Epinephrine Metabolism in Mammalian Brain after Intravenous and Intraventricular Administration

Abstract. *Epinephrine given intravenously or intraventricularly has a half-life in the brain of the rat of 2 to 2.5 hours. After intravenous administration of the drug the principal route of metabolism is* O*-methylation, whereas after intraventricular administration the principal route is conjugation.*

Depending upon its route of administration, epinephrine (adrenaline) apparently causes various behavioral and physiological effects in the central nervous system (*1*). Although epinephrine has been widely used in studies of the central nervous system, the metabolism or turnover of this compound in mammalian brain has not been investigated. Our findings suggest that it is metabolized with a half-life of under 3 hours and that metabolism varies depending upon the route of administration. The rapid metabolism and enzymatic synthesis of epinephrine in the brain (*2*) suggests that this potent compound may function as a neuroregulatory agent.

Axelrod, Weil-Malherbe, Wilson, and co-workers (*3*) have demonstrated a blood-brain barrier to epinephrine uptake in various areas of the rat brain. These investigators used a correction factor based on the average vascularity of the whole brain and from this they estimated the quantity of residual radioactivity in the vessels. However, our work and that of others (*4*) has shown that regional blood flow in the brain varies markedly. For this reason our data were obtained on animals after isotonic saline was perfused into the cranial vasculature.

Tritiated epinephrine was administered to a series of male rats as described in Table 1. Brain samples from three animals were pooled, and we then homogenized each fraction and performed the procedures of catecholamine metabolite separation of Kopin *et al.* with modifications by Iversen *et al.* (*5*). These procedures accomplish separation of epinephrine and its various metabolites by a combination of aluminum oxide and Dowex column chromatography and organic extraction of certain eluate and effluent fractions. Table 1 compares the amount of H^3-epinephrine recovered in each area 10 minutes after separation. The pineal body and pituitary gland, which are outside the blood-brain barrier, showed the greatest uptake; pineal uptake was approximately ten times greater than pituitary uptake. The hypothalamus showed a greater uptake than the midbrain, brain stem, or cortical regions. These other areas, however, did show definite uptake of the compound.

To compare the pattern of metabolism and turnover of epinephrine after intravenous administration with that after intraventricular administration, animals were given either intravenous H^3-epinephrine as before, or a smaller intraventricular dose of the compound by the technique of Noble *et al.* (*6*). The brains were perfused, dissected, and assayed as described above. Data for both intravenous and intraventricular injections 1 hour after administration were compared (Table 2). After intravenous administration the principal metabolites formed were metanephrine and vanilmandelic acid. Significant amounts of the dihydroxydeaminated catechols, dihydroxyphenylglycol, and dihydroxymandelic acid were formed only after intraventricular administration of epinephrine. After intraventricular injection, the main metabolic pathway in all areas studied is conjugation, in agreement with the results of Schanberg *et al.* (see *7*) for norepinephrine (NE).

Our data suggest that there are marked differences in the metabolic disposition of epinephrine depending upon its route of administration. These alterations in metabolic pathways may reflect varying functional roles for the hormone in the brain. Calculations of the turnover of epinephrine in the whole brain show an approximate half-life of 2.0 hours after intravenous administration and a half-life of 2.5 hours after intraventricular administration (*8*). These values should be considered in physiological and psychological experiments in which the compound is administered.

Substantial amounts of epinephrine are taken up by the pituitary and particularly by the pineal after intravenous

Table 1. Male Simonson rats weighing 300 to 350 g and anesthetized with ether were given 2.10 μg (116 μc) of H^3-epinephrine (New England Nuclear, 10.1 c/mmole) in an isotonic KCl carrier by injection into the femoral vein over 5 minutes. After the injection, the animals were perfused and decapitated, and their brains were removed and dissected. Each value represents the average of three animals.

Tissue	Nanograms of H^3-epinephrine per gram of tissue at 10 minutes
Pineal	37.5
Pituitary	3.18
Hypothalamus	0.306
Mesencephalon + diencephalon	0.212
Pons + medulla	0.204
Cerebral cortex	0.163

Table 2. H^3-epinephrine and its metabolites in the brain of the rat 1 hour after intravenous or intraventricular administration. In both procedures activity is expressed as H^3 disintegrations min^{-1} g^{-1} of tissue fraction. The other values represent the percentages of the total activity present as that metabolic fraction. Each value represents the average for three animals. Male Simonson rats (weighing 250 to 300 g) anesthetized with ether were given H^3-epinephrine either intravenously, as described in Table 1, or by injection into the lateral ventricle in a volume of 10 μl of phosphate buffer (*p*H 7.2). Intraventricular dose was 44 ng, 2.13 μc, of H^3-epinephrine (New England Nuclear, 10.1 c/mmole). E, epinephrine; MN, metanephrine; VMA, vanilmandelic acid; DHM, dihydroxymandelic acid; and DHPG, dihydroxyphenylglycol.

Route of administration	Total activity (dpm/g)	H^3-E (%)	H^3-MN (%)	H^3-VMA (%)	H^3-DHM + H^3-DHPG (%)	H^3-conjugated metabolites (%)
			Pineal			
Intraventricular	5.82×10^5	45.3	12.1	6.25	2.46	19.8
Intravenous	5.50×10^6	82.1	1.24	0.73	0.08	2.46
			Pituitary			
Intraventricular	1.23×10^5	32.4	10.6	9.8	12.6	26.7
Intravenous	2.81×10^5	44.5	17.2	12.4	0.12	6.30
			Whole brain			
Intraventricular	3.26×10^5	41.6	5.4	3.8	2.6	43.8
Intravenous	1.13×10^5	25.7	22.4	25.6	0.04	9.3

administration. After stress, when epinephrine is released from the adrenal medulla, the compound may be taken up by these two neuroendocrine organs and may thus affect function, for example, melatonin or adrenocorticotrophic hormone release (*9*). The ratio of H^3-epinephrine in the pineal to that in the whole brain at either 10 or 60 minutes after intravenous administration was 150:1; after intraventricular injection, the ratio was 2:1 (*10*). This finding raises the question of the ability of the pineal to exchange materials with the cerebral spinal fluid.

Although brain tissue can form epinephrine enzymatically (*2*), the endogenous concentrations of epinephrine in the brain of the rat are low. Bioassay of the hypothalamus suggests that epinephrine constitutes about 4 percent of the NE in the rat, whereas in the cat and the dog the corresponding values are 7 and 14 percent, respectively (*11*). However, turnover rates of the compound may have more relevance to the biologic role of epinephrine in the brain than absolute concentrations of the compound—which may merely be a measure of storage. Because of the limited knowledge about brain epinephrine (difficulties of assay have prevented investigators from studying regional and subcellular distribution), it is not possible to state whether exogenously administered material is handled similarly to endogenous material. Our data indicate that, when given intraventricularly, the half-life of epinephrine in the brain is at least as rapid as that of NE under similar conditions and that epinephrine is handled in a manner metabolically similar to that of intraventricularly administered NE (see *12*).

A great many studies have been conducted on the effects of mood-altering drugs or physiological and psychological states, or both, on brain NE and dopamine. However, there have been no such studies with epinephrine. Since the compound is made and metabolized by the brains of mammals, it is possible that some of the effects thought to be mediated through other catecholamines may be mediated through epinephrine (*13*).

ALAN M. STEINMAN
STANLEY E. SMERIN
JACK D. BARCHAS
Department of Psychiatry, School of Medicine, Stanford University, Stanford, California 94305

References and Notes

1. A. B. Rothballer, *Pharmacol. Rev.* **11**, 494 (1959); U. S. Von Euler, in *Neuroendocrinology*, L. Martini and W. F. Ganong, Eds. (Academic Press, New York, 1967); U. Feldberg, *A Pharmacologic Approach to the Brain from Its Inner and Outer Surface* (Williams and Wilkins, Baltimore, 1963).
2. R. Ciaranello, R. Barchas, G. Byers, D. Stemmle, J. Barchas, *Nature* **221**, 368 (1969); J. Barchas, A. Steinman, S. Smerin, J. Vernikos-Danellis, *Fed. Proc.* **27**, 711 (1968); P. L. McGeer and E. G. McGeer, *Biochem. Biophys. Res. Commun.* **17**, 502 (1964); L. A. Pohorecky, M. J. Zigmond, H. J. Karten, R. J. Wurtman, *Fed. Proc.* **27**, 239 (1968); ———, *J. Pharmacol. Exp. Ther.* **165**, 190 (1969); G. Milhaud and J. Glowinski, *C. R. Hebd. Seances Acad. Sci. Paris* **255**, 203 (1962); R. D. Ciaranello and J. D. Barchas, *Proc. Int. Union Physiol. Sci.* **7**, 87 (1968).
3. H. Weil-Malherbe, J. Axelrod, R. Tomchick, *Science* **129**, 1226 (1959); C. Wilson, A. Murray, E. Titus, *J. Pharm. Sci.* **135**, 1 (1962); J. Axelrod, H. Weil-Malherbe, R. Tomchick, *J. Pharmacol. Exp. Ther.* **127**, 251 (1959).
4. U. Nair, D. Palm, L. Roth, *Nature* **188**, 497 (1960); data obtained in our laboratory with I^{131}-albumin shows that the hypothalamus of the rat has a vascularity significantly higher than the remainder of the brain.
5. I. Kopin, J. Axelrod, E. Gordon, *J. Biol. Chem.* **236**, 2109 (1961); I. Kopin, *Methods Biochem. Anal.* **11**, 247 (1963); L. Iversen, J. Glowinski, J. Axelrod, *J. Pharmacol. Exp. Ther.* **151**, 273 (1966).
6. E. Noble, R. Wurtman, J. Axelrod, *Life Sci.* **6**, 281 (1966).
7. S. Schanberg, J. Schildkraut, G. Breese, I. Kopin, *Biochem. Pharmacol.* **17**, 247 (1968).
8. For the intravenous studies the time points used for the calculations ranged from 10 minutes to 3 hours. For the intraventricular studies the time points ranged from 1 to 6 hours.
9. R. Ciaranello, J. Barchas, J. Vernikos-Danellis, *Life Sci.* **8**, 401 (1969).
10. The ratio compares the disintegrations per minute per gram of tissue which actually represent H^3-epinephrine, that is, (total activity) × (percentage of H^3-epinephrine).
11. L. M. Gunne, *Acta Physiol. Scand.* **56**, 324 (1954); M. Vogt, *J. Physiol. (London)* **123**, 451 (1954).
12. S. Schanberg, J. Schildkraut, I. Kopin, *Biochem. Pharmacol.* **16**, 393 (1967); P. Draskoczy and C. Lyman, *J. Pharmacol. Exp. Ther.* **155**, 101 (1967); J. Glowinski, I. Kopin, J. Axelrod, *J. Neurochem.* **12**, 25 (1965); J. W. Maas and D. H. Landis, *J. Pharmacol. Exp. Ther.* **163**, 147 (1968).
13. J. Barchas, R. Ciaranello, A. Steinman, *Biol. Psychiat.* **1**, 31 (1969).
14. Supported by grants from NASA (NGR 05-020-168), ONR (Nr-102-715), and NIMH (16632 and 13259). J.B. holds NIMH career teacher award MH 10808.

24 March 1969; revised 26 May 1969

Magnetic Observations in Studies of Sea-Floor Spreading

The continuing stream of articles concerning sea-floor spreading suggests that many oceanographic geologists and geophysicists may be generally inexperienced in the use of terrestrial magnetic profiles. Larson and Spiess' report (*1*) illustrates my point. The authors seem to have difficulty explaining what they call "deep magnetics," and they review several hypotheses. In so doing, they introduce two terms which are in exact opposition to years of practical usage. Traditionally, "surface magnetics" refers to variations produced by mineral or rock concentrations near the solid surface of the earth; "deep magnetics" refers to anomalies and variations produced by deeper-buried, broader-dimensioned lithological units within the crust. "Sea surface profile" and "bottom profile" are terms consistent with the vast amount of airborne magnetic data obtained throughout the world over the past 20 years.

In airborne surveying practice, particularly as applied in mineral or petroleum exploration, the profile labeled here "deep magnetics" is a completely expected and normal result. The authors recognize the "proximity effect" (that is, flight altitude), but apparently they do not regard this as unusual or unique.

For example, surveys conducted at 150 m over basalts typically show the pattern observed. Raising the flight altitude to 450 m would show what they term "surface magnetics." Areas of glacial drift show the same features.

However, when such a phenomenon is observed over land, it is not explained in terms of "spreading" or "reversals"; rather, we regard it as a characteristic magnetic signature of recognized lithologic units, regardless of its cause, which is probably related more to conditions at the time of emplacement than to a sequential change of the earth's field.

Before others attempt to interpret this general type of observation, they should acquaint themselves with available aeromagnetic data, both on- and offshore, that will put their conclusions in a perspective dictated by nature's real variability in the "fine" as well as the "large" structure. Although the authors here deal mostly with fine structure, others who attempt to correlate "oceanographic ridges" with other phenomena should inspect the variability in the larger magnetic features found in the earth's field.

WILLIAM C. KELLOGG
Airborne Geophysics Division, Lockwood, Kessler & Bartlett, Inc., Pasadena, California 91101

Reference

1. R. L. Larson and F. N. Spiess, *Science* **163**, 68 (1969).

24 January 1969