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## Short Review

# Catecholamine Phenotyping: Clues to the Diagnosis, Treatment, and Pathophysiology of Neurogenetic Disorders

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**Abstract:** One purpose of clinical neurochemistry has been to indicate “activities” of catecholamine systems, by assaying levels of the effector compounds or their metabolites in body fluids such as plasma, cerebrospinal fluid, urine, or microdialysate. This review discusses a new purpose: relating specific catecholaminergic phenotypes to neurogenetic disorders. Distinctive catecholamine patterns in several neurogenetic conditions reflect enzyme deficiencies as direct or indirect effects of gene mutations. These neurochemical patterns can provide potentially important clues to the diagnosis, treatment, and pathophysiology of neurogenetic disorders. Linking genetic abnormalities with molecular mechanisms and clinical manifestations of disease represents a useful new direction in clinical neurochemistry. **Key Words:** Neurochemistry—Catecholamines—Norepinephrine—Dopamine—DOPA—Phenotype—Neurogenetics. *J. Neurochem.* **67**, 1781–1790 (1996).

Until recently, clinical catecholamine neurochemistry has been used mainly to examine release of catecholamines as effector chemicals in the brain and periphery, in order to indicate “activities” of central or peripheral neuronal systems. The development of assay techniques for simultaneous measurements of concentrations of catecholamines, the catecholamine precursor DOPA, and catecholamine metabolites, such as dihydroxyphenylglycol (DHPG), dihydroxyphenylacetic acid (DOPAC), methoxyhydroxyphenylglycol (MHPG), homovanillic acid (HVA), metanephrine (MN), and normetanephrine (NMN), has enabled detailed and comprehensive assessments of specific aspects of catecholaminergic function, including release, neuronal and extraneuronal uptake and metabolism, turnover, and synthesis (Eisenhofer et al., 1992).

The availability of these simultaneous assays has led to a novel application of clinical catecholamine neurochemistry: the delineation of neurochemical patterns associated with specific genetic abnormalities.

These patterns can provide potentially important clues to the diagnosis, treatment, and pathophysiology of neurogenetic disorders. This brief review summarizes what has been learned so far from this new approach.

Understanding the clinical significance of catecholamine phenotypic changes requires detailed knowledge about the sources and meanings of levels of DOPA, catecholamines, and catecholamine metabolites in human physiological fluids, such as plasma (Figs. 1 and 2, Table 1), and knowledge about the chromosomal sites of genes encoding proteins participating in the synthesis, storage, release, metabolism, and recycling of catecholamines (Table 2).

### GENETIC DISEASES WITH SPECIFIC CATECHOLAMINERGIC PHENOTYPES: SYNTHESIS

In mammals, catecholamine biosynthesis stems from a single enzymatic step—conversion of the amino acid tyrosine to the catechol amino acid L-DOPA by tyrosine hydroxylase (TH; EC 1.14.13.41; Fig. 1). Circulating catecholamines seem crucial for normal neurodevelopment, because genetic disorders of catecholamine biosynthesis typically produce severe neurological defects or fetal wastage. Thus, of mice with knockout of the TH gene, ~90% die in utero (Zhou et al., 1995).

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*Abbreviations used:* AD, aldehyde dehydrogenase; AR, aldehyde reductase (alcohol dehydrogenase, EC 1.1.1.1); BH<sub>4</sub>, tetrahydrobiopterin; COMT, catechol-*O*-methyltransferase; DA, dopamine; DBH, dopamine- $\beta$ -hydroxylase; DHPG, dihydroxyphenylglycol; DHPR, dihydropteridine reductase; DOPAC, dihydroxyphenylacetic acid; EPI, epinephrine; HVA, homovanillic acid; LAAAD, L-aromatic amino acid decarboxylase; MAO, monoamine oxidase; MHPG, methoxyhydroxyphenylglycol; MN, metanephrine; NE, norepinephrine; NMN, normetanephrine; PNMT, phenylethanolamine-*N*-methyltransferase; PST, phenolsulfotransferase; TH, tyrosine hydroxylase; VAT, vesicular amine transporter; VMA, vanillylmandelic acid.



TABLE 1. Sources and physiological meanings of concentrations of L-DOPA, catecholamines, and catecholamine metabolites

| Compound   | Source   | Meaning   |
|------------|--|---|
| L-DOPA     | Sympathetic nerves and unknown   | Alterations may reflect changes in TH activity and catecholamine biosynthesis   |
| DA         | Sympathetic nerves and unknown   | Alterations may reflect large increases in exocytotic release   |
| NE         | Sympathetic nerves and (to a much smaller extent) adrenal medulla                                | Alterations indirectly reflect exocytotic release, modulated by reuptake and presynaptic adrenoceptors  |
| EPI        | Adrenal medulla  | Index of adrenomedullary secretion  |
| DOPAC      | Enzymatic actions of MAO and AD on DA  | Reflects MAO and AD activities, indirectly reflects TH, DBH, vesicular and transmembrane transporters, and extraneuronal COMT activity                    |
| DHPG       | Enzymatic actions of MAO-A and AR on axoplasmic NE   | Reflects MAO-A and AR activities, indirectly reflects DBH, vesicular and transmembrane transporters, extraneuronal COMT activity, and vesicular NE stores |
| NMN        | Enzymatic actions of COMT on NE  | Reflects extraneuronal uptake and COMT activity in nonneuronal cells  |
| MN         | Enzymatic actions of COMT on adrenomedullary EPI mainly before entry of EPI into the circulation | Reflects extraneuronal uptake and COMT activity in nonneuronal cells  |
| MHPG       | Enzymatic actions of COMT on DHPG and of COMT and MAO on NE                                      | Reflects extraneuronal uptake and COMT activity in nonneuronal cells  |
| VMA        | Enzymatic actions of AD on MHPG in liver   | Reflects hepatic metabolism of circulating and locally generated MHPG   |
| HVA        | Enzymatic actions of COMT on DOPAC   | Reflects extraneuronal uptake and COMT activity in nonneuronal cells  |
| DA sulfate | Conjugation of DA, mainly in gut   | Possibly reflects inactivation of autocrine/paracrine DA  |

For abbreviations, see legend to Fig. 1.

Tyrosine hydroxylation requires tetrahydrobiopterin ( $BH_4$ ) as a cofactor. In humans, genetic deficiencies of  $BH_4$  synthesis or recycling, although compatible with survival to birth, obviate normal postnatal neurological development if not recognized and treated appropriately from early infancy.

#### Dihydropteridine reductase (DHPR) deficiency

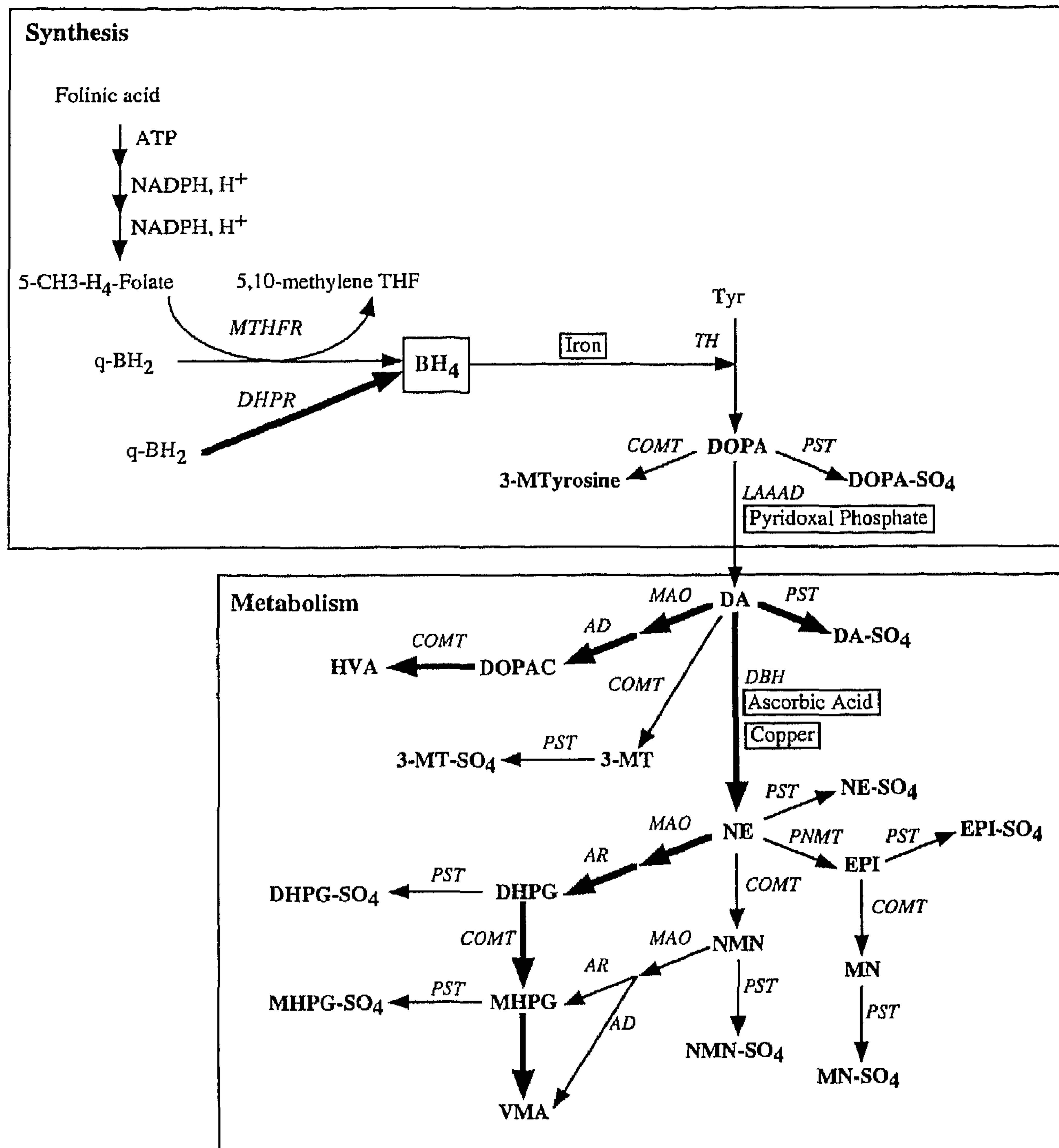
DHPR (EC 1.6.99.7) catalyzes the conversion of dihydrobiopterin to  $BH_4$ .  $BH_4$  is a required cofactor for hydroxylation not only of tyrosine but also of phenylalanine and tryptophan.  $BH_4$  also appears to play a role in maintaining the bioactive (tetrahydro) form of folic acid (Pollock and Kaufman, 1978). Because of impaired phenylalanine hydroxylation, patients with DHPR deficiency have a variant of phenylketonuria. In contrast to classical phenylketonuria (caused by specific mutations in the phenylalanine hydroxylase gene), where dietary restriction of phenylalanine beginning in infancy protects against mental retardation, patients with DHPR deficiency develop seizures and serious neurodevelopmental delays even *with* good dietary control of phenylalanine intake (Kaufman et al., 1975*a,b*).

These clinical problems presumably arise from deficient activities of TH and tryptophan hydroxylase and from defective folate metabolism. Corresponding biochemical consequences include the following: low CSF levels of metabolites of dopamine (DA) and norepinephrine (NE) (Fig. 1), such as DOPAC, HVA, DHPG, MHPG, and vanillylmandelic acid (VMA);

low CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid; and low CSF levels of tetrahydrofolate (Niederwieser et al., 1985; Goldstein et al., 1995). Therapy combining phenylalanine restriction with oral administration of L-DOPA, 5-hydroxytryptophan (precursor of serotonin), and folinic acid appears to improve neurodevelopmental outcomes in DHPR-deficient patients (Irons et al., 1987; Goldstein et al., 1995; Smooker et al., 1995).

At least 14 different mutations have been described at the DHPR locus (Matsubara et al., 1992; Dianzani et al., 1993; Smooker et al., 1993, 1995) on chromosome 4 (Sumi et al., 1990). Combinations of neurochemical assessments with mutation detection or functional characterization of abnormal DHPR alleles should help elucidate relationships between genotype and clinical phenotype in DHPR deficiency. Moreover, in a patient we studied (Goldstein et al., 1995), the pretreatment neurochemical findings (low but detectable plasma levels of DOPA and normal levels of NE, despite absent DHPR activity in erythrocytes and fibroblasts) led to the suggestion of a DHPR-independent mechanism for recycling  $BH_4$ , illustrating how neurochemical analyses in patients with rare disorders can also enhance general understanding of catecholamine metabolism.

As suggested by the pathways in Fig. 2, defects in GTP-cyclohydrolase I (EC 3.5.4.16) or 6-pyruvoyl tetrahydropterin synthase (no EC number listed) can also



**FIG. 1.** Overview of catecholamine synthetic and metabolic pathways. Note single pathway of catecholamine synthesis, via hydroxylation of tyrosine and decarboxylation of L-DOPA, compared with multiple pathways of catecholamine metabolism. *Abbreviations used:* 5-CH<sub>3</sub>-H<sub>4</sub>-folate, 5-methyltetrahydrofolate; THF, tetrahydrofolate; q-BH<sub>2</sub>, quinonoid dihydrobiopterin; MTHFR, methyltetrahydrofolate reductase; DHPR, dihydropteridine reductase; BH<sub>4</sub>, tetrahydrobiopterin; Tyr, tyrosine; TH, tyrosine hydroxylase; COMT, catechol-O-methyltransferase; PST, phenylsulfotransferase; 3-MTyrosine, 3-methoxytyrosine; LAAAD, L-aromatic amino acid decarboxylase; DOPA-SO<sub>4</sub>, L-DOPA sulfate; DA, dopamine; DA-SO<sub>4</sub>, dopamine sulfate; MAO, monoamine oxidase; AD, aldehyde dehydrogenase; AR, aldehyde reductase; DBH, dopamine-β-hydroxylase; NE, norepinephrine; 3-MT, 3-methoxytyramine; 3-MT-SO<sub>4</sub>, 3-methoxytyramine sulfate; PNMT, phenylethanolamine-N-methyltransferase; NMN, normetanephrine; EPI, epinephrine; MN, metanephrine; DHPG, dihydroxyphenylglycol; MHPG, methoxyhydroxyphenylglycol; EPI-SO<sub>4</sub>, epinephrine sulfate; NMN-SO<sub>4</sub>, normetanephrine sulfate; MN-SO<sub>4</sub>, metanephrine sulfate; DHPG-SO<sub>4</sub>, dihydroxyphenylglycol sulfate; MHPG-SO<sub>4</sub>, methoxyhydroxyphenylglycol sulfate; VMA, vanillylmandelic acid; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid.

produce atypical phenylketonuria due to defective BH<sub>4</sub> synthesis (Scriver et al., 1996). Complete deficiency of either enzyme leads to about the same clinical syndrome, with seizures, limb hypertonia, intermittent hyperthermia (Scriver et al., 1996), and predictable associated neurotransmitter abnormalities (Dhondt, 1984; Niederwieser et al., 1984). Heterozygosity for mutation at the GTP-cyclohydrolase I locus produces DOPA-responsive dystonia, as discussed later.

Deficiency of sepiapterin reductase (EC 1.1.1.153)

or of carbinolamine dehydratase (no EC number listed), other enzymes in BH<sub>4</sub> synthesis and recycling (Fig. 1) should also produce predictable clinical and neurochemical abnormalities. As carbinolamine dehydratase catalyzes a reaction that can also occur nonenzymatically, however, individuals with complete absence of this enzyme have mild clinical findings and only transient biochemical changes (Citron et al., 1993). Examples of sepiapterin reductase deficiency have not been reported to date.



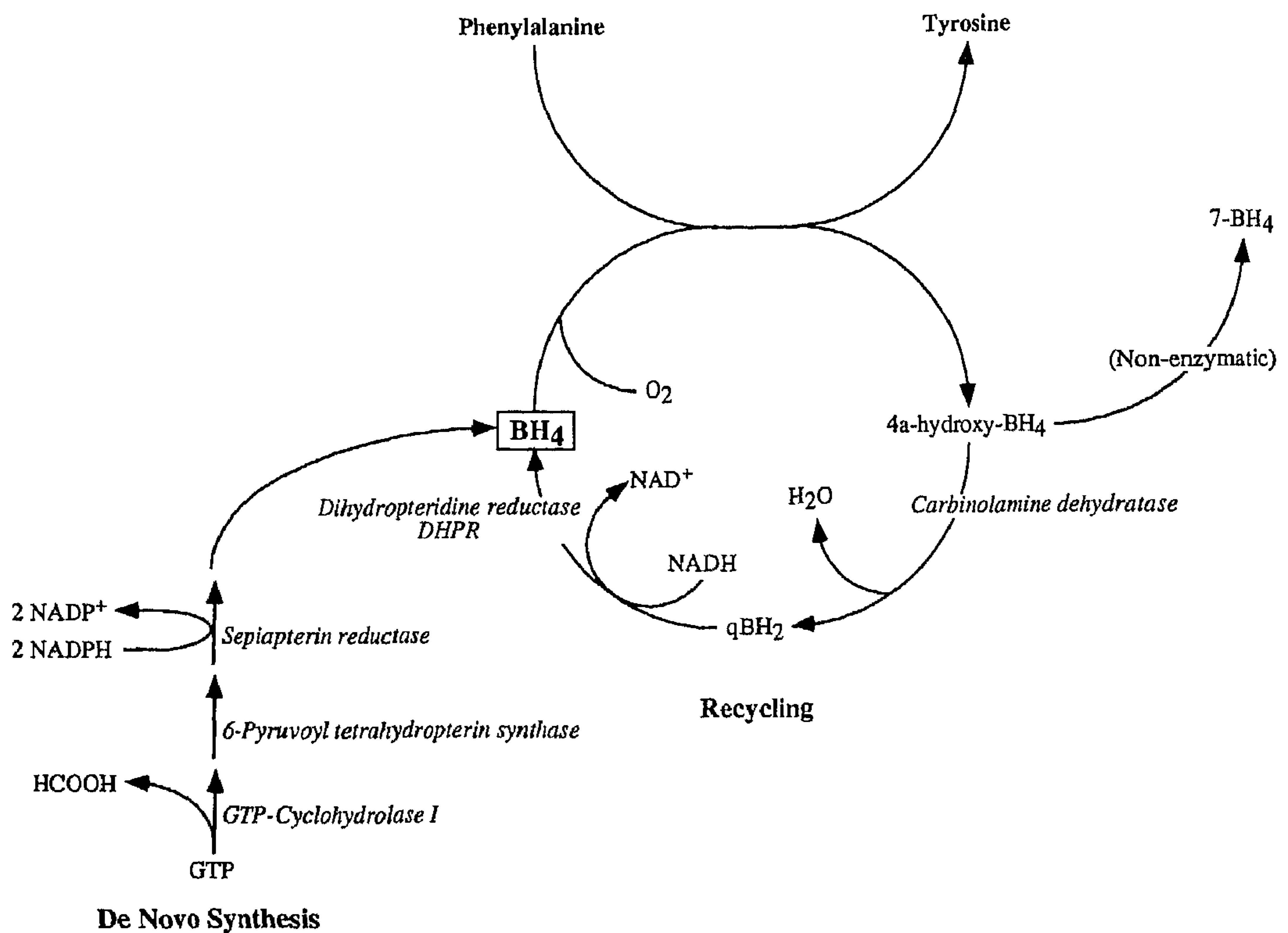


FIG. 2. Pathways of de novo synthesis and recycling of BH<sub>4</sub>. Abbreviations are as in the legend to Fig. 1.

### Vitiligo

Progressive depigmentation in vitiligo reflects neither a neurological nor a clearly inherited condition. This disorder, nevertheless, merits inclusion in this review, because vitiligo patients may have localized, cell type-specific abnormalities of catecholamine biosynthesis (Schallreuter et al., 1994). Affected individuals have three- to fivefold increases in epidermal GTP-cyclohydrolase I activity and decreased activity of carbinolamine dehydratase (Schallreuter et al., 1994). This combination increases formation of 7-BH<sub>4</sub> (Fig. 2), a by-product that potently inhibits phenylalanine hydroxylase (Adler et al., 1992; Davis et al., 1992). The genetic factors related to these alterations remain unknown.

Vitiligo patients have been reported to have increased rates of urinary excretion of HVA and VMA, especially during the onset and in progressive active phases (Morrone et al., 1992). Increased urinary excretion of norepinephrine has been noted in some affected individuals (Schallreuter et al., 1994). Data concerning plasma catecholamine levels have been inconsistent (Orecchia et al., 1994; Schallreuter et al., 1994), possibly due to a localized catecholaminergic abnormality. Additional genetic and neurochemical studies of patients with this disorder would be useful.

### L-DOPA-responsive dystonia

L-DOPA-responsive dystonia, which is inherited as an autosomal dominant trait, includes childhood-onset

dystonia, abnormal gait, marked diurnal fluctuation (symptoms aggravated in the evening and alleviated in the morning after rest), concurrent or later development of parkinsonism, and normal cognitive function. Oral L-DOPA treatment dramatically improves the neurologic symptoms.

It was the pattern of biochemical abnormalities in L-DOPA-responsive dystonia—low brain and CSF levels of DA, HVA, and BH<sub>4</sub> (Nygaard, 1993; Nygaard et al., 1994; Rajput et al., 1994; Takahashi et al., 1994)—that led initially to the prediction that the disorder would be found to arise from deficient DA synthesis due to decreased tyrosine hydroxylation. Genetic linkage analysis localized the putative mutant gene to chromosome 14q (Nygaard et al., 1993), but no candidate genes emerged from the genetic maps, until Ichinose and co-workers mapped the human GTP-cyclohydrolase gene to the L-DOPA-responsive dystonia critical region (Ichinose et al., 1994). The same workers demonstrated GTP-cyclohydrolase mutations in L-DOPA-responsive dystonia patients and documented severely reduced enzyme activity in affected patients. Numerous other GTP-cyclohydrolase mutations have since been reported in L-DOPA-responsive dystonia patients (Hirano et al., 1995; Furukawa et al., 1996), including a splice junction defect that produces skipping of exon 2 and predicts a truncated protein (Hirano et al., 1995). Thus, the neurochemical abnormalities in L-DOPA-responsive dystonia not only fit the genetic

abnormalities identified so far but also predicted the type of genetic defect.

Whether an individual possesses one or two mutant GTP-cyclohydrolase alleles profoundly influences the resultant neurological phenotype. Comparisons of neurochemical phenotypes in patients with autosomal recessive GTP-cyclohydrolase deficiency (atypical phenylketonuria) or autosomal dominant GTP-cyclohydrolase deficiency (L-DOPA-responsive dystonia) would be informative and potentially could provide insights about treatment possibilities.

#### **L-Aromatic amino acid decarboxylase (LAAAD) deficiency**

LAAAD (EC 4.1.1.28) catalyzes the conversion of L-DOPA to DA (Fig. 1) and of 5-hydroxytryptophan to serotonin. The enzyme requires pyridoxal-5'-phosphate (vitamin B<sub>6</sub>). A case report describing twins with profound deficiency of this enzyme (Hyland et al., 1992) noted that the probands, products of a consanguineous (first cousin) marriage, appeared normal at birth but developed slowly, with hypotonia and abnormal eye and limb movements by 2 months of age. A similarly affected older sibling had died when 9 months old. Both twins had low CSF and plasma levels of monoamines and high levels of DOPA and 5-hydroxytryptophan, from which the authors deduced the underlying enzymatic defect. As the parents each had intermediate LAAAD enzyme activity, the neurochemical findings suggested heterozygosity for a mutant LAAAD allele. Treatment of the affected twins during infancy with pyridoxine, bromocriptine, and tranylepromine produced some clinical benefit, although at 4 years of age neurodevelopment remained subnormal (Hyland et al., 1993). Treatment commencing earlier in infancy might be more successful.

To our knowledge, the exact mutation in this, or any other, inherited form of LAAAD deficiency has not yet been defined. The human gene encoding LAAAD has been mapped to chromosome 7 (Craig et al., 1992; Scherer et al., 1992) and cloned. Two protein isoforms, resulting from alternative mRNA splicing, have been identified (O'Malley et al., 1995).

#### **Dopamine- $\beta$ -hydroxylase (DBH) deficiency**

Although mutant mice lacking DBH (EC 1.14.17.1) die during fetal development (Thomas et al., 1995), humans with absent DBH activity have surprisingly few neurological signs. Orthostatic hypotension invariably occurs (Robertson et al., 1986), associated with extremely low or absent concentrations of NE, DHPG, VMA, and MHPG and increased concentrations of DA, DOPAC, HVA, and L-DOPA (Goldstein et al., 1989). The increase in plasma DOPA levels suggests compensatorily increased tyrosine hydroxylation in sympathetic nerves (Goldstein et al., 1987). Treatment with dihydroxyphenylserine, an amino acid converted to NE by decarboxylation, bypasses the enzymatic defect and produces remarkable clinical improvement in patients with DBH deficiency (Robertson et al., 1993). Treat-

ment with dihydroxyphenylserine also rescues DBH-deficient mice (Thomas et al., 1995).

As noted for LAAAD deficiency, no specific mutations have been reported to date for patients with congenital absence of DBH. The lack of immunoreactive DBH in plasma or CSF (O'Connor et al., 1994) suggests that the underlying molecular defect may involve abnormal expression of the DBH gene, such as by a mutation affecting the DBH promoter, splice junctions, or coding sequence.

#### **Menkes disease**

Menkes disease is an X-linked recessive cause of infantile neurodegeneration that results from mutations in a gene encoding a copper-transporting ATPase (Chelly et al., 1993; Mercer et al., 1993; Vulpe et al., 1993; Das et al., 1994). Clinical features include seizures, severe developmental delay, failure to thrive, connective tissue abnormalities, such as bladder diverticula and skin laxity, hair abnormalities ("pili torti"), and death in infancy or early childhood (Kaler, 1994). Other syndromes with less severe neurological phenotypes (e.g., occipital horn syndrome) have also been associated with mutations at this locus (Kaler et al., 1994). The clinical findings in Menkes disease and its variants result from reduced activities of copper-containing proteins, such as ceruloplasmin, cytochrome *c* oxidase, superoxide dismutase, lysyl oxidase, and DBH. Because the patients have impaired intestinal copper absorption, serum copper levels are low after the first 2 months of life.

Decreased DBH activity in patients with Menkes disease causes a distinctive, abnormal pattern of plasma and CSF catechols (Kaler et al., 1993b), with high concentrations of DOPA, DOPAC, and DA, low concentrations of DHPG (an index of intraneuronal NE turnover), and approximately normal concentrations of NE itself, consistent with compensatory increases in sympathetic nerve traffic and tyrosine hydroxylation. The neurochemical pattern (in particular, elevated ratios of DOPA/DHPG and DOPAC/DHPG) provides an excellent biochemical marker for this condition (Kaler et al., 1993b). Thus, analyses of plasma levels of catechols can diagnose or exclude Menkes disease in at-risk infants during the newborn period, when clinical signs are extremely subtle (Gunn et al., 1984) and other biochemical markers unreliable (Kaler et al., 1993a; Kaler, 1994). The abnormal pattern can also be detected in umbilical cord blood of affected patients, indicating DBH deficiency in utero and suggesting that analysis of catechol levels in cord blood may constitute a rapid, noninvasive test for Menkes disease in at-risk newborns (Kaler et al., 1993a, 1996).

Early treatment with parenteral copper improves the clinical outcome in some patients with Menkes disease (Kaler et al., 1996; Tumer et al., 1996). The success of such therapy, however, appears to depend on the particular gene mutation (Kaler et al., 1995, 1996; Kaler, 1996). Further analyses of clinical, biochemi-



cal, and molecular features should clarify the relative importance of mutation type and other factors in determining the likelihood of response to treatment, and improved understanding of the copper transport process mediated by the gene product and its homologues may facilitate development of novel therapies for this disorder. Correction of the abnormal neurochemical pattern could predict treatment efficacy.

### Familial dysautonomia

Familial dysautonomia, inherited as an autosomal recessive trait, produces a constellation of clinical findings that suggest deficient activities of multiple peripheral neurotransmitter systems, including catecholaminergic systems. Affected patients have neurogenic orthostatic hypotension, absent lingual papillae, no histamine-induced flare or overflow tears, and episodic paroxysmal hypertension, nausea, and vomiting. All familial dysautonomia patients identified to date have shared an Ashkenazic Jewish background, suggesting that one or a few mutations account for the majority of cases. The responsible gene has not yet been reported but has been localized to chromosome 9q35 (Blumenfeld et al., 1993), a region close to the map location of the DBH gene (9q34).

Familial dysautonomia patients have high rates of excretion of HVA and low rates of excretion of VMA (Smith et al., 1963). Although this pattern might suggest deficient DBH activity, most of the patients have normal plasma DA and DOPAC levels. Familial dysautonomia patients have high plasma DOPA/DHPG ratios (although less elevated than in Menkes disease patients), a failure to increase plasma NE levels during orthostasis [analogous to patients with acquired dysautonomias (Ziegler et al., 1976, 1977)], and low plasma EPI levels (Axelrod et al., 1996).

The plasma neurochemical pattern in familial dysautonomia does not appear to fit any single abnormality of catecholamine synthesis, storage, reuptake, or metabolism. Instead, the findings suggest more global arrested differentiation of peripheral catecholamine systems during embryological development. Studies of nerve growth factor and its receptors have not been rewarding so far (Breakefield et al., 1984; Slaughter et al., 1995). The phenotypic pattern, nevertheless, points to deficient innervation of the adrenal medulla and other organs. Mechanisms by which the bound nerve growth factor receptor signals the cell bodies remain poorly understood; from the neurochemical phenotype, one may speculate that the genetic abnormality involves a protein participating in these mechanisms. The DBH locus should be formally excluded.

### GENETIC DISEASES WITH SPECIFIC CATECHOLAMINERGIC PHENOTYPES: METABOLISM

Whereas catecholamine biosynthesis occurs mainly, if not exclusively, by a single pathway (tyrosine hy-

droxylation), catecholamine inactivation occurs by several alternative pathways that include at least three different intracellular enzymes (Fig. 1). From this, and from the absolute requirement of BH<sub>4</sub> for tyrosine hydroxylation, one might predict that, compared with the potentially devastating effect of mutations either in the TH gene itself or in genes encoding enzymes participating in synthesis or recycling of BH<sub>4</sub>, defects in genes encoding catecholamine-metabolizing enzymes would have less serious clinical consequences.

Mutations in genes that encode membrane catecholamine transporters or vesicular amine transporters (VATs) have not been reported, despite cloning of the genes and identification of their chromosomal locations (Table 2). A recent report described successful generation of mice with a knockout of the membrane DA transporter (Giros et al., 1996). The animals had hyperlocomotion, decreased food intake, abnormal maternal behavior, and an increased likelihood of premature death. Neurochemically, the animals had decreased electrical stimulus-induced DA release and decreased tyrosine hydroxylation in dopaminergic neurons. To our knowledge, no report to date has reported knockout or transgenic animals for the membrane NE transporter or for a VAT.

### Monoamine oxidase (MAO) deficiency

MAO (EC 1.4.3.4) isoenzymes inactivate catecholamines and their *O*-methylated metabolites (Fig. 1) and also deaminate other biogenic amines, such as serotonin. The genes encoding the two subtypes of MAO (MAO-A and MAO-B) lie adjacent to each other on the X chromosome. Oxidative deamination of serotonin depends on MAO-A; in vitro, both subtypes deaminate DOPA, DA, and NE.

Several inherited disorders involving MAO deficiency have been described. A kindred of Dutch men with impulsivity, aggressiveness, and antisocial behavior had isolated deficiency of MAO-A (Brunner et al., 1993b), with a point mutation in exon 8 of the MAO-A gene (Brunner et al., 1993a). The patients had increased urinary excretion of NMN, HVA, and VMA.

Patients with Norrie disease, inherited as an X-linked recessive trait, have blindness, deafness, and variable mental retardation. The Norrie disease gene is contiguous with the two MAO loci at Xp11.4-p11.3 (3,094, 3,075), the order from centromere to telomere being Norrie disease/MAO-B/MAO-A. Norrie disease patients can have deletions that include the Norrie disease locus and either the MAO-B locus or both MAO loci (Lenders et al., 1996). Two brothers with Norrie disease and selective MAO-B deficiency had minimal neurochemical alterations and no behavioral or psychomotor abnormalities. In contrast, a patient with deletion of all three loci had markedly increased levels of *O*-methylated amine metabolites and low levels of deaminated catecholamines, with severe mental deficiency, autistic-like behavior, atonic seizures, and altered peripheral autonomic function (Collins et al., 1992).

**TABLE 2.** Chromosomal locations of catecholamine-synthesizing, metabolizing, and inactivating genes

| Inactivating genes        |                          |  |
|---------------------------|--------------------------|--|
| Protein                   | Location                 | Comments   |
| PH                        | 12q-24.1                 | BH <sub>4</sub> cofactor; phenylketonuria              |
| GTP-cyclohydrolase I      | 14q21-q22                | L-DOPA-responsive dystonia                             |
| DHPR                      | 4p15.31                  | Atypical phenylketonuria                               |
| Carbinolamine dehydratase | 10q22                    | Mild phenylketonuria                                   |
| TH                        | 11 (short arm)           | Fe enzyme; BH <sub>4</sub> cofactor                    |
| Tyrosinase                | 11q14-q21                | Cu enzyme; albinism                                    |
| LAAAD                     | 7p13-p11                 | Pyridoxine cofactor; neonatal seizures, hypotonia      |
| Copper ATPase             | Xq13                     | Menkes disease   |
| DBH                       | 9q34                     | Cu enzyme; ascorbate cofactor; orthostatic hypotension |
| PNMT                      | 17                       |  |
| MAO-A                     | Xp11.23                  | Impulsivity, aggressive behavior                       |
| MAO-B                     | Xp11.4                   | Norrie disease (contiguous gene syndrome)              |
| COMT                      | 22q11.1-11.2             |  |
| PST                       | 16p11.2                  |  |
| NE transporter            | 16q12.2                  | Na <sup>+</sup> -dependent                             |
| DA transporter            | 5p15.3                   | Na <sup>+</sup> -dependent                             |
| VAT-1 (adrenal)           | 8p21.3                   |  |
| VAT-2 (brain)             | 10q25                    |  |
| AR                        | ?                        |  |
| AD                        | 1q32-q42, 3p12, 7q31-q35 |  |
|                           | 9q22                     |  |
|                           | 11p14-p15                |  |
|                           | 13q14-q21                |  |

PH, phenylalanine hydroxylase; VAT, vesicular amine transporter. For other abbreviations, see legend to Fig. 1.

These findings imply that MAO-A deficiency produces far more serious clinical consequences than does MAO-B deficiency. Some of these differences could depend on the importance of MAO-A in serotonin metabolism, because mice exposed to MAO inhibitors in utero have increased aggressive behavior (Cases et al., 1995) mitigated by blockade of serotonin synthesis.

### Pseudopheochromocytoma

Pheochromocytomas are adrenal tumors that synthesize and secrete catecholamines. The tumor, which usually is benign, typically presents as difficult-to-control hypertension, with paroxysms of severe high blood pressure, tachycardia, pallor, sweating, and headache. Because the tumor constitutes a rare, but curable, form of hypertension, hypertensive patients with these symptoms or signs often undergo diagnostic testing for pheochromocytoma. Kuchel and co-workers described a syndrome termed "pseudopheochromocytoma" (Kuchel et al., 1981), in which the patients have clinical findings consistent with pheochromocytoma, but instead of harboring the tumor, the patients have decreased plasma levels of conjugated catecholamines. Because sulfconjugation figures prominently in the inactivation of circulating catecholamines [especially DA (Kuchel et al., 1978; Ratge et al., 1991)], these patients might have a deficiency of phenolsulfotransferase (PST; EC 2.8.2.1). Plasma levels of DA sulfate vary widely across individuals and species (Toth et al., 1986; Dousa and Tyce, 1988), consistent with polymorphisms in the PST gene (Aksoy and Weinshil-

boum, 1995). Patients with complete deficiency of PST have not been described to date; the gene encoding PST was cloned recently (Aksoy et al., 1994; Aksoy and Weinshilboum, 1995). The location is near the gene responsible for Batten disease, an autosomal recessive disorder of lipofuscin metabolism (Taschner et al., 1995).

### Velo-cardio-facial syndrome and DiGeorge syndrome

Velo-cardio-facial syndrome includes cleft palate, craniofacial abnormalities, learning disorders, cardiac defects, and psychiatric illness in adolescence and adulthood. DiGeorge syndrome includes immunodeficiency, facial dysmorphism, mental disorders, and cardiac defects. Both syndromes have been associated with interstitial deletions of chromosome 22q11 (Scambler et al., 1992; Franke et al., 1994). A study of nine families with recurrent cardiac outflow tract defects found that five had transmitted deletions of chromosome 22q11 (Wilson et al., 1992). Chromosome 22q11 includes the locus of the gene encoding catechol-O-methyltransferase (COMT; EC 2.1.1.6). Thus, one may hypothesize that some patients with the velo-cardio-facial or DiGeorge syndrome may have only one functional COMT allele and decreased COMT activity (Dunham et al., 1992). Abnormal ratios of O-methylated to deaminated metabolites of catecholamines in plasma or urine could detect this. The relationship between COMT activity and clinical features of either syndrome remains unknown.



### von Hippel–Lindau disease and pheochromocytoma

von Hippel–Lindau disease is an autosomal dominant disorder featuring hemangioblastomas, cystic tumors, renal cell carcinomas, pancreatic cysts and tumors, epididymal cystadenomas, and pheochromocytomas (Choyke et al., 1995). von Hippel–Lindau disease patients with pheochromocytoma can have false negative results of screening tests based on plasma levels or urinary excretion of catecholamines or catecholamine metabolites, and measurement of plasma-free (unconjugated) NMN and MN appears to provide a more sensitive biochemical marker (Lenders et al., 1995). The von Hippel–Lindau disease gene, located on chromosome 3 (3p25), encodes a tumor suppressor gene (Latif et al., 1993; Herman et al., 1994; Linehan et al., 1995). Many mutations at different loci in this gene have been documented in individuals with the classic von Hippel–Lindau disease phenotype; however, familial pheochromocytoma seems to be associated with mutations at a specific locus (Crossey et al., 1995; Gross et al., 1996; Neumann et al., 1996).

### CONCLUSIONS

The wealth of knowledge regarding the synthesis and fate of catecholamines, the availability of sensitive and specific assays for L-DOPA, catecholamines, and most of their metabolites, and recent advances in molecular genetics afford the opportunity to glean new understanding of neurogenetic disorders that involve catecholamine metabolism. This review has presented several examples rather than a comprehensive picture of this new application of clinical neurochemistry. The pathways outlined in Figs. 1 and 2 suggest the existence of several other genetic defects, as yet undiscovered, with predictable neurochemical and clinical consequences.

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