Neurophysiol. **25**, 56 (1962)] showed PIR in an overstretched crayfish stretch receptor. E. R. Kandel and W. A. Spencer [*ibid.* **24**, 243 (1961)] demonstrated PIR following synaptic inhibition in hippocampal neurons of cats, and E. R. Kandel, W. T. Frazier, and H. Wachtel [*ibid.* **32**, 496 (1969)] showed similar bursts in *Aplysia* neurons. Postinhibitory rebound is a synonym for postanodal exaltation (PAE), a term used by P. Anderson and J. C. Eccles [*Nature (Lond.)* **196**, 645 (1962)], and is often treated as a synonym for the anodal break response analyzed in squid axons by A. L. Hodgkin and A. F. Huxley [*J. Physiol. (Lond.)* **116**, 497 (1952)]. Cellular mechanisms and early work are reviewed by T. Narahashi [*J. Cell. Comp. Physiol.* **64**, 73 (1964)]. P. G. Sokolove [*Biophys. J.* **12**, 1429 (1972)] discusses a possible mechanism for PIR in tonically active cells.

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10. Note the paradoxical effect of inhibition in increasing the rate of alternation.
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Brain Catechol Synthesis: Control by Brain Tyrosine Concentration

Abstract. *Brain catechol synthesis was estimated by measuring the rate at which brain dopa levels rose following decarboxylase inhibition. Dopa accumulation was accelerated by tyrosine administration, and decreased by treatments that lowered brain tyrosine concentrations (for example, intraperitoneal tryptophan, leucine, or parachlorophenylalanine). A low dose of phenylalanine elevated brain tyrosine without accelerating dopa synthesis. Our findings raise the possibility that nutritional and endocrine factors might influence brain catecholamine synthesis by controlling the availability of tyrosine.*

The rate at which the rat brain synthesizes serotonin varies with its tryptophan concentration (*1*); this, in turn, depends upon the ratio of the plasma tryptophan concentration to the sum of the concentrations of other neutral amino acids that compete with tryptophan for transport into the brain (*2*). The administration of insulin to, or the consumption of carbohydrates by, fasting rats increases this plasma ratio, and thereby accelerates brain serotonin synthesis (*2, 3*); in contrast, the consumption of high-protein rat chow elevates neither the plasma ratio nor the concentration of the indoleamine neurotransmitter in the brain (*2*).

There is abundant evidence that treatments that increase the physiological activity of catecholamine-containing cells cause parallel changes in the activity (*4*), and, ultimately, the concentration (*5*) of the enzyme tyrosine hydroxylase. Such evidence supports the concept that the rate-limiting factor controlling brain catecholamine synthesis can be tyrosine hydroxylase activity. We now present evidence that treatments which increase or decrease brain tyrosine concentrations can produce parallel changes in the rate at which the brain synthesizes catechols. Since the published Michaelis constant (K_m) for tyrosine of the tyrosine hydroxylase in brain homogenates [0.14 m*M* for whole rat brain (*6*), and 0.1 m*M* for sheep caudate nuclei (*7*)] appears to be high relative to brain tyrosine concentrations [approximately 0.08 m*M* (Table 1)], our data suggest that brain tyrosine concentration constitutes an additonal factor controlling catechol synthesis.

Brain catechol synthesis was estimated by measuring the accumulation of dopa during the hour after administration of the decarboxylase inhibitor RO4-4602 (*8*). We found that a dose of 800 mg/kg caused brain dopa concentrations to rise linearly for at least 1 hour, from unmeasurably low levels to approximately 250 ng/g. This treatment also elevated brain tyrosine by 20 to 40 percent, but had no significant effect on brain dopamine or norepinephrine concentrations during the interval examined.

Table 1. Effect of tyrosine or tryptophan administration on accumulation of dopa in rat brain. Rats received the decarboxylase inhibitor RO4-4602 (800 mg/kg intraperitoneally) and, after 15 minutes, tyrosine or tryptophan (50 mg/kg, intraperitoneally) or their diluent; they were killed 1 hour after the first injection. Data are given as means ± standard errors.

Treatment	Tyrosine (μg/g)	Dopa (ng/g)	*N*
None	14.7 ± 0.46	250 ± 10	28
Tyrosine	26.6 ± 0.80*	283 ± 10†	20
Tryptophan	12.1 ± 0.40*	170 ± 18*	10

* Differs from control, $P < .001$. † Differs from controls, $P < .05$.

Male rats, weighing 150 to 175 g (Charles River Breeding Laboratories), were given free access to a 26 percent protein diet (Charles River rat and mouse formula) and water and maintained under light (Vita-Lite, Duro-Test Co., North Bergen, N.J., 300 μw/cm^2) between 8:00 a.m. and 8:00 p.m. daily. In most experiments groups of rats were injected intraperitoneally with a solution of RO4-4602 between 10:00 a.m. and 11:00 a.m., and then were given injections of various amino acids or their diluent 15 minutes thereafter. The rats were killed 60 minutes after the first injection. Brains were weighed and assayed for tyrosine (*9*), dopa (*10*), and, in some cases, dopamine (*11*) and norepinephrine (*12*). Dopa concentrations were corrected for column recoveries averaging 72 percent.

The administration of a low dose (50 mg/kg) of tyrosine caused, after 45 minutes, an 81 percent increase in brain tyrosine and a 13 percent increase in the accumulation of dopa ($P < .05$) (Table 1). The same dose of tryptophan caused an 18 percent fall in brain tyrosine and a 32 percent decrease in dopa accumulation ($P < .001$). The failure of brain dopa accumulation to rise or fall as a linear function of tyrosine concentration after the administration of tyrosine or tryptophan suggests that the effects of one or both of these treatments on tyrosine hydroxylation involved more than simply changing the brain tyrosine concentration (for example, tryptophan might have inhibited tyrosine hydroxylase).

Brains of rats given leucine (100 mg/kg intraperitoneally), another neutral amino acid believed to be in the same transport group as tyrosine (*13*) contained significantly less tyrosine and dopa than the controls (Table 2); in contrast, the administration of similar doses of histidine, alanine, or lysine affected neither brain tyrosine nor the accumulation of brain dopa (Table 2).

A low dose of phenylalanine (50 mg/kg) elevated brain tyrosine without significantly accelerating dopa synthesis; a larger dose (100 mg/kg) failed to modify brain tyrosine, and also slowed the accumulation of dopa ($P < .01$). The dissociation between brain tyrosine concentration and dopa synthesis seen in animals given phenylalanine may reflect competition between tyrosine and phenylalanine for tyrosine hydroxylase (*14*); the biphasic effect of the two phenylalanine doses on brain tyrosine most likely results from two competing phenomena, that is, increased concentration of tyrosine in the plasma (caused by the conversion of phenylalanine to tyrosine, primarily in the liver), and competition between plasma phenylalanine and tyrosine for a common brain uptake mechanism (*13*). The injection of parachlorophenylalanine (PCPA) (300 mg/kg), a drug frequently used to inhibit tryptophan hydroxylase activity and serotonin synthesis, profoundly depressed both brain tyrosine and the accumulation of dopa ($P < .001$) (Table 2). This observation suggests that PCPA must be used with caution as an experimental tool in short-term studies requiring the selective suppression of serotonin biosynthesis.

These observations demonstrate that the rate at which catecholamine-containing neurons synthesize their neurotransmitter probably depends not solely on the activity of the enzyme tyrosine hydroxylase, but also on the availability of the precursor amino acid, tyrosine. Further studies will be needed to determine the relative importance of hydroxylase activity and tyrosine concentration in mediating the changes in catecholamine synthesis rate that may be occasioned by particular physiologic circumstances.

Table 2. Effects of various amino acids on accumulation of dopa in rat brain. Groups of seven to nine rats received the amino acid intraperitoneally 15 minutes after RO4-4602 (800 mg/kg, intraperitoneally) and 45 minutes before they were killed. Control rats received saline instead of the amino acid, and then the decarboxylase inhibitor. Data are given as percentages of controls ± the standard errors.

Treatment	Dose (mg/kg)	Tyrosine (%)	Dopa (%)
Leucine	100	78 ± 7*	75 ± 5†
Histidine	100	94 ± 3	99 ± 4
Alanine	100	104 ± 3	101 ± 5
Lysine	100	96 ± 2	99 ± 5
Phenylalanine	50	128 ± 7*	114 ± 8
Phenylalanine	100	103 ± 3	80 ± 5*
PCPA	300	53 ± 1†	48 ± 3†

* Differs from control means, $P < .01$. † Differs from control means, $P < .001$.

Our data suggest the following hypotheses concerning the conversion of tyrosine to catechols in mammalian brain: (i) The tyrosine concentrations of homogenates of whole brain do provide a good index of the size of the tyrosine pool actually available for conversion to catechols, inasmuch as tyrosine concentrations in whole brain are roughly predictive of brain catechol synthesis. (ii) Pathologic states that cause selective increases in the plasma concentrations of neutral amino acids (for example, phenylketonuria) may suppress brain catechol synthesis by lowering brain tyrosine concentrations (Table 2). (iii) The administration of any neutral amino acid other than the catecholamine precursors tyrosine and dopa might be expected to suppress catecholamine synthesis, just as the administration of any neutral amino acid other than tryptophan or 5-hydroxytryptophan (5-HTP) should suppress serotonin synthesis (by lowering brain tryptophan). Hence the physiologic and behavioral consequences of such amino acid drugs as PCPA, 5-HTP, and α-methyl-*p*-tyrosine can only tentatively be attributed to actions on specific populations of monoaminergic neurons. (iv) Catecholamine-containing brain neurons, like serotoninergic neurons (*1*), may participate in the mechanism by which the brain monitors the plasma amino acid pattern and the nutritional state.

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