Oral Load of Tyrosine or L-Dopa and Plasma Levels of Free and Sulfoconjugated Catecholamines in Healthy Men

JEAN-LOUIS CUCHE, JACQUES PRINSEAU, FRANÇOISE SELZ, GÉRARD RUGET, JEAN-LUC TUAL, LILIANE REINGEISSEN, MICHELLE DEVOSIN, ALAIN BAGLIN, JACQUES GUÉDON, AND DIDIER FRITEL

SUMMARY The levels of free and sulfoconjugated catecholamines were measured in the plasma of fasting, recumbent normal subjects before and after an oral load of the catecholamine precursors tyrosine or l-dopa. Basal values of sulfoconjugated catecholamines, measured in plasma samples diluted 1:100 were 7998 ± 540 pg/ml for dopamine sulfate, 2938 ± 281 pg/ml for norepinephrine sulfate, and 2958 ± 288 pg/ml for epinephrine sulfate (n = 37 tests in 15 men); these basal values are higher than those reported previously. Neither free nor sulfoconjugated catecholamine concentrations were changed by a tyrosine load (100 mg/kg) that induced a doubling of the plasma tyrosine level or by a meal low in phenylalanine and tyrosine (but otherwise supplying constituents of normal nourishment) that induced a greater than 50% reduction in the plasma tyrosine concentration. After an oral load of l-dopa (125 mg) the following were observed. (1) An extremely large increase (>100-fold) in dopamine sulfate levels was noted, an increase that was less marked in the same subjects given l-dopa (125 mg) plus the peripheral dopa-decarboxylase inhibitor carbidopa (12.5 mg); as expected, free dopamine concentration also was increased. (2) Neither free nor sulfoconjugated norepinephrine concentrations were altered. (3) Epinephrine sulfate but not free epinephrine concentration was increased (more than ten-fold) after l-dopa ingestion alone; this result was unexpected and has to be confirmed before considering its physiological meaning, if any. (Hypertension 7: 81–89, 1985)

KEY WORDS • dopamine • norepinephrine • epinephrine • phenylalanine- and tyrosine-restricted meal • carbidopa • plasma tyrosine level • radioenzymatic assay

CATECHOLAMINES (CA) are synthesized by specialized tissues in accordance with the precursors delivered to them. Precursors usually are delivered by the oral route, either physiologically (e.g., phenylalanine and tyrosine found in a standard diet) or pharmacologically (e.g., l-dopa in the treatment of Parkinson’s disease). Before the final stage of catecholamine synthesis precursors pass through several biochemical modifications, some of which are peculiar to the digestive tract. In humans, CA are conjugated mostly with sulfate\(^1\) to yield what are generally considered elimination products.\(^2\) Theoretically these conjugated compounds could be reserve forms, since the human organism has a sulfatase system and as dopamine sulfate has been described as a possible precursor of CA.\(^3\)\(^,\)\(^4\) Thus the major objective of the present study was to investigate the possible relationship between orally delivered catecholamine precursors and the plasma concentrations of their free and sulfoconjugated forms in healthy men. The only information presently available was derived from measurements of the urinary excretion of CA in patients with Parkinson’s disease treated with l-dopa.

Two points should be noted from these studies. On the one hand, an oral load of precursor does not necessarily induce a proportional stimulation of all metabolic pathways; for example, l-dopa induces an increase
in the concentration of dopamine and its metabo-
lites, whereas levels of norepinephrine and its metabo-
lites are only slightly increased (if at all) or are decreased. On the other hand, even if the major biosynthetic pathway of CA (i.e., tyrosine, dopa, dopamine, norepinephrine, and epinephrine) is now well established, other pathways, known as secondary metabolic pathways, may exist that are less well defined.

Material and Methods

Subjects

Thirty-seven studies were carried out in 15 normotensive healthy men (medical staff or medical students), whose average age was 24.4 years (range 20–33 years) and average weight was 67.9 kg (range 46–87 kg). Consent was obtained from each subject after the purpose of the study was fully explained. The protocol was approved by the Institut National de la Sante et de la Recherche Medicale.

After an overnight fast the subject arrived in the clinical investigation room at 0800 and adopted a recumbent position, which he maintained throughout the procedure. A small indwelling catheter was placed in an antecubital vein for blood sampling, and the cuff of an automatic apparatus for blood pressure and heart rate measurements (Dynamap 854, Applied Medical Research, Tampa, FL) was positioned on the other arm; blood pressure and heart rate remained unchanged in all groups of subjects studied. An hour was allowed for equilibration, before the first blood sample was drawn for basal catecholamine measurement.

Experimental Design

Group 1

After the basal blood sample had been taken, nine subjects were given an oral load of tyrosine, 100 mg/kg (prepared by Pharmacie Centrale des Hopitaux de Paris in the form of a 500-mg capsule mixed with lactose, 115 mg; Lot 83 M 058). A blood sample was taken 1, 2, and 4 hours thereafter. This sequence of sampling was repeated in the other five groups.

Group 2

The seven subjects in group 2 were kept fasting for the same period of time, and a blood sample was taken in accordance with the sequence described for group 1. This group served as the control.

Group 3

After the basal sample had been taken, eight subjects were given a meal low in phenylalanine and tyrosine, as described in Tables 1 and 2. Together with other normal dietary constituents, the meal contained rather large amounts of carbohydrates.

Group 4

After the basal sample, five subjects were given the same meal as the group 3 subjects, plus tyrosine (100 mg/kg), as described in group 1.

Group 5

After the basal sample, four subjects were given the meal low in phenylalanine and tyrosine (group 3), plus an oral load of L-dopa (125 mg). Bronaugh and colleagues have shown that the L-dopa dose is an important factor; after a low dose, 97% of urinary dopamine was conjugated, while the percentage was only 61% after a high dose. The dosage in our study — 125 mg — has been shown to be an intermediate dose, well within the physiological limits of conjugation in a normal human.

Group 6

The four subjects that formed this group were the same as those who formed group 5. After the basal blood sample, they were given a meal low in phenylalanine and tyrosine, plus L-dopa (125 mg) and carbidopa (12.5 mg), an inhibitor of peripheral decarboxylation of aromatic amino acids.

Methods

The levels of free and sulfoconjugated CA were measured according to radioenzymatic techniques described by Johnson and colleagues and Catechol-O-

<table>
<thead>
<tr>
<th>Meal constituents</th>
<th>Calories</th>
<th>Phenylalanine (mg)</th>
<th>Tyrosine (mg)</th>
<th>Proteins (gm)</th>
<th>Lipids (gm)</th>
<th>Carbohydrates (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple and dried plum</td>
<td>386</td>
<td>47</td>
<td>27</td>
<td>1.5</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>Apple juice</td>
<td>128</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butter</td>
<td>75</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Pain Hypo*</td>
<td>119</td>
<td>10.8</td>
<td>11.5</td>
<td>0.3</td>
<td>1.3</td>
<td>27</td>
</tr>
<tr>
<td>Mixture TY†</td>
<td>240</td>
<td></td>
<td></td>
<td>6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>948</td>
<td>60.8</td>
<td>38.5</td>
<td>61.8</td>
<td>9.3</td>
<td>154</td>
</tr>
</tbody>
</table>

*Deproteinized bread carbohydrate = 59.2%, cellulose = 0.9%, proteins = 0.6%, lipids = 2.8%, calcium, phosphorus, sodium, and potassium = 0.6%, phenylalanine = 0.024%, and tyrosine = 0.025% (Riet-Diet, Welfare Foods Stockport Ltd, Ponton, Stockport, U.K.)
†Laboratoire de la Pharmacie Centrale des Hopitaux, Paris, France
methylenedopa. All samples for a given subject in a given condition were run in the same assay, which minimized the effect of interassay variation. With each technical procedure an aliquot from a plasma pool was run as a quality control; the interassay coefficient of variation was 9.2% for dopamine, 11.8% for norepinephrine, and 10.2% for epinephrine (n = 36). Sensitivity and interassay coefficient of variation are in agreement with the data produced by the method of Peuler and Johnson.

The sulfoconjugated CA were measured in plasma samples, diluted with water 1:100. As shown in Figure 2, this procedure improved the recovery of internal standards. This recovery was between 60% and 85% when free CA were measured in nondiluted plasma samples, but increased to approximately 100% when sulfoconjugated CA were measured in diluted plasma samples. This phenomenon, the study of which was beyond the scope of the present investigation, does not interfere with the interpretation of our results. As a matter of fact, this interpretation was based on the comparison of data obtained before and after an oral load of catecholamine precursors. During the corresponding period of time, the recovery of the mean internal standard was unchanged for a given group of subjects (Figure 2). This phenomenon, however, induced a large modification in the so-called basal values of sulfoconjugated CA. As shown in Table 4, these basal values were in close agreement with previously published data, when obtained from nondiluted samples. They were increased, however, when obtained from 1:100 diluted samples; dopamine sulfate increased 2.6-fold, norepinephrine sulfate 5.2-fold, and epinephrine sulfate 17.6-fold.

Plasma tyrosine concentration was measured in accordance with a spectrofluorometric method. Data are expressed as mean ± SEM. A one-dimensional analysis of variance was used to test statistically significant differences. When a statistical significance (p < 0.05) for the mean effect was reached, a Dunnett's test was applied.

### Results

#### Plasma Tyrosine Concentrations

In group 1 a 100 mg/kg load of tyrosine was associated with a significant increase in the plasma tyrosine level (Figure 3). The magnitude of this increase is in agreement with previous reports and became evident soon after the oral load. The plasma tyrosine level remained unchanged in group 2. In group 3 the plasma tyrosine level fell by 50% after 4 hours. In group 4 the decrease in plasma tyrosine induced by the low phenylalanine and tyrosine meal was apparently offset by the decrease in plasma tyrosine induced by the low phenylalanine and tyrosine meal. In group 5 the plasma tyrosine level fell to the same extent as in the group 3 subjects.
FIGURE 1 4-O-methyldopamine does not co-chromatograph with metanephrine. Thin-layer chromatogram taken under ultraviolet light demonstrates a clear separation of 4-O-methyldopamine and metanephrine, the first moved ahead of the second. The chromatography solution of Da Prada and Zurcher was used. The radioenzymatic assay was slightly modified at the stage of the solution used to stop the methylation reaction. Cold-methylated derivatives (4 mM) were added alone or in association with this solution. Arrow indicates the direction of the migration. 1 = methoxytyramine, 2 = 4-O-methyldopamine, 3 = metanephrine, and 4 = normetanephrine.

TABLE 3 Thin-Layer Chromatographic Separation of Tritiated Methylated Metabolites of Dopamine (3H-methoxytyramine and 3H-4-O-methyl dopamine) and Related Catecholamine Metabolites, When Standard Dopamine Is Present Alone in the Radioenzymatic Assay

<table>
<thead>
<tr>
<th>Dopamine (ng)</th>
<th>3H-methoxytyramine cpm (%)</th>
<th>3H-4-O-methyl dopamine cpm (%)</th>
<th>3H-metanephrine cpm (%)</th>
<th>3H-normetanephrine cpm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>5,429 (69.4)</td>
<td>2,379 (30.4)</td>
<td>9 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.5</td>
<td>18,802 (68.9)</td>
<td>8,122 (30.6)</td>
<td>134 (0.5)</td>
<td>18 (0.1)</td>
</tr>
<tr>
<td>1.0</td>
<td>35,220 (68.5)</td>
<td>15,826 (30.8)</td>
<td>284 (0.5)</td>
<td>51 (0.1)</td>
</tr>
<tr>
<td>5.0</td>
<td>132,340 (68.4)</td>
<td>60,549 (31.2)</td>
<td>769 (0.4)</td>
<td>86 (0.1)</td>
</tr>
<tr>
<td>10.0</td>
<td>212,977 (67.9)</td>
<td>99,456 (31.7)</td>
<td>1227 (0.4)</td>
<td>106 (0.1)</td>
</tr>
</tbody>
</table>

Values shown are the means of two experiments. The assay of 4-O-methyldopamine contained in the gel spot was carried out identically to that described for methoxytyramine. Figures in parentheses represent the percentages of total radioactivity measured in each fraction.

Plasma Catecholamine Concentrations

In groups 1, 2, 3, and 4 free and sulfokonjugated catecholamine concentrations remained unchanged, except for an unexplained and transient increase in free dopamine in group 1 (Table 5) and a decrease in epinephrine sulfate in group 4 (Table 6).

Subjects in groups 5 and 6 were given a meal low in phenylalanine and tyrosine (Tables 1 and 2), plus L-dopa, 125 mg. When L-dopa was given alone (group 5), there was a large increase in free dopamine levels, with no change in either free norepinephrine or free epinephrine levels. Simultaneously, there was a large increase in dopamine sulfate levels (> 100-fold), associated with a lack of change in norepinephrine sulfate levels and an unexpected increase in epinephrine sulfate levels. The increases in dopamine sulfate and epinephrine sulfate concentrations were maximal approximately 2 hours after the L-dopa load. In group 6 the increase in dopamine sulfate levels was reduced when compared with that in group 5, and the increase in epinephrine sulfate levels was no longer statistically significant. In group 6 the mean concentration of free
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FIGURE 2 Data obtained before and after an oral load of catecholamine precursors. For each sample of a series for a given subject in a given experimental condition, the internal standard of each catecholamine was compared with its external standard (1 ng), and the result expressed as percentage of the latter. For each sample, the mean percentage of the internal standard for the three catecholamines (CA) was calculated. The figure illustrates their mean ± SEM in control (Control) and experimental (+1h, +2h, +4h) measurements in the six groups studied. The open symbols represent free CA, whereas closed symbols represent sulfoconjugated forms. △ = tyrosine load (group 1), ○ = fasting throughout (group 2), □ = low phenylalanine and tyrosine meal (group 3), ◀ = low phenylalanine and tyrosine meal plus tyrosine load (group 4), □ = L-dopa load (group 5), ◀ = L-dopa plus carbidopa (group 6).

For a given group, the mean internal standards were not statistically different from each other, thus whatever the mechanism underlying the apparent inhibition of the methyltransfer reaction in nondiluted samples, it is acceptable to compare the results obtained (see text).

TABLE 4 Plasma Concentration of Sulfoconjugated Catecholamines in Basal Conditions (Fasting Overnight, Recumbent for 60 min, 0800) in 15 Healthy Men (n = 37)

<table>
<thead>
<tr>
<th></th>
<th>Nondiluted sample</th>
<th>100 dilution with water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>3,115 ± 174</td>
<td>7,998 ± 540</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>565 ± 31</td>
<td>2,938 ± 281</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>168 ± 11</td>
<td>2,958 ± 288</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SEM

dopamine was slightly higher than in group 5, but was no longer statistically significant, probably because of the small number of subjects studied.

Discussion

It has been well established that tyrosine is the biochemical precursor of CA and that the concentration of tyrosine controls the rate of their biosynthesis. This effect requires that dietary tyrosine pass through the intestinal wall and reach the bloodstream; the plasma tyrosine level must be free to vary according to either the amount of dietary tyrosine delivered or the amount of tyrosine consumed by tissues. As shown by data in Figure 3, an oral load of tyrosine (100 mg/kg) induced an increase in the plasma tyrosine level (group 1), whereas a meal low in phenylalanine and tyrosine, by supplying the constituents of otherwise normal nourishment (Table 1), induced a decrease (groups 3, 5, and 6). This decrease may be due to stimulation of insulin release that in turn stimulates the uptake of tyrosine into skeletal muscle.

Despite these changes in plasma tyrosine levels, no major effects were observed on plasma concentration of either free or sulfoconjugated CA. This lack of change is unlikely to be due to stimuli of insufficient magnitude; both the increase in the plasma tyrosine levels induced by an oral load of 100 mg/kg and the decrease induced by a meal low in phenylalanine and tyrosine are likely to be at the extreme limits of physiological variation. An increase in the catecholamine turnover rate cannot be excluded. Such an increase could induce small changes in plasma catecholamine concentrations that may underlie the increase in the urinary excretion of CA observed after a comparable load of tyrosine in normal subjects.

The lack of change in sulfoconjugated CA after an oral load of tyrosine is at first glance at odds with the increase in both dopamine sulfate and norepinephrine sulfate levels observed after eating bananas. Tentatively one might consider that tyrosine, insensitive to sulfoconjugation, passes through the intestinal wall and then plays its different roles, one of them being that of catecholamine precursor, whereas the dopamine and norepinephrine supplied by bananas are recognized as foreign phenols and conjugated, for example, in the intestinal wall, to be rendered inactive and more easily eliminated.

After an oral load of L-dopa, there is good reason to suspect that a large fraction passes through the intestinal wall, even though one cannot rule out the possi-
concentration of free and sulfoconjugated dopamine and that only a small fraction reaches the central nervous system. The predominant role played by decarboxylation is partly confirmed by the fact that the magnitude of the dopamine sulfate increase was appreciably reduced when the same amount of L-dopa was given with carbidopa (group 6), an inhibitor of peripheral aromatic amino acid decarboxylation. It should be noted that the magnitude of the increase of dopamine sulfate was less than that with free dopamine, which suggests that the decarboxylation/sulfoconjugation axis is very efficient in normal men. Therefore, it is reasonable to suspect an increase in the digestive phenolsulfotransferase activity after an oral load of L-dopa, because this enzyme catalyzes the sulfoconjugation process and is especially efficient in the digestive tract.34,35 Has this increase in dopamine sulfate any physiological meaning? This study was not designed to answer this question. Nonetheless, it is interesting to recall that a decrease in blood pressure is frequently observed in patients treated with L-dopa and to note
that a recent, although preliminary, report demonstrates that an intravenous infusion of dopamine sulfate decreased blood pressure in anesthetized dogs.\textsuperscript{36}

We observed an increase in free dopamine levels in parallel with that of dopamine sulfate, as already reported in patients with Parkinson's disease.\textsuperscript{5} It is possible that the increase in dopamine concentration represents a manifestation of a saturation of the sulfocojugating process or platelet uptake, or both.\textsuperscript{6, 37} An increase in free norepinephrine levels would have been expected if the rise of free dopamine levels resulting from a generalized activation of the catecholamine biosynthetic pathway. As this was not the case, the origin of the increased circulating dopamine levels remains in question.

After l-dopa ingestion no statistically significant change in either free or sulfocojugated norepinephrine levels was observed (Table 7). This finding is in agreement with a report that demonstrated an increase in dopamine levels associated with a decrease in norepinephrine levels in both rat brain and heart after l-dopa administration,\textsuperscript{39} and with another report that showed a lack of change in the urinary excretion of free and sulfocojugated norepinephrine levels in patients with Parkinson's disease treated chronically with l-dopa.\textsuperscript{18}

Finally, after l-dopa administration (group 5), and to a lesser extent after l-dopa plus carbidopa administration (group 6), we measured an increase in epinephrine sulfate levels in plasma. It is unlikely that this increase was an artifact owing to incomplete chromatographic separation of the various catecholamines. Thus, as the data in Table 3 demonstrate, irrespective of the amount of dopamine present, the radioactivity measured in the metanephrine spot was very small (<0.5%). Additionally, the sulfocojugated CA were measured in 1:100 diluted samples whose radioactivity was between 200 and 1000 cpm, and the data in Figure 4 demonstrate that the contamination of metanephrine by methoxytyramine was just as small when cold-methylated derivatives were measured by high-performance liquid chromatography. The increase in epinephrine sulfate was an unexpected and rather surprising observation. Although theoretically explicable,\textsuperscript{40} this finding warrants confirmation, as in patients with Parkinson's disease treated chronically with l-dopa, urinary excretion of both free and sulfocojugated epinephrine has been reported to remain unchanged.\textsuperscript{18}

**Conclusion**

The present study, carried out in healthy men, demonstrates that large variations in the level of plasma tyrosine concentration, induced either by an oral load of tyrosine or by a meal low in phenylalanine and tyrosine, are not associated within the following 4 hours with measurable change in the plasma concentration of either free or sulfocojugated CA. This would suggest a rather large reserve pool of CA in the adrenergic tissue. On the other hand, a very mild oral load of l-dopa induces a significant enhancement of the plasma-free dopamine level and a tremendous increase in that of dopamine sulfate, which suggests that the decarboxylation/sulfocojugation axis is very efficient in normal men. Neither free norepinephrine and epinephrine nor norepinephrine sulfate concentrations were changed after l-dopa. Nonetheless, epinephrine sulfate was increased. This observation was unexpected and was independent of the biochemical procedure used to measure CA; it must be confirmed before considering any possible physiological meaning.

### Table 7: Plasma Catecholamine Concentrations in Four Healthy Men Given a Low Phenylalanine and Tyrosine Meal, plus Either l-Dopa (Group 5) or l-Dopa and Carbidopa (Group 6)

<table>
<thead>
<tr>
<th>Group</th>
<th>CA Levels (pg/ml)</th>
<th>Statistical Analysis</th>
<th>CA Levels (mg/ml)</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>+1 hr</td>
<td>+2 hr</td>
<td>+4 hr</td>
</tr>
<tr>
<td><strong>Group 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>5</td>
<td>570*</td>
<td>552†</td>
<td>298†</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>3</td>
<td>255</td>
<td>148</td>
<td>73</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>201</td>
<td>226</td>
<td>175</td>
<td>251</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>41</td>
<td>20</td>
<td>15</td>
<td>49</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>18</td>
<td>48</td>
<td>37</td>
<td>53</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>7</td>
<td>12</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td><strong>Group 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>35</td>
<td>1362</td>
<td>856</td>
<td>768</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>22</td>
<td>457</td>
<td>408</td>
<td>452</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>196</td>
<td>224</td>
<td>266</td>
<td>178</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>26</td>
<td>10</td>
<td>72</td>
<td>8</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>44</td>
<td>91</td>
<td>132</td>
<td>61</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>21</td>
<td>35</td>
<td>102</td>
<td>28</td>
</tr>
</tbody>
</table>

*p < 0.05 when compared with control
†p < 0.01 when compared with control
‡p < 0.001 when compared with control
CA = catecholamines
FIGURE 4  Measurement of a possible contamination of metanephrine by methoxytyramine. This is a montage. On the left-hand half, the usual thin layer chromatographic "trail" owing to cold methoxytyramine, metanephrine, and normetanephrine was arbitrarily divided according to dotted lines. On the right-hand half, methoxytyramine or metanephrine was added alone (4 mM each) in the solution used to stop the methylation reaction, and were measured by high performance liquid chromatography along the chromatographic "trail," which was divided accordingly. Most of the methoxytyramine or metanephrine localized where it was expected, and the contamination of metanephrine by methoxytyramine was negligible when measured by high-performance liquid chromatography, which is in agreement with data reported in Table 3.

Acknowledgments
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