Catechol-O-Methyltransferase and Blood Pressure in Humans

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Background—Whether catechol-O-methyltransferase (COMT), the enzyme that metabolizes extraneuronal norepinephrine, contributes to blood pressure regulation in humans is unknown.

Methods and Results—We studied incremental doses of the COMT inhibitor entacapone, the sympathetic stimulant yohimbine, and placebo in 7 patients with multiple system atrophy (Shy Drager syndrome). We selected these unique subjects because norepinephrine exerts an exaggerated increase in blood pressure in these patients. Autonomic regulation was characterized with intravenous phenylephrine, nitroprusside, and trimethaphan. Patients were extremely hypersensitive to phenylephrine and nitroprusside. Trimethaphan elicited a profound depressor response. Phenylephrine sensitivity increased only slightly during ganglionic blockade. Entacapone increased systolic blood pressure dose-dependently; however, the pressor response to yohimbine was \( \approx 3.5 \) times greater than the maximal response to entacapone.

Conclusions—COMT inhibition elicits a moderate, dose-dependent pressor response in the setting of severely impaired baroreflex buffering. Patients with multiple system atrophy allow for the characterization of subtle manipulations of norepinephrine turnover and blood pressure regulation in small numbers of subjects. (Circulation. 2002;106:460-465.)

Key Words: baroreflex ■ nervous system, autonomic ■ multiple system atrophy ■ Shy-Drager syndrome ■ receptors, adrenergic

Norepinephrine’s action on adrenergic receptors is strongly influenced by norepinephrine clearance. Released norepinephrine is largely reclaimed by postganglionic adrenergic neurons and repackaged or metabolized. The intraneuronal metabolism is mainly achieved by monoamine oxidase.1,2 A smaller percentage escapes the synapse and may enter the systemic circulation. This proportion of norepinephrine is taken up by extraneuronal tissue and is mainly metabolized by catechol-O-methyltransferase (COMT).3 COMT, a ubiquitous enzyme, is highly expressed in the liver and kidney. COMT gene polymorphisms are associated with a thermostable high-activity COMT or a thermolabile low-activity COMT.4,5 COMT’s effects on blood pressure are poorly understood. In animals, COMT inhibition exerts a pressor effect that is not observed in control subjects and in Parkinson patients with intact autonomic regulation.6-9 We hypothesized that patients with multiple system atrophy would be particularly suited to study the effect of COMT on blood pressure. Multiple system atrophy is a neurodegenerative disorder associated with disruption of central nervous cardiovascular control centers.10 Peripheral sympathetic neurons are, at least in part, functional.11,12 However, baroreflex control of sympathetic efferents is impaired. Therefore, pharmacologically induced changes in peripheral norepinephrine metabolism or vascular tone elicit a much larger blood pressure effect than in healthy subjects.13,14 We used the selective COMT inhibitor entacapone15 in patients with multiple system atrophy to test the hypothesis that COMT contributes to blood pressure regulation.

Methods

Study Subjects
We recruited 7 patients with multiple system atrophy (3 women and 4 men aged 54±1.5 years) from the movement disorder clinic.16 Five patients with Parkinson’s disease (1 woman and 4 men aged 63±1.3 years) but without autonomic dysfunction served as a control group. Written, informed consent was obtained after local institutional review board approval.

Protocol
Vasoactive medications were discontinued >5 half-lives before testing. Patients were given a diet free of interfering substances.
Studies were conducted at least 2.5 hours after a meal. Patients did not drink 1.5 hours before testing. On the first study day, blood pressure and heart rate were measured after an overnight supine rest and after standing 3 minutes. The following day, we conducted a series of cardiovascular autonomic reflex tests and pharmacological testing with trimethaphan, phenylephrine, and nitroprusside. On subsequent days, we tested the effect of orally administered placebo and the COMT inhibitor entacapone in incremental doses (Comtess, Orion). Four patients were also tested with 5 mg of yohimbine (Spiegel, Germany). In the patients with Parkinson’s disease, we tested the effect of placebo and 400 mg of entacapone.

**Autonomic Reflex Testing**

Sinus arrhythmia was assessed during controlled breathing (5-s inhalation and 5-s exhalation for 90 s). The sinus arrhythmia ratio was calculated as the ratio of the longest to the shortest RR interval during this 90-s period. Patients then performed a Valsalva maneuver and heart rate responses to isometric handgrip (30% maximum contraction for 1 minute) and cold pressor testing were also determined.

**Invasive Pharmacological Testing**

Heart rate was determined with continuous ECG and blood pressure by an indwelling catheter in the radial artery. Bolus phenylephrine and nitroprusside doses were administered via a heparin lock in an antecubital vein, and nitroprusside doses were administered via a heparin lock in an indwelling catheter in the radial artery. Bolus phenylephrine and nitroprusside were evaluated before ganglionic blockade. Thereafter, N1-cholinergic receptors were blocked by continuous trimethaphan infusion (Cambridge Pharmaceuticals) starting at 0.5 mg/min and increasing at 6-min intervals until one of the following end points was reached: presyncopal symptoms, no further decrease in blood pressure with increased infusion rates, or a reduction of systolic blood pressure to <75 mm Hg. The data were analog-digital converted (ECG, 1 kHz; blood pressure, 100 Hz). The peak detection (R-peak, systolic and diastolic blood pressure) was realized offline using PV-wave software (VisualNumerics).

**Baroreflex-Sequence Technique**

The spontaneous baroreflex slope was calculated as the slope of the linear regression lines between systolic blood pressure and the subsequent R-R intervals (within the same or the next heartbeat) using the sequence technique. Sequences with at least 3 intervals, 0.5-mm Hg blood pressure changes, and 5-ms R-R interval changes were analyzed only if the correlation coefficients were >0.85. The baroreflex slope was calculated as the mean value of the significant slopes obtained.

**Seated Medication Trials**

Seated medication trials were conducted as described previously. Briefly, brachial blood pressure and heart rate were automatically recorded every 5 minutes (Dinamap, Critikon). The cuff was kept at heart level throughout. After 30 minutes of baseline recording, we administered a placebo, 100, 200, or 400 mg of entacapone, or 5 mg of yohimbine by mouth with 50 mL of water. Seated blood pressure and heart rate were recorded every 5 minutes for the next 120 minutes. In 4 patients, we determined the effect of placebo and entacapone on venous plasma catecholamines.

**Statistics**

If not otherwise indicated, data are expressed as mean ± SEM. Individual areas under the curve (AUC; systolic blood pressure changes over time) were determined between 0 and 120 minutes after placebo, entacapone, and yohimbine. A drug response was quantified as AUCdrug − AUCplacebo. A value for AUCdrug − AUCplacebo > 0 mm Hg·min indicates that the response to drug was greater than the response to placebo. ANOVA testing for repeated measures was used for multiple comparisons. Nonlinear regression was used to analyze dose-response curves. P < 0.05 was considered statistically significant.
Results

Clinical Characteristics

Five patients with multiple system atrophy presented with predominant Parkinsonian symptoms that were consistent with striatonigral degeneration. Two patients had cerebellar dysfunction with sporadic olivopontocerebellar atrophy. Systolic blood pressure was $145\pm11$ mm Hg supine and decreased to $102\pm13$ mm Hg after 3 minutes of standing. Respiratory sinus arrhythmia and the Valsalva heart rate ratios were markedly attenuated, indicating impaired parasympathetic innervation to the heart. Impaired sympathetic function was indicated by the $47\pm15$ mm Hg decrease in systolic blood pressure during phase II of the Valsalva maneuver, the absence of a blood pressure overshoot during phase IV of the Valsalva maneuver, and the absent response to handgrip testing. Systolic blood pressure increased by $20\pm6$ mm Hg during cold pressor testing. Thus, the patients had moderate-to-severe autonomic impairment. A spontaneous baroreflex slope of $3\pm0.8$ ms/mm Hg is consistent with impaired baroreflex control of heart rate. Patients with Parkinson’s disease did not exhibit symptoms of autonomic failure. In these patients, systolic blood pressure was $106\pm8$ mm Hg in the supine position and $118\pm11$ after 3 minutes of standing. Respiratory sinus arrhythmia and responses to the Valsalva maneuver were within the normal range.

Figure 3. Changes in systolic blood pressure ($\Delta$SBP), diastolic blood pressure ($\Delta$DBP), and heart rate ($\Delta$HR) after ingesting 5.4 mg of yohimbine. Patients ingested yohimbine at 0 minutes.

Figure 4. Changes in systolic blood pressure ($\Delta$SBP) after ingesting placebo or 400 mg of entacapone in patients with multiple system atrophy (A) and in patients with Parkinson’s disease (B). Patients ingested medications at 0 minutes.

Figure 5. A, Mean AUC for systolic blood pressure change ($\Delta$SBP) over time with placebo and with incremental entacapone. B, Individual responses to different doses. The response was determined as the difference between the systolic blood pressure change AUC with entacapone and placebo. A difference $>0$ suggests that the patient had a greater response to entacapone than placebo. The responder proportion increased with increasing doses. C, Individual responses to 400 mg of entacapone in patients with Parkinson’s disease (response to entacapone minus response to placebo).
Responses to Complete Ganglionic Blockade

Figure 1 illustrates blood pressure changes with ganglionic blockade in patients with multiple system atrophy. Blood pressure was 147±12/75±24 mm Hg at baseline and decreased in all to 96±7/54±3 mm Hg during ganglionic blockade. The RR interval was 770±17 ms at baseline and did not change significantly.

Sensitivity to Phenylephrine and Nitroprusside

Phenylephrine and nitroprusside dose-dependently changed systolic blood pressure (Figure 2). We compared the responses in patients with multiple system atrophy with responses in healthy control subjects from a previous study. Patients with multiple system atrophy had a much greater response to both drugs than control subjects (P<0.001 by ANOVA between groups). Before ganglionic blockade, 25 μg of phenylephrine increased systolic blood pressure by 30±6 mm Hg in patients with multiple system atrophy and by 9±2 mm Hg in control subjects. Nitroprusside (0.4 μg/kg) decreased blood pressure by 30±4.7 mm Hg in patients with multiple system atrophy and by 8±2.7 mm Hg in control subjects. Ganglionic blockade potentiated the pressor response to 25 μg of phenylephrine 1.6±0.1-fold in patients with multiple system atrophy compared with 15±4-fold in healthy controls.

Response to Yohimbine

Figure 3 illustrates changes in systolic blood pressure, diastolic blood pressure, and heart rate with yohimbine. Blood pressure increased 20 minutes after yohimbine. The maximal increase above baseline was 55±9/17±5 mm Hg at 70 minutes after drug administration. The AUC of the systolic blood pressure change over time was 3500±870 mm Hg•min with 5.4 mg of yohimbine.

Inhibition of COMT

The baseline seated blood pressure before drug ingestion was 109±7/68±3 mm Hg with placebo, 110±8/74±3 mm Hg with 100 mg of entacapone, 105±6/73±5 mm Hg with 200 mg of entacapone, and 111±7/72±3 mm Hg with 400 mg of entacapone (P=NS by ANOVA). The change in systolic blood pressure over time, shown in Figure 4, was greater with 400 mg of entacapone than with placebo (P<0.001 by ANOVA). The change in systolic blood pressure at 120 minutes was 0.7±2 mm Hg with placebo and 11±4 with 400 mg of entacapone. Heart rate was 78±3 bpm before placebo and 79±3 bpm at 120 minutes after placebo. Heart rate was 83±3 bpm before 400 mg of entacapone and 79±3 bpm at 120 minutes afterward (P=0.09). Entacapone dose-dependently increased systolic blood pressure (Figure 5A). The AUC was 90±130 mm Hg•min with placebo, 650±300 mm Hg•min with 100 mg of entacapone, 960±310 mm Hg•min with 200 mg of entacapone, and 1000±330 mm Hg•min with 400 mg of entacapone. An AUC of 1000±330 mm Hg•min corresponds to an average systolic blood pressure increase of 8.5 mm Hg that is sustained for 120 minutes. We analyzed the dose-response relationship using nonlinear regression analysis (sigmoidal dose-response, r²=1) and found that the maximal response to entacapone was 1000±26 mm Hg•min (95% confidence interval, 950 to 1080 mm Hg•min). The ED₅₀ was 99±0.3 mg. Figure 5C illustrates individual responses (AUCentacapone−AUC placebo). The number of responders was 4 (57%), 5 (71%), and 6 (86%) with 100, 200, and 400 mg of entacapone, respectively. Two hours after drug ingestion, plasma norepinephrine concentrations were 3.1±0.44 nmol/L (530±75 pg/mL) with placebo and 3.1±0.62 nmol/L (520±105 pg/mL) with entacapone (mean dose, 300 mg). Plasma dopamine and epinephrine concentrations were similar with placebo and with entacapone. Plasma dihydroxyphenylglycol increased in all 4 patients tested (7.5±1.2 nmol/L [1279±210 pg/mL] with placebo and 15.6±4.0 nmol/L [2650±680 pg/mL] with entacapone).

In the 5 patients with Parkinson’s disease, the response to 400 mg of entacapone was similar to the placebo response (Figures 4B and 5C). The AUC of the change in systolic blood pressure was 188±92 mm Hg•min with placebo and −2±151 mm Hg•min with 400 mg of entacapone. An AUC of −2 mm Hg•min corresponds to a mean change in systolic blood pressure of 0 mm Hg. The response to 400 mg of entacapone was significantly smaller in patients with Parkinson’s disease than in patients with multiple system atrophy (P<0.05). Similarly, diastolic blood pressure and heart rate did not change with entacapone.

We used phenylephrine sensitivities in patients with multiple system atrophy and in control subjects to estimate the magnitude of the systolic blood pressure response to COMT inhibition for healthy subjects. We assumed that COMT inhibition leads to a similar decrease in norepinephrine metabolism in both groups. The dose of phenylephrine that increased systolic blood pressure 10 mm Hg in patients with multiple system atrophy (4.4 μg) elicits a 10.5-fold smaller response in healthy control subjects (0.95 mm Hg). Thus, the maximal response to COMT inhibition is ~10.5 times smaller in healthy subjects. This estimation is supported by the findings in patients with Parkinson’s disease.

Discussion

Selective COMT inhibition with entacapone increased systolic blood pressure in a dose-dependent fashion in patients with multiple system atrophy. However, the maximal pressor response was less than a third of the response to a moderate dose of the sympathetic stimulant yohimbine. In contrast, COMT inhibition with entacapone did not lead to a significant increase in blood pressure in healthy control subjects or in patients with Parkinson’s disease who had intact autonomic function.

Entacapone at these doses inhibits COMT activity in red blood cells by 60% to 80% in healthy volunteers. Maximal COMT inhibition is reached 45 to 60 minutes after ingestion. In contrast to tolcapone, entacapone is a peripheral COMT inhibitor. The compound does not enter the brain in sufficient quantities to inhibit COMT centrally. Clinically, entacapone is used in combination with L-DOPA to treat Parkinson disease. COMT inhibition decreases the O-methylation of L-DOPA and thereby improves L-DOPA availability in the brain. The O-methylated metabolite of L-DOPA may compete with L-DOPA for transport across the blood-brain.
barrier. Therefore, COMT inhibition may improve the delivery of L-DOPA into the brain. COMT inhibition also decreases the O-methylation of circulating norepinephrine and epinephrine. Catecholamine metabolism via monoamine oxidase is increased during COMT inhibition.9

A catecholamine metabolism inhibitor such as entacapone only increases blood pressure if sufficient norepinephrine is released from postganglionic adrenergic neurons occupying adrenoceptors on vascular smooth muscle cells. It may seem paradoxical that patients with autonomic impairment due to multiple system atrophy release sufficient amounts of norepinephrine. However, trimethaphan and the nonselective α-adrenoceptor antagonist phentolamine elicit a profound depressor response.11 The response to trimethaphan is markedly greater in patients with multiple system atrophy than in healthy subjects.23–25 Patients with pure autonomic failure,11 or patients with monogenic hypertension and brachydactyly,21 Indeed, sympathetic tone is sufficient to drive supine hypertension in these patients.11 Thus, increased sympathetic tone in the supine position seems to be a characteristic feature of multiple system atrophy. Yohimbine blocks α2 adrenoceptors in the central nervous system and at postganglionic sympathetic neurons. This effect leads to increased sympathetic outflow and norepinephrine release.18 Our patients had a large pressor response to a moderate dose of yohimbine. Furthermore, plasma norepinephrine concentrations in the supine position were within the normal range.20 These findings and the results of 6-[18F]fluorodopamine positron-emission tomography12 strongly support the notion that functioning sympathetic neurons are present in patients with multiple system atrophy.

COMT inhibition did not lead to a change in venous norepinephrine, epinephrine, or dopamine concentrations, whereas plasma dihydroxyphenylglycol concentrations increased markedly. Ordinarily, much of endogenous dihydroxyphenylglycol undergoes enzymatic conversion to methoxyhydroxyphenylglycol, a major end product of norepinephrine metabolism. The dihydroxyphenylglycol to methoxyhydroxyphenylglycol conversion is catalyzed by COMT. The increased plasma dihydroxyphenylglycol concentrations after entacapone treatment probably resulted from inhibition of this conversion and confirmed a sufficient drug dose to inhibit COMT. The subject number may have been too small to detect a subtle effect of COMT inhibition on plasma norepinephrine. Alternatively, in patients with multiple system atrophy, COMT inhibition may mainly affect plasma norepinephrine turnover in the synaptic cleft rather than circulating norepinephrine concentrations. Similarly, smaller intravenous doses of yohimbine led to a substantial increase in blood pressure in the absence of detectable changes in venous norepinephrine concentrations.18

The pressor response to COMT inhibition can only occur if the increment in norepinephrine acting on adrenergic receptors is large enough to overcome the restraining effect of the baroreflex. The greatest response to COMT inhibition is likely to occur in individuals with impaired baroreflex buffering23,26–30 and increased vascular sensitivity to norepinephrine. Both impaired baroreflex buffering and vascular hypersensitivity may be present in patients with multiple system atrophy.13,30,31 Either abnormality could explain the extreme hypersensitivity to phenylephrine. Interruption of the efferent part of the baroreflex with ganglionic blockade increased the sensitivity to phenylephrine profoundly in control subjects23 but only moderately in our patients with multiple system atrophy. This observation is consistent with severely impaired baroreflex buffering.21,23 Furthermore, baroreflex control of heart rate was reduced.32 Our findings suggest that the phenylephrine hypersensitivity in patients with multiple system atrophy is mainly due to impaired baroreflex buffering rather than vascular hypersensitivity.33 The baroreflex functional abnormalities, therefore, provided a sensitive means to study effects of COMT inhibition on blood pressure. Previous studies and our study suggest that the effect of COMT inhibition on blood pressure is minimal in the presence of intact baroreflex function.6

Until proven otherwise, COMT inhibitors should be used with caution in patients with impaired baroreflex function, in particular in combination with medications that enhance norepinephrine release, attenuate neuronal norepinephrine uptake, or stimulate adrenoceptors directly. COMT inhibition markedly augmented the chronotropic effect of isoproterenol and of epinephrine in an earlier study.34 Whether the pressor effect of COMT inhibition can be exploited to attenuate the depressor effect of L-DOPA and dopamine agonists in patients with Parkinsonism and autonomic impairment remains to be shown. We do not think that entacapone should be used for to treat orthostatic hypotension. Several commonly used pressor agents seem to be more efficacious and are less expensive than entacapone.13

One limitation of our study is that we tested the effect of placebo and incremental doses of entacapone in a sequential fashion. The reason we choose a sequential design is that we were concerned about possible side effects of entacapone in patients with multiple system atrophy given the extreme sensitivity of these patients to sympathetic stimulants.13,18

Our study supports the hypothesis that multiple system atrophy represents an excellent model to characterize the effect of subtle manipulations in norepinephrine metabolism on blood pressure regulation in small numbers of subjects.11,18 Even the sympathetic excitation induced by water drinking raises blood pressure profoundly in patients with multiple system atrophy.17 Our findings provide a rationale to study the effect of genetic and nongenetic variability in COMT activity on cardiovascular regulation. We expect the greatest effect of variability in COMT activity in the presence of impaired catecholamine metabolism via alternative pathways.

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