3). Others have concluded that whereas spontaneous blinks are highly variable and sometimes incomplete (*11*), they do not differ objectively from voluntary blinks (*2*). Our own preliminary observations confirm this conclusion (*12*) and support the extension of our findings to spontaneous blinks. Of still greater importance is the fact that we have already verified (*3, 7*) that voluntary blinks, like spontaneous ones, cause subjective interruptions of the visual scene that are much smaller than objective measurements would predict.

We conclude that the decrease in visual sensitivity that we measured cannot be attributed to optical factors. We attribute this decrease to a neural inhibitory mechanism in the brain. This mechanism, by decreasing the perceptual effect of the blink, contributes to the continuity of vision.

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References and Notes

1. Blinking is a temporary closure of both eyes that is under both voluntary and involuntary control. It has been categorized into three types: (i) voluntary blinks, which can be executed on external or internal command; (ii) spontaneous or periodic blinks, which are involuntary, centrally programmed, and which constitute most of normal blinking; and (iii) reflex blinks, whch are produced involuntarily in response to peripheral stimulation, such as a foreign body approaching or touching the eye (*2, 3*).
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4. We have assessed the light attenuation due to the eyelids by measuring absolute visual thresholds to 0.2-sec flashes in fully dark-adapted eyes. Using full-field (Ganzfeld) conditions, the thresholds for eyes closed were 1.8 to 2.0 log units higher than for eyes open.
5. Investigators have correctly distinguished between blink duration, which is typically reported to be 300 to 400 msec, and blackout duration, the time during which the upper lid covers the pupil, which is reported to range from 40 to 200 msec [R. W. Lawson, *Nature (London)* **162**, 531 (1948); A. T. Slater-Hammel, *Res. Q. Am. Assoc. Health Phys. Educ. Recreat.* **24**, 363 (1953)].
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7. We have confirmed this observation and have found that subjects confidently match the visual effect of a blink with that of a much briefer and shallower decremental pulse in the illumination of a visual field.
8. See, for example, F. C. Volkmann, L. A. Riggs, R. K. Moore, and K. D. White [in *Eye Movements and the Higher Psychological Functions*, J. W. Senders, D. A. Fisher, R. A. Monty, Eds. (Erlbaum, Hillsdale, N.J., 1978), p. 35]. We view this neural inhibition as a corollary discharge such as that described by R. W. Sperry [*J. Comp. Physiol. Psychol.* **43**, 482 (1950)]. Under certain conditions, saccades may also elicit a retinal component of visual impairment such as optical smear or masking of contours. These factors are not relevant to the suppression during blinks in the present experiments.
9. Our observations involved two techniques. First, we used a double Purkinje image eye tracker to measure the time during which the pupil was actually obscured during a blink and to indicate whether any movements occurred before the lids cut off the input to the tracker and after the lids reopened [T. N. Cornsweet and H. D. Crane, *J. Opt. Soc. Am.* **63**, 921 (1973)]. A second technique, modeled after that of Ginsborg and Maurice (*10*), involved subjective observations of a small spot of light which could be made to move either horizontally or vertically across a large field. When an observer succeeded in blinking just as the spot crossed the fovea, the trace of the spot appeared to be deflected, and the subjective deflection could be used to estimate the speed, duration, and extent of the eye movement which produced it. We estimate that just before a normal blink there is an inward and downward motion of the eyes of about 0.3 deg arc.
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12. In two subjects, neither the form of the blink as reflected in the EBG, nor the mean duration of pupil covering as measured on the eye tracker (*9*) was markedly different for voluntary and spontaneous blinks.
13. These experiments were conducted at Brown University, supported by grant EY 00744 from the National Eye Institute. We thank K. D. White, W. J. Donovan, K. Fuld, and J. Volkmann for their contributions. Preliminary reports of portions of this research were presented at the 1978 meeting of the Optical Society of America and at the 1979 meeting of the Association for Research in Vision and Ophthalmology.

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Sparing of the Brain in Neonatal Undernutrition: Amino Acid Transport and Incorporation into Brain and Muscle

Abstract. *Rates of tyrosine and lysine transport and incorporation into protein were measured in control and undernourished weanling rats. Undernutrition was induced by feeding lactating dams a low protein diet (12 percent casein) from birth to day 21. At weaning, body and brain weights of undernourished rats were 50 percent and 88 percent, respectively, of control values. Lysine and tyrosine transport rates into skeletal muscle were reduced by over 75 percent, more than twice the reduction seen in brain. Rates of amino acid incorporation into muscle protein were reduced by approximately 50 percent; the change in rate of incorporation into brain protein was not statistically significant. These data indicate that, in spite of marked retardation of amino acid transport into brain, the brain seems fully capable of maintaining normal rates of protein synthesis.*

Nutritional deprivation during critical periods of development in early life has profound and persistent effects on the body and brain (*1*). The fact that the growth impairment of the brain is smaller than that of the body as a whole has led to the concept of brain "sparing" (*2*). We have studied the mechanisms by which the brain is spared by measuring the transport of two amino acids, tyrosine and lysine, into brain and skeletal muscle and their incorporation into tissue protein. Both activities were sharply reduced in skeletal muscle of undernourished animals. In brain, the reduction of amino acid transport was about half that seen in muscle, yet the reduction in incorporation into brain protein was not statistically significant.

Female sperm-positive rats (*3*) were caged individually and housed in a temperature-controlled room with a 12 hour light and 12 hour dark (0900 to 2100 hours) diurnal cycle. The animals were fed a normal protein diet containing 25 percent casein (*4*) throughout gestation. At birth, litter size was made uniform by randomly distributing the rat pups among the lactating females, eight per litter. During lactation, experimental mothers were fed a low protein diet containing 12 percent casein (*4*), whereas control mothers continued on the 25 percent casein diet. The low protein intake reduces the volume of milk without altering its composition (*5*). Thus, throughout lactation the experimental pups were subjected to undernutrition by receiving suboptimal amounts of a diet of normal composition; during the third week of

Table 1. Body and brain weights of control and undernourished rats. The data are expressed as means ± standard error (N = 30).

Tissue	Weight (g)		Percentage decrease*
	Control	Experimental	
Body	60.6 ± 1.13	30.4 ± 0.93	49.8
Whole brain	1.438 ± 0.0166	1.267 ± 0.0117	11.9
Forebrain	1.128 ± 0.0121	1.009 ± 0.0105	10.5
Brainstem	0.128 ± 0.0049	0.115 ± 0.0030	10.3
Cerebellum	0.181 ± 0.0053	0.142 ± 0.0042	21.5

*$P < .001$, one-tailed t-test.

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life they were also subjected to malnutrition as they began to feed on the low protein and high carbohydrate diet supplied to the mother. This combination of undernutrition and malnutrition closely approximates the marasmus form of protein-calorie malnutrition seen in the human (*6*). At weaning, on day 21, rates of tyrosine and lysine transport into brain and skeletal muscle and rates of incorporation into protein were assessed by a procedure that provides a reliable index of the rates of amino acid transport and protein synthesis in vivo (*7*).

At weaning, the undernourished rats exhibited marked retardation in overall body growth (50 percent deficit in body weight) and a far smaller reduction in total brain weight (12 percent) (Table 1). These observations are consistent with the concept that the central nervous system is relatively spared from gross nutritional insult.

The transport rates of both tyrosine and lysine into skeletal muscle were reduced by 75 percent (Table 2). The magnitude of the transport reduction into brain was about half that in muscle. These data suggest that compensatory mechanisms come into play and attenuate the deficit in amino acid transport into brain.

Rates of tyrosine and lysine incorporation, an essential feature of tissue growth, were measured in both brain and skeletal muscle. Undernourished rats exhibited profound decreases in the rates of incorporation of both amino acids into muscle protein. In the brain, incorporation rates were not significantly reduced compared to control animals (Table 2). However, small decreases were observed in all three brain regions studied. It is of interest that in both muscle and brain the decreased rates of amino acid incorporation, an index of protein synthesis in vivo, paralleled the decrement in body and brain weight. Data on the concentrations of tyrosine and lysine in plasma and brain were consistent with these findings: both amino acids were reduced in the plasma but not in the brain (*8*).

The decreased rate of amino acid transport in muscle and brain has not, to our knowledge, been reported previously in neonatally undernourished animals. In previous studies (*9*) of amino acid uptake and incorporation in brain the results depended on the particular amino acid measured. Our data seem to represent a phenomenon of general significance because the two amino acids that we studied (tyrosine, a large neutral, and lysine, a basic amino acid) are carried by separate systems (*10*) but were similarly influenced. In addition, reduced rates of transport were observed both in the brain and in muscle. The decrease in amino acid incorporation into skeletal muscle protein could account for the observed retardation in body growth; thus, the impairment of protein synthesis is probably secondary to reduction in transport and availability of amino acids. Adequate supplies of essential amino acids have indeed been shown to control the overall rate of tissue protein synthesis (*11*). However, compared to the decrease in muscle protein, the brain exhibited a far smaller decrease in weight and amino acid incorporation in spite of the large reduction in amino acid transport.

This sparing effect on the brain may reflect an adaptive mechanism that, in the case of tyrosine and lysine incorporation into protein, involves more efficient utilization of amino acids. Reduced amino acid efflux from the brain may be one of the compensatory processes that helps to maintain adequate concentrations of cerebral amino acids. This concept is supported by the evidence that, especially with respect to tyrosine, brain concentrations are unchanged or even increased in undernourished rats whereas the concentrations in plasma and peripheral tissues are markedly decreased (*12*). Developmental patterns of cerebral amino acid metabolism are also altered by undernutrition (*13*). Thus, alternative factors that could account for the lack of a significant decrease in the rate of amino acid incorporation into brain protein are adaptive changes in amino acid metabolism or protein synthesis or protein degradation.

Although the brain seems to be spared from gross deficits in rate of growth and amino acid incorporation, other functionally important amino acid pathways do exhibit alterations related to the availability of normal supplies of amino acids. This is especially evident with respect to the utilization of the amino acids tyrosine and tryptophan as precursors of the monoamine neurotransmitters. Undernourished animals exhibit altered levels of norepinephrine and serotonin, in-

Table 2. Rates of transport and incorporation into protein of tyrosine and lysine in normal and undernourished rats. The rats (21 days old; 30 control, 30 undernourished) were injected subcutaneously with a mixture of [^{14}C]lysine (285 mCi/mmole) and [^{3}H]tyrosine (52.1 Ci/mmole) at a dose of 30.3 and 303.0 μCi/kg, respectively. They were killed by decapitation 2.5, 5.0, 7.5, 10.0, or 12.5 minutes after injection and their brains were removed and dissected into forebrain, brainstem, and cerebellum. Skeletal muscle samples were from the hind limbs. All tissues were stored at −70°C until processed. Total plasma radioactivities were determined by liquid scintillation spectrometry, with the external standard method being used for quench correction. The identity of the radioactive amino acid in plasma was confirmed by thin-layer chromatography (*18*). Free amino acids in the brain were extracted in ethanolic trichloroacetic acid (TCA) (*7*). Skeletal muscle samples were solubilized in 1*N* NaOH prior to ethanolic TCA extraction. Radioactivity in soluble and insoluble fractions of brain and muscle was measured. Transport and incorporation rates are expressed as nanomoles per gram (fresh weight) per minute (± standard error).

Tissue	Tyrosine			Lysine		
	Control	Experimental	Percentage decrease	Control	Experimental	Percentage decrease
			Amino acid transport			
Skeletal muscle	5.62 ± 0.779	1.48 ± 1.260*	73.7	50.3 ± 3.00	12.1 ± 1.89†	76.0
Whole brain	6.90 ± 0.595	3.99 ± 0.856‡	42.2	19.4 ± 2.13	10.1 ± 1.57§	47.9
Forebrain	6.83 ± 0.578	3.98 ± 0.766‡	41.7	17.7 ± 2.29	7.95 ± 0.376†	55.1
Brainstem	6.59 ± 0.585	3.72 ± 1.10‡	43.5	28.4 ± 2.75	20.5 ± 2.87‡	27.8
Cerebellum	7.26 ± 0.538	4.54 ± 1.04‡	37.5	24.2 ± 2.18	16.0 ± 2.52‡	33.9
			Amino acid incorporation			
Skeletal muscle	1.11 ± 0.152	0.57 ± 0.158‡	49.2	6.29 ± 1.690	2.12 ± 0.309‡	66.3
Whole brain	1.42 ± 0.091	1.25 ± 0.065	12.0	3.50 ± 0.489	2.93 ± 0.317	16.3
Forebrain	1.29 ± 0.939	1.11 ± 0.071	16.0	3.05 ± 0.551	2.55 ± 0.167	16.4
Brainstem	2.08 ± 0.116	1.96 ± 0.073	5.8	5.70 ± 0.523	5.10 ± 0.164	10.5
Cerebellum	1.75 ± 0.138	1.65 ± 0.133	5.7	4.63 ± 0.824	3.75 ± 0.328	19.0

*$P < .02$. †$P < .005$. ‡$P < .05$. §$P < .01$, one-tailed t-test.

creased tyrosine hydroxylase activity, and decreased norepinephrine turnover (*14*).

At weaning, a time when amino acid transport into brain is reduced, we have observed alterations in serotonin receptor binding (*15*) and in tyrosine hydroxylase activity in norepinephrine and dopamine areas of the brain (*16*). Thus, the sparing of the brain in undernutrition does not extend to all aspects of amino acid metabolism.

The biochemical changes that we observed in undernourished rats may represent important processes underlying the aberrations in brain function and behavior seen in adult animals and humans exposed to malnutrition early in life (*17*).

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8. The free amino acid concentrations on sulfosalicylic acid extracts of pooled samples of plasma and whole brain were:

Amino acid	Plasma (μmole/ml)		Brain (μmole/g)	
	Control	Experimental	Control	Experimental
Tyrosine	0.099	0.066	0.079	0.114
Lysine	0.635	0.410	0.466	0.383

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Multiple Daily Amphetamine Administration: Behavioral and Neurochemical Alterations

Abstract. *In rats, multiple daily amphetamine injections (2.5 milligrams per kilogram of body weight, injected subcutaneously every 4 hours for 5 days) resulted in a progressive augmentation in response, characterized by a more rapid onset and an increased magnitude of stereotypy. By contrast, offset times of both the stereotypy and the poststereotypy hyperactivity periods were markedly shortened. When the animals were retested with the same dose of amphetamine 8 days after the long-term treatment was discontinued, the time of offset of the stereotypy and hyperactivity phases had recovered to values found with short-term amphetamine treatment, whereas the more rapid onset of stereotypy persisted. Brain monoamine and amphetamine concentrations and tyrosine hydroxylase activity were determined in comparably treated rats at times corresponding to the behavioral observations. The behavioral data indicate that enhanced responsiveness to amphetamine following its repeated administration may contribute to the development of amphetamine psychosis.*

We have previously shown that repeated single daily injections of *d*-amphetamine in rats augment some features of the amphetamine response (*1*-*3*). Similar results have since been obtained in other species (*4*) and with repeated injections of other psychomotor stimulants (*5*). In humans, long-term administration of psychostimulants induces a schizophrenialike psychosis (*6*). On the basis of the behavioral augmentation produced in animals, we suggested that the heightened responsivity to amphetamine might be involved in the development of amphetamine psychosis (*1*-*3*). However, because amphetamine psychosis is most frequently associated with multiple daily drug administrations (*6*), development of a useful animal behavior model of this psychosis may require a more sustained level of amphetamine intoxication. In this regard, it has recently been reported that after 3 days of continuous amphetamine infusion in rats, motor stereotypies are replaced by increased social behaviors, such as fleeing and fighting (*7*). These results suggest that enhanced responsiveness to amphetamine may not be implicated in amphetamine psychosis. Therefore, we have extended our previous studies by characterizing the changes in behavior and in monoamine systems that occur with multiple daily injections of amphetamine in rats.

Male Wistar rats (325 to 375 g), obtained from Hilltop Laboratories, were housed individually in sound-attentuating activity chambers for 2 days before receiving 30 successive, subcutaneous injections of either saline or *d*-amphetamine sulfate (2.5 mg of free base per kilogram of body weight) at 4-hour intervals

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