Viagra slows the visual response to flicker

Andrew Stockman[1], Lindsay T. Sharpe[1], Adnan Tufail[2], Philip D. Kell[3] and Glen Jeffery[1]

As an undesirable side effect, sildenafil citrate (Viagra) partially inhibits the phosphodiesterase PDE6 [1], which plays an essential role in phototransduction (reviewed in [2,3]). PDE6 not only activates the visual transduction cascade, but also controls the time over which the visual response is integrated, thereby helping to maintain the size of the visual response within an optimal range as the light level is increased [4]. Consistent with an increase in temporal integration following Viagra ingestion, performance improvements have been reported for an identification task that relies on the integration of two temporally separated stimuli [5]. Using more conventional psychophysical measures of temporal sensitivity and resolution [6,7], we find that therapeutic 100 mg doses of Viagra can cause mild to moderate transient losses in human temporal visual sensitivity. These losses imply that in the more affected observers, Viagra may provide a unique tool for pharmacologically manipulating the activity of PDE6 in humans *in vivo*, and thus for investigating the role of PDE6 in light adaptation. At the light levels tested, the frequency-dependent sensitivity losses caused by the inhibition of PDE6 by Viagra are consistent with an almost doubling of the time over which visual events are normally integrated (from ~6.9 to 12.6 ms, assuming a single integration stage).

Observers were presented with a flickering red (650 nm) target superimposed in the centre of a moderate-intensity blue (481 nm) background field. They were asked to set the highest temporal frequency at which the flicker appeared to be just visible — also known as the temporal resolution limit or critical fusion frequency (c.f.f.) — as a function of the radiance of the 650 nm target. Under these conditions of adaptation, flicker detection is mediated by long-wavelength sensitive (L–) cones, and to a lesser extent by middle-wavelength sensitive cones (M–) cones. The results are shown in Figure 1 for observers L.T.S. (A) and G.J. (B). With increasing target radiance, their baseline (pre-Viagra) c.f.f. functions (open dotted circles) rise steadily until reaching a plateau between 38 and 52 Hz. Ingestion of Viagra induces moderate losses in c.f.f. for both subjects at all levels.

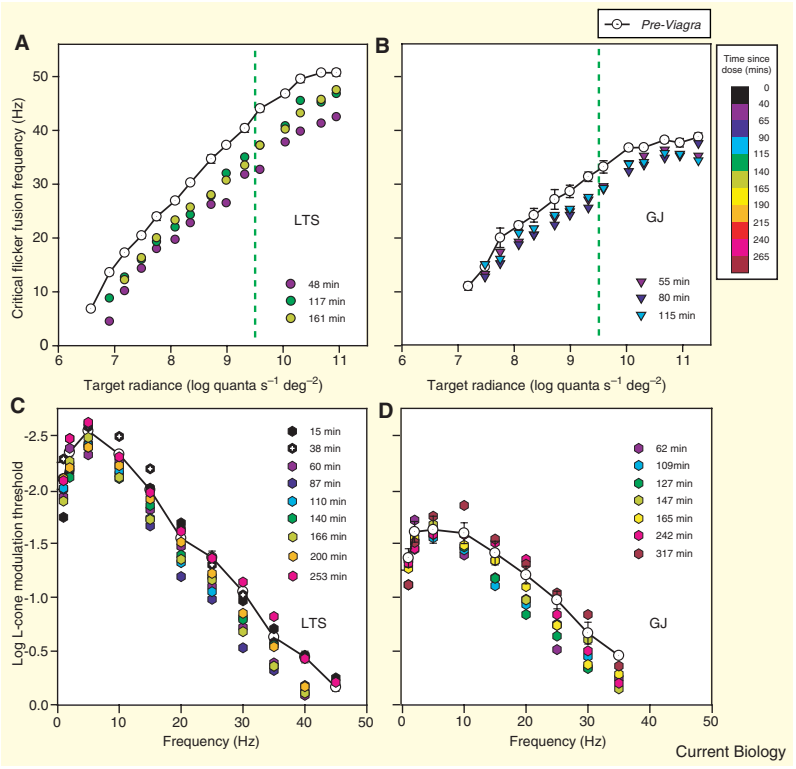

Figure 1. Critical flicker fusion (A,B) and modulation sensitivity (C,D) data for L.T.S. (A,C) and G.J. (B,D).

A centrally fixated flickering target of 4° of visual angle in diameter and 650 nm in wavelength was presented in the centre of a 9° background field of 481 nm. The background of 8.26 log quanta s^{-1} deg^{-2} at the cornea was there primarily to saturate the rods. The mean radiance of the 650 nm target was varied for the c.f.f. measurements and fixed at 9.52 log quanta s^{-1} deg^{-2} for the modulation sensitivity measurements. In each panel, the pre-Viagra baseline data (dotted open circles) are the averages of three or more separate measurements made before drug ingestion. The shapes of the coloured symbols denote the dose numbers: dose 1 (triangles); dose 2 (circles); dose 3 (inverted triangles); and dose 4 (hexagons). The time after dose ingestion is coded by the colour of the symbols (see key). The times noted are the midpoints of the time periods after dose ingestion during which a given curve was measured (from the first setting made at the end of a 3 min pre-adaptation period to the last setting). A c.f.f. curve required on average 12 min to complete, whereas a modulation sensitivity curve required 8 min. Crossed symbols distinguish between two runs made during the same colour-coded time window.

Below the plateau, the losses increase slightly with target radiance, reaching ~10 Hz for L.T.S. and 5 Hz for G.J. (coloured symbols).

To characterize the losses at frequencies below the c.f.f., we measured modulation thresholds as a function of temporal frequency. Subjects were asked to adjust the target modulation until the apparent flicker was just visible. Modulation is adjusted by varying the fraction of the light that flickers, while keeping the time-average intensity of the light constant. Figure 1 shows temporal modulation sensitivities for L.T.S. (C) and G.J. (D) measured at a 650 nm radiance

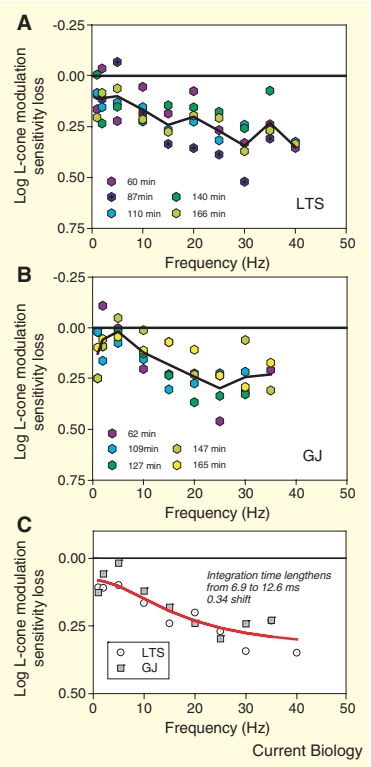

Figure 2. Modulation sensitivity losses for L.T.S. (A) and G.J. (B).

The data, from Figure 1, are plotted relative to the mean baseline measurements (horizontal lines). Symbol and symbol colours are as in Figure 1. The continuous lines are the mean losses, plotted in (C) for L.T.S. (dotted circles) and G.J. (grey dotted squares), which also shows the model fit (red line).

of 9.52 log quanta s^{-1} deg^{-2} (Figure 1, vertical dashed lines). Consistent with the changes in their c.f.f. data, both L.T.S. and G.J. show some losses of modulation sensitivity after ingesting Viagra at most frequencies. The relative losses compared with baseline are highlighted in Figure 2 for LTS (A) and GJ (B) for data collected between 60 and 166 min after Viagra ingestion, in which it becomes clear that the losses for both subjects increase with temporal frequency. This steepening suggests that Viagra is associated with a lengthening of the visual integration time.

We can model the mean losses (continuous lines in Figure 2A,B and symbols in 2C) and thus obtain a rough estimate of the change in the time constant of integration by assuming that the change occurs at a single integrating stage with an exponential decay (which we assume reflects the activity of some biochemical process or processes, such as the hydrolysis of cGMP catalyzed by PDE6). We model this change by applying a standard equation for a leaky integrator [8] and determining the change in integration time that will best account for our data (see Supplemental Data available online). Given that the mean data for L.T.S. (dotted circles) and G.J. (grey dotted squares) are similar, we have fitted this model simultaneously to both mean data sets. The model has three parameters: a baseline integration time, a Viagra-induced integration time and a frequency-independent sensitivity scaling factor.

The best-fitting model is shown by the continuous red line in the lower panel. The best-fitting parameters (± the asymptotic standard error for each parameter) are 6.91(±2.64) ms for the baseline integration time, 12.57(±3.79) ms for the Viagra-induced integration time, and 0.34(±0.05) log_{10} unit for the scaling factor. The scaling factor is needed to compensate for changes in sensitivity caused by the background becoming more effective when the integration time is lengthened (by 0.26 log_{10} unit for a 6.91–12.57 ms change in time constant). This increase in effectiveness is partially offset by the comparable increase in sensitivity to low frequency flicker, but not entirely so (a complete offset would be consistent with Weber's Law). The fact that the overall modulation sensitivity drops by 0.08 log10 represents a partial failure of light adaptation as Viagra presumably drives the system into a less optimal (nonlinear) part of its operating range. The data are clearly consistent with a lengthening of the integration time, but the precise values of the time constants are only moderately well constrained by the model, and should be considered as preliminary estimates.

By inhibiting PDE6, Viagra lengthens the time over which the visual response is integrated, thus impairing the overall ability of the eye to light adapt and to regulate its sensitivity.

Acknowledgements

This work was supported by a Wellcome Trust awarded to A.S. We thank Sabine Apitz, Bruce Henning and Rhea Eskew for helpful advice.

Supplemental data

Supplemental data including Experimental Procedures are available at http://www.current-biology.com/cgi/content/full/16/2/R44/DC1/

References

1. Wallis, R.M., Casey, J., Howe, L., Leishman, D., and Napier, C.M. (1998). Characterisation of retinal phosphodiesterase (PDE) isozymes and the effects of sildenafil *in vitro.* Ophthalmic Res. *30* (*suppl. 1*), 111.
2. Stryer, L. (1988). Molecular basis of visual excitation. Cold Spring Harb. Symp. Quant. Biol. *53*, 283–294.
3. Pugh, E.N., Jr., Nikonov, S., and Lamb, T.D. (1999). Molecular mechanisms of vertebrate photoreceptor light adaptation. Curr. Opin. Neurobiol. *9*, 410–418.
4. Nikonov, S., Lamb, T.D., and Pugh, E.N., Jr. (2000). The role of steady phosphodiesterase activity in the kinetics and sensitivity of the light-adapted Salamander rod photoresponse. J. Gen. Physiol. *116*, 795–824.
5. Mollon, J.D., Regan, B.C., Foo, R., and Morris, B.J. (2003). Sildenafil increases persistence of vision. Invest. Ophthalmol. Vis. Sci. *44* (*suppl*), 4097.
6. Hecht, S., and Verrijp, C.D. (1933). The influence of intensity, color and retinal location on the fusion frequency of intermittent illumination. Proc. Natl. Acad. Sci. USA *19*, 522–535.
7. De Lange, H. (1958). Research into the dynamic nature of the human fovea-cortex systems with intermittent and modulated light. I. Attenuation characteristics with white and colored light. J. Opt. Soc. Am. *48*, 777–784.
8. Watson, A.B. (1986). Temporal sensitivity. In Handbook of Perception and Human Performance, Volume *1*, K. Boff, L. Kaufman and J. Thomas, eds. (New York: Wiley), pp. 6–1-6–43.

[1]Institute of Ophthalmology, University College London, 11-43 Bath Street, London EC1V 9EL, UK. [2]Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, UK. [3]Archway Sexual Health Clinic, Whittington Hospital Highgate Hill and Institute of Urology, Middlesex Hospital, London N19 5NF, UK.