Biochemical Pharmacology, Vol. 27, pp. 621–626. Pergamon Press, 1978. Printed in Great Britain.

COMMENTARY

TRACE AMINES AND ALTERNATIVE NEUROTRANSMITTERS IN THE CENTRAL NERVOUS SYSTEM*

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The concept of chemically mediated synaptic neurotransmission in the central nervous system (CNS) is heavily biased by our still evolving understanding of peripheral cholinergic and sympathetic neurons. The better established amine neurotransmitter candidates (especially acetylcholine, the catecholamines and serotonin) account for only a fraction of the total nerve terminals in the mammalian CNS [1]. Attempts to advance beyond traditional concepts include a growing impression that other neuro-active substances, including amino acids and peptides, may account for even more of central neurotransmission than do the amines. In addition, with powerful new analytic techniques (especially radioenzymatic, and gas chromatographic-mass spectrometric methods), it has been possible to identify an increasing number of aromatic amines throughout the CNS, including phenylalkylamines, indolealkylamines and imidazoleamines [2–8]. There is increasing evidence that many such amines can be synthesized and stored in CNS nerve terminals and can be released by depolarizing stimuli [9–12], although their post-synaptic functional effects remain relatively obscure.

That most of these substances are present in low concentrations (ng/g, or less) has sometimes led to the impression that their occurrence may be incidental to the synthesis of other "more important" amines, such as the catecholamines or serotonin (5-HT), for example, by the action of relatively non-selective aromatic amino acid decarboxylases on their precursors, or by the interconversion of amines by recently appreciated hydroxylase or dehydroxylase (redox) pathways, presumably present in neuronal tissue [3, 7]. Low tissue concentrations of amines in some cases may reflect varying degrees of efficiency of their protection, notably by reserpine-sensitive storage in presynaptic vesicles [4, 9, 13], and hence, of vulnerability to monoamine oxidase (MAO). In the case of at least one of these substances, octopamine, it is now apparent that its turnover in most neuronal tissues is very rapid, and based on the production of deaminated metabolites, the daily synthesis of octopamine in the whole body closely approaches that of the catecholamines [14]. If turnover and production rates reflect the biologic activity of these amines, then they may be more important than had formerly been supposed, and low concentrations or limited vesicular storage need not exclude candidate neurohumors from further consideration.

There remains considerable uncertainty as to whether such "trace," "minor," or "alternative" aromatic amines arise in neurons or other brain cells along with better known amines, or whether there is a strict limitation of one amine to one neuron (an extension of Dale's view [15] that one neuron contains a given transmitter at all terminals). It is virtually certain at least that dopamine (DA) and norepinephrine (NE) can occur together in the same terminals and that preventing the accumulation of NE (as with an inhibitor of dopamine-beta-hydroxylase, DBH) favors substitution by DA in storage and release processes, although it is not known whether altered ratios of these two catecholamines have important physiological or pathological consequences. In peripheral target tissues, sympathectomy or treatment with 6-OH-dopamine leads not only to a depletion of the stores of both catecholamines, but also to a loss of a portion of the stores of octopamine and of tyramine. It has also been noted that tyramine and octopamine (beta-hydroxy-*p*-tyramine) occur in cardiac and CNS tissues in a regional distribution that approximately parallels the distribution of catecholaminergic innervation or of DBH activity. Furthermore, the ratio of tyramine–octopamine in rat striatum has been estimated to be 8:1 [7]; this may suggest that tyramine and DA coexist in DA-producing neurons, or that tissues low in DBH (or "tyramine-beta-hydroxylase") activity favor the production of both phenolic amines but in different cells. None of the available approaches definitively proves whether or not phenolic amines can arise separately in discrete non-catecholamine neurons, even in relatively simpler tissues outside the CNS, in part due to the ambiguity of effects of even selective surgical or pharmacologic lesioning methods. For example, sympathectomy or discrete brain lesions may simultaneously destroy neurons containing catecholamines and non-catecholamines, and 6-OH-dopamine may be taken up by some neurons containing amines other than catecholamines. An even more complicated situation occurs in the mollusc *Aplysia* in which octopamine, 5-HT and acetylcholine (ACh) have been

* Supported in part by U.S. PHS Grants MH-16674, MH-25515, AM-15347 and Career Scientist Award MH-74370 (to Dr. Baldessarini).

Table 1. Possible functions of trace amines in neurotransmission

A.	Neurotransmitters in their own discrete neuronal systems.
B.	"Cotransmitters" arising coincidentally with the biosynthesis of other amine neurotransmitters in neurons containing more than one amine product.
C.	Modulation of synthetic pathways of other amines (e.g. by intracellular effects on precursor availability, feedback or kinetics of rate-limiting enzymes).
D.	Modulation of access to, and storage in pre-synaptic vesicles, and of neuronal and extraneuronal uptake processes.
E.	Modulation of release by serving as "cotransmitters" (having their own post-synaptic effects), or by altering the quantal content of released "active" transmitter.
F.	Modulation of post-synaptic receptor agonism (which should reflect the net impact of molecules having different agonistic potencies and binding kinetics).
G.	Modulation of pre-synaptic receptor mechanisms or other membrane-mediated local feedback regulatory controls on transmitter synthesis and release.

found in the same neurons. Similar analyses of multiple transmitter candidates are not yet available for discrete or isolated mammalian neurons. The question of whether more than one candidate transmitter is synthesized and stored in one type of neuron may eventually yield to the application of highly selective and sensitive histochemical and immunohistologic analyses of brain tissue.

Various possible ways in which trace amines might exert important physiologic effects in synaptic neurotransmission are summarized in Table 1. These include the possibility that some aromatic amines may arise independently in discrete neurons that are not identical to recognized pathways, notably those containing catecholamines or indoleamines. Alternatively, if some aromatic amines arise coincidentally within neurons containing other neurotransmitters or enter them secondarily from other sites of production, they might serve as "cotransmitters," or might exert important pre-synaptic and post-synaptic modulating effects on the synthesis, storage, release or actions of other amine neurotransmitters [11].

Another approach to the possible role of aromatic amines in the CNS is to seek conditions in which they might accumulate at the expense of other physiologic neurotransmitters as a reaction to metabolic derangements in amine synthesis or storage, or as a consequence of certain drug treatments. If the amine is stored and released at nerve endings, but has different or lesser post-synaptic effects at target cells, it is usually designated a "false neurotransmitter," although a more neutral term such as "substitute" or "alternative" neurotransmitter is preferable to cover situations in which the substitute molecule may be not less, but equally, or even more active at post-synaptic receptor sites [11, 14]. The more commonly used term "false transmitter" has acquired an implication that the biological activity of the alternative molecule must be weak, or that failure of synaptic transmission is inevitably associated with its accumulation. Neither functional consequence is a necessary result. To fit the definition of "alternative transmitter," a molecule need only be accepted into appropriate neuronal storage sites from which release by depolarizing stimuli can occur. This definition might be broadened to allow for molecules that can be released by indirectly acting sympathomimetic amines or other drugs instead of, or in addition to, physiological stimuli.

The concept of alternative neurotransmitters arose to explain certain pharmacological observations concerning the peripheral sympathetic nervous system [11, 16, 17]. For example, the hypotensive effects of alpha-methylated analogs of *m*-tyrosine and DOPA (dihydroxyphenylalanine) were believed to result partly from their conversion by decarboxylation and beta-hydroxylation to relatively inactive structural analogs of the catecholamines. Similarly it was suggested that the hypotensive and antianginal effects of prolonged treatment with MAO inhibitors might be due to the accumulation in nerve endings of sympathetically inactive amine products usually destroyed by MAO. For such molecules to be accumulated vigorously in NE-containing nerve endings, at least one phenolic hydroxyl group is required, and to be accepted into pre-synaptic vesicles and be released by neural activity, another hydroxyl group on the benzene ring or on the beta-carbon of the ethylamine side chain seems to be needed [11, 16, 18]. Such compounds may be relatively weak directly acting sympathomimetic amines if they contain only two hydroxyl groups, and may or may not be weak if they have three hydroxyl groups (catechol plus beta-hydroxyl) plus an alpha-methyl group on the side chain. An initial hypothesis that alpha-methyl-DOPA is antiadrenergic because it is converted to alpha-methylated catecholamines that act as false or inactive neurotransmitters is over-simplified if not erroneous, although this concept may adequately explain the antiadrenergic actions of alpha-methyl-*m*-tyrosine, which is converted to the weak direct NE agonist, metaraminol. Current evidence indicates that alpha-methyl-norepinephrine is almost as potent as NE as an agonist of vascular adrenergic receptors in some preparations. It may also act in the CNS as an alpha-agonist to produce hypotensive effects, although the evidence on this point remains conflicting or equivocal, and it has even been suggested that alpha-methyl-NE and metaraminol may be antagonistic to CNS catecholamine receptors [19]. Nevertheless, the possibility remains that alpha-methylated catecholamines and phenolic phenethylamines may act as "superactive substitute neurotransmitters" with slow turnover and prolonged activity [20–22], due in part to protection from MAO by the alpha-methyl substituent [11, 14].

A useful general concept is that a number of endogenous or exogenous molecules may accumulate in

nerve terminals to mimic more or less successfully certain aspects of the metabolism and function of natural transmitters. This concept of substitute neurotransmitters allows inclusion of substances that may or may not be released by nerve depolarization and may or may not exert post-synaptic effects. This broadening of the concept includes the effects of metabolites of alpha-methylated amino acids and the amphetamines, as well as relatively nonspecific agents given increased selectivity because of their accumulation in nerve terminals, including neurotoxins (e.g. 6-OH-dopamine and dihydroxytryptamines) and local anesthetics (e.g. guanethidine and other post-ganglionic blocking agents) [11].

Such substitution phenomena might also occur in the CNS, not only in NE-containing neurons, but also with DA, 5-HT, ACh, and other putative neurotransmitters such as the excitatory and inhibitory amino acids and peptide-containing cells. For example, alpha-methyl-*m*-tyrosine leads to the formation not only of metaraminol (beta-hydroxylated), but also of alpha-methyl-*m*-tyramine, which can accumulate in and be released from striatal tissue, presumably at DA-containing nerve terminals [20, 23]. This evidence accords well with indications that a single phenolic hydroxyl group may be sufficient to support entry (e.g. of *p*- or *m*-tyramine or *p*-OH-amphetamine) into the site of release in striatal or limbic DA-rich tissues [10–12, 21], while two hydroxyl groups seem to be required for substitution in NE nerve terminals [11, 16, 18]. A further observation consistent with the idea that phenolic amines may serve as false DA transmitters in the striatum is the failure of *p*- or *m*-tyramine, octopamine, *p*-OH-amphetamine, α-methyl-*m*-tyramine, α-methyl-octopamine, or metaraminol to stimulate DA-sensitive adenylate cyclase in striatal homogenates (R. J. Baldessarini, N. Kula and K. Walton, unpublished observations). In addition to phenolic amines, serotonin may also be able to compete with DA for storage, and possibly also for release in the striatum; the converse may also occur as DA may be able to substitute for 5-HT at central 5-HT terminals [17, 24]. A possible example of false transmission with an amino acid is suggested by the ability of the neuropharmacologically inactive amino acid glutamine to compete for uptake into nerve endings with glutamate, a suggested excitatory neurotransmitter, and to be released [25]. Recent evidence further indicates that several structural analogs of choline can be taken into cholinergic nerve terminals by high-affinity uptake, be acetylated, stored and released in the presence of Ca^{2+} to exert weak muscarinic, and equivocal nicotinic effects [26]. Interestingly, some of these acetylated false cholinergic transmitters are poor substrates for acetylcholinesterase, a feature of their metabolism that, by analogy with the inability of alpha-methylated amines to be inactivated by MAO, may enhance their availability and effectiveness as substitute transmitters. It seems inevitable that similar findings will soon be forthcoming for neurons and other neurosecretory cells that produce and release biologically and neurophysiologically active peptides.

A wide variety of pharmacologic and metabolic conditions are known that might support the accumulation of substitute neurotransmitters. Many of these are summarized in Table 2. We have especially concentrated on hepatic failure and its attendant encephalopathy as an example of a condition in which abnormal metabolism of amines might occur [27–29]. Hepatic failure is an attractive model, since it includes clinical signs of altered function of peripheral adrenergic transmission in addition to neuropsychiatric signs of CNS dysfunction.

In hepatic failure, precursors of possible false transmitters are readily available. Aromatic amino acids are provided by protein catabolism, and their corresponding amines are produced in the gut by the action of bacterial amino acid decarboxylases. Normally, exogenous aromatic amines are largely catabolized by MAO, notably in the liver, and so are cleared from the portal blood. When hepatic function is impaired and blood is shunted around the liver, precursors can flood the systemic circulation and the nervous system. Aromatic amino acids can be locally decarboxylated in brain tissue to their corresponding amines by a relatively nonspecific decarboxylase; some can be locally beta-hydroxylated by DBH, another relatively nonspecific oxidizing enzyme localized in nerve endings, and replace NE.

The high cardiac output, low peripheral vascular resistance state, and the uremia (hepato-renal syn-

Table 2. Conditions favoring accumulation of substitute neurotransmitters at sympathetic nerve endings

A.	*Increased precursor availability*:
	1. Amino-acid therapy: L-DOPA, α-methyldopa, α-methyl-*m*-tyrosine, tryptophan, 5-OH-tryptophan.
	2. Amine therapy: amphetamines, tyramine, metaraminol.
	3. Portacaval venous shunts: surgical or in liver disease.
	4. Decreased utilization of amino acids due to toxins, drugs or metabolic disease.
	5. Metabolic-genetic error (e.g. phenylketonuria).
B.	*Decreased metabolism of amines*:
	1. Decreased MAO activity: drug-induced or spontaneous.
	2. Liver disease.
	3. Decreased DBH activity: drug-induced or spontaneous.
C.	*Drugs or toxins as substitute neurotransmitters*:
	1. Local anesthetics with localized actions (postganglionic blocking agents, e.g. guanethidine).
	2. Neurotoxins with localized actions (e.g. 6-OH-DA, dihydroxytryptamines introduced as drugs, or possibly as endogenously produced autotoxins).

drome) that occur in severe liver failure may result from the replacement of NE by weakly sympathomimetic amines, resulting in loss of arteriolar tone, opening of peripheral vascular shunts, perfusion of non-essential areas, and shunting of blood away from the kidneys. Similarly asterixis or flapping tremor, presumably a sign of extrapyramidal dysfunction, might result from a replacement of transmitters in the basal ganglia. Disturbances of consciousness in hepatic coma might result from the displacement of various transmitters from widely distributed central neurons, including mesolimbic DA-containing projections and NE-containing neurons associated with the ascending reticular activating system.

A false-transmitter hypothesis for hepatic coma is consistent with many of its clinical features [27–29]. Thus, shunting of portal blood around the liver and loss of hepatic function diminish the utilization of amino acids and catabolism of amines in portal blood. Ammonia and other nitrogenous products accumulate in the systemic circulation, but since the clinical condition would depend on the accumulation of amines in nerve endings, serum levels of ammonia need not necessarily reflect tissue levels of amines, particularly in the brain, and do not correlate closely with the neuropsychiatric status of patients with hepatic failure. Since bacteria produce amines from amino acids, protein loads from the diet or bleeding into the gut with portal venous congestion should increase the opportunity to accumulate amines and do in fact make hepatic encephalopathy worse in man and animals. Conversely, withholding proteins or sterilizing the gut with poorly absorbed antibiotics should reduce the formation of amines, and these steps often bring about clinical improvement of the patient's mental status.

In patients or animals with hepatic encephalopathy, elevated plasma or urinary levels of several aromatic amines have been observed repeatedly; although it is probably not uniquely significant *per se*, octopamine has been studied most intensively. Although it represents only one of many abnormalities, the accumulation of octopamine in blood, tissue, or urine seems to be a regular and predictable concomitant of dysfunction of neurotransmission, evidently contributing to its clinical utility as a predictor or correlate of hepatic coma [27–30]. In rats with surgically produced portacaval venous anastomoses or with acute hepatic failure induced by ligation of the hepatic blood supply, the neurological status correlated with decreased levels of NE in the brain and heart, with small decreases of brain DA, and with correspondingly increased amounts of octopamine, phenylethanolamine and 5-HT [28]. These increases may reflect decreased destruction of amines or greater availability of their precursors in the systemic circulation; increased entry of preformed hydroxylated amines (e.g. past a defective blood–brain barrier) is less likely, since brain octopamine increased prior to increases in blood octopamine [31]. With both dogs and monkeys with similar surgically induced hepatic encephalopathy, levels of octopamine and phenylethanolamine in cerebrospinal fluid (CSF) recovered through a lateral cerebroventricular cannula closely corresponded to the level of arousal and consciousness [31].

Such amines might act as flase transmitters by their accumulation in catecholamine-containing nerve terminals on a competitive basis, displacing the physiological transmitter stoichiometrically. However, in peripheral sympathetic terminals, even replacement of substantial proportions of the NE stores (say 50 per cent) with other amines need not decrease the amount of NE released, and conversely, altered transmission can occur after only partial replacement of the natural transmitter [11]. Since it is likely that newly synthesized pools of neurotransmitters may be released preferentially [1, 11, 16, 17, 26], interference with the synthesis of neurotransmitters may have more profound functional consequences than simple replacement of the transmitter from pre-synaptic storage pools. Changes in synthesis may arise from altered patterns of plasma amino acid levels. Profound and remarkably similar abnormalities in tissue levels of many amino acids occur in animals with a portacaval shunt and in man during hepatic failure in association with encephalopathy [27–30]. Derangements in amino acids may lead to altered synthesis of physiological amine neurotransmitters, as well as increases in the synthesis of amines by decarboxylase enzymes not normally saturated with these substrates, leading to the accumulation of aromatic animes in unusual concentrations and distributions. For example, elevations of brain octopamine levels in the rat with a portacaval shunt correspond closely to the rise in brain tyrosine levels [31]. In addition, increased levels of octopamine or indoleamines and their metabolites in the rat brain after portacaval anastomosis are associated with increases of plasma tyrosine or free tryptophan, respectively, and decreases of branched-chain neutral aliphatic amino acids, and can be shifted toward normal by infusions of leucine, isoleucine and valine [33, 34]. Since phenylalanine can compete with tyrosine as a substrate for tyrosine hydroxylase [1], the rate-limiting step of catecholamine synthesis, excess phenylalanine may impede the production of DOPA from tyrosine and further increase the production of tyrosine as well. Since glutamine is regularly elevated in hepatic encephalopathy, its suggested role as a false amino acid transmitter [25] may also be significant in the pathophysiology of hepatic failure [28, 29].

Correction of abnormal distributions of amines in central nerve endings may contribute to the clinical neurological benefits of L-DOPA in hepatic encephalopathy, or this may merely represent a nonspecific effect of increased arousal [27, 35]. Recently, a novel approach to the therapy of hepatic encephalopathy has been introduced, based on a better understanding of the metabolism of aromatic amines and amino acids. This involves some attempts to correct the pattern of increased circulating and CNS levels of aromatic amino acids and decreased levels of their competitors for entry into the brain, the branched-chain and other neutral aliphatic amino acids [14, 19, 28]. Dealing directly with the abnormal levels of amino acids, Fischer *et al.* [31, 36] recently reversed hepatic coma in the dog and the monkey with a portacaval venous anastomosis by infusions of nutrient solutions containing reduced quantities of phenylalanine, tyrosine, and methionine and increased concentrations of branched-chain neutral amino acids (valine, leucine and isoleucine). Moreover, the elevated CSF levels of

aromatic amino acids and amines returned to normal 12 hr after the start of an infusion of amino acids which normalized the proportions of plasma amino acids. Simultaneously, the animals awakened from hepatic coma and remained neurologically normal as long as the correcting amino acid infusion was continued; when the infusions were stopped, the animals once again returned to the encephalopathy, with corresponding returns of abnormal CSF levels of amino acids and amines [32]. Preliminary results with similar infusions in patients with hepatic encephalopathy have produced a similar improvement of their neuropsychiatric status [29]. This and most other treatments that ameliorate hepatic encephalopathy (protein restriction, gut sterilization, as well as infusion of amino acid mixtures low in precursors of aromatic amines) have also been found to normalize amino acid and amine levels in animals tissues [29].

Other clinical examples of excessive availability of aromatic amino acids or simple amines include the treatment of Parkinsonism with L-DOPA, or of mood disorders or myoclonus with serotonin precursors, and the use of amphetamines—all of which may result in profound behavioral changes (Table 2). Since L-DOPA leads to accumulations of DA in non-dopaminergic neurons, and since L-DOPA and the amphetamines form hydroxylated amine products that accumulate in the CNS, they may affect the brain by a substitute transmitter mechanism. For example, "tolerance" to the effects of the amphetamines might be due to the accumulation of their hydroxylated metabolites [11, 14].

In addition to increased availability of precursors, increased accumulations of probable substitute transmitters can be caused by decreased destruction of amines (Table 2). Although this possibility has been suggestively related to the anti-autonomic effects of prolonged use of MAO inhibitors [16], whether their antidepressant and psychotogenic effects may be partly mediated by increased accumulations of amines other than the catecholamines or serotonin in the CNS is not known. One intriguing possibility is that the reported decreases of MAO activity in the blood platelets of chronic schizophrenics [37] and manic-depressives [38] might provide an opportunity for substitute amines to accumulate and thereby to compromise the function of central aminergic synapses, if such enzyme deficiencies are physiologically significant and if they occur in brain or liver as well as in blood.

Whether any of the concepts presented above are relevant to metabolic or neuropsychiatric illnesses other than hepatic encephalopathy is unclear. In addition to the asterixis and coma that commonly accompany severe hepatic failure, a variety of psychotic changes and the syndrome of catatonia have also been described in such patients, and the accumulation of false transmitters and loss of other transmitters may be important in their pathophysiology. One disease that does have a marked excess of circulating aromatic amino acids and an overproduction of phenethylamines is phenylketonuria. Whether the neuropsychiatric aspects of this or any other heritable metabolic dysfunction are due to accumulations of substitute transmitters (Table 2) is unknown. Since there are many metabolic errors and many putative neurotransmitters, the possibilities for future research along this line are broad.

Trace amines should be considered in the development of other testable hypotheses about the pathophysiology of the still idiopathic neuropsychiatric disorders. There may be physiologically important abnormalities in such conditions associated directly with the metabolism of such amines and their activity as CNS neurohumors or their interactions with other neurotransmitters. So far there is little evidence for such abnormalities based on clinical metabolic studies of patients [14]. This deficiency of supportive clinical metabolic findings is a shortcoming of virtually all hypotheses attempting to link amine metabolism in the brain to abnormal mood, behavior or thinking, plausible though they may seem based on animal or clinical pharmacological studies [39, 40].

In summary, we have reviewed the present status of concepts involving the presence of "minor" or trace amines in the central nervous system. Such substances are likely to arise metabolically in association with the synthesis of other amine neurotransmitters and may have regulatory or other physiologically important actions as cotransmitters. Some may even arise independently in unique neurons that do not synthesize more "classical" transmitters. Unusual accumulations of trace amines, possibly leading to their acting as substitute or "false" neurotransmitters, may occur in response to a variety of drug treatments and may contribute to the pathophysiology of some metabolic diseases. Their possible role in other idiopathic neurological or psychiatric disorders might also be explored further.

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