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The mysterious trace amines: Protean neuromodulators of synaptic transmission in mammalian brain☆

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Abstract

The trace amines are a structurally related group of amines and their isomers synthesized in mammalian brain and peripheral nervous tissues. They are closely associated metabolically with the dopamine, noradrenaline and serotonin neurotransmitter systems in mammalian brain. Like dopamine, noradrenaline and serotonin the trace amines have been implicated in a vast array of human disorders of affect and cognition. The trace amines are unique as they are present in trace concentrations, exhibit high rates of metabolism and are distributed heterogeneously in mammalian brain. While some are synthesized in their parent amine neurotransmitter systems, there is also evidence to suggest other trace amines may comprise their own independent neurotransmitter systems. A substantial body of evidence suggests that the trace amines may play very significant roles in the coordination of biogenic amine-based synaptic physiology. At high concentrations, they have well-characterized presynaptic ''amphetamine-like'' effects on catecholamine and indolamine release, reuptake and biosynthesis; at lower concentrations, they possess postsynaptic modulatory effects that potentiate the activity of other neurotransmitters, particularly dopamine and serotonin. The trace amines also possess electrophysiological effects that are in opposition to these neurotransmitters, indicating to some researchers the existence of receptors specific for the trace amines. While binding sites or receptors for a few of the trace amines have been advanced, the absence of cloned receptor protein has impeded significant development of their detailed mechanistic roles in the coordination of catecholamine and indolamine synaptic physiology. The recent discovery and characterization of a family of mammalian G protein-coupled receptors responsive to trace amines such as β-phenylethylamine, tyramine, and octopamine, including socially ingested psychotropic drugs such as amphetamine, 3,4-methylenedioxymethamphetamine, *N*,*N*-dimethyltryptamine, and lysergic acid diethylamide, have revitalized the field of scientific studies investigating trace amine synaptic physiology, and its association with major human disorders of affect and cognition.

Keywords: β-Phenylethylamine; Tyramine; Tryptamine; Octopamine; Receptor; Trace amine; Synaptic transmitter; Neuromodulator; Afeect; Cognition; Schizophrenia; Depression

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Abbreviations: L-AADC, aromatic L-amino acid decarboxylase; COMT, catechol-*O*-methyltransferase; DBH, dopamine β-hydroxylase; DMT, *N*,*N*-dimethyltryptamine; INMT, indolethylamine-*N*-methyltransferase; MAO-A/B, monoamine oxidase A/B; NMT, *N*-methyltransferase; PNMT, phenylethanolamine *N*-methyltransferase; TH, tyrosine hydroxylase

☆ Protean: readily assuming different shapes or forms.

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1. The mysterious trace amines

The label ‘‘trace amine’’ (or ‘‘micro-amines’’, as sometimes they have been described) refers to the structurally related group of amines and their isomers, *p*-octopamine, *m*-octopamine (*p*- and *m*-OA) *p*- and *m*-tyramine (*p*- and *m*-TYR), tryptamine (TRP), β-phenylethylamine (β-PEA) and perhaps including *N*,*N*-dimethyltryptamine (DMT)[1] (Fig. 1).

All trace amines are closely associated metabolically with the dopamine, noradrenaline and serotonin neurotransmitter systems (Philips et al., 1974; Axelrod and Saavedra, 1977). Like OA, these compounds are present at trace concentrations (0.1–100 ng/g tissue) and are distributed *heterogeneously* in mammalian brain tissue (Boulton, 1976a; Boulton and Juorio, 1982). All trace amines exhibit very high rates of biosynthesis and catabolism (Boulton, 1984). In the case of β-PEA and TRP, this high rate of turnover is strongly believed to be related to their lack of vesicular storage mechanisms and their greater affinity for monoamine oxidase B (MAO-B) (Dyck, 1984). The term ‘‘trace amine’’ is certainly a misnomer for it implies an accidental or incidental role for these molecules in the processes of the synaptic physiology or metabolism of dopamine, noradrenaline and serotonin (Robertson, 1981).

Since these amines are believed by some to be localized exclusively in dopamine, noradrenaline, or serotonin systems, their greater rates of turnover there suggest that the trace amines may have very significant roles in the *integrative* activity relating to the synaptic physiology of these amines. In fact, dopamine is found at trace levels in visual cortex. Iontophoresis of dopamine there produces similar long-term inhibitory post-synaptic potentials (IPSPs) as are elicited following the iontophoresis of dopamine on neurons in the striatum, where dopamine is present at roughly four times greater levels (Reader et al., 1988). Thus, although it in no way suggests, the lack of significant concentrations of a neurochemical – such as TRP and DMT – at some site in the nervous system should never imply an absence of more important functions (Jones, 1983). Indeed as will be detailed below, a substantial body of observations suggests that TYR, TRP, OA, and particularly β-PEA may play very *significant*

[1] DMT is ubiquitously present within the plant and animal kingdoms (Ott, 1993). DMT is perhaps most well known for its presence in the plant *Psychotria viridis*, which is used together with the vine *Banisteriopsis caapi*, to prepare the hallucinogenic concoction, ayahuasca (or yagè), used by indigenous tribes of the Amazon in their shamanic rituals (Metzner, 1999). DMT is also a normal constituent of human blood and urine (Franzen and Gross, 1965; Karkkainen et al., 2005). More controversial is the presence of DMT in brain. Some researchers posit that the synthesis of DMT in brain is not physiologically significant (Thompson et al., 1999; however, consider the arguments of Jones, 1983; Reader et al., 1988). Other researchers propose that DMT levels increase in the mammalian brain during stress, whereupon DMT may act as an endogenous anxiolytic (for discussion, see Jacob and Presti, 2005).

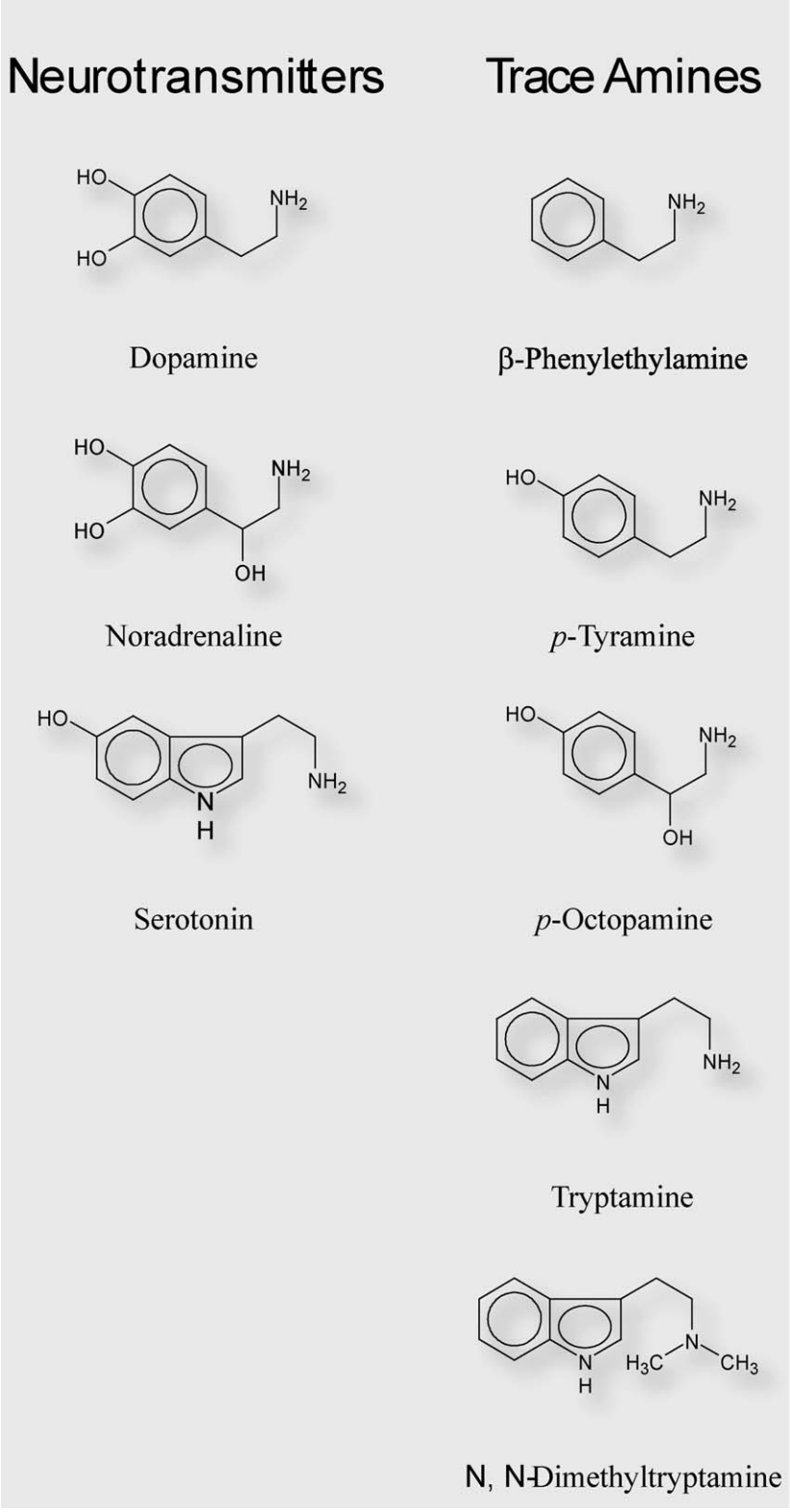

Fig. 1. Structure of the mammalian biogenic amines. The trace amines β-phenylethylamine, tyramine and tryptamine are synthesized from the decarboxylation by aromatic L-amino acid decarboxylase of their precursor amino acids. Octopamine is synthesized from the hydroxylation of tyramine by dopamine-β-decarboxylase. *N*,*N*-dimethyltryptamine is synthesized from a two-step methylation reaction each catalyzed by indolethylamine-*N*-methyltransferase, yielding *N*-methyltryptamine and subsequently *N*,*N*-dimethyltryptamine (Mandell and Morgan, 1971). The trace amines are also *N*-methylated to the corresponding active secondary amines by phenylethanolamine *N*-methyltransferase or *N*-methyltransferase. All trace amines are catabolized to their corresponding inactive metabolites by monoamine oxidase-A/B (see text for details).

roles in the coordination of biogenic amine-based synaptic physiology.

Such coordination may involve particular signaling pathways activated by receptors specific for the trace amines. The recent discovery, partial neuroanatomical mapping, and pharmacological characterization of two G protein-coupled human trace amine associated receptors, TAAR1 and TAAR4, activated by TRP, *p*-TYR and β-PEA, as well as amphetamine, 3,4-methylenedioxymethamphetamine (MDMA, ''ecstacy''), *N*,*N*-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD) (Borowsky et al., 2001; Bunzow et al., 2001; Cikos et al., 2001), substantiates this idea enormously.

Trace amines are characterized by a variety of features that they hold in common. As stated, these substances are distributed *heterogeneously* in mammalian brain. This distribution closely parallels the origins and terminal projection domains of the dopamine, noradrenaline and serotonin neurotransmitter systems (Philips, 1984). They are present at *trace* levels in these same areas (Philips et al., 1974), compared with their presence at microgram levels in the ganglia and nerves of various invertebrate species (Klemm and Axelsson, 1973), as well as compared with dopamine and noradrenaline levels in the mammalian brain (Versteeg et al., 1976). Like OA, they all exhibit *greater* turnover rates than dopamine or noradrenaline (Durden and Phillips, 1980; Durden et al., 1988; Philips and Boulton, 1979). This greater turnover rate may in fact be due to the increased sensitivity of these amines to oxidative deamination by MAO-A/B, owing to their lack of comparable storage mechanisms (Wu and Boulton, 1975; Philips and Boulton, 1979; Durden and Phillips, 1980).

As suggested by other investigators, based on their synaptosomal localization (Boulton and Baker, 1975; Baldessarini and Vogt, 1972), sensitivity to reserpine, and Ca^{2+}-dependent release following depolarizing stimuli such as electrical activation or high K^+ stimulation (Boulton and Baker, 1975; Boulton et al., 1977, 1975; Baldessarini, 1971b; Baldessarini and Vogt, 1972; Dyck, 1989), at least four possible communication roles exist for the trace amines (for review, see Berry, 2004). They may serve as either *co-transmitters* in dopamine, noradrenaline or serotonin neurotransmitter systems (Saavedra and Axelrod, 1976). The trace amines may function as distinct *neurotransmitters* in their own unique trace aminergic systems (Boulton, 1976b; Sabelli et al., 1978; Hicks, 1977). Due to their close structural similarities to dopamine, noradrenaline and serotonin, the trace amines may serve as substitute or *false* neurotransmitters in both peripheral noradrenaline-containing (Kopin, 1968) and central dopamine or noradrenaline systems (Fischer and Baldessarini, 1971; Baldessarini and Fisher, 1978) during disease states, such as hepatic encephalopathy (Fogel et al., 1990), or following L-DOPA therapy for Parkinsonism (Baldessarini and Vogt, 1972). Finally, they may potentially serve in the mammalian brain as *neuromodulators* of the catecholamines insofar as is concerned their biosynthesis, carrier-mediated vesicular uptake (Baldessarini and Fisher, 1978; Boulton, 1976b; Bailey et al., 1987; Dyck, 1983; Matthaei et al., 1976), Ca^{2+}-dependent release (Bailey et al., 1987), pre- or post-synaptic receptor binding (Cheng et al., 1990; Locock et al., 1984; Borowsky et al., 2001), post-synaptic responses (Boulton, 1976a,b; Jones, 1984; Paterson, 1993; Boulton, 1979; Borowsky et al., 2001; Bunzow et al., 2001), and/or carrier-mediated cytoplasmic uptake (Raiteri et al., 1977; Sangiah et al., 1979).

Even with the recent discovery of G-protein-coupled receptors (GPCRs) responsive to the trace amines and the consequent resurgent interest of the role of the trace amines in mammalian synaptic physiology, a shortage of contemporary molecular studies will severely limit the depth in which the activities of any trace amine, particularly OA, can be discussed; they instead may be discussed as a class, the class of trace amines. A number of distinguishing characteristics support this choice. Firstly, the trace amines can be grouped together based on their close structural similarities to each other and to dopamine and noradrenaline. Secondly, they also can be grouped based on their common metabolic associations with catecholamine and indoleamine systems in the mammalian brain. Thirdly, and perhaps most significantly of all, they can be bound together based on their unique abilities to *potentiate* the synaptic efficacy of dopamine, nor adrenaline and serotonin synaptic transmission.

The following review will be concerned with the distributions of the trace amines with dopamine or noradrenaline neurotransmitter systems; that is, are the trace amines indigenous molecules of the dopamine or noradrenaline systems? If this is indeed the case, then they may serve as neuromodulators or co-transmitters with dopamine or noradrenaline in these systems. Whereas if they exist in the brain *independently* of the dopamine or noradrenalin systems, then the trace amines may function as neurotransmitters in their own unique trace aminergic systems. In fact in certain regions of the mammalian brain they may fulfill both roles.

If they perform either of these roles, then what is the nature of the release of the trace amines? Are the trace amines released vesicularly or are they released non-specifically by diffusion from their sites of biosynthesis? We will also attempt to classify them and discuss their *communication* roles in the brain. Are the trace amines neurotransmitters, neuromodulators or neurohumoral agents in the mammalian brain? Are they *fast* synaptic ionotropic neurotransmitters or *slow*-acting metabotropic neuromodulatory agents? On the other hand, might they play both roles?

2. Trace amines and human disorders of affect and cognition

A single man stands like a bird-watcher,
And scuffles the pepper and salt snow
From a discarded, gray
Westinghouse Electric cable drum.
He cannot discover America by counting
The chains of condemned freight-trains
From thirty states. They jolt and jar
and junk in the siding below him.
He has trouble with his balance.
His eyes drop,
And he drifts with the wild ice
Ticking in the seaward down the Hudson,
Like the blank sides of a jig-saw puzzle—Lowell (1999)

It perhaps should not be unexpected that the trace amines have been implicated in most neuropsychiatric disorders that are associated with catecholamine and indoleamine system

dysfunctions, given the fact that the trace amines have a storied history of modulating signaling events that occur at presynaptic and post-synaptic sites for these systems. Alterations in trace amine function are thought to be involved in the etiology of a variety of neuropathological conditions, including hallucinations, schizophrenia, major depression, anxiety states, anorexia, obsessive-compulsive disorders, attention deficit hyperactivity disorder (ADHD), bipolar disorder and hepatic encephalopathy (for excellent reviews, see Boulton, 1980; Dourish and Boulton, 1981; Wolf and Mosnaim, 1983; Davis and Boulton, 1994; Fogel et al., 1990; Ciprian-Ollivier and Cetkovich-Bakmas, 1997; Janssen et al., 1999; Kim and Von Zastrow, 2001; Kusaga et al., 2002; Branchek and Blackburn, 2003; Lindemann and Hoener, 2005).

2.1. Depression

The original hypothesis for depressive illness stated that depression is caused by a deficiency in biogenic amine transmitters (Schildkraut, 1967; Lapin and Ovxenkrug, 1969). Antidepressant drugs such as the tricyclics, tetracyclics, selective serotonin reuptake inhibitors (SSRIs) and MAO inhibitors all increase brain biogenic amine functional availability and improve neurotransmission at catecholamine- and/or indoleamine-mediated synapses. Reserpine, a drug that interferes with biogenic amine packaging in synaptic vesicles and depletes dopamine, noradrenaline and serotonin from the terminals, causes depressive states in some patients who take the substance as an anti-hypotensive agent (Carlsson et al., 1963).

It has been proposed that alterations in trace amine activity could result in a reduced effectiveness of catecholamine- and serotonin-mediated transmission (Dewhurst, 1968; Sabelli and Mosnaim, 1974). In line with this reasoning, Sandler et al. (1979) found that urinary excretion of trace amines are significantly diminished in depressed patients (cf., DeLisi et al., 1984). Similarly the major metabolite of β-PEA, phenylacetic acid, considered a useful indicator for clinical states, is reduced in patients with some forms of depression (Davis and Boulton, 1994). Importantly, the long-term administration of β-PEA, or its precursor, L-phenylalanine, significantly improves the affective state of depressed individuals (Sabelli et al., 1996).

2.2. Schizophrenia

β-PEA is also implicated in the neuropathology of schizophrenia (for reviews, see Sandler and Reynolds, 1976; O'Reilly and Davis, 1994), in part due to the evidence that β-PEA is an agonist at dopamine receptors, but more to the point, based on the observations that administration of high doses of β-PEA not only increases locomotion and induces stereotypic behaviors in rats and monkeys (Tinklenberg et al., 1978; Dourish, 1985; Paterson et al., 1990) in a manner analogous to amphetamine but also in humans at high doses β-PEA will induce schizophrenia-like episodes by stimulating ascending mesolimbic and mesocortical pathways (Connell, 1958; Snyder et al., 1967; Angrist et al., 1974; Laruelle et al., 2003; for review, see O'Reilly and Davis, 1994). This has lead to the proposal that β-PEA is the brain's "endogenous" amphetamine (Janssen et al., 1999). The most direct evidence for the involvement of β-PEA in schizophrenia are the observations that urinary (Yoshimoto et al., 1987; Myojin et al., 1989) as well as plasma β-PEA levels are increased in schizophrenics (Potkin et al., 1979; Shirkande et al., 1995); however other studies did not demonstrate this relationship (cf., Beckmann et al., 1983; Szymanski et al., 1987).

Clearly the precise mechanisms of β-PEA psychogenic activity are still a mystery, but if there is a link between β-PEA and schizophrenia, it would be likely that the site of action is the dopamine D_2 receptor because many efficacious antipsychotic drugs are dopamine D_2 receptor antagonists (for review, see Laruelle et al., 2005). A simple explanation for β-PEA involvement in schizophrenia would be that in response to *elevated* aromatic L-amino acid decarboxylase (L-AADC) activity – the rate limiting enzyme necessary for the biosynthesis of trace amines including β-PEA – trace amine concentrations would increase and this would be expected to alter activity at dopamine D_2 receptors and perhaps TAAR1 expressed within the limbic forebrain (see Borowsky et al., 2001; Bunzow et al., 2001). Our hypothesis is supported by findings that L-AADC activity is increased in the brains of patients having psychoses (Reith et al., 1994), and chronic administration of antipsychotic or psychogenic drugs, such as LSD and PCP, also up-regulate L-AADC mRNA (Buckland et al., 1992, 1997) and protein levels in rat brain (Zhu et al., 1992, 1993).[2]

With the discovery of GPCRs responsive to β-PEA and other trace amines a new avenue of investigation has materialized focusing on these trace amine GPCRs and human psychopathologies. Polymerase chain reaction (PCR) screening for TAARs coupled with chromosomal mapping using probes derived from the amplified TAAR PCR products identified a number of additional human trace amine associated receptors (TAAR9, TAAR6 and TAAR8) (Borowsky et al., 2001; Bunzow et al., 2001). Interestingly, the genes for these GPCRs, including TAAR1 and TAAR4, are tightly clustered on human chromosome 6q23.2 (Borowsky et al., 2001; Bunzow et al., 2001; for review, see Lindemann and Hoener, 2005). This region is nested within a wider region (6q13–q26) demonstrating genome-wide suggestive linkage in a number of pedigrees to bipolar affective disorder and schizophrenia (Cao et al., 1997; Rice et al., 1997; Cichon et al., 2001; Ewald et al., 2002; Dick et al., 2003; Middleton et al., 2004; Venken et al., 2006).

The association of the trace amine associated receptor genes of human chromosomal region 6q23.2 with these disorders is heightened by the presence of multiple single nucleotide polymorphisms in TAAR4 and TAAR6, which are associated with schizophrenic or bipolar pedigrees (Duan et al., 2004; Bly, 2005; Jamra et al., 2005). However, for TAAR6, screening of schizophrenic pedigrees from other ethnicities has not

[2] The human ventral striatum (nucleus accumbens), which is implicated in the pathogenesis of schizophrenia, contains neurons, D-cells that express L-AADC. Interestingly, D-cells are significantly reduced in the brains of autopsied schizophrenics (Ikemoto et al., 2003; for reviews, see Ikemoto, 2002; Ikemoto, 2004; see also Sections 4.3 and 4.4).

demonstrated a linkage between these polymorphisms and schizophrenia (Duan et al., 2005; Ikeda et al., 2005; Amann et al., 2006; Venken et al., 2006). Similarly, a mutant variant of TAAR9 did not segregate with ADHD or bipolar disorder (Vanti et al., 2003). The relationship between trace amine receptor genes and these human cognitive disorders remains unclear.

3. Synthesis and metabolism of the trace amines

> Forever and ever, persistent matter must change its form. Grasping the clue of causality, mechanical, physical, chemical and organic phenomenon greedily push to the fore, snatching matter from one another, for each would reveal its own inherent idea (Schopenhauer, 1966).

The trace amines, β-PEA, p-TYR, OA and TRP, are all synthesized directly by the enzymatic decarboxylation by L-AADC of the respective precursor amino acids, or as in the case of OA by additional conversion from TYR by dopamine-β-hydroxylase (Boulton and Wu, 1973; Boulton, 1976a; Durden and Phillips, 1980; Bowsher and Henry, 1983; for review, see Lindemann and Hoener, 2005). DMT is synthesized by two successive methylation reactions. The first forms *N*-methyltryptamine from tryptamine while the second produces *N*,*N*-dimethyltryptamine (DMT) from the methylation of *N*-methyltryptamine (Mandell and Morgan, 1971; for discussion, see Jacob and Presti, 2005).

The trace amines are catabolized to biologically inactive molecules predominately by MAO, with different selectivities for MAO-A and MAO-B (Philips and Boulton, 1979). In addition to these main metabolic pathways, the trace amines can be converted by non-specific *N*-methyltransferase (NMT) and phenylethanolamine *N*-methyltransferase (PNMT) to the corresponding secondary amines, synephrine, *N*-methylphenylethylamine and *N*-methyltyramine (Saavedra et al., 1973, 1974; again for review, see Lindemann and Hoener, 2005).

4. Phenotypic localization of trace amines in mammalian brain

Considering the fact that the classical neurotransmitters account for only a *small* proportion of the total nerve terminals in the mammalian brain, the presence of additional neurotransmitter systems, if only minor, such as for TRP, TYR, or OA, would appear to be *not* such an unlikely possibility (Baldessarini and Karobath, 1973). While initial immunohistochemical localization of TYR in the rat brain has produced negative results (Osborne, 1985), more recently, Kitahama et al. (2005) demonstrated *strong* TYR immunoreactivity in the rat median eminence and mediobasal hypothalamus. These authors also noted *weak* TYR immunoreactivity within nigrostriatal dopamine neurons and terminals and noradrenergic neurons of the locus coeruleus, observations that corroborate the lesioning studies of Juorio and Jones (1981) described in detail below.

While the *concept* of the development of antibodies to β-PEA has been criticized based on apparently inevitable cross-reactivites with the catecholamines, particularly dopamine (Paterson et al., 1990), TRP and OA immunoreactivity in the rat brain have been successfully demonstrated using polyclonal antisera to TRP (Geffard et al., 1987) and OA (Burchett, 1994). Specifically, TRP and OA immunoreactivity are present in the dorsal and medial raphe, as well as in the locus coeruleus, substantia nigra (SN)-ventral tegmental area (VTA), and in additional mesencephalic regions (Dabadie et al., 1990; Burchett, 1994).

Additionally, OA immunoreactivity is present in more rostral limbic forebrain regions, such as the amygdala, hippocampus, globus pallidus, and caudate-putamen and nucleus accumbens (Burchett, 1994). Using a double-labeling technique Dabadie et al. (1990) and later Dabadie and Geffard (1993) examined the possible co-localization of TRP with dopamine and TRP with serotonin, respectively, in the SN and the raphe nuclei and in the regions between the raphe nuclei and the SN. Dabadie and associates (Dabadie et al., 1990; Dabadie and Geffard, 1993) revealed that the TRP immunoreactivity within the raphe nuclei and in the regions between the raphe nuclei and the SN is *not* present in the same cells with dopamine; in the dorsal raphe TRP is not only present in cells with serotonin but is also present *solely* in TRP-containing-serotonin-*negative* neurons. Thus, it appears that a heterogeneous population of TRP and OA neurons exists in the rat brain which does not express dopamine, but which overlaps anatomically with the classical catecholamine and indoleamine systems, and which is also present more widely in mesencephalic and in additional forebrain regions.

4.1. Is octopamine synthesized exclusively within noradrenaline neurons?

In addition to the immunocytochemical techniques, experiments performed to date attempting to clarify the relationship between the catecholamine-containing neurons and the trace amines have relied primarily on a combination of electrolytic and chemical lesioning of the dopamine, noradrenaline or serotonin cell bodies or their pathways, followed by quantitative analytical measures of the concentrations of dopamine, noradrenaline or serotonin and the relative trace amine(s) at various times following the lesion.

In all cases, these experiments have led to a body of indirect, if sometimes ambiguous, evidence suggestive of either unique trace amine systems or the association of the respective trace amines with other catecholamine transmitter systems. Specifically, studies which turned out to be inconclusive compared the rate and progress of decrease of noradrenaline and OA following chemical lesioning with the neurotoxin 6-OHDA, a drug which destroys catecholamine-containing nerve terminals and results in a degeneration of their terminal projections, effecting a depletion of dopamine and noradrenaline (Thoenen and Tranzer, 1968). The data only were able to suggest that OA is either present entirely in noradrenaline-containing cells, or that an independent population of OA-containing cells exists which also is sensitive to 6-OHDA (Baldessarini, 1971a). Similar conclusions were reached by Juorio (1988a), following the subcutaneous administration of the noradrenaline neurotoxin DSP-4, which depleted

hypothalamic noradrenaline and OA. This resulted in the suggestions that *p*-OA is either present within noradrenaline terminals within the hypothalamus, or that OA cells exist there that are sensitive to DSP-4 (Juorio, 1988a).

Studies comparing the relative disappearance of OA and noradrenaline following electrolytic lesions of the locus coeruleus by Hicks et al. (1987) showed that in the hippocampus, midbrain, hypothalamus and cerebellum, there were significant differences in the patterns of noradrenaline and OA disappearance over time following the lesion. However, in the anterior and posterior cortex and striatum, the post-lesion patterns of disappearance were similar. This led these authors to suggest that in the former regions, OA cells may exist independently of the noradrenaline terminals from the locus coeruleus, while in the latter regions OA is co-localized in noradrenaline terminals from the locus coeruleus (Hicks et al., 1987).

4.2. Is tyramine synthesized exclusively within dopamine neurons?

In addition to the body of evidence discussed above relating to OA and noradrenaline, other studies by Juorio and Jones (1981) focused on the possibility of a relationship between *m*-TYR and *p*-TYR with dopamine neurons and their projections to the striatum. Unilateral electrolytic lesions of the SN pars compacta (SNc) combined with analytical measurements of concentrations of dopamine, *p*- and *m*-TYR from the striatum at survival times of 2, 11, and 25 days, led these authors to conclude that both *m*- and *p*-TYR are located within dopamine-containing cells of the SNc, and/or in fibers passing through the SNc. In contrast, after only 1 day, lesions placed dorsally to the SNc resulted in a profound increase in levels of *m*-TYR, a decrease in levels of *p*-TYR, and no change in dopamine levels after 1 day. This temporal dissociation of the metabolism of *m*-TYR from dopamine suggested to Juorio and Jones (1981) that these differences indicated evidence for the existence of a population of *m*-TYR-containing cell bodies lying dorsal to the SNc and which also project to the striatum. The additional *p*- and *m*-TYR in the striatum might arise from dopamine-containing neurons in the SNc, or in its immediate vicinity.

4.3. Is tryptamine synthesized exclusively within serotonin or dopamine neurons?

Lesioning studies provided the first preliminary evidence for the possible *independent* existence of TRP from serotonin neurons. Specifically, electrolytic lesions of the dorsal and median raphe reduced forebrain serotonin by 70%, but TRP levels were reduced by only 30% (Knott et al., 1974; Marsden and Curzon, 1974). Subsequently Juorio and colleagues (Juorio and Greenshaw, 1985, 1986; Juorio et al., 1987) investigated the extent of the localization of TRP with dopamine or serotonin neurons and their projections to the striatum. Those experiments led to the conclusion that concentrations of TRP in the hypothalamus, striatum and hippocampus were not dependent upon the integrity of the dorsal or medial raphe, but were dependent upon the integrity of the SNc. Specifically, these researchers found that whereas electrolytic lesions of the dorsal and medial raphe followed by analytical measurements of concentrations of TRP and serotonin in the striatum, hypothalamus and hippocampus demonstrated significantly reduced levels of serotonin, there was a failure of the lesion to change concentrations of TRP even up to 1–2 weeks following lesioning (Juorio and Greenshaw, 1985).

By contrast, measurements of TRP and dopamine in the striatum 7 days following a unilateral electrolytic lesion of the SN demonstrated significant reductions of TRP and dopamine. Unilateral injections of 6-OHDA or 5, 7-DHT into the SN combined with measurements of TRP in the striatum, nucleus accumbens, and olfactory tubercles demonstrated that levels of dopamine and TRP were unaffected following 5, 7-DHT lesioning, but they were reduced dramatically following 6-OHDA lesions of the SN and of the striato-nigral projection. Together these results suggest that the TRP present within the striatum does not arise from the dorsal or medial raphe, and that either TRP is found in dopamine-containing neurons and their terminals in the striatum, or that a 6-OHDA-sensitive, TRP-containing group of neurons exists, or transverses, the domain of the striato-nigral projection.

Building up the picture from these studies, Dabadie et al. (1990) demonstrated a unique population of TRP neurons in the SN and its vicinity, but these TRP neurons did not stain for dopamine. It may be that these TRP cells are the D-cells observed by Jaeger et al. (1984). D-cells are found in the SN and contain L-AADC but lack tyrosine hydroxylase and tryptophan hydroxylase (Jaeger et al., 1984; Ikemoto, 2002). Thus, D-cells are able to synthesize β-PEA from phenylalanine (Lovenberg et al., 1962), TRP from L-tryptophan (Warsh et al., 1979), TYR from L-tyrosine, but not dopamine from L-DOPA. In fact, D-cells may be the 6-OHDA-sensitive and 5,7-DHT-insensitive neurons from which TRP is derived in the striatum in the study of Juorio et al. (1987). Thus, these TRP neurons in the SN may comprise a component of the striato-nigral projection.

4.4. Is β-phenylethylamine synthesized exclusively within dopamine neurons?

Studies with *p*-TYR, *m*-TYR, or β-PEA suggest that these amines may either co-exist with dopamine in the SN and thus within the nigrostriatal projection, or with axons that containing these trace amines may pass through the SN and striatum (Juorio, 1988a; Nguyen et al., 1989). In a study employing a quite similar experimental design to that of Juorio et al. (1987) and Greenshaw et al. (1986) lesioned the SN either electrically or chemically with 6-OHDA and found that concentrations of both dopamine and β-PEA were reduced substantially in the striatum. Electrical or chemical lesioning of the dorsal and medial raphe had no effect on levels of β-PEA and dopamine in the striatum. This implies that β-PEA is present in dopamine-containing neurons and in the nigro-striatal projection, but not in serotonin-containing neurons of the raphe or in their projections to the striatum. The experiments by Greenshaw et al. (1986) did not discriminate between the sites of β-PEA biosynthesis, that is, whether β-PEA is synthesized in

dopamine-containing neurons in the SN, or in D-cells, or in both dopamine and D-cells.

Juorio et al. (1991) designed experiments to ascertain more directly whether β-PEA is present in dopamine-containing neurons or in D-cells of the SN and their projection to the striatum. These researchers demonstrated that the electrical stimulation of the SN produced an increase in dopamine turnover and a decrease in the biosynthesis of β-PEA and *p*-TYR in the striatum. This effect was dependent upon the activity of TH since the inhibition of TH by α-methyl-*p*-tyrosine reversed these changes. These results demonstrate three important points. Electrical stimulation of the SN leads to a decrease in β-PEA biosynthesis. The levels of β-PEA in the striatum are dependent upon tyrosine hydroxylase activity since α-methyl-*p*-tyrosine prevented these changes. Finally, β-PEA is synthesized in tyrosine hydroxylase-containing dopamine neurons, and not in D-cells, which are present in the SN and which may project to the striatum.

While these studies intimate that β-PEA may be *exclusively* present with dopamine in the SN, additional experimentation suggests that L-AADC is expressed in additional non-dopaminergic regions. Li et al. (1992b) used cultured rat glia derived from the striatum and C6 glioma cells to show that both the cell lines express L-AADC mRNA and protein. Despite the fact that L-AADC mRNA and protein were expressed at lower levels than those found in kidney, this indicated that nondopaminergic glial cells from the striatum can potentially synthesize TYR, TRP and β-PEA. In fact, the cellular distribution of L-AADC in non-catecholaminergic and non-indoleaminergic neurons may be more extensive than previously known. Eaton et al. (1993) applied the technique of *in situ* hybridization using an anti-sense probe directed towards the L-AADC mRNA and mapped the distribution of those cells that express the L-AADC mRNA in the rat brain. In addition to the expression of the L-AADC mRNA in the traditional catecholaminergic and indolaminergic nuclei, L-AADC mRNA was also expressed, albeit at a lower level, in non-catecholaminergic or non-indolaminergic cells in the medial prefrontal cortex, olfactory bulb, thalamic nuclei, cranial-nerve nuclei, deep cerebellar nuclei and pyramidal neurons of the hippocampus. These results suggest that the L-AADC enzyme has a more *expansive* role than just simply the synthesis of catechol and phenolic amines (for review, see Berry et al., 1996).

5. Trace amines as neurotransmitters or neuromodulators

As stated in Young (1988) and in accordance with semantic information theory, a system is an aggregation of material entities that endures through time and whose entities influence each other. Information is communicated, or transmitted, by a sender in one part of a physico-chemical system through a communication channel, or medium, to a receiver in another part of the system. The purpose of this transfer of information in biological systems is to assist homeostasis.

Consistent with these principles, Fuxe and Agnati (1991) have characterized chemical communication between neurons in the brain based on a number of criteria.[3] Additionally, distinct types, or modes, of chemical communication in the brain have been described based on the presence or absence of synaptic profiles and the distance between their sites of release and the receptors involved in producing a cellular response stereotypical to that effector. This refers to the so-called, *synaptic* or *non-synaptic* modes of release.[4]

Ultrastructural evidence suggests the varicosities of noradrenaline and serotonin axons in the cerebral cortex rarely are apposed to membrane specializations, or synaptic complexes that typically are identified with synaptic transmission (Descarries et al., 1975, 1977). These observations prompted the suggestion (Beaudet and Descarries, 1978) that noradrenaline and serotonin may be released non-synaptically to diffuse through the extracellular fluid as *humoral* agents to reach their distant target cells. Subsequent ultrastructural evidence has confirmed in large part the rare occurrence of differentiated junctional specializations associated with noradrenaline- and serotonin-containing axons in the cerebral cortex (Séguéla et al., 1989, 1990). For dopamine, the majority of available quantitative ultrastructural evidence suggests a high incidence of junctional specializations associated with dopamine-containing axon terminals in the cerebral cortex (Séguéla et al., 1988). Together with the known lack of neuroanatomical overlap between noradrenaline and serotonin receptors and the sites of the release of these substances (Beaudet and Descarries, 1978), these observations have implied that the vast majority of noradrenaline and serotonin in the cerebral cortex may be released non-synaptically, while the majority of dopamine in the cerebral cortex may be released synaptically.

Using the dopamine, noradrenaline and serotonin systems described above as representative examples, two general modes of chemical communication in the mammalian brain may exist based on the presence or absence of pre- or post-synaptic membrane specializations associated with synaptic connectivity of the chemical communication agent. These involve *wiring* and *volume* transmission. Wiring transmission is believed to operate via synaptic connectivity while volume transmission operates via the non-synaptic release and diffusion of chemical molecules via a leaking pathway, such as the extracellular fluid, to access their high-affinity receptors expressed on remote target cells (Agnati et al., 1986a,b; Fuxe and Agnati, 1991; Fuxe et al., 1989).[5]

[3] These comprise the distance between the sites of release of synaptic mediators and their respective receptors, the concentration of the signals in the communication medium, and the affinity of the receptors for the communication molecule.

[4] Synaptic release has been identified with molecules that typically induce fast [in milliseconds (ms)] post-synaptic potentials (PSPs) in their target cells. These are the *transmitters*. Non-synaptic release, by contrast, has been associated with molecules that induce relatively slower [in seconds (s)] modulatory, PSPs on their target cells; these are the *modulators*.

[5] There are a number of physico-chemical factors which will limit the extent of transmission (diffusion) of a volume communication molecule from its site(s) of release: the local synaptic and neuropilar geometry, the polarity of the communication molecule, the presence of and spatial distribution of sinks for the molecule, such as binding proteins and/or receptors, and finally the spatial distribution of and rates of enzymatic biosynthesis and catabolism by enzymes for that molecule.

5.1. Ionotropic and metabotropic chemical communication

In dopamine and noradrenaline systems, regardless of the mechanism of release, both synaptic or non-synaptic release of the catecholamine is associated with *slow* G-protein-mediated *neuromodulatory* responses in post-synaptic target neurons (Hepler and Gilman, 1992). Thus, defining the mode of release does not necessarily distinguish a neurotransmitter from a neuromodulator, and it thus seems as though the distinction may indeed be arbitrary. It may be that there are no neurotransmitters, but only modulators of modulators! Nevertheless, neuromodulators traditionally have been differentiated from neurotransmitters based on a number of additional characteristics. These most often are based on the nature of the post-synaptic response, which is complex, and/or the time course of action, which often is slow to materialize (Dismukes, 1979; Hartzel, 1981; Fuxe and Agnati, 1991; Greengard, 2001).

Following the classification scheme of McGeer et al. (1978), two general categories of chemical synaptic communication may be proposed to exist in the brain, based on the nature of the post-synaptic response: *ionotropic* and *metabotropic* transmission. *In vitro* neurophysiological studies suggest that, similar to many of the fast-ON and fast-OFF IPSPs or excitatory PSPs (EPSPs) that conventional amino acid neurotransmitters like glutamate and γ-aminobutyric acid (GABA) have on neurons (Iversen, 1984), many of the post-synaptic responses causing changes in neuronal firing seen with the trace amines also may be of a direct and rapid nature (see Section 10). These effects appear to be fast, on the order of approximately ms in duration, and therefore may be termed *ionotropic* responses because they are mediated by the opening or closing of post-synaptic, receptor-gated ion channels.[6]

Other types of post-synaptic responses of trace amines, like those influencing the effects of dopamine, noradrenaline or serotonin, are more complex, have longer latencies, are longer lasting (>1 s), and specifically amplify or *potentiate* the post-synaptic IPSPs or EPSPs induced by dopamine, noradrenaline or serotonin (see Section 9). These may be termed *metabotropic* because they stimulate or inhibit the biosynthesis of second-messengers, such as the $InsP_3/Ca^{2+}$ response, 1,2-diacylglycerol (DAG), and cyclic nucleotides, such as cyclic adenine monophosphate (cAMP), by the activation of G proteins which then either stimulate or inhibit various effector enzymes that synthesize those second messengers (Noda et al., 2004).

6. A classic model of trace amine function

In a seminal article, Boulton (1976b) suggested that the trace amines may have both *direct* and *indirect* modulatory effects on synaptic transmission mediated by the major catecholamine and indolamine neurotransmitters dopamine, noradrenaline or serotonin. The direct effects involve either the synaptic vesicular release of the trace amine, or following its biosynthesis, non-vesicular spontaneous *diffusion* from the presynaptic nerve terminal (Attwell et al., 1993). The indirect effects involve the uptake block and/or release of dopamine, noradrenaline or serotonin from their presynaptic vesicular storage sites. These modulatory effects of the trace amines may occur by preactivation, simultaneous activation, or post-activation of particular biochemical components of the dopamine, noradrenaline or serotonin-based signal transduction system (Brinton, 1990).

Boulton (1976b) suggested that the *direct* modulatory effects would alter the sensitivity of some biophysical parameter of the post-synaptic membrane of cells possessing GPCRs for dopamine, noradrenaline or serotonin, presumably by ionotropic or metabotropic means. Specifically, the tonic or phasic-vesicular or diffusional release of trace amines from their presynaptic sites of synthesis would induce miniature PSPs (mini-PSPs) – analogous to those described by Katz (1971) – in the post-synaptic membrane of cells bearing catecholamine or indolamine GPCRs. These sub-threshold mini-PSPs would function to *prime* a circumscribed area of the postsynaptic membrane by continually maintaining just that local area of the post-synaptic membrane affected in a state of *enhanced sensitivity*. This enhancement or *synergy* between the trace amines – particularly TRP – and the catecholamines or serotonin, may be necessary for enhancing the specificity and fidelity of information transfer within cells sensitive to their combined effects (Jones and Boulton, 1980b; see Section 10.3).

To be of value, this enhancement of dopamine, noradrenaline or serotonin synaptic efficacy would require several prerequisites. The actions of the trace amine(s) could be exerted *tonically* or *phasically*. To be of value, the phasic release of the trace amine would require temporal and/or spatial association with the post-synaptic, GPCR-mediated metabotropic electrochemical effects of dopamine, noradrenaline or serotonin on their target cells. The temporal association events would require biochemical interactions to take place *simultaneously* or otherwise *synchronously*, while the spatially coordinated events would have the signal transduction processes coupled in the same patch of post-synaptic membrane.

In contrast to the phasic effects, in Boulton's model the trace amines may also be *continuously* present at the catecholamine or indolamine synapse in the extracellular fluid, at levels which at least for β-PEA are comparable to that of dopamine (Henry et al., 1988). This *tonic* presence comprises a system that entails the continuous simultaneous activity of the trace amines for the modulation of the dopamine, noradrenaline or serotonin synapse. This may be important for enhancing the excitability of neurons, as has been observed for the tonic activation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate (Sah et al., 1989).

One must be mindful also that the trace amines may, by phasic preactivation, initiate or *sensitize* particular biochemical processes that outlast the presence of the modulator in the synaptic cleft. In either case, this continual presence affords the trace amines the potential for the maintenance of the initial conditions necessary for either the coordination of, or

[6] It is believed these fast PSPs permit the cell to perform a large number of computations in a short period of time (McCormick, 1990); while slow PSPs are believed to be important in the long-term control of membrane excitability, and not in the high-frequency transfer of information (Hartzel, 1981).

maintenance of, particular modes of dopamine, noradrenaline or serotonin post-synaptic signal transduction (Jones, 1983).

Since the post-synaptic effects of the catecholamines and serotonin are themselves considered to be *modulatory* for other types of synaptic transmitter, it may be that the trace amines are indeed modulators, or *adjunctive* modulators of neuromodulators, and perturbations in their adjunctive modulatory roles, whether through stress or psychiatric disease, may have subtle effects on catecholamine- or serotonin-dependent cognitive or motor functions.

7. Multi-focal or *protean* neuromodulatory activities of the trace amines

In accordance with the views of Boulton (1976b), the response(s) to the trace amines could be interpreted in the context of involving multiple or *protean* pre- or post-synaptic, metabotropic-mediated events incorporating intracellular signal transduction mechanisms similar to those utilized by other, better-understood effects of more conventional neuromodulatory agents (Kaczmarek and Levitan, 1987):

- As characterized below these neuromodulatory, or metabotropic responses induced by the trace amines, may depend ultimately on the *lipophilic* properties of the trace amines.
- They also may occur through the direct trace-amine, GPCR-mediated activation of intracellular mechanisms of signal transduction, which associate either *additively* or *synergistically* with a biochemical step of the dopamine, noradrenaline or serotonin-based mechanisms of signal transduction.
- They may occur indirectly through the mechanism of *allosteric* activation of proteins of the dopamine, noradrenaline or serotonin-based post-synaptic mechanisms of signal transduction.

7.1. Lipophilicity of the trace amines

The non-polar nature, or lipophilicity, of the trace amines, in particular TRP and β-PEA, may play an indirect role in the types of modulation mentioned above. Oldendorf (1971) has established a relative lipophilicity series for the efficacy of β-PEA, TRP, TYR, dopamine, and noradrenaline for crossing the blood–brain barrier. The degree of this lipophilicity unit is highly correlated with the lipid permeability of the relevant amine.[7] Thus, β-PEA and TRP, due to their greater lipophilicity values relative to dopamine and noradrenaline, TYR and OA, may readily diffuse from their presynaptic sites of biosynthesis, and partition preferentially into other sub-cellular compartments of the cell or into the plasma membrane of neighboring post-synaptic neurons.

[7] β-PEA > TRP > noradrenaline > dopamine > TYR. β-PEA is seen as the most lipophilic of the trace amines and TYR the least. While OA was not studied, the fact that it possesses an additional β-hydroxyl group indicates that it is more water soluble than TYR. Similarly, the possession of twin methyl groups by DMT suggests it is more lipophilic than β-PEA. So a revised series may be conceived as: DMT > β-PEA > TRP > noradrenaline > dopamine > OA > TYR.

Research into the physicochemical requirements for, and mechanisms of action of protein kinase C (PKC), has demonstrated a complex process for activation that depends upon concentrations of intracellular Ca^{2+}, the phospholipid phosphatidylserine, and the biosynthesis of the membrane-delimited, non-polar DAG molecule (Zidovetzki and Lester, 1992). The activation of PKC is dependent on, and sensitive to, local membrane instabilities such as the physicochemical fluctuations of the phospholipid bilayer induced following biosynthesis of DAG. Physicochemical fluctuations in the structure of the plasma membrane, such as those induced by the biosynthesis of DAG, have been demonstrated as serving important allosteric modulating factors in determining protein–lipid interactions and the state of activation of PKC-dependent signal transduction systems (Zidovetzki and Lester, 1992).

Non-polar trace amines such as DMT, TRP and β-PEA may induce similar changes in membrane phase in post-synaptic membranes similar to the changes induced by DAG. By spatial or temporal association, or second messenger *cross-talk*, these phase changes may contribute either directly or indirectly to the post-synaptic, metabotropic modulatory responses evoked by β-PEA, TRP and TYR.

7.2. Vesicular or non-vesicular release of the trace amines

While the experiments reviewed below may imply the existence of a vesicular release mechanism for β-PEA, TRP and TYR, since in fact these trace amines exhibit a particulate, i.e., synaptosomal, localization (Boulton and Baker, 1975), the *majority* of the empirical evidence available does not support this model for those amines. Reserpine is a drug that depletes catecholamine storage (Carlsson et al., 1963) and it is well known that dopamine, noradrenaline and serotonin are localized to a reserpine-sensitive pool of synaptic vesicles (Shore et al., 1955; Bertler, 1961; Stjärne and Lishajko, 1966). It is likely that β-PEA, TRP and TYR are absent from such synaptic vesicles since reserpine treatment by itself (Boulton et al., 1977) or in the presence of MAO-inhibitors (Juorio, 1988b) results in either no change in, or an increase in, β-PEA concentrations, respectively.

This lack of a specific vesicular storage mechanism for β-PEA, TRP and TYR explains their *greater turnover rates* as compared with dopamine or noradrenaline, which are stored in vesicles (Durden and Phillips, 1980). Similarly, studies dealing with synaptic release have demonstrated that β-PEA and TRP are poorly taken up, stored, and released from striatal brain slices following stimulation by neuronal depolarization via electrical or K^+-induced stimulation (Dyck, 1984, 1989; Dyck et al., 1982). These manipulations all typically lead to the release of vesicularly localized synaptic transmitter molecules.

By contrast, it is known that the following types of release can occur: Ca^{2+}-dependent, electrically evoked, or K^+-evoked synaptosomal release of [^{3}H]-β-PEA from striatal slices (Niddam et al., 1985), of [^{3}H]-TRP from slices of spinal cord (Snodgrass and Iverson, 1974), and electrically-sensitive, K^+-sensitive, or veratridine-sensitive release of *m*-TYR and *p*-TYR

in the presence and the absence of MAO inhibitors from slices of the striatum (Dyck, 1984, 1988, 1989; Dyck et al., 1982). The investigations by Dyck (1989) also suggest the release of [^{3}H]-TRP could occur according to the criteria of a false transmitter (Kopin, 1968), since the measurements of [^{3}H]-TRP by Snodgrass and Iverson (1974) were undertaken in the presence of the MAO inhibitor pargyline.

OA exhibits a subcellular (i.e., synaptosomal) distribution similar to noradrenaline (Molinoff and Axelrod, 1972). OA also is present in noradrenaline terminals in the CNS, since the administration of 6-OHDA severely reduced the ability of rat brain slices to release both [^{3}H]-noradrenaline and [^{3}H]-OA following electrical or K^+-induced depolarization (Baldessarini and Vogt, 1971, 1972). This same study also demonstrated that *p*-TYR is poorly released by the same stimuli which released noradrenaline and OA.

Thus, the empirical evidence for a vesicular release model of *p*-TYR appears contradictory. Still, the majority of evidence suggests that either TYR and OA may function as conventional transmitters or co-transmitters in catecholamine terminals by virtue of the presence of cellular mechanisms for their cytoplasmic transport, vesicular uptake, storage, and release from presynaptic nerve terminals. On the other hand, the cellular mechanisms for cytoplasmic transport, vesicular uptake, storage and release of β-PEA and TRP do not appear to exist. Therefore β-PEA and TRP are unlikely to function conventionally as synaptic transmitters or co-transmitters in mammalian brain according to these criteria.

7.3. Trace amines as indirect releasing agents

In general, the responses of trace amines may be divided into two major groups: those that affect the post-synaptic neuron directly by mimicking the physiological effects of the catecholamines or serotonin without interacting with the pre-synaptic terminal, and those that affect the function of the catecholamine- and/or indoleamine-releasing mechanism. This latter process is referred to as the *indirect* mechanism of action while the former is the *direct* mechanism.

Indirect stimulation of the pre-synaptic terminal by the trace amines, or by amphetamine, MDMA or cocaine through modulating the reuptake of neurotransmitter, or stimulating release from storage vesicles, could result in a net increase of neurotransmitter release and subsequent activation of the post-synaptic catecholamine, indoleamine or trace amine receptors (Borowsky et al., 2001; Sotnikova et al., 2004; Miller et al., 2005). The trace amines can potentially stimulate the pre-synaptic neuron through several mechanisms:

- Inhibition of transmitter reuptake by binding to a specific site of the membrane protein transporter, such as the dopamine transporter (DAT).
- Activation of neurotransmitter synthesis by blocking pre-synaptic dopamine D_2 auto-receptors.
- Displacement of vesicular and cytoplasmic catecholamines, which then passively diffuse into the synaptic cleft through a Ca^{2+}-independent process.

It is also possible that at certain synapses, the trace amines could function as *mixed-action agonists*, having the property of directly stimulating post-synaptic receptors while simultaneously increasing the activity of, and neurotransmitter release from, the pre-synaptic terminal. In such cases, the trace amine function would require careful analysis for the accurate description of the relative proportion of each of its separate mechanisms of action.

7.3.1. Evidence for tyramine and octopamine

TYR is sympathomimetically active and is used as an experimental tool to study the mechanisms of noradrenaline release in sympathetic neurons. TYR, β-PEA and other indirectly acting sympathomimetics have chemical structures similar to ephedrine and amphetamines, and, as such, are taken into the pre-synaptic terminal by the same amine membrane transporter. They then affect the release of noradrenaline by displacing it from the cytoplasmic pools of vesicles and causing it to diffuse into the synaptic cleft (Raiteri et al., 1977; Knoll et al., 1996). By binding to the catecholamine membrane transporter the sympathomimetics also interfere with the amine reuptake mechanism and prolong the post-synaptic effects of the transmitter molecules already in the cleft (Raiteri et al., 1977); some sympathomimetics have a mixed action.

Specifically, the central stimulatory effects of ephedrine are caused by stimulation of post-synaptic β-nor adrenaline receptors and an increase in noradrenaline release, activating α- and β-noradrenaline receptors. TYR may not normally function in the brain as a catecholamine releaser because its concentration in blood and tissues is kept low by rapid deamination by MAO-A/B (Philips, 1984).

However, when patients treated for depression with MAO inhibitors consume certain foods rich in TYR, a severe hypertensive crisis can be provoked. The hypertensive reaction is caused by TYR-induced noradrenaline release. In patients chronically treated with MAO inhibitors, TYR levels are steadily increased. Once in the noradrenergic terminal, TYR is transported into synaptic vesicles and rapidly converted by dopamine-β-hydroxylase into OA. OA partially displaces noradrenaline and may serve as a false neurotransmitter in the periphery. Because of the partial substitution of noradrenaline with OA, and the inability of OA to potently stimulate post-synaptic α- and β-noradrenaline receptors, patients receiving chronic doses of MAO inhibitors suffer from hypotension.

7.3.2. Evidence for β-phenylethylamine

In the periphery, TYR and β-PEA act as indirect sympatomimetics to increase the activity of the sympathetic neuron. In the CNS, the trace amines and chemically similar drugs may function as psychostimulants and antidepressants by enhancing catecholaminergic and indoleaminergic neurotransmission. This enhancement seems to be based on *protean* mechanisms with the *net* result being the increase of neurotransmitter release and *potentiation* of post-synaptic catecholamine or indoleamine GPCR signaling pathways, or possible trace amine-GPCR-mediated effects (Bunzow et al., 2001). The strongest evidence available that the trace amines

can function as indirectly acting agonists comes from studies using β-PEA (Nakamura et al., 1998), TYR (Knoll et al., 1996), and TRP (Jones and Boulton, 1980b).

β-PEA administered intraventricularly rapidly increases the extracellular dopamine concentrations in the rat striatum through competitive inhibition of dopamine reuptake by the DAT within nigrostriatal dopaminergic terminals (Sato et al., 1996). β-PEA-induced dopamine release from striatal slices can also be modulated by dopaminergic autoreceptor agonists and antagonists (Yamada et al., 1998). In the presence of the presynaptic dopamine autoreceptor agonist quinpirole, a molecule that reduces dopamine release from the nigrostriatal terminals, perfusion with β-PEA results in an attenuation (by 30%) of dopamine release. Striatal dopamine release induced by the dopamine D_2 selective antagonist sulpiride, also is attenuated by β-PEA (Yamada et al., 1998). Trace amines can also increase the efflux of newly synthesized dopamine. Geracitano et al. (2004) deduced that the inhibition of nigral dopamine neurons produced by perfused TYR or β-PEA was due to enhanced efflux of dendritic dopamine and the resulting activation of synthesis, modulating dopamine D_2 autoreceptors.

Although the precise mechanisms of autoreceptor-regulated transmitter release are still not clear, these findings suggest that at least two mechanisms exist for *indirectly* acting catecholamine modulation by β-PEA in the striatum. First, β-PEA may act by blocking the reuptake of dopamine by the DAT, and secondly it may modulate inhibitory dopamine D_2 autoreceptors. These suggestions receive support from the observation that β-PEA is a dopamine receptor agonist in the striatum, and that it can act by enhancing the behavioral and electrophysiological effects of dopamine on post-synaptic striatal neurons (Rodriguez and Barroso, 1995; Barroso and Rodriguez, 1996).

The *indirect* effects of β-PEA are not restricted to dopamine-containing neurons. β-PEA and TYR enhance the release of both noradrenaline and dopamine from catecholamine-containing terminals in mammalian brain (Knoll et al., 1996). In the nucleus accumbens of the rat, *in vivo* microdialysis of β-PEA increases the extracellular concentrations of both dopamine and serotonin (Nakamura et al., 1998). Similar results have been obtained from the glomerular layer of the rat olfactory bulb, where higher doses of β-PEA (10.0 mg/kg) increase the concentrations of dopamine and noradrenaline as measured by an electrochemical detection method (Mesfioui et al., 1998).

Accumulating evidence suggests that under certain conditions the trace amines and other catecholamine enhancers, such as (−)-deprenyl, can inhibit the catabolic actions of MAO-A/B. Although the trace amines are substrates for MAO-A/B, certain trace amine analogs can function as MAO inhibitors. For example, introducing a chloride or fluoride atom into the phenyl ring of β-PEA or TRP changes them from MAO substrates to MAO inhibitors (Kinemuchi et al., 1988). Similarly, the introduction of a methyl group into the β-position of β-PEA results in a derivative that is a selective MAO-B inhibitor. α-methylation of TYR results in TYR analogs that are strong MAO inhibitors. Systemic administration of those compounds in the rat induces hallucinogen-like abnormal beaviors (Arai et al., 1995).

In summary, the trace amines can have strong reinforcing or enhancing effects on the major catecholamine and indoleamine systems of the brain by an action on the presynaptic terminals. Thus, the trace amines can function as indirectly acting agonists there through an enhancement of transmitter release, by blocking reuptake, via stimulating transmitter synthesis, or because of a suppression of MAO catabolic activity.

8. Trace amine-binding sites in mammalian brain

If in fact the trace amines, such as TYR and OA, do function as synaptic transmitters or co-transmitters within catecholaminergic systems and thereby act as chemical agents of the *wiring* mode of neurotransmission, then according to the criteria of Laduron (1988) there should be reversibly saturable, high affinity and regionally specific binding sites. These binding sites would represent either/or pre- or post-synaptically localized receptors that would be readily demonstrable and would present *contiguously* with the presynaptic sites of release of the trace amines in the mammalian brain. One would also expect to find these sites particularly concentrated in the striatum, cerebral cortex, and hypothalamus, where these trace amines are present at their highest tissue levels. While there remains a scarcity of studies focusing on the immunocytochemical localization of the trace amines in mammalian brain, there is a substantial body of research that has focused on the characterization of trace amine binding sites, their distributions and pharmacological specificities in mammalian brain.

In general, two neuroanatomical patterns of distribution of trace amines and their cognate receptors are possible: a trace amine-receptor overlap, or a *matching*. This latter situation would be when the distribution of a particular trace amine, as visualized through immunocytochemistry or autoradiography and its binding site(s), are spatially coexistent. The second possibility is a so-called trace amine-receptor *mismatch*, in which there is a spatial disparity between the sites of release of the trace amine and its receptor.[8] If such a situation were to pertain for trace amines, this easily might imply that the trace amines could function extrasynaptically as *humoral* agents for interaction with relatively more distant (>1.0 mm) receptors via *volume transmission* (Fuxe and Agnati, 1991).

8.1. Evidence for tyramine

Borowsky et al. (2001) identified a trace amine receptor, TAAR1 that is most sensitive to TYR (EC_{50} = 214.0 nM) and less sensitive to OA and dopamine, noradrenaline and serotonin, in generating cAMP biosynthesis within COS-7 cells. [^{3}H]-TYR displayed high affinity, saturable binding to TAAR1 (K_d = 20.0 nM) from these cells. Bunzow et al. (2001) also separately described this receptor. Strikingly, TAAR1

[8] For the majority of chemical mediators of synaptic transmission, a mismatch of receptors with transmitters is more often the *rule* rather than the exception in mammalian brain (Herkenham and McLean, 1986; Herkenham, 1987; Herkenham, 1991).

generates cAMP comparable to or slightly less than that generated by TYR, when exposed to LSD and DMT, or amphetamine and MDMA,[9] indicating a possible *direct* receptor-mediated mode of action for these drugs in addition to their well-described effects on serotonergic 5-$HT_{2A/C}$ receptors, and catecholamine uptake and vesicular storage, respectively (Bunzow et al., 2001; for reviews, see Seiden et al., 1993; Marek and Aghajanian, 1998; Jacob and Presti, 2005). Thus, TAAR1 may well contribute a *novel* mode of action to the hallucinogenic drugs, and to the stimulant and reinforcing properties of the psychostimulants. In fact, GPCRs responsive to both trace amines and these drugs suggest a novel possibility that some of the physiological effects of all these molecules may involve a common molecular signaling pathway in neurons (Ciprian-Ollivier and Cetkovich-Bakmas, 1997).

Of the five human TAARs, only TAAR1 mRNA expression has been mapped in mammalian brain. Using *in situ* hybridization histochemistry the TAAR1 mRNA has been localized within the mouse brain by both groups. TAAR1 mRNA is expressed densely within the olfactory bulb, cerebral cortex and ventral horn of the spinal cord; moderately expressed within the thalamus, hypothalamus, hippocampus, SN-VTA, locus coeruleus and dorsal raphe, with lower levels of TAAR1 expression detected from the cerebellum, dorsal root ganglion, basal ganglia and amygdala (Borowsky et al., 2001; Bunzow et al., 2001). Unfortunately, only the TAAR1 and TAAR4 are directly activated by trace amines, while other TAARs are not (Borowsky et al., 2001). These receptor proteins are members of a *novel* and highly related family of GPCR molecules expressed within human, rat, mouse and chimpanzee tissues (Lindemann et al., 2005; Lewin, 2006).

Another high affinity and specific binding site for TYR has been identified and characterized in the mammalian brain (Vaccari, 1988). It is not known whether this binding site is a trace amine receptor, in particular TAAR1. This binding site bound *p*-TYR with nanomolar affinity (K_d = 10.8–14.4 nM) and was highly concentrated in dopamine- and noradrenaline-rich regions such as the striatum and hypothalamus (Vaccari, 1986). Pharmacological characterization of this *p*-TYR binding site has demonstrated that it is specific for *p*-TYR:*p*-OA was described as being only a weak displacer of *p*-TYR binding but *p*-TYR was displaced potently by all other compounds recognized as uptake inhibitors of dopamine: amphetamine, nomifensine, and methamphetamine. In addition reserpine, an irreversible inhibitor of the dopamine and noradrenaline vesicular transporters, was the most potent competitor of *p*-TYR binding (Vaccari, 1986). Moreover, mechanical lesions of the nigro-striatal pathway resulted in a 79% reduction of *p*-TYR binding in the striatum (Vaccari, 1986). The *p*-TYR binding site thus appears to be associated with presynaptic dopamine-containing nerve terminals. Based on this evidence this *p*-TYR binding site is proposed to be a site on the vesicular membrane transporter for dopamine (Vaccari, 1993).

8.2. Evidence for octopamine

A neurotransmitter role for OA is well described, where OA is considered the invertebrate counterpart to noradrenaline (Roeder et al., 2003). In invertebrates, OA is necessary for a wide variety of physiological processes and behaviors (Kravitz, 1988; Hammer and Menzel, 1998). The pharmacological characterization of OA binding sites from the locust neuromuscular junction using select agonists and antagonists has yielded a description of at least two distinct subclasses of OA receptor, OA_1 and OA_2 (Evans, 1981). The OA_2 subclass has been differentiated further based on the selectivity of the evoked responses for different agonists, and these receptors have been described as OA_{2a} and OA_{2b} subtypes (Evans, 1981). These subclasses of receptor are coupled to different second messenger systems, that is the OA_1 receptor appears to be coupled to an increase in intracellular levels of Ca^{2+} (Evans, 1984a) and both subtypes of the OA_2 receptors appear to be coupled to increases in the synthesis of cAMP (Evans, 1984b,c). A pharmacologically distinct class of OA receptor similar to the OA_2 subclass of OA receptor has been identified in the CNS of the locust (Guillen et al., 1989). This OA_3 receptor also is coupled to increases in cAMP and is found highly concentrated in the optic lobes of the locust (Roeder and Nathanson, 1993). Additional OA GPCRs have recently been discovered. These receptors – DmOct β_{1R}, DmOct β_{2R} and DmOct β_{3R} – are expressed within *Drosophila* neurons, have homology to mammalian β-noradrenaline receptors and are able to drive the expression of cAMP when expressed within CHO cells (Maqueria et al., 2005).

A subtype of noradrenaline receptor, the β_3 receptor, has been demonstrated to bind to OA with an affinity comparable to that of noradrenaline or other noradrenaline agonists (Galitzky et al., 1993). However, this receptor is present only in peripheral tissues and is not known to be expressed in mammalian brain (Granneman et al., 1991). Thus evolutionary descendents of the OA_1, OA_2 or OA_3 receptors or their subtypes or other atypical α- or β-noradrenaline receptor subtypes may be present in the spinal cord and/or the cerebral cortex to mediate the post-synaptic effects of OA.

A mammalian CNS receptor strongly activated by OA remains elusive. The TAAR1 discovered by Borowsky et al. (2001) is weakly activated by OA and generates cAMP when expressed from COS-7 cells (EC_{50} = 4029.0 nM) (Borowsky et al., 2001). While the TAAR1 mRNA is expressed in brain regions which have been shown to be responsive to OA (see Hicks and McLennan, 1978a,b), it is unclear as to the contribution of the TAAR1 to the physiological effects characterized by those researchers.

[9] Bunzow et al. (2001) determined the rank order of EC_{50} values for the trace amines, isomers and related molecules in generating cAMP from the TA_1 receptor expressed within HEK293 cells as follows from lowest to highest: *p*-tyramine < β-PEA < tryptamine < *S*(+)-amphetamine < *R*(−)-amphetamine = DMT < (±)-synephrine < (±)-octopamine < (±)-MDMA < *m*-tyramine ≤ dopamine < serotonin ≪ noradrenaline = adrenaline (for a comparative summary of the EC_{50} values with different TAARs generated by Bunzow et al., 2001; Borowsky et al., 2001; Lindemann et al., 2005; see Lewin, 2006).

8.3. Evidence for tryptamine and dimethyltryptamine

TRP also displayed a capacity – albeit weak – to stimulate cAMP biosynthesis from the TAAR4 when expressed from COS-7 cells (Borowsky et al., 2001). Nonetheless, the existence of saturable and reversible (K_d = 1.5–5.0 nM) [^{3}H]-TRP binding site(s) in the rat brain has been known for years (Kellar and Casio, 1982; Wood et al., 1984; Altar et al., 1986; Perry, 1986). The distribution of TRP binding sites in the rat brain is heterogeneous, with the highest concentrations found in the striatum, cortex, and hippocampus (Nguyen et al., 1989). In the human brain, [^{3}H]-TRP also binds with high affinity in a saturable and reversible manner (Mousseau and Butterworth, 1994). These binding sites also are unevenly distributed with the highest densities found in the hippocampus and thalamus and lower densities expressed within the medulla and cerebellum. TRP binding sites are distributed heterogeneously within the neocortical layers (Mousseau and Butterworth, 1995). The density of these binding sites parallels their regional concentration differences (Philips et al., 1974; Warsh et al., 1979; Larson and Dalo, 1986).

In rats treated chronically with the MAO-A inhibitor clorgyline, the number of TRP binding sites decreases significantly but there is no change in the affinity of [^{3}H]-TRP in the cerebral cortex (Casio and Kellar, 1986; Graham and Langer, 1987). These findings suggest that TRP may interact with a functional post-synaptic receptor since a commonly observed response to reducing the normal ligand–receptor interaction through chemical lesioning is the increase in receptor sensitivity and excitability of the post-synaptic neuron. This phenomenon is observed after chronic treatment with 6-OHDA. In rats treated with 6-OHDA, alterations in [^{3}H]-TRP binding properties in the striatum have been found (Nguyen et al., 1989). Six weeks after unilateral 6-OHDA lesions in the SN, striatal [^{3}H]-TRP binding is increased whereas concentrations of TRP are decreased. At the same time, ipsilateral to the lesion caudate neurons show a dramatic (10–15-fold) increase in the inhibition of neuronal firing rate in response to intravenous administration of TRP. This suggests there is an alteration in receptor sensitivity that most likely is due to the loss of TRP (Nguyen et al., 1989).

The results from these studies suggest that TRP is released from 6-OHDA-sensitive, dopamine-containing terminals in the striatum and that [^{3}H]-TRP binding sites are not located on terminals containing dopamine because it is known that TRP affects the activity of the post-synaptic neuron after the terminals are lesioned (Nguyen et al., 1989).

Behavioral and pharmacological studies in rats suggest DMT behaves as an agonist at serotonin 5-HT$_{2C}$ and 5-HT$_{2A}$ receptors (Smith et al., 1998). A non-serotonin receptor specific for DMT expressed within rat brain has been speculated upon (Barker et al., 1981). This DMT receptor may be the receptor which has been characterized within rat brain synaptosomal membranes as having a sub-nanomolar affinity for DMT and LSD, and when stimulated by these molecules is capable of driving the biosynthesis of cAMP (Bearden et al., 1977). DMT also exhibits a strong capacity – comparable to that of TYR – of eliciting cAMP biosynthesis from TAAR1 when expressed within HEK293 cells (Bunzow et al., 2001).

8.4. Evidence for β-phenylethylamine

It has been suggested that β-PEA may activate TAAR1 expressed within neurons or their projections to the SN-VTA or the basal ganglia (Borowsky et al., 2001; Miller et al., 2005; Berretta et al., 2005; Ishida et al., 2005a; Ishida et al., 2005b). Like TYR, β-PEA potently activates cAMP biosynthesis (EC_{50} = 240.0 nM) coupled to TAAR1 when expressed from either COS-7 or HEK293 cells (Borowsky et al., 2001; Bunzow et al., 2001). β-PEA also generates cAMP from activation of TAAR4 from heterologous COS-7 cells, but with a much lower potency (EC_{50} = 1.9 μM) (Borowsky et al., 2001).

Taguchi et al. (2005a) as well as Kato et al. (2001) suggest activation of the cortical TAAR1 may underlie the systemic administered β-PEA-stimulated release of striatal acetylcholine, through activation of the corticostriatal α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) glutamatergic pathway. Paterson et al. (1990) has suggested that β-PEA may underlie the *potentiation* of dopamine synaptic efficacy by the direct allosteric activation of a unique target protein coupled to post-synaptic mechanisms of catecholamine signal transduction, such as the β-PEA receptor described by Hauger et al. (1982).

In the work of Hauger et al. (1982) β-PEA binding was not displaced by many compounds, including a variety of psychotherapeutic agents that bind to cholinergic, dopaminergic or noradrenergic receptors. β-PEA binding is localized preferentially in the hypothalamus and striatum where there is a relatively great amount of β-PEA (Durden and Davis, 1993). Thus there is the potential for β-PEA to act at other sites, such as receptors, independently of the effects of β-PEA on uptake and release at the noradrenaline and dopamine vesicular carrier (Raiteri et al., 1977).

One major caveat is that since β-PEA binding to MAO-B is very strong, the receptor-binding assay of Hauger et al. (1982) should have been performed in the presence of an MAO-B inhibitor but this was not done. Thus, β-PEA may have been binding to MAO-B, the enzyme responsible for its catabolism. When the binding conditions of Hauger et al. (1982) were repeated in the presence of the MAO-B inhibitors pargyline and (−)-deprenyl, the β-PEA binding either was significantly reduced using lower concentration of the inhibitors, or eliminated using higher concentrations of the inhibitors, in a concentration-dependent manner (Li et al., 1992a).

9. Trace amines as *slow* metabotropic neuromodulatory agents

Another protean theme that has emerged from an additional body of physiological studies is the question of the *modulatory* metabotropic effect that the trace amines appear to have on synaptic transmission mediated by other transmitters in the rat brain. This neuromodulatory effect very likely occurs *independently* of the above-mentioned, indirect carrier-mediated effects of β-PEA, *p*-TYR and *p*-OA on the release of dopamine or noradrenaline from presynaptic terminals, since commonly it is elicited following iontophoretic ejection of the trace amines at *low* doses (0–20.0 nA), levels of ejection which show no

measurable effect of the trace amine itself on the baseline rate of firing of the neuron studied. These presumptive metabotropic effects may involve a number of different mechanisms:

- As modulators of the physico-chemical state of the neuronal phospholipid bilayer, since to some degree the trace amines are all *lipophilic*.
- By interacting directly with post-synaptically localized metabotropic GPCRs.
- By the *allosteric* activation of a signaling protein of another neurotransmitter-based signal transduction pathway.

Collectively, the state of activation of a potentially diverse array of unknown trace amine-sensitive signaling proteins in the cells that possess GPCRs for dopamine and noradrenaline or other neurotransmitters may be susceptible to modulation by those trace amines. For example, in dopaminergic neurons of the SN, TYR and β-PEA have a depressant effect on the $GABA_B$-mediated *slow* inhibitory $G\alpha_{i/o}$ protein-mediated inwardly-rectifying potassium (GIRK) channels within these neurons, by activating G proteins that interfere with the coupling between the $GABA_B$ receptors and GIRK channels (Federici et al., 2005; Berretta et al., 2005).

It bears mentioning that all or any combination of these *protean* mechanisms, ionotropic, metabotropic, uptake/releasing effects, and/or changes in membrane phase, may be in operation to a lesser or greater extent at any dopamine, noradrenaline or serotonin synapse, and thus may contribute to the post-synaptic, electro-chemical responses to the trace amines.

9.1. A hallmark synergy: vasopressin and noradrenaline

In contrast to the direct, fast ionotropic responses (*vide infra*) and the indirect presynaptic releasing effects, the metabotropic post-synaptic effects induced by TYR, β-PEA and TRP are much *slower*. This suggests mediation through a second messenger-mediated response that is dose-dependent, one that would be elicited only following low-level (0–20.0 nA) iontophoretic administration of the respective trace amine which is specific for and dependent upon the simultaneous presence of dopamine, noradrenaline or serotonin (Jones, 1981a; Jones, 1982a; Jones and Boulton, 1980a,b; Paterson, 1988, 1993; Paterson et al., 1990). In particular cases this response persists following lesioning of the dopamine, noradrenaline or serotonin pathway or nucleus (Jones, 1982b, 1984; Paterson, 1988). These additional post-synaptic effects frequently have been shown to exert a *potentiating*, enhancing or *synergistic* action (Jones and Boulton, 1980b; Jones, 1981a, 1982d; Paterson et al., 1990), indicating that the combined post-synaptic effects are greater than the sum of the additive effects with dopamine and/or noradrenaline on the rates of firing of the target cells.

A hallmark neuromodulatory interaction is that between noradrenaline and the neuropeptide, arginine vasopressin (AVP) in the hippocampus. The administration of 250 nM AVP has no measurable effect on basal levels of cAMP from hippocampal slices, whereas the administration of 10.0 μM noradrenaline results in a three-fold increase in cAMP over basal levels from these slices. When AVP (50.0–250.0 nM) and 10.0 μM noradrenaline are co-administered, cAMP levels are *potentiated* significantly (five-fold) over basal levels of cAMP. Thus the co-temporaneous presence of AVP is able to potentiate the cAMP response of the cell to noradrenaline (Brinton and McEwen, 1989). If Gardner and Jensen (1981) are correct, this synergistic effect of AVP upon noradrenaline-induced intracellular second-messenger responses will involve the *nonlinear* association between different second messenger systems.

The trace amine-dopamine, -noradrenaline or -serotonin association may also involve ''cross-talk'' between two different second messenger systems (Paterson and Boulton, 1988). For the noradrenaline-AVP interaction, this certainly appears to be the case. The AVP-induced modulation of noradrenaline-coupled cAMP synthesis is dependent upon a dose-dependent increase in intracellular levels of Ca^{2+} by AVP (Brinton and McEwen, 1989).

9.2. Models of β-phenylethylamine and tryptamine function

The significant lipophilicity of β-PEA (especially) but also TRP and TYR suggests that while they may all block and release vesicularly stored dopamine, noradrenaline or serotonin when their concentrations are elevated – a situation which may occur during stress psychiatric disease states or under the influence of MAO-B-inhibiting psychotherapeutic drugs (e.g. (−)-deprenyl) (Knoll et al., 1996) – they are unlikely to be stored and released in a similar mode to how the conventional catecholamine and indolamine synaptic transmitters are stored and released. Dyck (1984) suggested that the poor transport, retention and release of β-PEA and TRP prior to and following depolarizing stimuli implies that these amines are predominantly released *rapidly* from the respective tissue preparations by *diffusion*, rather than by a depolarizing stimulus. The diffusional nature of this release of β-PEA and TRP could be explained on the basis of the lipophilic nature of these trace amines, while the relatively more polar *m*-TYR, *p*-TYR and OA may be stored in synaptic vesicles and released following a depolarizing stimulus. In fact, OA and TYR may escape from the peri-synaptic space and modulate more distal (>1.0 mm) elements of the neuronal circuitry via diffusion through the extracellular fluid through processes of volume transmission (Fuxe and Agnati, 1991).

Thus TYR and OA, like the major catecholamines, may be conceived of as *humoral* agents of interneuronal communication by exerting long-range *tonic* physiological effects on more distal neuronal synaptic elements. On the other hand, the high rates of turnover and lipophilicity of β-PEA and TRP suggest that following their biosynthesis and diffusion, these trace amines will more than likely become trapped in more proximal subcellular compartments or neighboring neural membranes.

9.2.1. β-Phenylethylamine

It is possible also that the tonic or phasic diffusional release of the trace amines following their biosyntheses may contribute to the post-synaptic, metabotropic responses after the fashion as described originally by Boulton (1976b) (see Section 6). In the

latter case, Paterson et al. (1990) have suggested the following model that is compatible with that offered by Boulton (1976b) to explain the direct post-synaptic modulatory effects of β-PEA on catecholamine-sensitive, post-synaptic target cells.

Following the biosynthesis of β-PEA from the decarboxylation of L-phenylalanine by L-AADC in dopamine- or noradrenaline-containing nerve terminals (Lovenberg et al., 1962), the lipophilic nature of β-PEA will afford the trace amine with the potential to diffuse from the presynaptic nerve terminal. Since the site of synthesis of β-PEA is in the presynaptic nerve terminal containing dopamine, and its catabolic enzyme MAO-B is located in astrocytes (Levitt et al., 1982), β-PEA exists in a graded, steady-state concentration in the synaptic cleft, its prevailing level dependent on its rate of biosynthesis in dopamine-containing neurons and catabolism in astrocytes. According to Paterson et al. (1990), in the synaptic cleft β-PEA may then modulate post-synaptic dopamine receptor signaling, or the presynaptic activity of dopamine through some unknown mechanism, perhaps via the TAAR1 expressed within the SN-VTA and basal ganglia.

9.2.2. Tryptamine

The lesioning data (Juorio and Greenshaw, 1985, 1986; Juorio et al., 1987) suggest that the TRP present in the striatum is not derived from the cells in the dorsal or medial raphe, but is derived from either dopamine neurons in the SN or neurons which are 6-OHDA-sensitive but are 5,7-DHT-insensitive and which also project to the striatum. As cited above, recent immunohistochemical data suggest that although TRP is present in both the dorsal and medial raphe and the SN, the TRP present in the SN is not localized in dopamine-containing neurons there (Dabadie et al., 1990). One possibility that reconciles the lesioning and immunohistochemical data is that the TRP present in the striatum is derived from TRP cells in the SN that project to the striatum and which are 6-OHDA-sensitive and 5,7-DHT-insensitive. These TRP cells may be the D-cells observed in the SN by Jaeger et al. (1984). The physiological investigations by Jones and Boulton (1980b) and Jones (1982b,c,d) suggest a complex functional relationship between TRP and serotonin in the striatum. Other studies posit that TRP resides in dopamine neurons since there is a functional relationship between synaptic concentrations of dopamine and the biosynthesis of TRP (Juorio, 1982) that may be mediated by dopamine D_2 autoreceptor regulation of L-AADC activity (Rossetti et al., 1990).

In an attempt to reconcile this discrepancy, information provided by Juorio and Paterson (1990) supports a proposed model that suggests that TRP is synthesized in dopamine neurons in the SN that project to the striatum. Juorio and Paterson (1990) suggest that following the biosynthesis of TRP by L-AADC from tryptophan, TRP is released as a *paracrine* agent by diffusion, to modulate the activities of adjacent target cells. This modulation may occur through allosteric sites of either pre- and/or postsynaptic serotonin receptors, or via unique TRP receptors not located on dopamine terminals (Nguyen et al., 1989), but located on post-synaptic GABAergic or cholinergic neurons.

10. Could the trace amines function as *fast* ionotropic synaptic neurotransmitters?

In contrast to their *slow* metabotropic modulatory effects and indirect releasing effects on presynaptic uptake in dopamine, noradrenaline and serotonin neurons, if the trace amines do function as *fast* synaptic, ionotropic neurotransmitters or co-transmitters in dopamine, noradrenaline or serotonin systems, then accordingly the definitions of Burnstock (1976) and the criteria proposed by Barchas et al. (1978) for a synaptic neurotransmitter should pertain. Thus, there should be present in the mammalian brain mechanisms for their vesicular uptake and storage, Ca^{2+}-dependent release, Na^{+}-dependent cytoplasmic re-uptake following release, recycling into synaptic vesicles or enzymatic deactivation, and the presence of trace amine receptors mediating their pre- and/or post-synaptic ionotropic responses, contiguous with their vesicular release sites (Herkenham, 1991). As elaborated above, many of these criteria have been fulfilled by various trace amines. However, there remains a lack of extensive empirical support for the trace amines to exert fast ionotropic responses and thus to fulfill a role as a *fast* synaptic transmitter or co-transmitter in processes of synaptic transmission mediated by dopamine, noradrenaline or serotonin.

10.1. Evidence for β-phenylethylamine and tyramine

Nevertheless, a number of electrophysiological studies performed *in vitro* have suggested that the actions of the trace amines are of a *direct*, post-synaptic nature. This would mean that the trace amines may be capable of functioning in a manner very similar to other conventional *fast* synaptic transmitters such as glutamate. Like the majority of the iontophoretic responses to noradrenaline and dopamine elicited from cortical or caudate neurons, the predominant response to iontophoretic administration of the trace amines is an *inhibition* of cell firing. Specifically, while iontophoretic studies have observed that β-PEA can either increase or decrease the firing rates of visual cortical cells in a manner similar to noradrenaline (Giardina et al., 1972), in other instances the effects of β-PEA on the same cells affected by noradrenaline were *opposite* to the effects of noradrenalin. Giardina et al. (1972) remarked that these latter observations are clearly at odds with the view that the effects of β-PEA are due to the presynaptic release of noradrenaline or by the activation of noradrenergic receptors. In fact, they suggest that in the cerebral cortex distinct β-PEA receptors may exist.

In other cases, the iontophoretic administration of β-PEA produces an inhibition of the rate of firing of cortical or caudate neurons. Other researchers have suggested that this effect is a direct, post-synaptic and receptor-mediated action (Antelman et al., 1977). Even though it appeared necessary to eject the substances with relatively large currents of administration, the iontophoretic expulsion of β-PEA, *p*-TYR and OA demonstrated that these compounds might produce *fast* inhibitory effects on both cortical and caudate neurons (Henwood et al., 1979).

Intracellular recordings demonstrated similar findings of depressions of the responses of spinal cord neurons using

iontophoresis of *p*-OA, *p*-TYR, dopamine and noradrenaline (Engberg et al., 1976). In an extracellular recording study on single cerebellar Purkinje neurons investigating the effects of *p*-TYR, Hoffer et al. (1971) concurred with the earlier unit recording data, while Jones and Boulton (1980b) observed that the iontophoretic effects of β-PEA, *p*-TYR and *m*-TYR were *similar* to dopamine on cells of cortex and caudate.

10.2. Evidence for octopamine

Hicks and McLennan (1978a,b) demonstrated that whereas the effects of noradrenaline on neurons of the spinal cord and cerebral cortex were predominantly inhibitory, the effects of OA on the same neurons inhibited by noradrenaline were more *variable* in nature. They noted that some spinal and cortical neurons are *excited* by OA, while others were inhibited. In both spinal cord and cortex, the inhibitory effects of noradrenaline were blocked by the mixed β_1- and β_2-nor adrenaline receptor antagonist propranolol, whereas this antagonist had no effect on the excitatory or inhibitory responses to OA. Similarly, in the cerebral cortex, the dopamine antagonist, α-flupenthixol was ineffective in antagonizing the actions of OA. The effects of OA on spinal and cortical neurons thus appeared unlikely to be mediated by β_1- or β_2-noradrenaline receptors and like the opposing effects of β-PEA on visual cortical neurons (Giardina et al., 1972), the *opposing* effects of OA could be interpreted as evidence for the existence of differentially distributed OA receptor subtypes within the spinal cord, even though pharmacologically specific OA receptors have yet to be demonstrated in vertebrates (see Borowsky et al., 2001; Bunzow et al., 2001).

10.3. Evidence for tryptamine

In one of the earliest-performed iontophoretic studies, Curtis (1962) failed to detect an electrophysiological response to the ejection of TRP on the spontaneous firing rate of spinal cord interneurons. A consensus of later experimental investigations has determined that TRP iontophoresis has a strong *inhibitory* effect on the spontaneous firing rate of lateral geniculate (Curtis and Davis, 1962; Aghajanian and Haigler, 1975), amygdaloid and dorsal raphe neurons (Aghajanian and Haigler, 1975) and cortical neurons in the cat (Krnjevic and Phillis, 1963). However, in the above investigations, it was generally assumed that the responses to TRP were as a serotonin receptor agonist.

The investigations of Jones (1982b,c) and Jones and Boulton (1980b) further differentiated the iontophoretic actions and interactions of TRP and serotonin on single rat cortical neurons. Specifically, these authors observed that serotonin induces both excitatory and inhibitory effects on cortical neurons in nearly equal amounts, and the effects of TRP on cortical neurons are invariably *inhibitory* and more potent than those elicited by serotonin alone. Further iontophoretic studies on the interactions between TRP and serotonin demonstrated that TRP may *not* be a serotonin receptor agonist, but rather a neuromodulator of serotonin synaptic transmission. Specifically, weak (0–10 nA) iontophoretic administration of TRP at ejecting currents that do not produce an effect on baseline firing of the cortical neuron actually *potentiate* the inhibitory effects of serotonin; similar weak applications of TRP antagonize the excitatory effects of serotonin on these neurons or in some cases actually reverse them into an inhibitory response (Jones and Boulton, 1980b).

Based on these observations Jones and Boulton (1980b) suggested that TRP is an agonist at inhibitory serotonin receptors and an antagonist at excitatory serotonin receptors. These researchers further observed that the inhibitory effects of TRP were more potent, of a rapid onset and were longer lasting than those of serotonin. An interesting observation was that 40% of the cortical neurons excited by serotonin were *inhibited* by TRP (Jones, 1982b). Thus, like the opposing post-synaptic effects of OA on single cells of the cortex and spinal cord (Hicks and McLennan, 1978a,b), these later data suggested that specific receptors mediating the activity of TRP also may exist in the cerebral cortex.

Furthermore, and most importantly, the inhibitory effects of TRP on cortical cells persists following electrolytic lesions of serotonin pathways (Jones, 1982b, 1984), suggesting the effects of TRP are truly post-synaptic and not due to the presynaptic release of serotonin. In fact, the mixed serotonin 5-HT_1/5-HT_2 antagonist metergolide blocked the inhibitory effect of TRP, but not serotonin. This last observation led Jones (1982c) to suggest that the post-synaptic activity of TRP is not as a serotonin receptor agonist, but may have post-synaptic actions independent of serotonin.

Finally, single-shock stimulation of the raphe nuclei evokes a complex biphasic response from cortical cells (Jones, 1982c). This response involves a short-latency inhibitory phase followed by a long-latency excitatory phase and in some instances, this is followed by a long-latency inhibitory phase. It appears the early inhibitory phase may be mediated by TRP, while the later excitatory phase may be mediated by serotonin. Significantly, weak iontophoretic administration of TRP reduced the long-latency excitatory phase but left the short-latency inhibitory phase unaltered and in some instances actually *potentiated* the latter (Jones, 1982d).

Further support for TRP as a mediator of the early inhibitory response of cortical neurons to raphe stimulation comes from the use of precursor loading. Either L-tryptophan for TRP or L-5-hydroxytryptophan for serotonin demonstrated the short latency inhibitory responses, and the longer latency excitation responses of cortical neurons to raphe stimulation were enhanced by L-tryptophan, while 5-hydroxytryptophan, on the other hand, enhanced the excitatory effects only (Jones and Broadbent, 1982a). Similar support for a unique TRP response comes from the follow-up studies by these authors. Intravenous administration of fluoxetine, which inhibits the reuptake of both TRP and serotonin, or zimelidine, which inhibits serotonin only, demonstrated that fluoxetine potentiated both the inhibitory and excitatory responses of cortical neurons to raphe stimulation, while zimelidine potentiated only the excitatory responses (Jones and Broadbent, 1982b). Finally, the activity of TRP can be distinguished from serotonin when various behavioral parameters are explored (Jones, 1981b). In general, these complex interactions between TRP and serotonin may be important for

TRP in controlling the balance between the excitatory and inhibitory effects of serotonin on cortical neurons (Jones, 1982e).

In general, the iontophoretic ejection of *p*-TYR, *m*-TYR, *p*-OA and β-PEA elicits *rapid* hyperpolarizations at currents of administration comparable to, or slightly greater than, those necessary for hyperpolarizations elicited by dopamine and noradrenaline (Boakes et al., 1976; Bevan et al., 1978; Henwood et al., 1979; Jones and Boulton, 1980b). Whereas the responses to these trace amines have been described as weaker and more variable than those induced by dopamine and noradrenaline (Bevan et al., 1978; Jones and Boulton, 1980a), they are readily reversible, longer lasting, and in a few cases have been reported as occurring *independently* of any indirect presynaptic release of dopamine and noradrenaline or serotonin (Hoffer et al., 1971; Engberg et al., 1976; Jones, 1982b). In other cases, however, indirect presynaptic releasing effects or effects operating through alterations of uptake mechanisms ascribed to the large iontophoretic currents of administration of the respective trace amine may be responsible of the depressant actions (Henwood et al., 1979). In fact, indirect, presynaptic-releasing effects have been offered as explanations for the depressant effects of *p*-TYR (Boakes et al., 1976; Bevan et al., 1978; Jones, 1983).

11. Coda

In assessment of all the data and analyses described above, the following empirical evidence may be advanced in support of independent trace amine (particularly TYR) systems in the mammalian brain:

- Striatal TRP is not derived from serotonin neurons of the raphe. Instead, either striatal TRP may be derived from dopamine terminals that arise from neurons of the SN or a unique population of TRP neurons exist that projects to the striatum.
- In the locus coeruleus a population of OA cells exists *independently* from those that synthesize noradrenaline, and this population projects to the hippocampus, midbrain, hypothalamus and cerebellum.
- An independent population of *m*-TYR cell bodies exists, situated dorsal to the SN and which projects to the striatum.
- TYR and OA may function as conventional neurotransmitters or co-transmitters within dopamine and/or noradrenaline terminals in the striatum. The polar *m*-TYR, *p*-TYR and OA may be stored in synaptic vesicles and released following a depolarizing stimulus. These trace amines may also be conceived of as potential *humoral* agents of interneuronal communication.
- β-PEA and TRP are released *rapidly* from the respective tissue preparations by *diffusion*. This can be explained on the basis of the lipophilic nature of these trace amines. Thus TRP and β-PEA are *unlikely* to function as conventional neurotransmitters or co-transmitters in dopamine and/or noradrenaline terminals in the striatum.
- A TYR binding site is associated with pre-synaptic dopamine terminals within the striatum. This may correspond to the TAAR1 that is expressed weakly there. TAAR1 responds very strongly to TYR when expressed from heterologous cell lines.
- A TRP binding site exists within the striatum that is not expressed within dopamine terminals. A TRP binding site may also exist within the cerebral cortex.
- A distinct β-PEA binding site may exist within the cerebral cortex. This receptor may correspond to the TAAR1 expressed at high levels there. When expressed within a heterologous cell line TAAR1 is activated strongly by β-PEA.
- Considerable evidence exists for TYR, β-PEA and TRP as indirectly acting agonists within the striatum based on studies examining their actions when those substances are administered at high doses.
- At low dose iontophoretic administration these trace amines *potentiate* post-synaptic actions of dopamine, noradrenaline or serotonin. In other cases low dose iontophoretic administration of these trace amines also exert electrophysiological responses that can be in *opposition* to that of dopamine and serotonin, suggesting *specific* trace amine receptors may be mediating these effects.

The discovery of a class of GPCRs, one member of which, TAAR1, is potently activated by β-PEA and TYR in cell culture, has provided a missing piece to a puzzle that has perplexed biogenic amine researchers for decades. The eventual characterization and neuroanatomical mapping of the additional human members of this GPCR family, along with a description of the signaling mechanism(s) they evoke and their degree of intracellular ‘‘cross-talk’’ with additional intracellular signaling pathways, will surely change our perceptions in regard to the integrative post-synaptic roles the trace amines play in dopamine, noradrenaline and serotonin signaling in brain. Towards that end, gene knockouts of the TAAR1 or TAAR4 in mice will afford the opportunity to study the contribution of TYR and β-PEA signaling as well as the recreationally abused drugs amphetamine, MDMA and LSD in the absence of these receptors in well-established behavioral and pharmacological paradigms of psychostimulant and hallucinogenic activity in mammalian brain.

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