remains that their oculomotor performance can limit their visual abilities. These limitations must be taken into account when interpreting their visual performance.

EILEEN KOWLER
Department of Psychology,
Rutgers University,
New Brunswick, New Jersey 08903
ALBERT J. MARTINS
Department of Psychology,
University of Maryland,
College Park 20742

References and Notes

1. Existing studies of oculomotor development used eye monitors that cannot detect eye rotations less than 1° or confound eye rotation with head translations [N. H. Mackworth and J. S. Bruner, *Hum. Dev.* **13**, 149 (1970); E. Vurpillot, *J. Exp. Child Psychol.* **6**, 632 (1968); J. A. Whiteside, *ibid.* **18**, 313 (1974); M. Cohen and L. Ross, *ibid.* **26**, 517 (1978)].
2. Eye movements were recorded with a double Purkinje image eye tracker (SRI Generation III) [T. N. Cornsweet and H. D. Crane, *J. Opt. Soc. Am.* **63**, 921 (1973)]. The noise level of the tracker, expressed as the standard deviation of position of an artificial eye, was 0.5 minute of arc on the horizontal and 0.67 minute of arc on the vertical meridian. The tracker is insensitive to head translation. Voltage outputs of the tracker were filtered at 50 Hz (−3 dB) and fed to an analog-to-digital converter that sampled eye position at 100 Hz. Movements of the right eye were recorded with the left eye occluded and the head stabilized by a bite board.
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4. Alignment and calibration were carried out in the first session. Calibration factors were determined from the children's tracking of a large-amplitude (8.2°), low-frequency (0.4 step per second) square wave (Fig. 1C). Median eye position was estimated for intervals between the large tracking saccades. The children's calibration factors were within the 10 percent range of variation we have measured with a large sample of adults whose calibration factors have been measured with the same instrument in lengthy and elaborate calibration sessions. Both children remained attentive and cooperative throughout. They were willing and able to sit still, bite on the bite board, and look at the target for many consecutive minutes during each recording session. No special procedures were used to reward or to train the children in order to facilitate comparison with prior studies of adults. The correlation between the children's eye movements and the general pattern of target motions (Fig. 1) suggests that they understood and were trying to follow our simple instructions to look at the target.
5. The bivariate contour ellipse area [(minutes of arc)^2], as calculated, describes the region in which the line of sight was located 68 percent of the time.
6. Saccade vector magnitudes were measured by taking the differences between the steady-state saccade-offset and -onset eye positions. The large overshoots at the end of saccades (Fig. 1A) were not included in the measures of saccade vector magnitude. These large overshoots are generated by movements of the fourth Purkinje image when the crystalline lens moves within the lens capsule because of inertia.
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8. The children's saccade rates and vector magnitudes were almost the same as those of the rhesus monkey before extensive fixation training [A. A. Skavenski, D. A. Robinson, R. M. Steinman, G. T. Timberlake, *ibid.* **15**, 1269 (1975)].
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10. Mean retinal image vector speed (that is, mean eye speed averaged over all 100-msec saccade-free intervals) was 42.3 minutes of arc per second for Philip [standard deviation (S.D.) = 21.7, N = 1505] and 47.5 minutes of arc per second for Jennifer (S.D. = 26.3, N = 542). The average retinal image vector speed of D.F. was 13.7 minutes of arc per second (S.D. = 9.0, N = 954). D.F.'s retinal image speeds fell within the range of retinal image speeds of other adults [(*9, 11*); A. Skavenski, R. Hansen, R. M. Steinman, B. J. Winterson, *Vision Res.* **19**, 675 (1979)].
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13. Preschool children may perform as well as adults when visual tasks do not require precise fixation. For example, recent reports suggest that visual acuity reaches adult levels by about 2 years of age [D. L. Mayer and V. Dobson, *Invest. Ophthalmol. Visual Sci.* **19**, 566 (1980)]. Stimuli in this study were large (9°) high-contrast square wave gratings. Thus, saccades on the order of several degrees would still permit the bars of the grating to remain imaged on the fovea. The contribution of retinal image speed to performance of this task is more difficult to evaluate because performance of some visual tasks is not impaired by imposed retinal image motion slower than 2° per second [B. J. Murphy, *Vision Res.* **18**, 521 (1978); G. Westheimer and S. P. McKee, *J. Opt. Soc. Am.* **65**, 847 (1975)].
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Increased Axonal Proteolysis in Myelin-Deficient Mutant Mice

Abstract. *Protein degradation within retinal ganglion cell axons in vitro is 50 to 110 percent faster than normal in mutant mice exhibiting deficiencies of myelin in the central nervous system. Proteolysis is increased proximally and distally within retinal ganglion cell axons of mice carrying the jimpy mutation or its allele, myelin synthesis deficiency, and is increased distally within those axons of quaking mice. The proteolytic defect is axon (neuron)-specific since the rate of protein degradation within glial cells is normal. Increased axonal proteolysis does not bear a simple relation to hypomyelination since shiverer, another mouse mutant deficient in central myelin, displayed normal rates of axonal protein degradation under the same conditions. These observations suggest an abnormal axon-glial interaction in mice with primary glial defects and raise the possibility that the functioning of histologically normal axons (neurons) may be altered in dysmyelinating diseases.*

Biochemical interactions between neurons and glia seem to be important in normal brain development (*1*). The interplay between axons and glia during myelinogenesis has been well documented (*2, 3*), although our understanding of these interactions at the molecular level is limited. In large part, this limitation stems from the problem of distinguishing biochemical events in neurons from those in glia, while preserving the anatomical relationships between these cells.

A strategy was developed that permits proteolysis to be studied specifically within the axons of mouse retinal ganglion cells (RGC) and separately within neighboring glial cells throughout postnatal development (*4, 5*). After labeling RGC proteins in vivo by intravitreal injection of radioactively labeled amino acid, I exploited the ability of the neuron to segregate by axoplasmic transport a population of labeled proteins that is specifically neuronal in origin. Glia in the optic pathway were selectively labeled in vitro by taking advantage of the negligible protein synthetic capacity of axons (*6*). Proteolysis in RGC axons or glial elements of the primary optic pathway was studied in vitro in the excised, but intact, optic nerves to preserve anatomic relationships. The rates of protein degradation measured under these conditions approximate those estimated in vivo (*4*).

This approach was applied to mice with genetic disorders that profoundly impair myelin formation but apparently spare neurons and their processes (*7–11*). In two mutant strains, jimpy (*jp* and *jp^{msd}*) (*7–9*) and quaking (*qk*) (*8*), protein degradation at physiological *p*H was abnormally elevated within RGC axons but not in adjacent glial cells. Since the primary genetic defect in *jp* and *qk* mice is believed to reside in glial cells (*12*), the observation that neuronal proteolysis is increased suggests that axon-glial interactions, and possibly neuronal function, are abnormal in these mice.

Mice, originally from Jackson Laboratories (Bar Harbor), were bred in controlled-environment rooms on a 12-hour day-night cycle. The *jp* mutation, a sex-linked recessive trait (*7, 8*), was bred on a C57BL/6J-CBA hybrid background.

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This strain also carried the mutation tabby (*Ta*), a marker gene which allows hemizygous animals to be identified at birth (*10*). Myelin synthesis deficiency (jp^{msd}), an allele of *jp* which is a milder phenotypic expression of the defect (*9*), and *qk*, an independent autosomal mutation (*8*), were carried on the C57BL/6J-C3H background. Shiverer (*shi*), a second autosomal recessive mutation (*11*), was obtained and bred on a nonspecific genetic background. The ages chosen for analysis represented the stage when seizures, tremor, and ataxia were most prominent.

Differences in the rate of protein degradation in RGC axons were observed in control mice of different genetic background (*13*). The rate in optic nerves from C57BL/6J-C3H mice was comparable to that previously reported in normal C57BL/6J mice (*4*) and significantly higher [$t(39) = 2.87$, $P < .01$] than the rate in C57BL/6J-CBA hybrid mice and in *shi* mice on a heterogeneous genetic background (Table 1). These differences are not related to age, since stable adult rates are obtained by the third postnatal week (*14*).

Protein degradation in RGC axons proceeded twice as fast in *jp* and jp^{msd} mice as in control mice (Table 1). This elevated rate was observed proximally (optic nerve) and, to a lesser extent, distally (optic tract) within RGC axons. In *qk* mice, protein degradation was increased but only in distal axonal regions [$t(24) = 3.77$, $P < .001$]. By contrast, the rate of protein degradation in RGC axons from *shi* mice was normal. Secondary nutritional effects of the mutations did not seem to influence these protein degradative rates, since runted control mice (C57BL/6J-CBA and C57BL/6J-C3H) exhibited normal rates of protein degradation. The *Ta* marker for the *jp* mutation had no apparent effect, since proteolytic rates were comparably elevated in *jp* mice with and without the *Ta* phenotype.

Since calcium stimulates the rate of protein degradation in RGC axons (*4*), the possibility that enhanced access of calcium to the axonal proteolytic system might account for the higher degradative rates in hypomyelinated axons was examined. Adding calcium ionophore (A23187) to the incubating medium or freeze-thawing the optic nerves or tracts several times before protein degradation analysis increases the influx of exogenous calcium into the axon (*15*) and in preliminary experiments did not disrupt the cellular specificity of the degradation measurement. Either procedure increased protein degradation approximately twofold in optic tract and fivefold in optic nerve, although the effects were not additive. When freeze-thawed optic nerves or optic tracts from *jp* and *qk* mutants were exposed to calcium ionophore (10 μg/ml), the axonal proteolytic

Table 1. Protein degradation in RGC axons of abnormal and myelin-deficient mutant mice. The *jp* and jp^{msd} mice were analyzed at 3 to 4 weeks of age, and *qk* and *shi* at 3 to 4 months. Protein degradation in RGC axons was measured as previously described (*4*) with several modifications. Mice were anesthetized with Avertin (*4*), and 0.25 μl of L-[^{3}H]proline (15 μCi) in phosphate-buffered saline was injected into the vitreous of each eye through the use of a glass micropipette apparatus. The *qk*, *shi*, and jp^{msd} mice were decapitated 5 days, and *jp* mice 4 days, after the proline injection. Each optic nerve or optic tract was placed in 0.35 ml of Hepes buffer [25 m*M* Hepes (*p*H 7.4), 6 m*M* KCl, 110 m*M* NaCl, 4 m*M* $CaCl_2$, choramphenicol 0.3 mg/ml, 9.5 m*M* cycloheximide, 6.5 m*M* glucose]. One of each pair of nerves or tracts, serving as a background control sample, was immediately homogenized and mixed with 0.125 ml of 50 percent trichloroacetic acid (TCA). The other paired specimen was incubated at 37°C for 1.5 hours and then similarly homogenized. The radioactivity (dis/min) in the TCA-soluble and TCA-insoluble fractions of each sample was then determined. The rate of protein degradation was operationally defined as the fraction of labeled free amino acid and TCA-soluble peptides released from protein per unit time at 37°C. This fraction was calculated as the ratio of TCA-soluble radioactivity to total radioactivity. The rate of degradation was expressed as that fraction after 1 hour of incubation at 37°C minus "background"—the corresponding value obtained from the paired tissue specimen that was homogenized immediately after dissection—multiplied by 100. Each value in the table is the mean ± standard error of the mean for the number of mice given in parentheses. Mutant and control values were compared by *t*-tests for independent samples.

Genetic background	Mutation	Rate of axonal protein degradation					
		Optic nerve region			Optic tract region		
		Mutant	Control	Percentage of control	Mutant	Control	Percentage of control
C57BL/6J-CBA	*Ta jp/y*	2.77 ± 0.29 (11)	1.39 ± 0.14 (11)	199‡	5.39 ± 0.59 (7)	3.63 ± 0.27 (10)	148*
C57BL/6J-C3H	jp^{msd}/y	3.26 ± 0.44 (10)	1.92 ± 0.18 (15)	170†	4.02 ± 0.36 (8)	2.79 ± 0.16 (8)	145†
C57BL/6J-C3H	*qk/qk*	2.82 ± 0.27 (15)	2.43 ± 0.23 (15)	116	5.27 ± 0.52 (12)	3.19 ± 0.25 (14)	165‡
Mixed	*shi/shi*	1.27 ± 0.24 (6)	1.27 ± 0.08 (6)	100	2.30 ± 0.31 (5)	2.24 ± 0.31 (6)	103

*$P < .01$. †$P < .005$. ‡$P < .001$.

Table 2. Protein degradation in retinas and optic nerve glia of normal and myelin-deficient mice. For isolated retinas, the procedure was the same as that described in Table 1. To label glial proteins, optic nerves from an uninjected mouse were incubated for 50 minutes at 37°C in Hepes buffer (with cycloheximide and chloramphenicol omitted) containing L-[^{3}H]leucine (3 mCi in 0.4 ml). Free leucine associated with the nerves after the labeling procedure was reduced by three successive 2-minute incubations of the nerves in unlabeled Hepes buffer (containing cycloheximide and chloramphenicol) (*25*). The rate of degradation at *p*H 7.4, linear for more than 1.5 hours, was measured as described for axonal proteins (Table 1).

Genetic background	Mutation	Rate of protein degradation					
		Retinas			Optic nerve glia		
		Mutant	Control	Percentage of control	Mutant	Control	Percentage of control
C57BL/6J-CBA	*Ta jp/y*	1.55 ± 0.21 (3)	1.73 ± 0.13 (4)*	90	8.05 ± 0.56 (5)	7.61 ± 0.36 (9)	106
C57BL/6J-C3H	jp^{msd}/y	0.89 ± 0.10 (7)	0.86 ± 0.08 (8)	103	8.20 ± 0.53 (8)	6.80 ± 0.43 (10)	121
C57BL/6J-C3H	*qk/qk*	0.63 ± 0.11 (8)	0.71 ± 0.11 (8)	96	5.96 ± 0.42 (10)	5.42 ± 0.18 (19)	110
Mixed	*shi/shi*	1.30 ± 0.08 (5)	1.04 ± 0.13 (4)	126	5.33 ± 0.76 (4)	5.82 ± 0.44 (7)	92

*$P < .001$, C57BL/6J-CBA controls versus C57BL/6J-C3H controls.

rates differed from control rates by approximately the same margin as in the earlier experiments [versus control: jp^{msd} nerves, 140 percent, $t(18) = 3.16$, $P < .01$; jp^{msd} tracts, 145 percent, $t(18) = 2.88$, $P < .01$; *qk* tracts 209 percent, $t(10) = 4.69$, $P < .001$]. Increased penetration of exogenous calcium into axons does not seem to be the cause of the axonal proteolytic abnormalities.

The retina, containing neurons but no central nervous system myelin (*16*), is histologically normal in *jp* and *qk* mice (*17*). The rate of protein degradation in isolated retina from each of these mutants is normal (Table 2). However, the rate of retinal protein degradation in C57BL/6J-CBA controls was twice that in C57BL/6J-C3H control animals (Table 2). This difference in proteolytic rates was not related to age, since adult rates of protein degradation are attained by the third postnatal week (*14*).

By modifying the protein-labeling procedure, protein degradation within optic nerve glial cells could be measured in vitro. Incorporation of label into proteins proceeded at a linear rate for more than 1 hour when optic nerve or optic tract segments were incubated in vitro with L-[^{3}H]leucine. Since axonal protein synthesis is negligible under these conditions (*6*), the ^{3}H-labeled proteins are derived from nonneuronal elements of the optic nerve (*18*). When the rates of protein degradation in optic nerve glia of *jp*, jp^{msd}, and *qk* were measured, no differences from unaffected controls were observed (Table 2).

These results suggest that protein degradation can be studied selectively in neurons (axons) and in glial cells of the optic pathway while largely preserving their normal anatomic relationships. The proteolytic rates in axons and in glial elements vary independently under different physiological conditions (*5*). This experimental approach has made it possible to detect abnormalities of axonal proteolysis in myelin-deficient mutant mice not revealed when conventional cell-free techniques for measuring proteolytic activity are used (*14*).

The alleles *jp* and jp^{msd} exhibited similar axonal proteolytic defects despite substantial quantitative differences in the severity of the disorder, including the dysmyelination (*9*). Quaking mice, affected at another genetic locus, displayed a different abnormal pattern, while mice carrying a third independent mutation, *shi*, exhibited normal axonal protein degradation at physiological *p*H.

The neuronal proteolytic defect in these mutants, therefore, does not bear a simple relationship to the extent of hypomyelination. It is possible, however, that increased axonal proteolysis occurs in response to some other aspect of defective glial metabolism. Alternatively, since proteolytic activity normally decreases during postnatal development (*14, 19*), the increase in axonal proteolysis in *jp* and *qk* may reflect an arrest of axonal development that precedes or accompanies the glial developmental arrest. Abnormal proteolysis would then represent an immaturity of the axon rather than a reactive pathological state. Indeed, central nervous axons from *jp* mice do not exhibit the normal increase in diameter associated with the myelination (*20*). Elevated activity of calcium-activated neutral proteases (*15, 21*), known to be present in RGC axons (*4, 14*), might be involved in this failure of axonal enlargement, especially in view of their particular affinity for axonal structural proteins (*15*).

If more widespread in the brain, enhanced axonal proteolytic activity would provide a possible basis for certain reported neuronal abnormalities in *jp* and *qk* mice including subtle axonal degenerative or dystrophic changes (*22*). Calcium-activated neutral proteinase might play a role since it is believed to mediate early morphological and biochemical events during Wallerian degeneration (*15*). However, increased activity of acidic proteinase has been observed in RGC axons from *jp*, *qk*, and *shi* mice (*14*) and may also contribute to these pathological changes.

Recent findings that myelination and demyelination are associated with physiological and morphological alterations of the axon (*23*), suggest that glial and axonal function are interdependent. The proteolytic abnormalities in morphologically normal RGC axons from *jp* and *qk* mice may be possible clues to the biochemical nature of such glia-axon interactions. The additional implication that neuronal dysfunction may underlie certain neurologic deficits in these myelin disorders may be relevant to the pathobiology of other dysmyelinating diseases (*24*).

RALPH A. NIXON
Ralph Lowell Laboratories,
Mailman Research Center,
McLean Hospital, and
Department of Psychiatry,
Harvard Medical School,
Belmont, Massachusetts 02178

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