weight) were well below those used in treatment of viral infections of hamsters by Sidwell *et al.* (*2*).

Inoculated animals were killed with ether and examined on gestation day 14. Tables 1 and 2 show that ribavirin had a potent effect in inducing fetal deaths (resorptions) as well as malformations. The most common abnormalities were limb defects. Others listed in Table 2 were eye malformations, ranging from microphthalmia to complete absence of the eye (anophthalmia), encephaloceles, exencephaly, rib defects, and one case of occult spina bifida.

The range of abnormalities of the extremities (single missing digit to complete amelia) were similar to those induced by cadmium in the same animal model (*3*) as well as to those which resulted from the unfortunate use of thalidomide in early human pregnancies (*4*). Should ribavirin be licensed for marketing, warning to prevent its use in the pregnant woman would seem mandatory for, if the findings in hamsters are applicable to man, ribavirin might cause either fetal death or congenital anomalies.

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30 July 1976; revised 16 September 1976

Monocular Deprivation: Morphological Effects on Different Classes of Neurons in the Lateral Geniculate Nucleus

Abstract. *Retrograde axonal transport of horseradish peroxidase from areas 17 and 18 of the cat's visual cortex labels, principally, the small (X) and large (Y) cells, respectively, of the lateral geniculate nucleus. Quantitative analysis of the sizes of these morphologically identified neurons after monocular deprivation shows that the arrest of cell growth in the deprived laminae involves mainly Y cells.*

The lateral geniculate nucleus (LGN) of the cat contains neurons of widely varying sizes and shapes (*1*, *2*). In particular, there is a small population of very large cells, which is clearly visible in Nissl-stained sections.

If one eye of a kitten is deprived of vision by suturing the eyelids together within a sensitive period during the first 3 months of life there is a retardation of neuronal growth in the laminae of the LGN innervated by the deprived eye, compared with the laminae receiving axons from the experienced eye (*3*), and very large cells are not detectable in the deprived laminae. However, it is not clear whether there is an overall lack of growth of cells of all sizes, or whether the large cells are affected specifically and become indistinguishable from the small cells.

There is physiological evidence that the responses from a specific cell type become harder to record in the deprived laminae of the LGN of cats with monocular lid suture (*4*). The hypothesis that LGN cells can be divided into different types stems from the observation that retinal ganglion cells which project to the main laminae of the LGN can be classified, on the grounds of their response properties, into X and Y cells (*5*). This classification has a morphological basis: Y cells in the retina probably correspond to the largest ganglion cells, and X cells to the smaller ones (*6*). Furthermore, retinal Y cells conduct rapidly to the thalamus where they relay with Y-type cells in the LGN, which have fast conducting axons to the visual cortex; retinal X-type cells, however, influence geniculate X cells, and thence the cortex, by slower axons (*7*). Rapid conduction is a feature of large axons, derived, presumably, from large neuronal somata. The specific loss found after monocular deprivation was in the percentage of recordable Y cells in the LGN, and it has been postulated that the lack of morphologically large cells after monocular lid closure is correlated with these findings (*8*). We now have morphological evidence that monocular deprivation does indeed cause a selective failure of growth among the Y cells of the LGN.

We sought a method of labeling X cells and Y cells selectively in the LGN of the cat, based on the observation that lesions of area 17 of the visual cortex cause retrograde cell degeneration mainly in small or medium cells, while after lesions of both areas 17 and 18 the large cells are also involved (*9*). This suggests that the small cells project mainly to area 17 and the Y system to both 17 and 18, a hypothesis supported by physiological evidence (*7*).

In the present study, horseradish peroxidase (HRP) (Sigma type VI or Boehringer grade 1) was injected into the visual cortex of five cats anesthetized with Althesin or Ketamine. One of these animals (N1) was a normal adult and the others were kittens 10 to 12 weeks old which had undergone suture of the right eyelids at the age of 1 week (MD1, MD3, and MD4) or 40 days (MD2). The injections were restricted to area 17 on one side of each brain and to area 18 on the other. A total of 1 to 2 μl of 30 percent HRP distributed over three or four penetrations was injected by pressure in each hemisphere, either through a Hamilton microsyringe needle or a glass micropipette. After a survival time of 1 to 3 days, the animals were perfused through the heart with a buffered mixture of aldehydes. A block containing the visual cortex and the LGN was washed in buffered sucrose, frozen, and sectioned coronally at 40 μm; the sections were incubated in di-

Table 1. Results of measurements of cross-sectional areas of LGN neurons.

Animal	Injection (side and area)	Mean cell areas in LGN ipsilateral to cortical injection (μm^2)					
		All cells sampled			Labeled cells		
		Undeprived lamina	Deprived lamina	Difference* (%)	Undeprived lamina	Deprived lamina	Difference* (%)
MD1	Left 17	328	190	42	317	241	24
MD3	Left 17	399	266	33	402	291	28
MD4	Right 17	361	278	23	350	301	14
MD1	Right 18	317	204	36	401	188	53
MD2	Right 18	506	333	34	682	344	50
MD3	Right 18	491	274	44	532	255	52
MD4	Left 18	522	279	47	592	216	64

*Difference as percentage of larger figure. All differences are significant at $P < .005$ (Student's t-test).

aminobenzidine containing hydrogen peroxide (*10*). Mounted sections were examined by light- and dark-field microscopy and most were lightly counterstained with cresyl violet.

After qualitative examination, counterstained sections were used for quantitative study. Outline drawings of LGN neurons containing HRP reaction product were made at a magnification of 1000 with the aid of a microscope drawing tube. In the same way, cells within the same high-power field which were stained for Nissl substance, but which did not contain reaction granules, were also outlined. Usually 10 to 15 acceptable neurons were present in each field; cells were only selected if they had clear plasma and nuclear membranes and a distinct nucleolus. Drawings were made on paper fixed to a digital graphics tablet (Tektronix 4953), and a Nova 2 computer was used on line to calculate the cross-sectional area of each cell, perform statistical analysis, and provide histograms of cell size.

In the normal adult cat (N1), we injected HRP into the left area 17 and the right area 18. On both sides, LGN neurons containing reaction granules were visible in laminae A, A1, and the C complex, but on the right side, ipsilateral to the injection in area 18, labeled cells were also present in the medial interlaminar nucleus and, to a lesser extent, in the posterior nucleus, pulvinar, and nucleus lateralis posterior, in accordance with earlier reports (*2, 11, 12*). Figure 1, A and B, shows histograms of the areas of 138 cells from the left LGN (combining laminae A and A1), and 144 cells from the right. The cells containing HRP product are plotted as solid bars within the histograms of the whole population. It is clear that the marked neurons on the right are larger than those on the left (by 28 percent); although there is considerable overlap, more large cells are filled retrogradely after an injection in area 18 than after one in area 17. This observation supports the concept that the postulated Y cells have been labeled selectively by injection of HRP in area 18, and confirms the independent results of Gilbert and Kelly (*11*). The histograms show that the distribution of the total cell populations on the two sides varies somewhat. This is not entirely surprising because the samples are not from precisely the same antero-posterior level in the LGN. However, the mean total cell size on the two sides is similar, while the differences in both mean and distribution of the labeled cells between sides are large.

In the four monocularly deprived cats (MD1 to MD4) HRP was injected into area 17 on one side and into area 18 on the other with the intention of marking, principally, the X cells and the Y cells, respectively, of the LGN. We measured cell areas as before, but collected the data for lamina A1 and the binocular part of lamina A separately. The effect of monocular deprivation in these experiments was to produce differences in mean cell area ranging from 23 to 47 percent between laminae A and A1 on the same side and between corresponding laminae on opposite sides (Table 1). In three kittens (MD1, MD3, MD4) good labeling of cells was obtained after injection into area 17; in the fourth kitten (MD2) the reaction in the LGN related to the area 17 injection was too weak for sufficient cells to be measured. In two of the kittens (MD1, MD2) the area 17 injection was on the left, contralateral to

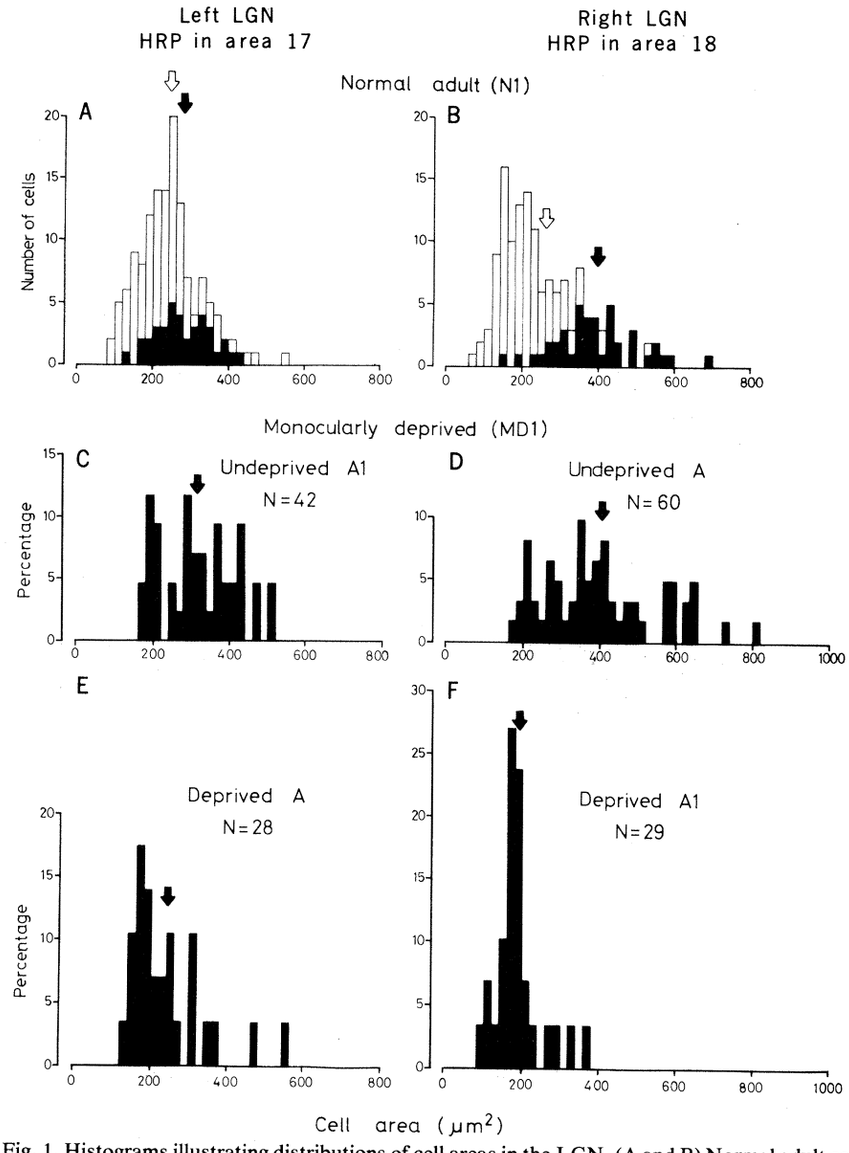

Fig. 1. Histograms illustrating distributions of cell areas in the LGN. (A and B) Normal adult cat (N1). HRP was injected into the left area 17 (A) and the right area 18 (B). Measurements from laminae A and A1 are combined. The outline histograms illustrate the distributions of all cells measured; the solid blocks within these histograms show neurons that contain HRP reaction product and that are presumed to be mainly X cells on the left and Y cells on the right. Open arrows indicate the mean values for total populations (essentially the same on the two sides), and solid arrows the means for HRP-labeled cells. The slight difference in overall distribution on the two sides is probably due to sampling variations. (C to F) Kitten MD1, subjected to right monocular deprivation. Solid histograms show the data for HRP-labeled cells alone, again presumed X cells on the left (C and E) and Y cells on the right (D and F). Results are given separately for the undeprived pair of laminae (left A1 and right A) and the deprived pair (left A and right A1). Since the overall distribution and mean cell size were similar in the two laminae of each pair, data for unlabeled cells are omitted for clarity. Ordinates are expressed as percentages, and the number in each sample is indicated.

the eye closure, and in the other (MD4) on the right, ipsilateral to the deprived eye. In all three kittens, in the nondeprived laminae, there was no significant difference between the mean size of the total cell population and that of the marked cells. However, the marked cells in the deprived laminae were from 14 to 28 percent smaller than those in the nondeprived laminae. A comparison of the histograms of cell size (Fig. 1, C and D) shows a somewhat higher peak of the small cells in the deprived laminae, compared with a broader, flatter distribution in the normal laminae.

The results of cell measurements in the LGN on the side of the area 18 injection are very different. HRP was injected into the right area 18, ipsilateral to the lid suture in MD1 to MD3; the injection was on the left in MD4. In the LGN ipsilateral to the area 18 injection, labeled cells from the nondeprived laminae were up to 26 percent larger than the mean of all cells measured, but in the deprived laminae labeled cells were of similar size to the mean. Comparison of the size of marked cells between the normal and the deprived laminae revealed a striking difference, of from 50 to 64 percent, and the histograms (Fig. 1, E and F) show a very clear shift from a wide, relatively flat distribution in the undeprived laminae to a sharply peaked distribution entirely within the small cell population in the deprived laminae. The "shrinkage" of these presumed Y cells, marked by injection of HRP in area 18, is much more than that of the neurons labeled after injection in area 17, most of these cells probably being X cells. In fact, inspection of Table 1 shows that, in those animals where both sides were successfully injected, labeled Y cells are 12 to 28 percent smaller than labeled X cells in the deprived laminae (*13*).

We draw the following conclusions. In a normal adult cat, HRP injected into area 18 reaches a greater proportion of the large neuronal somata in the LGN than when injected into area 17. There are good physiological and anatomical data to permit identification of the largest neurons of the LGN with the fast-conducting Y system projecting mainly to area 18. When HRP is injected in area 18, one can, therefore, postulate that the Y cells of the LGN on the side injected will be labeled. We have shown here that, in monocularly deprived kittens, reaction product is restricted to very small cells of the deprived laminae, which can be taken to represent the diminished Y cells. When the injection is in area 17, which should cause predominant labeling of X cells, the marked neurons in the deprived laminae are smaller than those in the nondeprived laminae but to a much lesser degree. Thus, the present experiments provide morphological evidence that monocular deprivation in cats does have a relatively specific effect on the Y cell system.

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14. Supported by grants from the Fonds National Suisse de la Recherche Scientifique (3/2460/74), the Medical Research Council, London (G/972/463/B), and the European Training Programme in Brain and Behaviour Research. C.B. held a fellowship from the Roche Research Foundation during a visit to Lausanne. We thank M. Gissler and M. Dürsteler for computer programming, and M. C. Cruz, R. M. Cummings, and B. Rhodes for technical help.

6 July 1976; revised 6 October 1976

Selective Blockade of Hypothalamic Hyperphagia and Obesity in Rats by Serotonin-Depleting Midbrain Lesions

Abstract. *Adult female rats, depleted of 70 percent of forebrain serotonin by dorsal and median raphe lesions, showed little overeating of food pellets and obesity following medial hypothalamic lesions. However, these rats showed the same reduced acceptance of sucrose solutions, enhanced rejection of quinine solutions, and exaggerated weight gain on a high-fat diet as did other rats made obese by medial hypothalamic lesions alone. Since raphe lesions alone produced none of these effects, the pattern of behaviors observed suggests a hitherto unknown (perhaps secondary) role for brain serotonin metabolism in selective aspects of the medial hypothalamic syndrome.*

It has been estimated that 20 to 40 percent of all North Americans are obese (*1*). Considering the known health risks of excessive weight, it is not surprising that many animal models have been studied to understand its pathophysiology. The most prominent model employs rats with medial hypothalamic (MH) lesions. The marked behavioral similarities between the obese human and this experimental analog (*2*) suggest common underlying disorders.

The complex behavioral changes attendant upon MH injury imply alterations to multiple neuronal systems (*3*). Efforts to define these systems have recently focused on the role of monoamines (*4, 5*). Several reports indicate that damaged hypothalamic or forebrain (or both) serotonin (5-hydroxytryptamine or 5-HT) systems contribute to MH hyperphagia and obesity (*6*). Seemingly incompatible with this suggestion are findings that chronic 5-HT depletion by midbrain raphe lesions does not elevate food intake and body weight (*7*). We present evidence clarifying this paradox, namely, that such raphe damage can largely prevent the overeating and obesity characteristic of MH injury. These findings imply a secondary rather than a primary role for 5-HT in MH hyperphagia.

Forty-two adult female rats (Wistar strain, High Oaks Ranch, Ontario) were individually housed in a colony with light (0800 to 2000 hours) and temperature (22° ± 1°C) controlled and given free access to weighed amounts of Purina food pellets (on cage floor) plus tap water (in 100-ml Wahmann bottles). Half had received dorsal and median raphe lesions