found to be elevated; however, these were within the normal range and far below those associated with hyperglycemia (*10*). Accordingly, maternal insulin and fetal glucose concentrations (control, 16.7 ± 12.5 mg/100 ml; growth hormone treated, 20.5 ± 19.5 mg/100 ml; $t = 0.3395$, $P > .05$) were unaffected by the growth hormone administration. Explanation for the increase in maternal weight gain is unclear. Whereas the protein anabolic effect of growth hormone and metabolic adjustments during pregnancy would suggest increased protein deposition, our findings do not indicate general mobilization of the protein source for transfer to the fetus. In view of the large increase in brain growth, it is likely that metabolic alterations would be evident in concentration estimations; however, further studies of metabolic turnover may be required.

Although maternal nutrition appears largely unaffected, placental growth was stimulated as measured by the incorporation of ^{14}C-TdR into placental DNA (Table 1). Correlation of placental growth with elevated brain weight further supports placental regulation of fetal growth. Where this has been found to be retarded, as in malnutrition or intrauterine growth retardation (*11*), fetal growth is curtailed, an action attributed to impaired fetal nutrient supplies (*12*). Although our data provide the only evidence relating placental overgrowth, it cannot be incorporated into a similar nutritional hypothesis, which suggests that the role of the placenta needs reconsideration, perhaps in terms of production or transfer of trophic factors.

Contrary to the proposal of Zamenhof *et al.* (*3*), elevated cellular content was thus obtained in fetuses from well-nourished dams given growth hormone. This discrepancy cannot be attributed to maternal diet since both daily food intake and composition are comparable. However, Zamenhof *et al.* report mean litter numbers of 6 and 11 for control and growth hormone groups, respectively, whereas no change was observed in our study, and this may account for the inconsistency between their and our findings. The administration of growth hormone during pregnancy appears to produce a unique effect on brain growth. Similar specificity was observed by Zamenhof, Mosley, and Schuller (*1*). These results indicate more than stimulation during a vulnerable period, for other prenatal factors, such as malnutrition (*13*), have a generalized influence at birth, affecting body as well as brain development. Rather, the specificity of growth hormone action indicates a selective effect on growth of the brain. Pituitary growth hormone does not cross the placenta (*14*), and thus its action must be mediated by secondary changes. From our study, however, this is not via nutrient mobilization. Alternatively, a second messenger, such as somatomedin, or a similar trophic substance, perhaps of placental origin, may be able to directly influence fetal brain growth. Indeed the specificity of growth hormone action suggests the presence of a trophic substance which is unique to the brain.

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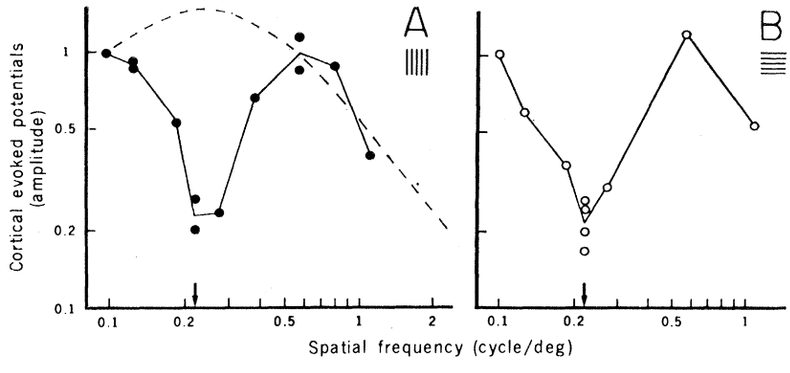
Geniculate Neural Plasticity in Kittens after Exposure to Periodic Gratings

Abstract. *Kittens were exposed for 2 hours a day to a periodic vertical grating during the first 10 weeks after birth, and otherwise kept in darkness. The spatial frequency of the grating fell in the range of highest contrast sensitivity of normal cats. After the 10-week exposure period, cortical evoked potentials and lateral geniculate mass responses to alternating gratings showed a reduced amplitude for the spatial frequency of exposure. This reduction was independent of grating orientation. An analysis of orientational sensitivity of cortical units did not show any bias in favor of the vertical orientation.*

It has been demonstrated that if a kitten is brought up in a visual environment containing only bars of a given orientation, the visual cortex of the kitten develops only neurons subserving that orientation (*1, 2*). Cortical neurons in cats and in monkeys, besides being selective for the orientation of the visual stimulus, are specific for the spatial frequency of it (*3*). Thus we performed an experiment in which the only visual experience offered to a kitten, otherwise kept in darkness, was a grating of a given spatial frequency. We always used square-wave gratings with vertical bars and with spatial frequency corresponding to the peak of the contrast sensitivity curve of the cat. We found that cortical and geniculate neural responses to a grating of the same spatial frequency as that to which the animals were exposed were reduced as compared with the responses to other spatial frequencies. This reduction of cortical and geniculate responses was independent of the orientation of the grating. Moreover, an analysis of the orientational selectivity of cortical units did not show any bias in favor of the vertical orientation.

The kittens were kept from birth in a completely dark room. From the age of 2 to 3 weeks, they were exposed to a periodic grating for 2 to 3 hours a day, 6 days a week. The spatial frequency of the grating was 0.22 cycle/deg for some of the kittens and 0.45 cycle/deg for the others. These two spatial frequencies fall in the range of highest contrast sensitivity of the cat (*4, 5*). This routine was stopped when the kittens were 2½ or 3 months old. Seven kittens were exposed to gratings by being suspended in the middle of a cylinder 2 m in diameter, the walls of which were painted with periodic black and white vertical stripes. The kittens stood on the floor of a small plastic



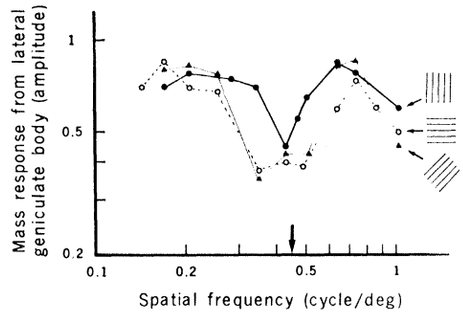


Fig. 1 (left). Amplitude of cortical evoked potentials as a function of the spatial frequency of the stimulus grating from a kitten exposed to a vertical grating of 0.22 cycle/deg. (A) The points represent the amplitude of evoked potentials (in arbitrary units) in response to a vertical grating having a contrast of 20 percent and phase alternation of 8 hertz. For the spatial frequency of the early exposure (arrow) and for two other spatial frequencies on either side of it, the recordings were repeated twice at different times. The dashed line was obtained by fitting the results from a similar experiment performed under the same experimental conditions on a 3-month-old control kitten reared in a normal visual environment. (B) The amplitude of evoked potentials in response to a horizontal grating is shown for the experimental kitten. Fig. 2 (right). Amplitude of the mass response of the lateral geniculate body recorded from the optic radiations in response to alternating gratings of various orientations (vertical, horizontal, and 45 deg from vertical) and spatial frequencies. The recordings were performed on a kitten that had been exposed to a grating of 0.45 cycle/deg (arrow). The contrast of the stimulus grating was 30 percent and its frequency of alternation was 8 hertz.

transparent cylinder 30 cm in diameter. They wore a white collar that restricted their visual field to approximately 100 deg. The floor and the roof of the plastic cylinder restricted the visual field along the vertical so that possible changes in spatial frequency due to changes in viewing distance were at most of the order of 10 percent. Five kittens were exposed to gratings with a procedure similar to that of Hirsch and Spinelli (*1*). Each of these kittens wore masks rigidly attached to the head and looked at two periodic vertical gratings mounted in the mask, one in front of each eye, at a distance of 3 cm. The gratings were focused on the kitten retina by means of suitable lenses mounted before the eyes.

The electrophysiological experiments were begun soon after the termination of the exposure. Twelve kittens were studied. Under halothane anesthesia, an endotracheal tube and a venous cannula were inserted. A plastic chamber was cemented around two small openings of the skull overlying area 17 of the cortex and the lateral geniculate body. Anesthesia was then terminated, and the animal was immobilized with curare and artificially ventilated with room air. The recording session lasted 5 to 6 hours; afterward, the animal was left to recover its natural respiration and put back in the dark room. Recordings were made every other day.

During recording the animal was fixed to the table by bolting the rim of the plastic chamber to a suitable metal mounting. The pupils were dilated with atropine, and contact lenses with artificial pupils 4 mm in diameter were applied to both eyes. Refraction was corrected with additional lenses.

Cortical potentials were recorded by means of screws implanted in the skull above the cortical projection of the area centralis (area 17). Geniculate activity either at the level of the optic radiations or at the level of the geniculate body was recorded by means of tungsten microelectrodes. An averaging computer was used to improve the signal-to-noise ratio. The electrical activity was recorded in response to gratings of various spatial frequencies and suitable contrast (*6*), generated on the face of an oscilloscope. The gratings were alternated in phase at a rate of 8 hertz, so that the bright bars replaced the dark ones without any change in the average luminance (*4*). The center of the oscilloscope screen was placed in correspondence to the projection of the area centralis of one eye when cortical evoked potentials were recorded, or in correspondence to the receptive field of the cortical orgeniculate single unit or multiunits. The cortical potentials were evoked by presenting the kitten with an alternating sinusoidal grating of vertical orientation and of variable spatial frequency (*4*). In general, the amplitude of the evoked potentials for the spatial frequency at which the kitten had been exposed was smaller as compared with those for higher and lower frequencies.

The amplitude of the cortical evoked potentials obtained in one kitten is reported in Fig. 1A as a function of the spatial frequency. The amplitude of the evoked potentials is much smaller for the frequencies around 0.22 cycle/deg, the frequency of the early exposure, than for lower or higher frequencies. In contrast to the dip in this curve, the analogous curve obtained for the same value of contrast in a kitten reared in a normal visual environment peaks around 0.2 cycle/deg.

In 8 of our 12 kittens, the amplitude of the evoked response to the spatial frequency at which the kitten had been exposed was much smaller than the responses at both lower and higher frequencies. In three other kittens the same effect was present and significant, although less marked. In one kitten, we did not find any evidence of the phenomenon using the evoked potential technique.

The results in Fig. 1A are relative to a vertical grating, that is, a grating parallel to the grating of exposure. In the same kitten a similar dip in the spatial frequency curve was obtained for the evoked potentials in response to a horizontal grating (Fig. 1B) and for oblique gratings. This result, confirmed in other kittens, indicates that the effect of grating exposure is selective for spatial frequency but not for orientation. Therefore we looked for the effect in the neurons of the lateral geniculate body, the responses of which are not sensitive to stimulus orientation. We recorded the output of the

lateral geniculate body from the optic radiations by means of a semimicroelectrode (tip diameter, about 20 μm). This electrode recorded simultaneously from many units, the amplitude of the impulses being practically uniform. The activity was then fed into a band-pass filter with cutoffs at 6 and 600 hertz. The filter output was sent to an averaging computer. The averaged responses to an alternating grating looked approximately sinusoidal. The amplitude of the responses obtained from a kitten for gratings of various spatial frequencies and orientations are reported in Fig. 2. The frequency of the grating to which the kitten had been exposed was 0.45 cycle/deg. All three curves, for the vertical, horizontal, and oblique gratings, show a dip in the region of this frequency. This experiment has been repeated in six kittens.

When recordings of the response to gratings located in the central part of the visual field were made with the same technique from the optic tract, we did not find any significant reduction of the response for the spatial frequency of the early exposure. This experiment however, may not be conclusive, since the recording electrode might select populations of fibers unaffected by exposure.

In initial experiments, a reduction in sensitivity for the spatial frequency of exposure was found also at a single unit level, both in some geniculate cells and in some complex neurons of the striate cortex. In our experiments the cortical cells did not show any tuning in favor of the vertical orientation, the orientation of the periodic grating to which the kittens were exposed (*7*).

It is known from psychophysical experiments in man that inspection of a grating of high contrast strongly increases the contrast threshold for a grating of the same spatial frequency (*8*). We demonstrated that the simple cortical neurons of the adult cat respond similarly (*9*). If a grating of high contrast drifts across the receptive field of a cortical neuron, its response to a grating of low contrast is dramatically reduced for 25 to 30 seconds. The reduction is limited to a narrow band of spatial frequencies around that of the high contrast grating to which the neuron receptive field was exposed. This is exactly the same phenomenon reported here for kittens, except that the neural modification brought about by early exposure is probably permanent (*10*). In kittens the modification of neural responses occurs primarily at the geniculate level, where the receptive fields are concentrically organized. It is not surprising, therefore, that the phenomenon was independent of orientation.

Our experiments seem to contradict the generally accepted concept that exposure to a given pattern during the critical period increases the sensitivity of the visual system for that pattern. We have found an instance in which this sensitivity is decreased.

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Cyclic Guanosine Monophosphate: Elevation in Degenerating Photoreceptor Cells of the C3H Mouse Retina

Abstract. *As a result of an early deficiency in cyclic nucleotide phosphodiesterase activity, guanosine 3′,5′-monophosphate accumulates in retinal photoreceptor cells before they begin to degenerate. It is suggested that degeneration of the photoreceptor cells is related to an imbalance in their metabolism or function which is caused by the elevated levels of cyclic guanosine monophosphate.*

The neural retina of the mouse is organized in layers that contain morphologically and functionally distinct classes of neurons (*1*). The outer layers contain the light-sensitive photoreceptor cells with their characteristic rod outer segments, and the innermost layers contain the ganglion cells and their axons, which converge to form the optic nerve. The bipolar or inner nuclear layer, which contains several neuronal cell types, is sandwiched in between these layers.

An autosomal recessive mutation (*rd*) of C3H/HeJ mice (*2*) results in the degeneration of all the photoreceptor cells of this retina during the second and third postnatal week (*1*). The inner bipolar and ganglion layers survive the disease and retain their layered organization. Biochemical studies have shown that the C3H retina is abnormal before the first signs of degeneration can be observed in the photoreceptor cells at the eighth postnatal day (*3*).

During the development of the normal retina, a receptor-specific phosphodiesterase (PDE), which hydrolyzes cyclic nucleotides to 5′-mononucleotides, increases in activity as the photoreceptor cells differentiate and mature. In the developing C3H retina, this enzyme activity is never observed. The receptor-specific PDE has been studied in homogenates of the normal retina (*3*) and in isolated rod outer segments of photoreceptor cells (*4*), where it exhibits a low affinity for cyclic nucleotides [high Michaelis constant (K_m) for PDE]. But the role of this high K_m-PDE in the metabolism or function of normal photoreceptor cells, as well as the identity of its substrate in vivo, has remained speculative.

We have considered adenosine 3′,5′-monophosphate (cyclic AMP) and guanosine 3′,5′-monophosphate (cyclic GMP) as possible substrates for the high K_m-PDE reaction in vivo. Quantitative histochemical and biochemical studies have revealed that (i) cyclic AMP is concentrated in the inner layers of the retina where it is associated with neuronal function and (ii) the content of cyclic AMP and the activity of adenylate cyclase are both low in normal photoreceptor cells (*5*). That the metabolism of cyclic AMP is minimal in photoreceptor cells is also suggested by investigations of the immature retina of C3H mice, where cyclic AMP concentrations do not increase in the photoreceptor cells, even though the cells are deficient in cyclic nucleotide PDE activity (*5*). These findings cast serious doubt as to