Control of brain monoamine synthesis by diet and plasma amino acids[1,2,3]

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ABSTRACT The rates at which monoaminergic neurons in rat brains synthesize their neurotransmitters depend on the availability of the amino acid precursors tryptophan (for serotonin) and tyrosine (for dopamine and norepinephrine). The administration of tryptophan, the injection of insulin, or the consumption of a single protein-free high-carbohydrate meal all elevate brain tryptophan levels and, soon thereafter, the levels of serotonin and its major metabolite 5-hydroxyindole acetic acid. The addition of protein to the meal suppresses the increases in brain tryptophan and serotonin, because protein contributes to plasma considerably larger amounts of the other neutral amino acids (e.g., leucine, phenylalanine) than of tryptophan, and these other amino acids compete with tryptophan for uptake into the brain. The elevation of brain tyrosine (by injection of the amino acid or consumption of a single 40% protein meal) accelerates brain catecholamine synthesis, as estimated by measuring brain dopa accumulation after decarboxylase inhibition, or brain catecholamine accumulation after inhibition of monoamine oxidase. These observations suggest that serotonin- and catecholamine-containing brain neurons are normally under specific dietary control. *Am. J. Clin. Nutr.* 28: 638–647, 1975.

Mammalian brains employ as neurotransmitters three primary monoamines synthesized from the amino acids, tyrosine and tryptophan: they are the catecholamines dopamine and norepinephrine, and the indoleamine serotonin. Studies summarized in this report show that food consumption, by determining the concentrations of tryptophan and tyrosine in the brain, physiologically controls the rates at which serotoninergic catecholaminergic neurons produce their neurotransmitters (1, 2).

The tyrosine in brain neurons (3) can derive from the circulation, the breakdown of brain proteins, or possibly, the intraneuronal hydroxylation of brain phenylalanine (which may be catalyzed by tyrosine hydroxylase (4)) (Fig. 1). Circulating tyrosine derives either from dietary protein, i.e., as tyrosine, or as phenylalanine, which is converted to tyrosine through the action of hepatic phenylalanine hydroxylase, or from the outward flux of free tyrosine from tissue pools. This flux is controlled by hormones such as insulin, which facilitates the uptake of most amino acids into skeletal muscle and certain other tissues, thereby decreasing their plasma concentrations. The mechanism that controls tyrosine and tryptophan flux between the brain and the extracellular fluid apparently differs from that operating in most other tissues, in that this flux is primarily controlled not by direct effects of insulin or other hormones on neurons, but by competition with other neutral amino acids for a common transport system (5–7). This competition is described in greater detail below.

Tryptophan, an essential amino acid, cannot be made in the body: hence brain tryptophan can originate only from the lysis of brain proteins and from circulating tryptophan derived from the diet or from other tissue pools (3) (Fig. 2). Both tyrosine and tryptophan are utilized within brain neurons to form peptides and proteins, as well as for monoamine syn-

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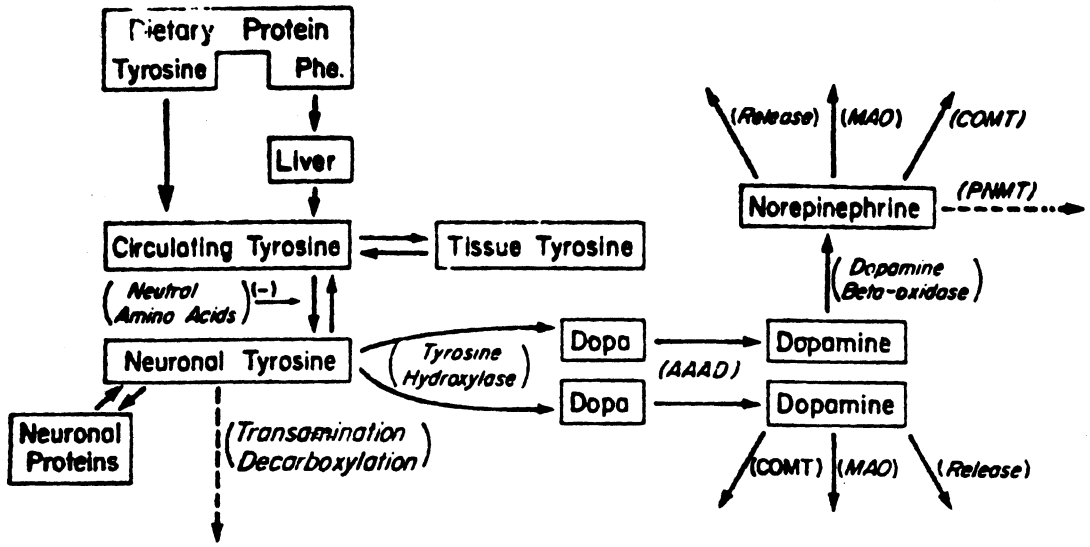

FIG. 1. Control of catecholamine synthesis in brain neurons. Phe. = phenylalanine, MAO = monoamine oxidase, COMT = catechol-*O*-methyl transferase, PNMT = phenylethanolamine-*N*-methyl transferase, AAAD = aromatic L-amino acid decarboxylase, - - - - indicates unproved pathway.

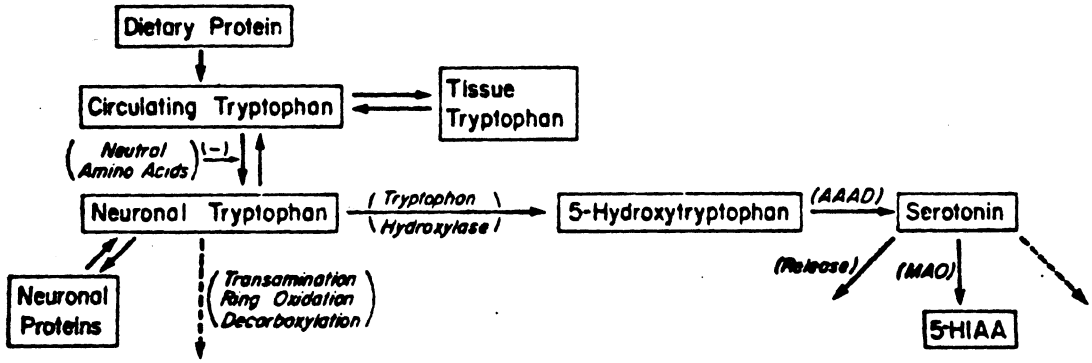

FIG. 2. Control of serotonin synthesis in brain neurons. AAAD = aromatic L-amino acid decarboxylase, MAO = monoamine oxidase, - - - - indicates unproved pathway.

thesis; both compounds may also be decarboxylated or transaminated to a minor extent (8).

Biosynthetic pathways for brain monoamines

The initial steps in the biosynthesis of the catecholamines and serotonin involve the hydroxylations of tyrosine and tryptophan to form the corresponding amino acids dihydroxyphenylalanine (dopa) and 5-hydroxytryptophan (5-HTP) (Figs. 1 and 2). These reactions are catalyzed by two distinct enzymes, tyrosine hydroxylase and tryptophan hydroxylase, which are highly localized within catecholamine-producing and serotonin-producing cells, respectively. Both enzymes utilize a reduced pteridine as a cofactor (4, 9). Catecholamines can compete with this cofactor for attachment to a binding site on the tyrosine hydroxylase molecule, and may thereby inhibit the hydroxylation of tyrosine in vivo (10); serotonin apparently does not compete for this site, and thus does not suppress its own biosynthesis by end-product inhibition. Dopa and 5-HTP are then decarboxylated to form the corresponding monoamines dopamine and serotonin (Figs. 1 and 2). It is generally believed that the decarboxylations of both substrates are catalyzed by a single enzyme, aromatic L-amino acid decarboxylase (11); however the finding that intracisternal 6-hydroxydopamine selec-

tively decreases the ability of brain homogenates to decarboxylate dopa, but not 5-HTP (12), has caused this view to be questioned. Neither dopa nor 5-HTP is normally found in significant concentrations within mammalian brain, hence their decarboxylations must be very rapid, even though their tissue concentrations are well below the K_m of the decarboxylating enzyme or enzymes (11). Some brain neurons utilize dopamine as their neurotransmitter; in others, containing the enzyme dopamine β-oxidase, dopamine is simply an intermediate in the biosynthesis of norepinephrine, their true neurotransmitter. Phenylethanolamine-*N*-methyl transferase (PNMT), the enzyme that catalyzes the conversion of norepinephrine to the hormone epinephrine within the adrenal medulla, has also been identified in mammalian brain (13); it is therefore possible that epinephrine might also function as a catecholamine neurotransmitter in the brain.

Control of monoamine synthesis by brain amino acid concentrations

It is widely recognized that the rates at which brain neurons synthesize monoamine neurotransmitters can be controlled by the activities of the hydroxylase enzymes. Various types of evidence tend to support this view: for example, short-term increases in the physiological activity of catecholaminergic neurons, caused by direct electrical stimulation (14, 15) or by drug- or stress-induced changes in presynaptic activity (16), can accelerate the conversion of labeled tyrosine to a catechol, possibly by decreasing the end-product inhibition of tyrosine hydroxylase by norepinephrine. Longer periods of enhanced presynaptic input increase the activities of tyrosine hydroxylase (17) and tryptophan hydroxylase (18) measured in vitro, and may also increase the rate of formation of the tyrosine hydroxylase enzyme protein, as assayed immunochemically (19).

We have been interested in the possibility that monoamine synthesis might depend not only on the amounts or activities of rate-limiting enzymes, but also on the tissue concentrations of their amino acid precursors. A series of experiments described below has led us to conclude that the major physiological factor that normally controls the rate at which serotonin-containing brain neurons synthesize their neurotransmitter is the availability of tryptophan; indeed, the functional significance of these neurons may derive from their ability to serve as "sensors," which couple serotonin synthesis to brain tryptophan level and, thereby, to the pattern of amino acids in the plasma. More recent studies suggest that brain tyrosine levels may also affect the rate at which brain neurons synthesize catecholamines.

Brain tryptophan and serotonin synthesis

Our interest in the possibility that amino acid availability might affect monoamine synthesis arose initially from observations on temporal changes in plasma amino acid concentrations. We found that if plasma samples were collected from untreated humans or rats at various times of day or night, their concentrations of tryptophan and of most other amino acids fluctuated characteristically during each 24-hour period (20, 21). Among human subjects who ate three meals per day, tryptophan levels were lowest at 2–4 AM, and rose by 50–80% to attain a plateau in the late morning or early afternoon. In rats, the daily nadir and peak occurred 8–10 hours later (22); a difference consistent with the nocturnal feeding behavior of this species. The plasma amino acid rhythms were shown not to be generated simply by the cyclic ingestion of dietary protein, inasmuch as they persisted in human volunteers who ate essentially no protein for 2 weeks (21). Subsequent studies by others showed that the rhythms did disappear in subjects placed on a total fast (23); this implies that they are not truly circadian, but of nutritional origin (perhaps resulting from the postprandial release of insulin and other hormones which modify tissue uptake of amino acids).

The existence of plasma amino acid rhythms suggested that the quantities of these compounds available to the brain and to other tissues for the synthesis of proteins and low molecular weight derivatives might also change diurnally, perhaps in response to food consumption. To explore the possible significance of plasma amino acid rhythms, we elected to examine the possibility that experimentally induced fluctuations of the same amplitude as those occurring diurnally might cause parallel

changes in the rate at which a particular amino acid was incorporated into proteins, or converted to a particular low molecular weight compound. The amino acid whose plasma concentration seemed most likely to influence its metabolic fate was tryptophan, the least abundant amino acid in most tissues and foods (3). Daily rhythms in the ingestion of tryptophan-containing proteins (and, presumably, in the concentration of tryptophan delivered to the liver via the portal venous circulation) had previously been shown to generate parallel rhythms in the aggregation of hepatic polysomes (24) and in the synthesis of the enzyme tyrosine transaminase in the liver (20).

As the dependent variable in our studies, we looked for changes in brain serotonin content among rats with a spontaneous daily rhythm or treatment-induced fluctuation in plasma tryptophan. Three lines of evidence had suggested that the amount of tryptophan available to the brain might control serotonin synthesis: *1*) the existence of a daily rhythm in the brain concentrations of both tryptophan and serotonin (3, 25); *2*) the likelihood, based on K_m measurements, that the concentrations of tryptophan in brain would not be sufficient to saturate tryptophan hydroxylase (9); and *3*) the great increases in the brain concentrations of serotonin and its chief metabolite, 5-hydroxyindole acetic acid (5-HIAA), that could be obtained by injecting large doses of tryptophan (50–1,600 mg/kg, i.p.) (26).

Initial experiments were designed to determine whether brain serotonin concentrations could be increased by raising the level of brain tryptophan from its daily nadir to values just below peak nocturnal levels. The administration of L-tryptophan (12.5 mg/kg, i.p.; less than 5% of the tryptophan that a 200-g rat would consume daily in 10–20 g of rat chow) at noon produced peak elevations in plasma and brain tryptophan that were within the nocturnal range of untreated rats (Figs. 3 and 4), and caused brain serotonin levels to rise by 20–30% ($P < 0.01$) within 1 hour of treatment. Doses of 25 and 50 mg/kg caused proportionately greater increases in both brain tryptophan and brain serotonin. Larger doses of tryptophan, which caused brain tryptophan concentration to rise well beyond its physiological range, produced no further increments in brain serotonin (Fig. 5).

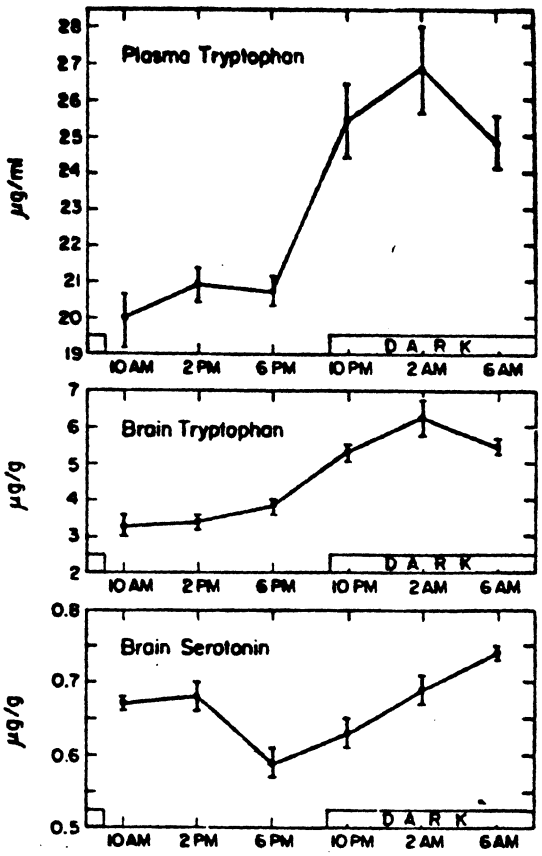

FIG. 3. Daily rhythms in plasma tryptophan, brain tryptophan, and brain serotonin. Groups of 10 rats kept in darkness from 9 PM to 9 AM were killed at intervals of 4 hours. Vertical bars indicate standard errors of the mean.

The increase in brain serotonin produced by the very small doses of tryptophan showed that changes in plasma and brain tryptophan on the order of those occurring diurnally could influence brain serotonin synthesis. However, a substrate-induced rhythm in serotonin synthesis is probably not the only factor causing daily rhythms in brain serotonin; brain serotonin levels might also reflect rhythms in serotonin release or intraneuronal metabolism.

Now that small increases in plasma tryptophan had been shown to cause parallel changes in brain serotonin, we next attempted to determine whether physiological decreases in the plasma amino acid could similarly depress serotonin synthesis. Rats similar to those used in the previous experiments were fasted overnight and then received a dose of insulin (2 IU/kg, i.p.) known to lower plasma concentra-

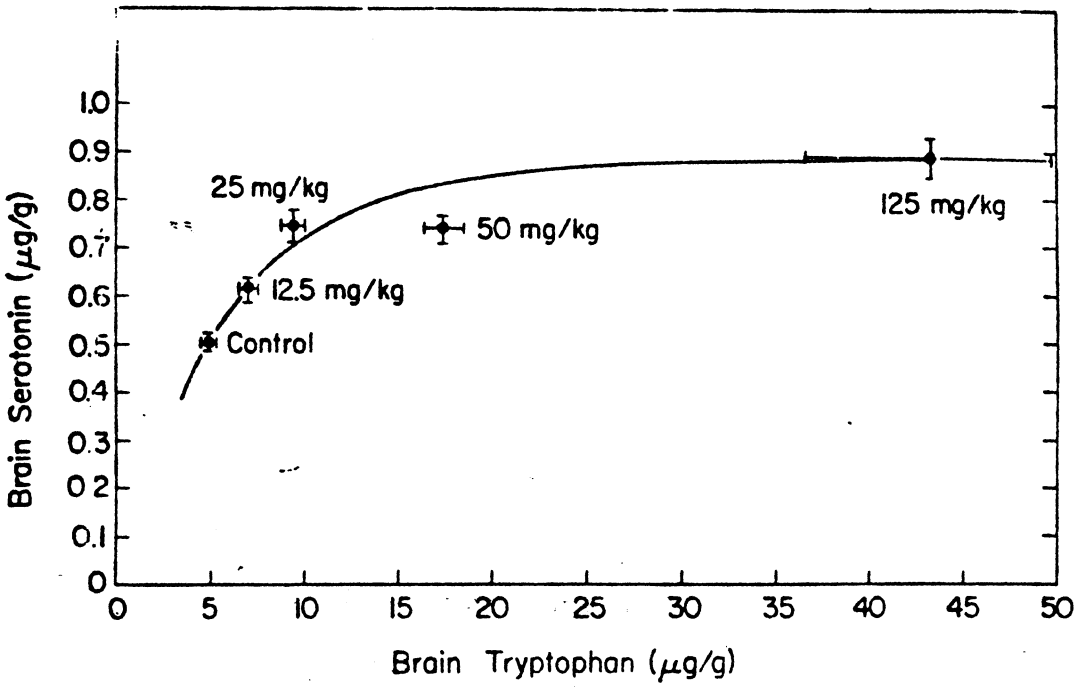

FIG. 4. Dose-response curve relating brain tryptophan and brain serotonin. Groups of 10 rats received L-tryptophan (12.5, 25, 50, or 125 mg/kg, intraperitoneally) at noon, and were killed 1 hour later. Horizontal bars represent standard errors of the mean for brain serotonin. All brain tryptophan levels were significantly higher than control values ($P < 0.001$). All brain serotonin levels were significantly higher than control values ($P < 0.01$). Plasma tryptophan rose 22% over control levels in rats injected with the 12.5 mg/kg dose ($P < 0.02$) (27).

tions of glucose and most amino acids. To our surprise, the hormone did not lower plasma tryptophan, but instead increased its concentration by 30–40% (28). This effect was independent of the route by which the insulin was administered; it was associated with a 55% fall in plasma glucose, and with major reductions in the plasma concentrations of most other amino acids, including the neutral amino acids generally believed to compete with tryptophan for uptake into the brain (5, 29). Two hours after rats received the insulin, brain tryptophan levels were elevated by 36% ($P < 0.01$), and brain serotonin by 28% ($P < 0.01$) (30).

The increase in brain serotonin observed in rats receiving insulin might have been artefactual, resulting not from increased availability of substrate, but from central reflexes activated by hypoglycemia. To determine whether the physiological secretion of insulin in normoglycemic rats also increased plasma and brain tryptophan and brain serotonin, these indoles were measured in rats fasted for 15 hours and then given free access to a carbohydrate diet. Plasma tryptophan levels were significantly elevated 1, 2, and 3 hours after food presentation; plasma tyrosine concentrations were depressed at all three times studied. Brain tryptophan and serotonin were significantly elevated at 2 and 3 hours (Table 1) (27, 30).

Since carbohydrate consumption, by eliciting insulin secretion, raised plasma tryptophan levels, and, ultimately, the concentrations of tryptophan and serotonin in the brain, we anticipated that the consumption of a "balanced" diet that simultaneously presented both carbohydrates and protein would cause an ever greater rise in brain serotonin: in addition to elevating plasma tryptophan by causing insulin secretion, the tryptophan in the dietary protein would contribute directly to plasma tryptophan; brain tryptophan and serotonin would presumably increase accordingly. However, when we gave fasted rats access to diets containing natural protein, or complete mixtures of amino acids, we found that the expected major increase (about 60%, $P < 0.001$) in plasma tryptophan was accompanied by no increases in brain tryptophan or serotonin (6, 7) (Fig. 5).

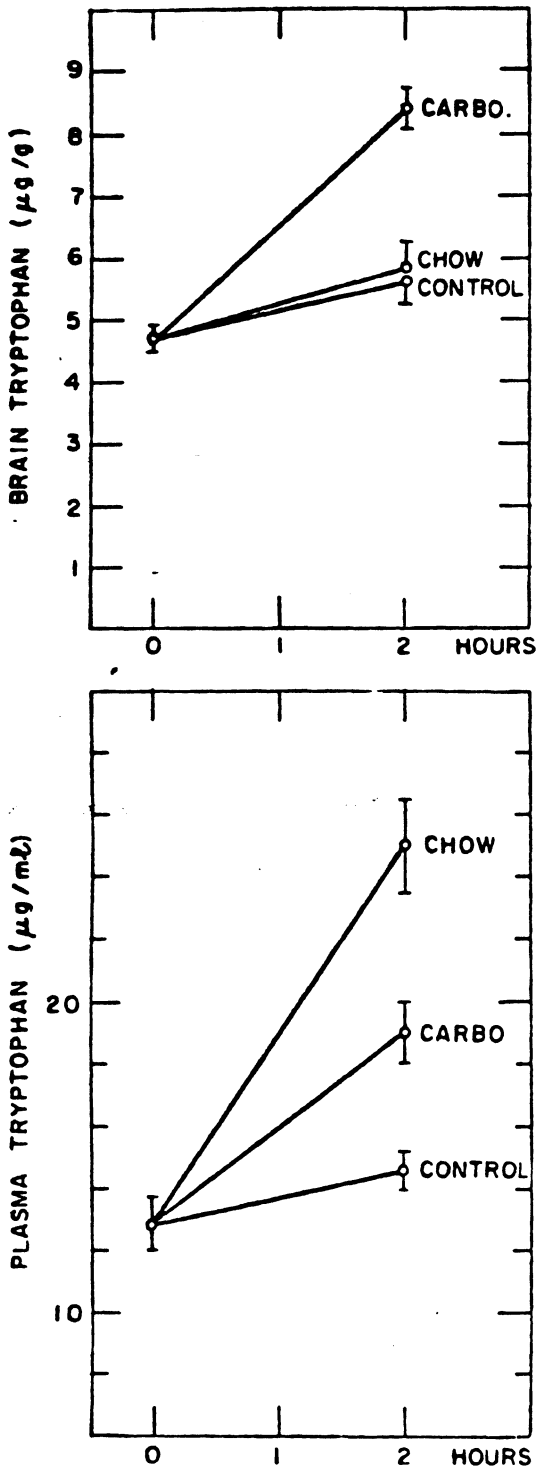

FIG. 5. Changes in brain and plasma tryptophan concentrations following the consumption of different foods. Groups of 6 rats were killed 1 or 2 hours after diet presentation. Vertical bars represent standard errors of the mean. Two hour plasma tryptophan levels were significantly greater in rats consuming either diet than in fasting controls (chow: $P < 0.001$; carbohydrate: $P < 0.01$). Two-hour brain tryptophan levels were significantly elevated above controls only in rats consuming the carbohydrate-plus-fat diet ($P < 0.001$) (7).

It seemed possible that brain tryptophan failed to increase after protein ingestion because the plasma concentrations of other, competing, amino acids (5, 29) increased even more than that of tryptophan. To test this hypothesis, we allowed groups of animals to eat either a synthetic diet containing carbohydrates plus all of the amino acids in the same proportions as are present in an 18% casein diet, or this diet minus five of the amino acids thought to share a common transport system with tryptophan (tyrosine, phenylalanine, leucine, isoleucine, and valine) (5). Both diets significantly increased plasma tryptophan levels above those found in fasted controls. However, large increases in brain tryptophan, serotonin, or 5-HIAA occurred only when the competing neutral amino acids were deleted from the diet (6). When these studies were repeated omitting aspartate and glutamate (two acidic amino acids) from the diet instead of the five neutral amino acids, plasma tryptophan concentrations again increased 70–80% above those of fasted controls ($P < 0.001$); however, brain tryptophan, serotonin, and 5-HIAA remained unaffected.

On the basis of these observations, we postulated that brain tryptophan and 5-hydroxyindole levels did not simply reflect plasma tryptophan, but depended also on the plasma concentrations of other neutral amino acids. This relationship was confirmed by an analysis correlating brain tryptophan concentration with the ratio of plasma tryptophan to the five competing amino acids in individual rats given diets containing various amounts of each amino acid (6). This analysis yielded a correlation coefficient of 0.95 ($P < 0.001$ that $r = 0$), whereas the correlation between brain tryptophan and plasma tryptophan alone was less striking ($r = 0.66$; $P < 0.001$ that $r = 0$). Similarly, the correlation coefficient for brain 5-hydroxyindoles (serotonin plus 5-HIAA) versus the plasma amino acid ratio was 0.89 ($P < 0.001$), whereas that of 5-hydroxyindoles versus tryptophan alone was only 0.58 ($P < 0.001$). The reason that brain tryptophan and serotonin had appeared, in our earlier studies,

TABLE 1.
Effect of carbohydrate ingestion on brain serotonin concentrations and on plasma and brain tryptophan

	Time after presentation of food, hours			
	0	1	2	3
Plasma tryptophan	10.86 ± 0.55	13.56 ± 0.81[b]	14.51 ± 0.70[c]	13.22 ± 0.65[b]
Brain tryptophan	6.78 ± 0.40	8.32 ± 0.63[a]	11.24 ± 0.52[c]	9.81 ± 0.50[c]
Brain serotonin	0.549 ± 0.015	0.652 ± 0.046	0.652 ± 0.012[c]	0.645 ± 0.017[c]
Plasma tyrosine	13.03 ± 0.29	9.55 ± 0.34[c]	8.67 ± 0.26[c]	9.03 ± 0.21[c]

Plasma amino acid concentrations are in μg/ml. Brain tryptophan and serotonin concentrations are in μg/g brain, wet weight. Average animal weight was 160 g. [a] $P < 0.05$ differs from 0-hour group. [b] $P < 0.02$ differs from 0-hour group. [c] $P < 0.001$ differs from 0-hour group. Reproduced from (28).

to depend on plasma tryptophan alone was that all of the physiological manipulations that had been examined (tryptophan injections, insulin injections, carbohydrate consumption) raised the numerator in the plasma tryptophan–to–competitor ratio while either lowering the denominator or leaving it unaltered. Only when rats consumed protein were both the numerator and the denominator elevated. The effect of food consumption on 5-hydroxyindole synthesis in rat brain may now be modeled as in Fig. 6.

In humans, although serum tryptophan does not increase after glucose consumption or insulin injection as in rats, it also does not substantially decrease (31). In contrast, the plasma concentrations of the competing neutral amino acids fall markedly (20). Hence the plasma ratio of total tryptophan to the sum of the competing neutral amino acids increases, just as it does in rats. We might than anticipate that brain tryptophan and serotonin levels would also rise in humans following insulin injection or carbohydrate consumption. (Of course, it has not been possible to test this assumption directly.)

Tryptophan in plasma is distributed between two pools: about 10–20% circulates as the free amino acid, while the remainder is bound to serum albumin (32). None of the other amino acids binds appreciably to plasma proteins. Because binding in general implies storage, several investigators have suggested that the plasma-free tryptophan pool determines the availability of circulating tryptophan to brain and other tissues (33).

A variety of lipid-soluble compounds which bind to albumin in the blood (e.g., hormones, drugs, nonesterified fatty acids (NEFA)) may displace each other. Thus, for example, increasing the serum concentration of NEFA in vitro causes the concentration of albumin-bound tryptophan to fall, and that of free tryptophan to rise (34). In collaboration with Drs. Bertha Madras and Hamish Munro, we examined this relationship in vivo by feeding rats diets that were expected to alter serum NEFA levels, and then measuring the changes in serum-free and albumin-bound tryptophan. We then examined the correlations between diet-induced changes in brain tryptophan or 5-hydroxyindoles and *1*) serum-free tryptophan, *2*) serum total tryptophan, and *3*) the ratio of serum tryptophan to the sum of the competing neutral amino acids (35). These studies showed that diet-induced changes in brain tryptophan do not correlate at all with what happens to serum-free tryptophan. For example, the consumption by rats of a carbohydrate diet decreases serum-free tryptophan (presumably via the insulin-mediated decline in serum NEFA), but increases brain tryptophan and 5-hydroxyindoles (probably by raising the serum ratio of tryptophan to competing neutral amino acids). Thus, the binding of serum tryptophan to albumin does not appear to limit the availability of the amino acid to the brain. Indeed, the physiological significance of tryptophan binding appears to be just the opposite: it allows serum tryptophan levels to remain elevated after insulin is secreted, at a time when the serum concentrations of the amino acids that compete with it for brain uptake are declining. Thus albumin binding makes it possible for carbohydrate consumption to elevate brain tryptophan and, consequently, to increase the synthesis of 5-hydroxyindoles.

An increase in brain serotonin content,

whether it be induced by diet or by any other treatment, will be physiologically significant only if it is associated with a corresponding change in the amount of the neurotransmitter that is secreted into synaptic clefts. This, in turn, will probably depend on two factors, i.e., the number of action potentials traversing serotoninergic neurons, and the number of neurotransmitter molecules released per action potential. Of course, no direct methods are available for measuring the number of serotonin molecules released into brain synapses; hence it is not possible to test directly the existence of a relationship between the increased brain serotonin levels in rats that have recently consumed a carbohydrate meal, and the amount of the neurotransmitter released. We are currently attempting to estimate serotonin release by indirect methods, e.g., by examining the amounts liberated in vitro following the electrical stimulation of brain slices, or by determining whether various brain outputs that seem to be associated with serotoninergic neurons (e.g., temperature regulation, pituitary secretion, pain sensitivity) are differentially modified by the consumption of carbohydrates or proteins. Large doses of tryptophan, which cause major increases in brain 5-hydroxyindole levels, have been shown to decrease the rate of firing of serotoninergic neurons (36); this effect may be mediated by a multisynaptic reflex arc, or by the effects of increased serotonin release on presynaptic serotonin receptors (37). However, there is no evidence that such physiologic increases in brain serotonin as occur after carbohydrate consumption modify the rate of firing of serotonin neurons. Thus it may not be overly optimistic for us to speculate that, within the normal dynamic range, a physiologic increase in neuronal serotonin content can be associated with a corresponding increase in the rate at which the serotonin is secreted into synapses. This speculation is supported by the finding that diet-induced changes in brain serotonin are always accompanied by parallel increases in brain 5-HIAA.

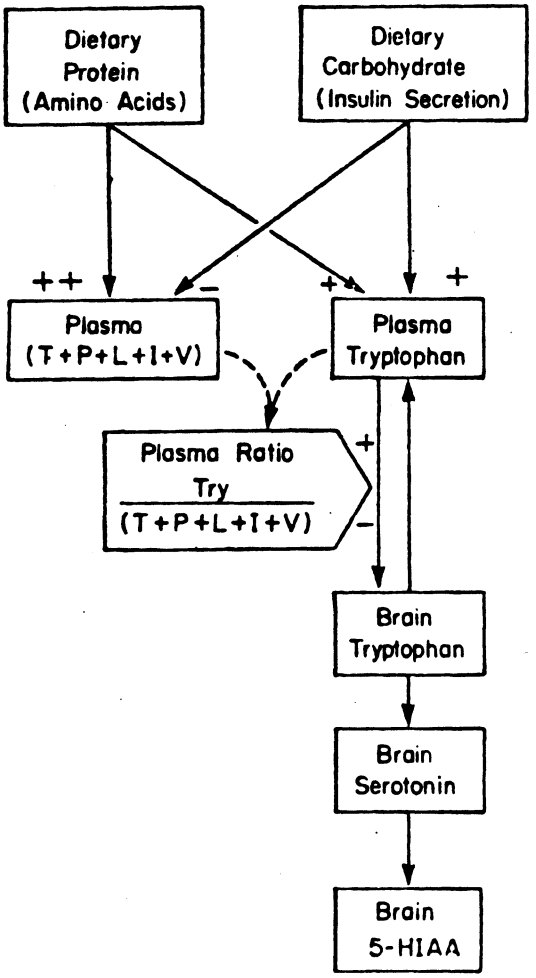

FIG. 6. Proposed sequence describing diet-induced changes in brain serotonin concentration in the rat. The ratio of tryptophan to the combined levels of tyrosine, phenylalanine, leucine, isoleucine, and valine in the plasma is thought to control the tryptophan level in the brain (6).

When rats are treated with chlorimipramine, a drug that blocks the presynaptic uptake of serotonin and thus probably potentiates its postsynaptic effects, brain 5-HIAA levels fall. This observation has been interpreted as reflecting a decrease in the rate of firing of serotoninergic neurons, mediated either by a multisynaptic reflex arc or by presynaptic receptors responding to increased amounts of serotonin within synaptic clefts. Our associate, Dr. Jacob Jacoby, has shown that the consumption of a carbohydrate meal by chlorimipramine-treated rats elevates brain serotonin and 5-HIAA levels: the increments in brain 5-hydroxyindoles are comparable to those observed in untreated animals (38). We interpret these observations as showing that the "external" feedback control of the physiological activity of serotonin neurons does not override the "internal" physiological regulation of serotonin synthesis by diet and brain tryptophan. Dr.

Jacoby has also found that carbohydrate consumption further elevates brain serotonin levels in animals in which pretreatment with a monoamine oxidase inhibitor has already markedly increased brain serotonin (38). We interpret this finding as evidence that intraneuronal serotonin concentrations do not normally exert feedback control over serotonin synthesis. Both of the above factors—the rate at which the neuron fires and the intraneuronal concentration of the monoamine—would be expected to have major effects on the synthesis of brain catecholamines.

Brain tyrosine and catecholamine synthesis

The of the enzyme tyrosine hydroxylase is on the same order of magnitude as the concentration of this amino acid in whole brain (39) (Table 2). This raises the possibility that relatively small changes in brain tyrosine might also influence catechol synthesis by changing the saturation of tyrosine hydroxylase. To explore this possibility, we have recently initiated studies on brain catechol synthesis in animals given treatments that modify brain tyrosine concentrations. We first employed for this purpose an approach developed by Dr. Arvid Carlsson, which involves measuring the rate at which dopa accumulates in brain soon after the pharmacologic inhibition of the enzyme aromatic L-amino acid decarboxylase (37). Since brain dopa levels are usually barely measurable, this approach has the advantage of great sensitivity.

When changes in brain tyrosine were induced by injecting tyrosine itself or other neutral amino acids (which lower brain tyrosine by competing with it for uptake from the extracellular fluid (5)), highly significant correlations were observed with the rate of accumulation of dopa (Table 2) (40). Similar correlations were also noted in subsequent experiments in which brain catecholamine synthesis rates were estimated by measuring the accumulation of dopamine and norepinephrine in the hour after administration of a monoamine oxidase inhibitor: tyrosine administration accelerated, and valine administration slowed, catecholamine accumulation.

These observations provide initial evidence that brain tyrosine *can* control the rates of catecholamine synthesis. In order to determine whether brain tyrosine actually *does* affect catecholamine synthesis, it would be necessary to show that tyrosine levels do, in fact, normally change in untreated animals, and that when they do, catechol synthesis follows suit. This may turn out to be the case. In preliminary studies we have observed that rats given a single high-protein (40%) meal undergo major elevations in both brain tyrosine level and brain dopa accumulation (i.e., after decarboxylase inhibition). As described above, this diet does not elevate, and may actually suppress, brain tryptophan levels and serotonin synthesis. Its effect on brain tyrosine probably results from the relatively high proportions of tyrosine and phenylalanine—part of which is converted to tyrosine in the liver—within dietary proteins. Perhaps it is not too early to suggest that the consumption of a protein-free or a protein-containing meal selectively facilitates the activity of one neuronal population or another, i.e., serotoninergic or catecholamingeric neurons, respectively.

TABLE 2.
Relationship between brain tyrosine concentration and the synthesis of brain dopa

Treatment	Tyrosine, μg/g	Dopa, ng/g	No.
Control	15.12 ± 0.50	194 ± 11	15
Tyrosine, 20 mg/kg	19.42 ± 0.83[c]	207 ± 14	8
Tyrosine, 50 mg/kg	26.74 ± 0.74[c]	217 ± 7	22
Tyrosine, 100 mg/kg	32.72 ± 0.85[c]	224 ± 8[a]	6
Tryptophan, 50 mg/kg	12.89 ± 0.67[b]	153 ± 8[b]	9
Leucine, 50 mg/kg	10.16 ± 1.38[b]	160 ± 8[a]	4

All groups (including control rats) received RO4-4602 (800 mg/kg i.p.), and were killed 60 min later. Animals indicated also received an intraperitoneal injection of an amino acid 15 min after the first injection. Data are presented as mean ± standard error. [a] $P < 0.05$ differs from control. [b] $P < 0.01$ differs from control. [c] $P < 0.001$ differs from control.

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