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# ENZYMATIC CONVERSION OF NOREPINEPHRINE TO EPINEPHRINE BY THE BRAIN[1]

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ABSTRACT

POHORECKY, LARISSA A., MICHAEL ZIGMOND, HARVEY KARTEN AND RICHARD J. WURTMAN: Enzymatic conversion of norepinephrine to epinephrine by the brain. J. Pharmacol. Exp. Ther. **165**: 190–195, 1969. The epinephrine-forming enzyme phenylethanolamine-N-methyl transferase (PNMT) can be demonstrated in various brain regions of the rat, cat, hen and turtle. The activity of the enzyme is greatest when either norepinephrine or phenylethanolamine is used as its substrate in the olfactory tubercle and olfactory bulb. PNMT activity is elevated in the olfactory tubercle among rats treated with dexamethasone for 7 days. After the injection of $H^3$-norepinephrine into the lateral cerebral ventricle, a large fraction of the amine is converted to $H^3$-epinephrine and stored in the olfactory bulb.

The conversion of norepinephrine to epinephrine is catalyzed by the enzyme phenylethanolamine-N-methyl transferase (PNMT) (Kirshner and Goodall, 1959). Previous reports have indicated that in mammals this enzyme is highly localized within the adrenal medulla. Although low levels of epinephrine-forming activity were demonstrated in the heart and in two of five brainstems studied in rabbits (Axelrod, 1962), no evidence was presented that these organs actually synthesized the amine *in vivo*.

Small amounts of epinephrine (5–15% of the total catecholamine content) have been identified in the mammalian brain using bioassay techniques (von Euler, 1946; Holtz, 1950; Vogt, 1954; Paasonen and Dews, 1958), and somewhat larger proportions of this amine have been found in the chicken brain (Callingham and Cass, 1965). Using fluorescence assays, some investigators (Kovacs and Faredin, 1961; Stupfel and Roffi, 1961; McGeer and McGeer, 1964; Gunne, 1962) found epinephrine in mammalian brains while others (Bertler and Rosengren, 1959; Sano *et al.*, 1960; Shore and Olin, 1958) did not. McGeer and McGeer (1964) observed that a small fraction of the $H^3$-norepinephrine or $C^{14}$-tyrosine injected directly into monkey or cat brainstem and caudate could be recovered as isotopically labeled epinephrine.

As we shall show, the epinephrine-forming enzyme is present in the brains of the turtle, chicken, rat and cat, especially in structures related to olfaction. PNMT activity in the rat olfactory tubercle is elevated after rats are treated with dexamethasone, a synthetic glucocorticoid. The olfactory bulb in this species N-methylates $H^3$-norepinephrine placed in the lateral ventricles and stores the resulting $H^3$-epinephrine.

MATERIALS AND METHODS. $H^3$-norepinephrine (7 c/mmol) and $C^{14}$-adenosylmethionine (50 mc/mmol) were obtained from the New England Nuclear Corporation, Boston, Mass. Thin-layer chromatographic plates (cellulose powder, MN 300) were purchased from the Brinkmann Instruments Company, Westbury, N.Y.

*Animals.* Control and hypophysectomized female Sprague-Dawley rats weighing 200 to 250 g were housed in individual cages in a room maintained at 20°C and illuminated from 6 A.M. to 6 P.M.; Purina chow and water were available *ad libitum*. Other species (mongrel cats, chickens and one turtle) were killed soon after they were received. The rats, chickens and turtle were all killed by decapitation; the cats received a lethal dose of pentobarbital.

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All of the regions of the rat brain were examined for PNMT, but in the other species only selected areas were assayed. Initially, the brain dissections were performed in a cold room; however, no significant differences were observed in PNMT activity when this procedure was carried out at room temperature provided that the brain was kept on ice. After dissection, the tissues were frozen on Dry Ice and stored at −20°C until assay.

*Brain dissection.* Rat brains were divided into eight regions. The olfactory bulbs were severed at the anterior border of the olfactory tubercle. The tubercle was then circumscribed along its ventral surface with a scalpel and pinched off with tweezers. Two transverse cuts were then made through the brain. The first passed through the anterior border of the tubercle, thus separating an area of cerebral cortex. The second passed through the optic chiasm just posterior to the anterior commissure. The brain section between these cuts was further divided into neocortex, a small amount of hypothalamus (*i.e.*, just below the anterior commissure) and septal area. The remaining telencephalon was separated from the brainstem by placing the brain on its ventral surface and peeling the telencephalon from posterior to anterior. The neocortex was separated from the hippocampus along the lateral ventricle and pooled with the frontal neocortex described above. The brainstem was then placed on its dorsal surface. The raised ventral portion of the hypothalamus which surrounds the infundibulum and includes the mammillary bodies and the tuber cinereum was outlined with vertical cuts. A midsagittal cut was made through the hypothalamus, and the tissue was separated along its ventricular surface. The hypothalamus was then removed in two symmetrical portions; the roof of the third ventricle was used as the dorsal boundary and the cuts outlined previously were used as the posterior and lateral limits. Next, the cerebellum was removed from anterior to posterior by transecting the peduncles close to the cerebellum. The remaining brainstem was divided into three parts: thalamus (defined dorsally by the anterior border of the colliculi and ventrally by the previous hypothalamic cut), mesencephalon (including the colliculi on its dorsal surface and bounded ventrally by the anterior border of the pons) and the pons-medulla. The same landmarks were used in dissecting the brains in the other species.

*PNMT assay.* For the enzyme assay, tissue samples were weighed, homogenized in 1 ml of cold water (4 ml for cerebral cortex) and centrifuged at 100,000 × *g* for 30 min. A 100-μl aliquot of the supernatant fluid was mixed with 100 μg of norepinephrine bitartrate or phenylethanolamine (Wurtman *et al.*, 1967), 1 mμmol of S-adenosylmethionine-$C^{14}H_3$ and 10 μmol of pH 7.9 phosphate buffer in a final volume of 500 μl. After this mixture was incubated for 30 min at 37°C, the enzymatic reaction was stopped by the addition of 200 μl of 1 N hydrochloric acid, and the epinephrine-$C^{14}$ formed was extracted into butanol, as described previously by Axelrod (1962). The radioactivity in 2-ml aliquots of the washed organic phase was measured in a liquid scintillation spectrophotometer, using a naphthalene–dioxane phosphor. Catechol-O-methyltransferase (COMT) activity was assayed as described by Wurtman and Axelrod (1966).

All enzyme assays were run in duplicate; zero-time incubations were used as blanks to estimate the radioactivity contributed by the small amount of unchanged S-adenosylmethionine-$C^{14}$ which is extracted into butanol.

*Chromatography of catecholamines.* Epinephrine and norepinephrine were separated by thin-layer chromatography. Aliquots (10–25 μl) of the supernatant fluid obtained from perchloric acid extracts of brain regions were spotted on cellulose plates, along with $H^3$-catecholamine standards that had been mixed with brain supernatants from untreated animals. Unlabeled epinephrine, norepinephrine, normetanephrine and, in some experiments, dihydroxymandelic acid (DHMA) and dihydroxyphenyl glycol (DHPG) were also co-chromatographed with each plate. After drying, the plates were developed in a phenol-water mixture (8:2, w/w) for 4 hr (Choulis, 1967). The spray described by Schneider and Gillis (1965) was used for developing the unlabeled catecholamines and metanephrines, and the resulting fluorescent compounds were made visible under ultraviolet light. The regions of the plates that contained radioactive material were then divided into 10 equal sections with the origin at the second and the front at the ninth. Each section was eluted with 200 μl of 0.1 N hydrochloric acid and its radioactivity was measured as described above.

RESULTS. *Regional distribution of PNMT in the rat brain.* The rat brain was divided into eight regions, as described in METHODS. PNMT activity was unevenly distributed throughout the brain (tables 1 and 2). When norepinephrine was used as its substrate, the highest enzyme activity was found in the olfactory area, especially in the olfactory tubercle (39.7 ± 4.7 mμmol/g/hr). In the olfactory bulb, the activity was 22.0 ± 0.7 mμmol/g/hr; because the bulb weighed much more than the tubercle,

its total epinephrine-forming activity was higher.

The same regional distribution of PNMT activity was found whether norepinephrine or phenylethanolamine was used as the substrate in the enzyme assay. With phenylethanolamine, enzyme activity was greatest in the olfactory tubercle (21.0 ± 2.0 mμmol/g/hr) and olfactory bulb (20.2 ± 1.5 mμmol/g/hr) (table 2). Some PNMT activity could be detected with both substrates in all of the brain regions studied.

The use of norepinephrine as substrate resulted in the formation of more $C^{14}$-labeled product than did phenylethanolamine (table 2). Previous studies had indicated that phenylethanolamine was at least as good a substrate for PNMT as norepinephrine (Wurtman *et al.*, 1968). This discrepancy could have resulted from several factors: 1) PNMT has been shown to exist in at least two molecular forms (Wurtman *et al.*, 1968); it is possible that some forms of the enzyme preferentially methylate its physiologic substrate, norepinephrine. 2) It was possible that some of the methylated product produced when norepinephrine was used as substrate might have been normetanephrine, formed through the action of COMT, and not epinephrine. To determine whether the distribution of brain COMT was similar to that of PNMT, brain regions were assayed for the formation of $C^{14}$-labeled product using phenylethanolamine, norepinephrine alone or norepinephrine fortified by the addition of magnesium (table 2). The latter assay indicated that COMT is distributed in the rat brain more or less evenly; hence, the selective localization of PNMT to olfactory structures is not an artifact resulting from the formation of normetanephrine.

Further evidence that the radioactive product formed by incubating brain supernatants with norepinephrine was not the O-methylated derivative, $C^{14}$-normetanephrine, was obtained by chromatographing the butanol extracts in a thin-layer system (phenol–$H_2O$, 8:2, w/w). Essentially all of the radioactivity beyond the origin had the same $R_f$ as authentic epinephrine.

*Regional distribution of PNMT in the brains of the other species.* The distribution of PNMT was also investigated in brains from cats, chickens and one turtle. In general, the same pattern of distribution was found in all of the species studied (table 3): the highest enzyme concentration was always found in the olfactory tubercle or bulb.

*Effects of hypophysectomy or dexamethasone treatment on PNMT activity in the rat brain.* PNMT is induced in the mammalian adrenal medulla by adrenocortical steroids (Wurtman and Axelrod, 1965, 1966) which are preferentially delivered to the medulla in high concentrations (Wurtman, 1966). To determine

TABLE 1

*Regional distribution of phenylethanolamine-N-methyl transferase activity in rat brain*

| Region | Weight | No. of Rats | PNMT Activity |
|---|---|---|---|
| | *mg* | | *units*[a] |
| Olfactory tubercle | 30.7 ± 5.4 | 4 | 39.7 ± 4.7 |
| Olfactory bulb | 80.6 ± 5.7 | 10 | 22.0 ± 0.7 |
| Pons-medulla | 205.2 ± 4.3 | 3 | 12.6 ± 1.3 |
| Septum | 170.0 ± 12.6 | 5 | 12.5 ± 1.1 |
| Hypothalamus | 55.7 ± 8.3 | 5 | 10.2 ± 1.8 |
| Cerebral cortex | 660.2 ± 11.6 | 2 | 9.0 ± 0.8 |
| Hippocampus | 131.9 ± 8.6 | 5 | 8.5 ± 0.8 |
| Cerebellum | 276.1 ± 8.5 | 5 | 7.9 ± 0.4 |

[a] One unit of PNMT activity equals 1 mμmol of $C^{14}$-epinephrine formed from norepinephrine and $C^{14}$-S-adenosylmethionine per gram of tissue per hour. Data are expressed as mean ± standard error.

TABLE 2

*Methylation of amines by $C^{14}$-S-adenosylmethionine*[a]

| Region | Amount of $C^{14}$-Product Formed with: | | |
|---|---|---|---|
| | Phenylethanolamine | Norepinephrine | Norepinephrine + Magnesium |
| | *mμmol/g/hr* | | |
| Olfactory tubercle | 21.0 ± 2.0 | 30.6 ± 3.2 | 59.5 ± 10.2 |
| Olfactory bulb | 20.2 ± 1.5 | 26.7 ± 9.0 | 72.2 ± 4.3 |
| Brainstem | 9.3 ± 0.1 | 14.7 ± 1.4 | 59.0 ± 5.1 |
| Hypothalamus | 10.9 ± 2.6 | 10.3 ± 1.2 | 48.7 ± 12.1 |
| Cerebral cortex | 5.6 ± 0.3 | 10.3 ± 1.5 | 44.2 ± 4.2 |
| Hippocampus | 6.2 ± 0.1 | 10.6 ± 0.6 | 43.0 ± 8.1 |
| Cerebellum | 6.3 ± 0.5 | 8.2 ± 0.6 | 55.7 ± 7.9 |

[a] Aliquots of the supernatant fluid obtained from brain regions of four rats were incubated with phenylethanolamine, norepinephrine or norepinephrine and magnesium as described in METHODS. Data are expressed as mean ± standard error.

whether PNMT in the brain was dependent upon circulating glucocorticoids, its activity was measured in the several brain regions of rats whose adrenocortical function had been depressed by hypophysectomy performed 12 days previously. Although adrenal PNMT activity decreased considerably in these animals (from 3.91 ± 0.35 to 1.78 ± 0.40 mμmol/gland/hr), no change was observed in brain PNMT activity among any of the regions investigated (table 4).

To examine the possibility that brain PNMT activity might be enhanced by elevated blood corticoid levels, we gave unoperated rats dexamethasone (1 mg/kg/day) i.p. for 7 days, after which PNMT activity was measured in the olfactory structures. PNMT activity was significantly elevated (by 36%) in the olfactory tubercle by this treatment (table 4).

*In vivo synthesis of epinephrine from norepinephrine in the olfactory area.* To determine whether the olfactory structures could actually synthesize epinephrine from norepinephrine *in vivo*, we injected 50 μc of $H^3$-norepinephrine into the lateral ventricles of three rats (Noble *et al.*, 1967); the $H^3$-catecholamines were subsequently extracted from these tissues. Animals were sacrificed by decapitation 1 hr after receiving the norepinephrine. The olfactory bulb and tubercle were removed, homogenized in 1 ml of 0.4 N perchloric acid and centrifuged at 100,000 × *g*, and aliquots of the supernatant fluid were counted or chromatographed as described above. Peaks of radioactivity corresponding to norepinephrine ($R_f$ = 0.35) could be demonstrated in extracts of both olfactory bulb and tubercle (table 5). However, a clear epinephrine peak ($R_f$ = 0.79) was found only in the olfactory bulb. About 20% of the total radioactivity was located between the regions corresponding to norepinephrine and epinephrine; its $R_f$ was similar to that of authentic normetanephrine ($R_f$ = 0.66) (table 5).

The remaining supernatant fluids were pooled for each of the regions. The catecholamines were extracted using an alumina column (Whitby *et al.*, 1961), and aliquots of the effluents and eluates were counted or chromatographed. Most of the radioactivity in the effluents was found in the area corresponding to normetanephrine. In the eluate from the olfactory tubercles, most of the radioactivity (50%) was found in the norepinephrine area; however, a small peak (10%) had the same $R_f$ as authentic $H^3$-epinephrine (table 5). In the eluate from the olfactory bulbs, sharp peaks of radioactivity were found in the areas corresponding

TABLE 3

*Regional distribution of PNMT activity in brains of various species*[a]

| Region | Distribution of Activity in: | | |
|---|---|---|---|
| | Cat | Chicken | Turtle |
| | *units* | | |
| Olfactory bulb | 5.3 (3.7-6.9) | 35.7 (17.4-64.4) | 6.6 |
| Olfactory tubercle | 16.8 (16.8) | | |
| Hypothalamus | 9.2 (8.2-10.1) | | 4.0 |
| Hippocampus | 2.7 (2.0-3.3) | 12.9 (10.3-15.4) | |
| Pons-medulla | 4.6 (4.1-5.0) | 10.1 (7.2-14.4) | |
| Cerebral cortex | 2.9 (2.7-3.1) | | |
| Telencephalon | | 6.8 (4.0-11.2) | 5.7 |
| Cerebellum | 6.9 (5.9-7.9) | 5.5 (4.7-6.0) | 3.0 |
| Thalamus | 5.5 (5.1-5.9) | | |
| Mesencephalon | 7.3 (5.9-8.8) | | |
| Thalamus-mesencephalon | | 8.6 (5.3-10.0) | |

[a] Brains were examined from two cats, three chickens and one turtle. One unit of PNMT activity equals 1 mμmol of $C^{14}$-epinephrine formed from norepinephrine and $C^{14}$-S-adenosylmethionine per gram of tissue per hour. Results are given as mean, with range in parentheses.

TABLE 4

*Effect of hypophysectomy or treatment with dexamethasone on PNMT activity in rat brain*[a]

| Region | Activity after Treatment | | |
|---|---|---|---|
| | Control | Hypophysectomy | Dexamethasone |
| | *units* | | |
| Olfactory tubercle | 46.8 ± 3.8 | 54.0 ± 9.8 | 63.5 ± 2.7[b] |
| Olfactory bulb | 22.0 ± 0.8 | 21.2 ± 1.4 | 19.9 ± 0.3 |

[a] Groups of five animals were hypophysectomized or treated with dexamethasone (1 mg/kg/day) or a placebo. Twelve days after hypophysectomy or 7 days after the start of dexamethasone treatment, the animals were killed and their brains dissected and assayed for PNMT activity. One unit of enzyme activity equals 1 mμmol of $C^{14}$-epinephrine formed from norepinephrine and $C^{14}$-S-adenosylmethionine per gram of tissue per hour.

[b] Dexamethasone-treated group differs from control animals, $P < .02$.

TABLE 5

*Synthesis of $H^3$-epinephrine in olfactory structures*

| Compound | $R_f$[a] | Whole Supernatant | | Alumina Eluate | | Effluent | |
|---|---|---|---|---|---|---|---|
| | | Olfactory tubercle | Olfactory bulb | Olfactory tubercle | Olfactory bulb | Olfactory tubercle | Olfactory bulb |
| | | %[b] | | %[b] | | %[b] | |
| Epinephrine | 0.73 | 3 | 26 | 10 | 30 | | |
| Normetanephrine | 0.66 | 18 | 18 | | | 27 | 22 |
| Norepinephrine | 0.35 | 41 | 30 | 51 | 33 | | |

[a] The $R_f$ for each pure compound was the same using either unlabeled material or labeled amine mixed with tissue supernatant fluids from untreated animals.

[b] Percentage of total radioactivity in supernatant, eluate or effluent.

to both epinephrine and norepinephrine (30% and 33%, respectively) (table 5).

To rule out the possibility that the radioactive peak thought to be epinephrine actually represented deaminated catechols also eluted from the alumina columns, authentic DHMA and DHPG were co-chromatographed along with unlabeled or radioactive epinephrine and norepinephrine in the above solvent system. The $R_f$'s of both DHMA and DHPG were 0.36 and 0.64, respectively; that of epinephrine was 0.79.

Discussion. The studies described in this report indicate that, although PNMT activity is highly concentrated in the adrenal medulla, significant amounts of the enzyme are also present in brains of certain mammals, birds and reptiles. It has previously been shown that the brain of an amphibian, *Rana pipiens*, contains large amounts of PNMT. The enzyme in the frog is widely distributed but does not appear to be induced by glucocorticoids (Wurtman *et al.*, 1968). The increase in PNMT activity in rat brains after treatment with dexamethasone suggests that the enzyme in mammalian brain is like mammalian adrenal PNMT in that it can be induced by adrenocortical steroids.

The distribution of brain PNMT in the cat, rat, chicken and turtle is nonhomogeneous; highest activity is present in the olfactory tubercle or olfactory bulb among all of these species. Endogenous epinephrine has not yet been identified in mammalian olfactory structures. However, these tissues are known to contain norepinephrine (Dalström *et al.*, 1965; Valzelli and Garatini, 1968), and our experiments indicate that they are able to convert norepinephrine to epinephrine and to store the resulting amine. Thus, the possibility that epinephrine might function as a neurotransmitter in mammalian olfactory structures should be considered. There is evidence that epinephrine serves this function in the amphibian brain; Segura and Biscardi (1967) have found that electrical stimulation of the spinal roots reduces the epinephrine content in the olfactory bulbs of the toad.

It has previously been shown that ovarian hormones influence norepinephrine biosynthesis in the rat brain (Anton-Tay and Wurtman, 1968). Our studies suggest that adrenocortical hormones also modify brain catecholamine metabolism.

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