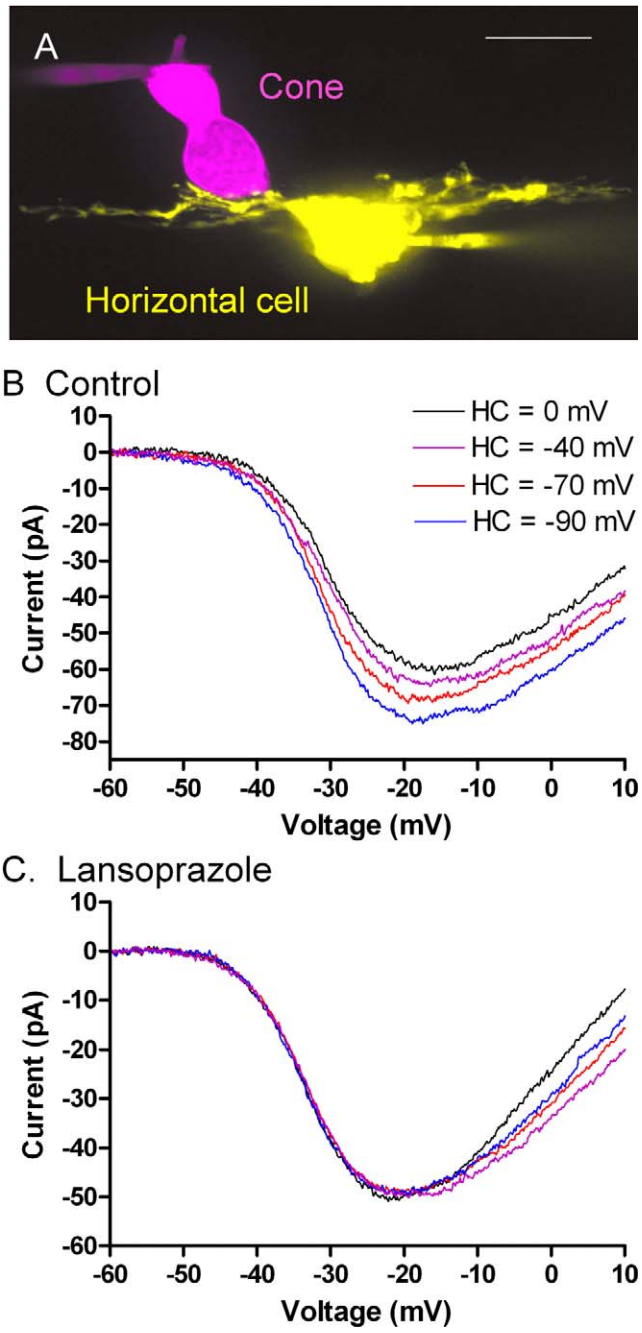

Figure 1. (**A**) Confocal stack showing a fluorescently stained cone and horizontal cell pair used for simultaneous whole-cell recordings. Sulfarhodamine B (*magenta*; 0.5 mg/mL) was introduced into the cone through the patch electrode near the top of the cell. The horizontal cell was labeled with Lucifer Yellow (*yellow*, 2 mg/mL). (**B**) Effects of horizontal cell–membrane potential on cone I_{Ca} measured using a ramp voltage protocol (–90 to +60 mV, 0.5 mV/ms). The overlaid traces show measurements of cone I_{Ca} when the postsynaptic horizontal cell–membrane potential (V_m) was changed from 0 mV (*black*) to –40 mV (*purple*), –70 mV (*red*), and –90 mV (*blue*). (**C**) Changes in horizontal cell V_m had little effect on cone I_{Ca} measured in the same cell pair after bath application of lansoprazole (100 μM) for 3 minutes.

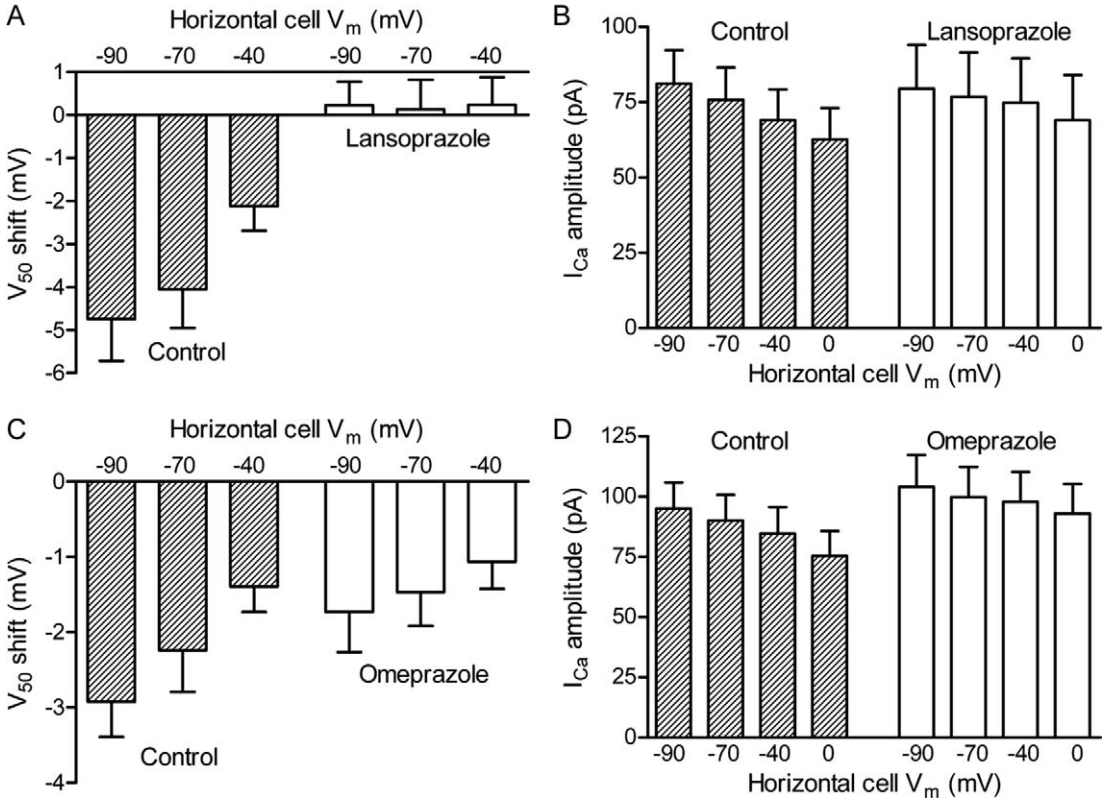

Figure 2. Effects of lansoprazole and omeprazole on feedback from horizontal cells to cone I_{Ca}. (**A**) Voltage shifts in cone I_{Ca} were quantified by determining the voltage at which the current was half-maximal (V_{50}). Data are plotted relative to V_{50} measured when the horizontal cell was voltage clamped at 0 mV. The *hatched bars* on the *left* show control data; data from the same cell pairs measured after bath application of lansoprazole (100 μM) are shown by the *open bars* on the *right* ($N = 10$ pairs). Lansoprazole significantly reduced the change in V_{50} induced by voltage clamping the horizontal cell at –40 ($P < 0.0047$, paired *t*-test); –70 ($P < 0.0044$); and –90 mV ($P < 0.0012$). (**B**) Peak amplitude of I_{Ca} measured in control and lansoprazole. (**C**) Voltage shifts measured in control conditions and following bath application of omeprazole (100 μM; $N = 10$ pairs). Omeprazole significantly reduced the change in V_{50} induced by voltage clamping the horizontal cell at –70 ($P < 0.0066$) and –90 mV ($P < 0.0044$). (**D**) Peak amplitude of I_{Ca} measured in control and omeprazole. Amplitude differences did not attain statistical significance.

cone I_{Ca} recorded when the horizontal cell membrane potential was –90 mV (approximating the potential in bright light; blue trace). From this comparison, one can see that hyperpolarization of the horizontal cell caused a negative shift in voltage dependence of cone I_{Ca} (leftward shift) and increased its peak amplitude. These effects increase the amplitude of I_{Ca} at the cone's normal resting potential of ca. –35 mV and this increase in I_{Ca} helps to restore synaptic output from the cone during a light flash. However, in the presence of lansoprazole (100 μM, Sigma-Aldrich), the cone I_{Ca} did not respond to changes in the horizontal cell membrane potential, indicating that the normal feedback response was lost (Fig. 1C).

The shift in I_{Ca} activation was quantified by determining the voltage at which cone I_{Ca} was half maximal (V_{50}). Figure 2A shows the change in cone I_{Ca} V_{50} as a function of horizontal cell–membrane potential. Data were normalized by comparing V_{50} values measured when the horizontal cell was voltage clamped at –40, –70, or –90 mV to the V_{50} obtained when the horizontal cell was held at 0 mV. Figure 2B shows the peak amplitude of cone I_{Ca} as the horizontal cell hyperpolarizes. In the presence of lansoprazole (Sigma-Aldrich), the cone I_{Ca} exhibited no change in V_{50} in response to hyperpolarization of the horizontal cell and the change in peak current amplitude was diminished. Omeprazole caused a similar but weaker disruption in horizontal cell feedback, as shown by the reduction in the V_{50} voltage shifts (Fig. 2C) and amplitude changes (Fig. 2D). These effects were restored when omeprazole and lansoprazole were washed out of the bath (not shown), indicating the disruption in horizontal cell-cone feedback was reversible.

Discussion

Our results demonstrate that proton pump inhibitors with the core structure 2-pyridyl-methylsulfinyl benzimidazole can induce or enhance visual hallucinations in wet macular degeneration patients with a breakdown of the outer blood-retinal barrier. Four of the five patients had chronic subretinal neovascular membranes in only one eye, indicating that unilateral disease is sufficient to disrupt visual processing with these drugs. The hallucinations are reversible with timely discontinuation of the proton pump inhibitors, but may be more difficult to reverse after years of drug use.

Our clinical data support the premise that the signals inducing the patterned visual hallucinations in this group of patients are retinal in origin and are dependent on activation of the visual transduction cascade. The patients report their hallucinations are most noticeable in bright light, disappear after 20 to 30 minutes of darkness, and are never present when they awake at night. The patients also report that their images disappeared when the retinal circulation is temporarily decreased and return when the circulation is restored.

The clinical data further suggest that enhancement of the visual hallucinations with proton pump inhibitors may also involve the suppression of normal horizontal cell-cone

Table. Clinical Features of Visual Hallucinations in Patients on PPIs

Patient	Age, y	Sex	Visual Acuity		Exudative Disease	Drug/Duration	Images	Reversible
			Right Eye	Left Eye				
1	80	F	20/40	20/400	Left eye	Omeprazole ×2 days	Blue confetti	Yes
2	90	F	20/25	20/400	Left eye	Pantoprazole ×2 weeks	Black polka dots	Yes
3	98	F	20/50	20/60	Right eye	Omeprazole ×5 months	Colored circles	Yes
4	90	F	CF	20/200	Right eye	Lansoprazole ×3 years	Black dots, crosses, violet flowers	No
5	89	F	20/400	CF	Both	Omeprazole ×4 years	Black dots and colors	No

CF, counting fingers.

feedback mechanisms. Patients describe a subjective loss of contrast sensitivity, which is governed by the feedback interactions between horizontal cells and cones and the formation of center-surround receptive fields.[11,15,16,25]

Simultaneous paired whole-cell recordings from cones and horizontal cells in an animal model showed that these compounds disrupt normal horizontal cell–cone feedback interactions. Previous data from a number of studies has shown that pH neutralizing buffers, such as HEPES, can block horizontal cell feedback,[9,10,26] and thereby abolish both color-opponency and the center-surround receptive field arrangement of parasol ganglion cells.[13,20] Under our experimental conditions, the effect of lansoprazole (Sigma-Aldrich) and omeprazole (Sigma-Aldrich) on horizontal cell-cone feedback is similar to the effect of HEPES, supporting the idea that the oral proton pump inhibitors may interfere with a proton-related mechanism of surround formation in this patient population.[13]

Negative feedback from horizontal cells to cones modulates the voltage-dependence of cone calcium currents.[27] At the resting membrane potential, the relationship between calcium current amplitude and membrane voltage is quite steep and so small shifts along the voltage axis induced by small changes in proton levels can have large effects on release. The net result of this feedback interaction is to subtract the effects of the average surrounding light levels from more localized changes in illumination falling on the cone, thereby facilitating contrast discrimination.

Photoreceptor calcium currents are uniquely sensitive to the effects of protons on membrane surface charge because of their relatively depolarized resting membrane potential and unusually low threshold for calcium current activation.[28] Changes in extracellular pH produce less pronounced effects at most other neuronal synapses because the resting membrane potentials for most neurons are typically below the threshold for calcium current activation.

While pH buffers have consistently been shown to block horizontal cell feedback to photoreceptors, the mechanisms by which they do so remain controversial, in part because changes in pH that have been proposed to influence horizontal-cell-to-cone feedback are likely to be highly localized to the synapse and not readily measurable by conventional techniques (reviewed by Thoreson and Mangel[11]).

Proton pump inhibitors typically cause an irreversible inhibition of H^+ secretion in gastric parietal cells. In our experimental conditions, the disruption of horizontal cell-cone feedback was reversible. One explanation for this apparent discrepancy is that the timing of the drug exposure in our experimental system may have been insufficient for complete inhibition of ATPase activity. The washout of drugs in our system was typically begun 5 to 7 minutes after application, which is less than the time necessary for pyridyl-methylsulfinyl-benzimidazoles to fully inhibit ATPase activity.[29] It is notable that the effect of omeprazole (Sigma-Aldrich) was weaker than lansoprazole (Sigma-Aldrich), consistent with its slower rate of inhibition.

However, along with the possibility of species differences, it is worth considering that these drugs may disrupt feedback at sites other than H^+ and K^+ pumps. For example, these drugs have been shown to inhibit phosphatases,[30] Na-K-ATPases,[31] and swelling-dependent chloride channels.[32] They also alter muscle contractility in various tissues perhaps by acting on L-type calcium channels.[33–36] Antibodies to H+-K+-ATPases do not appear to label retinal neurons,[37] and the competitive H^+, K^+ blocker, SCH 28080, did not block horizontal cell–cone feedback in our experimental system. On the other hand, aside from a slight increase in peak amplitude of the calcium current with omeprazole (Sigma-Aldrich) illustrated in Figure 2D, we did not see any consistent changes in the current/voltage relationships of cones during application of these drugs that would suggest actions at other targets. Additional insight into how these drugs alter horizontal cell–cone feedback awaits further study.

The concentrations that were used in the animal model are more than 10-fold higher than plasma concentrations typically attained in patients.[38,39] Given that lansoprazole 100 μM (Sigma-Aldrich) completely blocked horizontal cell to cone feedback and such blockade abolishes center-surround receptive fields and color opponency, it is likely that the presence of lansoprazole (Sigma-Aldrich) at higher concentrations in patients would produce much more profound visual disturbances.

We observed interindividual variation in the response to these drugs in AMD patients with exudative disease. Although we do not fully understand why some patients have visual disturbances and others do not, some of this variation could be accounted for by individual differences in the plasma concentrations of these drugs, due to genetic variation in the hepatic cytochrome P450 isoenzymes that metabolize the drugs.[38] Patients who are low metabolizers of these drugs have plasma concentrations that are 5-fold higher than the typical rapid metabolizers.

In conclusion, the new idea that visual hallucinations in the Charles Bonnet Syndrome are related to a loss of neuronal feedback inhibition is consistent with the longstanding concept proposed by David Cogan that hallucinations are "release phenomena" that can occur with pathology anywhere in the visual processing pathway.[5]

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