THE EFFECTS OF TYROSINE AND OTHER NUTRIENTS ON NEUROTRANSMITTER SYNTHESIS IN THE BRAIN AND RETINA

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Traditionally, concern about the possible effects of nutritional state on the central and peripheral nervous systems has been focused on malnutrition—the possibility that chronic inadequacies in the intakes of vitamins, proteins, and other key nutrients, especially very early in life, may cause permanent damage in neuronal development, synaptogenesis, and even in behavior. Our current interest is in a different aspect of nutrition—brain (or nutrition-neuron) relationships, viz, in the possibility that normal variations in the quantities of certain nutrients reaching the brain may cause parallel changes in brain function. The nutrients that mostly concern us are compounds such as tyrosine, choline, and tryptophan, which are converted by particular neurons into neurotransmitters (the catecholamines, acetylcholine, and serotonin, respectively). There is now abundant evidence that, under appropriate conditions, variations in the plasma concentrations of these neurotransmitter-precursors can affect brain composition and function. Moreover, the deliberate administration of very large quantities of certain nutrients to patients may alter neuronal function in predictable and useful ways, thus allowing the nutrients to serve as drugs. Research has only just begun on the possibility that such variations can similarly affect neurotransmitter synthesis within retinal neurons; it would be surprising, however, if they do not.

Plasma Composition and Neurotransmitter Synthesis

The amount of information that a group of like-neurons can transmit during a particular interval depends on three main factors: the number of neurons in the nucleus (or the number of synapses that these neurons make), the average rate at which these neurons happen to be firing, and the average number of neurotransmitter molecules that the neuron releases each time it fires. All of these factors, however, are subject to change. The number of synapses might either increase or decrease if neurons are indeed "plastic" in an anatomic sense. However, the number of neurons inexorably does change in a single direction (downwards) with age. Any neuron’s frequency of firing will typically accelerate or decelerate, increasing when it is bombarded with excitatory neurotransmitters released from other neurons, and decreasing in response to inhibitory transmitters. Studies performed during the past decade have shown that the numbers of neurotransmitter molecules that certain types of neurons release per firing probably also vary over wide ranges; moreover, these variations bear predictable relationships to the concentrations of particular compounds in the blood stream, and thus to food consumption. The neurotransmitter molecules known to exhibit these relationships are serotonin, acetylcholine, and the catecholamines; the controlling compounds in the plasma are the essential* large

* From the brain’s standpoint, tyrosine is an essential amino acid. Consumption of an amino acid mixture containing other competing LNAA, but lacking tyrosine, will sorely impair catecholaminergic neurotransmission.
neutral amino acids (LNAAs) and, for acetylcholine, choline. These plasma compounds are either precursors for neurotransmitters themselves, or, as described below, are in competition with the precursors for uptake into the brain.

Five general laws govern the relationships between the synthesis of neurotransmitters and the plasma levels of their precursors. First, the limiting step in the biosynthesis of the transmitter must be catalyzed by a low-affinity enzyme—tryptophan hydroxylase, choline acetyltransferase, or tyrosine hydroxylase—which, at normal substrate concentrations, is unsaturated with the neurotransmitter precursor. Secondly, this enzyme must not be subject, under normal circumstances, to significant intracellular feedback control by end-product inhibition. Thirdly, the amount of the enzyme’s substrate (the neurotransmitter precursor) that is present within the neuron must depend on its concentration in the plasma—either because the neuron is unable to make the precursor (for example, tryptophan), and obtains it solely by influx from the plasma, or because the neuron tends to lose the precursor by efflux into the plasma (for example, choline), such that the efflux rate varies inversely with the precursor’s plasma concentration. Fourthly, a mechanism must exist which facilitates the precursor’s passage from the blood stream to the brain (ie, a blood-brain barrier transport system); moreover, the affinity of this mechanism for the circulating precursor must, like that of the rate-limiting enzyme, be relatively low. A selective increase in plasma tyrosine levels must enhance the mechanism’s saturation with tyrosine, and must thereby facilitate tyrosine’s entry into the brain.

A single transport mechanism, probably comprising a single system of macromolecules, mediates the facilitated diffusion of all of the LNAAs across the blood-brain barrier. The \( K_m \) of this mechanism for LNAAs per se, is of the same order of magnitude as the total plasma LNAAs concentration; hence, each of the LNAAs competes with all of the others for uptake sites. As a consequence, the rate at which circulating tyrosine enters the brain depends both on plasma tyrosine levels and, inversely, on plasma levels of tryptophan, phenylalanine, leucine, isoleucine, valine, threonine, methionine, and histidine (and to a lesser extent, on a few additional amino acids). The most important competing LNAAs, by virtue of their relatively high affinities for the carrier and their high plasma concentrations, are the aromatic and the branched-chain amino acids. Hence, brain tyrosine levels can be predicted at any moment by a "plasma tyrosine ratio" whose numerator is the concentration of tyrosine, and whose denominator is the sum of the plasma concentrations of tryptophan, phenylalanine, and the branched-chain triad. Similar ratios predict brain levels of other neurotransmitter precursors such as tryptophan. The predictive power is slightly improved if more individual LNAAs are included in the denominator, and if corrections are made for differences in the affinities of individual LNAAs for the transport carrier. In the case of circulating tryptophan, transport across the blood-brain barrier is retarded to a very small extent by the amino acid’s low-affinity, high-capacity binding to albumin. The power of the blood-brain barrier transport mechanism to grab and hold circulating tryptophan is, generally, so much greater than that of circulating albumin that, for all practical purposes, no correction in the plasma tryptophan ratio is usually needed for that portion of circulating tryptophan which happens to be albumin-bound at the moment that it enters brain capillaries. No normal plasma constituents which significantly affect choline’s flux from brain to blood have yet been identified; however, certain drugs such as deanol and lithium may have this effect.

The fifth general law is that plasma levels of the precursors must, in fact, change under normal conditions. For example, choline levels must be allowed to rise after choline is consumed (as the free base or as a constituent of lecithin or sphingomyelins), and plasma LNAAs must be able to rise or fall postprandially (elevated by the amino acids in dietary protein; depressed—in most cases, but not in the case of tryptophan—by the insulin released subsequent to carbohydrate consumption). If feedback mechanisms existed which kept plasma choline or LNAAs levels within narrow ranges (similar to those regulating plasma osmolarity or glucose levels), then, even though neurons might have the capacity to respond to variations in plasma composition, they would never be called upon to do so.

Nutrient Consumption and Neurotransmitter Synthesis

Since plasma choline and LNAAs are not regulated, the factors that normally cause them to rise and fall assume great importance as potential determinants of brain function. Clearly the most important such factor is eating, or, more specifically, the composition of that which is eaten. Each meal produces, within minutes of its initiation, predictable changes in plasma choline and LNAAs levels; minutes later, equally predictable changes are observed in brain neurotransmitters. In humans, a meal that is rich in lecithin (or, for milk-consuming infants, sphingomyelins) will rapidly elevate blood choline and presumably neuronal acetylcholine levels; the lack of a dietary choline source for 12–24 hours will cause a gradual fall in plasma choline and the lack of a
post-prandial increase in neuronal acetylcholine. A protein-poor meal will, by virtue of its ability to initiate insulin secretion, cause marked reductions ( >50%) in plasma leucine, isoleucine, and valine levels; at the same time, plasma tryptophan will not fall at all but may rise. Consequently, the plasma tryptophan ratio increases, and brain serotonin quickly follows. This protein-poor meal also causes plasma tyrosine levels to fall, but not by as great a proportion as the branched-chain amino acids; hence, the tyrosine ratio may increase slightly, causing a small acceleration in norepinephrine's synthesis and release.14 Consumption of a high-protein meal causes a paradoxical fall in the tryptophan ratio10 and a major rise in the tyrosine ratio,12 followed by the anticipated changes in brain monoamine synthesis. The fall in the tryptophan ratio reflects the fact that tryptophan tends to be very scarce in dietary protein (0.5–1.6% of total amino acids); hence, even though plasma tryptophan levels rise post-prandially, this increase is much less than that of the competing LNAA. The rise in the tyrosine ratio after protein consumption reflects the fact that proteins contain two molecules that tend to elevate plasma tyrosine, ie, tyrosine itself and phenylalanine, most of which is converted to tyrosine in each pass through the portal circulation.

The demonstration of altered amounts of transmitters following different kinds of meals leads to the question of what the possible function of such precursor control may be. Because serotonin-producing neurons exhibit characteristic inverse responses to the proportion of protein in each meal, they are able to function as sensors of food-induced changes in plasma composition; throughout the dynamic range of plasma compositions associated with eating protein-free to high-protein meals, serotonin neurons produce and release more or less of their transmitter, thereby “informing” other brain neurons about metabolic state.10 No similar teleological explanation has yet been proposed for the question of why cholinergic or catecholaminergic neurons are susceptible to precursor control.

Use of Nutrients to Modify Neurotransmitter Synthesis

The extent to which naturally occurring foods can be used to influence neurotransmitter synthesis is limited by the fact that foods contain, in addition to the desired transmitter precursor, other compounds that compromise the precursor's effectiveness (eg, other LNAA in the case of tryptophan or tyrosine) or that limit the dose that can be administered (eg, the cholesterol and calories that accompany the lecithin in eggs or liver). Hence, if transmitter precursors are to be used clinically, it seems likely that they will be presented most effectively to the patient either in pure form (with or without excipients), as though they were drugs; as constituents of specially-prepared diet mixtures (akin to the phenylalanine-free synthetic foods used in treating phenylketonuria); or as intravenous solutions. That the precursors are vastly more effective when removed from their natural setting as food constituents and given instead in pure form is demonstrated by comparing the changes in the plasma tyrosine ratio that follow protein consumption with those changes following administration of tyrosine itself. A two- to three-fold increase in plasma tyrosine level was produced by giving normal volunteers either a single meal containing 33–50 g of protein12 or 33–50 mg/kg of tyrosine15,16; however the former treatment caused no significant elevation in the plasma tyrosine ratio, while the latter treatment doubled this ratio. Giving tryptophan (or tyrosine) along with a carbohydrate can potentiate its effect on its monoamine product; the resulting secretion of insulin and fall in LNAA allows a larger proportion of each dose to enter the brain.*

Tyrosine and the Synthesis and Release of Catecholamines

Despite the demonstration that exogenous administration of tyrosine can lead to an increase in both plasma tyrosine levels and the plasma tyrosine ratio, it has not been reported to cause rapid elevation in brain catecholamine levels. This stands in contrast to the situation for some of the other neurotransmitter precursors, eg, tryptophan or choline, whose administration leads to rapid elevations in brain levels of their transmitter products. This apparently negative relationship led many investigators to assume that catecholamine synthesis was not under significant precursor control, a view that was buttressed by the availability of alternative candidates for control mechanisms (eg, end-product inhibition of tyrosine hydroxylase by its catechol products; unsaturation of tyrosine hydroxylase with its pteridine cofactor). It was not until studies using decarboxylase inhibitors showed that brain catechol formation varies with brain tyrosine level17 that this earlier view was challenged. From a position of hindsight, it is possible now to understand why precursor control of catecholamine synthesis was relatively late in being recognized. The fact that brain dopamine or norepinephrine levels do not change appreciably in the hour or two after tyrosine is administered may reflect the relatively slow turnover

* Unpublished observations.
of these transmitters (compared with serotonin or acetylcholine) and the heterogeneity of their storage. It is possible that even a doubling in the synthesis of the most important norepinephrine pool would not cause a detectable rise in brain norepinephrine levels until many hours had passed (ie, if the other, larger pools turn over more slowly). It is also possible that changes in transmitter levels would have been detected had particular sets of catecholaminergic neurons, and not the whole brain, been examined, or even that the doses of tyrosine that were supposed to have elevated brain tyrosine levels did not actually do so (and that this went undetected because plasma tyrosine ratios were not measured). In any case, abundant evidence has since been obtained that tyrosine levels can control not only brain catechol synthesis (in decarboxylase-inhibited animals), but also catecholamine release, as reflected by brain levels of dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) for dopamine and MOPEG-sulphate for norepinephrine.

The extent to which catecholaminergic neurons are affected by tyrosine levels apparently depends on their firing frequencies. Dopamine release from nigrostriatal neurons is unaffected by major changes in tyrosine levels under resting conditions, but is markedly enhanced following treatment with haloperidol or reserpine (which block dopamine receptors and dopamine storage, respectively), or partial lesioning of the nigrostriatal tract (which accelerates the firing of the surviving neurons). Norepinephrine synthesis and release are enhanced slightly in the brains of otherwise untreated animals when brain tyrosine levels have been elevated, but this effect is potentiated when noradrenergic neurons are caused to fire more rapidly than normal (for example, in hypertensive rats, or among animals placed in a cold environment). Adrenal chromaffin cells similarly secrete more epinephrine when rats or humans are given tyrosine, and this response is enhanced in shock. A relationship between neuronal firing rates and precursor-dependence seems to characterize cholinergic neurons as well; thus, the choline concentration in the medium has little effect on the spontaneous release of acetylcholine from motor neurons innervating the rat diaphragm, but markedly augments the acetylcholine release caused by stimulating the phrenic nerve electrically. The particular mechanism that couples neuronal firing rate to precursor dependence may, in catecholaminergic cells, have to do with activation of the tyrosine hydroxylase, which enhances its affinity for (and saturation with) the tetrahydrobiopterin cofactor, rendering it more dependent on the tyrosine. The mechanism operating in cholinergic neurons awaits characterization.

Neurotransmitter Synthesis Affecting Neurotransmitter Release

Under what conditions may a change in a neurotransmitter's synthesis, caused by giving its precursor, be expected to modify the amount of transmitter actually released each time the neuron fires? The central nervous system could effectively dampen whatever effects precursor administration may have on catecholaminergic or cholinergic neurotransmission, simply by changing neuronal firing rates. If, for example, a particular cholinergic neuron released twice as much acetylcholine per firing for a period following choline's administration, the brain could keep this change from seriously affecting neurotransmission by reducing the neuron's firing rate by half. Under what conditions might such modulations not be expected to occur? Three situations suggest themselves. The first occurs if the neurons in question are designed to function as sensors, coupling their output signal (neurotransmitte: release per unit time) to the level of something being sensed (for example, the plasma tryptophan ratio, post-prandially). In this circumstance, their design would include the lack of multisynaptic feedback loops, which, in the normal, dynamic, range might suppress their firing rates in inverse proportion to the amounts of transmitter released per firing. The second situation occurs if neurotransmitter release is not controlled by multisynaptic feedback loops (eg, from peripheral autonomic or motor neurons, or the adrenal medulla). Thus, for example, choline administration causes major and prolonged increases in preganglionic neurotransmission, as reflected by epinephrine release from the adrenal medulla and tyrosine hydroxylase induction in the medulla and in sympathetic ganglia; tyrosine administration also causes increases in urinary norepinephrine and epinephrine levels in the absence of overt stress. The third situation occurs if the neurons are "sick" and are unable to release as much transmitters as usual—either because they are too few in number (eg, in aging, or Alzheimer's Disease, or Parkinson's Disease), or because of an impairment in the release mechanism (eg, in tardive dyskinesia).

This third situation underlies the current interest in therapeutic uses of neurotransmitter precursors. It seems likely that, if a particular precursor-dependent transmitter (eg, dopamine) is utilized by a number of different brain tracts, and if a disease affects one of the tracts, causing it to release too few neurotransmitters per unit time, then that tract's function may be selectively restored by giving tyrosine, without causing excessive dopaminergic tone in the other, "healthy", dopaminergic tracts. Available clinical and experi-
mental evidence, though meager, tends to support this expectancy. Tyrosine administration increases dopamine's release from tuberoinfundibular neurons and thereby suppresses prolactin secretion in hyperprolactinemia, but not when plasma prolactin levels are normal.\textsuperscript{15} Tyrosine's administration to patients with mild Parkinson's Disease ameliorates their clinical signs without causing the signs of dopaminergic hyperactivity seen with dopaminergic agonists (nausea; hallucinations; psychosis).\textsuperscript{28} Tyrosine rapidly increases brain stem MOPEG-sulfate levels and lowers blood pressure in hypertensive animals, but has relatively little effect on either index in normotensives.\textsuperscript{20} Choline (or lecithin) and physostigmine share an ability to ameliorate the abnormal movements characteristic of tardive dyskinesia,\textsuperscript{29} but precursor administration fails to produce the marked side effects—manifestations of generalized cholinergic activation—seen after physostigmine administration. Future studies should bear out the apparent ability of neurotransmitter precursor molecules to target their sites of action to those synapses at which more of their transmitter products happen to be needed.

**Retinal Cells in Which Neurotransmitter Synthesis May Be Precursor-Dependent**

Many of the putative neurotransmitters found in brain tissue have been identified also in retina (eg dopamine, acetylcholine, glycine, substance P).\textsuperscript{*}

Dopamine in the retina fulfills many of the classical criteria for CNS neurotransmitters. First of all, its presence has been demonstrated autoradiographically and histochemically within specific retinal cells (eg, amacrine cells).\textsuperscript{32,33} Secondly, the enzymes required (34–36) for dopamine's synthesis and degradation also are present. Retinal tyrosine hydroxylase apparently exists in two states, a basal state in dark-adapted retinas and an activated state in light-exposed retinas. The activated enzyme has a greater affinity for the tetrahydrobiopterin cofactor ($K_m = 0.70$ mM vs 1.40 mM).\textsuperscript{35} Retinal monoamine oxidase activity is predominantly of the B type.\textsuperscript{37} Third, tritiated dopamine is taken up by the retina and released when the eye is stimulated by exposure to light.\textsuperscript{38,39} Fourth, direct application of dopamine to postsynaptic retinal ganglion cells suppresses their spiking frequency;\textsuperscript{40} dopamine application also diminishes the responses of horizontal cells to light.\textsuperscript{41} Finally, depletion of dopamine (eg by reserpine or $\alpha$-methyl-paratyrosine) causes animals to become more sensitive to light, possibly by increasing retinal sensitivity.\textsuperscript{34,42}

Retinal tyrosine hydroxylase is highly sensitive to light; exposure of rats to 400 lux of fluorescent light activates the enzyme within 15 minutes.\textsuperscript{35} The enzyme normally undergoes light-related daily rhythm (in rats on a standard 12 hour light/dark cycle) with peaks occurring during the daylight hours.\textsuperscript{34} Maximal and rapid stimulation occurs when animals have been dark-adapted, ite, placed in the dark for 11–96 hours and then exposed to light; enzyme activity then doubles within 15 minutes of light exposure.\textsuperscript{34,35} If dopamine synthesis in retinal cells is sensitive to available tyrosine levels, it might be anticipated that the greatest responses to tyrosine administration will be observed during the light phase of the cycle, when the enzyme is in an activated state.

Dopamine receptors have also been demonstrated in the retina, predominantly of the D-1 type which are linked to adenylate cyclase and bind $^3H$-spiroperidol.\textsuperscript{43} Receptor activity and sensitivity also vary depending on the presence or absence of light, and hence with the quantities of dopamine that have been interacting with receptor sites. Sensitivity (ie, maximum stimulation of adenylate cyclase) is highest in dark-adapted rats, when dopamine release has been minimal, and lowest in the light-adapted animal.\textsuperscript{44} Retinal dopamine neurons may represent a particularly useful model system for studying catecholamine synthesis and its regulation in a relatively homogeneous and accessible population of cells, in which the synthetic enzyme, tyrosine hydroxylase, can be activated by a simple physiologic stimulus—light.

It is not known whether the carrier system mediating the passage of tyrosine and other LNAAs into the retina is the same as that which operates at the blood-brain barrier. Thus, it is not known at this time whether blood tyrosine levels alone, or the tyrosine to LNAAs ratio, determines precursor (tyrosine) availability in the retina.

Acetylcholine probably also is a neurotransmitter in the retina. Cholinesterase-positive neurons are found among the amacrine cells,\textsuperscript{35,46} as is choline acetyltransferase activity.\textsuperscript{47} Moreover, retinas release acetylcholine when stimulated with a flashing light.\textsuperscript{48}

It appears certain that an indole-containing cell also exists in retina, but whether or not the indole is serotonin remains controversial.\textsuperscript{49–51} No serotonin-type histochemical fluorescence can be detected before or after animals receive tryptophan loads;\textsuperscript{49} moreover, retinas contain only very low levels of serotonin and no demonstrable tryptophan hydroxylase activity.\textsuperscript{50} Tritiated serotonin can be taken up by retinal cells, but this alone does not prove a neurotransmitter role.\textsuperscript{51} Perhaps retinal serotonin functions as the precursor for melatonin. N-acetylserotonin, the melatonin pre-

\*See Ehinger B, this issue.
cursor, has also been found in rat retina, it undergoes a characteristic diurnal rhythm, with high levels in the dark phase and low levels in the light phase. Retinas also contain hydroxyindole-O-methyl transferase, the enzyme that converts N-acetylserotonin to melatonin.53

Effects of Tyrosine Administration on Retinal Dopamine Synthesis and Release

We have very recently started to examine the possibility that treatments which change retinal tyrosine levels can thereby modify dopamine synthesis in, and its release from, the amacrine cells. In studies performed to date, tyrosine levels have been manipulated by administering tyrosine itself or giving other individual LNAA. However, it should be remembered that major changes in tyrosine levels within brain7 and other tissues21 can occur after the consumption of individual meals of appropriate composition; perhaps similar changes also occur within the retina. In our studies, dopamine metabolism is assessed by measuring retinal levels of dopamine itself and of a major dopamine metabolite, DOPAC. If a treatment caused an increase in DOPAC without decreasing DA, this strongly suggests that it accelerated the synthesis and release of the neurotransmitter itself.

Our preliminary studies have utilized male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA), housed in suspended metal cages exposed to Vita-Lite (Duro-Test Corp., North Bergen, NJ) (300 µW/cm²; 11–33 lux illumination inside rat cages) from 7AM to 7PM and given access to food (Charles River Rat and Mouse Formula) and tap water ad libitum, except during fasting experiments when only water was available. Free amino acids (L-tyrosine, L-leucine, L-valine (Sigma Chemical Co., St. Louis, MO or Regis Chemical, Morton Grove, IL) were ad-

Fig. 1. Effect of tyrosine on retinal dopamine and DOPAC. Groups of male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA, N = 5) were injected intra-peritoneally with a suspension of L-tyrosine (100 mg/kg in saline) and killed by decapitation 15, 30, 60, or 120 minutes later. Injections were performed between the 8th and 9th hours of the daily light period. Eyes were quickly removed and frozen on dry ice; retinas were subsequently dissected on an ice-cold glass plate. Retinal dopamine and DOPAC were measured by HPLC with electrochemical detection.55 Serum tyrosine was measured by the method of Waa1kes and Udenfriend. Data are presented as ng/pair of retinas ± standard errors of the means.
ministered by intraperitoneal injection of a suspension or solution in 0.9% saline; control rats were injected with saline. The animals were decapitated. Blood was collected in tubes on ice. After centrifugation at 1000 g for 20 minutes (Beckman TJ-6R, Beckman Instruments, Irvine, CA), the serum was frozen at −20°C. Aliquots were assayed for tyrosine fluorimetrically using an Amino-Bowman SPF (American Instrument Co., Silver Spring, MD). Eyes were frozen on dry ice and stored at −70°C. Retinas were dissected from the frozen eyes on an ice-cold glass plate. A single-edge razor blade was used to slice off the cornea. Pressure from blunt forceps applied to the rear of the eyeball then pushed out the lens and the frozen vitreous humor with much of the retina adhering to it. A micro spatula was used to scrape off the retina from this frozen liquid and from the inside of the eyeball. This portion was determined to contain at least 71% of the dopamine present in whole eyes. Retinal samples were sonicated in 200 μl of 0.1 N HClO₄ (Cell Disruptor W-225 R, Heat Systems-Ultrasoundics, Plainview, NY) and centrifuged at 10,000 g for 15 minutes (Eppendorf 5413, Brinkmann, Westbury, NY). Supernatant fluids were assayed for dopamine and DOPAC using HPLC with electrochemical detection (BioAnalytical Systems, West Lafayette, IN).

Standards (tyrosine, dopamine, DOPAC, and dihydroxybenzyamine) were obtained from the Sigma Chemical Co. or the Regis Chemical Co., and HPLC grade solvents from the Baker Co. (Phillipsburg, NJ) or from Burdick & Jackson (Muskegon, MI).

Injection of tyrosine (100 mg/kg, ip) to fasted rats caused the expected significant rise in serum tyrosine levels (from 11.4 to 16.4 μg/ml) within 15 minutes (Fig. 1). The tyrosine/LNAA ratio was not measured.) Serum tyrosine remained elevated for at least 2 hours. The retinal contents of dopamine and its acid metabolite, DOPAC, rose in parallel with serum tyrosine during this interval, maximal increases (28% and 40%, respectively) being observed after 15 minutes.

Dose-response studies were then done by injecting fasted rats with 10, 30, or 100 mg/kg tyrosine, and decapitating them 30 minutes later. The animals exhibited dose-related increases in serum tyrosine that were statistically significant at the two higher doses (Fig. 2). Similar patterns were observed for retinal dopamine and DOPAC. Although, in this experiment, the changes in DA and DOPAC were not significant, they were of the same magnitude as those noted in our other experiments, ie, at 100 mg/kg, dopamine levels rose by 20% and DOPAC by 48%.

If animals received both tyrosine (100 mg/kg) and a mixture of other LNAA (valine and leucine; total dose 150 mg/kg) intraperitoneally, the effects of the tyrosine on both serum tyrosine and retinal DOPAC were blocked (Fig. 3); tyrosine and DOPAC levels were reduced to control levels.

Published data indicate that retinal tyrosine levels (0.038 μM/g) are well below those in brain (0.083 μM/g) and well below the Km for retinal tyrosine hydroxylase (0.13 mM). Hence, our observations on tyrosine induced DA synthesis are compatible with a mechanism involving enhanced saturation of tyrosine hydroxylase.

Since retinal light exposure activates retinal tyrosine hydroxylase activity, and since the activated enzyme is, in other tissues, known to be considerably more responsive to added tyrosine than the unactivated form, we are currently examining the extent to which the effects of tyrosine on retinal dopamine synthesis depend on ambient lighting state. In preliminary experiments we have found that light exposure per se is associated with significantly higher retinal DOPAC levels than dark exposure; among animals in light for 14 consecutive hours, DOPAC levels were 3.4 ± 0.2 ng/pair of retinas; among those in light for 12 hours followed by darkness for 2 hours,
retinal DOPAC was only 1.9 ± 0.2 ng/pair of retinas. Retinal DA levels were not significantly different in the two groups (4.7 ± 0.2 vs 3.8 ± 0.4 ng/pair).

These observations encourage the anticipation that changes in plasma composition, such as those following nutritional interventions, will be found to affect retinal function by modifying the quantities of neurotransmitter precursors that are available to retinal neurons. The extent to which retinal cholinergic and indole-containing neurons respond to changes in choline and tryptophan levels is currently under investigation.

References


43. Watling KJ, Dowling JE, Iversen LL. Dopamine receptors in the retina may all be linked to adenylyl cyclase. Nature 1979;281:578–580.


