Vascular smooth muscle from a strain of genetically hypertensive rats is less reactive to specific (norepinephrine and serotonin) and nonspecific (KCl) smooth muscle contractile substances than is comparable tissue from normotensive animals. The mechanism responsible for this abnormality may be related to the intrinsic contractility of the muscle, since all of the agonists were affected to about the same degree. On the other hand, stimulation of beta adrenergic sites in aortas from both hypertensive and normotensive rats with isoproterenol produced the classical relaxation. Thus, hypertension in the SHR is not due to the absence of beta receptors in the vascular tree. Reduction of alpha receptor activity plus slight enhancement of beta activity may be a compensatory mechanism to reduce the elevated blood pressure. Other compensatory mechanisms may be operative in the SHR; for example, the biosynthesis and release of catecholamines are reduced (*7*). However, since the tissue response to a nonspecific stimulant, such as KCl, is depressed, it would seem that in the SHR the responsiveness of the muscle itself to contract is reduced rather than there being a specific modification of the alpha and beta receptors. Schild *et al.* (*8*) have shown an interaction between calcium and stimulating agents, such as epinephrine, and relaxing drugs, such as isoproterenol. The calcium content of vascular smooth muscle from SHR may perhaps be altered so that the effect of a stimulating drug is reduced while that of the relaxing agent is enhanced.

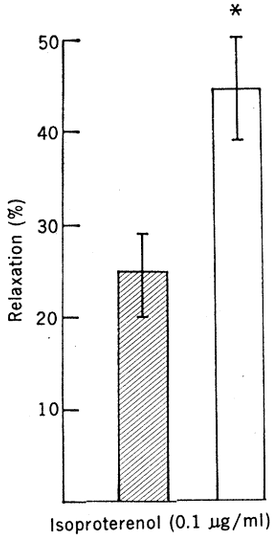

Fig. 2. A comparison of the relaxant beta responses of thoracic aortic strips from four normotensive and seven spontaneously hypertensive rats to isoproterenol. The aortic tissue was made to contract with 3 μg of serotonin per milliliter. Data given as means ± S.E. The asterisk indicates a statistically significant difference, $P < .05$. Shaded bar, normotensive animals; open bar, SHR.

SYDNEY SPECTOR
Roche Institute of Molecular Biology, Nutley, New Jersey 07110
JEROME H. FLEISCH
HARRIET M. MALING
BERNARD B. BRODIE
Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda, Maryland 20014

References and Notes

1. A. N. Brest and J. H. Moyer, *Hypertension—Recent Advances* (Lea and Febiger, Philadelphia, 1961).
2. K. Okamoto and K. Aoki, *Jap. Circ. J.* **27**, 282 (1963).
3. ———, S. Nosaka, M. Fukushima, *ibid.* **28**, 943 (1964).
4. J. R. Williams, T. R. Harrison, A. Grollman, *J. Clin. Invest.* **18**, 373 (1939).
5. R. F. Furchgott and S. Bhadrakom, *J. Pharmacol. Exp. Ther.* **108**, 129 (1953).
6. J. H. Fleisch and H. M. Maling, *Fed. Proc.* **28**, 285 (1969); ———, B. B. Brodie, *Pharmacologist* **11**, 231 (1969).
7. W. J. Louis, S. Spector, R. Tabei, A. Sjoerdsma, *Lancet* **1968–I**, 1013 (1968); *Circ. Res.* **24**, 85 (1969).
8. K. A. P. Edman and H. O. Schild, *J. Physiol. (London)* **169**, 404 (1963); H. O. Schild, *Brit. J. Pharmacol. Chemother.* **31**, 576 (1967).

22 July 1969

Histamine and Spermidine Content in Brain during Development

Abstract. *Histamine concentration in fetal rat brain is high at 17 days gestation but decreases sharply just before birth. Values subsequently increase to a maximum postnatal concentration 5 to 10 days after birth, and then steadily decline to low adult values by time of weaning. Spermidine follows a pattern similar to that of histamine but with a 24- to 48-hour lag. The developmental pattern for histamine in the central nervous system is different from that for other neural amines. It appears that the marked fetal and neonatal changes in brain histamine correlate best with periods of rapid cell proliferation and growth during brain maturation.*

Although histamine occurs in the brain of various species, its function in the central nervous system is unclear. In the brain, histamine is concentrated mainly in the gray matter, and has a regional and subcellular localization analogous to other neural amines having probable transmitter function (*1*). Data obtained from peripheral systems show that increased capacity to form histamine is correlated with periods of greatest mitotic activity in rapidly growing tissues (*2*). The possibility exists that histamine may be involved in growth processes in the central nervous system as well as in neurotransmission. We determined the histamine levels (total histamine, expressed per brain and per gram of brain) in developing rat brain and compared them to levels of other amines and to phases of cell growth and differentiation. Spermidine, which similarly increases in peripheral tissues during rapid growth (*3*), was also measured in developing rat brain.

Sprague-Dawley rats (*4*) obtained at 10 days gestation were kept in individual cages where they gave birth and remained with their litters until the time of weaning. The rats were given free access to water and Purina laboratory chow. All animals were killed by decapitation. To provide a relatively constant sample weight, a varying number of brains were pooled depending on their size. The samples were immediately homogenized in cold 0.4*N* perchloric acid; the homogenate was centrifuged and the supernatant adjusted to *p*H 7.5 with tris(hydroxymethyl)aminomethane. Histamine and spermidine were adsorbed to Amberlite CG-50 (*5*). Columns were then washed with distilled water and eluted with 1*N* HCl. Spermidine was determined by reaction with *o*-phthalaldehyde (*6*). Histamine was extracted from the eluate and assayed by a modification of the method of Anton and Sayre (*7*). The modification entailed the substitution of a potassium phosphate-perchloric acid wash (solution identical to initial extraction media) for the chloroform wash. All samples were read in an Aminco-Bow-

Table 1. Regional changes in histamine during brain development. Each determination represents pooled brain parts from three to five animals of the same litter. Values are expressed as nanograms of histamine per gram of brain.

Brain section	Conceptual age (days)			
	28	32	40	70
Cortex	239	129	47	42
	304		49	44
	286			
Brainstem	172	127	113	94
	188		128	98
	138			
Cerebellum	160	119	56	30
	248		35	32
	195			

man spectrophotofluorometer. Optimal activation and fluorescence occurred at 340 and 420 nm for spermidine and at 350 and 440 nm for histamine. Internal histamine and spermidine standards were run with each analysis.

Histamine concentration in fetal brain was higher at 17 days gestation (earliest time examined) than at any subsequent time, but decreased sharply just before birth. Levels increased to maximum postnatal concentrations 5 to 10 days later and then steadily declined to low adult values by the time of weaning (Fig. 1A). The large fluctuations in perinatal histamine concentration cannot be explained by the small changes in brain weight. The slow decline starting 27 days after conception might appear related to increasing brain weight; however, a similar decline occurs when values are expressed on a per brain basis (Fig. 1B). Six days after birth the concentration of histamine was higher in cortex than in cerebellum or brain stem, but by adulthood this relation was reversed due to a larger decrease in histamine concentration in the cortex (Table 1).

The developmental pattern for histamine in the central nervous system is distinctly different from that for other monoamines. Whereas dopamine (*8*), norepinephrine (*9*), and serotonin (*10*) content steadily increases in brain from late gestation to maturity, histamine content is highest during early development but declines to very low amounts 3 weeks after birth. Similarly, while histamine decreases fivefold at parturition, other neural amines either remain stable during this period or continue to increase.

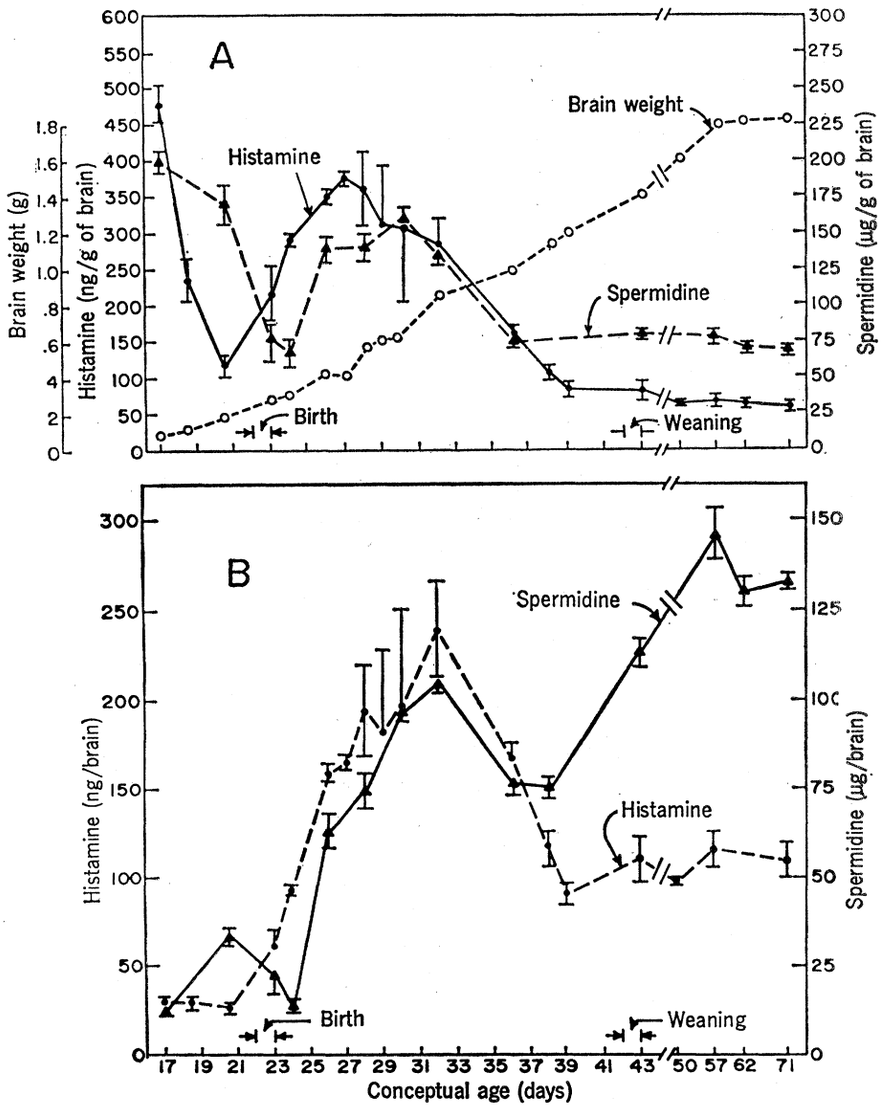

Fig. 1. Histamine and spermidine content in rat brain during development. Each point represents the mean ± S.E.M. of at least five separate determinations. Weight expressed as average wet weight per brain. (A) Variation per gram of brain. (B) Variation per brain.

It would appear that the marked fetal and neonatal fluctuations in brain histamine correlate best with the major periods of proliferation and growth during brain maturation. Histamine concentration is highest in late gestation when neuronal proliferation is maximal (*11*). After birth the rapid increase in brain histamine parallels the accelerated growth of nerve processes (*11*). Histamine levels decline as the overall growth rate subsides. It is interesting that rates of increase in DNA phosphorus and brain weight also peak in developing rat brain 10 days after birth (*12*).

The content of spermidine in brain during development follows the general pattern of histamine content (Fig. 1) but with an apparent 24 to 48 hour lag at points of maximum fluctuation. A number of studies implicate spermidine in nucleic acid metabolism and in rapid cell growth (*3*). Michaelson (*13*) has reported that brain spermidine in the guinea pig is associated with the nuclear fraction and with the fraction corresponding to nerve endings.

Tissue concentrations reflect a balance between synthesis, uptake, binding, and catabolism. Since the major pathway of histamine catabolism is by oxidative deamination (*14*), the absence of histaminase in the fetus (*15*) may contribute to the high concentration of histamine in fetal brain. Histamine is formed by the decarboxylation of histidine. We analyzed brain for histidine decarboxylase (*16*) in rats at 17 days gestation and in adult rats. Fetal liver and adult stomach were also examined. Whereas high activity was found in liver and stomach, no detectable activity was observed in fetal or adult brain. Therefore, the histamine measured in brain may enter from peripheral sites of synthesis. Moreover, the brain during fetal and neonatal development exhibits altered permeability for many substances (*11*). Our studies in neonatal rats show that C^{14}-histamine penetrates readily into brain after subcutaneous administration. After 30 minutes the concentration in the brain is 10 to 30 percent of that in the blood. Thus, higher concentrations of histamine in fetal brain may reflect increased peripheral histamine formation which appears to occur during early development (*17*). However, the potent histaminolytic activity in the placenta

and in maternal plasma during the later half of pregnancy makes it unlikely that the increased brain histamine originates in the mother (*18*).

Our data suggest that histamine and spermidine are involved in processes related to rapid tissue growth in the central nervous system. It would appear that hormonal and other adaptive factors associated with birth and growth may be controlling influences. A further possible role for histamine in neurotransmission, however, cannot be excluded on the basis of present findings.

LARRY A. PEARCE
SAUL M. SCHANBERG
Departments of Neurology and *Pharmacology, Duke University Medical Center* and *Veterans Hospital, Durham, North Carolina 27706*

References and Notes

1. H. M. Adam, in *Regional Neurochemistry*, S. S. Kety and J. Elkes, Eds. (Pergamon Press, London, 1961), p. 293; K. Kataoka and E. de Robertis, *J. Pharmacol. Exp. Ther.* **156**, 114 (1967).
2. G. Kahlson, E. Rosengren, C. Steinhardt, *J. Physiol. (London)* **169**, 487 (1963); G. Kahlson and E. Rosengren, *Experientia* **19**, 182 (1963); C. G. Ahlström, M. Johnston, G. Kahlson, *Life Sci.* **5**, 1633 (1966); M. Johnston and G. Kahlson, *Brit. J. Pharmacol.* **30**, 274 (1967).
3. G. A. Harrison, *Biochem. J.* **25**, 1885 (1931); *ibid.* **27**, 1152 (1933); G. Moruzzi and C. M. Caldarera, *Arch. Biochem. Biophys.* **105**, 209 (1964); H. Shimizu, Y. Kakimoto, I. Sano, *ibid.* **110**, 368 (1965).
4. Sprague-Dawley strain purchased from Blue Spruce Farms, Altamont, N.Y.
5. J. A. Huff, V. E. Davis, H. Brown, *J. Lab. Clin. Med.* **67**, 1044 (1966).
6. Although both spermidine and histamine are present in the column eluate, fluorescence due to histamine is not measurable with histamine concentration as low as that of brain at the dilutions used.
7. A. H. Anton and D. F. Sayre, *J. Pharmacol. Exp. Ther.* **166**, 285 (1969).
8. N. Karki, R. Kuntzman, B. B. Brodie, *J. Neurochem.* **9**, 53 (1962).
9. H. C. Agrawal, S. N. Glisson, W. A. Himwich, *Int. J. Neuropharmacol.* **7**, 97 (1968).
10. D. S. Bennett and N. J. Giarman, *J. Neurochem.* **12**, 911 (1965).
11. A. McIlwain, in *Biochemistry of the Developing Nervous System* (Little Brown, Boston, 1966).
12. J. Dobbing, in *Progress in Brain Research, Brain Barrier Systems*, A. Lajtha and D. H. Ford, Eds. (Elsevier, New York, 1968), vol. 29, p. 417.
13. I. A. Michaelson and P. Z. Coffman, *Biochem. Pharmacol.* **16**, 2085 (1967).
14. S. H. Snyder, J. Glowinski, J. Axelrod, *J. Pharmacol. Exp. Ther.* **153**, 8 (1966).
15. J. B. Dixon, *J. Physiol. (London)* **147**, 144 (1959); M. Roberts and J. M. Robson, *ibid.* **119**, 286 (1953).
16. R. J. Levine and D. E. Watts, *Biochem. Pharmacol.* **15**, 841 (1966).
17. J. M. Telford and G. B. West, *J. Physiol. (London)* **157**, 306 (1961); D. Aures, *Fed. Proc.* **27**, 244 (1968).
18. S. E. Lindell and H. Westling, in *Handbook of Experimental Pharmacology*, O. Eichler and A. Farrah, Eds. (Springer-Verlag, New York, 1966), vol. XVIII/I, p. 734.
19. Supported by NIH grants MH-13688 and NB-06233. L.A.P. is a Research Fellow in Neurology, NB-1804 NINDS. S.M.S. is recipient of Research Scientist Award K5-6489, NIMH. We thank Miss B. Horne and Mrs. A. Draper for technical assistance.

2 June 1969; revised 2 September 1969

Visual Receptive Fields of Neurons in Inferotemporal Cortex of the Monkey

Abstract. *Neurons in inferotemporal cortex (area TE) of the monkey had visual receptive fields which were very large (greater than 10 by 10 degrees) and almost always included the fovea. Some extended well into both halves of the visual field, while others were confined to the ipsilateral or contralateral side. These neurons were differentially sensitive to several of the following dimensions of the stimulus: size and shape, color, orientation, and direction of movement.*

Evidence from neuropsychological, electrophysiological, and anatomical experiments suggests that inferotemporal cortex in the monkey is involved in visual function. Removal of inferotemporal cortex produces a severe impairment in learning visual discriminations but does not affect visual acuity, the integrity of the visual fields, or discrimination learning in other modalities (*1*). Visual evoked responses may be recorded from macroelectrodes on inferotemporal cortex (*2*), and single neurons in inferotemporal cortex are responsive to visual but not auditory stimulation (*3*). Inferotemporal cortex receives afferents from prestriate cortex and from the pulvinar (*4*), and both these structures are known to respond to visual stimuli (*5, 6*). In order to analyze further the role of inferotemporal cortex in vision, we studied the response of single neurons in inferotemporal cortex to presentation of a variety of visual stimuli.

The results presented here are based on seven *Macaca mulatta* weighing 3.4 to 8.2 kg. Two days before the start of recording they were implanted, under aseptic conditions and Nembutal anesthesia, with the base of an Evarts microdrive and with two bolts for subsequent fixation of the head (*7*), and then returned to their home cage. At the start of the recording session, the animals were anesthetized with intravenous Surital for the duration of a tracheotomy and then immobilized with a continuous intravenous infusion of gallamine triethiodide in a solution of 5 percent dextrose in lactated Ringer's (Abbott Laboratories), artificially respired, and anesthetized with a mixture of 30 percent oxygen and 70 percent

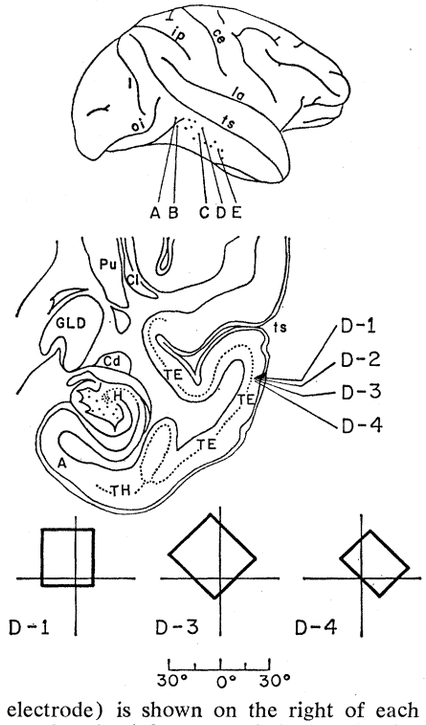

Fig. 1. (Top) Side view of right hemisphere of *Macaca mulatta*. The dots on inferotemporal cortex show approximate site of entry of microelectrode passes. The passes in which the cells with receptive fields illustrated in Figs. 1 to 3 were recorded are designated with the letters *A* to *E*. (Middle) Coronal section through pass *D*, illustrating the approximate locations of cells whose receptive fields are shown below or in Fig. 2. *A*, Allocortex; *ce*, central sulcus; *Cd*, caudate nucleus; *Cl*, claustrum; *GLD*, lateral geniculate body; *H*, hippocampus; *ip*, intraparietal sulcus; *l*, lunate sulcus; *la*, lateral fissure; *oi*, inferior occipital sulcus; *Pu*, putamen; *ts*, superior temporal sulcus; *TA*, *TE*, and *TH* designate cytoarchitectonic areas of von Bonin and Bailey (*9*). (Bottom) Size and position of receptive fields of three neurons recorded on pass *D*. Each rectangle is the largest rectangle oriented parallel or at 45 degrees to the meridians of the visual field, which could be fitted entirely within each receptive field. In each case, the stimuli used to define the field were the most adequate found. The cross in each figure represents the horizontal and vertical meridians of the visual field. The right visual field (which was always ipsilateral to the electrode) is shown on the right of each vertical meridian. All receptive fields shown are for the left eye. Unit D-1, receptive field plotted with 1- by 5-degree blue bar. Unit D-3, plotted with 1- by 5-degree white bar, and 5- by 10-degree dark rectangle. Unit D-4, plotted with 1- by 5-degree white bar. The receptive field for Unit D-2 is shown in Fig. 2. The scale is in degrees of visual angle.