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Tritiated Uridine Labeling of the Retina: Variations Among Retinal Quadrants, and Between Right and Left Eyes*

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We have determined the pattern of RNA labeling (uridine incorporation) in the normal retina of the domestic cat. One eye in each of eight cats was labeled by injecting [^{3}H]uridine into the vitreous cavity. Two of the labeled eyes had the lens and vitreous removed 10 days before labeling. Three additional animals received intravenous (i.v.) injections of [^{3}H]uridine. All animals were injected 4 hr into the light period and fixed 24 hr later; then the retinas were divided into quadrants (ST = superior temporal, SN superior nasal, IT = inferior temporal, and IN = inferior nasal). The ST quadrant contains the area centralis and the SN quadrant the optic nerve head. Autoradiograms were prepared from plastic sections 1 μm thick taken near the centre of each quadrant. In animals receiving intravitreal [^{3}H]uridine, the ganglion cells and the inner and outer nuclear layers (INL; ONL) were heavily labeled; the synaptic layers and the retinal pigment epithelium (RPE) were very lightly labeled. Amacrines were the heaviest labeled cells in the INL; cones were more heavily labeled than rods in the ONL. This finding indicates that amacrines and cone photoreceptors may be synthesizing RNA more actively than other retinal neurons. In animals receiving intravenous [^{3}H]uridine the pattern of labeling was the same as above except that the RPE was heavily labeled. Because cells in the ST quadrant appeared to be more heavily labeled than the same cell types in the other retinal quadrants, silver grains over the ONL in each quadrant were counted as grains μm^{-2} or grains per rod nucleus. In all cases rod nuclei in the ST quadrant are about twice as heavily labeled as in the SN, IT and IN quadrants ($P < 0{\cdot}001$, Student's *t*-tests). In addition, in three animals with i.v. injections, rods in the ST quadrant of the right eye are more heavily labeled than in the ST quadrant of the left eye ($P < 0{\cdot}005$, Student's *t*-tests). Because of the 24-hr incubation period and the nuclear location of the labeling, the species of RNA being observed in this study is probably small nuclear RNA (snRNA). Our results show that there are large differences in uridine labeling of different regions of the retina, with the highest labeling in the quadrant containing the area centralis (the region of high visual acuity). In addition, the right eyes have a higher labeling with uridine than the left eyes. These data indicate regional and interocular differences in retinal metabolism.

Key words: retina; uridine; RNA; autoradiography.

1. Introduction

One of the responses of neurons to injury is a change in RNA metabolism (Watson, 1965). Because of this we carried out a series of experiments to determine if changes in the pattern of RNA synthesis occur after a retinal detachment. The first of these experiments, reported here, is the determination of the labeling pattern with [^{3}H]uridine in the normal retina.

The incorporation of [^{3}H]uridine is commonly used as a measure of RNA synthesis, although such experiments require careful consideration of certain parameters, such as the incubation period (Jakoubek, 1976) and the lighting cycle (Hollyfield and Basinger, 1980; Schmidt, 1983). Delivery of the radioactive compound to the retina by intravitreal injection has the advantage of requiring significantly less amounts of material than delivery through the vasculature. It does, however, have the potential for biasing the pattern of labeling by virtue of the injection site within the vitreous cavity, the potential of the vitreous to influence delivery to the retina, and the fact that all of the label diffuses into the retina from the vitreal border. To address these issues, the lens and vitreous were removed from one eye in each of two animals and the [^{3}H]uridine was injected into a fluid-filled vitreous cavity; in three additional animals the tracer was delivered by intravenous injection.

2. Materials and Methods

Animals and Labeling

Eleven adult cats (at least 6 months old) were maintained on a 12 hr L:12 hr D lighting cycle for at least 2 weeks prior to use in this experiment. The animals were anesthetized with an i.m. injection of 0·5 ml xylazine (20 mg ml^{-1}; Miles Labs., KS) plus 0·16 ml ketamine (100 mg ml^{-1}; Parke-Davis, NJ). One eye in each of six cats (three right eyes and three left eyes) was labeled by injecting 200 μCi of [^{3}H]uridine (in 0·2 ml aqueous solution; 40–48 Ci $mmol^{-1}$ = 1·33–1·78TBq $mmol^{-1}$ specific activity; Amersham, IL) into the vitreous cavity. Two animals had their lens and

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vitreous removed from their right eyes (detailed methods in Anderson et al., 1983) 10 days prior to the uridine injection. In each of the eyes with intravitreal injections, the needle was positioned approximately 3 mm posterior to the limbus, along the temporal midline, and inserted into the approximate center of the vitreous cavity (determined by the depth and angle of penetration). Three animals received i.v. injections into the left saphenous vein (20 mCi into each of two animals delivered continuously over 10 min; 50 mCi into the third over 15 min. All animals were injected 4 h into the light period. Twenty-four hours after injection the animals were anesthetized as above and then killed with an intracardiac injection of 3·0 ml sodium pentobarbital (50 mg ml^{-1}; Abbott Labs., IL). The eyes were enucleated, the anterior one-third of the globes were excised and the eye-cups were fixed (overnight at 4°C) by immersion in 1% formaldehyde (from paraformaldehyde) plus 1% glutaraldehyde in 0·086 M sodium phosphate buffer, pH 7·2. The eye-cups were subsequently divided into quadrants (superior temporal = ST, superior nasal = SN, inferior temporal = IT, and inferior nasal = IN; see Fig. 1), rinsed in 0·137 M sodium phosphate buffer (three changes for 15 min, each at room temperature), post-fixed in 2% osmium tetroxide in 0·086 M sodium phosphate buffer (1·5 hr at room temperature), and dehydrated in a graded ethanol series (30, 50, 70, 85, 95, 100, 100 and 100%, each for 15 min at room temperature). The ethanol was replaced with 100% propylene oxide (two changes for 15 min, each at room temperature) and infiltrated with a 1:1 mixture of propylene oxide and Araldite 6005 (rotated overnight in capped vials at room temperature). The tissue was removed from the infiltrate and placed on filter paper to remove residual propylene oxide (45°C oven for 20 min) and then placed in fresh Araldite resin and polymerized for 1 day at 45°C and an additional day at 60°C.

Autoradiography

Tissue sections 1 μm thick were cut from the center of each quadrant using an LKB III ultramicrotome. The sections were placed on glass microscope slides and dipped into a 1:1 solution of Kodak NTB-2 and distilled H_2O maintained at 43°C in the dark. The slides were exposed from 2 to 3 weeks (intraocular injections; the right eyes required 2 weeks, whereas the left eyes required 3 weeks) or up to 14 months (i.v. injections; both eyes incubated for the same period of time for a direct comparison) at 4°C, developed for 2 min in D-19 (20°C), H_2O-washed, fixed, H_2O-rinsed and stained with azure II–methylene blue–toluidine blue in sodium borate (each 0·25%). Slides from the quadrants of each eye (both eyes in the case of animals with i.v. injections) were processed together to assure equal treatment.

Grain Counts

Silver grains over the outer nuclear layer in each quadrant were counted as grains μm^{-2} (minimum of 3200 μm^2 per quadrant) or grains per individual rod nucleus (minimum of 100 rod nuclei per quadrant). All counts were performed using a Zeiss Universal light microscope at 2000× magnification. The image of a digitizing tablet (Zeiss MOP-3) was projected on to the visual field with a camera lucida to obtain area measurements and grain counts.

3. Results

Figure 1 diagrammatically shows how the cat retinas were divided into quadrants. Tissue sections for autoradiography were taken from the center of each quadrant (○, Fig. 1). A representative autoradiograph of a normal retina labeled by an intravitreal injection of [^{3}H]uridine is presented in Fig. 2. In each cell type the labeling was heaviest in the nucleus, with frequent heavy labeling bordering (i.e. surrounding) the nucleoli. The ganglion cells, the inner nuclear layer (INL) and the outer nuclear layer (ONL) were heavily labeled while the synaptic layers and the retinal pigment epithelium (RPE) were very lightly labeled. Amacrine cells were the most heavily labeled cells in the INL and cone nuclei were more heavily labeled than rods in the ONL. In all eyes with intraocular injections, the pattern was the same within each quadrant (Fig. 3).

Because the pattern was the same in each quadrant, but the cells in the ST quadrant appeared to be more heavily labeled, silver grains were counted over rod photoreceptor nuclei in each quadrant (Fig. 4). Rods in the ST quadrant were about twice as heavily labeled when compared against rods in each of the other three

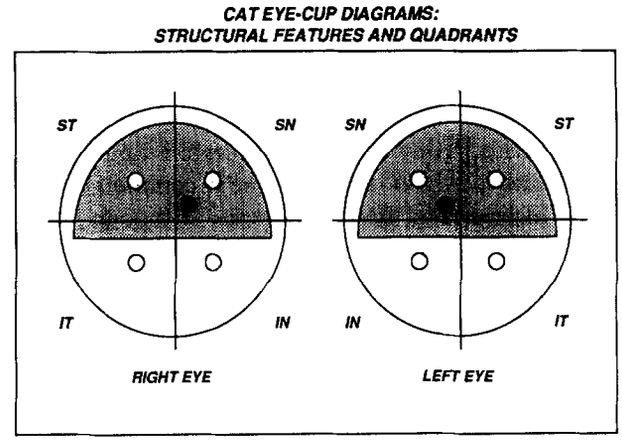

FIG. 1. Diagram of the posterior one half of a cat's right and left eyes, showing the division into quadrants; the tapetum lucidum (▨); the approximate centre of each quadrant where the samples for this study were obtained (○); the optic nerve head (●). ST = superior temporal; SN = superior nasal; IT = inferior temporal; IN = inferior nasal.

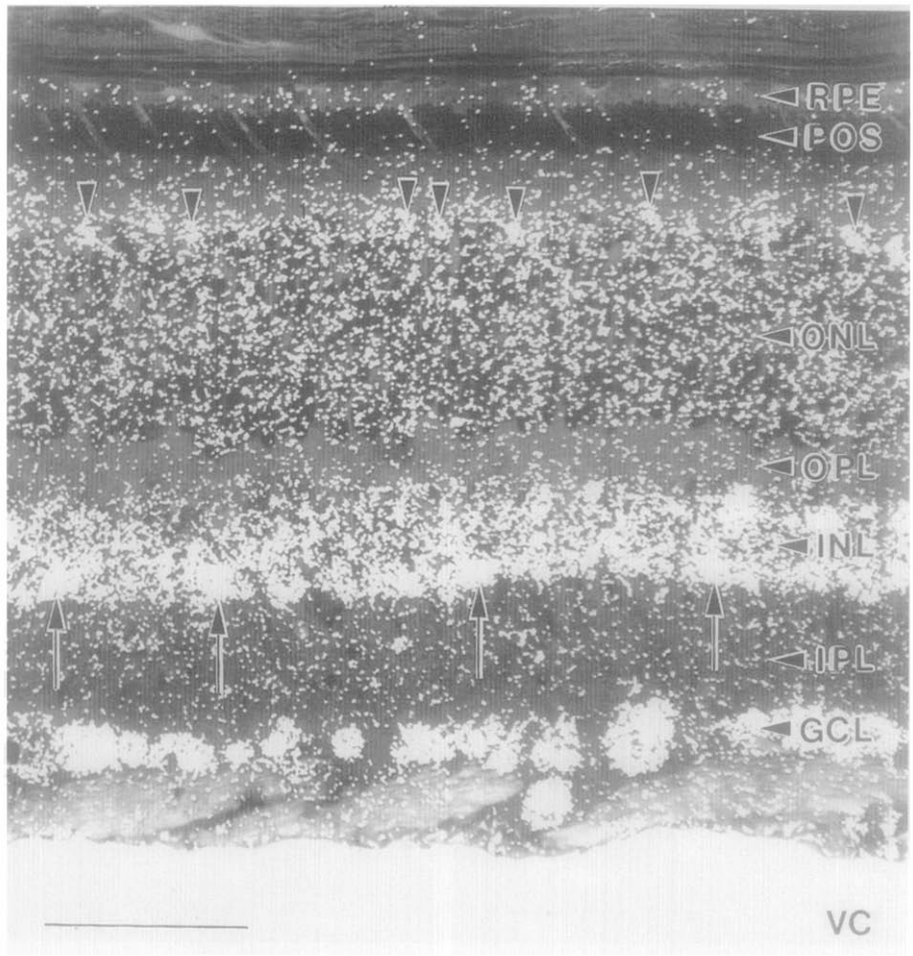

FIG. 2. A light-microscopic autoradiograph (double exposure; dark field, bright field), showing the pattern of retinal RNA synthesis (uridine incorporation as indicated by the white grains) 24 hr after injecting 200 μCl of [^{3}H]uridine into the vitreous cavity (VC) of a normal cat eye. The ganglion cells (GCL), the inner nuclear layer (INL) and the outer nuclear layer (ONL) are heavily labeled while the synaptic layers (IPL; OPL) and the retinal pigment epithelium (RPE) are lightly labeled. Cone nuclei (vertical arrowheads) are more heavily labeled than rod nuclei in the ONL, while amacrines (arrows) appear to be the most heavily labeled cells in the INL. IPL = inner plexiform layer; OPL = outer plexiform layer: POS = photoreceptor outer segments. Bar = 50 μm.

quadrants (individual comparisons between ST and each of the other three quadrants, using Student's *t*-test, resulted in each $P < 0{\cdot}001$). When counts were analyzed in a similar manner, in each eye, from all of the animals with intravitreal injections (Fig. 5), the results were the same (with each $P < 0{\cdot}001$): (*a*) in right and left eyes, (*b*) in eyes with and without lens and vitreous, and (*c*) when counts are expressed as grains per rod nucleus or grains μm^{-2} (data not shown). When counts from the individually injected eyes were combined for a four-quadrant analysis (i.e. all ST combined, all SN combined, etc.), an analysis of variance showed that the labeling in the four quadrants was not random ($P < 0{\cdot}005$). In addition, the Newman–Keuls multiple range test showed that the ST quadrant is the non-random quadrant when compared against the other three quadrants, whereas the other three quadrants when intercompared showed a random distribution. The data from the individually injected eyes is summarized in Fig. 6 as a percentage of maximum labeling: ST = 100%, IT = 48% (range = 24–79%), SN = 40% (range = 17–62%), and IN = 28% (range = 10–57%).

The exposure times of the autoradiograms suggested that there may be differences in uridine labeling between right and left eyes in this experiment. To obtain sufficient levels of silver grains over the photoreceptors in the animals with intravitreal injections, autoradiograms of the right eyes required only 2 weeks of exposure time, whereas autoradiograms of the left eyes required three weeks (see Materials and Methods, and Fig. 5). This data suggested that the right eyes may have incorporated more [^{3}H]uridine than the left eyes. However, since each eye was from a different animal, confirmation of this finding required a comparison of right and left eyes from the same animal after systemic (i.v.) labeling.

The same labeling pattern was observed after [^{3}H]uridine was injected intravenously as after the intravitreal injections, except for a much heavier labeling of the RPE (Fig. 7). As before, silver grain counts over rod nuclei revealed maximal labeling in

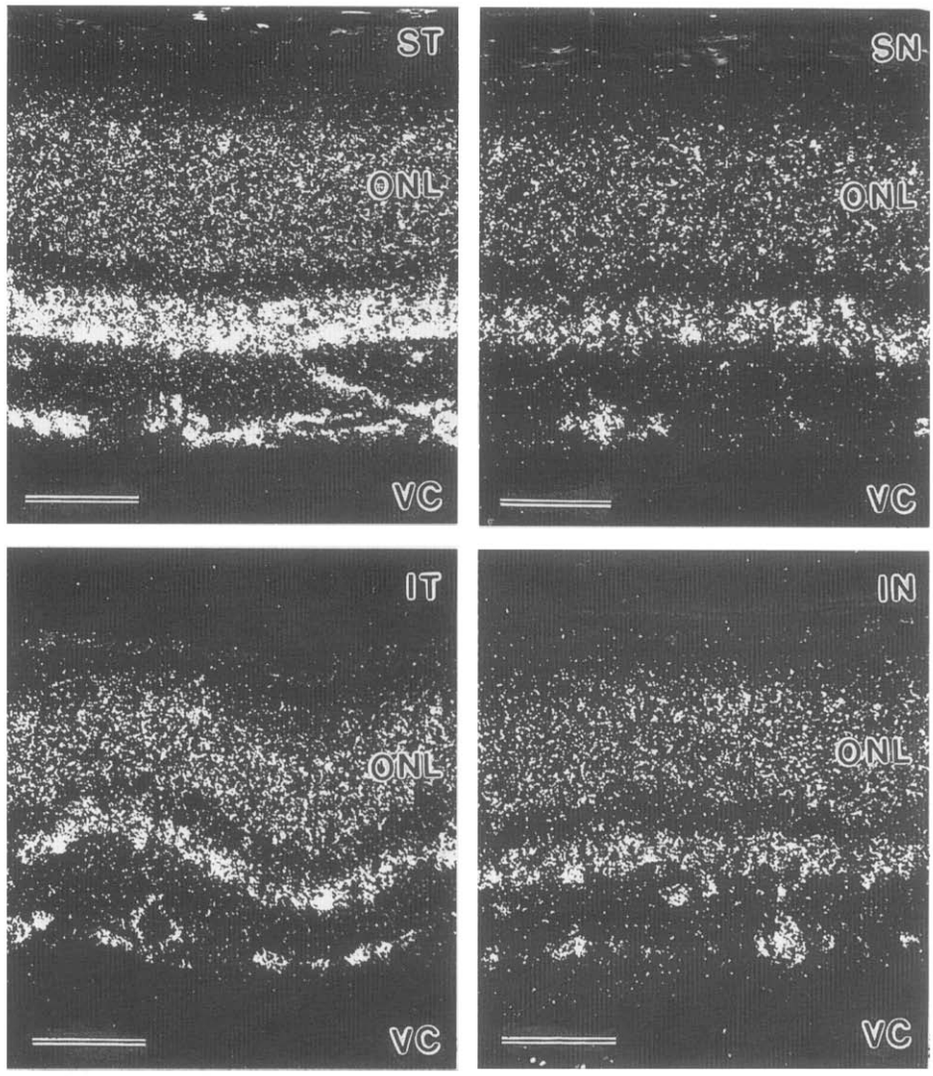

FIG. 3. Four light-microscopic autoradiographs (dark-field exposures) from the four quadrants of one eye. Tissue sections (1 μm thick) from all four quadrants were processed simultaneously to avoid variables during the autoradiography procedures. Light-meter setting, exposure time, developing time, magnification, etc., are also identical. ST = superior temporal; SN = superior nasal; IT = inferior temporal; IN = inferior nasal. Cells in the ST quadrant appear to be more heavily labeled than the corresponding cell types in the other quadrants. ONL = outer nuclear layer; VC = vitreous cavity. Bar = 50 μm.

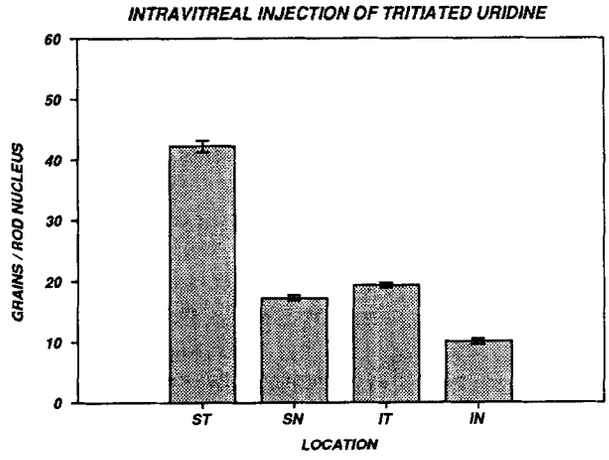

FIG. 4. A histogram showing the mean silver grain counts, ($\pm$S.E.M.; a minimum of 100 nuclei counted for each mean) per rod photoreceptor nucleus, from the right eye of a cat labeled with [^{3}H]uridine. Retinal location is indicated by superior temporal (ST), superior nasal (SN), inferior temporal (IT) and inferior nasal (IN). The grain counts per rod nucleus in the superior temporal quadrant are significantly higher than in the other retinal quadrants (see text for details).

the ST quadrants of both right and left eyes (Fig. 8). When counts were compared between the ST quadrants of the right and left eyes in each animal (Student's t-test, Fig. 9), it was clear that the right eye was more heavily labeled than the left eye in each animal (each $P < 0{\cdot}001$). In addition, when the RE/ST data were grouped together and compared to the grouped LE/ST, the RE/ST was significantly different from the LE/ST (Student's t-test; $P < 0{\cdot}005$). These results corroborated the data obtained following intravitreal labeling.

4. Discussion

The particular species of RNA labeled in this study has not been determined. Because of the 24-hr incubation period and the nuclear location, the best possibility is small nuclear RNA (snRNA; Darnell, Lodish and Baltimore, 1986). Immediately after transcription, snRNA moves to the cytoplasm and combines with specific proteins. These RNA–protein

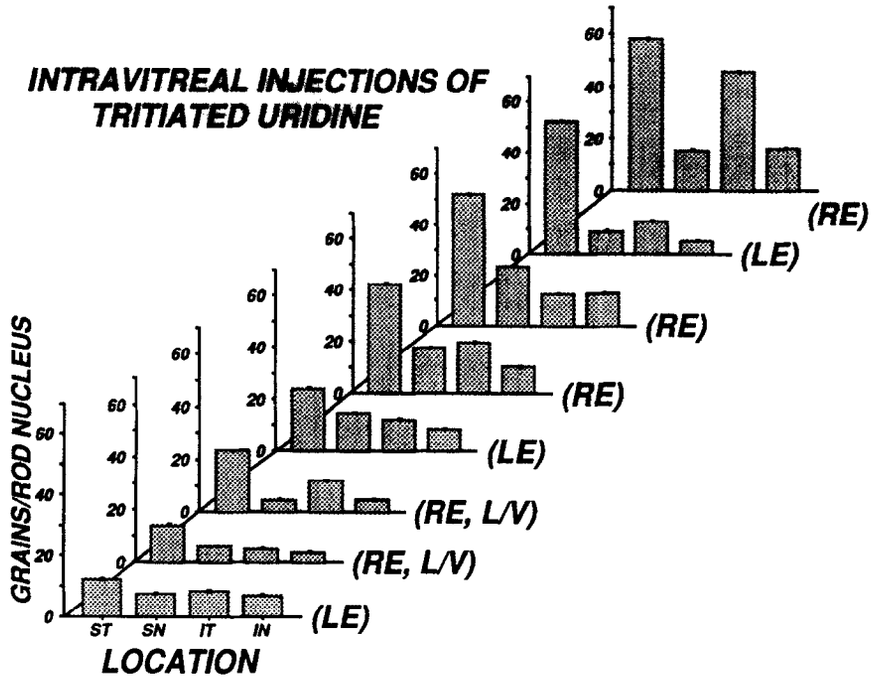

FIG. 5. Histograms expressing the mean grain count per rod photoreceptor nucleus from individual cats labeled with [^{3}H]uridine. Retinal location is indicated by superior temporal (ST), superior nasal (SN), inferior temporal (IT) and inferior nasal (IN). Right eye (RE), left eye (LE), and whether the eye had the lens and vitreous removed (L/V) is indicated along the abscissa for each cat. The error bars represent ±S.E.M.. The grain counts per rod nucleus in the ST quadrants are significantly higher than they are in the other retinal quadrants (see text for details).

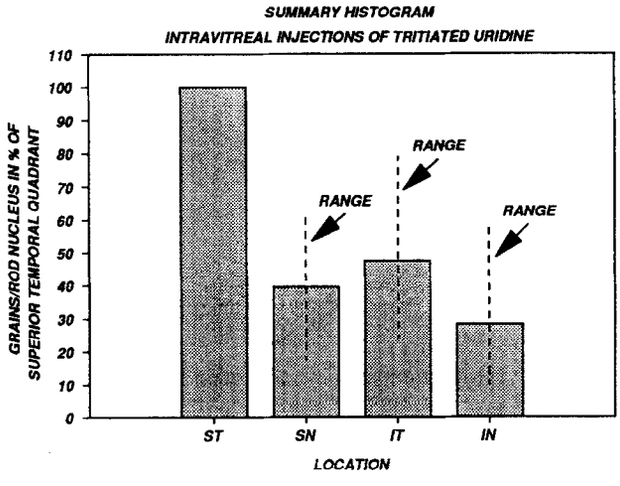

FIG. 6. A summary histogram expressing the pattern of labeling of rod photoreceptors in all eight cats as a percentage of the maximum. In all eyes the superior temporal (ST) quadrant = 100%, superior nasal (SN) = 40% (range = 17–62%), inferior temporal (IT) = 48% (range = 24–79%) and inferior nasal (IN) = 28% (range = 10–57%).

complexes then move to the nucleus and are called small nuclear ribonucleoprotein particles (snRNP). The function of the snRNP is not completely known, but they are very stable and may have a regulatory role in the nucleus (Zieve, Feeney and Sauterer, 1986), probably in splicing nuclear mRNA precursors (Sharp, 1987).

Regional variations within the retina have been reported, for example, in (*a*) development (Donovan, 1966; Johns, Russoff and Dubin, 1979; Rapaport and Stone, 1983), (*b*) the onset of some retinal diseases (Aguirre, Stramm and O'Brien, 1985), (*c*) rod outer segment length and rhodopsin content (Rapp et al., 1985), (*d*) photoreceptor sensitivity to light damage (Kuwabara and Gorn, 1968; LaVail, 1976; Rapp and Williams, 1980), (*e*) photoreceptor axial absorbance (Penn, Howard and Williams, 1985), and (*f*) the distribution and kinetics of visual pigments (Kemp, Faulkner and Jacobson, 1988). In many of these instances the maximal effect is in the superior retina. The data in this study show that there are actual metabolic differences in photoreceptor cells from different regions of the eye and may help us understand some of the regional variations reported in these earlier studies.

It has been shown that RNA synthesis in visual cells can be altered by changing the lighting conditions (Rasch et al., 1961; Byzov, 1965; Bok, 1970; Hollyfield and Basinger, 1980; Schmidt, 1983) with a higher level of total RNA synthesis in light than in dark. Our study shows tritiated uridine labeling to be highest in the quadrant containing the area centralis (the region of high visual acuity; Steinberg, Reid and Lacey, 1973; Morrison, 1982). This result is consistent, whether the tritiated uridine is injected into a normal vitreous cavity, into a fluid-filled globe (vitreous and lens removed), or into the saphenous vein. The possibility that stimulation of photoreceptors may increase their production of total RNA suggests that the heavier labeling of cells near the area centralis may be due to a higher level of visual stimulation. Alternatively, these cells may, for unknown reasons, have a higher rate of RNA metabolism and, perhaps,

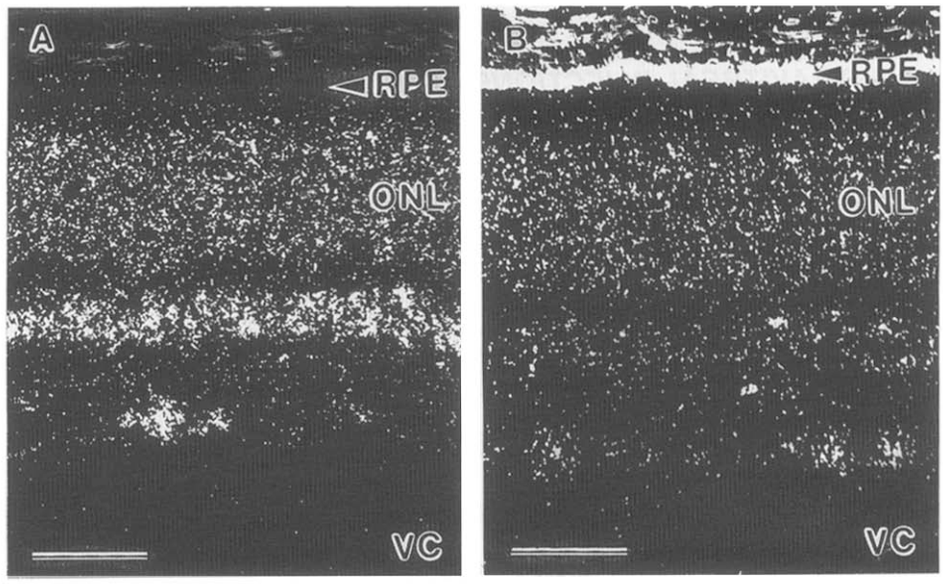

FIG. 7. Two light-microscopic autoradiographs (dark-field exposures), showing the similarities and the differences between the retinal labeling pattern after intravitreal and intravenous injections of [^{3}H]uridine. RPE = retinal pigment epithelium; ONL = outer nuclear layer; VC = vitreous cavity. Bar = 50 μm. A, Intravitreal injection of [^{3}H]uridine. B, Intravenous injection of [^{3}H]uridine. Note the very high labeling of the RPE that is not observed in the retinas following intravitreal injections.

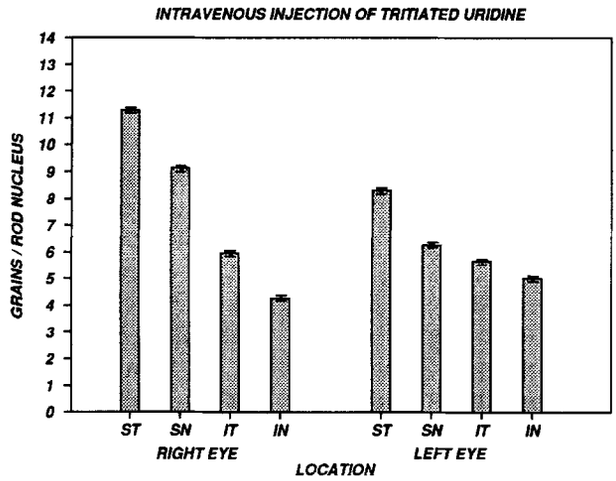

FIG. 8. A histogram showing the mean silver grain counts (±S.E.M.) per rod photoreceptor nucleus from one cat injected i.v. with [^{3}H]uridine. Retinal location is indicated by superior temporal (ST), superior nasal (SN), inferior temporal (IT) and inferior nasal (IN). Within each eye, photoreceptors in the ST quadrant are significantly more heavily labeled than in the other quadrants. In addition, photoreceptors in the ST quadrant of the right eye are significantly more heavily labeled than in the ST quadrant of the left eye (see text for details).

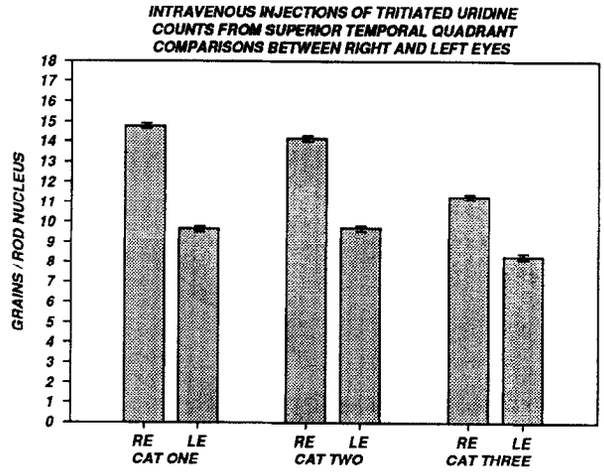

FIG. 9. A histogram showing the mean silver-grain count (±S.E.M.) per rod photoreceptor nucleus in the superior temporal quadrants of three cats injected i.v. with [^{3}H]uridine. In each animal, photoreceptors in the superior temporal quadrant of the right eye are significantly more heavily labeled than in the superior temporal quadrant of the left eye (see text for details).

metabolism in general. The ST quadrant overlies the taptum lucidum and thus is exposed to light reflected back through the retina by that layer; the SN quadrant also overlies the tapetum but shows consistently less labeling than the ST quadrant.

Comparing the uridine-labeling levels of individually injected eyes (intravitreal injections) suggested the possibility that the right eyes were more heavily labeled than the left eyes. This data was corroborated in all three animals that received intravenous injections. The mechanism underlying the consistently higher labeling of the right eye is currently unknown. It seems unlikely that it is produced by an unequal delivery of tracer to the two eyes. Slowly injecting the tritiated uridine into the left saphenous vein should allow an even distribution of the label in the blood stream as it travels to the heart, through the lungs, back to the heart, and then out of the aorta to the carotid arteries (Allen, 1980a, b; Walker, 1980). This method of administration should deliver the tritiated uridine equally to both eyes. This conclusion is supported by the data from the eyes labeled intravitreally; it is unlikely that in each of eight cases the right eye was given relatively more tracer than the left eye.

Since visual stimulation can increase RNA synthesis

(Rasch et al., 1961; Byzov, 1965; Bok, 1970; Hollyfield and Basinger, 1980; Schmidt, 1983), the higher RNA labeling observed in the superior temporal region of the right eyes may simply correlate with the dominance of this region during vision (Rovamo and Virsu, 1979; Stone and Johnson, 1981; Fahle, 1983, 1987; LeVay et al., 1985). If this hypothesis is correct then the cells of layers 2, 3 and 5 of the posterior-medial area of the right lateral geniculate nucleus (LGN) would be expected to be more metabolically active than other LGN cells because they receive their input from ganglion cells of the superior temporal region of the right eye. The labeling differential might also be expected to occur in the monocular cells of layer 4 in the primary visual cortex (Hubel and Wiesel, 1979). Further studies with [^{14}C]deoxyglucose (Kennedy et al., 1976) and cytochrome oxidase histochemistry (Wong-Riley, 1979), utilizing a high-resolution quantitative analysis under normal and experimental conditions, would help to clarify these issues.

In addition, the results of this study indicate that caution should be observed when making experimental comparisons between different regions of one eye or when using one eye as a control for the other in experimental measurements.

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