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Dark Adaptation in Hyperprolactinemic Women

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In a study to test the hypothesis that hyperprolactinemia is caused by subclinical zinc deficiency, dark-adaptation curves of seven women with primary hyperprolactinemia and seven normal women were measured to assess tissue zinc status. Although plasma zinc levels, final dark-adapted thresholds, and the time courses of rod dark-adaptation did not differ significantly between patients and normal subjects, the median cone plateau of the hyperprolactinemic patients was significantly higher (0.66 log units) than that of normal subjects. It appears unlikely that derangements of vitamin A metabolism, for which zinc is a cofactor, explains this unanticipated and subtle abnormality in dark adaptation of the hyperprolactinemic women. Invest Ophthalmol Vis Sci 30:1177–1180, 1989

It is well known that zinc-dependent vitamin A metabolism in the visual cycle affects dark adaptation.[1] Therefore, in a study to test the hypothesis that primary hyperprolactinemia is caused by subclinical zinc deficiency, measurements of dark adaptation were undertaken to assess tissue zinc status.[2] Because alterations in the zinc–vitamin A pathway have a greater effect on rod than cone function, dark-adaptation testing concentrated on delineation of rod function.[3]

Materials and Methods. Seven hyperprolactinemic and seven normal women were studied after obtaining written informed consent. Eligibility was determined by two fasting and resting prolactin levels. Hyperprolactinemia was defined as 30 ng/ml or greater and normal was 5 to 20 ng/ml. Computed tomography or magnetic resonance imaging of each hyperprolactinemic woman showed no evidence of extrasellar pituitary tumor, although two had evidence of intrasellar microadenomas. All subjects had normal blood counts and normal renal, thyroid and hepatic functions. No subjects were taking prescription medications, and none had taken oral contraceptives within three months of testing. The patients and normal subjects were similar in age (median: 31 years; range: 25 to 37 years vs. median: 30 years; range: 22 to 35 years). The patients had documented hyperprolactinemia for a median of 3.6 years (range: 1.0 to 6.0 years).

Thorough ophthalmological examinations of all women demonstrated no abnormalities, except one had mild amblyopia and exotropia after treatment of congenital esotropia. Pupillary responses and ophthalmoscopy revealed no signs of optic nerve disease.

Visual function studies were random with respect to the menstrual cycle. All patients had 20/20 corrected acuity in each eye, except the strabismic patient who had 20/25 acuity in one eye. Visual fields were full for both I_{4e} and I_{2e} targets in both eyes of each woman. No color vision defects were demonstrated using the Farnsworth–Munsell 100 Hue test.

Dark adaptation curves were obtained using a Maxwellian view adaptometer. After 30 min of dark adaptation from room light, five settings of the dark adapted threshold were made using a 1.6° diameter, blue ($\lambda < 510$ nm) test spot presented 15° temporal to the fovea. After this, a 20° patch of retina concentric with the test spot was exposed to a white light producing 6.1 log scotopic trolands retinal illumination for 2 min; such a light is known to bleach 95+% of rhodopsin.[4] After the bleaching light was extinguished, thresholds were determined using the

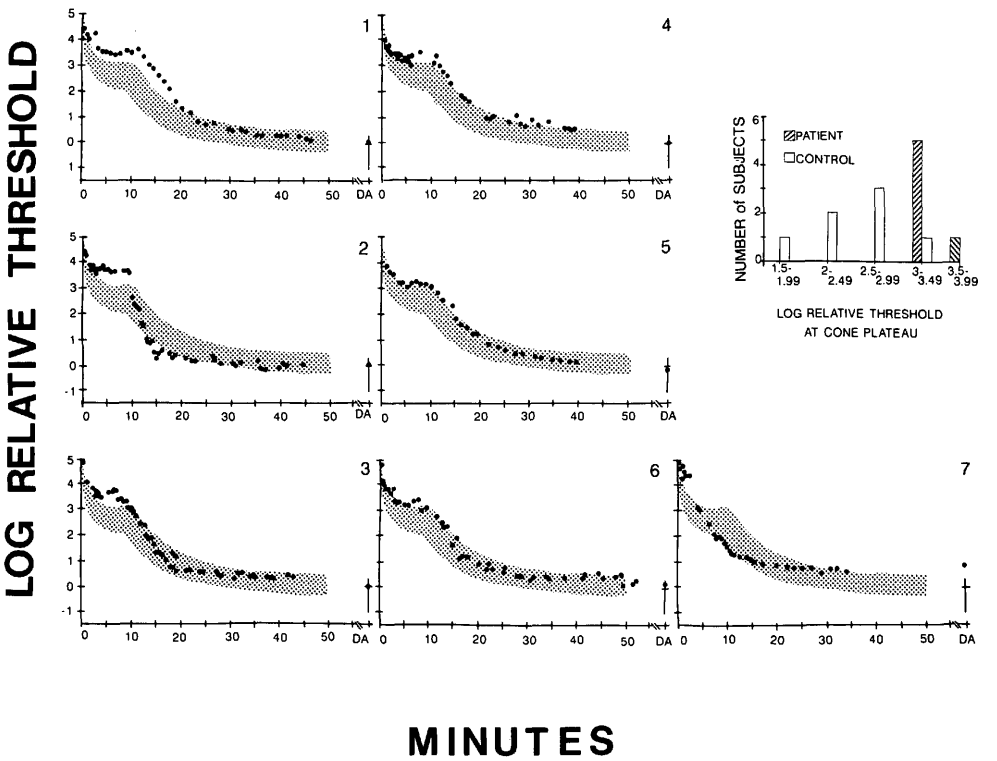

Fig. 1. The threshold elevation above the dark-adapted threshold at various times in the dark after the bleaching light had been extinguished is shown for each patient. The patient numbers on the panels correspond to those in Table 1. The shaded area depicts the locus of thresholds and the bar the range of dark-adapted (DA) thresholds of the seven control subjects. On the vertical axis, 0 represents the controls' median, dark-adapted value, which is 4.34 log equivalent quanta (500 nm)/second/cm^2. The histogram in the inset shows the distribution of patients' and controls' thresholds at the cone plateau.

method of limits until the thresholds had returned to the pre-bleach level.

The course of recovery of log scotopic threshold after bleaching was assumed to be exponential with time constant T. The threshold data were fit by

$$\text{Log } I_t = \text{Log } I_D + ke - (t - t_{C/R}/T) \qquad (1)$$

using an iterative routine until a least-squares solution was reached. I_t is the threshold, I_D the pre-bleach, dark-adapted threshold, k the range in log units of the best fitting exponential,[5] and $t_{C/R}$ the time of the cone-rod break.

Within 36 hr of the dark adaptation study, a fasting blood sample was obtained for plasma zinc, serum prolactin, retinol, retinol-binding protein, and albumin. The samples for prolactin, retinol-binding protein, albumin, and zinc were stored at −20°C and run in one batch. The samples for fasting retinol were wrapped in aluminum foil, stored at −70°C and run in two batches to minimize storage effects. Prolactin was measured using a monoclonal immunoradiometric assay (Hybritech, San Diego, CA), and retinol-binding protein by radial immunodiffusion (Behring Diagnostics, La Jolla, CA). Zinc was assayed by atomic absorption spectrophotometry,[6] and retinol by high pressure liquid chromatography.[7] Within assay coefficients of variation were zinc 6.2% and prolactin 4.2%.

Results. The dark adaptation curves (Fig. 1) show that the cone plateaus of the three patients were above the normal range, three were at the upper boundary of the normal range and for Patient 7 could not be determined. The median threshold (Table 1) at the patients' (n = 6) cone plateau was 0.66 log units higher than that of the seven control subjects (U = 0; $P < 0.001$).

Table 1. Summary of dark adaptation results

	*Cone plateau**	*t, C/R', sec*	*T, Rod, branch, sec*	*RMS deviation*	*Dark-adapted threshold†*
A. Patients					
1	3.37	675	504	0.0207	+0.10
2	3.76	570	175	0.0299	+0.03
3	3.39	555	354	0.0305	0.00
4	3.10	660	529	0.0454	0.00
5	3.10	620	583	0.0194	−0.20
6	3.15	720	579	0.0347	+0.35
7	cannot determine		279	0.0214	+0.75
Median	3.26	640	504	0.0299	+0.03
B. Controls					
1	2.70	690	586	0.0169	−0.30
2	1.80	545	354	0.0222	0.00
3	3.00	680	565	0.1015	0.20
4	2.60	645	425	0.0123	0.20
5	2.77	630	562	0.0113	0.00
6	2.30	750	708	0.0180	−0.30
7	2.00	900	606	0.0274	−0.30
Median	2.60	680	565	0.0180	0.00
C. Comparison of patients and controls; Mann-Whitney U-Test					
U	0	14.0	14.0	13.0	17.5
P	*<0.001*	*0.18*	*0.10*	*0.08*	*0.19*

* Log units above normal, median dark-adapted threshold.

† Log units above (+) or below (−) normal, median dark-adapted threshold.

The final dark-adapted thresholds of patients and controls did not differ significantly (Fig. 1, Table 1). Furthermore, the rate of rod threshold recovery, which is probably more susceptible to the effects of vitamin A deficiency than the final dark-adapted threshold,[3] was similar for patients and controls. There was no significant difference between T for patients and controls (Table 1). Partial bleaching[5] is a possible explanation for the low value of T for Patient 2.

The blood test results (Table 2) showed only prolactin was significantly different between patients and controls. The parameters of the dark adaptation curves (threshold at cone plateau; time course of rod dark adaptation; dark-adapted rod threshold) were not correlated with prolactin or the visual cycle factors in either the patients or controls.

Table 2. Fasting blood levels

	Patients (n = 7)		*Controls (n = 7)*	
	Median	*Range*	*Median*	*Range*
Prolactin (ng/ml)	52.1*	42.2–159.7	11.3	6.0–15.5
Zinc (μg/dl)†	59.2	52.0–69.6	64.4	57.2–85.6
Retinol (mg/dl)	41.0	30.0–58.0	49.0	26.0–60.0
Retinol binding protein (mg/dl)	3.1	2.4–3.7	3.4	2.5–4.3
Albumin (g/dl)	4.7	4.4–4.9	4.6	4.3–5.0

* Significantly higher than normal; Mann-Whitney U = 0; $P < 0.001$.

† Normal mean ± SD (n = 182 women, ages 20 to 50 years): 97 ± 20 μg/dl; range: 49–143 μg/dl.

Discussion. These findings do not support the initial hypothesis of subclinical zinc deficiency in hyperprolactinemia. The data show an unanticipated, subtle abnormality of dark adaptation in women with primary hyperprolactinemia. Despite the normal 100 Hue test results, we suspect that decreased cone sensitivity, represented by the elevated cone plateau, is the physiologically important difference between patients and controls. An extended rod branch with normal time constant and final threshold can be uncovered in normal subjects using the after-flash psychophysical technique of Alpern.[8]

At present, an explanation for reduced cone sensitivity is not apparent. However, mechanisms involving retinal dopamine are among those to consider in patients with primary hyperprolactinemia who have derangements of hypothalamic–pituitary dopamine physiology, which renders dopamine agonists an effective treatment of prolactinomas (eg, ref. 9). No matter what mechanisms underlie the patients' elevated cone plateau, investigations of the functions of receptoral and post-receptoral cells would be expected to further define the determinants of visual sensitivity during dark adaptation of patients with hyperprolactinemia.

Key words: hyperprolactinemia, zinc, dark adaptation, cone sensitivity

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