0031-6997/81/3204-0315$02.00/0
PHARMACOLOGICAL REVIEWS
Vol. 32, No. 4
Printed in U.S.A.

Precursor Control of Neurotransmitter Synthesis

R. J. WURTMAN, F. HEFTI,* AND E. MELAMED†

Laboratory of Neuroendocrine Regulation, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts

I. Introduction

THIS review summarizes our knowledge of the ability of certain neurons to synthesize more or less of their particular neurotransmitters when plasma concentrations of their precursors rise or fall. The transmitters for which there is now the best evidence of precursor control are serotonin, the catecholamines dopamine and norepinephrine, and acetylcholine (227, 92, 86); their circulating precursors are the amino acids tryptophan and tyrosine and the quaternary base choline. The review first describes factors that determine the amounts of these precursors available to the neurons and the intracellular mechanisms that couple precursor availability to neurotransmitter synthesis. It next considers the circumstances that must exist in order for changes in plasma composition to affect neurotransmitter synthesis, as well as the factors that determine whether an increase in the synthesis of a neurotransmitter will, in fact, lead to an increase in its release. Finally, it summarizes data presently available on the physiologic and behavioral effects of neurotransmitter precursors and on their utility, present or potential, in the treatment of neurologic and psychiatric diseases.

* Dr. Hefti's current address is Max-Planck-Institut für Psychiatrie, Abt. Neurochemie, Martinstried, Federal Republic of Germany.

† Dr. Melamed's current address is Department of Neurology, Hadassah University Hospital, Jerusalem, Israel.

Neurotransmitter precursors tend to be much less potent modifiers of neurotransmission than the true drugs that interact with synaptic macromolecules. (As used here, the term "drugs" excludes normal dietary constituents like tyrosine, tryptophan, or choline, which also are invariably present in the circulation.) In general, the precursors are unable to combine directly with neurotransmitter receptors, having first to be converted to agonists by one or more enzymes in the presynaptic neuron. As discussed below (section III), the rate at which this conversion occurs may vary considerably from neuron to neuron and time to time, depending on the neuron's firing frequency, among other things. [One possible exception to the statement that the precursors lack intrinsic synaptic activity may be choline, which has been reported to have one-eighth the muscarinic activity of acetylcholine when applied iontophoretically to neurons in the cat's sensorimotor cortex (120), and which also exhibits very weak muscarinic activity in synaptosomal binding studies (99).] Moreover, all of the neurotransmitter precursors are rapidly metabolized [as demonstrated by the constancy of their fasting plasma levels, regardless of how much protein (64) or lecithin (101) was consumed during the day before the fast] and their status as ligands for ubiquitous transport systems keeps their tissue levels from continuing to rise when they are administered chronically. These disadvantages may become advantages if the precursors are used clinically. For example, precisely because they do not accumulate in tissues after repeated administrations, their concentrations in plasma remain excellent indices of tissue levels at all times; precisely because their conversion to neurotransmitter molecules is often coupled to neuronal firing frequency, they can be kept from causing generalized cholinergic or adrenergic activation by local feedback modulations. The phenomenon of precursor control may, in a sense, be viewed like the talking horse of circus side shows: what is surprising is not its limited vocabulary, but the fact that it talks at all. That the consumption of particular nutrients can affect brain composition and that administration of such nutrients can perhaps be used to modify neuronal functions remains surprising, but may also provide a basis for useful new therapeutic and research strategies.

About 20 or 25 compounds are currently conceived to be neurotransmitters in the mammalian central nervous system (108). These compounds fall into three chemical groups: amines (serotonin, dopamine, norepinephrine, epinephrine, acetylcholine, histamine); certain peptides (such as thyrotropin-releasing hormone, luteinizing hormone-releasing hormone, somatostatin, endorphins, and substance P); and some nonessential amino acids (glutamine, aspartate, glycine) and their metabolites (GABA, taurine, beta-alanine). Some evidence for susceptibility to precursor control is available for all of the neurotransmitter amines except epinephrine, which apparently has yet to be examined; and for the amino acid glycine, whose levels in spinal cord synaptosomes are elevated in rats treated with the essential amino acid threonine (135). It seems unlikely a priori that the synthesis of peptide transmitters will be found to depend on plasma levels of their precursor amino acids, since intraneuronal concentrations of the immediate precursors in peptide formation, amino acid molecules coupled to their respective tRNAs, normally depend not on amino acid levels but on the extent to which the enzymes that bind the amino acid to the tRNA are saturated. In the brain, these tend to be high-affinity enzymes (13). The extent to which circulating precursors control the production of transmitters (other than glycine) that are nonessential amino acids or their products awaits characterization. In some cases, even the identities of these precursors have yet to be established with certainty. Thus, the ability to be affected by precursor availability and plasma composition may characterize only a very small proportion of synapses, i.e. those using an amine or perhaps glycine as their transmitter. However, these tend to be the same synapses as those acted upon by most of the neuropharmacologic agents whose actions are understood, and as those known to be involved in particular diseases. This raises hopes that additional clinical testing of the precursors will point to useful new therapies.

II. Precursor Availability

All neurotransmitters whose syntheses are now known to be influenced by precursor availability are produced from compounds that must be obtained, in whole or in part, from the diet. Tryptophan (like threonine) cannot be synthesized at all by mammalian cells, and is truly an essential amino acid. Tyrosine is formed in the liver, and to a limited extent in the brain (107), from phenylalanine; however, phenylalanine itself is an essential amino acid and its conversion to tyrosine is probably insufficient to satisfy the body's need for tyrosine. Choline, like tyrosine, can be formed in liver and in brain (18, 18a) by hydrolysis of endogenously synthesized lecithin. However, the major portion of the choline in the circulation (especially postprandially) derives from dietary lecithin (101). Small amounts also come from the free choline in such foods as cauliflower (223) or the sphingomyelin in milk (223). Like other nutrients, the neurotransmitter precursors are stored in the organism within very large metabolic pools, in the form of tissue proteins and membrane lecithins; thus failure to consume them for short periods causes relatively small decreases in their plasma levels beyond those observed after a normal overnight fast.

As described below, consumption of a meal can increase plasma tryptophan, choline, or tyrosine concentrations as much as severalfold for short periods of time (the number of hours needed to digest and absorb the meal) (fig. 1A), if the meal happens to include foods rich in protein or lecithin (101, 64, 105). If the meal lacks lecithin, it will have no effect on plasma choline (101); if it lacks protein, it will actually *lower* plasma levels of

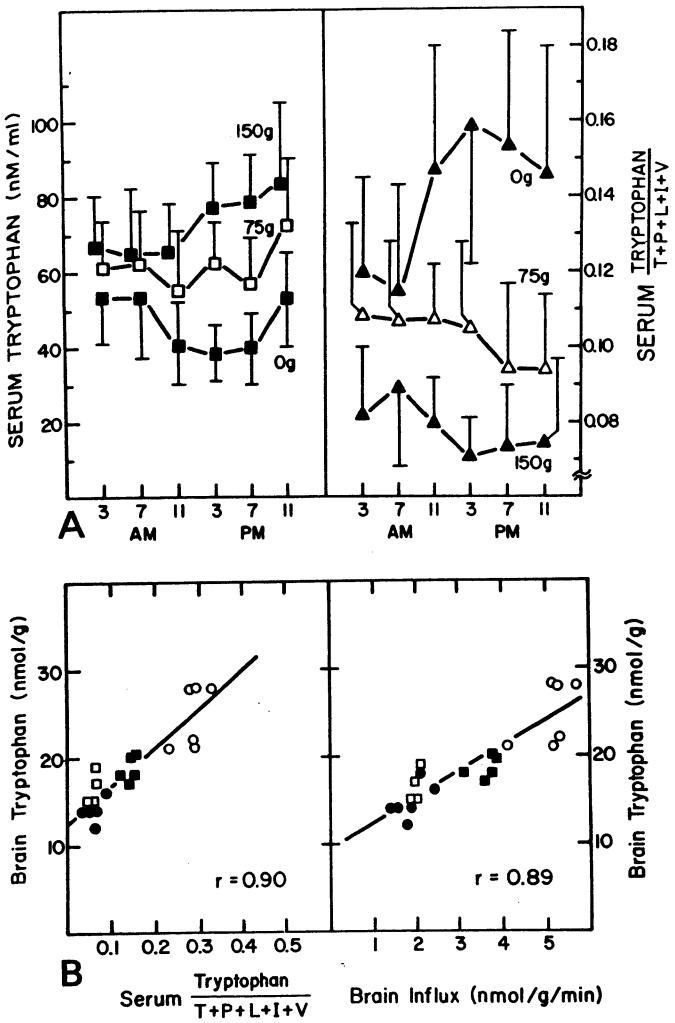

FIG. 1A. Relation between dietary protein content and plasma tryptophan levels (or tryptophan ratios) in healthy male subjects consuming 0, 75, or 150 g of protein daily and having plasmas sampled at 4-hr intervals. Vertical bars indicate standard deviations. Each point represents blood taken on the fourth and fifth days (data pooled) from seven subjects consuming the indicated diet for 5 consecutive days; all subjects consumed all three diets. Plasma tryptophan levels (in humans and experimental animals) vary directly with dietary tryptophan content, while the plasma tryptophan ratios vary inversely with dietary protein (64).

FIG. 1B. Relationship between brain tryptophan levels and the serum tryptophan ratio, or the calculated brain tryptophan influx, in individual animals consuming (for 2 hr) single meals of different protein content. ● = fasting controls; ○ = animals ingesting 0% protein; ■ = rats consuming 18% protein; □ = rats consuming 40% protein. Data were analyzed by linear regression; the values of the correlation coefficient differed significantly from 0 ($P < .01$, t-test) (60).

most of the amino acids because of the insulin secretion it elicits (64, 226). In order for a circulating precursor to affect brain neurotransmitter synthesis, it is a prerequisite that such increases (or decreases) in its plasma concentration be *allowed* to occur. That is, there must not be feedback mechanisms that keep plasma precursor levels from changing after consumption of meals or after ingestion of the precursors themselves. Were such feedback mechanisms to operate for plasma choline and amino acids (as they do, for example, for plasma glucose, temperature, and osmolarity), maintaining their concentrations within narrow ranges regardless of the amounts consumed, then neurotransmitter synthesis would be independent of plasma composition. In the absence of feedback mechanisms, diseases that disrupt a metabolic "sink" for an amino acid or choline, like phenylketonuria (72) or hepatic failure (172), can cause very major changes in their plasma levels, and may thereby alter neurotransmitter synthesis (160, 67, 137) and cause important neurologic sequelae. A normal condition, that of the newborn, also is associated with major elevations in plasma levels of a neurotransmitter precursor: plasma choline levels in human infants and late fetal and neonatal choline levels in experimental animals are more than 3-fold those of adults (235) and are even higher than levels induced in adult subjects given lecithin or choline to treat neurologic diseases. This elevation probably reflects the delayed development of choline-metabolizing enzymes in the liver; its effect on cholinergic function awaits examination.

A second phenomenon that must exist in order for plasma precursor levels to affect neurotransmitter synthesis is the presence of mechanisms within the blood-brain barrier that allow precursor molecules in the circulation to equilibrate with those in brain extracellular fluid (fig. 2) (166, 60, 168). If the blood-brain barrier for tryptophan or choline, for example, really were an absolute barrier, then brain levels of these transmitter pre-

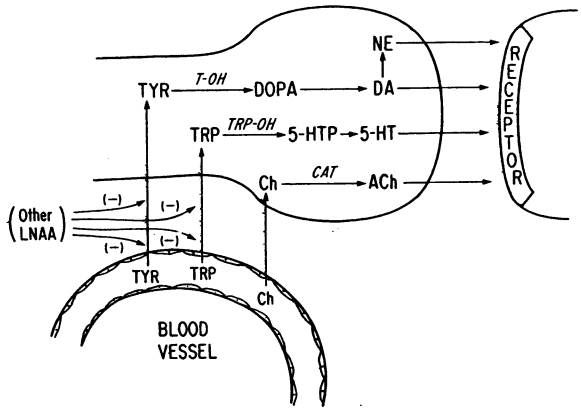

FIG. 2. Schematic diagram illustrating the blood-brain barrier mechanisms mediating the transport of neurotransmitter precursors into the brain's extracellular space, the uptake of these compounds into neurons, and their conversion to the neurotransmitters. Choline (Ch) apparently is taken up by a noncompetitive system and is converted to acetylcholine (ACh) by the enzyme choline acetyltransferase (CAT). The uptakes of tryptophan (TRP) and tyrosine (TYR) at both the blood-brain barrier and the neuronal membrane are competitive with each other and with other large neutral amino acids (LNAA). The rate at which tryptophan is converted to 5-hydroxytryptophan (5-HTP) and thence to serotonin (5-HT) is controlled by the enzyme tryptophan hydroxylase. Similarly, the syntheses of the catecholamine transmitters, dopamine (DA) and norepinephrine (NE), from tyrosine via DOPA, can depend on the concentration of intraneuronal tyrosine available to tyrosine hydroxylase. (Any particular neuron produces *only* ACh, 5-HT, or a catecholamine.)

cursors would be unaffected by their consumption or administration. In fact, the capillary endothelia that comprise the blood-brain barrier contain two specific transport systems for neurotransmitter precursors: one for choline (168, 38) and another for such large neutral amino acids (LNAA) as tryptophan, tyrosine, threonine, the branched-chain amino acids (leucine, isoleucine, and valine), phenylalanine, and methionine (fig. 3) (166, 168). Neither transport system is energy-requiring, nor can either maintain a concentration gradient: rather, both serve to facilitate the diffusions of their substrates from blood into brain (influx) or in the opposite direction (efflux). At steady-state, brain choline levels probably are higher than those in arterial plasma (4b, 35), probably reflecting the de novo synthesis of choline in brain or its liberation from circulating phospholipids (4b, 18, 18a); hence, the prevailing direction of choline flux is from brain to blood (52). Consumption of a choline-rich meal or a therapeutic dose of lecithin raises blood choline levels; this both accelerates the influx of choline into the brain and, by diminishing its concentration gradient from brain to blood, slows its efflux. The blood-brain barrier transport of choline constitutes a locus at which drugs can act to influence cholinergic functions. Thus, deanol (dimethyl-aminoethanol) competes with choline (149) for influx, an observation that may explain why high doses (that temporarily exceed the capacity of the liver to convert them to choline) may actually impair cholinergic functions. Lithium salts apparently suppress the efflux of choline more than its influx (150, 54); this potentiates the increases in brain choline levels and acetylcholine synthesis caused by a given dose of choline or lecithin.

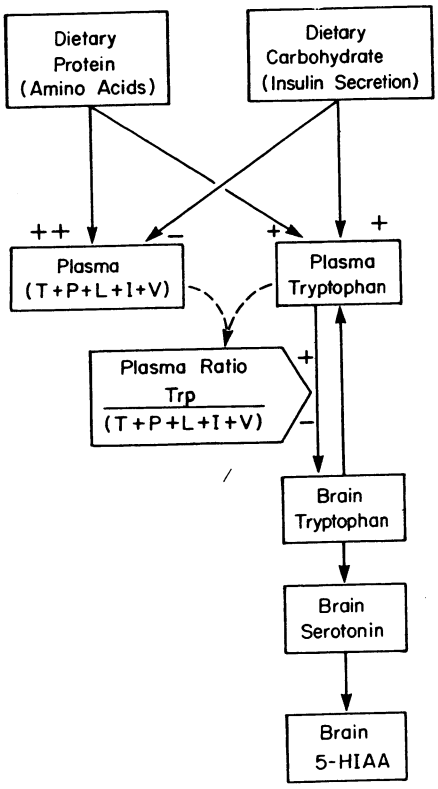

FIG. 3. Schematic diagram illustrating relationships between food consumption, plasma amino acid levels, and brain serotonin synthesis and release. Carbohydrate consumption elicits insulin secretion, which markedly lowers plasma levels of LNAA other than tryptophan (e.g. tyrosine, phenylalanine, leucine, isoleucine, and valine). This increases the plasma tryptophan ratio, which facilitates the transport of tryptophan into the brain. The resulting increase in the saturation of tryptophan hydroxylase enhances the synthesis and release of the neurotransmitter serotonin. The addition of protein to a meal tends to diminish the plasma tryptophan ratio because all dietary proteins contain proportionately much less tryptophan than other LNAA; thus they tend to lower brain tryptophan levels and diminish serotonin synthesis and release (61).

The kinetics of LNAA transport across the blood-brain barrier are such that transport is competitive between the individual amino acids. This reflects the fact that a single mechanism mediates the brain uptake of all the LNAA, and that its K_m for them is about equal to their total plasma concentration (167, 230). Hence, the entry of circulating tryptophan (or tyrosine) into the brain can be accelerated *either* by raising plasma tryptophan (or tyrosine) levels or by lowering plasma levels of other LNAA (166, 60, 63). Insulin enhances brain serotonin synthesis primarily by reducing the denominator of this ratio (fig. 3). Insulin administration (or its secretion after carbohydrate consumption) has little effect on plasma tryptophan levels but markedly lowers plasma levels of the other LNAA (63); this increases the *plasma tryptophan ratio* (the ratio of the tryptophan concentration to the sum of the other competing LNAA concentrations), thereby facilitating the flux of tryptophan into the brain. Brain tryptophan levels are raised, thus increasing the saturation of the enzyme (tryptophan hydroxylase) that controls the rate at which neurons synthesize serotonin (130). The reason that plasma tryptophan levels do not fall after insulin is secreted has to do with that property of tryptophan, unique among natural amino acids, of traveling in the circulation largely bound to albumin (142) by a low-affinity, high-capacity mechanism (133, 118, 196). Ordinarily, as much as 75% to 80% of the total amount of nonpeptide tryptophan in the blood stream is albumin-bound. When insulin is secreted, plasma levels of nonesterified fatty acids (NEFA) fall, because insulin facilitates the uptake of NEFA into fat-producing cells. As these NEFA molecules are stripped off the circulating albumin (to which almost all are bound normally), the affinity of albumin for tryptophan increases substantially (167, 133, 118, 127); hence, plasma levels of albumin-bound tryptophan rise. This rise in bound tryptophan makes up for the fall in plasma "free" tryptophan (which is proportionate to the declines in the other aromatic LNAA). Apparently, the *total* amount of tryptophan in the plasma (i.e. albumin-bound plus free) determines the amount of the amino acid that is potentially accessible to the brain; this is because the affinity for tryptophan of the blood-brain barrier transport mechanism, estimated from its V_{max}/K_m ratio (167, 230), is considerably greater than the affinity for tryptophan of albumin. When an albumin-bound tryptophan molecule passes through brain capillaries, the likelihood that it will dissociate from

the albumin and be taken up into the brain is only about 22% less than that of a corresponding "free" tryptophan molecule (234).

Tryptophan tends to be very scarce in most dietary proteins (about 1% of the total amino acid content) (226); moreover, unlike the branched-chain LNAA, portal venous tryptophan is extensively metabolized in the liver (177a). Hence, when a given amount of protein is consumed in a meal, its direct contribution of tryptophan molecules to the systemic circulation is proportionately much less than its contribution of the other LNAA. The net effect of any meal on the plasma tryptophan ratio will be the resultant of two processes, i.e. the postprandial secretions of insulin (which markedly lowers blood levels of the branched-chain LNAA, but not of tryptophan) and the passage into the circulation of some of the amino acids in the dietary protein (which contributes many more molecules of the other LNAA than of tryptophan). If a given meal contains about 10% protein (18% for the rat), the net increase in plasma tryptophan will be approximately proportionate to that in the other plasma LNAA; the plasma tryptophan ratio will thus remain unchanged, as will brain tryptophan and serotonin levels (figs. 1 and 3) (60, 63). Below this level of protein, the insulin-mediated postprandial fall in plasma LNAA will not be sufficiently compensated by the direct contribution of LNAA from dietary protein; hence, the plasma tryptophan ratio will rise. Conversely, if the protein content of the meal is increased beyond this proportion, then the marked increase in other plasma LNAA will cause the plasma tryptophan ratio to fall below initial levels, suppressing brain serotonin synthesis (63) (fig. 1). Serotonin-releasing brain neurons can thus function as *variable ratio sensors*, making and probably releasing more or less of their transmitter in inverse proportion to the protein content of the most recently eaten meal. As discussed below, the brain may utilize this property in decisions about food choices (224).

Unlike tryptophan, tyrosine is fairly abundant in dietary proteins. Moreover, at least half of the phenylalanine in protein is converted to tyrosine in each passage through the hepatic circulation (55). Plasma tyrosine levels are lowered by insulin, which stimulates the uptake of tyrosine into skeletal muscle (226), but not proportionately as much as levels of the branched-chain LNAA, leucine, isoleucine, and valine (which, unlike the aromatic LNAA, are metabolized primarily in muscle). These factors cause the effects of particular diets on plasma factors affecting brain tyrosine uptake to differ considerably from those affecting tryptophan. A protein-free meal will cause no change or a small increase in the *plasma tyrosine ratio* (the ratio of the tyrosine concentration to the sum of the other competing LNAA concentrations), while the addition of protein will increase this ratio (80) and potentially accelerate catecholamine synthesis (80, 81) (fig. 2). A large dose of tyrosine will raise brain tyrosine levels, but will lower those of tryptophan and other LNAA. Similarly, a large tryptophan dose can lower brain tyrosine and may thereby compromise central catecholaminergic transmission (229). It can be anticipated that a variety of synthetic amino acid mixtures will be developed by investigators and clinicians who wish to cause an increase, decrease, or no change in one monoamine neurotransmitter, while primarily altering another. If the mix also contains sufficient carbohydrate, the effect of its amino acid content on brain tyrosine or tryptophan will be amplified by the resulting insulin-mediated fall in other plasma LNAA.

A third factor that must operate in order for plasma composition to affect neurotransmitter synthesis relates to the kinetics of the participating blood-brain barrier transport system. It must be of the *low-affinity* type, and must not be saturated with its substrate (i.e. the precursor of the neurotransmitter) at physiologic plasma concentrations. For example, if the affinity of the choline transport carrier (reflected in its K_d or K_m for its ligand) were such that, at normal plasma choline levels, the carrier was fully saturated, then further increases in plasma choline caused by lecithin administration would have no effect on the flux of choline across the blood-brain barrier or its steady state levels in the brain. Both the choline and LNAA transport systems exhibit low-affinity kinetics (fig. 1B); hence, brain levels of choline, tryptophan, and tyrosine vary with the plasma choline level and with the plasma tryptophan or tyrosine ratios (166, 60, 34). The predictability of this relationship is important clinically: it is not necessary actually to obtain samples of brain tissue, or even cerebrospinal fluid, in order to estimate the changes in brain choline, tyrosine, or tryptophan that occur after a given meal or treatment; one need measure only plasma choline or LNAA concentrations (101, 64). Very little information is available about the capillary macromolecules that underlie the blood-brain barrier transport systems or the factors that influence their concentrations in endothelial cells (168). There is evidence that in at least one disease state, acute hepatic failure, the transport V_{max} for some LNAA into the brain is increased (137); the associated rise in brain tryptophan may contribute to the development of hepatic coma (137).

Do neurons making a particular transmitter possess special mechanisms for taking up its precursor from the extracellular fluid of the brain? Insufficient data are available to justify a firm answer to this question; however, those data that exist do not make a strong case for such special uptake systems. Cholinergic nerve terminals are thought by some (232, 121), but not all (116), investigators to contain a high-affinity mechanism (K_m = 1 μM) that catalyzes the uptake of choline from the synaptic cleft; this presumably allows terminals to reutilize choline formed intrasynaptically (from the hydrolysis of acetylcholine by acetylcholinesterase) for resynthesis of the transmitter (232, 121, 116, 16). However, the kinetics of this uptake mechanism cannot account for observed rates of acetylcholine production in the brain (26) or phrenic nerve (16a) nor for the phenomenon of precursor

control. The high-affinity mechanism is probably too well saturated with choline at basal intrasynaptic choline levels [estimated to be as high as 1 mM (53)] to allow choline or lecithin administration to cause it to transport more of the precursor (121). Like other cells, cholinergic neurons also contain a high-capacity, low-affinity uptake system (16) (K_m = 100 μM), and this mechanism probably mediates the uptake of most of the choline in extracellular fluid that is destined to become acetylcholine (16, 16a, 128). Isolated brain nerve terminals (synaptosomes) contain two mechanisms catalyzing the uptake of tyrosine and, probably, tryptophan (157, 23). One of these exhibits high-affinity (K_m = approximately 8 μM); the other is low-affinity, and perhaps even diffusional, since it continues to take up additional tyrosine beyond the point that no more amino acid can be dissolved in the medium. Both mechanisms exhibit competition among LNAA; the pattern of competition is similar to that of the blood-brain barrier uptake system. At physiologic LNAA concentrations, at least half the tyrosine that passes from the extracellular fluid of the brain to nerve terminals apparently does so via the low-affinity mechanism (157). Synaptosomal tyrosine-uptake mechanisms are present in all brain regions, but their concentrations vary in a manner roughly paralleling the distribution of catecholaminergic terminals (156). In summary, when plasma choline or LNAA levels change, qualitatively similar alterations probably occur in all brain neurons.

III. Mechanisms Coupling Intraneuronal Precursor Levels to Neurotransmitter Synthesis

In order for treatment-induced changes in plasma and brain tryptophan, choline, or tyrosine levels to cause parallel alterations in the syntheses of their neurotransmitter products, the enzyme catalyzing the key step in this biotransformation *must* be capable of generating more product when exposed to increased concentrations of its substrate. This requires that the enzyme not be saturated fully with the precursor or, stated another way, that the affinity of the enzyme for its substrate (as indicated by the Michaelis-Menten constant) be poor in relation to available substrate concentrations. It also requires that the enzyme not be subject to significant feedback inhibition by its products.

The first requirement is fulfilled by the rate-limiting enzymes that produce catecholamines, serotonin, and acetylcholine. The K_m of tyrosine hydroxylase for tyrosine, studied in vivo [approximately 25 μM (25)] and in vitro (115), is probably in the same range as the tyrosine concentrations in brain homogenates, which suggests that the enzyme normally is only about 50% to 75% saturated (25). There is a similar relationship with tryptophan hydroxylase [K_m = approximately 25 μM in vivo (25)] and brain tryptophan (130, 24, 94). Choline acetyltransferase, which forms acetylcholine from choline and acetyl-coenzyme A, has a far lower affinity for choline (that is, a much higher K_m, approximately 400 μM) than usual brain choline concentrations (34, 218); its V_{max} in brain areas like corpus striatum is also far higher than their estimated rates of in vivo acetylcholine synthesis.

There are at least three theoretical loci at which feedback mechanisms might operate to dampen the acceleration of synthesis of a neurotransmitter that follows administration of its precursor. The first is within the neuron itself and involves direct inhibition by the product of the enzyme (the neurotransmitter) of the rate-limiting enzyme. The second includes an extracellular link: release of the transmitter into the synaptic cleft, followed by its interaction with *presynaptic* dendritic autoreceptors located on its neuron of origin. Such receptors could "inform" the neuron that more transmitter was being released, and thereby activate intracellular mechanisms (perhaps involving allosteric changes in the same rate-limiting enzyme) for slowing transmitter synthesis. The third presupposes a multisynaptic reflex arc that diminishes the firing rate of the precursor-dependent neuron when the amount of transmitter released per firing has increased. An additional intracellular mechanism would couple the change in the firing frequency of the neuron to the activity of the rate-limiting enzyme.

Treatments that raise brain tryptophan levels accelerate brain serotonin synthesis and increase brain concentrations of both serotonin and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) (36, 63). In vitro studies with tryptophan hydroxylase have not provided evidence that the enzyme is subject to significant direct inhibition by its product serotonin (130, 73). Furthermore, a treatment that increased brain serotonin levels in vivo (administration of a monoamine oxidase inhibitor) failed to block the further increase in serotonin synthesis caused by administering tryptophan (111). Large doses of tryptophan that elevate brain tryptophan levels beyond their normal dynamic range do slow the firing of serotonin-containing raphe neurons (74); this diminishes serotonin release and might also suppress serotonin synthesis. These observations suggest that feedback control of brain serotonin synthesis is minimal within the normal dynamic range of brain tryptophan levels (i.e. those levels associated with eating various foods or taking low doses of tryptophan). However, it should be noted that treatments that cause unphysiologic changes in brain tryptophan (i.e. administering 1 g/kg of an LNAA; consuming a tryptophan-free diet) can cause tryptophan hydroxylase activity to change in the opposite direction (162).

Choline acetyltransferase exists in several isomeric forms (136, 184, 217), at least one of which (184) may be inhibited by acetylcholine concentrations similar to those found within vesicles (16). Within intact neurons, however, choline acetyltransferase exists mainly in the cytoplasm, where acetylcholine concentrations are thought to be low (16). Corpora striata from rats given a choline dose adequate to cause a prolonged increase in acetylcholine levels exhibit no decrease in choline acetyltransferase activity during the interval in which acetylcholine is elevated, and a small increase in the enzyme's activity

on the following day (65). Tardive dyskinesia patients receiving therapeutic doses of lecithin for a year (75) exhibit no tolerance to lecithin, as would be anticipated if the resulting increase in acetylcholine levels inhibited choline acetyltransferase.

The situation is somewhat more complex in the case of catecholaminergic neurons, where end-product inhibition of tyrosine hydroxylase has been demonstrated both directly, in vitro (161), and in vivo among animals given monoamine oxidase inhibitors to raise catecholamine levels (131). Catechols can inhibit the enzyme by interfering with the binding of its cofactor, reduced biopterin (161). However, it has never been shown that intraneuronal catecholamine levels can increase in vivo sufficiently to inhibit tyrosine hydroxylase activity *except* when animals are treated with a monoamine oxidase inhibitor. Such drugs change *both* the level and the intracellular distribution of the catecholamines, causing the transmitters to accumulate in the cytoplasm of the cell in the vicinity of tyrosine hydroxylase, where they normally are undetectable.

Catecholamine synthesis and release are also modulated by extracellular feedback mechanisms involving both presynaptic or dendritic autoreceptors and changes in neuronal firing rates (59, 164). Presynaptic alpha receptors, activated by norepinephrine or clonidine and blocked by phenoxybenzamine, suppress the release of ^{3}H-norepinephrine from electrically-stimulated perfused tissues containing noradrenergic terminals; their effect has been reported to diminish when neuronal firing rates increase (123, 191, 114). That similar feedback mechanisms also act in vivo to buffer neurons from tyrosine-induced changes in catecholamine synthesis is suggested by the fact that tyrosine administration has never clearly been shown to elevate brain or tissue catecholamine levels. The hydroxylation of tyrosine to DOPA is accelerated by tyrosine administration in brains of rats given a drug that blocks the subsequent conversion of DOPA to catecholamines (229, 25); however, this response need not imply that tyrosine administration also accelerates the synthesis of DOPA when its conversion to a catecholamine is not blocked.

Despite evidence for extracellular feedback control of tyrosine hydroxylation, the availability of tyrosine does indeed affect catecholamine synthesis and turnover under a variety of conditions. For example, levels of homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) in the caudate nucleus (which may provide an indication of changes in the rate at which dopamine is released from nigrostriatal neurons) are increased by tyrosine administration in rats pretreated with haloperidol (179) or reserpine (194) (which block dopamine receptors and dopamine storage, respectively); or after partial lesioning (more than 75%) of the nigrostriatal tract (144) [which apparently accelerates the firing frequencies of surviving dopaminergic neurons (4)]. Tyrosine also enhances the increase in striatal dopamine levels in rats given gamma-butyrolactone (193), which itself activates nigrostriatal tyrosine hydroxylase (154) and increases striatal dopamine levels (189) while suppressing nigrostriatal impulse flow. Tyrosine enhances norepinephrine synthesis and release in brains of normal animals subjected to cold stress (80), and in brainstems of spontaneously hypertensive rats not otherwise treated (195). What all these experimental situations appear to have in common is their propensity either to accelerate the firing of the tyrosine-dependent catecholaminergic neurons or to diminish the local feedback responses mediated by presynaptic catecholamine receptors. Thus, the extent to which a catecholaminergic terminal exhibits precursor-dependence at any time seems to depend on its physiologic activity at that time. The hypothetical mechanism that couples the frequency of neuronal depolarization to tyrosine-responsiveness awaits characterization; it could involve changes in the activity of tyrosine hydroxylase, perhaps mediated by phosphorylation of the enzyme, which might increase its V_{max} and affinity for its pteridine cofactor (112). Alternatively, it could result from the reported tendency of presynaptic receptors to become less effective in suppressing catecholamine release when neuronal firing frequencies increase (123, 191).

An apparent relationship between frequency of depolarization and responsiveness to increased precursor levels seems also to characterize cholinergic and serotoninergic neurons. For example, increasing the choline concentration in the medium has only a small effect on the spontaneous release of acetylcholine from motor neurons innervating the rat diaphragm (fig. 4) (16, 16a) or from brain preparations (216); yet, choline markedly augments acetylcholine release when the phrenic nerve (16, 16a) is stimulated electrically in the physiologic range, or when the brain slices (195a) or minces (26) are exposed to potassium ions. Based on such evidence, a tentative principle can be proposed concerning the extent to which *any* neuron containing a precursor-dependent transmitter will be affected by actual changes in that precursor's availability: precursor dependency becomes manifest, or is enhanced, under conditions that accelerate the frequency with which a neuron becomes depolarized. This "law" is, of course, based only on empirical observations and in no way implies that precursor levels are the major factor that modulate the synthesis of any transmitter under any conditions.

Why is it that administration of tyrosine apparently fails to elevate brain dopamine or norepinephrine levels if, as proposed, tyrosine hydroxylase is less than fully saturated with its amino acid substrate, not significantly affected by allosteric end-product inhibition, and capable of being activated when catecholaminergic neurons fire? Perhaps very large fractions of the dopamine or norepinephrine are stored in metabolic or cellular pools that turn over very slowly; even major increases in the size of the "active," tyrosine-dependent pool could thereby go unnoticed. Alternatively, perhaps investigators simply have not yet utilized optimal experimental conditions

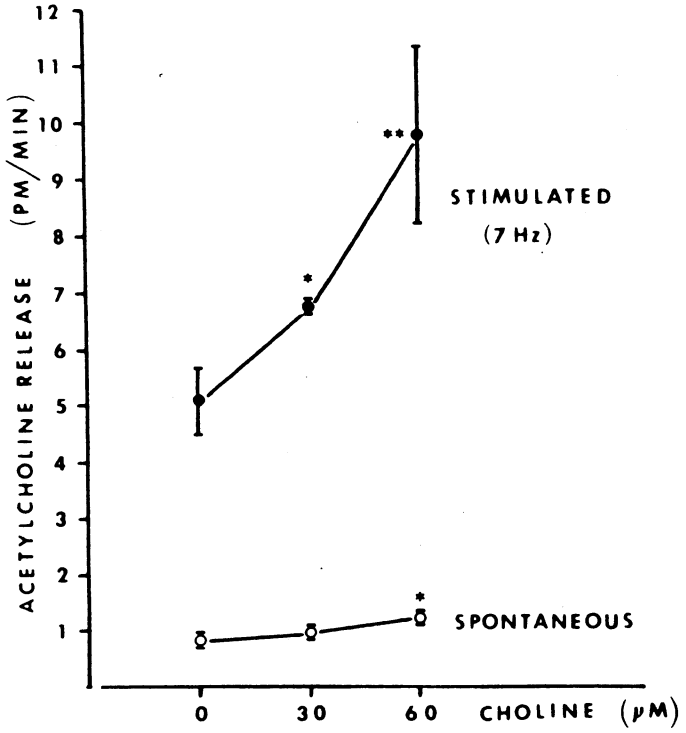

FIG. 4. Relation between choline availability and acetylcholine release. An intact rat phrenic nerve-diaphragm was incubated in the presence of various choline concentrations and a cholinesterase inhibitor; acetylcholine release was measured in the resting state and after electrical stimulation of the nerve (7 Hz; 0.2 msec; 0.6 V). In the resting state, increasing choline concentration in the medium had only a slight effect on acetylcholine release; with nerve-stimulation precursor, availability had a major influence on the amount of acetylcholine released ($^*P < 0.01$) (16).

(e.g. treatments that chronically increase neuronal firing frequencies) or have not yet examined catecholamine levels in brain regions containing the most responsive groups of catecholaminergic neurons.

IV. Precursor Availability and Neurotransmission

The total amount of information that a group of neurons can transmit during any particular interval probably depends on several factors, one of which is the number of neurotransmitter molecules that their presynaptic terminals are releasing during that interval. This, in turn, depends on the total number of synapses that the neurons make, the average frequency with which the neurons happen to be firing, and the average amount of transmitter released at each synapse per firing. If precursor-induced changes in neurotransmitter *synthesis* are to be of any physiologic relevance, then such changes must cause increases in the amount of transmitter *released*, both per depolarization and per unit time. This may or may not modify postsynaptic responses, depending on such additional factors as whether unoccupied postsynaptic receptors are available to respond to the additional neurotransmitter molecules. [Precursor administration may also affect the number of receptor molecules; the presence of choline in the diet has been reported to increase the number of nicotinic receptors in the brain (155).] But an increase in transmitter release is a prerequisite, if precursor-induced changes in transmitter synthesis are to have functional significance. If most brain neurons are controlled by feedback mechanisms, involving presynaptic receptors or multisynaptic reflex arcs, that keep neurotransmitter release per unit time constant, despite fluctuations in the levels of transmitter within presynaptic terminals, then when, if ever, does precursor availability actually affect neurotransmission? There are a number of situations, outlined below, in which this seems probable.

A. Neurons That Lack Multisynaptic Feedback Loops

Peripheral sympathetic neurons (and chromaffin cells) in humans (3) and experimental animals (4a) release more catecholamines after tyrosine has been administered or a protein-rich meal has been consumed. That the resulting increase in urinary catecholamine levels represents increased catecholamine release and not, for example, alterations in catecholamine metabolism, is indicated by the fact that levels of catecholamine metabolites in the urine also rise; that this reflects accelerated catecholamine synthesis and not simply release of stored material is indicated by the failure of tissue catecholamine levels to decline (4a).

Another locus at which the effect of a precursor on neurotransmitter release may not be modulated by multisynaptic feedback loops involves preganglionic cholinergic neurons terminating in sympathetic ganglia (208) or in the adrenal medulla (204). In both tissues, chronic administration of choline (2 to 4 days) causes persistent increase in tyrosine hydroxylase activities within the postsynaptic cells. The time-course and actinomycin sensitivity of these increases suggest that they reflect enzyme induction (204). When the firing frequencies of the preganglionic cholinergic neurons are accelerated [by pretreating animals with reserpine (205), dibenzylene, 6-hydroxydopamine, or insulin (206), or by placing them in a cold environment (206)], the induction by choline of postsynaptic tyrosine hydroxylase is markedly amplified; the two treatments potentiate each other. [That the locus of action of choline is within the adrenal, on acetylcholine release per firing, and not via a centrally mediated acceleration in the frequency of splanchnic nerve firing, is suggested both by this potentiation and by the fact that centrally acting muscarinic agonists like oxotremorine fail to reproduce choline's effects on sympathoadrenal tyrosine hydroxylase activity (208a)].

B. Neurons That Are Components of Positive Feedback Loops

If a neuron releases a precursor-dependent *excitatory* neurotransmitter directly onto its own receptors, or if its depolarization, acting transsynaptically, causes it to receive greater quantities of excitatory transmitters from other neurons and thus to fire more frequently, then the initial increase in transmitter release after precursor administration may enhance subsequent responses to the

precursor. There might be such a situation in cholinergic interneurons within the basal ganglia (140). These neurons may synapse onto themselves, adjacent cholinergic neurons, and nigrostriatal terminals, as well as onto the perikarya of other neurons. Choline or lecithin administration increases acetylcholine levels in (34, 102), and release from, these neurons, as indicated by the resulting activation of tyrosine hydroxylase (207, 176a) (within nigrostriatal terminals) and the increase in caudate HVA levels (98). The concurrent increase in caudate choline acetyltransferase activity (65) suggests that the cholinergic neurons are also activated by the choline. The effect of choline on caudate acetylcholine levels is enhanced in animals receiving atropine [(i.e., comparing these levels with those observed in animals receiving atropine alone (215, 213)], presumably because the muscarinic antagonist acts via multisynaptic pathways to accelerate the firing of the cholinergic interneurons. The long-axon neurons of the septohippocampal tract show much smaller changes in acetylcholine content after choline administration (65, 215) than do caudate interneurons. Perhaps the septohippocampal cells fail to receive positive feedback signals after choline administration and thus fail to increase their firing frequencies and become more choline-dependent.

C. Neurons That Normally Release Variable Quantities of Neurotransmitter per Firing without Engaging Feedback Responses

If the mechanisms controlling the firing frequencies of a group of neurons allow the neurons to release widely varying amounts of neurotransmitter per unit time without undergoing feedback changes in firing, then precursor availability might be expected to exert undampened effects on neurotransmitter output within this broad range.

One group of neurons that may manifest this kind of control is the serotonin-releasing cells of the raphe nucleus. The rate at which they synthesize and release neurotransmitter apparently varies directly with tryptophan availability throughout the physiologic range of brain tryptophan concentrations (more than 2-fold) (62). Raphe firing does decrease when animals are given very large doses of tryptophan (74), indicating that there *is* an upper limit to serotonin release beyond which the neurons are subject to feedback control, but not when they receive smaller doses (20a). The ability of serotoninergic neurons to serve as variable ratio sensors, releasing more or less of their transmitter in response to changes in plasma amino acid pattern, may allow them to provide the rest of the brain with useful information about peripheral metabolic state, which can then be used to formulate behavioral strategies. Serotoninergic neurons apparently participate in a complex neural-behavioral mechanism controlling appetites for carbohydrates. If animals are pretreated with a drug that, like carbohydrate consumption (62), increases serotonin release, and if they are then given a choice between various diets, they selectively reduce their consumption of carbohydrates while sustaining protein intake (224, 225). This effect is independent of whether the carbohydrates in the test foods happen to be sweet (225).

D. Physiologic Situations in Which Neurons Undergo Sustained Increases in Firing Frequency

As outlined above, the extent to which the cholinergic neurons of the rat's phrenic nerve respond to elevated choline concentrations by releasing more acetylcholine (fig. 4) varies with their firing frequency (16). Indirect evidence for a similar relationship between firing frequency and precursor responsiveness has been obtained for striatal cholinergic neurons by destroying some of them with locally injected kainic acid (129). Subsequent systemic administration of choline chloride failed to elevate acetylcholine levels significantly on the intact side, but doubled these levels in the surviving cholinergic neurons within the lesioned striata. (Presumably, these neurons were firing more frequently than those on the intact side.)

The mechanism underlying the apparent relationship between firing frequency and precursor dependence remains to be established; it could involve, among other things, activation of a biosynthetic enzyme, suppression of the inhibitory effects of an autoreceptor, or an effect of an ion whose flux is altered by depolarization. The relation between firing frequency and precursor responsiveness appears to be general, and is well illustrated by the ability of exogeneous tyrosine to raise *or* lower blood pressure depending upon which of the animal's noradrenergic neurons happens to be most active at the time of its administration. Noradrenergic neurons at several loci participate in the control of blood pressure (165). Norepinephrine release from peripheral sympathetic nerves tends to elevate blood pressure, while its application to or release from certain brainstem sites tends to lower blood pressure (presumably by diminishing sympathetic outflow) (49). If normotensive rats (mean systolic blood pressure = 100 to 130 mm Hg) receive a given dose of tyrosine (100 to 200 mg/kg, i.p.), blood pressure falls only slightly or not at all (195); in human subjects it also fails to change (82, 143). If the same tyrosine dose is given to a spontaneously hypertensive rat (mean systolic blood pressure = 170 to 210 mm Hg), blood pressure falls by 28 to 46 mm Hg for several hours (195); however, if that dose is given to a *hypotensive* animal (mean blood pressure = 63 mm Hg, 45 min after hemorrhage of 20% of calculated blood volume), systolic pressure *rises* by 31 mm Hg (36a). Treatments that increase blood pressure accelerate the release of norepinephrine from brainstem neurons terminating in the anterior hypothalamus (171) (as well, presumably, as the firing of noradrenergic neurons in this region), while those that produce hypotension activate sympathoadrenal structures and catecholaminergic terminals in the posterior hypothalamus (185). Hence, the most economical explanation for the paradoxical ability of tyrosine to raise *or* lower blood pressure, depending on physiologic state, is that in the case of the

hypertensive animal, the precursor enhances norepinephrine release selectively within one set of brainstem neurons (because these happen to be firing frequently), while in shock peripheral sympathetic neurons and adrenomedullary cells are activated and thus tyrosine-sensitive.

Intravenous tyrosine lowers blood pressure slightly in normotensive rats, and markedly reduces blood pressure in animals with renovascular or DOCA-salt hypertension. These changes are associated with a reduction in heart rate and with increases in plasma dopamine and epinephrine, but not norepinephrine (20a). [Tryptophan has about half the blood-pressure-lowering activity of tyrosine (195), possibly acting by increasing serotonin release from bulbospinal neurons, while branched-chain LNAA lack any effect on blood pressure and, when administered with tyrosine, block its effect (195).]

Similar relationships between precursor-dependence and apparent firing frequency have, as discussed above, been shown to occur in nigrostriatal dopaminergic neurons (179, 144) and in preganglionic sympathetic cholinergic neurons [e.g. in rats given hypotensive agents (206)]. Thus, short-term physiologic conditions that accelerate the firing of precursor-dependent neurons may overcome the feedback mechanisms that would otherwise maintain the constancy of neurotransmitter *release*, and allow the neuron to couple precursor availability to transmitter release.

E. Neurologic Diseases That Cause either a Decreased Number of Synapses or Decreased Transmitter Release per Unit Time

Neurodegenerative disorders that diminish the number of presynaptic terminals issuing from a precursor-dependent brain nucleus may be associated with accelerations in the average firing rates of the surviving neurons (15), enhancing their sensitivity to precursor control (Fig. 5). This formulation provides a theoretical basis for testing neurotransmitter precursors in Alzheimer's disease, postanoxic myoclonus, and Parkinson's disease. It also offers an explanation for the specificity of action that seems to be associated with the therapeutic use of neurotransmitter precursors. If the brain contains, for example, 10 groups of cholinergic neurons, and if all but one of these groups are intact and functioning normally, it might be anticipated that only this one group would be substantially affected by precursor administration. The elevation in brain choline levels would initially enhance acetylcholine release from all 10 groups, but in the nine normal nuclei, this effect would rapidly be dampened by presynaptic or multisynaptic feedback mechanisms. This situation apparently occurs in patients treated for tardive

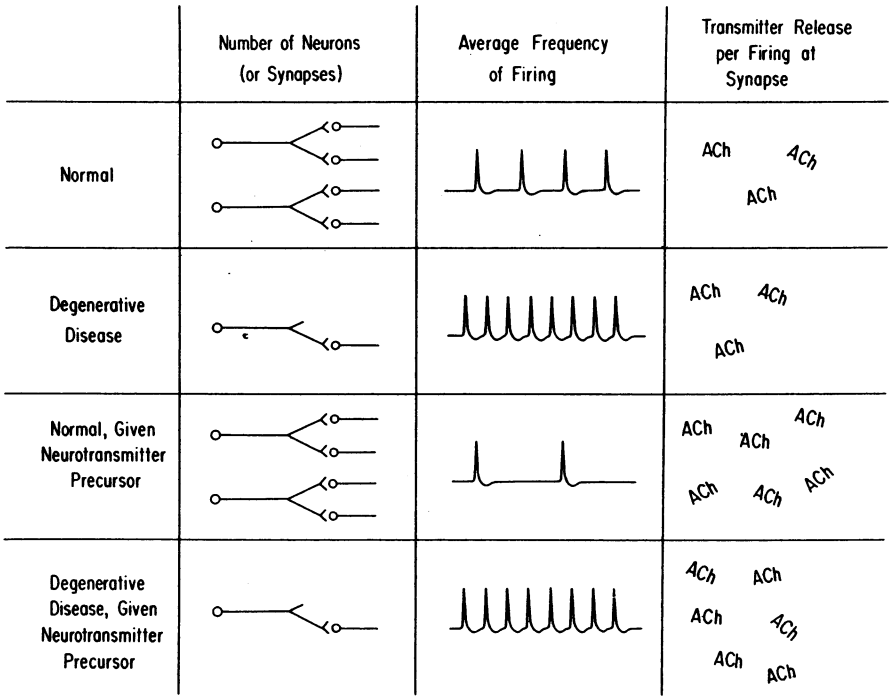

FIG. 5. Mechanism by which precursor administration may enhance neurotransmission in neurodegenerative diseases. Diagram is based on assumptions that (a) synthesis of the neurotransmitter is precursor-dependent; (b) disease neurons are components of a negative feedback loop that controls the rate at which they fire; and, (c) neurons have overlapping fields of innervation, such that those that survive the disease process can partly take over the functions of those that have degenerated. In normal brain (illustrated by two neurons, each making two synapses per firing and firing at a certain rate), precursor administration does increase the amount of transmitter released per firing. However, feedback mechanisms quickly cause a compensatory decrease in the firing rate, causing net release of transmitter per unit time in return to normal. In brains of untreated patients with neurodegenerative diseases, transmitter release at each affected synapse is presumed to be unchanged. However, there is a compensatory increase in the rates at which the surviving neurons fire (i.e. to increase net neurotransmitter output from the nucleus per unit time). Even though transmitter output at each synapse is increased when precursor is administered, no compensatory decrease occurs in firing rates because total transmitter output at all of the surviving synapses is still subnormal. Hence, precursor administration is able to cause a continuing increase in transmitter release.

dyskinesia with lecithin (or choline), but not in those treated with physostigmine. [This disorder, discussed in section VI A 1, is probably associated with inadequate release of acetylcholine from cholinergic caudate neurons, without a demonstrated decrease in the number of such neurons (41).] Both treatments afford relief in a sizeable fraction of patients (12), the former probably by increasing the synthesis of acetylcholine and the latter by blocking its enzymatic degradation within the synapse. However, physostigmine causes numerous side effects associated with generalized cholinergic hyperactivity, while lecithin produces few such effects. After physostigmine administration, there is nothing that normal cholinergic neurons can do to modulate the ubiquitous effect of the drug on cholinergic neurotransmission; the horse has already left the metabolic barn, so that even if the neurons stop firing completely, excess acetylcholine will still be present in the synapse. In contrast, after lecithin administration normal neurons can utilize feedback processes to attenuate, and even block, unneeded increases in cholinergic transmission.

V. Neuroendocrine and Behavioral Effects of Neurotransmitter Precursors

A growing body of indirect evidence involving studies on autonomic and neuroendocrine functions and on animal behaviors suggests that precursor administration can, by increasing neurotransmitter release, modify the physiologic activities of postsynaptic cells. Some of the autonomic responses have been discussed above; an abbreviated summary follows here of the neuroendocrine and behavioral changes. Obviously, the neurotransmitter precursors have numerous additional fates, and their effects on physiologic and behavioral processes could result from products of such other metabolic pathways.

A. Neuroendocrine

Tyrosine administration had no effect on serum prolactin levels in normal animals but lowered the elevated levels produced by giving animals reserpine (2.5 mg/kg) twice daily for 4 days (194). Tyrosine was ineffective in rats with acute hyperprolactinemia (i.e. those given a single dose of reserpine 4 hr earlier), an observation thought compatible with other evidence that at least 16 hr are required for exogenous prolactin to activate tuberoinfundibular dopaminergic neurons (93). That activation of these neurons, and a consequent increase in dopamine secretion into the pituitary portal vessels, underlie the prolactin-lowering effect of tyrosine is supported by the finding that tyrosine significantly elevated hypothalamic HVA and DOPAC levels in chronically reserpinized animals, but not in untreated control rats (194).

Male rats fed a tryptophan-free diet for 14 days, which reduced brain serotonin by about half, exhibited greater increases in serum prolactin and corticosterone when given "serotoninergic stimuli" (5-hydroxytryptophan, alone or in combination with fluoxetine, an uptake-blocker) than control animals fed a normal chow diet (32). This apparent supersensitivity was similar to that previously observed in rats pretreated with a serotonin neurotoxin and was not observed in animals given a dopaminergic antagonist (haloperidol) to induce prolactin release. Administration of tryptophan (50 or 100 mg/kg, i.p.) or of MK-212, a serotoninergic agonist, to male rats significantly enhanced the amplitude of pulsatile growth hormone secretion (monitored by drawing blood at 15-min intervals via an indwelling cannula) (6); valine alone had no effect on the growth hormone surges but suppressed the effect of tryptophan when given concurrently. Tryptophan administration also may increase plasma growth hormone levels in humans (222, 158, 83, 106); however, careful dose-response and time-course studies apparently have not yet been done on this response. Tryptophan consumption in the morning appeared to lower plasma corticotrophin and cortisol levels in human subjects in one study (222) but raised them in another (151a); higher blood tryptophan levels were attained in the latter study. Tryptophan consumed later in the day failed to modify adrenocortical function (106). The long-term consumption of 6 mg/kg of tryptophan daily by humans (58), or the acute administration of larger doses (83a, 106, 188a, 219), failed to affect serum prolactin levels. Tryptophan administration also had no effect on basal or TRH-stimulated TSH and prolactin levels in human sera (58) or on serum FSH or LH (106).

Consumption of a single low-choline meal fortified with 3 g of choline chloride or an equivalent amount of lecithin failed to modify serum concentrations of prolactin, cortisol, insulin, or glucose (examined 0.5, 1, 4, or 8 hr later) (65).

B. Behavioral

Indirect evidence derived from studies on experimental animals suggests that serotoninergic neurons are involved in a wide variety of behaviors, including sleep (113), feeding (224, 225, 21, 192), temperature control (159), pain sensitivity (97, 231, 48, 147), locomotor activity (124, 148), aggression (182), and myoclonus (84). Several of these behaviors are affected by treatments that modify brain tryptophan. Thus, pain sensitivity is increased in rats consuming tryptophan-poor diets and is restored to normal by the addition of tryptophan to the diet (132, 146). Tryptophan administration (100 or 800 mg/kg, i.p.) to rats similarly produced hypoalgesia in one study (200), but in other studies tryptophan either failed to affect pain sensitivity (104) or decreased the analgesic action of morphine (103).

Reports of tryptophan effects on locomotor activity and aggressive behavior have also been contradictory; addition of 0.25% or 0.5% L-tryptophan to the basal diet increased aggression in mice after 2 weeks but not after 6 weeks, and had no effect on locomotor activity (201). In contrast, decreases in dietary tryptophan were reported to facilitate mouse-killing in killer rats and induced this behavior in nonkiller rats (78). Several inves-

tigators have described increases in locomotor activity (68, 134, 110, 139) and even the emergence of stereotyped behavior (110, 139) after tryptophan administration in rats or mice also injected with various drugs; however, other investigators who gave tryptophan alone observed decreases in locomotor activity (151, 199, 203). (The basis of this decrepancy may be drug-induced changes in the metabolism of tryptophan leading to the accumulation of biologically active compounds like tryptamine.) Marsden and Curzon (138) also observed increased locomotor activity by animals given sufficient parachlorophenylalanine to reduce brain serotonin; both effects were completely reversed by 150 mg/kg of tryptophan, partially reversed by 100 mg/kg, and unaffected by 25 mg/kg. Jacobs et al. (110) observed changes in locomotor activity in rats injected with tryptophan, but not in animals fed tryptophan-free or tryptophan-supplemented diets. The chronic consumption of a corn-based, tryptophan-poor diet decreased apomorphine-induced stereotypy in rats (178). Consumption of a similar, maize-based diet enhanced the acoustic startle reflex in rats (212). Tryptophan-deficient diets augmented mounting sexual behavior in male rats; this effect was reversed by adding tryptophan to the diet (39, 71). L-Tryptophan administration also potentiated the myoclonic behavior induced by giving rats *p*-chloroamphetamine, a serotonin neurotoxin (22).

Plasma amino acid patterns and brain serotonin release affect food choice, but there is disagreement as to which food constituents are influenced. Ashley and Anderson (7) first noted that the plasma tryptophan/LNAA ratios observed in rats consuming various diets tended to correlate inversely with the proportion of protein that they had consumed (i.e. when given access to two or more diets each containing different concentrations of protein). In subsequent studies, they reported that adding tryptophan to the diets of weanling rats caused them to diminish their intakes of protein (221). In contrast, Wurtman and Wurtman observed that treatments that enhanced central serotoninergic transmission (e.g. administration of drugs like fenfluramine or fluoxetine, with or without tryptophan) selectively diminished carbohydrate consumption while sustaining protein intake (224, 225). They postulated (225) that serotoninergic neurons are components of a behavioral feedback loop that regulates carbohydrate consumption, selectively causing further carbohydrate intake to decline after animals eat carbohydrate-rich, protein-poor meals that elevate the plasma tryptophan/LNAA ratio. The basis of this difference in interpretation may be the way experiments have been done in the different laboratories, i.e. investigators have sometimes failed to keep the intake of one dietary component, protein or carbohydrate, constant while varying the other. In other studies, Latham and Blundell (125) observed that tryptophan administration diminished the total amount of food that animals consumed during the subsequent 24 hr and reduced meal size.

Only a few studies have utilized experimental animals to examine the effects of tryptophan loading on sleep. Hartmann (95) found that administration of high doses of L-tryptophan, (450 or 800 mg/kg) significantly reduced sleep latency in rats without affecting other sleep parameters. Other investigators (220) reported that injection of a low dose of tryptophan (30 mg/kg) decreased sleep latency, but a larger dose (120 mg/kg) not only failed to affect sleep latency but also increased wakefulness.

Relatively few data are available on the behavioral effects of tyrosine in experimental animals. Thurmond et al. (202) reported that animals consuming a tyrosine-supplemented (4%) diet exhibited increased aggressive behavior but no changes in locomotor activity. In contrast, Gibson et al. (79) observed that doses of tyrosine as low as 50 mg/kg, i.p., caused marked increases in open-field activity, measured 1 hr after the injection. Tryptophan (20 to 320 mg/kg) and phenylalanine (25 to 400 mg/kg) were ineffective in this situation, but phenylalanine, found by others to increase open-field activity and aggressive behavior in mice (201), shared tyrosine's ability to diminish the period of immobility observed when mice were placed in a Plexiglas cylinder containing water (79). [This effect was similar to that produced by many antidepressant drugs (175, 174).] In other studies, the hypothermic effect of *d*-amphetamine, thought to result from release of brain dopamine (233), was suppressed in animals pretreated with valine, an LNAA that, by competing with tyrosine for brain uptake (29), might diminish the pool of dopamine available for release.

Few data also are available on the behavioral effects of choline or lecithin in animals. In one study, rats kept for 2 weeks on a choline-deficient diet displayed no changes in locomotor activity, but animals fed a choline-supplemented diet exhibited increased motor activity, which, paradoxically, could be reversed by choline injections (214). A recent study (14) that examined the effects of dietary choline on memory and learning in aging mice yielded interesting and promising information. Senescent mice were placed on either choline-deficient or choline-enriched diets for a period of 4.5 months. The animals were then trained in a single-trial passive avoidance task and tested for its retention 24 hr and 5 days later; their performance was compared with that of mice of similar ages fed a control diet. Old mice exhibited the expected marked decrease in retention of task learning. However, there were striking differences between the choline-deficient and the choline-supplemented animals; the latter group (13 months old) performed as well as younger mice (3 months old), whereas the younger choline-deficient animals performed as poorly as aged control mice. These observations suggest that dietary manipulations affecting choline availability may modulate the decline in learning ability and memory functions that occur with aging. The concurrent administrations to aged rats of choline and Piracetam, a drug that may accelerate acetylcholine release from septohippocampal cholinergic neurons

(230a), caused improvements in retention that were several times greater than those observed after choline or Piracetam alone (14a).

VI. Clinical Applications of Neurotransmitter Precursors

A. Choline or Lecithin

1. Tardive Dyskinesia. Within months of the first demonstrations (34,100) that choline administration could elevate brain acetylcholine levels in rats, Davis et al. (43) reported marked clinical improvement after giving oral choline to a patient with tardive dyskinesia. This disorder is induced in many psychiatric patients by administering any of the neuroleptic drugs currently marketed in the United States (41, 12). It tends to appear during chronic drug treatment or after drug discontinuation and is characterized by involuntary choreic movements mainly involving the orobuccolingual musculature. Presumably, the disorder arises because the neuroleptics, by chronically blocking striatal dopamine receptors, cause these receptors to become supersensitive to the inhibitory effects of dopamine (77). Since some of these receptors are present on cholinergic neurons, their supersensitivity probably causes a chronic decrease in the firing rates of the cholinergic neurons and thus in the release of acetylcholine. Clinical improvement has also been observed with drugs that suppress central catecholaminergic transmission (119), or after i.v. administration of physostigmine (117), which presumably acts by enhancing cholinergic transmission. However, physostigmine does not constitute a useful therapeutic agent in tardive dyskinesia because of its parenteral route of administration and its tendency to cause a generalized increase in cholinergic tone, which leads to severe side effects. (In fact, before the introduction of choline, no clinically useful agent was available that, administered to patients orally, appeared to increase cholinergic tone within the brain.) Soon after the initial report of the efficacy of choline in tardive dyskinesia (43), ingestion of choline chloride was shown to produce dose-dependent increases in plasma and CSF choline levels (87), suggesting that in humans as in rats, the exogeneous compound raises the quantity of choline available for brain acetylcholine synthesis.

Many subsequent studies (43, 45, 197, 8, 75), including one performed using a double-blind crossover protocol (90), have confirmed the utility of choline in treating tardive dyskinesia. Side effects, which have been minimal, have included a fishy skin odor (resulting from degradation of the ingested free choline to trimethylamine by intestinal bacteria), mild gastrointestinal symptoms, and urinary incontinence. In rare cases, it caused transitory depression, usually in people with a prior history of depressive disorders (197). Although the choline ameliorates a side effect of neuroleptic drugs, it apparently does not block the therapeutic action of these drugs in patients who continue to need them.

Normally, less than 1% of the choline present in food occurs as the free base. Most of the dietary choline is instead ingested in the form of lecithin (223), which is hydrolyzed to choline after its uptake into hepatic and, possibly, intestinal mucosal cells (105). Because studies in normal subjects showed that ingestion of an equimolar lecithin dose was far more effective than the free base in raising plasma choline levels (228), lecithin was also tested in tardive dyskinesia (75, 89, 9, 109) and found to be at least as effective as choline without producing the fishy odor. The general adoption of lecithin therapy as a means of treating tardive dyskinesia has been slowed by the unavailability of sufficiently pure lecithin preparations. Until recently, virtually all of the allegedly "pure" lecithin marketed in America actually contained 20% or less phosphatidylcholine (223), a consequence of a 1938 ruling equating, for commercial purposes, the terms "phosphatide" and "lecithin." This problem may be resolved soon; several companies are developing lecithin preparations that are more than 80% pure.

2. Huntington's Disease. Choline acetyltransferase activity (presumably a marker for the number of cholinergic synapses) is markedly depressed in brains examined postmortem (17), suggesting that central cholinergic tone may be deficient in Huntington's disease. Furthermore, administration of physostigmine diminished choreic movements transiently in some afflicted subjects (198). Two groups of investigators have described suppression by oral choline of abnormal movements in patients with Huntington's disease (8, 47); however, other investigators found only minor and transitory improvement, or no improvement, after treatment with choline or lecithin (5, 88). In a proposed animal model for Huntington's disease (129), in which rats were given intrastriatal injections of the parenchymal neurotoxin kainic acid, systemic choline administration markedly increased acetylcholine levels in the lesioned striata despite the severe damage done by the neurotoxin to most of the cholinergic neurons. It seems unlikely, therefore, that the failure of choline to improve chorea in the majority of Huntington's disease patients would be due to inadequate formation of acetylcholine in surviving cholinergic terminals. Possibly this failure reflects a reduction in the number of postsynaptic cholinergic receptors (56). Alternatively, it could reflect the involvement in Huntington's disease of numerous other synapses besides those using acetylcholine (141, 189a); changes in neurotransmission mediated by these other compounds would not be expected to respond to an increase in the availability of choline.

3. Alzheimer's Disease. The possibility that lecithin or choline might be useful in treating memory disorders associated with Alzheimer's disease or with aging, per se ("benign senescent forgetfulness"), was suggested by observations that brains of afflicted patients exhibit a major, and possibly selective (19, 42), decrease in choline acetyltransferase activity. In addition, memory function

in normal humans is markedly impaired, in a pattern similar to that observed in patients, after blockade of central cholinergic receptors with scopolamine, and it is restored by physostigmine (51). Central cholinergic receptors apparently are intact in Alzheimer's disease (169), suggesting that if a treatment like lecithin or physostigmine did succeed in increasing brain acetylcholine levels, receptors would be available to take advantage of this increase. Of course, advanced Alzheimer's disease may reflect more than a single, homogeneous brain disorder. It is characterized by major reductions in the mass of the brain (70), and may, in particular patients, involve numerous additional neuronal populations besides those utilizing acetylcholine as their transmitter (2, 42a). A number of reports have been published on memory function in patients given choline or lecithin (20, 183, 188, 57, 31, 170, 177, 66, 152). Most have described open-label studies, but at least two (69, 105a) have shown clinical improvement with a double-blind, placebo-controlled protocol. In the first, five patients receiving 12 g of choline bitartarate daily for 2 weeks exhibited significant improvements in auditory and visual word recognition, and near-significant improvements in testing by mental status questionnaire. In the second, seven of 11 patients receiving lecithin for 2 to 8 weeks showed 50% to 200% improvement in "long-term storage." Choline has also been reported to improve the performance of poor initial learners among normal volunteers doing serial-learning and selective-reminding tasks (187, 186). However, too few data are presently available from well controlled studies to substantiate conclusions as to the effectiveness of acetylcholine precursors in improving memory function within any population.

Serious problems confront the investigator who would perform such a study. There is little consensus as to whether the data generated by any particular "objective" memory test are predictive of functionally significant memory changes in the patient's normal environment. Similarly, there is no method available for distinguishing patients with exclusively cholinergic deficits from those with lesions of other neurons, and there is no agreement as to how the severity of a particular patient's disease should be defined. Finally, the unavailability of adequately pure, palatable lecithin preparations severely limits the ability of investigators to initiate experiments.

Perhaps the most effective way to utilize acetylcholine precursors in treating memory disorders will be to coadminister them with a low dose of a cholinesterase inhibitor (170).

4. Psychiatric Disorders. Some evidence suggests that inadequate central cholinergic transmission may be involved in the pathogenesis of schizophrenia and mania (44); moreover, lithium apparently potentiates the effect of exogenous choline on brain acetylcholine levels (150). Hence, Cohen et al. (33) gave partially purified lecithins to patients also receiving neuroleptics or lithium. When a relatively impure preparation was tested (up to 30 g/day of 51% to 55% lecithin), one patient out of four improved markedly and two showed slight improvement, but treatment had to be discontinued because of gastrointestinal side effects. When patients received a preparation containing lecithin of greater than 90% purity (15 to 30 g/day) instead, all four subjects responded without significant side effects. Lithium carbonate administration occasionally causes a myasthenia-like syndrome that disappears when the drug is withdrawn (163). Since lithium is known to affect the bidirectional flux of choline across various membranes (150), this syndrome may involve impaired choline uptake into terminals of motor neurons. Choline chloride (up to 20 g/day) administered in a single-blind crossover study failed to modify the clinical ratings of nine schizophrenic subjects (46).

5. Ataxia. It was suggested that patients with classical, recessively inherited Friedreich's ataxia suffer a defect in the pyruvate dehydrogenase enzyme complex that might, by diminishing acetyl-CoA synthesis, impair brain acetylcholine synthesis (11). Barbeau (8, 9) has described improvements in such patients during treatment with choline or lecithin; treatment both diminished the ataxia and seemed to slow its progression. Oral choline chloride (4 to 5 g/day) produced sustained benefit in a single patient with cerebellar ataxia (126). In another study (125a), one of 13 patients with a variety of ataxic disorders showed a reproducible, dose-related, placebo-controlled improvement in motility and hand functions while taking oral choline.

6. Tourette's Syndrome. Administration of i.v. physostigmine or oral choline reduced the tics observed in two patients with Tourette's syndrome (190). One investigator noted major and continuing improvement when three patients with this disorder were treated with oral lecithin (40 to 50 g/day, 20% pure) (10), but another group (with a double-blind, placebo-controlled protocol) failed to detect improvement in six subjects who ingested 45 g/day of 55% lecithin for 4 weeks (173).

7. Myasthenic Syndrome. Administration of oral choline chloride (210 mg/kg/day for 3½ weeks) to a woman with myasthenic syndrome caused a significant improvement in neuromuscular transmission, as assessed by recording the compound action potential amplitude of the thenar muscles in response to supramaximal nerve stimulation (119b); data were interpreted as showing that the choline caused at least a 40% increase in the release of an immediately available ACh pool. Intravenous administration of choline bitartrate (total dose equivalent to 38 mg/kg of choline chloride, given over 70 min) was without acute effect.

B. Tryptophan

1. Depression. That serotonin release from brain neurons may be inadequate in some patients with depression is suggested by reported reductions in the levels of 5-HIAA within their CSF (209), and in brain serotonin levels in people who committed suicide (181). Attempts to treat depression with doses of tryptophan calculated to raise brain serotonin levels have had limited success;

it improved depression (37) or mania (176) in some cases but not in others (145, 28). This discrepancy may reflect the etiologic and biochemical heterogeneity of affective disorders. While some depressed patients may suffer from a deficiency in brain serotonin, depression in others may reflect reduced noradrenergic transmission (180) or be unrelated to monoamines entirely. In one study that examined other LNAAs in addition to plasma tryptophan, manic depressive patients with normal plasma tryptophan ratios were found to be unresponsive to oral tryptophan, while others with "relative tryptophan deficiencies" (i.e. reduced plasma tryptophan ratios) exhibited clear therapeutic responses (153). Very high tryptophan doses might be less effective than lower doses if the higher doses impair brain tyrosine uptake and thereby interfere with brain catecholamine synthesis (229). Tyrosine itself may be useful therapeutically in treating some people with depression (76, 83b). Perhaps the precursor strategy most likely to be useful in treating depression may involve mixtures of tryptophan and tyrosine, along with a carbohydrate to reduce plasma LNAA levels by eliciting insulin secretion (226). Tryptophan potentiated the clinical efficacy of clomipramine, an antidepressant drug that blocks serotonin reuptake (211), but not of the more potent zimelidine (211a).

2. Posthypoxic Intention Myoclonus. This specific myoclonic syndrome is a sequel to transient brain hypoxia such as occurs during cardiorespiratory arrest (122). Its association with reduced CSF 5-HIAA levels and the tendency of some patients to respond therapeutically to 5-hydroxytryptophan suggest that the syndrome may arise from a loss of serotonin-releasing neurons (85). Administration of tryptophan, alone or combined with a monoamine oxidase inhibitor, suppressed the myoclonic movements in some patients, but apparently not in others (50, 27, 210, 119a).

3. Appetite Control. On the basis of animal studies showing that treatments that enhance serotoninergic transmission also caused animals to select to consume less dietary carbohydrate (225), experiments were performed on the effects of giving tryptophan or *dl*-fenfluramine, a serotonin-releasing anorexic drug, on carbohydrate consumption by human subjects (225a). Eleven healthy subjects with a documented tendency to consume relatively large quantities of carbohydrate snacks received each treatment or its placebo for 5 days, separated by 5-day washout periods; treatment was given 1 hr before the anticipated daily period of maximal carbohydrate snacking, and food consumption (snacks and meals) was recorded during the subsequent 4 hr. Fenfluramine consistently reduced carbohydrate snacking in seven subjects, and diminished it significantly in the group as a whole; tryptophan consistently diminished carbohydrate snacking in three of the subjects, but not in the group as a whole; the placebos were without effect. Tryptophan also diminished mealtime carbohydrate consumption in four of the five subjects who consistently ate meals during the 4-hr test periods. These observations were interpreted as showing that treatments that enhance central serotoninergic transmission can suppress carbohydrate appetite in some individuals. Perhaps some obese people fail to display an adequate brain serotonin response to dietary carbohydrates and thus desire more carbohydrate-rich foods than other people. Tryptophan administration has also been associated with a reduction of appetite in depressed patients (30).

4. Tryptophan Malabsorption. Lehmann has described a syndrome characterized by malabsorption of an oral tryptophan load (100 mg/kg administered in a beverage at 8 A.M., after an overnight fast), confusion, depression, and signs of dementia (126a). The clinical findings were exacerbated by oral L-dopa (which further impaired the absorption of tryptophan) and were ameliorated by supplemental tryptophan or consumption of a high-protein diet.

5. Sleep. Serotonin release may also be involved in the induction of particular sleep stages. Oral administration of tryptophan has been reported to reduce sleep latency and to increase subjective sleepiness in subjects with long sleep latencies (96). A single, 1-g dose was insufficient to diminish the times required for subjects to attain stage 1 or stage 2 sleep; however, people who took this dose with a carbohydrate tended to have the shortest sleep latencies (1).

C. Tyrosine

To our knowledge, no papers have been published describing well controlled studies in which tyrosine was examined as a possible treatment for a catecholamine-related disorder. Indeed, very few articles have been published on even the biochemical consequences of administering tyrosine to normal people. Fasting subjects given 100 to 150 mg/kg of the amino acid as a single oral dose exhibit 2- to 3-fold increases in plasma tyrosine levels; the increases last up to 8 hr and are accompanied by parallel changes in the plasma tyrosine ratio (82). Consumption of 100 mg/kg of the amino acid with meals, in three divided doses, also elevates plasma tyrosine levels and the tyrosine ratio in spite of the contribution of amino acids from the dietary protein (143); this suggests that the use of pure amino acids to increase neurotransmitter synthesis need not be done at the expense of adequate protein nutrition. Administration of tyrosine to patients with Parkinson's disease caused elevations in the levels of tyrosine and the dopamine metabolite HVA within the CSF (91). This elevation indicates that the exogenous amino acid does enter the human brain and can subsequently affect the synthesis and release of its neurotransmitter products. Studies on experimental animals (control rats or those given probenecid) showed that striatal HVA levels are unaffected by tyrosine administration unless animals also receive a treatment that activates nigrostriatal neurons (cf. 179). Thus, the effect of tyrosine on HVA levels in human CSF probably does not reflect interference with the efflux of HVA.

The possibility that tyrosine might be useful in selected

cases of Parkinson's disease is supported by its effects in animals with partial unilateral destruction of the nigrostriatal system. The surviving hyperactive dopaminergic neurons become precursor-dependent, releasing more dopamine after tyrosine administration than contralateral, control neurons (that receive equivalent amounts of the tyrosine) (144). There is postmortem evidence (e.g. increased HVA/dopamine ratios in striatum) that surviving nigrostriatal neurons in Parkinsonian patients also are hyperactive (15), a change that allows them partially to compensate for the lost neurons. Under such conditions, exogenous tyrosine might amplify dopamine synthesis in, and its release from, these neurons. The now classical treatment of Parkinson's disease with L-DOPA (40) involves use of a catecholamine precursor, but unlike treatment with tyrosine, not one that is normally present in dietary proteins nor one converted to catecholamines solely within cells that normally produce these transmitters. (Exogenous DOPA is converted to dopamine within all cells, in the striatum and elsewhere, that contain the enzyme aromatic L-amino acid decarboxylase.) This nonspecificity may underlie some of the side effects associated with long-term L-DOPA treatment.

As described above, depression may, in some cases, be associated with deficient central noradrenergic transmission (180); if so, tyrosine might, by increasing brain norepinephrine synthesis, be useful in such patients. Published data describing a single patient, studied with a placebo-controlled experimental design, suggested that this may be the case (76); similar observations were made elsewhere on two depressed patients who previously had responded only to amphetamines (83b). Therapeutic trials with tyrosine or tryptophan might be useful in distinguishing subgroups of depressed patients suffering from central noradrenergic or serotoninergic deficiencies.

Since tyrosine reduces elevated plasma prolactin levels in rats (194), probably by increasing dopamine release from the median eminence, treatment with this amino acid may also be useful for some humans with hyperprolactinemia. Tyrosine also reduces blood pressure in hypertensive rats (195), but elevates blood pressure in animals with hemorrhagic shock (36a). Intravenous administration of tyrosine to healthy dogs (1 to 4 mg/kg) diminishes the vulnerability of their myocardium to induction of ventricular fibrillation by electric currents delivered to the right ventricle (180a). This effect is blocked by concurrent administration of valine, a competing LNAA, and is associated with cardiodynamic changes indicative of diminished stellate outflow (180b). The utility of tyrosine in the treatment of human autonomic or cardiovascular disorders awaits evaluation.

VII. Summary

Studies performed during the past decade have shown that the rates at which certain neurons produce and release their neurotransmitters can be affected by precursor availability, and thus by the changes in plasma composition that occur after ingestion of the precursors in purified form or as constituents of foods. Thus, tryptophan administration or a carbohydrate meal will increase the plasma ratio of tryptophan to other large neutral amino acids, thereby raising brain tryptophan levels, increasing the substrate saturation of tryptophan hydroxylase, and accelerating the synthesis and release of serotonin. Tyrosine administration or a high-protein meal similarly elevates brain tyrosine and can accelerate catecholamine synthesis in the CNS and sympathoadrenal cells, while the consumption of lecithin or choline increases brain choline levels and neuronal acetylcholine synthesis.

The physiologic and biochemical mechanisms that must exist in order for nutrient consumption to affect neurotransmitter synthesis have been characterized and include: 1) the lack of significant feedback control of plasma levels of the precursor; 2) the lack of a real "blood-brain barrier" for the precursor, i.e. the ability of the plasma level of the precursor to control its influx into, or efflux from, the CNS; 3) the existence of a *low*-affinity (and thus unsaturated) transport system mediating the flux of the precursor between blood and brain; 4) *low*-affinity kinetics for the enzyme that initiates the conversion of the precursor to the transmitter; and, 5) the lack of end-product inhibition of the enzyme, in vivo, by its ultimate product, the neurotransmitter.

The extent to which neurotransmitter synthesis in any particular aminergic neuron happens to be affected by changes in the availability of its precursor probably varies directly with the neuron's firing frequency. This relationship allows precursor administration to produce selective physiologic effects by enhancing neurotransmitter release from some but not all of the neurons potentially capable of utilizing the precursor for this purpose. It also allows the investigator to predict when administering the precursor might be useful for amplifying a physiologic process, or for treating a pathologic state. (For example, tyrosine administration *raises* blood pressure in hypotensive rats, *lowers* it in hypertensive animals, and has little effect on blood pressure in normotensive animals; the elevation in blood pressure probably reflects enhanced catecholamine release from sympathoadrenal cells, while the reduction in hypertensive animals probably results from increased catecholamine release within the brainstem.) Such predictions are now being tested clinically in many institutions.

Available evidence suggests that lecithin or choline administration can diminish the frequency of abnormal movements in patients with tardive dyskinesia. These precursors are also being tested—alone or in combination with drugs—in mania, the senile memory disorders, the myasthenic syndrome, and other diseases that are known to be associated with inadequate cholinergic function, or even those that respond empirically to short-term treatment with cholinesterase inhibitors (e.g. certain ataxias). When the precursors are effective, they also have the

distinct advantage over alternative therapies of producing few of the side effects associated with generalized cholinergic activation. Tyrosine and tryptophan are similarly being tested in the treatment of depression, disorders of appetite and sleep, cardiovascular disturbances, and other states thought to involve inadequate release of a catecholamine or serotonin.

Even though plasma levels of the precursors can be increased by eating normal foods, it seems likely that their clinical use, if justified by results of future studies, will be based on giving relatively large doses of synthetic preparations that contain highly purified lecithins or amino acids, alone or in mixtures. The ability of such large doses to treat a disease or modify a physiologic state cannot be taken as evidence that that disorder or state is nutritional in origin. Rather, the nutrients are probably acting pharmacologically, as amplifiers, causing neurons to liberate more transmitter molecules per unit time than they normally would.

Acknowledgments. The authors' research was supported in part by grants from the National Institutes of Health, the National Institute of Mental Health, and the National Aeronautics and Space Administration. Dr. F. Hefti is a recipient of a fellowship from the Swiss National Science Foundation.

REFERENCES

1. ADAM, K., AND OSWALD, I.: One gram of L-tryptophan fails to alter the time taken to fall asleep. Neuropharmacology **18:** 1025–1027, 1979.
2. ADOLFSSON, R., GOTTFRIES, C. G., ROOS, B. E., AND WINBAL, B.: Postmortem distribution of dopamine and homovanillic acid in human brain, variations related to age, and a review of the literature. J. Neural Transm. **45:** 81–105, 1979.
3. AGHARANYA, J., ALONSO, R., AND WURTMAN, R. J.: Changes in catecholamine excretion following tyrosine ingestion in normally fed human subjects. Amer. J. Clin. Nutr. **34:** 82–87, 1981.
4. AGID, Y., JAVOY, F., AND GLOWINSKI, J.: Hyperactivity of remaining dopaminergic neurons after partial destruction of the nigrostriatal dopaminergic system in the rat. Nature New Biol. **245:** 150–151, 1973.

4a. ALONSO, R., AGHARANYA, J. C., AND WURTMAN, R. J.: Tyrosine loading enhances catecholamine excretion by rats. J. Neural Transm. **49:** 31–43, 1980.

4b. ANSELL, G. B., AND SPANNER, S.: The source of choline for acetylcholine synthesis. *In* Cholinergic Mechanisms and Psychopharmacology, ed. by D. L. Jenden, pp. 431–445, Plenum Press, New York, 1977.

5. AQUILONIUS, S. M., AND ECKERNAS, S. A.: Plasma concentrations of free choline in patients with Huntington's chorea on high doses of choline chloride. N. Engl. J. Med. **293:** 1105–1106, 1975.
6. ARNOLD, M. A., AND FERNSTROM, J. D.: L-Tryptophan injection enhances pulsatile growth hormone secretion in the rat. Endocrinology **108:** 331–335, 1981.
7. ASHLEY, D. V. M., AND ANDERSON, G. H.: Correlation between the plasma tryptophan to neutral amino acid ratio and protein intake in the self-selecting weanling rat. J. Nutr. **105:** 1412–1421, 1975.
8. BARBEAU, A.: Emerging treatments: replacement therapy with choline or lecithin in neurological diseases. Can. J. Neurol. Sci. **5:** 157–160, 1978.
9. BARBEAU, A.: Lecithin in neurologic disorders. N. Engl. J. Med. **299:** 200, 1978.
10. BARBEAU, A.: Cholinergic treatment in the Tourette Syndrome. N. Engl. J. Med. **302:** 1310–1311, 1980.
11. BARBEAU, A., BUTTERWORTH, R. F., NGO, T., BRETON, G., MELANCON, S., SHAPLOTT, D., GEOFFROY, G., AND LEMIEUX, B.: Pyruvate metabolism in Friedreich's ataxia. Can. J. Neurol. Sci. **3:** 379–388, 1976.
12. BARBEAU, A., GROWDON, J. H., AND WURTMAN, R. J.: Choline and Lecithin in Brain Disorders, New York, Raven Press, 1979.
13. BARRA, H. S., UNATES, L. E., SAYAVEDRA, M. S., AND CAPPUTTO, R.: Capacities of binding amino acids by tRNAs from rat brain and their changes during development. J. Neurochem. **19:** 2287–2297, 1972.
14. BARTUS, R. T., DEAN, R. L., GOAS, A. J., AND LIPPAS, A. S.: Age related changes in passive avoidance retention: Modulation with dietary choline. Science **209:** 301–303, 1980.

14a. BARTUS, R. T., DEAN, R. L., SHERMAN, K., AND FRIEDMAN, E.: Enhancement of aged rodent retention via pharmacological modulation of choline availability. Abstr. Soc. Neurosci. **6:** 112, 1980.

15. BERNHEIMER, H., BIRKMAYER, W., HORNYKIEWICZ, O., JELLINGER, K., AND SEITELBERGER, F.: Brain dopamine and the syndromes of Parkinson and Huntington. J. Neurol. Sci. **20:** 415–455, 1973.
16. BIERKAMPER, G. G., AND GOLDBERG, A. M.: Effect of choline on the release of acetylcholine from the neuromuscular junction. *In* Choline and Lecithin in Brain Disorders, Nutrition and the Brain, ed. by A. Barbeau, J. H. Growdon, and R. J. Wurtman, vol. 5, pp. 243–251, Raven Press, New York, 1979.

16a. BIERKAMPER, G. G., AND GOLDBERG, A. M.: Release of acetylcholine from the vascular perfused rat phrenic nerve-hemodiaphragm. Brain Res. **202:** 234–237, 1980.

17. BIRD, E. D., AND IVERSEN, L. L.: Huntington's chorea: Postmortem measurement of glutamic acid decarboxylase, choline acetyltransferase and dopamine in basal ganglia. Brain **97:** 457–472, 1974.
18. BLUSZTAJN, J. K., ZEISEL, S. J., AND WURTMAN, R. J.: Synthesis of lecithin (phosphatidylcholine) from phosphatidylethanolanine in bovine brain. Brain Res. **179:** 319–327, 1979.

18a. BLUSZTAJN, J. K., AND WURTMAN, R. J.: Biosynthesis of choline by rat brain synaptosomes. Nature, in press, 1981.

19. BOWEN, D. M., SMITH, C. B., WHITE, P., AND DAVISON, A. N.: Neurotransmitter related enzymes and indices of hypoxia in senile dementia and other abiotrophies. Brain **99:** 459–496, 1976.
20. BOYD, W. D., GRAHAM-WHITE, J., BLACKWOOD, G., GLEN, I., AND MCQUEEN, J.: Clinical effects of choline in Alzheimer's senile dementia. Lancet **2:** 711, 1977.

20a. BRAMWELL, G. J.: Factors affecting the activity of 5-HT-containing neurones. Brain Res. **79:** 515-519, 1974.

20b. BRESNAHAN, M. R., HATZINIROLAOU, P., BRUNNER, H. R., AND GAVRAS, H.: Effects of tyrosine infusion in normotensive and hypertensive rats. Amer. J. Physiol. **239:** H206–H211, 1980.

21. BRIESCH, S. T., ZEMLAN, F. P., AND HOEBEL, B. G.: Hyperphagia and obesity following serotonin depletion by intraventricular para-chlorophenylalanine. Science **192:** 382–384, 1976.
22. BROWN, D. R., AND GROWDON, J. H: L-Tryptophan administration potentiates serotonin-dependent myoclonic behavior in the rat. Neuropharmacology **19:** 343–347, 1980.
23. BRUINVELS, J.: Effects of sodium and potassium ions on the uptake of noradrenaline and its precursor tyrosine. Life Sci. **20:** 437–444, 1977.
24. CARLSSON, A., AND LINDQVIST, M.: The effect of L-tryptophan and some psychotrophic drugs on the formation of 5-hydroxytryptophan in the mouse brain in vivo. J. Neural. Transm. **33:** 23–42, 1972.
25. CARLSSON, A., AND LINDQVIST, M.: Dependence of 5-HT and catecholamine synthesis on precursor amino-acid levels in rat brain. Naunyn Schmiedeberg's Arch. Pharmacol. **303:** 157–164, 1978.
26. CARROLL, P. T., AND GOLDBERG, A. M.: Relative importance of choline transport to spontaneous and potassium depolarized release of Ach. J. Neurochem. **25:** 523–527, 1975.
27. CHADWICK, D., HALLETT, M., HARRIS, R., JENNER, P., REYNOLDS, E. H., AND MARSDEN, C. D.: Clinical, biochemical, and physiological features distinguishing myoclonus responsive to 5-hydroxytryptophan, tryptophan with a monoamine oxidase inhibitor, and clonazepam. Brain **100:** 455–487, 1977.
28. CHAMBERS, C. A., AND NAYLOR, G. J.: A controlled trial of L-tryptophan in mania. Brit. J. Psychiat. **132:** 555–559, 1978.
29. CHIEL, H. J., AND WURTMAN, R. J.: Suppression of amphetamine-induced hypothermia by the neutral amino acid valine. Psychopharmacol. Commun. **2:** 207–217, 1976.
30. CHOUINARD, G., YOUNG, S. N., ANNABLE, L., AND SOURKES, T. L.: Tryptophan-nicotinamide, imipramine and their combination in depression. Acta Psychiat. Scand. **59:** 395–414, 1979.
31. CHRISTIE, J. E., BLACKBURN, I. M., GLEN, I. A., ZEISEL, S., SHERING, A., AND YATS, C. M.: Effects of choline and lecithin on CSF choline levels and cognitive functions in patients with presenile dementia of the Alzheimer type. *In* Nutrition and the Brain, ed. by A. Barbeau, J. H. Growdon, and R. J. Wurtman, vol. 5, pp. 377–387, Raven Press, New York, 1979.
32. CLEMENS, J. A., BENNETT, D. R., AND FULLER, R. W.: The effect of a tryptophan free diet on prolactin and corticosterone release by serotoninergic stimuli. Horm. Metab. Res. **12:** 35–38, 1980.
33. COHEN, B. M., MILLER, A. L., AND LIPINSKI, J. F.: Lecithin in mania: A preliminary report. Amer. J. Psychiat. **137:** 242–243, 1980.
34. COHEN, E. L., AND WURTMAN, R. J.: Brain acetylcholine: Increase after systemic choline administration. Life Sci. **16:** 1095–1102, 1975.
35. COHEN, E. L., AND WURTMAN, R. J.: Brain acetylcholine; control by dietary choline. Science **191:** 561–562, 1976.
36. COLMENARES, J. L., WURTMAN, R. J., AND FERNSTROM, J. D.: Effect of ingesting a carbohydrate-fat meal on the levels and synthesis of 5-hydroxyindoles in various regions of the rat central nervous system. J. Neurochem. **125:** 825–829, 1975.

36a. CONLAY, L. A., MAHER, T. J., AND WURTMAN, R. J.: Tyrosine increases blood pressure in hypotensive rats. Science, in press, 1981.

37. COPPEN, A., HERZBERG, B., AND MAGGA, R.: Tryptophan in the treatment of depression. Lancet **2:** 1178–1180, 1967.
38. CORNFORD, E. M., BRAUN, L. D., AND OLDENDORF, W. H.: Carrier mediated blood-brain barrier transport of choline and certain analogs. J. Neurochem. **30:** 299–308, 1978.
39. CORRULA, M. O., PICOTI, G. B., GENOVESE, E., AND MONTEGAZZA, P.:

Stimulatory effect of a maize diet on sexual behavior in male rats. Life Sci. **20:** 159–164, 1977.

40. COTZIAS, G. C., PAPAVASILIOU, P. S., AND GELLENE, R.: Modification of Parkinsonism: Chronic treatment with L-Dopa. N. Engl. J. Med. **280:** 337–345, 1969.
41. CRANE, G.: Tardive dyskinesia in patients treated with major neuroleptics: A review of the literature. Amer. J. Psychiat. **124:** 40–48, 1968.
42. DAVIES, P., AND MALONEY, A. J. F.: Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet **2:** 1903, 1976.

42a. DAVIES, P., KATZMAN, R., AND TERRY, R. D.: Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer disease and Alzheimer senile dementia. Nature (London) **288:** 279–280, 1980.

43. DAVIS, K. L., BERGER, P. A., AND HOLLISTER, L. E.: Choline for tardive dyskinesia. N. Engl. J. Med. **293:** 152, 1975.
44. DAVIS, K. L., BERGER, P. A., HOLLISTER, L. E., AND BARCHAS, J. D.: Cholinergic involvement in mental disorders. Life Sci. **22:** 1865–1872, 1978.
45. DAVIS, K. L., HOLLISTER, L. E., BARCHAS, J. D., AND BERGER, P. A.: Choline in tardive dyskinesia and Huntington's disease. Life Sci. **19:** 1507–1519, 1976.
46. DAVIS, K. L., HOLLISTER, L. E., AND BERGER, P. A.: Choline chloride in schizophrenia. Amer. J. Psychiat. **136:** 1581–1584, 1979.
47. DAVIS, K. L., HOLLISTER, L. E., AND BERGER, P. A.: Studies on choline chloride in neuropsychiatric disease: Human and animal data. Psychopharmacol. Bull. **14:** 56–58, 1978.
48. DEAKIN, J. F. W., AND DOSTROVSKY, J. O.: Involvement of the periaqueductal grey matter and spinal 5-hydroxytryptaminergic pathways in morphine analgesia: effects of lesions and 5-hydroxytryptamine depletion. Brit. J. Pharmacol. **63:** 159–165, 1978.
49. DEJONG, W., ZANDBERG, P., AND BOHUS, B.: Role of noradrenaline in the central control of blood pressure in normotensive and spontaneously hypertensive rats. Arch. int. Pharmacodyn. Thér. **213:** 272–284, 1975.
50. DELEAN, J., RICHARDSON, J. C., AND HORNIKIEWICZ, O.: Beneficial effects of serotonin precursor in postanoxic action myoclonus. Neurology **26:** 863–868, 1976.
51. DRACHMAN, D. A.: Memory and cognitive function in man: does the cholinergic system have a specific role? Neurology **27:** 783–790, 1977.
52. DROSS, K., AND KEWITZ, H.: Concentration and origin of choline in the rat brain. Naunyn Schmiedeberg's Arch. Pharmacol. **274:** 91–106, 1972.
53. DUNANT, Y., AND ISRAEL, M.: Acetylcholine turnover in the course of stimulation. *In* Cholinergic Mechanisms, ed. by P. G. Waser, pp. 161–167, Raven Press, New York, 1975.
54. EHRLICH, B. E., DIAMOND, J. M., BRAUN, L. D., CORNFORD, I. M., AND OLDENDORF, W. H.: Effects of lithium on blood-brain barrier transport of the neurotransmitter precursor choline, tyrosine, and tryptophan. Brain Res. **193:** 604–607, 1980.
55. ELWYN, D. H.: The role of the liver in regulation of amino acid and protein metabolism. *In* Mammalian Protein Metabolism, ed. by H. N. Munro, Chpt. 38, pp. 523–557, Academic Press, New York, 1970.
56. ENNA, S. J., BIRD, E. D., BENNETT, J. F., BYLUND, D. B., YAMAMURA, H. I., IVERSEN, L. L., AND SNYDER, S. H.: Huntington's chorea: Changes in neurotransmitter receptors in brain. N. Engl. J. Med. **294:** 1305–1309, 1976.
57. ETIENNE, P., GAUTHIER, S., JOHNSON, G., COLLIER, B., MENDIS, T., DASTOOR, D., COLE, M., AND MULLER, H. F.: Lecithin in Alzheimer's disease. Lancet **2:** 837, 1978.
58. FABER, J., HAGEN, C., KIRKEGAARD, C., BIRK-LAURIDSEN, U., AND MOLLER, S. E.: Lack of effects of L-tryptophan on basal and TRH-stimulated TSH and prolactin levels. Psychoneuroendocrinology **2:** 413–415, 1977.
59. FARNEBO, L. O., AND HAMBERGER, B.: Drug-induced changes in the release of ^{3}H-monoamines from field stimulated rat brain slices. Acta Physiol. Scand. Suppl. **371:** 35–44, 1971.
60. FERNSTROM, J. D., AND FALLER, D. V.: Neutral amino acids in the brain: Changes in response to food ingestion. J. Neurochem. **30:** 1531–1538, 1978.
61. FERNSTROM, J. D., AND WURTMAN, R. J.: Brain serotonin content: Physiological dependence on plasma tryptophan levels. Science **173:** 149–152, 1971.
62. FERNSTROM, J. D., AND WURTMAN, R. J.: Brain serotonin content: Increase following ingestion of carbohydrate diet. Science **174:** 1023–1025, 1971.
63. FERNSTROM, J. D., AND WURTMAN, R. J.: Brain serotonin content: Physiological regulation by plasma neutral amino acids. Science **178:** 414–416, 1972.
64. FERNSTROM, J. D., WURTMAN, R. J., HAMMERSTROM-WIKLUND, B., RAND, W. M., MUNRO, H. N., AND DAVIDSON, C. S.: Diurnal variations in plasma concentrations of tryptophan, tyrosine, and other neutral amino acids: Effect of dietary protein intake. Amer. J. Clin. Nutr. **32:** 1912–1922, 1979.
65. FERNSTROM, M. H., AND WURTMAN, R. J.: Increase in striatal choline acetyltransferase activity after choline administration. Brain Res. **165:** 358–361, 1979.
66. FERRIS, S. H., SATHANANTHAN, G., REISBERG, B., AND GERSHON, S.: Long-term choline treatment of memory-impaired elderly patients. Science **205:** 1039–1040, 1979.
67. FISCHER, J. E., ROSEN, H. M., EBEID, A. M., JAMES, J. H., KEANE, J. M., AND SOETERS, P. B.: The effects of normalization of plasma amino acids on hepatic encephalopathy in man. Surgery **80:** 77–91, 1976.
68. FOLDES, A., AND COSTA, E.: Relationship of brain monoamine and locomotor activity in rats. Biochem. Pharmacol. **29:** 1617–1621, 1975.
69. FOVALL, P., DYSKEN, M. W., LAZARUS, L. W., DAVIS, J. M., KAHN, R. L., FINKLE, S., AND RATTAN, P.: Choline bitartrate treatment of alzheimer-like dementias. Commun. Psychopharmacol. **4:** 141–143, 1980.
70. FOX, J. H., TOPEL, J. L., AND HUCKMAN, M. S.: Use of computerized tomography in senile dementia. J. Neurol. Neurosurg. Psychiat. **38:** 948–953, 1975.
71. FRATTA, W., BIGGIO, G., AND GESSA, G. L.: Homosexual mounting behavior induced in rats and rabbits by a tryptophan-free diet. Life Sci. **21:** 379–389, 1977.
72. FRIEDMAN, P. A., KAUFMAN, S., AND KANG, E. S.: Nature of the molecular defect in phenylketonuria. Nature (London) **240:** 157–159, 1972.
73. FRIEDMAN, P. A., KOPPELMAN, A. H., AND KAUFMAN, S.: Partial purification and characterization of tryptophan hydroxylase from rabbit hindbrain. J. Biol. Chem. **247:** 4165–4173, 1972.
74. GALLAGER, D. W., AND AGHAJANIAN, G. K.: Inhibition of firing of raphe neurons by tryptophan and 5-hydroxytryptophan: Blockade by inhibiting serotonin synthesis with Ro 4-4602. Neuropharmacology **15:** 149–156, 1976.
75. GELENBERG, A. J., DOLLER-WOJCIK, J. C., AND GROWDON, J. H.: Choline and lecithin in the treatment of tardive dyskinesia: Preliminary results from a pilot study. Amer. J. Psychiat. **136:** 772–776, 1979.
76. GELENBERG, A. J., WOJCIK, J. D., GROWDON, J. H., SVED, A. F., AND WURTMAN, R. J.: Tyrosine for the treatment of depression. Amer. J. Psychiat. **137:** 622–623, 1980.
77. GERLACH, J., REISBY, N., AND RANDRUP, A.: Dopaminergic hypersensitivity and cholinergic hypofunction in the pathophysiology of tardive dyskinesia. Psychopharmacologia **34:** 21–35, 1974.
78. GIBBONS, J. L., BURR, G. A., BRIDGER, W. H., AND LEIBOWITZ, S. F.: Manipulations of dietary tryptophan: Effects on mouse killing and brain serotonin in the rat. Brain Res. **169:** 139–153, 1979.
79. GIBSON, C. J., DEIKEL, S. M., YOUNG, S. N., AND BINIK, Y. M.: Behavioural and biochemical effects of tryptophan, tyrosine, and phenylalanine in mice. Psychopharmacologia, submitted for publication.
80. GIBSON, C. J., AND WURTMAN, R. J.: Physiological control of brain catecholamine synthesis by brain tyrosine concentration. Biochem. Pharmacol. **26:** 1137–1142, 1977.
81. GIBSON, C. J., AND WURTMAN, R. J.: Physiological control of brain norepinephrine synthesis by brain tyrosine concentration. Life Sci. **22:** 1399–1406, 1978.
82. GLAESER, B. S., MELAMED, E., GROWDON, J. H., AND WURTMAN, R. J.: Elevation of plasma tyrosine after a single oral dose of L-tyrosine. Life Sci. **25:** 265–272, 1979.
83. GLASS, A. R., SCHAFF, M., AND DIAMOND, R. C.: Absent growth hormone response to L-tryptophan in acromegaly. J. Clin. Endocrinol. Metab. **48:** 664–666, 1979.

83a. GLASS, A. R., SMALLRIDGE, R. C., SCHAAF, M., AND DIAMOND, R. C.: Absent prolactin response to L-tryptophan in normal and acromegalic subjects. Psychoneuroendocrinology **5:** 261–265, 1980.

83b. GOLDBERG, I. K.: L-Tyrosine in depression. Lancet **2:** 364, 1980.

84. GROWDON, J. H.: Changes in motor behavior following the administration of serotonin neurotoxins. Ann. N.Y. Acad. Sci. **305:** 510–523, 1978.
85. GROWDON, J. H.: Serotoninergic mechanisms in myoclonus. J. Neural Transm. **15**(suppl.): 209–216, 1979.
86. GROWDON, J. H.: Neurotransmitters in the diet: Their use in the treatment of brain disorders. *In* Nutrition and the Brain, ed. by R. J. Wurtman and J. J. Wurtman, vol. III, pp. 117–181, Raven Press, New York, 1979.
87. GROWDON, J. H., COHEN, E. L., AND WURTMAN, R. J.: Effects of oral choline administration on serum and CSF choline levels in patients with Huntington's disease. J. Neurochem. **28:** 229–231, 1976.
88. GROWDON, J. H., COHEN, E. L., AND WURTMAN, R. J.: Huntington's disease: Clinical and chemical effects of choline administration. Ann. Neurol. **1:** 418–422, 1977.
89. GROWDON, J. H., GELENBERG, A. J., DOLLER, J., HIRSCH, M. J., AND WURTMAN, R. J.: Lecithin can suppress tardive dyskinesia. N. Engl. J. Med. **298:** 1029–1030, 1978.
90. GROWDON, J. H., HIRSCH, M. J., WURTMAN, R. J., AND WIENER, W.: Oral choline administration to patients with tardive dyskinesia. N. Engl. J. Med. **297:** 524–527, 1977.
91. GROWDON, J. H., AND MELAMED, E.: Effects of oral L-tyrosine administration on CSF tyrosine and HVA levels in patients with Parkinson's disease. Neurology **30:** 396, 1980.
92. GROWDON, J. H., AND WURTMAN, R. J.: Dietary influences on the synthesis of neurotransmitters in the brain. Nutr. Rev. **37:** 129–136, 1979.
93. GUDELSKY, G. A., AND MOORE, K. E.: A comparison of the effects of haloperidol on dopamine turnover in the striatum, olfactory tubercle, and median eminence. J. Pharmacol. Exp. Ther. **202:** 149–156, 1977.
94. HAMON, M., AND GLOWINSKI, J.: Regulation of serotonin synthesis. Life Sci. **15:** 1533–1548, 1974.
95. HARTMANN, E.: L-Tryptophan: A rational hypnotic with clinical potential. Amer. J. Psychiat. **134:** 366–370, 1977.
96. HARTMANN, E.: L-Tryptophan as a hypnotic agent: A review. Waking and Sleeping **1:** 155–161, 1977.

97. HARVEY, J. A., AND LINTS, C. E.: Lesions in the medial forebrain bundle: Delayed sensitivity to electric shock. Science **148:** 250–252, 1965.
98. HAUBRICH, D. R., AND PFLUEGER, A. B.: Choline administration: Central effect mediated by stimulation of acetylcholine synthesis. Life Sci. **24:** 1083–1090, 1979.
99. HAUBRICH, D. R., RISLEY, E. A., AND WILLIAMS, M.: Effects of deanol, choline, and its metabolites on binding of ^{3}H-quinuclidinyl benzilate to rat brain membranes. Biochem. Pharmacol. **28:** 3673–3674, 1979.
100. HAUBRICH, D. R., WANG, P. F. L., HERMAN, R. L., AND CLODY, D. E.: Increase in rat brain acetylcholine induced by choline or deanol. Life Sci. **17:** 975–980, 1975.
101. HIRSCH, M. J., GROWDON, J. H., AND WURTMAN, R. J.: Relations between dietary choline or lecithin intake, serum choline levels and various metabolic indices. Metabolism **27:** 953–960, 1978.
102. HIRSCH, M. J., AND WURTMAN, R. J.: Lecithin consumption elevates acetylcholine concentrations in rat brain and adrenal gland. Science **207:** 223–225, 1978.
103. HO, I. K., BRASE, D. A., LOH, H. H., AND WAY, E. L.: Influence of L-tryptophan on morphine analgesia, tolerance, and physical dependence. J. Pharmacol. Exp. Ther. **193:** 35–43, 1975.
104. HOLE, K., AND MARSDEN, C. A.: Unchanged sensitivity to electric shock in L-tryptophan treated rats. Pharmacol. Biochem. Behav. **3:** 307–309, 1975.
105. HOUTSMULLER, M. T.: Metabolic fate of dietary lecithin. *In* Nutrition and the Brain, ed. by A. Barbeau, J. H. Growdon, and R. J. Wurtman, vol. 5, pp. 83–94, Raven Press, New York, 1979.
105a. HU, R., VROULIS, G., AND SMITH, R. C.: Effects of lecithin on memory and behavior in Alzheimer's type dementia. Abstracts, Gerontology Society of America, 33rd Scientific Meeting, p. 128, 1980.
106. HYYPPA, M. T., JOLMA, T., LIIRA, J., LANGVIK, V. A., AND KYTOMAKI, O.: L-Tryptophan treatment and the episodic secretion of pituitary hormones and cortisol. Psychoneuroendocrinology **4:** 29–35, 1979.
107. IKEDA, M., LEVITT, M., AND UDENFRIEND, S.: Hydroxylation of phenylalanine by purified preparations of adrenal and brain tyrosine hydroxylase. Biochem. Biophys. Res. Commun. **18:** 482–488, 1965.
108. IVERSEN, L. L.: The chemistry of the brain. Sci. Amer. **241:** 134–149, 1979.
109. JACKSON, I. V., NUTTALL, E. A., IBE, L. O., AND PEREZ-CRVET, J.: Treatment of tardive dyskinesia with lecithin. Amer. J. Psychiat. **136:** 1458–1462, 1979.
110. JACOBS, B. L., EUBANKS, E. E., AND WISE, W. D.: Effect of indolealkylamine manipulations on locomotor activity in rats. Neuropharmacology **13:** 575–583, 1974.
111. JACOBY, J., COLMENARES, J. L., AND WURTMAN, R. J.: Failure of decreases of serotonin uptake or monoamine oxidase inhibition to block the acceleration in brain 5-hydroxyindole synthesis that follows food consumption. J. Neural Transm. **37:** 25–32, 1975.
112. JOH, T. H., TURK, D. H., AND REIS, D. J.: Direct phosphorylation of brain tyrosine hydroxylase by cyclic AMP-dependent protein kinase mechanism and enzyme activation. Proc. Nat. Acad. Sci. U.S.A. **75:** 4744–4748, 1978.
113. JOUVET, M.: Biogenic amines and the states of sleep. Science **163:** 32–41, 1969.
114. KALSNER, S.: Limitations of presynaptic adrenoreceptor theory: The characteristics of the effects of nonadrenaline and phenoxybenzamine on stimulation induced efflux of ^{3}H-nonadrenaline in vas deferens. J. Pharmacol. Exp. Ther. **212:** 232–239, 1980.
115. KAUFMAN, S.: Properties of the pterin-dependent aromatic amino acid hydroxylases. *In* Aromatic Amino Acids in the Brain, Ciba Foundation Symposium 22, pp. 85–108, Elsevier, Amsterdam, 1974.
116. KESSLER, P. D., AND MARCHBANKS, R. M.: Choline transport is not coupled to acetylcholine systhesis. Nature (London) **279:** 542–544, 1979.
117. KLAWANS, H. L., AND RUBOVITS, R.: Effect of cholinergic and anticholinergic agents on tardive dyskinesia. J. Neurol. Neurosurg. Psychiat. **27:** 941–947, 1974.
118. KNOTT, J., AND CURZON, G.: Free tryptophan in plasma and brain tryptophan metabolism. Nature (London) **239:** 452–453, 1972.
119. KOBAYASHI, R. M.: Drug therapy of tardive dyskinesia. N. Engl. J. Med. **296:** 257–260, 1977.
119a. KOSKINIENI, M., HYYPPA, M., SALNIO, K., SALNI, T., SARNA, S., AND UOTILA, L.: Transient effect of L-tryptophan in progressive myoclonus epilepsy without Lafora bodies: Clinical and neurophysiological studies. Epilepsia **21:** 351–357, 1980.
119b. KRANZ, H., CADDY, D. J., WILLIAMS, A. M., AND GAY, W.: Myasthenic syndrome: Effect of choline, plasmaphoresis, and test for circulating factor. J. Neurol. Neurosurg. Psychiat. **43:** 483–488, 1980.
120. KRNJEVIC, K., AND REINHARDT, W.: Choline excites cortical neurons. Science **206:** 1321–1323, 1979.
121. KUHAR, M. J., SETHY, V. H., ROTH, R. H., AND AGHAJANIAN, G. K.: Choline: Selective accumulation by central cholinergic neurons. J. Neurochem. **20:** 581–593, 1973.
122. LANCE, J. W., AND ADAMS, R. D.: The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. Brain **86:** 111–136, 1963.
123. LANGER, S. Z., DUGOCOVICH, M. L., AND CELUCH, S. M.: *In* Chemical Tools in Catecholamine Research, ed. by O. Almgren, A. Carlsson, and J. Engel, vol. II, pp. 183–191, North-Holland Publishing Co., New York, 1975.
124. LASSEN, J. D.: The effect of *p*-chloroamphetamine on motility in rats after inhibition of monoamine synthesis, storage, uptake and receptor interaction. Psychopharmacologia **34:** 243–254, 1974.
125. LATHAM, C. J., AND BLUNDELL, J. E.: Evidence for the effect of tryptophan on the pattern of food consumption in free feeding and food deprived rats. Life Sci. **24:** 1971–1978, 1979.
125a. LAWRENCE, G. M., MILLAC, P., STOUT, G. S., AND WARD, J. W.: The use of choline chloride in ataxic disorders. J. Neurol. Neurosurg. Psychiat. **43:** 452–454, 1980.
126. LEGG, N. J.: Oral choline in cerebellar ataxia. Brit. Med. J. **2:** 1403–1404, 1978.
126a. LEHMANN, J.: How to investigate tryptophan malabsorption and the value of repeated tryptophan loads. *In* Origin, Prevention, and Treatment of Affective Disorders, ed. by M. Schou and E. Stromgren, pp. 125–138, Academic Press, London, 1979.
127. LIPSETT, D., MADRAS, B., WURTMAN, R. J., AND MUNRO, H. N.: Serum tryptophan levels after carbohydrate ingestion: Selective decline in non-albumin-bound tryptophan coincident with reduction serum-free fatty acids. Life Sci. **12:** 57–64, 1973.
128. LÖFFELHOLZ, K., LINDMAR, R., AND WEIDE, W.: Relationship between choline and acetylcholine release in the autonomic nervous system. *In* Nutrition and the Brain, vol. 5, ed. by A. Barbeau, J. H. Growdon, and R. J. Wurtman, pp. 233–241, Raven Press, New York, 1979.
129. LONDON, E. D., AND COYLE, J. T.: Pharmacological augmentation of acetylcholine levels in kainate-lesioned rat striatum. Biochem. Pharmacol. **27:** 2962–2965, 1978.
130. LOVENBERG, W., JEQUIER, E., AND SJOERDSMA, A.: Tryptophan hydroxylation in mammalian systems. Advan. Pharmacol. **6A:** 21–25, 1968.
131. LOVENBERG, W., AND VICTOR, S. J.: Regulation of tryptophan and tyrosine hydroxylase. Life Sci. **14:** 2337–2353, 1974.
132. LYTLE, L. D., MESSING, R. B., FISHER, L., AND PHEBUS, L.: Effect of chronic corn consumption on brain serotonin and the response to electric shock. Science **190:** 692–694, 1975.
133. MADRAS, B. K., COHEN, E. L., MESSING, R., MUNRO, H. N., AND WURTMAN, R. J.: Relevance of serum-free tryptophan to tissue concentrations. Metabolism **23:** 1107–1116, 1974.
134. MAGYAR, R. L., GILLINA, J. C., AND WYATT, R. J.: Tolerance to the increased locomotor activity produced by L-5-hydroxytryptophan following peripheral decarboxylase inhibition in mice. Psychopharmacologia **57:** 342–350, 1978.
135. MAHER, T. J., AND WURTMAN, R. J.: L-Threonine administration increases glycine concentrations in the rat central nervous system. Life Sci. **26:** 1283–1286, 1980.
136. MALTHE-SORENSON, D., AND FONNUM, F.: Multiple forms of choline acetyltransferase in several species demonstrated by isoelectric focusing. Biochem. J. **127:** 229–236, 1972.
137. MANS, A. M., BEIBUYCK, J. F., SAUNDERS, S. J., KIRSCH, R. E., AND HAWKINS, R. A.: Tryptophan transport across the blood-brain barrier during acute hepatic failure. J. Neurochem. **33:** 409–418, 1979.
138. MARSDEN, C. A., AND CURZON, G.: Studies on the behavioral effects of tryptophan and *p*-chlorophenylalanine. Neuropharmacology 15: 165–171, 1976.
139. MARSDEN, C. A., AND CURZON, G.: The contribution of tryptamine to the behavioral effects of L-tryptophan in tranylcypromine treated rats. Psychopharmacologia **57:** 71–76, 1978.
140. MCGEER, P. L., AND MCGEER, E. G.: Central cholinergic pathways. *In* Nutrition and the Brain, vol. 5, ed. by A. Barbeau, J. H. Growdon, and R. J. Wurtman, pp. 177–199, Raven Press, New York, 1979.
141. MCGEER, P. L., MCGEER, E. G., AND FIBIGER, H. C.: Choline acetylase and glutamic acid decarboxylase in Huntington's chorea. Neurology **23:** 912–917, 1973.
142. MCMENAMY, R. H., AND ONCLEY, J. L.: The specific binding of L-tryptophan to serum albumin. J. Biol. Chem. **233:** 1436–1447, 1978.
143. MELAMED, E., GLAESER, B. S., GROWDON, J. H., AND WURTMAN, R. J.: Plasma tyrosine in normal humans: Effects of oral tyrosine and protein-containing meals. J. Neural Transm. **47:** 299–306, 1980.
144. MELAMED, E., HEFTI, F., AND WURTMAN, R. J.: Tyrosine administration increases striatal dopamine release in rats with partial nigrostriatal lesions. Proc. Nat. Acad. Sci. U.S.A. **77:** 4305–4309, 1980.
145. MENDELS, J., STINNETT, J. L., BURNS, D., AND FRAZER, A.: Amine precursors and depression. Arch. Gen. Psychiat. **32:** 22–30, 1975.
146. MESSING, R. B., FISHER, L., PHEBUS, L., AND LYTLE, L. D.: Interaction of diet and drugs in the regulation of brain 5-hydroxyindoles and the response to painful electric shock. Life Sci. **18:** 707–714, 1976.
147. MESSING, R. B., AND LYTLE, L. D.: Serotonin-containing neurons: Their possible role in pain and analgesia. Pain **4:** 1–21, 1977.
148. MESSING, R. B., PHEBUS, L., FISHER, L. A., AND LYTLE, L. D.: Effects of *p*-chloroamphetamine on locomotor activity and brain 5-hydroxyindoles. Neuropharmacology **15:** 157–163, 1976.
149. MILLINGTON, W. R., MCCALL, A. L., AND WURTMAN, R. J.: Deanol acetoamidobenzoate inhibits the blood-brain barrier transport of choline. Ann. Neurol. **4:** 302–306, 1978.
150. MILLINGTON, W. R., MCCALL, A. L., AND WURTMAN, R. J.: Lithium and brain choline levels. N. Engl. J. Med. **300:** 196–197, 1978.

151. MODIGH, K.: Effects of L-tryptophan on motor activity in mice. Psychopharmacologia **30:** 123–134, 1973.

151a. MODLINGER, R. S., SCHONMULLER, J. M., AND ARORA, S. P.: Adrenocorticotropin release by tryptophan in man. J. Clin. Endocrinol. Metab. **50:** 360–363, 1980.

152. MOHS, R. C., DAVIS, K. L., TINKLENBERG, J. R., HOLLISTER, L. E., YESAVAGE, J. A., AND KOPELL, B. S.: Choline chloride treatment of memory deficits in the elderly. Amer. J. Psychiat. **136:** 1275, 1979.

153. MØLLER, S. E., KIRK, L., AND FREMMING, K. H.: Plasma amino acids as an index for subgroups in manic-depressive psychosis: Correlation to effect of tryptophan. Psychopharmacologia **49:** 205–213, 1976.

154. MORGENROTH, V. A., III, WALTERS, J. R., AND ROTH, R. H.: Dopaminergic neurons—Alteration in the kinetic properties of tyrosine hydroxylase after cessation of impulse flow. Biochem. Pharmacol. **25:** 655–661, 1976.

155. MORLEY, B. J., ROBINSON, G. R., BROWN, G. B., KEMP, G. E., AND BADLEY, R. J.: Effects of dietary choline on nicotinic acetylcholine receptors in brain. Nature (London) **266:** 848–850, 1977.

156. MORRE, M. C., HEFTI, F., AND WURTMAN, R. J.: Regional variations in brain tyrosine levels following tyrosine administration. J. Neural Transm. **49:** 45–50, 1980.

157. MORRE, M., AND WURTMAN, R. J.: Characteristics of synaptosomal tyrosine uptake: Relation to brain regions and to presence of other amino acids. Life Sci., **28:** 65–75, 1981.

158. MULLER, E. E., BRAMBILLA, F., CAVAGNINI, F., PERACCHI, M., AND PANERAI, A.: Slight effect of L-tryptophan on growth hormone release in normal subjects. J. Clin. Endocrinol. Metab. **39:** 1–5, 1974.

159. MYERS, R. D., AND YAKSH, T. L.: Control of body temperature in the unanesthetized monkey by cholinergic and aminergic systems in the hypothalamus. J. Physiol. (London) **202:** 483–500, 1969.

160. NADLER, H. L., AND HSIA, D. Y.: Epinephrine metabolism in phenylketonuria. Proc. Soc. Exp. Biol. Med. **107:** 721–723, 1961.

161. NAGATSU, T., LEVITT, M., AND UDENFRIEND, S.: Tyrosine hydroxylase: The initial step in norepinephrine biosynthesis. J. Biol. Chem. **239:** 2910–2917, 1964.

162. NECKERS, L. M., BIGGIO, G., MOJA, E., AND MEEK, J. L.: Modulation of brain tryptophan hydroxylase activity by brain tryptophan content. J. Pharmacol. Exp. Ther. **201:** 110–116, 1977.

163. NEIL, J. F., HIMMELHOCH, J. M., AND LICATA, S. M.: Emergence of myasthenia gravis during treatment with lithium carbonate. Arch. Gen. Psychiat. **33:** 1090–1092, 1976.

164. NOWYCHY, M. C., AND ROTH, R. H.: Dopaminergic neurons: Role of presynaptic receptors in the regulation of transmitter biosynthesis. Progr. Neuropsychopharmacol. **2:** 139–158, 1978.

165. PALKOVITS, M., AND ZABORSZKY, L.: Neuroanatomy of central cardiovascular control. Nucleus tractus solitarii: Afferent and efferent neuronal connections in relation to the baroreceptor reflex arc. Progr. Brain Res. **47:** 9–34, 1977.

166. PARDRIDGE, W. M.: Regulation of amino acid availability to the brain. *In* Nutrition and the Brain, ed. by R. J. Wurtman and J. J. Wurtman, vol. 1, Raven Press, New York, 1977.

167. PARDRIDGE, W. M.: The role of blood-brain barrier transport of tryptophan and other neutral amino acids in the regulation of substrate-limited pathways of brain amino acid metabolism. J. Neural Transm. **15**(suppl.): 43–54, 1979.

168. PARDRIDGE, W. M., AND OLDENDORF, W. H.: Transport of metabolic substrates through the blood-brain barrier. J. Neurochem. **28:** 5–12, 1977.

169. PERRY, E. K., PERRY, R. H., BLESSES, G., AND TOMLINSON, B. E.: Necropsy evidence of central cholinergic deficits in senile dementia. Lancet **1:** 189, 1977.

170. PETERS, B. H., AND LEVIN, H. S.: Effects of physostigmine and lecithin on memory in Alzheimer disease. Ann. Neurol. **6:** 219–221, 1979.

171. PHILIPPU, A., DIETL, H., AND SINHA, J. N.: Rise in blood pressure increases the release of endogenous catecholamines in the anterior hypothalamus of the cat. Naunyn Schmiedeberg's Arch. Pharmacol. **310:** 237–240, 1980.

172. PLUM, F., AND HINDFELT, B.: The neurological complications of liver disease. *In* Handbook of Clinical Neurology: Metabolic and Efficiency Diseases of the Nervous System, ed. by P. J. Vinten and G. W. Bruyn, vol. 31, Amsterdam, North-Holland, 1976.

173. POLINSKY, R. J., EBERT, M. H., CAINE, E. D., LUDLOW, C., AND BASSICH, C. J.: Cholinergic treatment in the Tourette syndrome. N. Engl. J. Med. **302:** 1310, 1980.

174. PORSOLT, R. D., BERTIN, A., BLAVET, N., DENIAL, M., JALFRE, M.: Immobility induced by forced swimming in rats: Effects of agents which modify central catecholamine and serotonin activity. Eur. J. Pharmacol. **57:** 201–210, 1979.

175. PORSOLT, R. D., BERTIN, A., AND JALFRE, M.: Behavioral despair in mice: A primary screening test for antidepressants. Arch. int. Pharmacodyn. Thér. **229:** 327–336, 1977.

176. PRANGE, A. J., WILSON, I. C., LYNN, C. W., ALLTOP, L. B., AND STIKELATHER, A.: L-Tryptophan in mania: Contribution to a permissive hypothesis of affective disorders. Arch. Gen. Psychiat. **30:** 56–62, 1974.

176a. RASTOGI, R. B., NAIR, N. P. V., AND LAL, S.: A comparative study of choline and lecithin treatment on dopamine (DA) synthesis and turnover in the striatum and hippocampus of rats. Abstr. Soc. Neurosci. **6:** 516, 1980.

177. RENVOIZE, E. B., AND JERRAM, T.: Choline in Alzheimer's disease. N. Engl. J. Med. **301:** 330, 1979.

177a. ROSS, D. S., FERNSTROM, J. D., AND WURTMAN, R. J.: The role of dietary protein in generating daily rhythms in rat liver tryptophan pyrrolase and tyrosine transaminase. Metabolism **22:** 1175–1184, 1973.

178. SAHAKIAN, B. J., WURTMAN, R. J., BARRL, J. K., MILLINGTON, W. R., AND CHIEL, H. J.: Low tryptophan diet decreases brain serotonin and alters response to apomorphine. Nature (London) **279:** 731–732, 1979.

179. SCALLY, M. C., ULUS, I. H., AND WURTMAN, R. J.: Brain tyrosine level controls striatal dopamine synthesis in haloperidol-treated rats. J. Neural Transm. **43:** 103, 1977.

180. SCHILDKRAUT, J. J.: The catecholamine hypothesis of affective disorders: a review of supportive evidence. Amer. J. Psychiat. **122:** 509–522, 1965.

180a. SCOTT, N. A., DESILVA, R. A., LOWN, B., AND WURTMAN, R. J.: Tyrosine administration decreases vulnerability to ventricular fibrillation in the normal canine heart. Science, **211:** 727–729, 1981.

180b. SCOTT, N. A., VERRIER, R., LOWN, B., AND WURTMAN, R. J.: Mechanisms mediating influence of tyrosine on vulnerability to ventricular fibrillation. Clin. Res., in press, 1981.

181. SHAW, D. M., CAMPS, F. E., AND ECCLESTON, E. G.: 5-HT in the hindbrain of depressive suicides. Brit. J. Psychiat. **113:** 1407–1411, 1967.

182. SHEARD, N. H.: The effect of *p*-chlorophenylanine on behavior in rats: Relation to brain serotonin and 5-hydroxyindoleacetic acid. Brain Res. **15:** 524–528, 1969.

183. SIGNORET, J. L., WHITELEY, A., AND LHERMITTE, F.: Influence of choline on amnesia in early Alzheimer's disease. Lancet **2:** 837, 1978.

184. SINGH, V. K., MCGEER, E. G., AND MCGEER, P. L.: Two isoenzyme forms of choline acetyltransferases in human nigrostriatal nuclei. Proceedings of the 5th Annual Meeting of the Society for Neuroscience, p. 384, New York, 1975.

185. SINHA, J. N., DIETL, H., AND PHILIPPU, A.: Effect of a fall in blood pressure on the release of catecholamines in the hypothalamus. Life Sci. **26:** 1751–1760, 1980.

186. SITARAM, N., WEINGARTNER, H., CAINE, E. D., AND GILLIN, J. C.: Choline: Selective enhancement of serial learning and encoding of low imagery words in man. Life Sci. **22:** 1555–1560, 1978.

187. SITARAM, N., WEINGARTNER, H., AND GILLIN, J. C.: Human serial learning: Enhancement with arecholine and choline and impairment with scopolamine. Science **201:** 274–276, 1978.

188. SMITH, C. M., SWASH, M., EXTON-SMITH, A., PHILLIPS, M. H., OVERSTALL, P. W., PIPER, M. E., AND BAILEY, M. R.: Choline therapy in Alzheimer's disease. Lancet **2:** 318, 1978.

188a. SMYTHE, G. A.: The role of serotonin and dopamine in hypothalamic-pituitary function. Clin. Endocrinol. Metab. **7:** 325–341, 1977.

189. SPANO, P. F., TAGLIAMONTE, A., TAGLIAMONTE, P., AND GESSA, G. L.: Stimulation of brain dopamine synthesis by gamma-hydroxybutyrate. J. Neurochem. **18:** 1831–1836, 1971.

189a. SPINDEL, E., WURTMAN, R. J., AND BIRD, E. D.: Increased TRH content of the basal ganglia in Huntington's disease. N. Engl. J. Med. **303:** 1235–1236, 1980.

190. STAHL, S. M., AND BERGER, P. A.: Cholinergic treatment in the Tourette syndrome. N. Engl. J. Med. **302:** 1311, 1980.

191. STARKE, K., AND ALTMANN, K. P.: Inhibition of adrenergic neurotransmission by clonidine: An action on prejunctional alpha-receptors. Neuropharmacology **12:** 339–347, 1973.

192. SULLER, C. F., AND STRICKLER, E. M.: Hyperphagia and increased growth in rats after intraventricular injection of 5,7-dihydroxtryptamine. Science **192:** 385–387, 1976.

193. SVED, A. F., AND FERNSTROM, J. D.: Tyrosine availability and dopamine synthesis in the striatum: Studies with gamma-butyrolactone. Life Sci., submitted for publication.

194. SVED, A. F., FERNSTROM, J. D., AND WURTMAN, R. J.: Tyrosine administration decreases serum prolactin levels in chronically reserpinized rats. Life Sci. **25:** 1293–1300, 1979.

195. SVED, A. F., FERNSTROM, J. D., AND WURTMAN, R. J.: Tyrosine administration reduces blood pressure and enhances brain norepinephrine release in spontaneously hypertensive rats. Proc. Nat. Acad. Sci. U.S.A. **76:** 3511–3514, 1979.

195a. SWARTZ, B. E., AND JENDEN, O. J.: Acetylcholine dynamics in rat hippocampal slices. Abstr. Soc. Neurosci. **6:** 151, 1980.

196. TAGLIAMONTE, A., BIGGIO, G., VARGIU, L., AND GESSA, G. L.: Free tryptophan in serum controls brain tryptophan level and serotonin synthesis. Life Sci. **12:** 277–287, 1973.

197. TAMMINGA, C. A., SMITH, R. C., ERICKSON, S. E., AND DAVIS, J. M.: Cholinergic influences in tardive dyskinesia. Amer. J. Psychiat. **134:** 769–774, 1977.

198. TARSY, D., LEOPOLD, N., AND SAX, D. S.: Physostigmine in choreiform movement disorders. Neurology **24:** 28–33, 1974.

199. TAYLOR, M.: Effects of L-tryptophan and L-methionine on activity in rat. Brit. J. Pharmacol. **58:** 117–119, 1976.

200. TELNER, J., LEPORE, F., AND GUILLEMOT, J. P.: Effects of serotonin content on pain sensitivity in the rat. Pharmacol. Biochem. Behav. **10:** 657–661, 1979.

201. THURMOND, J. B., KRAMARCY, N. R., LASLEY, S. M., AND BROWN, J. W.: Dietary amino acid precursors: Effects on central monoamines, aggression,

and locomotor activity in the mouse. Pharmacol. Biochem. Behav. **12:** 525–532, 1980.

)2. THURMOND, J. B., LASLEY, S. M., CORKING, A. L., AND BROWN, J. W.: Effects of dietary tyrosine, phenylalanine, and tryptophan on aggression in mice. Pharmacol. Biochem. Behav. **6:** 475–478, 1977.

)3. TRICKLEBANK, M. D., SMART, J. L., BLOXAM, D. L., AND CURZON, G.: Effects of chronic experimental liver dysfunction and L-tryptophan on behavior in the rat. Pharmacol. Biochem. Behav. **9:** 181–189, 1978.

)4. ULUS, I. H., HIRSCH, M. J., AND WURTMAN, R. J.: Transsynaptic induction of adrenal tyrosine hydroxylase activity by choline: Evidence that choline administration increases cholinergic transmission. Proc. Nat. Acad. Sci. U.S.A. **74:** 798–800, 1977.

)5. ULUS, I. H., SCALLY, M. C., AND WURTMAN, R. J.: Choline potentiates the transsynaptic induction of adrenal tyrosine hydroxylase by reserpine, probably by enhancing the release of acetylcholine. Life Sci. **21:** 145–148, 1977.

)6. ULUS, I. H., SCALLY, M. C., AND WURTMAN, R. J.: Enhancement by choline of the induction of adrenal tyrosine hydroxylase by phenoxybenzamine, 6-hydroxydopamine, insulin, or exposure to cold. J. Pharmacol. Exp. Ther. **204:** 676–682, 1978.

)7. ULUS, I. H., AND WURTMAN, R. J.: Choline administration: Activation of tyrosine hydroxylase in dopaminergic neurons of rat brain. Science **194:** 1060–1061, 1976.

)8. ULUS, I. H., WURTMAN, R. J., SCALLY, M. C., AND HIRSCH, M. J.: Effect of choline on cholinergic function. *In* Cholinergic Mechanisms and Psychopharmacology, ed. by D. H. Jenden, pp. 525–538, Plenum Press, New York, 1977.

)8a. ULUS, I. H., AND WURTMAN, R. J.: Selective response of rat peripheral sympathetic nervous system to various stimuli. J. Physiol. (London) **293:** 513–523, 1979.

)9. VAN PRAAG, H. M., AND KORF, J.: Serotonin metabolism in depression: Clinical application of the probenecid test. Int. Pharmakopsychiat. **9:** 35–51, 1974.

10. VAN WOERT, M. H., AND SETHY, V. H.: Therapy of intention myoclonus with L-5-hydroxytryptophan and a peripheral decarboxylase inhibitor, MK486. Neurology **25:** 135–140, 1975.

11. WALINDER, J., SKOTT, A., CARLSSON, A., NAGY, A., AND ROOS, B. E.: Potentiation of the antidepressant action of clomipramine by tryptophan. Arch. Gen. Psychiat. **33:** 1384–1389, 1976.

11a. WALINDER, J., CARLSSON, A., PERSSON, R., AND WALLIN, L.: Potentiation of the effect of antidepressant drugs by tryptophan. Acta Psychiatr. Scand. **280:** suppl. 61, 243–247, 1980.

12. WALTERS, J. K., DAVIS, M., AND SHEARD, M. H.: Tryptophan-free diet: Effects on the acoustic startle reflex in rats. Psychopharmacologia **62:** 103–109, 1979.

13. WECKER, L., DETTBARN, W. D., AND SCHMIDT, D. E.: Choline administration: Modification of the central actions of atropine. Science **199:** 86–87, 1978.

14. WECKER, L., AND SCHMIDT, D. E.: Central cholinergic function relationship to choline administration. Life Sci. **25:** 375–384, 1979.

15. WECKER, L., AND SCHMIDT, D. E.: Neuropharmacological consequences of choline administration. Brain Res. **184:** 234–238, 1980.

16. WERTER, M. H., MISGELD, U., BAK, I. J., AND JENDEN, D. J.: Electrophysiological and biochemical examination of the cholinergic system in rat neostriatal slices. Abstr. Soc. Neurosci. **5:** 81, 1979.

17. WHITE, H. L., AND WU, J. C.: Kinetics of choline acetyltransferase by isoelectric focusing. J. Neurochem. **21:** 939–948, 1973.

218. WHITE, H. L., AND WU, J. C.: Kinetics of choline acetyltransferase (E.C. 2,3,1,6) from human and other mammalian central and peripheral nervous tissues. J. Neurochem. **20:** 297–308, 1973.

219. WIEBE, R. H., HANDWERGER, S., AND HAMMOND, C. B.: Failure of L-tryptophan to stimulate prolactin secretion in man. J. Clin. Endocrinol. Metab. **45:** 1310–1312, 1977.

220. WOJCIK, W. J., FORNAL, C., AND RADULOVACKI, M.: Effect of tryptophan on sleep in the rat. Neuropharmacology **19:** 163–167, 1980.

221. WOODGER, T. L., SIREK, A., AND ANDERSON, G. H.: Diabetes, dietary tryptophan and protein intake regulation in weanling rats. Amer. J. Physiol. **236:** 307–311, 1979.

222. WOOLF, P. D., AND LEE, L.: Effect of the serotonin precursor tryptophan on pituitary hormone secretion. J. Clin. Endocrinol. Metab. **45:** 123–133, 1977.

223. WURTMAN, J. J.: Sources of choline and lecithin in the diet. *In* Nutrition and the Brain, ed. by A. Barbeau, J. H. Growdon, and R. J. Wurtman, vol. 5, pp. 73–81, Raven Press, New York, 1979.

224. WURTMAN, J. J., AND WURTMAN, R. J.: Fenfluramine and fluoxetine spare protein consumption while suppressing caloric intake by rats. Science **198:** 1178–1180, 1977.

225. WURTMAN, J. J., AND WURTMAN, R. J.: Drugs that enhance central serotoninergic transmission diminish elective carbohydrate consumption by rats. Life Sci. **24:** 895–904, 1979.

225a. WURTMAN, J. J., AND WURTMAN, R. J.: Suppression of carbohydrate consumption as snacks and at mealtime by *dl*-fenfluramine or tryptophan. *In* Anorectic Agents: Mechanisms of Actions and of Tolerance, ed. by S. Garrattini, Raven Press, New York, in press, 1981.

226. WURTMAN, R. J.: Diurnal rhythms in mammalian protein metabolism. *In* Mammalian Protein Metabolism, ed. by H. N. Munro, vol. IV, pp. 445–479, Academic Press, New York, 1970.

227. WURTMAN, R. J., AND FERNSTROM, J. D.: Control of brain neurotransmitter synthesis by precursor availability and nutritional state. Biochem. Pharmacol. **25:** 1691–1696, 1976.

228. WURTMAN, R. J., HIRSCH, M. J., AND GROWDON, J. H.: Lecithin consumption raises serum-free choline levels. Lancet **2:** 68–69, 1977.

229. WURTMAN, R. J., LARIN, F., MOSTAFAPOUR, S., AND FERNSTROM, J. D.: Brain catechol synthesis: Control by brain tyrosine concentration. Science **185:** 183–184, 1974.

230. WURTMAN, R. J., AND PARDRIDGE, W. M.: Summary: circulating tryptophan, brain tryptophan, and psychiatric disease. J. Neural Transm. **15**(suppl.): 227–236, 1979.

230a. WURTMAN, R. J., MAGIL, S. G., AND REINSTEIN, D. K.: Piracetam diminishes hippocampal acetylcholine levels in rats. Life Sci., in press, 1981.

231. YAKSH, T. L., AND WILSON, P. R.: Spinal serotonin terminal system mediates antinociception. J. Pharmacol. Exp. Ther. **208:** 446–453, 1973.

232. YAMAMURA, H. I., AND SNYDER, S. H.: High affinity transport of choline into synaptosomes of rat brain. J. Neurochem. **21:** 1355–1374, 1973.

233. YEHUDA, S. L., AND WURTMAN, R. J.: Release of brain dopamine as the probable mechanism for the hypothermic effect of D-amphetamine. Nature (London) **240:** 477–478, 1972.

234. YUWILER, A., OLDENDORF, W. H., GELLER, E., AND BRAUN, L.: Effect of albumin binding and amino acid competition on tryptophan uptake into brain. J. Neurochem. **28:** 1015–1023, 1977.

235. ZEISEL, S. H., EPSTEIN, M. F., AND WURTMAN, R. J.: Elevated choline concentration in neonatal plasma. Life Sci. **26:** 1827–1831, 1980.