Sources and Significance of Plasma Levels of Catechols and Their Metabolites in Humans

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ABSTRACT

Human plasma contains several catechols, including the catecholamines, norepinephrine, epinephrine, and dopamine; their precursor, L-3,4-dihydroxyphenylalanine (L-DOPA); and their deaminated metabolites, dihydroxyphenylglycol, the main neuronal metabolite of norepinephrine, and dihydroxyphenylacetic acid, a deaminated metabolite of dopamine. Products of metabolism of catechols include 3-methoxytyrosine (from L-DOPA), homovanillic acid and dopamine sulfate (from dopamine), normetanephrine, vanillylmandelic acid, and methoxyhydroxyphenylglycol (from norepinephrine), and metanephrine (from epinephrine). Plasma levels of catechols and their metabolites have related but distinct sources and therefore reflect different functions of catecholamine systems. This review provides an update about plasma levels of catechols and their metabolites and the relevance of those levels to some issues in human health and disease.

Soon after the description, near the end of the 19th century, of the profound cardiovascular effects of injected adrenal extract, and the purification and identification of epinephrine as the vasoactive principal of the adrenal gland, researchers began to develop chemical means to assess activity of what came to be called the sympathoadrenomedullary system.

The first chemical method for such measurement was colorimetric, based on the unusual susceptibility of epinephrine to oxidize, forming a brownish compound, “adrenochrome.” Early attempts to measure circulating levels of epinephrine and related compounds chemically failed, mainly because the potency of epinephrine corresponds to very low normal concentrations in the bloodstream. Bioassays such as used by Cannon were the first to detect successfully epinephrine release into the circulation. Cannon later developed and exploited a preparation based on the magnitude of the increase in heart rate in animals with denervated hearts; abolition of the increase by adrenalectomy confirmed the hormone’s adrenal source. Subsequent chemical methods depended on fluorescence detection (after the trihydroxyindole reaction or ethylenediamine condensation) or radioenzymatic assays (after methylation with S-adenosylmethionine and catechol-O-methyltransferase. Ironically, current sensitive chemical methods using liquid chromatography with electrochemical detection depend on the same catechol oxidation as did the original colorimetric method.

For almost the whole of the first half of the last century, epinephrine was the only catecholamine to receive attention. Cannon proposed—erroneously—that epinephrine was not only the main vasoactive hormone released by the adrenal gland but also the chemical messenger released from sympathetic nerves. This fit with his concept of a unitary sympathoadrenomedullary system, which would help maintain homeostasis (a word he coined) during emergencies but would not be necessary in day-to-day life. Fifty years after the discovery of epinephrine, norepinephrine, rather than epinephrine, was finally identified as the main sympathetic neurotransmitter regulating the cardiovascular system in mammals. Although the notion of a single, emergency sympathoadrenomedullary system remains prominent in current research and practice, it is evident that in many situations the sympathetic nervous and

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adrenomedullary hormonal systems are regulated separately and that there is a continuous basal level of sympathetic nervous activity.

Human plasma contains six readily detectable catechols, compounds containing two adjacent hydroxyl groups on a benzene ring. The main plasma catechols are the three catecholamines; their precursor, L-3,4-dihydroxyphenylalanine (DOPA, levodopa); and their deaminated metabolites dihydroxyphenylacetic acid (DOPAC), from dopamine, and dihydroxyphenylglycol (DHPG, DOPEG), from norepinephrine.

Catecholamines undergo a complex fate, mediated by several enzymes, including aldehyde reductase (AR), aldose reductase, aldehyde dehydrogenase (AD), alcohol dehydrogenase (ADH), catechol-O-methyltransferase (COMT), dopamine-ß-hydroxylase (DBH), monoamine oxidase (MAO) types A and B, monoamine-preferring phenolsulfotransferase (SULT1A3, or m-PST), and phenylethanolamine-N-methyltransferase (PNMT), in various combinations. Because these enzymes are expressed differently among tissues, circulating levels of the products have distinctive sources and reflect specific aspects of sympathetic neuronal and adrenomedullary hormonal system functions (Table 1).

This brief review provides an update about plasma levels of catechols and their metabolites and illustrates the relevance of those levels to several issues in human health and disease. Separate sections deal with norepinephrine, epinephrine, and dopamine and their metabolites, followed by indices of catecholamine biosynthesis.

SYMPATHETIC NORADRENERGIC FUNCTION

Plasma Norepinephrine

Norepinephrine in the bloodstream emanates mainly from networks of sympathetic nerves that enmesh blood vessels—especially arterioles—throughout the body and pervade organs such as the heart and kidneys. The caliber of the arterioles determines total peripheral resistance to blood flow. The sympathetic innervation of the smooth muscle cells in arteriolar walls therefore represents a focal point in neural regulation of blood pressure. In the heart, sympathetic nerves form lattice-like networks around myocardial cells and also supply coronary arterial vessels.

Because of the close architectural association between the sympathetic nerves and myocardial and arteriolar smooth muscle cells, one might predict an important role of sympathetic nerves in regulation of cardiovascular performance.

Only a very small proportion of norepinephrine released from sympathetic nerves reaches the bloodstream unchanged. The main route of inactivation of norepinephrine is by reuptake into the nerve terminals. Under resting conditions, however, most of the norepinephrine produced in sympathetic nerves is metabolized before entry of the transmitter into the interstitial fluid or plasma (Figure 1).

Since plasma norepinephrine is derived from sympathetic nerves, plasma norepinephrine levels have been widely used to indicate sympathetic nervous system activity. The relationship between plasma norepinephrine levels and sympathetic nerve traffic is not simple. The plasma concentration depends on both the rate of release of norepinephrine into the plasma and the rate of its removal of from the plasma. Thus, a high plasma norepinephrine level does not necessarily indicate a high rate of sympathetic nerve traffic; a decrease in removal from the plasma also can increase plasma norepinephrine levels, without a change in the rate of sympathetic nerve traffic. Second, the sympathetic nervous system consists of myriad nerves distributed throughout the body, and stressors can activate sympathetic nerve traffic hetereogeneously to different organs. For blood sampling from humans, most researchers use the antecubital vein. Since sympathetic nervous activity in the forearm and hand arm influences levels of norepinephrine in antecubital venous plasma, those levels may not accurately reflect changes in sympathetic nervous activity elsewhere in the body during stress. Only a small amount of plasma norepinephrine comes from the adrenal gland under resting conditions, but during some stress responses, such as acute glucoprivation, the adrenal contribution to plasma norepinephrine increases. Third, since only a small proportion of norepinephrine released from sympathetic nerve endings actually reaches the circulation unchanged, small variations in efficiency of the cell membrane norepinephrine transporter can markedly alter the amount of norepinephrine reaching the plasma. Fourth, any of several endogenous biochemicals—including norepinephrine itself, by activating presynaptic α_2-

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adrenoceptors—have the potential to modulate release of norepinephrine from the nerve terminals. In clinical studies, α_2-adrenoceptor stimulation has been shown to inhibit norepinephrine release into the bloodstream in the heart and forearm. And fifth, in some pathological states and in response to a variety of sympathomimetic amines, norepinephrine is released from sympathetic nerve terminals by a non-exocytotic mechanism differing from the calcium-dependent, exocytotic mechanism of release in response to sympathetic nerve traffic. Cardiac ischemic anoxia is an example of such a pathologic state. Increased net leakage of norepinephrine from vesicular storage sites builds up norepinephrine concentrations in the axoplasm, and exit of norepinephrine via the cell membrane norepinephrine transporter can then lead to norepinephrine entry into the interstitial fluid. Sympathomimetic amines such as tyramine and amphetamine, increase plasma norepinephrine levels, by this non-exocytotic mechanism.

While these considerations do not invalidate plasma norepinephrine levels in arm venous blood in diagnosis, assessment of drug effects, or prognosis, it is evidenct that plasma norepinephrine levels must be interpreted with care, keeping in mind the purpose of the test, the characteristics of the patient, the possible interacting effects of medications, and other factors that can influence the obtained results.

Plasma norepinephrine kinetics

In virtually all organs, some of released norepinephrine enters the venous drainage. The rate of entry of norepinephrine into the arterial plasma ("total body spillover") can be measured using a tracer kinetic method, based on dilution of infused ^{3}H-norepinephrine by endogenous norepinephrine. Because of ^{3}H-norepinephrine extraction from the circulation in the forearm tissues, use of antecubital venous plasma levels of ^{3}H-norepinephrine overestimates whole body norepinephrine clearance. Healthy people release about 0.3-0.5 micrograms per minute (1.7-3.0 nmoles/min) of norepinephrine into arterial plasma, resulting in too low a plasma norepinephrine concentration to exert hormonal effects.

By applying the same tracer dilution principle, one can calculate norepinephrine spillover in organs such as the heart, kidneys, mesenteric organs, forearm, and brain. This avoids a problem

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inherent to calculation of total body norepinephrine spillover, which is the possibility of missing localized changes in norepinephrine release when sympathetic outflows change heterogeneously among organs. Measurement of regional norepinephrine spillover also has some limitations. Local spillover increases as blood flow increases, unless regional extraction of arterial norepinephrine decreases correspondingly.

Without other neurochemical information, one cannot distinguish norepinephrine release from neuronal reuptake as determinants of norepinephrine spillover, in the whole body or in specific organs. A recent modification, based on dilution not only of ^{3}H-norepinephrine but also of ^{3}H-normetanephrine by the corresponding endogenous compounds, has enabled such a distinction (Kopin et al., 1998). In the kidneys, norepinephrine release into interstitial fluid averages three times norepinephrine spillover, in skeletal muscle 12 times norepinephrine spillover, and in the heart more than 20 times norepinephrine spillover, due to efficient local neuronal reuptake of norepinephrine from the interstitial fluid.

Many studies have noted that both plasma norepinephrine concentrations and directly recorded skeletal muscle sympathetic activity increase with subject age; the increased plasma norepinephrine concentrations appear to reflect both increased spillover and decreased clearance (Esler et al., 1995).

Plasma Dihydroxyphenylglycol (DHPG)

Dihydroxyphenylglycol (DHPG) is formed from norepinephrine in the cytoplasm of sympathetic nerves, by sequential deamination of norepinephrine to form dihydroxyphenylglycoaldehyde (DOPEGAL, DHPGALD) and reduction of the aldehyde by aldehyde reductase or aldose reductase (Figures 1 and 2). DHPG diffuses rapidly across the cell membrane into the extracellular fluid and from there into extraneuronal cells, where it is metabolized by COMT to form methoxyhydroxyphenylglycol (MHPG), or into the bloodstream.

Norepinephrine in the cytoplasm of sympathetic nerves has two sources; most comes from continuous vesicular leakage, and a small, variable amount comes from uptake of norepinephrine released in response to sympathetic nerve traffic. Plasma DHPG has in essence the same sources

(Goldstein et al., 1988). Since vesicular leakage and axoplasmic deamination of norepinephrine are the main constituents of norepinephrine turnover, plasma DHPG provides a biochemical index of norepinephrine turnover, a parameter distinct from norepinephrine release.

Combined measurements of plasma norepinephrine and DHPG levels provide unique information about sympathetic nervous function. When sympathetically-mediated exocytosis increases, plasma levels of both norepinephrine and DHPG increase—the former because a small proportion of released norepinephrine spills over into the bloodstream, and the latter because a portion of the released norepinephrine is taken up into the nerve terminals and deaminated. Increases in plasma norepinephrine levels from diminished reuptake of norepinephrine are not attended by increases in plasma DHPG levels (Goldstein et al., 1988).

Furthermore, measurements of tritiated and endogenous norepinephrine and DHPG provide estimates of rates of vesicular leakage, intraneuronal deamination of norepinephrine, and the proportion of released norepinephrine that undergoes reuptake into the nerve terminals (Eisenhofer et al., 1992). These estimates indicate a tremendously high exchange rate of amines between the axoplasm and the vesicles; turnover of norepinephrine as a result of intraneuronal deamination after leakage from vesicles into the axoplasm; and reuptake of endogenously released norepinephrine, the efficiency of which varies from organ to organ and is especially prominent in the heart.

Plasma Normetanephrine

Catechol-O-methyltransferase (COMT) catalyzes the O-methylation of the 3-hydroxyl group of most catechols. The O-methylated derivative of L-DOPA is 3-methoxytyrosine, of dopamine mainly 3-methoxytyramine, of norepinephrine normetanephrine, and of epinephrine metanephrine. The term, “metanephrines,” refers to the latter two compounds.

In most cells, the O-methylated compounds that contain amine groups undergo further metabolic breakdown by MAO. Deamination of 3-methoxytyramine yields homovanillic acid (HVA) and of normetanephrine and metanephrine yields MHPG. In cells that have monoamine-preferring phenolsulfotransferase (SULT1A3) activity, the non-acidic metabolites,

methoxytyramine, normetanephrine, metanephrine, and MHPG, undergo extensive sulfate-conjugation. Glucuronides of these compounds may be excreted in the bile or, via entry into the circulation, in the urine.

High levels of COMT are found in the liver, kidneys and other extraneuronal cells, as well as in adrenomedullary chromaffin cells (Eisenhofer et al., 1998b). Formation of normetanephrine in the body therefore occurs from extraneuronal uptake and metabolism of norepinephrine released from sympathetic terminals and also from O-methylation within the adrenal gland. Because of the importance of reuptake and intraneuronal deamination of endogenously released norepinephrine, plasma levels of normetanephrine are much lower than those of DHPG, despite similar clearances of these compounds from the plasma. The rate of extra-adrenal production of normetanephrine, however low, provides a unique marker of extraneuronal metabolism of norepinephrine.

Patients with pheochromocytomas virtually always have high plasma normetanephrine or metanephrine levels, reflecting metabolism of norepinephrine or epinephrine in the tumor before release of the catecholamines into the circulation (Lenders et al., 1995). Plasma levels of metanephrines (normetanephrine and metanephrine) constitute the most sensitive blood test to detect pheochromocytoma devised so far (Lenders et al., 2002). The sensitivity exceeds that of plasma norepinephrine and epinephrine levels, because catecholamines produced in the tumor undergo metabolism continuously by COMT, even if they do not reach the bloodstream.

Most pheochromocytomas secrete predominantly norepinephrine, many produce both norepinephrine and epinephrine, and more rarely others secrete predominantly epinephrine. The differences in catecholamine secretion reflect differences in expression of catecholamine biosynthetic enzymes and can explain differences in presenting symptoms. Paroxysmal hypertension and symptoms such as palpitations, anxiety, dyspnea and hyperglycemia are more common in patients with pheochromocytomas producing epinephrine than producing norepinephrine. Pheochromocytomas in patients with multiple endocrine neoplasia, Type 2 (MEN 2) produce epinephrine and have an adrenergic phenotype, while those from patients with

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von Hippel-Lindau (VHL) disease have a distinctively noradrenergic phenotype (Eisenhofer et al., 2001). Thus, differences in biochemical and clinical presentation of pheochromocytoma can reflect the underlying mutation.

The common painkiller, acetaminophen (Tylenol™), interferes with the assay for plasma normetanephrine. Patients undergoing blood sampling for assays of plasma levels of metanephrines should not take any medications containing acetaminophen for at least 3 days before the test.

Plasma Methoxyhydroxyphenylglycol (MHPG)

Methoxyhydroxyphenylglycol (MHPG) in human plasma is derived from multiple sources, including (a) deamination of normetanephrine after its cellular uptake; (b) deamination of normetanephrine after cellular uptake and intracellular O-methylation of norepinephrine; (c) O-methylation of DHPG after its uptake from the circulation; and (d) O-methylation of DHPG after its uptake from the interstitial fluid but before its entry into the circulation. Of these sources, the most prominent is the last (Eisenhofer et al., 1994).

The metabolic fate of circulating MHPG is also complex and includes sulfation, glucuronidation, urinary excretion, and especially conversion to VMA in the liver. Because of the complex and multiple determinants of plasma MHPG levels, one must interpret those levels carefully.

Although earlier work suggested that plasma MHPG, or plasma MHPG-sulfate, might reflect release of norepinephrine in the brain, in fact plasma levels of these metabolites derive mainly from norepinephrine released in the periphery.

Plasma Vanillylmandelic Acid (VMA)

MHPG is converted to vanillylmandelic acid (VMA), by oxidation catalyzed by human class I alcohol dehydrogenase (ADH) . The aldehyde product is oxidized further by class II alcohol dehydrogenase (also called piADH). Virtually all of VMA production in humans can be accounted for by conversion from MHPG.

Only small amounts of VMA are formed from O-methylation of dihydroxymandelic acid

(DHMA, DOMA), which actually is a minor metabolite of norepinephrine in humans. Thus, circulating VMA and MHPG come mainly from DHPG (Eisenhofer et al., 1996). Some of hepatic VMA production appears to be from uptake of circulating DHPG, but most is derived from uptake of circulating MHPG (Figure 3).

Noradrenergic Neuropharmacology

Tricyclic antidepressants and monoamine oxidase inhibitors, which are used to treat depression, produce characteristic changes in patterns of norepinephrine metabolites. Inhibition of Uptake-1 by tricyclics increases norepinephrine spillover for a given amount of sympathetic nerve traffic; however, their actions in brain reduce sympathetic nerve traffic, so that plasma norepinephrine levels may remain unchanged; plasma DHPG levels, however, fall, probably due partly to decreased reuptake of released norepinephrine. Plasma MHPG levels also fall. Inhibition of MAO-A markedly decreases plasma DHPG levels, whereas inhibition of MAO-B is much less effective, consistent with the sympathoneuronal source of plasma DHPG and selective expression of MAO-A in sympathetic nerves.

Cocaine is a classical inhibitor of Uptake-1. In conscious humans, intranasal cocaine also increases sympathetic nerve discharge. The combination of increased sympathetic outflows and attenuation of neuronal reuptake results in increases in plasma norepinephrine levels . The cell membrane norepinephrine transporter plays a important role in the inactivation of norepinephrine in the human heart. By blocking this inactivation, cocaine markedly increases delivery of norepinephrine to cardiac adrenoceptors, providing a ready explanation for cardiac toxicity from cocaine. Clonidine is an α_2-adrenoceptor agonist that acts in the central nervous system to decrease sympathetic nervous system outflows and also in the periphery at presynaptic receptors to decrease norepinephrine release from sympathetic nerve terminals. By both effects, clonidine decreases plasma norepinephrine levels. In patients with pheochromocytoma, a tumor that produces catecholamines, plasma norepinephrine levels can be increased because of release of norepinephrine into the bloodstream independently of the sympathetic nervous system. In such patients, failure of clonidine to reduce plasma norepinephrine constitutes a positive diagnostic test

result (Grossman et al., 1991). Conversely, the combination of a high plasma norepinephrine level and a large fall in blood pressure in response to clonidine may identify patients with "hypernoradrenergic hypertension" (Goldstein et al., 1985).

Yohimbine exerts effects opposite to those of clonidine. Intravenous infusion of yohimbine increases sympathetic neural outflows and blocks α_2-adrenoceptors on sympathetic nerve terminals, thereby increasing plasma norepinephrine levels. Yohimbine challenge testing can assess whether a patient with neurogenic orthostatic hypotension has releasable norepinephrine stores (Robertson et al., 1986), which can be a target for treatment. Yohimbine challenge testing can also reveal excessive norepinephrine release in patients with anxiety or panic disorder (Charney et al., 1984).

Indirectly acting sympathomimetic amines, such as dextroamphetamine and tyramine, release norepinephrine from sympathetic nerve endings. These drugs are substrates for both the cell membrane norepinephrine and vesicular monoamine transporters. By intravesicular alkalinization, they enhance norepinephrine leakage from storage vesicles into the axoplasm. They also interfere with the efficiency of the cell membrane norepinephrine transporter, resulting in transport of the axoplasmic norepinephrine into the extracellular fluid. In humans, infusion of tyramine or dextroamphetamine therefore increases plasma norepinephrine levels. During tyramine infusion, plasma DHPG levels increase to a proportionately larger extent than do plasma norepinephrine levels (Goldstein and Holmes, 1997), probably because of the greater buildup of norepinephrine in the axoplasm than in the extracellular fluid.

Foodstuffs such as hard cheeses and red wines contain large amounts of tyramine. Normally, dietary tyramine is metabolized in the gastrointestinal tract and liver before the amine can enter the systemic circulation. In patients taking an MAO inhibitor, tyramine is able to reach the sympathetic nerve terminals, and after neuronal and vesicular uptake of tyramine, paroxysmal hypertension can result from release of vesicular norepinephrine—a phenomenon termed the "cheese effect." Because of the susceptibility to severe hypertension due to the cheese effect, MAO inhibitors have not had wide usage as antidepressants, despite their clinical efficacy.

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α-methyl-para-tyrosine (Demser™) blocks tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis. Repeated administration of α-methyl-para-tyrosine decreases plasma levels of DOPA, DOPAC, norepinephrine, and DHPG. The drug is used clinically prior to surgery to remove a pheochromocytoma.

Carbidopa inhibits L-aromatic-amino-acid decarboxylase, which catalyzes conversion of levodopa to dopamine. Since carbidopa does not pass through the blood-brain barrier, administration of carbidopa with levodopa increases delivery of levodopa to the brain, while decreasing nausea and vomiting resulting from production of dopamine from levodopa outside the brain (hence the brand name, "Sinemet™," from the Latin for "without vomiting," for the combination of levodopa/carbidopa). Carbidopa increases plasma levels of endogenous DOPA and decreases renal dopamine production from circulating DOPA.

ADRENOMEDULLARY HORMONAL SYSTEM FUNCTION

Plasma Epinephrine

Since cells of the adrenal medulla secrete their contents directly into the bloodstream, plasma epinephrine levels generally reflect neural outflow to the adrenal medulla. Thus, increments in adrenomedullary secretion of catecholamines resulting from manipulations of circulatory reflexes or from administration of drugs into the brain correlate with increments in directly recorded adrenal nerve activity (Yoshimatsu et al., 1987).

Plasma levels of epinephrine are very low in antecubital venous plasma of healthy volunteers at rest—as little as 30 pmol/L—lower than plasma levels of norepinephrine, which normally average about 1 nmol/L. In contrast with plasma levels of norepinephrine, which generally increase with advancing age, those of epinephrine tend to decrease. Plasma epinephrine levels and urinary epinephrine excretion also tend to be lower in obese than in lean people and in women than in men. Inconsistencies in the literature on these topics may reflect incomplete controls for demographic and metabolic factors, variable numbers of subjects, and inter-laboratory differences in assay reliability.

Plasma epinephrine concentrations increase markedly and to a greater extent than do

norepinephrine concentrations in response to hypoglycemia, hemorrhagic hypotension, asphyxiation, circulatory collapse, and distress, presumably reflecting relatively greater adrenomedullary hormonal than sympathetic neuronal activation. Even mild, asymptomatic hypoglycemia elicits larger increases in epinephrine than norepinephrine levels, and in the relatively benign form of circulatory failure represented by fainting, plasma epinephrine concentrations increase with smaller increases in plasma norepinephrine concentrations (Goldstein et al., 1982).

Tracer kinetic studies have demonstrated epinephrine spillover in the heart in severe exercise, panic attacks, and in some patients with essential hypertension (Esler, 2000). Although extra-adrenal epinephrine synthesis and phenylethanolamine-N-methyltransferase have been reported in the heart, it is likely that the epinephrine released in the heart is derived from uptake from the circulation.

Addison's disease, usually due to an autoimmune adrenalitis of the adrenal cortex, includes impaired adrenal medullary secretion of epinephrine. The medulla is intact but plasma levels of epinephrine are decreased (Bornstein et al., 1995). This occurs despite glucocorticoid replacement, indicating that the normal high intraadrenal steroid levels are required for an adequate production of catecholamines in the human adrenal medulla. Epinephrine secretion is also impaired in secondary adrenocortical insufficiency in children with hypocorticotropic hypopituitarism, further supporting the importance of a local source of steroids for adrenal medullary release of catecholamines.

. Patients with severe 21-hydroxylase deficiency have markedly decreased plasma concentrations of epinephrine associated with incomplete formation of the adrenal medulla (Merke et al., 2001). These patients also have low plasma concentrations of metanephrine, consistent with decreased adrenal medullary stores of epinephrine.

Plasma Metanephrine

As for norepinephrine in sympathetic nerves, under resting conditions metabolism of epinephrine in the adrenal medulla takes place before the hormone enters the bloodstream. Since

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adrenomedullary chromaffin cells possess COMT, metanephrine constitutes a major metabolite of epinephrine before its release into extracellular fluid, whereas in sympathetic nerves, which contain MAO-A but not COMT, DHPG constitutes the main metabolite of norepinephrine before norepinephrine release into extracellular fluid.

The fate of epinephrine that enters the bloodstream differs quantitatively from that of norepinephrine. Epinephrine is a poorer substrate than norepinephrine for Uptake-1 and a better substrate for Uptake-2. It is also a better substrate than norepinephrine for COMT. Because of these differences, more of circulating epinephrine than norepinephrine is metabolized by extraneuronal uptake and O-methylation.

Plasma metanephrine levels are roughly the same as plasma normetanephrine levels, even though plasma norepinephrine levels exceed epinephrine levels by about 5- to 10-fold. The relatively high metanephrine concentration results from a much greater rate of production of epinephrine than of norepinephrine in adrenomedullary chromaffin cells, metabolism of adrenomedullary catecholamines by COMT, and a relatively high proportion of metabolism of circulating circulating epinephrine by the same enzyme.

Adrenergic Pharmacology

In response to stressors posing global metabolic threats, such as acute glucoprivation, emotional distress, and hemorrhagic hypotension, increments in plasma epinephrine levels exceed those of norepinephrine levels (Pacak et al., 1998).

Drugs that stimulate nicotinic, angiotensin II, or glucagon receptors increase plasma epinephrine levels.

Epinephrine stimulates $ß_2$-adrenoceptors more potently than does norepinephrine. Physiological increases in circulating epinephrine concentrations decrease the serum K^+ concentration, by increasing active Na^+-K^+ transport across cell membranes, especially in skeletal muscle (Clausen, 1983). $ß_2$-Adrenoceptor agonists can be used clinically to treat hyperkalaemia; conversely, exercise can induce hyperkalemia in patients taking ß-adrenoceptor blockers.

ß-Adrenoceptor agonists also increase norepinephrine release into plasma, by stimulating sympathetic outflows reflexively in response to decreased vascular resistance and by occupying ß-adrenoceptors on sympathetic nerves. Concurrently, plasma epinephrine levels fall (Eisenhofer et al., 1987). Occupation of cardiac ß-adrenoceptors increases cardiac norepinephrine spillover (Thompson et al., 1998).

Because of the effect of adrenocortical steroids on activity of phenylethanolamine-N-methyltransferase (PNMT) in adrenomedullary chromaffin cells, manipulations of hypothalamo-pituitary-adrenocortical activity affect plasma epinephrine levels more than they do plasma norepinephrine levels. Indeed, plasma epinephrine levels in many situations vary more closely with those of corticotropin (ACTH) than those of norepinephrine.

Secondary adrenocortical insufficiency may result from exogenous glucocorticoid administration. The mechanism involves suppression of intra-adrenal cortisol production through negative feedback of the hypothalamo-pituitary-adrenocortical axis. Low epinephrine levels in severe asthma patients treated with glucocorticoids may be explained by iatrogenic adrenocortical insufficiency (Mathe and Knapp, 1969). Similar impairment of adrenal medullary function might be expected in other patients on glucocorticoid treatment regimens.

PERIPHERAL DOPAMINERGIC FUNCTION

Plasma Dopamine

Until recently, dopamine outside the brain was considered only as a biochemical intermediate in the production of the body's other two catecholamines, norepinephrine and epinephrine (adrenaline). Plasma dopamine concentrations are similar to those of epinephrine, but because of the much lower potency of dopamine than of epinephrine, circulating dopamine does not act as a hormone. Furthermore, stressors that elicit release of norepinephrine from sympathetic nerves produce much larger increases in plasma norepinephrine levels than in plasma dopamine levels. Relatively meager understanding about the sources and clinical significance of plasma levels of dopamine therefore contrasts with rather clear understanding about those of plasma epinephrine and norepinephrine.

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Plasma Dihydroxyphenylacetic acid (DOPAC)

DOPAC is the product of oxdiation of the aldehyde produced by deamination of dopamine. Whereas the aldehyde intermediate produced upon oxidative deamination of norepinephrine undergoes metabolism mainly by aldehyde reductase and aldose reductase, forming DHPG, the aldehyde intermediate upon deamination of dopamine is metabolized mainly by aldehyde dehydrogenase and alcohol dehydrogenase, forming DOPAC.

Plasma DOPAC levels averages about 50 times that of dopamine, due to much slower clearance of DOPAC than of dopamine from the circulation.

At least some of plasma DOPAC is from metabolism of dopamine in the cytoplasm of sympathetic nerves. Blockade of the vesicular monoamine transporter by reserpine increases plasma DOPAC levels (Eisenhofer et al., 1988). Meanwhile, blockade of tyrosine hydroxylase by α-methyl-para-tyrosine treatment decreases plasma DOPAC levels (Goldstein et al., 1987), and patients with pure autonomic failure associated with diffuse loss of sympathetic nerves have low plasma DOPAC levels (Goldstein et al., 1989). Immobilization in rats rapidly increases plasma DOPAC levels, concurrently with increases in plasma catecholamine levels; blockade of catecholamine biosynthesis by α-methyl-para-tyrosine prevents the stress-induced increases in plasma DOPAC (Kvetnansky et al., 1992).

Plasma DOPAC is also formed from metabolism of dopamine in non-neuronal cells of the gastrointestinal tract (Eisenhofer et al., 1995; Eisenhofer et al., 1996). Meal ingestion increases plasma DOPAC levels (Goldstein et al., 1999), although the determinants of the dietary influences remain unknown.

Several neurogenetic diseases of catecholamine synthesis or metabolism produce distinctive abnormalities of plasma levels of DOPAC. In patients with dihydropteridine reductase (DHPR) deficiency, failure to regenerate tetrahydrobiopterin (BH_4), which is absolutely requiredfor tyrosine hydroxylation, results in low plasma DOPAC levels (Goldstein et al., 1995). In contrast, in DBH deficiency, failure to convert dopamine to norepinephrine leads to high plasma DOPAC levels and low DHPG levels (Goldstein et al., 1989). Menkes disease is an X-linked recessive

disorder of a copper ATPase, and since DBH is a copper enzyme, patients with Menkes disease have decreased DBH activity, resulting in high plasma DOPAC:DHPG and high dopamine:norepinephrine ratios (Kaler et al., 1993). In deficiency of L-aromatic-amino-acid decarboxylase, plasma levels of DOPA are high, whereas levels of DOPAC, DHPG, and dopamine sulfate are low, consistent with decreased conversion of DOPA to dopamine (Swoboda et al., 1999). The genes encoding the two subtypes of MAO exist very close to each other on the X-chromosome. Deficiency of MAO-A presents clinically entirely differently from that of MAO-B. Whereas MAO-B deficiency produces few if any neurobehavioral consequences, MAO-A deficiency produces an inherited tendency to violent anti-social behavior. Patients with MAO-A deficiency have very low plasma DOPAC levels, whereas patients with MAO-B deficiency have normal plasma DOPAC levels (Lenders et al., 1996), consistent with the intraneuronal site of MAO-A.

Carbidopa is combined with levodopa in Sinemet™, to inhibit decarboxylation of levodopa to dopamine outside the brain. Although carbidopa effectively inhibits L-aromatic-amino-acid decarboxylase, the attained plasma levodopa concentration is so high (about 10,000 nmol/L) that plasma DOPAC levels typically increase by more than 20-fold (from about 7 to about 180 nmol/L). Thus, patients taking Sinemet™ actually have substantially increased production and metabolism of dopamine outside the brain.

Plasma Dopamine Sulfate

With the exception of VMA, all the catecholamines and their metabolites are metabolized to sulfate conjugates, by a specific sulfotransferase isoenzyme (SULT1A3). In humans, a single amino acid substitution confers the enzyme with particularly high affinity for dopamine and the O-methylated metabolites of catecholamines, including normetanephrine, metanephrine and methoxytyramine. The SULT1A3 isoenzyme is found in high concentrations in gastrointestinal tissues, which therefore represent a major source of sulfate-conjugated catecholamines and their metabolites (Eisenhofer et al., 1999).

In humans, at least 95% of dopamine in plasma circulates in sulfoconjugated form. Plasma

dopamine sulfate results importantly from ordinary dietary constituents. In fasting normal volunteers, ingestion of a standard meal increases plasma dopamine sulfate levels more than 50-fold, with proportionately smaller increases in plasma levels of dopamine (Goldstein et al., 1999).

There are also substantial non-dietary sources of plasma dopamine sulfate. Thus, patients with deficiency of L-aromatic amino acid decarboxylase have low plasma dopamine sulfate levels (Swoboda et al., 1999). Since dopamine infusion into such patients markedly increases plasma dopamine sulfate levels, plasma dopamine sulfate derives at least partly from circulating dopamine; however, at least 90% of the sulfoconjugation of dopamine normally takes place before the dopamine enters the bloodstream, with little of plasma dopamine sulfate forming from circulating dopamine.

Although most organs produce little dopamine sulfate, as judged from increments in plasma levels of the compound between the arterial inflow and venous outflow, an exception is the mesenteric organs. Indeed, in the body as a whole dopamine sulfate production appears to come mainly from conjugation of dopamine in the gastrointestinal tract (Eisenhofer et al., 1999).

The formation of dopamine sulfate depends on synthesis of dopamine from L-DOPA in the cells. The relative contributions from uptake of circulating L-DOPA and from intracellular synthesis of L-DOPA remain incompletely understood.

Plasma dopamine sulfate does not derive to any important extent from dopamine in sympathetic nerves. Thus, patients with pure autonomic failure or the Shy-Drager syndrome have normal plasma levels of dopamine sulfate. Dopamine sulfate levels respond relatively little to acute exposure to various stressors such as exercise.

The diagram in Figure 4 summarizes our current view about the sources and physiological significance of plasma dopamine sulfate levels. First, meal ingestion markedly increases plasma dopamine sulfate levels. This could result from actual ingestion of L-DOPA, dopamine, or dopamine sulfate, from conversion of ingested tyramine to dopamine, from actions of tyrosinase to generate L-DOPA in the gastrointestinal lumen, or from increased release and metabolism of endogenous dopamine in gastrointestinal lining cells. None of these explanations apply to plasma

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dopamine sulfate detected after an overnight fast. Second, tyrosine generated from breakdown of dietary protein can enter sympathetic nerves or other cells containing tyrosine hydroxylase, resulting in production of L-DOPA outside the gastrointestinal tract. Some of this L-DOPA enters the bloodstream, and uptake and decarboxylation of circulating L-DOPA provides a means to generate dopamine sulfate continuously from endogenous dopamine. Third, since dopamine sulfate derives to a relatively small extent from circulating dopamine, in fasting subjects the rate of entry of dopamine sulfate into plasma might reflect dopamine production in the gastrointestinal tract.

Plasma Homovanillic Acid (HVA)

Plasma HVA levels are derived mainly from O-methylation of DOPAC. This explains why COMT inhibition increases plasma DOPAC levels as HVA levels fall. The liver and kidneys possess high levels of COMT activity; however, in humans, a substantial proportion of HVA production takes place in mesenteric organs (Eisenhofer et al., 1998a).

Dopaminergic Pharmacology

In addition to the well-known functions of dopamine as a neurotransmitter in the brain, dopamine also probably functions as an autocrine-paracrine substance, participating in functions of several organs outside the brain.

This role is most well understood in the case of the kidneys. Exogenously administered dopamine dilates renal blood vessels, increases glomerular filtration, and increases sodium excretion, via specific receptors in the kidneys and also via inhibition of aldosterone secretion from the adrenal cortex. Proximal tubular cells both express dopamine receptors and produce dopamine, after uptake of L-DOPA from the circulation and decarboxylation catalyzed by L-aromatic-amino-acid decarboxylase (LAAAD). In humans, virtually all of dopamine in urine comes from renal uptake and decarboxylation of L-DOPA (Wolfovitz et al., 1993), and only a small fraction is from filtration of plasma dopamine. Dopamine produced in the adrenal cortex also appears to be derived from uptake and decarboxylation of circulating L-DOPA (Buu and Lussier, 1990).

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Because of the role of dopamine in natriuresis, drugs that inhibit LAAAD or block dopamine receptors tend to attenuate natriuretic responses, such as to sodium chloride administration, lower body positive pressure, or protein ingestion.

PLASMA DOPA

L-DOPA is the precursor of the catecholamines and the immediate product of the rate-limiting step in catecholamine biosynthesis, conversion of tyrosine to L-DOPA by the enzyme tyrosine hydroxylase. L-DOPA therefore occupies a pivotal position in the function of effector systems that use catecholamines.

In humans, plasma levels of L-DOPA exceed those of norepinephrine by about 10-fold, due to much more rapid clearance of norepinephrine than of L-DOPA from the plasma. Until recently it was thought that all the L-DOPA synthesized in sympathetic nerve endings was rapidly converted to dopamine. Release of L-DOPA from sympathetic nerve endings into the bloodstream would not be expected; however, in humans there virtually always are increments of plasma L-DOPA levels between the arterial inflow and venous outflow in the limbs, heart, head, leg, adrenal gland, and gut (Goldstein et al., 1991).

Patients with sympathectomized limbs have no or reduced regional arteriovenous increments in L-DOPA levels (Goldstein et al., 1987). Patients with diseases associated with loss of sympathetic terminals in the heart have an analogous absence of the increment in plasma L-DOPA levels between the arterial inflow and coronary sinus outflow (Goldstein et al., 1997); and in laboratory animals, chemical destruction of sympathetic nerve terminals eliminates regional arteriovenous increments in plasma L-DOPA levels in the hindlimb, gut, and kidneys . These findings are consistent with a sympathoneural origin of plasma L-DOPA levels.

Acute changes in arterial plasma L-DOPA levels probably reflect acute changes in the overall rate of synthesis of norepinephrine in sympathetic nerves. Thus, in rats, immobilization increases L-DOPA levels in arterial plasma within a few minutes, and blockade of catecholamine biosynthesis or of sympathetic nerve traffic prevents these increases. Nevertheless, in rats, chemical sympathectomy does not completely eliminate arterial plasma L-DOPA, and in dogs,

chemical sympathectomy does not reduce arterial plasma L-DOPA levels. In humans, pure autonomic failure is associated with decreased—but by no means absent—plasma L-DOPA levels (Goldstein et al., 1989). These findings suggest important additional, non-neuronal sources of L-DOPA in arterial plasma.

The source of this residual L-DOPA is unknown. In normal volunteers, meal ingestion increases plasma L-DOPA levels (Goldstein et al., 1999). Chemical sympathectomy with 6-hydroxydopamine spares both the adrenal medulla and sympathetic ganglion cells, and in both cell types 6-hydroxydopamine increases rates of catecholamine synthesis. Increased L-DOPA release from adrenomedullary or sympathetic ganglionic cells could partly maintain arterial plasma L-DOPA levels. The possibility of L-DOPA synthesis in non-neuronal cells, perhaps by tyrosinase, must also be considered.

The fact that L-DOPA is the immediate product of the rate-limiting step in catecholamine synthesis has led to the hypothesis that changes in regional L-DOPA spillover into the bloodstream provide an *in vivo* index of changes in regional norepinephrine synthesis in sympathetic nerves. In every situation examined so far, changes in tyrosine hydroxylase activity are reflected by similar changes in plasma L-DOPA levels. Plasma L-DOPA levels can detect derangements of catecholamine synthesis in a variety of disorders, including tumors and inherited neurological diseases. Neuroblastoma constitutes one of the most common solid tumors of children. By the time of diagnosis of this viciously malignant cancer, the fate of the patient often has been sealed. As the name of the tumor suggests, neuroblastoma cells derive from the neural crest in embryological development, and they contain tyrosine hydroxylase. Patients harboring a neuroblastoma have high—sometimes spectacularly high—plasma L-DOPA levels (Eldrup et al., 2001).

Patients with malignant pheochromocytoma, another tumor of catecholamine-synthesizing cells, also have elevated plasma L-DOPA levels (Goldstein et al., 1986). Malignant pheochromocytoma cells appear to be so undifferentiated that although they can hydroxylate tyrosine to form L-DOPA, they do not decarboxylate L-DOPA efficiently to form dopamine or

hydroxylate dopamine to form norepinephrine.

High plasma L-DOPA levels occur in a third type of cancer, malignant melanoma (Letellier et al., 1997). The tumor cells do not contain tyrosine hydroxylase, but they do contain high levels of tyrosinase, and L-DOPA is produced in phase I melanogenesis, either from direct oxidation of tyrosine or from dopaquinone.

Tyrosine hydroxylase is vital for normal neurological development. For tyrosine hydroxylase to function, other enzymes are also required for synthesis of tetrahydrobiopterin (BH_4), which is absolutely necessary for tyrosine hydroxylase to convert tyrosine to L-DOPA. Autosomal dominant mutations of the gene encoding GTP cyclohydrolase I, the rate-limiting enzyme for the biosynthesis of BH_4, produce DOPA-responsive dystonia, or hereditary progressive dystonia with marked diurnal fluctuation. Autosomal recessive GTP cyclohydrolase I deficiency, with complete loss of the enzyme activity, produces severe, progressive neurodegeneration. Autosomal recessive DOPA-responsive dystonia can also arise from mutation of the tyrosine hydroxylase gene itself. One would predict low plasma DOPA levels in these diseases.

In contrast, as noted above, diseases associated with deficient activities of enzymes involved in the cascade of catecholamine synthesis, such as of DBH, produce a biochemical pattern with high plasma L-DOPA levels and low or absent levels of norepinephrine or the norepinephrine metabolite DHPG. The buildup of plasma L-DOPA probably results not only from the low enzymatic activity but also from increased tyrosine hydroxylation in sympathetic nerves. A high ratio of plasma L-DOPA:DHPG occurs in DBH deficiency (Biaggioni et al., 1990), Menkes disease (Kaler et al., 1993), and familial dysautonomia (Axelrod et al., 1998).

In order to maintain norepinephrine stores, the rate of synthesis of norepinephrine must balance the rate of turnover. This explains why the regional rate of entry of L-DOPA into the circulation correlates better with regional spillover of DHPG, an index of norepinephrine turnover, than with indices of norepinephrine release, as discussed in the section about DHPG.

After uptake into cells, L-DOPA can be metabolized by at least two enzymes—L-aromatic-

amino-acid decarboxylase (LAAAD, also called L-DOPA decarboxylase, or DDC) and catechol-O-methyltransferase (COMT). LAAAD converts L-DOPA to dopamine. COMT converts L-DOPA to 3-methoxytyrosine. Both enzymes figure prominently in the clinical use of L-DOPA to treat Parkinson's disease. The catechol hydrazide drugs, carbidopa and benserazide, inhibit LAAAD outside the brain and so are used in combination with L-DOPA to augment the proportion reaching the brain . COMT constitutes an important part of the enzymatic "blood-brain barrier" for catechols including L-DOPA. COMT inhibitors (e.g., tolcapine, entacapone) supplement Sinemet™ effects by increasing the bioavailability of L-DOPA and the efficiency, smoothness, and duration of delivery of L-DOPA to the brain.

PERSPECTIVE

Plasma levels of endogenous catechols and their metabolites vary remarkably widely over a several thousand-fold range (Table 2). Concentrations of these compounds are determined not only by the rate of entry into the plasma but also by the clearance from the plasma. At one extreme, plasma levels of catecholamines are kept very low because of rapid clearance from the plasma; at the other, plasma levels of the sulfate-conjugated metabolites are generally high because of slow clearance from the plasma. Because of extensive removal of catecholamines from the plasma during passage of blood through tissues of the forearm, catecholamine clearances based on sampling antecubital venous blood overestimate those from arterial plasma. One must be careful about drawing inferences about functions of catecholamine systems based on plasma measurements of single analytes, obtained from single sites such as the antecubital vein.

Nevertheless, measurements of levels of DOPA, catecholamines, and their metabolites—especially measured in combination—can provide important or even unique information relevant to diagnosis, pathophysiology, and treatment effects for several diseases. We predict future discoveries and insights based on clinical catecholamine neurochemistry.

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FIGURE LEGENDS

Figure 1: Determinants of Plasma Norepinephrine (NE) and Dihydroxyphenylglycol (DHPG) Levels. Plasma NE levels are determined mainly by release from vesicles by exocytosis and reuptake via the cell membrane norepinephrine transporter (NET), via the Uptake-1 process. Other influences include enzymatic activities of tyrosine hydroxylase (TH), L-aromatic-amino-acid decarboxylase (LAAAD), and dopamine-ß-hydroxylase (DBH), as well as activity of the vesiculr monoamine transporter (VMAT). In contrast, plasma DHPG levels are determined mainly by monoamine oxidase (MAO) in sympathetic nerves, net leakage of NE from vesicles into the axoplasm, reuptake of released NE, and extraneuronal O-methylation of DHPG catalyzed by catechol-O-methyltransferase (COMT). Note that both metabolism of NE to DHPG and DHPG to MHPG occurs extensively before entry of either NE or DHPG into the bloodstream.

Figure 2: Metabolism of Dopamine and Norepinephrine (NE). The main pathways in humans are in bold arrows. The minor metabolites, dihydroxymandelic acid (DHMA) and dihydroxyphenylethanol (DOPET), are not shown. Abbreviations: AD = aldehyde dehydrogenase; ADH = alcohol dehydrogenase; AR = aldehyde reductase; COMT = catechol-O-methyltransferase; DBH = dopamine-ß-hydroxylase; DHPG = dihydroxyphenylglycol; DOPAC = dihydroxyphenylacetic acid; HVA = homovanillic acid; MAO = monoamine oxidase; MHPG = methoxyhydroxyphenylglycol; PST = phenolsulfotransferase; NMN = normetanephrine; SAM = S-adenosyl methionine; VMA = vanillylmandelic acid.

Figure 3: Sources of Plasma Levels of Vanillylmandelic Acid and Metanephrines Note that plasma VMA derives mainly from hepatic uptake and conversion of MHPG, which in turn derives mainly from DHPG produced in sympathetic nerves.

Figure 4: Sources of Dopamine (DA) Production and Metabolism in the Gastrointestinal Tract. There are multiple, interacting pathways of dopamine production and metabolism. Dopamine can be produced from DOPA synthesized by the intracellular actions of tyrosine hydroxylase (TH) on tyrosine (TYR) or intraluminal actions of tyrosinase found in foods such as

cereal grains. DOPA can also be supplied by uptake of circulating DOPA. DOPA is converted intracellularly to DA by L-aromatic-amino-acid decarboxylase (LAADC). Dopamine is metabolized by several enzymes, including catechol-O-methyltransferase (COMT), monoamine-preferring phenolsulfotransferase (PST), and monoamine oxidase (MAO) types A and B, followed by aldehyde dehydrogenase and alcohol dehydrogenase in various combinations. The main end-product of DA metabolism is homovanillic acid (HVA). Other metabolites include DA-sulfate (DA-S), 3-methoxytyramine (3-MT); 3-methoxytyrosine sulfate (3-MT-S) , and dihydroxyphenylacetic acid (DOPAC). Circulating concentrations of these metabolites vary inversely with their clearances from the plasma and do not necessarily reflect relative contributions of the different pathways.

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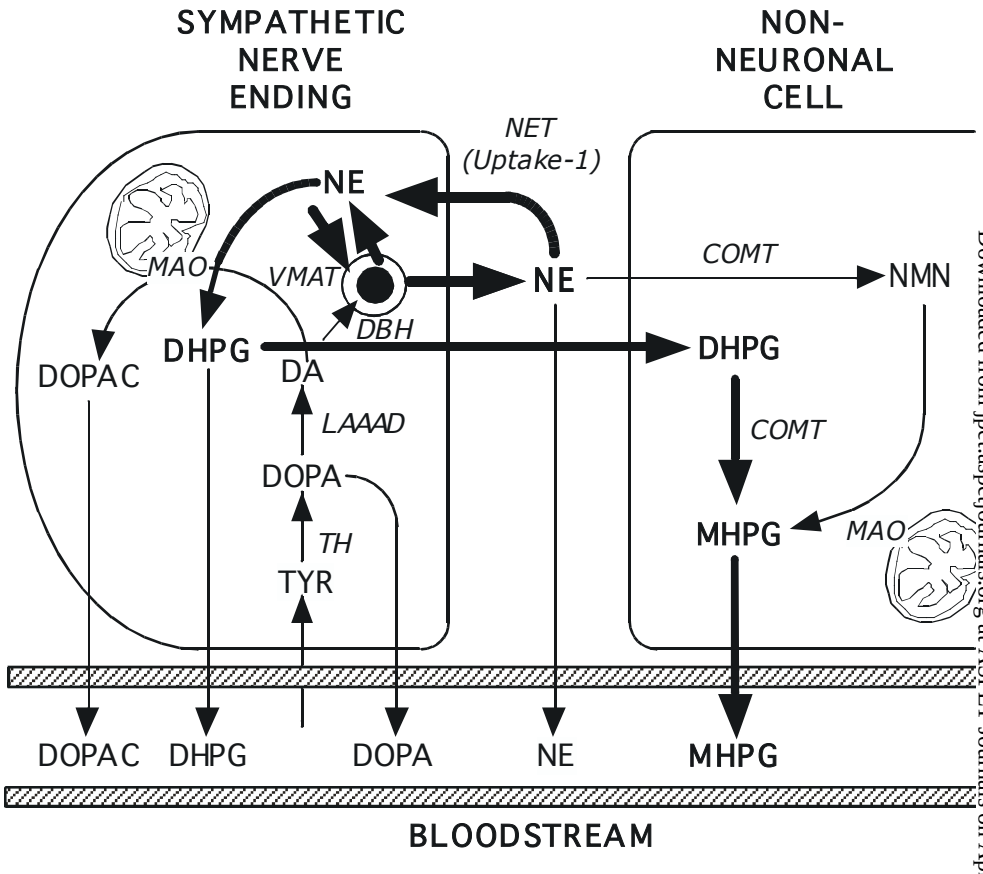

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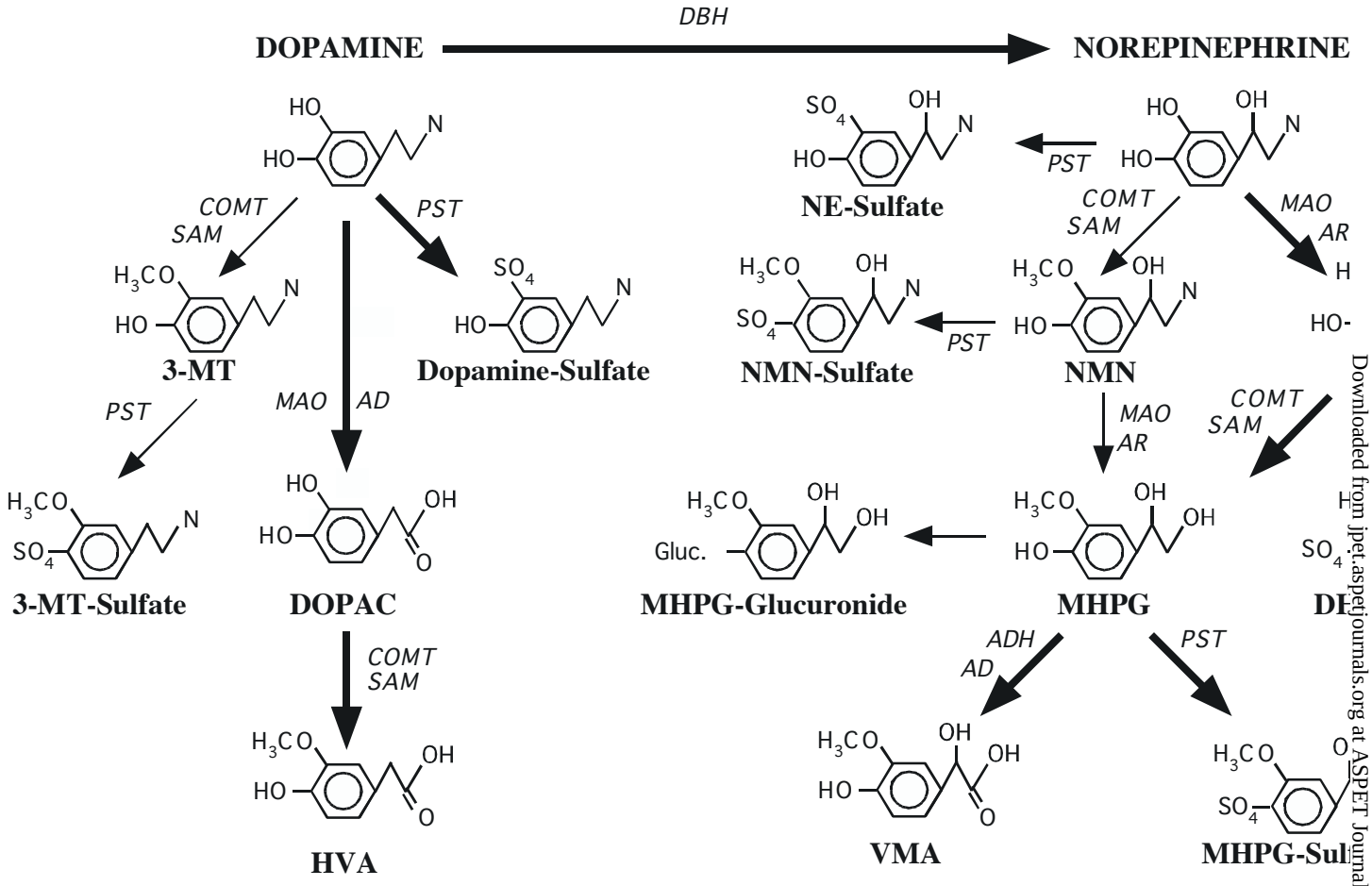

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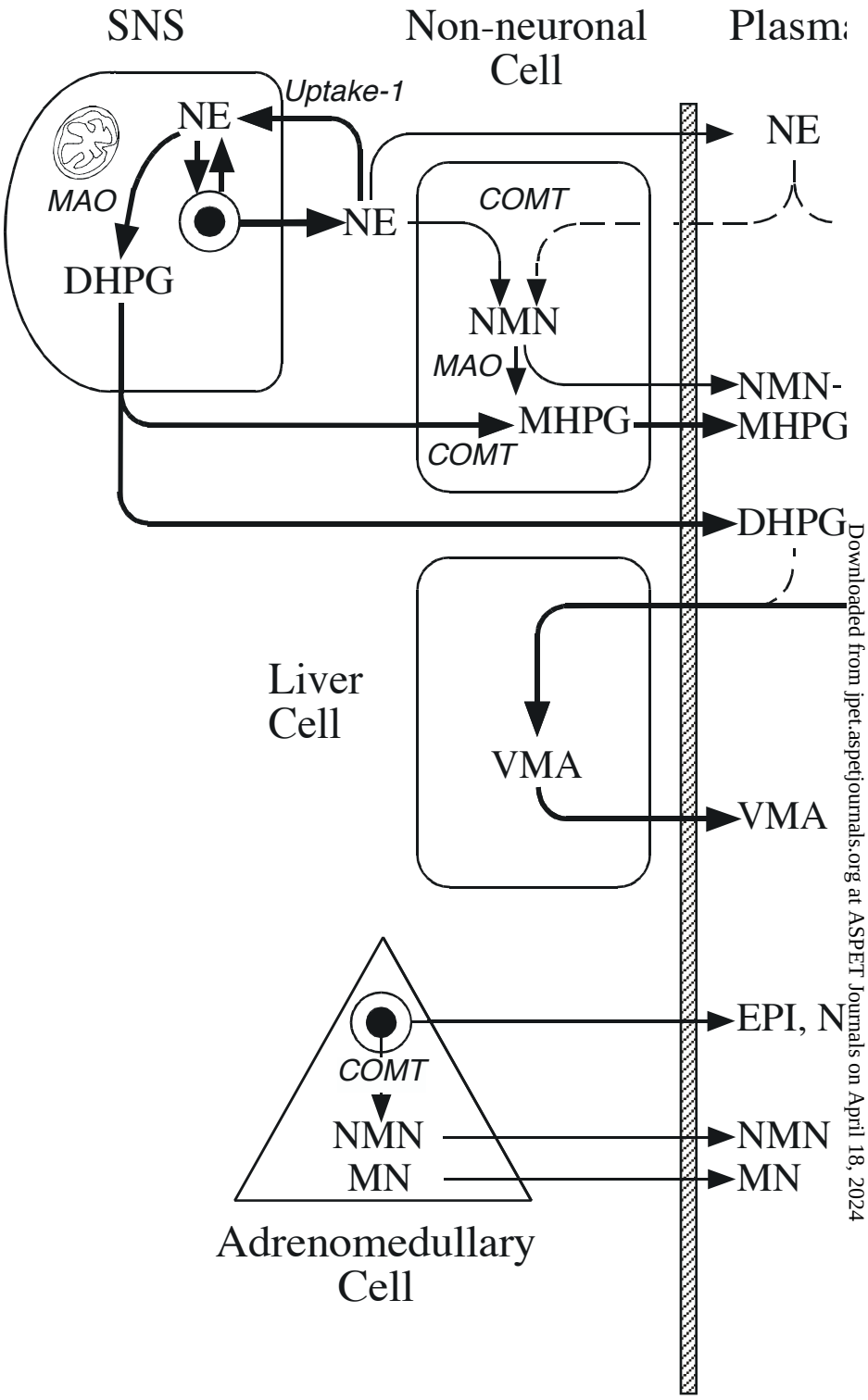

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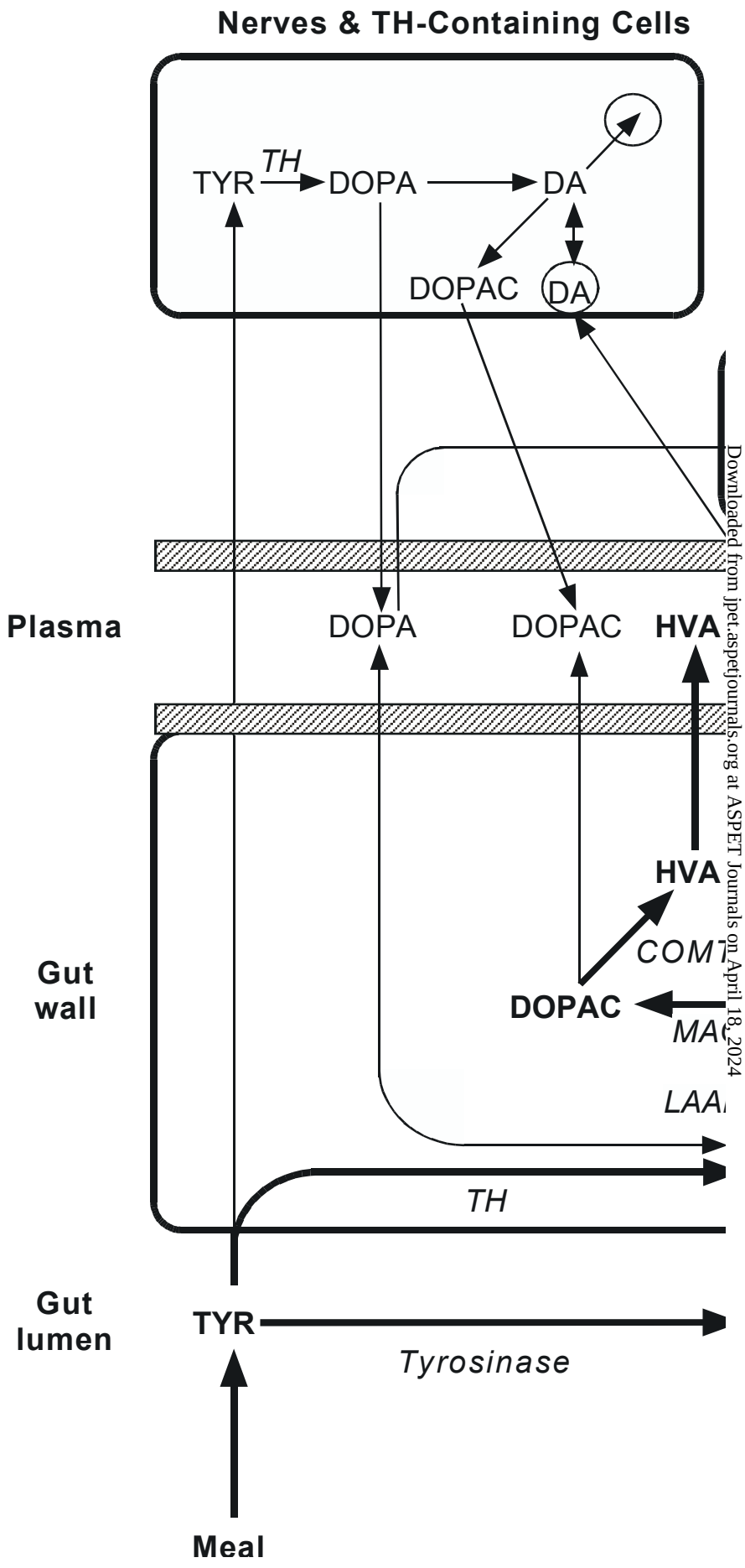

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TABLE 1

Sources and Significance of Plasma Catechols and Metabolites

Compound	Determinants	Significance
Norepinephrine	Sympathetic nerves	Sympathetic nerve traffic Prognosis (e.g., heart failure)
	Uptake-1 activity	NET function
	Dopamine-ß-hydroxylase	DBH deficiency
	LAAAD	LAAAD deficiency
	BH_4	DHPR deficiency GTP cyclohydrolase-I deficiency
DHPG	VMAT/Vesic. Leakage	NE turnover
	NE reuptake	NET function
	MAO-A	MAO-A deficiency Familial Dysautonomia Menkes disease
MHPG	DHPG	NE turnover
	COMT activity	Altered COMT function
MHPG-Sulfate	MHPG SULT1A3	
MHPG-Glucuronide	MHPG Glucuronidase	Hepatic function
NMN	Adrenal medulla	Pheochromcytoma diagnosis
	Sympathetic nerves	Uptake-2 activity
	COMT activity	Altered COMT function
NMN-Sulfate	NMN SULT1A3	
VMA	MHPG	Hepatic function
	Alcohol dehydrogenase Aldehyde dehydrogenase	
Epinephrine	Adrenal medulla	Distress Shock Glucoprivation Calorigenesis/Obesity Asphyxia
MN	Adrenal medulla	Pheochromocytoma diagnosis

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		21-Hydroxylase deficiency severity
MN-Sulfate	MN SULT1A3	
DA	Non-neuronal gut cells Circulating L-DOPA Sympathetic nerves	Menkes disease diagnosis DBH deficiency diagnosis
DA-Sulfate	Mesenteric organs Diet SULT1A3	? Gastrointestinal TH activity
DOPAC	Sympathetic nerves MAO-A Extraneuronal MAO	TH activity MAO-A activity Extraneuronal MAO activity Altered COMT function
HVA	COMT activity DOPAC	Altered COMT function
3-M-Tyramine	COMT activity	Altered COMT function
3-M-Tyramine-Sulfate	3-M-Tyramine SULT1A3	
DOPA	Sympathetic nerves Diet Melanocytes ? Extraneuronal TH	TH activity LAAAD deficiency DBH deficiency DHPR deficiency GTP cyclohydrolase deficiency Tyrosinase activity Malignant melanoma Neuroblastoma diagnosis Malignant pheo. diagnosis
3-MT	COMT DOPA	Altered COMT function
3-MT-Sulfate	3-MT SULT1A3	

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TABLE 2

Plasma Levels, Clearances, Spillovers, and Half-Times of Catechols and Their Metabolites

Compound	Level *nmol/L*	Clearance *L/min*	Spillover *nmol/min*	Half-Time *min*
Noradrenergic				
VMA	30	0.6	21	32
MHPG-S	23	0.3*	7.4*	
MHPG	20	1.3	25	28
DHPG-S	6.6	0.3*	1.7*	
NMN-S	6.6	0.1*	0.7*	>60
DHPG	4.7	2.4	12	
NE-S	3.4	0.1*	0.5*	
Norepinephrine	1.0	1.7	2.6	2
NMN	0.3	1.4	0.4	<4
Adrenergic				
MN-S	3.9	0.1*	0.5*	>60
Epinephrine-S	0.5	0.2*	0.1*	
MN	0.3	1.4	0.5	<4
Epinephrine	0.2	2.3	0.5	~3
Dopaminergic				
HVA	70	0.8	63	40
DA-S	9.7	0.1*	1.3	148

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TABLE 2, CONTINUED

Plasma Levels, Clearances, Spillovers, and Half-Times of Catechols and Their Metabolites

Compound	**Level** *nmol/L*	**Clearance** *L/min*	**Spillover** *nmol/min*	**Half-Time** *min*
DOPAC	8.9	0.5*	>4.1*	
3-MTyramine-S	2.8	0.12*	0.3*	>60
DA	0.1	2.8**	0.3	~2
3-MTyramine	0.03	0.5	0.02	
DOPA				
3-MTyrosine	87	0.005	0.4	
DOPA	8.9	0.9	7.4	
3-MTyrosine-S	2.8	0.1	0.3	>60
DOPA-S	2.1			

(*) Calculation based on renal removal or urinary excretion and therefore may underestimate total body clearance and spillover.

(**) Calculation based on one-half the published clearance from antecubital venous plasma.