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Sources and Physiological Significance of Plasma Dopamine Sulfate

DAVID S. GOLDSTEIN, KATHRYN J. SWOBODA, JOHN M. MILES, SIMON W. COPPACK, ANDERS ANEMAN, COURTNEY HOLMES, ISAAC LAMENSDORF, AND GRAEME EISENHOFER

Clinical Neuroscience Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892; Children's Hospital Division of Genetics, Harvard Medical School, Boston, Massachusetts 02115; The Diabetes and Nutrition Research Laboratory, St. Luke's Hospital, Kansas City, Missouri 64111; UCL Medical School, Whittington Hospital, London NI9 3UA, United Kingdom; University of Göteborg, Göteborg S-41390, Sweden

ABSTRACT

Dopamine in the circulation occurs mainly as dopamine sulfate, the sources and physiological significance of which have been obscure. In this study, plasma concentrations of dopamine sulfate were measured after a meal, after fasting for 4 days, and during iv L-DOPA, nitroprusside, or trimethaphan infusion in volunteers; after dopamine infusion in patients with L-aromatic-amino-acid decarboxylase deficiency; in arterial and portal venous plasma of gastrointestinal surgery patients; and in patients with sympathetic neurocirculatory failure. Meal ingestion increased plasma dopamine sulfate by more than 50-fold; however, prolonged fasting decreased plasma dopamine sulfate only slightly. L-DOPA infusion produced much larger increments in dopamine sulfate than in dopamine; the other drugs were without effect. Patients with L-aromatic amino acid decarboxylase deficiency had decreased dopamine sulfate levels, and patients with sympathetic neurocirculatory failure had normal levels. Decarboxylase-deficient patients undergoing dopamine infusion had a dopamine sulfate/dopamine ratio about 25 times less than that at baseline in volunteers. Surgery patients had large arterial-portal venous increments in plasma concentrations of dopamine sulfate, so that mesenteric dopamine sulfate production accounted for most of urinary dopamine sulfate excretion, a finding consistent with the localization of the dopamine sulfoconjugating enzyme to gastrointestinal tissues. The results indicate that plasma dopamine sulfate derives mainly from sulfoconjugation of dopamine synthesized from L-DOPA in the gastrointestinal tract. Both dietary and endogenous determinants affect plasma dopamine sulfate. The findings suggest an enzymatic gut-blood barrier for detoxifying exogenous dopamine and delimiting autocrine/paracrine effects of endogenous dopamine generated in a "third catecholamine system." (*J Clin Endocrinol Metab* **84:** 2523–2531, 1999)

THE FACT that urinary excretion rates of dopamine and its metabolites exceed those of norepinephrine and its metabolites (1) has posed a paradox in clinical neurochemistry. Norepinephrine is the neurotransmitter of the sympathetic nervous system, and epinephrine is the main effector of the adrenomedullary hormonal system. Although dopamine plays a prominent neurotransmitter role in the central nervous system, central neural release and metabolism of dopamine contribute relatively little to circulating concentrations and urinary excretion rates of dopamine and its metabolites (2–4). If in the periphery dopamine acted only as a transient intermediate in the biosynthesis of norepinephrine and epinephrine, then why would there be such a high rate of production of metabolites of dopamine with respect to those of norepinephrine?

The sources and physiological significance of plasma dopamine sulfate have constituted a related mystery. In humans, at least 95% of dopamine in plasma circulates in the sulfoconjugated form (5). From where does plasma dopamine sulfate originate, and what do plasma dopamine sulfate concentrations mean?

According to one suggestion, conjugated catecholamines reflect and provide a marker of long term sympathetic nervous system "tone" (6), with dopamine sulfate functioning physiologically as a precursor of norepinephrine (7). According to another, dopamine sulfate has a mainly dietary source, because ingestion of a standard meal or of foodstuffs with high monoamine contents (*e.g.* bananas) produces large increases in plasma dopamine sulfate concentrations (8, 9). According to a third, plasma dopamine sulfate derives from intravascular sulfoconjugation, because dopamine infusion produces large increases in plasma concentrations of dopamine sulfate (10), and platelets contain abundant phenolsulfotransferase (11).

We have suggested that, rather than dopamine sulfate levels reflecting integrated sympathoadrenal activity, metabolic breakdown of dietary dopamine, or intravascular effects of platelet phenolsulfotransferase, dopamine sulfate could reflect metabolism of dopamine in a "third catecholamine system" (12). In this system, dopamine, synthesized from decarboxylation of L-DOPA in nonneuronal cells, would act locally as an autocrine/paracrine effector and undergo inactivation by sulfoconjugation before entry into the bloodstream.

In the present study, we evaluated these four hypotheses

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Address all correspondence and requests for reprints to: Dr. David S. Goldstein, Building 10, Room 6N252, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892. E-mail: daveg@box-d.nih.gov.

by measuring plasma dopamine sulfate levels in selected patient groups and in normal volunteers under several experimental conditions, with the following rationale. If plasma dopamine sulfate resulted only from ordinary dietary constituents, then ingestion of a standard meal would increase plasma dopamine sulfate concentrations, and prolonged fasting would decrease plasma dopamine sulfate levels to near zero. We therefore studied normal volunteers after they had ingested a standard meal and after they had fasted overnight and for 4 days, the latter corresponding to more than about 20 plasma half-times of dopamine sulfate (13, 14).

If plasma dopamine sulfate depended on the metabolism of endogenously formed dopamine, as opposed to dopamine in the diet, then patients lacking L-aromatic amino acid decarboxylase would have low plasma dopamine sulfate concentrations. We therefore studied patients with L-aromatic amino acid decarboxylase deficiency, who had fasted overnight, before and during prolonged (≥48 h) iv infusion of dopamine.

The latter manipulation provided a means to estimate the proportion of plasma dopamine sulfate derived from the metabolism of dopamine before and after entry of dopamine into the bloodstream. If circulating dopamine sulfate were derived from circulating dopamine, then during prolonged dopamine infusion in patients with L-aromatic amino acid decarboxylase deficiency, the ratio of plasma dopamine sulfate/dopamine would approach the normal ratio at baseline, which is about 50:1. To estimate the half-time of plasma dopamine sulfate in the absence of production from endogenous dopamine, we measured plasma dopamine sulfate concentrations in the more severely affected L-aromatic amino acid decarboxylase-deficient patient after cessation of prolonged dopamine infusion.

If dopamine sulfate were formed only after cellular uptake of circulating L-DOPA, then the ratio of plasma dopamine sulfate to plasma L-DOPA at baseline would equal the ratio of the increment in plasma dopamine sulfate to the increment in plasma L-DOPA during L-DOPA infusion. On the other hand, if plasma dopamine sulfate were derived from locally generated L-DOPA, such as by actions of tyrosine hydroxylase in cells, then during L-DOPA infusion the increment in plasma dopamine sulfate to the increment in plasma L-DOPA would be less than the ratio of plasma dopamine sulfate to L-DOPA at baseline.

If plasma dopamine sulfate depended on the release of dopamine from sympathetic nerves, then administration of drugs with known stimulatory or inhibitory effects on the release of catecholamines from sympathetic nerves would produce predictable changes in plasma dopamine and dopamine sulfate concentrations, and patients with sympathetic neurocirculatory failure would have decreased plasma dopamine sulfate concentrations. We therefore measured plasma dopamine sulfate in normal volunteers during infusion of the ganglion blocker, trimethaphan, which decreases postganglionic sympathetic nerve traffic, or of the vasodilator, sodium nitroprusside, which produces reflexive sympathetic stimulation. We also measured concentrations of plasma dopamine sulfate in patients with sympathetic neurocirculatory failure associated with loss of sympathetic nerve terminals (peripheral autonomic failure) or with decreased sympathetic nerve traffic (the Shy-Drager syndrome) (15). To evaluate the contribution of the liver to plasma dopamine sulfate, we compared dopamine sulfate concentrations in portal venous and hepatic arterial and venous plasma in fasting patients undergoing gastrointestinal surgery.

If dopamine sulfate were released into the bloodstream substantially by extrahepatic mesenteric organs, where catecholamines are synthesized at least partly nonneuronally (16, 17), then the arterial-portal venous increment in plasma dopamine sulfate levels multiplied by the portal venous plasma flow would constitute a major proportion of the total body production of dopamine sulfate, as indicated by the urinary excretion rate of dopamine sulfate. We therefore estimated the rate of entry of dopamine sulfate into the portal venous plasma in patients undergoing gastrointestinal surgery.

To examine tissue expression of the phenol-sulfating form of phenolsulfotransferase (P-PST) and the monoamine-sulfating form of phenolsulfotransferase (M-PST), responsible for dompamine sulfation, Western blotting was performed on human postmortem tissues from several organs, including liver, kidneys, small intestine, and duodenum.

Subjects and Methods

Subjects

The subjects included 22 healthy volunteers, 2 patients with L-aromatic amino acid decarboxylase deficiency, 6 patients with peripheral autonomic failure, 9 patients with Shy-Drager syndrome, and 8 patients with nonmetastatic gastrointestinal carcinoma. Each subject (or parent of a minor subject) gave informed written consent before participation in clinical protocols, which were approved by the Intramural Research Boards of the National Heart, Lung, and Blood Institute, the National Institute of Neurological Disorders and Stroke, the Office of Human Subjects Research at the National Institutes of Health, or the St. Luke's Hospital. Normal subjects were healthy volunteers who had normal screening medical history, physical examination, electrocardiogram, and blood and urine tests (complete blood count, clotting parameters, serum electrolytes, hepatic and renal function tests, and urinalysis).

Dietary manipulations

In six subjects (four men and two women; mean age, 26 yr; age range, 23–30 yr), plasma concentrations of dopamine sulfate and other catechols were measured after an overnight fast, after 4 days of fasting, and before and after the ingestion of a standard meal. Blood samples were obtained through an indwelling radial arterial catheter at 30, 20, 10, and 0 min before and at 60, 80, 100, and 120 min after ingestion of the standard morning meal (50% carbohydrate, 30% fat, and 20% protein). Each subject ate *ad libitum* until admission to the Clinical Research Center at 1700 h, ingested a standard meal (50% carbohydrate, 30% fat, and 20% protein) at 1730 h, had a fat-free snack at 2300 h, and thereafter took nothing by mouth except ice water or decaffeinated, calorie-free beverages until the 24-h collection ended at 0600 h the next morning. At 1000 h that morning, the subjects consumed another standard meal (50% carbohydrate, 30% fat, and 20% protein).

In four of these subjects, urine was collected for 24 h, beginning at 0600 h. The subjects then fasted for a total of 4 days, with repetition of the 24-h urine collection ending at 0600 h on the last day.

L-DOPA infusion

In six subjects (four men and two women; mean age, 39 yr; age range, 24–51 yr) studied at the NIH Clinical Center, antecubital venous catheters were inserted percutaneously in each arm. L-DOPA at a dose of 0.33 μg/min·kg was infused iv for 5–6 h, with blood sampled from the contralateral iv catheter (18).

Trimethaphan infusion

In eight men (mean age, 31 yr; age range, 23–40 yr) studied at the NIH Clinical Center, a brachial arterial catheter and peripheral venous iv catheters were placed. Trimethaphan (500 mg in 250 or 500 cc) was infused iv via a controlled infusion pump for at least 30 min. The infusion rate (starting rate, 15 or 30 cc/h) was increased until it produced symptoms and signs of ganglion blockade, such as dry mouth, tachycardia, and decreased pulse pressure (19).

Nitroprusside infusion

In two 28-yr-old men studied at the NIH Clinical Center, a brachial arterial catheter and peripheral venous iv catheter were placed. Sodium nitroprusside (50 mg in 500 cc) was infused iv via a controlled infusion pump for at least 20 min. The infusion rate (starting rate, 0.5 μg/kg·min) was increased until a rate that produced a clear, persistent increase in pulse rate and about a 5-mm Hg fall in mean arterial pressure (19).

Patients with L-aromatic amino acid decarboxylase deficiency

Plasma samples were assayed from two pediatric patients with L-aromatic amino acid decarboxylase deficiency studied at the Children's Hospital. Both patients had neurochemical findings characteristic of this disorder, including high plasma levels of DOPA and low concentrations of dopamine and its deaminated metabolite dihydroxyphenylacetic acid.

As part of an experimental therapeutics trial, both patients underwent prolonged (≥48 h) iv infusion of dopamine. Blood samples were obtained before and during the infusion. In one of the patients, who had virtually undetectable L-aromatic amino acid decarboxylase activity, blood was also sampled at various time points after cessation of the dopamine infusion.

Patients with sympathetic neurocirculatory failure

Arterial plasma samples were assayed from six men with peripheral autonomic failure (mean age, 70 yr; age range, 64–76 yr) and nine patients with the Shy-Drager syndrome (six men and three women; mean age, 59 yr; age range, 47–78 yr) studied at the NIH Clinical Center. Peripheral autonomic failure was diagnosed from persistent orthostatic hypotension, abnormal blood pressure responses during and after performance of the Valsalva maneuver, absent cardiac norepinephrine spillover, and absent cardiac 6-[^{18}F]fluorodopamine-derived myocardial radioactivity (15) without signs of central neurodegeneration. Shy-Drager syndrome was diagnosed from persistent orthostatic hypotension, abnormal blood pressure responses during and after performance of the Valsalva maneuver, signs of central neural degeneration, normal cardiac norepinephrine spillover, and normal or increased cardiac 6-[^{18}F]fluorodopamine-derived myocardial radioactivity (15).

Patients undergoing gastrointestinal surgery

Portal venous and arterial blood samples were obtained, and hepatic arterial and portal venous blood flows were measured under fasting conditions in eight adult patients at the Sahlgrenska University Hospital (Göteborg, Sweden) during elective upper abdominal surgery for nonmetastatic gastric or pancreatic carcinoma (20).

Assays

Plasma concentrations of free (unconjugated) catechols were assayed by liquid chromatography with electrochemical detection after batch alumina extraction (21, 22). Concentrations of sulfoconjugated catechols were assayed similarly after incubating aliquots of the alumina supernates with sulfatase (50μL of a water-diluted solution containing 95 mU of enzyme Type VI, Sigma Chemical Co., St. Louis, MO) at 37 C for 20 min (23). Intra-assay coefficients of variation were 4.8% for dihydroxyphenylglycol, 1.9% for norepinephrine, 1.9% for L-DOPA, 3.0% for epinephrine, 8.1% for dopamine, and 3.9% for dihydroxyphenylacetic acid. Interassay coefficients of variation were 8.6% for dihydroxyphenylglycol, 6.5% for norepinephrine, 7.3% for L-DOPA, 10.3% for epinephrine, 10.6% for dopamine, and 14.5% for dihydroxyphenylacetic acid.

Western blots

Human postmortem tissue harvested at the NIH Clinical Center within 18 h of death was assayed for contents of M-PST and P-PST. An antibody to human M-PST/P-PST, raised in sheep against purified recombinant M-PST and cross-reacting with P-PST (24), was kindly provided by Dr. Michael Coughtrie (University of Dundee, Dundee, Scotland). Tissue samples (25 mg) from liver, kidney, small intestine, lung, pancreas, duodenum, heart, and spleen were homogenized in 250 mL of a triple-detergent lysis buffer (50 mmol/L Tris HCl at pH 8, containing 1 mmol/L EDTA, 150 mmol/L NaCl, 0.02% sodium azide, 0.1% SDS, 1% Nonidet P-40, 0.5% sodium deoxycholate, and a cocktail of protease inhibitors; Sigma Chemical Co.). After centrifugation at 12,000 *g* for 3 min, aliquots of the clear supernatant fluid, each containing 15 μg protein, were mixed with a loading buffer (50 mmol/L Tris HCl buffer at pH 6.8, containing 2% SDS, 2.5% glycerol, and 10% mercaptoethanol), immediately heated at 100 C for 5 min, and then chilled on ice. The denatured proteins were subjected to electrophoresis on a 10% SDS-Tris-glycine gel and transferred to Immobilon-P Transfer membranes (Millipore Corp., Bedford, MA) using a Bio-Rad transblot apparatus (Bio-Rad Laboratories, Inc., Hercules, CA). After transfer, the membranes were blocked for 90 min in 5% FCS in Tris-buffered saline (50 mmol/L Tris HCl at pH 7.4, containing 0.9% NaCl and 0.05% Tween-20). The membranes were then treated with antihuman M-PST/P-PST primary antibody at a 1:1000 dilution for 90 min, washed three times for 10 min each time with Tris-buffered saline, and incubated for 45 min with secondary antibody (Anti-Sheep IgG, Pierce Chemical Co., Rockford, IL) conjugated to horseradish peroxidase at a 1:40,000 dilution. Detection of the two bands corresponding to P-PST (32 kDa) and M-PST (34 kDa) was achieved by the enhanced chemiluminescence method (New England Nuclear, Boston, MA).

Data analysis and statistics

Mean concentrations were expressed ± SEM. For single comparisons within subjects, two-tailed, dependent means *t* tests were used. For multiple comparisons, ANOVAs were conducted on logarithm-transformed data. $P < 0.05$ defined statistical significance.

Results

Dietary manipulations

Ingestion of a standard meal produced more than a 50-fold increase in the mean plasma level of dopamine sulfate, with proportionately much smaller, but nevertheless highly significant ($P < 0.001$), increases in plasma concentrations of dopamine, L-DOPA, and dihydroxyphenylacetic acid in all subjects (Fig. 1). Meal ingestion also produced significant ($P < 0.001$) increases in plasma concentrations of other sulfate-conjugated catechols, including L-DOPA sulfate, epinephrine sulfate, and norepinephrine sulfate (Table 1); however, relative increases in these concentrations were much less than the increases produced in dopamine sulfate.

Compared with overnight fasting, fasting for 4 days was associated with nonsignificant decreases in plasma concentrations of L-DOPA and dihydroxyphenylacetic acid and a significant decrease in plasma concentrations of dopamine sulfate ($P = 0.01$; Fig. 2). Because of low subject numbers and interindividual variability, changes in urinary excretion rates of these compounds did not attain statistical significance.

Drug infusions

During infusion of L-DOPA, concentrations of plasma L-DOPA increased to about 10 times the baseline levels. Con-

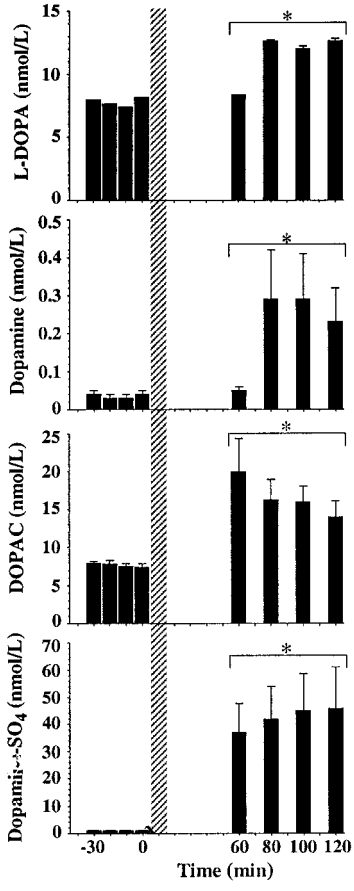

FIG. 1. Effects of ingestion of a standard meal on mean (±SEM) plasma concentrations of L-DOPA, dopamine (DA), dihydroxyphenylacetic acid (DOPAC), and DA-sulfate (DA-S) in healthy volunteers. *Cross-hatching* indicates the approximate time of meal ingestion, commencing at 0 min. *, Significant difference ($P < 0.001$) from baseline by ANOVA.

TABLE 1. Plasma concentrations of L-DOPA sulfate, epinephrine sulfate and norepinephrine sulfate before and after mean ingestion

	DOPA Sulfate nmol/L	Epinephrine Sulfate mol/L	Norepinephrine Sulfate nmol/L
Before meal ingestion (min)			
−30	2.1 ± 0.2	0.34 ± 0.08	3.2 ± 0.6
−20	2.0 ± 0.2	0.37 ± 0.08	3.2 ± 0.5
−10	1.9 ± 0.2	0.36 ± 0.07	3.2 ± 0.5
0	2.1 ± 0.3	0.36 ± 0.05	3.1 ± 0.5
After meal ingestion (min)			
60	3.2 ± 0.4	0.89 ± 0.21	4.4 ± 0.8
80	3.3 ± 0.7	0.95 ± 0.21	4.7 ± 0.6
100	3.2 ± 0.8	0.90 ± 0.19	5.6 ± 0.8
120	3.7 ± 0.6	0.93 ± 0.16	4.5 ± 0.7

centrations of dopamine sulfate increased by 3.4-fold, and dopamine increased by 2-fold (Fig. 3). The absolute increment in plasma dopamine sulfate (113 nmol/L) was similar to that in L-DOPA (96 nmol/L) and 56 times that in plasma dopamine (2 nmol/L).

Despite clear decreases in plasma norepinephrine levels in trimethaphan-treated subjects and increases in nitroprusside-treated subjects, neither trimethaphan nor nitroprusside affected plasma concentrations of dopamine sulfate (Fig. 4).

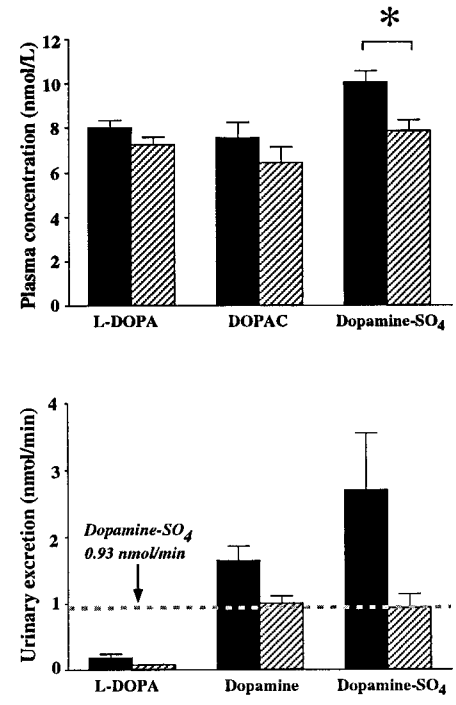

FIG. 2. Effects of fasting overnight (*black*) or for 4 days (*cross-hatched*) on mean (±SEM) plasma concentrations (*top*) of L-DOPA, dihydroxyphenylacetic acid (DOPAC), and dopamine sulfate (Dopamine-SO_4) and urinary excretion rates (*bottom*) of L-DOPA, dopamine, and dopamine sulfate (Dopamine-SO_4) in healthy volunteers. *, Significant difference ($P < 0.01$) from fasting overnight by ANOVA.

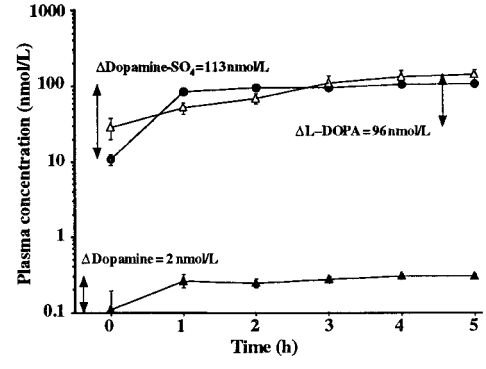

FIG. 3. Effects of iv infusion of L-DOPA on mean (±SEM) plasma levels of L-DOPA (*black circles*), dopamine (*black triangles*), and dopamine sulfate (*open triangles*) in healthy volunteers. Note: logarithmic scale of y-axis.

L-Aromatic amino acid decarboxylase-deficient patients

Both L-aromatic amino acid decarboxylase-deficient patients had decreased plasma concentrations of dopamine sulfate (Fig. 5). The patient with the more severe deficiency of L-aromatic amino acid decarboxylase, as indicated neurochemically by little or no detectable dopamine or dihydroxyphenylacetic acid in plasma, had a plasma dopamine sulfate level that was less than 1% of normal.

During prolonged infusion of dopamine, both patients with L-aromatic amino acid decarboxylase deficiency had large increases in plasma concentrations of dopamine and dopamine sulfate (Fig. 5).

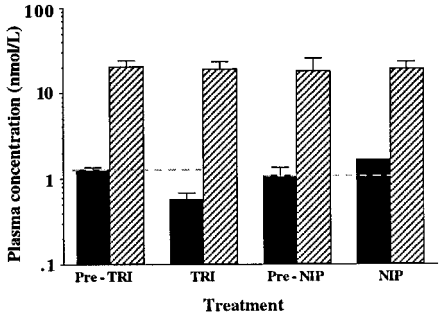

FIG. 4. Effects of iv infusion of trimethaphan (TRI) or sodium nitroprusside (NIP) on mean (±SEM) plasma concentrations of norepinephrine (*black bars*) and dopamine sulfate (*cross-hatched bars*) in healthy volunteers. Note: logarithmic scale of y-axis.

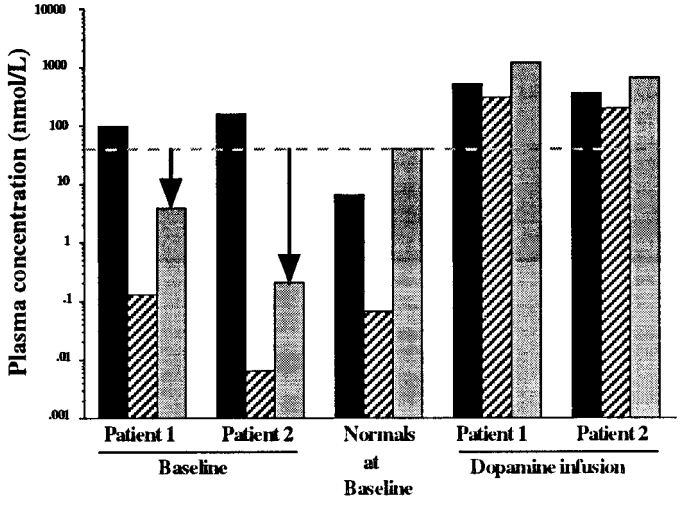

FIG. 5. Plasma concentrations of L-DOPA (*black bars*), dopamine (*cross-hatched bars*), and dopamine sulfate (*gray bars*) in patients with deficiency of L-aromatic-amino-acid decarboxylase (DDC) at baseline and during prolonged infusion of dopamine and in normal control subjects at baseline. *Vertical arrows* indicate the decreased baseline plasma concentrations of dopamine sulfate in patients compared with normal control values. Note: logarithmic scale of y-axis.

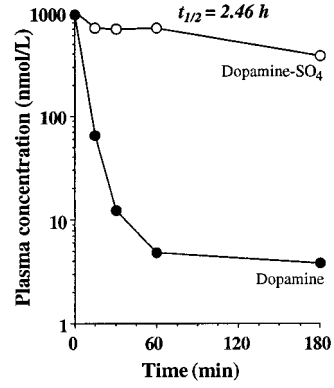

FIG. 6. Plasma concentrations of dopamine (*filled objects*) and dopamine sulfate (*open objects*) in a patient with deficiency of L-aromatic-amino-acid decarboxylase. The patient had undergone iv infusion of dopamine continuously for 4 days, with blood samples taken at various time points after discontinuation of the infusion. Note: logarithmic scale of y-axis.

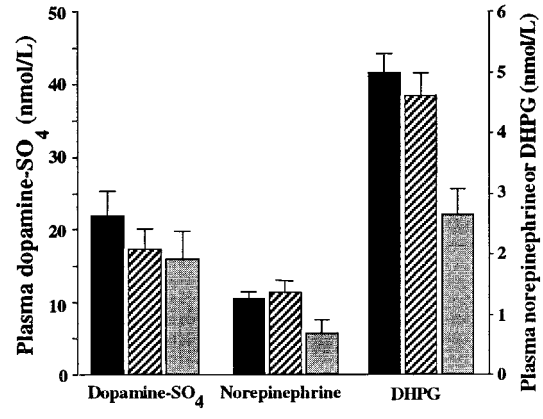

FIG. 7. Mean (±SEM) plasma concentrations of dopamine sulfate (Dopamine-SO_4), norepinephrine, and dihydroxyphenylglycol (DHPG) in patients with sympathetic neurocirculatory failure due to peripheral autonomic failure (*gray bars*) or the Shy-Drager syndrome (*cross-hatched bars*) and in normal volunteers (*black bars*).

In the patient with more severe L-aromatic amino acid decarboxylase deficiency, after cessation of dopamine infusion plasma dopamine sulfate levels declined with a half-time of 2.46 h (Fig. 6). In a patient with Shy-Drager syndrome who received dopamine iv for 3 min, plasma concentrations of dopamine sulfate declined subsequently with a half-time of 3.32 h.

Peripheral autonomic failure patients

Patients with peripheral autonomic failure had normal plasma concentrations of dopamine sulfate and DOPA, with significantly decreased plasma concentrations of norepinephrine and dihydroxyphenylglycol, compared with values in healthy volunteers (Fig. 7). Patients with Shy-Drager syndrome had normal plasma concentrations of all of these catechols.

Gastrointestinal surgery patients

Fasted patients undergoing gastrointestinal surgery had consistent arterial-portal venous increments in plasma concentrations of L-DOPA, dopamine, and dopamine sulfate (Table 2). Portal venous concentrations of L-DOPA and dopamine exceeded the corresponding hepatic venous concentrations, whereas the mean hepatic-portal venous difference in plasma dopamine sulfate was not statistically significant. From the mean arterial-portal venous increment in the plasma dopamine sulfate concentrations and the mean portal venous flow rate (486 ± 17 mL/min), mesenteric dopamine sulfate spillover was estimated to be 1.18 ± 0.31 nmol/min, accounting for most of renal extraction and urinary excretion of dopamine sulfate.

Western blots

Both M-PST and P-PST were detected in small intestine, duodenum, pancreas,and lung (Fig. 8). Small intestine showed the greatest expression of both isoenzymes. In contrast, only P-PST was detected in liver, where it was present in considerable quantity. Both P-PST and M-PST were undectable in heart and spleen, and only trace amounts of P-PST were detected in kidney.

TABLE 2. Arterial and portal and hepatic venous plasma concentrations of catechols (means ± SEM) in patients undergoing gastrointestinal surgery, and urinary excretion of catechols in normal volunteers after overnight or four days of fasting

Catechol	Arterial	Portal vein	Hepatic vein
L-DOPA (nmol/L)	7.40 ± 0.71	8.76 ± 0.84[a]	7.28 ± 0.56
DA (nmol/L)	0.32 ± 0.06	0.93 ± 0.17[a]	0.23 ± 0.03
DA-S (nmol/L)	13.39 ± 2.1715.91 ± 2.47[a]		15.47 ± 2.64
Portal plasma flow (mL/min)		486 ± 17	
Plasma L-DOPA delivery (nmoles/min)		3.60 ± 0.35	
Mesenteric Organ dopamine sulfate production rate (nmol/min)		1.18 ± 0.31	
Portal DA-S production rate (nmoles/min)		1.18 ± 0.31	
Urinary L-DOPA excretion rate (nmoles/min)			
Overnight fasting		0.18 ± 0.06	
After 4 days of fasting		0.07 ± 0.10	
Urinary DA excretion rate (nmoles/min)			
Overnight fasting		1.64 ± 0.22	
After 4 days of fasting		1.00 ± 0.11	
Urinary DA-S excretion rate (nmoles/min)			
Overnight fasting		2.70 ± 0.86	
After 4 days of fasting		0.93 ± 0.21	

[a] Significant difference from arterial, $P < 0.01$.

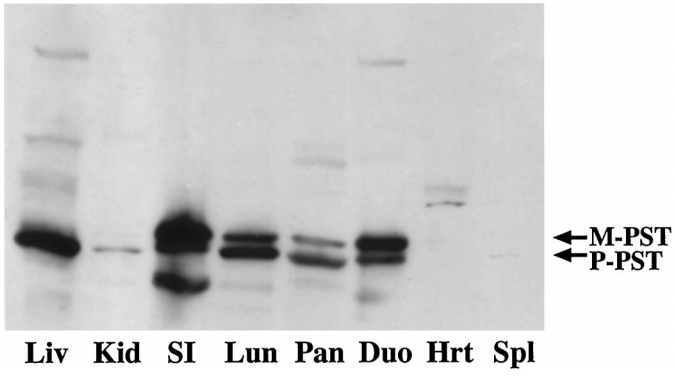

FIG. 8. Western blot analysis of M-PST and P-PST in human liver (Liv), kidney (Kid), small intestine (SI), lung (Lun), pancreas (Pan), duodenum (Duo), heart (Hrt), and spleen (Spl). Positions of M-PST and P-PST are shown on the *right*. The amount of total protein was 15 μg for each sample.

Discussion

The present results indicate that plasma dopamine sulfate originates from both dietary intake and synthesis and metabolism of endogenous dopamine, especially in the gastrointestinal tract. The former may reflect a gut-blood barrier to detoxify catecholamines derived from exogenous sources and the latter a third catecholamine system, in which sulfoconjugation delimits the actions of dopamine as an autocrine-paracrine factor.

Ingestion of a standard meal increased plasma concentrations of dopamine sulfate by more than 50-fold, with proportionately smaller increases in plasma concentrations of L-DOPA and dopamine. The marked stimulatory effect of meal ingestion on concentrations of plasma dopamine sulfate confirms previous reports (8, 25).

Because of the relatively low amounts of L-DOPA in food (8), the increased plasma L-DOPA concentrations after meal ingestion in the present study did not result from L-DOPA itself as a dietary constituent, and probably reflected increased production of endogenous L-DOPA. This could occur by metabolic breakdown of dietary protein to generate tyrosine and by the actions of tyrosinase, which is abundant in cereal grain (26), or from increased tyrosine hydroxylation in gastrointestinal nerves or nonneuronal cells (16, 17). Other literature has disagreed about the effects of meal ingestion on plasma L-DOPA (8, 25).

The much larger meal-related increases in plasma dopamine sulfate concentrations could have reflected the ingestion of dopamine (10) and dopamine sulfate (8), increased L-DOPA production in the gastrointestinal lumen or cells, or increased release and metabolism of stored endogenous dopamine (16, 27). The present results cannot distinguish among these possibilities.

The results also point to substantial nondietary, *i.e.* endogenous sources of plasma dopamine sulfate. If plasma dopamine sulfate only reflected dietary intake of foodstuffs containing dopamine or dopamine sulfate, then patients with L-aromatic amino acid decarboxylase deficiency would have approximately normal plasma dopamine sulfate levels. Instead, both of these patients had low plasma concentrations of dopamine sulfate, and in the more severely affected patient, in whom L-aromatic amino acid decarboxylase activity was virtually absent, the plasma dopamine sulfate level was less than 1% of normal. The low plasma dopamine sulfate levels in the L-aromatic amino acid decarboxylase-deficient patients did not result from an associated decrease in M-PST activity, because during infusion of dopamine, both patients had above normal plasma dopamine sulfate concentrations. These findings are consistent with the hypothesis that plasma dopamine sulfate derives at least partly from endogenously produced dopamine.

The results in fasting normal volunteers provide support for this view. The plasma half-time of dopamine sulfate probably is less than 6 h (10). In the present study, after cessation of long-term dopamine infusion in the patient with virtually absent L-aromatic amino acid decarboxylase, the plasma half-time of dopamine sulfate was 2.5 h. If plasma dopamine sulfate derived solely from dietary constituents, then after several days of fasting, given the plasma half-time of dopamine sulfate, healthy humans would have negligibly low

plasma dopamine sulfate levels. Instead, in the present study, plasma dopamine sulfate concentrations averaged only slightly less after 4 days of fasting than after an overnight fast. This finding not only confirms that plasma dopamine sulfate has substantial endogenous sources but also indicates that in humans who have fasted overnight, plasma dopamine sulfate levels probably mainly reflect metabolism of dopamine produced from endogenous L-DOPA.

As dopamine infusion into L-aromatic amino acid decarboxylase-deficient patients markedly increased plasma dopamine sulfate levels, plasma dopamine sulfate derives at least partly from circulating dopamine (10); however, the relatively small ratio of dopamine sulfate/dopamine (~4:1) in the L-aromatic amino acid decarboxylase-deficient patients, compared with the much higher ratio in healthy humans (>50:1 in the present study), indicates that at least 90% of the dopamine sulfate conjugation normally takes place before dopamine enters the bloodstream, and very little dopamine sulfate is formed from circulating dopamine.

During L-DOPA infusion, increased dopamine sulfate formation depends on the intracellular synthesis of dopamine. The reasonable agreement between the ratio of the increment in dopamine sulfate (113 nmol/L) to dopamine (0.2 nmol/L) during L-DOPA infusion, 565 (113:0.2), and the ratio of baseline levels of dopamine sulfate to dopamine, 280 (28/0), is consistent with dependence of dopamine sulfate formation on the intracellular synthesis of dopamine from L-DOPA. Analogously, if sources other than circulating L-DOPA generated intracellular dopamine, at baseline the ratio of plasma dopamine sulfate to plasma L-DOPA would exceed the ratio of increments during L-DOPA infusion. In the present study, the ratio of plasma dopamine sulfate to plasma L-DOPA at baseline, 2.3 (28:12), was about twice the ratio of the increment in dopamine sulfate to the increment in L-DOPA, 1.2 (113:96). Thus, about half of the plasma dopamine sulfate appears to derive from intracellular synthesis of dopamine after uptake of circulating L-DOPA. The remaining half probably derives from intracellular synthesis of L-DOPA.

The present results indicate that plasma dopamine sulfate does not derive to any important extent from dopamine in sympathetic nerves. First, patients with peripheral autonomic failure, who have loss of sympathetic terminals, and patients with Shy-Drager syndrome, who have decreased or absent sympathetic nerve traffic (15), had normal plasma concentrations of dopamine sulfate, confirming a previous report in less well characterized groups (28). Second, infusion of the ganglion blocker trimethaphan, at a dose that virtually abolishes directly recorded postganglionic sympathetic nerve traffic (29) and elicits substantial decreases in plasma norepinephrine levels, did not affect plasma dopamine sulfate concentrations. Third, infusion of nitroprusside at a dose that reflexively increases sympathetic nerve traffic and plasma norepinephrine concentrations (30) did not affect plasma dopamine sulfate levels. These findings agree with previous reports about small or absent responses of dopamine sulfate concentrations during acute exposure to various stressors (31, 32).

Most organs produce little dopamine sulfate, as judged from arterio-venous increments in plasma concentrations of the compound (33). An exception is the mesenteric organs (17). In the present study, patients undergoing gastrointestinal surgery (preparation for which always entails proscription of all oral intake) had consistent arterial-portal venous increments in dopamine sulfate concentrations. The estimated rate of mesenteric dopamine sulfate spillover (1.18 ± 0.31 nmol/min) was similar to the mean rate of urinary excretion of dopamine sulfate after 4 days of fasting in normal volunteers (0.93 nmol/min) and about 44% of the mean rate after an overnight fast. Previously published values for urinary excretion of dopamine sulfate in nonfasting subjects have averaged about 1.9 nmol/min (34). Thus, most dopamine sulfate production in the body as a whole derives from conjugation of dopamine in the gastrointestinal tract. This is also consistent with Western blot data in this and another study (24), showing that considerable amounts of M-PST, the phenolsulfotransferase isoenzyme responsible for dopamine sulfation (35), are localized to the tissues of the gastrointestinal tract.

As noted above from the L-DOPA infusion data, about half of the dompamine sulfate is produced from uptake of circulating L-DOPA, so that the remaining half (~3.6 nmol/min) would reflect L-DOPA synthesized within the gastrointestinal tract. Assayed concentrations of tyrosine hydroxylase activity (under saturating conditions) in humans average about 0.070 nmol/min·g in stomach tissue and about 0.040 nmol/min·g in duodenal tissue (17). Considering that the mass of the mesenteric organs amounts to several kilograms, the organs appear to contain a sufficient capacity for tyrosine hydroxylation to account for the estimated rate of local L-DOPA synthesis. Moreover, the present results demonstrate the expression of M-PST in duodenum and small intestine.

The absence of an arterio-venous increment in dopamine sulfate between the portal and hepatic veins indicates that the liver is not an important source of plasma dopamine sulfate. Consistent with this conclusion and in agreement with another study (24), postmortem tissue from human liver expressed the phenolsulfotransferase isoenzyme, P-PST, but not the isoenzyme, M-PST, responsible for dopamine sulfation. Lack of importance of the liver for sulfate conjugation of dopamine is also consistent with the findings of Tyce and colleagues (36), who found normal plasma dopamine sulfate concentrations in patients about to undergo liver transplants for severe hepatic failure.

Plasma L-DOPA appears to have both dietary and nondietary (37) sources. Regional entry of L-DOPA into plasma in organs such as the heart and skeletal muscle depends on tyrosine hydroxylation in local sympathetic terminals (38–43); however, the present findings clearly show that dietary factors also influence plasma L-DOPA concentrations. Thus, the notion that plasma levels of L-DOPA reflect total body tyrosine hydroxylase activity (38) may be valid only in fasting individuals.

The findings have several potential physiological and pharmacological ramifications. M-PST in mesenteric organs could contribute (along with catechol-*O*-methyltransferase and monoamine oxidase) to a gut-blood barrier, effectively detoxifying ingested catecholamines before they could enter the bloodstream. Thus, oral ingestion of bananas produces little if any increase in circulating concentrations of uncon-

jugated catecholamines but produces large increases in concentrations of dopamine sulfate (44, 45); after oral ingestion of a catecholamine, a major proportion is excreted in the urine in the sulfate-conjugated form (46).

Subjects with polymorphisms of the gene encoding M-PST (47–49), resulting in decreased sulfoconjugation of dopamine, might be susceptible to emetic, cardiovascular, or other side-effects of L-DOPA or dopamine. In particular, one may hypothesize that hypertensive paroxysms associated with high plasma levels of unconjugated and low levels of conjugated catecholamines in patients with pseudopheochromocytoma (50) may reflect low gastrointestinal M-PST activity, rendering the patients susceptible to toxic effects of ingesting foodstuffs that have high monoamine contents (9).

Drugs that inhibit sulfoconjugation of dopamine would be expected to augment actions of L-DOPA, as phenylsulfotransferase inhibition would increase the bioavailability of L-DOPA and interfere with sulfoconjugation of L-DOPA itself. The extent to which phenolsulfotransferase contributes to bioavailability of L-DOPA or to the blood-brain barrier for circulating L-DOPA is unknown.

M-PST could also function to delimit the actions of dopamine as an autocrine-paracrine factor in the gastrointestinal tract (51). Mesenteric organs express dopamine receptors (27), and administration of drugs that alter occupation of dopamine receptors affects bicarbonate secretion and sodium-hydrogen ion exchange in the gastrointestinal tract (52) in a manner consistent with the gastroprotective actions of dopamine (53, 54). M-PST in gastrointestinal walls would prevent locally generated dopamine from entering the bloodstream and exerting hormonal effects.

Patients with autonomic failure in the setting of Parkinson's disease can have cardiac sympathetic denervation (15), consistent with the view that, in at least some patients, the disease results from a diffuse neurodegenerative process (55). One may speculate that if a subgroup of patients with Parkinson's disease had not merely nigrostriatal but also diffuse deficiency of dopamine synthesis (56, 57), then the fasting, untreated patients would have decreased plasma levels of dopamine sulfate. Deficient functioning of a nonneuronal, gastroprotective, dopaminergic third catecholamine system could then help to explain the poorly understood high frequency of gastrointestinal ulceration in Parkinsonian patients (54, 58).

The diagram in Fig. 9 summarizes our current view about the sources and physiological significance of plasma dopamine sulfate. First, meal ingestion markedly increases plasma dopamine sulfate concentrations. 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 applies to plasma 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 the production of L-DOPA outside the gastrointestinal tract. Some of this L-DOPA enters the bloodstream, and uptake and decarboxylation of circulating L-DOPA provide a means to generate dopamine sulfate continuously from endogenous dopamine. Third, dopamine sulfate derives to a relatively small extent from circulating dopamine.

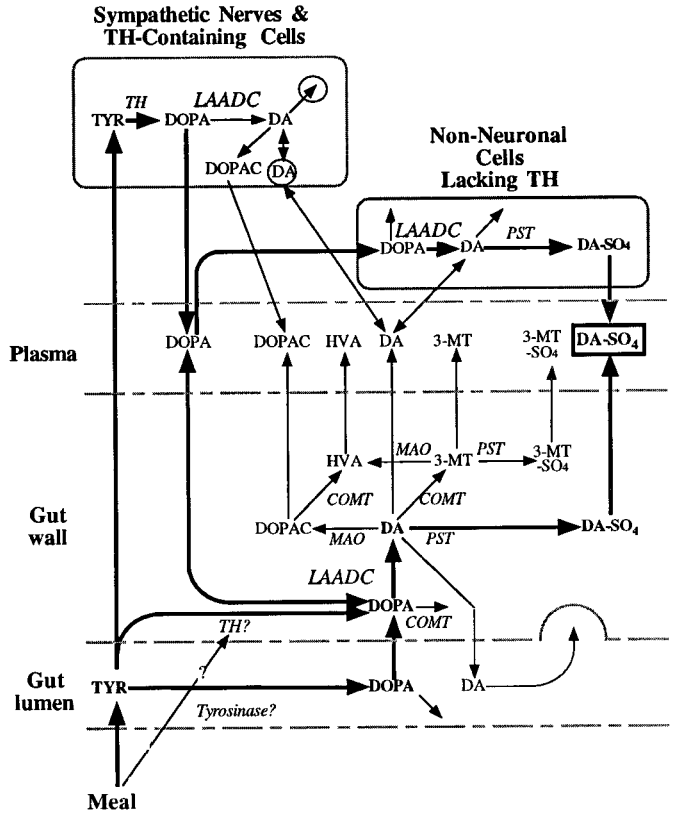

FIG. 9. Sources of plasma dopamine sulfate. *Thick lines* reflect proposed main routes of dopamine sulfate production in humans.

By this reasoning, in fasting subjects, the rate of entry of dopamine sulfate into plasma should indicate the rate of dopamine production in the gastrointestinal tract. The extent to which dopamine formation in mesenteric organs depends on tyrosine hydroxylation in sympathetic nerves or in nonneuronal cells is currently under study.

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