Letter to the editor: Comments on retinal metabolic state in P23H and normal retinas

Barry S. Winkler
Eye Research Institute, Oakland University, Rochester, Michigan

TO THE EDITOR: Acosta et al. (1) have asked whether changes in energy-dependent processes occur before the onset of photoreceptor degeneration in the proline-23-histidine (P23H-3) rat model of retinitis pigmentosa. On the basis of whole retinal measurements of selected metabolites and enzymes in normal (Sprague-Dawley, SD) and mutant retinas as a function of age, they have concluded that “photoreceptor apoptosis in the P23H-3 retina occurs in an environment of increased LDH, ATPase activity, and higher-than-normal ATP levels” (see pg. C764) and that “the retina is working in an environment of higher-than-normal metabolism” (see pg. C770). In my view, however, the results of Acosta et al. (1) do not support any firm conclusions regarding the precise relationship between energy metabolism/demand and photoreceptor degeneration in this mutant model.

Time-course data comparing LDH activity between normal and mutant retinas are shown in Fig. 1, A and B in Acosta’s paper. The authors state that, “at P1-P21, LDH activity was higher in the P23H-3 than SD retinas” (see pg. C767) and “given the significant increase in the LDH activity ratio at early ages, we conclude that the P23H-3 retina is highly metabolically active before and during the early stages of retinal degeneration” (see pg. C767). This time period of study is indeed critical because apoptosis in the P23H-3 retina begins at day 10 and increases to a peak at day 20, and thereafter the rate of apoptosis falls over the next several months (4). A close inspection of the LDH activity ratio in Fig. 1B, however, shows that on 4 (P4, P6, P12, and P15) of the 8 days that were sampled between P1 and P21, there were only small (\(<5\%\) ) statistically insignificant differences in LDH activity between SD and mutant retinas.

Even more consequential concerns relate to the measurements of retinal ATP content shown in Fig. 2A of Acosta et al.’s paper. They report that the averaged ATP content in 60-day SD retinas is 5 mmol/g protein. A reasonable estimate for the total (homogenate) protein content of an adult rat retina is 1 mg. Using this value, their ATP value can be expressed as 5 \(\mu\)mol/mg protein or 5 \(\mu\)mol/retina. When one considers that the wet weight of single adult rat retina is about 10 \(\mu\)l, then on a concentration basis (5 \(\mu\)mol ATP/10 \(\mu\)l), the ATP concentration in Acosta et al.’s retinas is 500 mM. This is clearly not correct. Indeed, we (3) have reported that a normal adult rat retina contains 12 nmol ATP/retina or 1.2 mM. An additional significant criticism of using whole retinal ATP measurements to make conclusions about metabolic changes specifically in photoreceptor cells comes from the work of Berger et al. (2) who measured ATP content on frozen sections of retinas from rabbit (mostly rods), ground squirrels (mostly cones), and monkeys (mixed rods and cones). In all species, the predominant fraction of ATP is located in the inner retinal layers, e.g., the inner nuclear, inner plexiform, ganglion cell, and nerve fiber layers.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES