Deuterium Oxide Normalizes Blood Pressure and Vascular Calcium Uptake in Dahl Salt-Sensitive Hypertensive Rats

Sudesh Vasdev, Victor Prabhakaran, and Carol Ann Sampson

This study examined the effect of 25% deuterium oxide in drinking water on systolic blood pressure, uptakes of calcium, and rubidium 86 by aortas of Dahl salt-sensitive rats on 0.4% (low) and 8% (high) sodium chloride (salt) diet. Twenty-four rats were divided into four groups. Groups I and II were on the low salt diet and groups III and IV on the high salt diet from 6 weeks of age. Additionally, at 10 weeks of age groups I and III were placed on 100% water and groups II and IV on 25% deuterium oxide. At 14 weeks, systolic blood pressure, uptakes of calcium, and rubidium 86 by aortas were significantly higher ($p<0.01$) in rats on the high salt diet as compared with those on the low salt diet. Deuterium oxide intake normalized systolic blood pressure and aortic calcium uptake but not aortic rubidium 86 uptake in hypertensive rats on the high salt diet. Deuterium oxide had no effect on blood pressure or aortic calcium uptake in rats on the low salt diet. The parallel increase in systolic blood pressure and vascular calcium uptake suggests that increased calcium uptake mechanisms are associated with hypertension in salt-sensitive Dahl rats. Furthermore, deuterium oxide appears to normalize elevated blood pressure in salt-sensitive hypertensive rats by normalizing elevated vascular (aortic) calcium uptake. (Hypertension 1990;15:183–189)

Abnormal contractile activity of the vascular smooth muscle is considered as one cause for the development of essential hypertension. The contractile activity of vascular smooth muscle is regulated by the levels of intracellular free Ca$^{2+}$. It has been suggested that factors leading to an increased concentration of calcium ions within the vascular smooth muscle cell may be responsible for the increased contraction of the smooth muscle and the development of hypertension. Such factors may be an increased entry of calcium ions through the cell membrane, through either voltage-operated calcium channels or receptor-operated calcium channels or an increased release of calcium ions within the smooth muscle cells. Calcium influx through cell surface calcium channels is a major contributing factor to cytosolic free calcium.

Calcium antagonists inhibit both the calcium influx through Ca$^{2+}$ channels and Ca$^{2+}$ release from the Ca$^{2+}$-regulating sarcoplasmic reticulum and the Ca$^{2+}$ binding sites on the membrane of vascular smooth muscle. Intra-arterial infusion of the calcium channel blockers verapamil and nifedipine produce marked vasodilation in humans. These calcium channel blockers also produce a greater relaxation response in blood vessels of spontaneously hypertensive rats compared with those of normotensive rats. Oral administration of these calcium channel blockers decrease blood pressure in hypertensive human subjects, as well as spontaneously hypertensive and Dahl salt-sensitive hypertensive rats but not in normotensive human subjects, normotensive Wistar-Kyoto and Dahl normotensive rats.

Deuterium oxide ($D_2O$), a stable nonradioactive isotope of water has been shown to inhibit mouse ventricular myocardial contraction with concomitant reduction in calcium uptake. It has also been shown to reduce the L-type calcium channel conductance in isolated guinea pig myocytes. We have shown recently that 25% $D_2O$ in drinking water when given to spontaneously hypertensive rats prevents the onset of hypertension and normalizes elevated aortic calcium uptake. The present study examined the effect of 25% $D_2O$ administration on salt-induced hypertension and aortic calcium and 86Rb uptake in Dahl salt-sensitive hypertensive rats.
Methods

Animals, Diet, and Administration of Deuterium Oxide

Twenty-four male Dahl salt-sensitive rats from Harlan Sprague-Dawley (Indianapolis, Indiana) were used in this study. All rats consumed standard rat chow containing 0.4% sodium chloride from weaning up to 6 weeks of age. These rats were then divided into four groups. Groups I and II were fed a low (0.4%) and groups III and IV a high (8%) salt (sodium chloride) diet for 4 weeks. During this period, all rats had free access to tap water. At 10 weeks, drinking water of groups I and III was replaced with 100% H2O and groups II and IV with 25% D2O in H2O for another four weeks. Body weight and blood pressure of all rats were recorded weekly. Food and water intakes were recorded every second day. At the end of the experiment (age 14 weeks), rats were anesthetized with intraperitoneal sodium pentobarbital (10 mg/100 g body wt). After thoracic cage resection, blood was drawn into a vacutainer tube by intracardiac puncture for serum biochemistry. Thoracic aortas were excised immediately for calcium and 86Rb uptake measurement. Liver, heart, and kidneys were dissected and weighed.

Laboratory Analysis

Plasma renin activity and serum aldosterone were determined by standard commercially available radioimmunoassay kits from New England Nuclear Corp. (Boston, Massachusetts) and Diagnostic Products Corp. (Los Angeles, California), respectively. Sodium, potassium, calcium, magnesium, and creatinine in serum were assayed on autoanalyzers with ion-specific electrodes for sodium and potassium, compleximetric method for calcium and magnesium, and reaction rate Jaffe method for creatinine.

Measurement of Calcium Uptake by Thoracic Aortas

Calcium uptake by thoracic aortic tissues was measured as described previously.18–20 Briefly, rats were anesthetized, killed, and thoracic aortas immediately excised and dissected free of connective tissue in a constantly oxygenated HEPES buffer (pH 7.4) solution containing: 150 mM NaCl, 4.5 mM KCl, 10 mM D-glucose, 5 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), 1.5 mM CaCl2, and 1 mM MgCl2. Aortas were then cut into 2–3 mm long segments. After an equilibration period of 2 hours at 37°C subsequent to tissue excision, aortic rings (in tissue holders) were incubated in 5 ml constantly oxygenated buffer containing 45Ca2+ (5 μCi/ml) for 20 minutes at 37°C in a constantly shaking water bath. Subsequently, tissues were washed in cold (2°C) buffer for 2 minutes, followed by a second cold (2°C) buffer wash for 45 minutes to remove free 45Ca2+. Under these conditions, efflux of intracellular calcium is prevented and only the extracellular calcium is effectively washed away.19,20 The tissues were then blotted, wet weights measured, and transferred to counting vials containing 100 μl H2O and 1 ml Protosol (New England Nuclear) and placed in a water bath for 2 hours at 60–70°C. After digestion, 100 μl glacial acetic acid was added to each vial followed by 10 ml liquid scintillation fluid (BDH Chemicals, Toronto, Canada), and the solution was counted in a Beckman liquid scintillation counter (Beckman Instrs., Fullerton, California). The uptake of Ca2+ was expressed as micromoles Ca2+ per kilogram wet weight of tissue per 20 minutes. This net uptake represents total Ca2+ influx minus efflux in the aortas.

Measurement of 86Rb+ Uptake of Thoracic Aortas of Dahl Salt-Sensitive Rats

We assessed vascular sodium pump activity by measuring 86Rb+ uptake in vitro in thoracic aortic rings by an essentially similar method as described previously.20,21 After an equilibration period of 2 hours subsequent to tissue excision, aortic rings (in tissue holders) were incubated in 5 ml constantly oxygenated HEPES buffer containing 86Rb+ (2–10 μCi/ml) for 30 minutes at 37°C in a constantly shaking water bath. After this period, tissues were placed in ice cold (2°C) unlabeled buffer for 2 minutes to wash the radioisotope in the extracellular compartment. The tissues were blotted carefully and wet weights taken immediately. The tissues were digested in counting vials by adding 100 μl H2O and 1 ml Protosol and heated in a water bath for 2 hours at 60–70°C. After digestion, 100 μl glacial acetic acid was added to each vial followed by 10 ml liquid scintillation fluid (BDH). Aliquots of incubation media were taken and processed to estimate total added counts. The vials were counted in a Beckman liquid scintillation counter and the uptake of 86Rb+ based on K+ molarity (4.5 mM) expressed as micromoles per kilogram wet weight per minute. The ouabain-insensitive portion of 86Rb+ uptake was determined by incubating the same tissues with a maximally effective concentration of ouabain (2 mM) for 60 minutes before and during 86Rb+ uptake. The ouabain-insensitive portion of the 86Rb+ uptake was equivalent to the amount of 86Rb+ uptake observed after a similar exposure to a combination of iodoacetate acid (1 mM) and 2,4-dinitrophenol (0.1 mM) (data not shown). The ouabain-sensitive portion of 86Rb+ uptake was determined by subtracting the ouabain-insensitive uptake from the total uptake.

Systolic Blood Pressure Measurements

Systolic blood pressure was recorded weekly using a tail-cuff method (model 5A Amplifier, ITTC Life Science Instrs., Woodland Hills, California). Each pressure value was obtained by averaging four individual readings.

Statistical Analysis

All data are expressed as mean±SD. Statistical analysis of results were performed by Students t test (unpaired).
TABLE 1. Effect of Oral Deuterium Oxide Treatment on Body Weight, Systolic Blood Pressure, and Biochemical Parameters of Dahl Salt-Sensitive Rats on Low and High Salt Diet

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low salt</th>
<th>High salt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% H2O</td>
<td>25% D2O</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>381±35</td>
<td>390±34</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122±6</td>
<td>117±8</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>144±4</td>
<td>142±2</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.4±0.42</td>
<td>4.6±0.59</td>
</tr>
<tr>
<td>Serum magnesium (mmol/l)</td>
<td>0.80±0.12</td>
<td>0.74±0.11</td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.52±0.08</td>
<td>2.47±0.07</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>44±12</td>
<td>38±6</td>
</tr>
<tr>
<td>Plasma renin activity (ng/US)</td>
<td>2.3±0.36</td>
<td>4.1±0.99§</td>
</tr>
<tr>
<td>Serum aldosterone (pmol/l)</td>
<td>850±400</td>
<td>609±207</td>
</tr>
</tbody>
</table>

Values are mean±SD. n=6 in each group. Starting at 6 weeks of age, rats were given either a low (0.4% NaCl) or high (8% NaCl) salt diet for 4 weeks. At that time both groups of rats were given either 100% H2O or 25% deuterium oxide (D2O) as their drinking water for 4 weeks.

*Significantly different (p<0.05) from low salt diet group.
†Significantly different (p<0.001) from all other groups.
§Significantly different (p<0.05) from all other groups.
**Significantly different (p<0.05) as compared with 100% H2O group.

Results

Effect of Oral Intake of Deuterium Oxide on Serum Biochemistry, Body Weight, Food, and Water Intake

The initial body weights of the rats in the four groups were not significantly different (Table 1). However, the mean values of final body weights of the rats on the high salt diet were less (p<0.05) as compared with rats on the low salt diet. There was no significant difference in the mean body weights between those rats with similar salt intakes on 100% H2O and those on 25% D2O. Twenty-five percent D2O used as drinking water had no significant effect on body weight of the rats. Serum sodium was significantly lower (p<0.05) in the rats on the high salt diet receiving 25% D2O. Although serum potassium was higher in the rats on the high salt diet receiving D2O, it was not statistically significant from other groups. Serum magnesium, calcium, and creatinine were not significantly different between the groups.

Mean values of plasma renin activity and serum aldosterone of rats on the high salt diet were significantly lower (p<0.05) as compared with rats on low salt diet. Treatment with 25% D2O significantly increased (p<0.05) plasma renin activity as compared with rats on 100% H2O with similar salt intakes. Of the rats on the high salt diet, those on 25% D2O had significantly lower (p<0.05) mean serum aldosterone when compared with those on 100% H2O. The mean systolic pressure was significantly higher in the rats on the high salt diet and 100% H2O (p<0.001) as compared with all other groups. The mean systolic blood pressure of the rat group on the high salt diet and 25% D2O was normal and not significantly different from that of the two groups of rats on the low salt diet. Mean values±SD for food intake at the 14th week of the experimental period were 27±6, 33±5, 27±5, and 21±5 g/day/rat in rats on low salt and 100% H2O, low salt and D2O, high salt and 100% H2O, and high salt and D2O, respectively. The mean values of food intake of rats on high salt and D2O (21±5 g/day/rat) was significantly low (p<0.01) as compared with rats on low salt and D2O (33±4 g/day/rat). Mean values±SD for water intake were 37±6, 38±2, 141±22, and 95±10 ml/day/rat in rats on low salt and 100% H2O, low salt and D2O, high salt and 100% H2O, high salt and D2O, respectively. Rats on high salt consumed significantly (p<0.001) more water than rats on low salt. Rats on high salt and 25% D2O consumed significantly (p<0.05) less water than those on high salt and 100% H2O.

Effect of Oral Intake of Deuterium Oxide on Systolic Blood Pressure of Dahl Salt-Sensitive Rats

Mean±SD values of systolic blood pressure of Dahl salt-sensitive rats in groups III and IV on the high salt diet were significantly higher at 8 weeks (2 weeks of high salt diet) and 10 weeks (4 weeks of high salt diet) as compared with their initial values and of rats on low salt diet of same age (Table 2). Mean±SD values of rats on high salt and H2O (group III) were significantly higher at the 11th, 12th, 13th, and 14th week of the high salt diet as compared with other groups. When rats on the high salt diet (group IV) at 10 weeks were started on 25% D2O as their drinking water, their systolic blood pressure was significantly lower (p<0.01) as compared with rats on high salt and 100% H2O at the 11th, 12th, 13th, and 14th weeks. Systolic blood pressure of rats on high salt and D2O at the 13th and 14th weeks was not statistically different from rats on low salt diet. D2O (25%) effectively normalized salt-induced increase in blood pressure in Dahl salt-sensitive rats.
TABLE 2. Effect of Oral 25% Deuterium Oxide Treatment on Systolic Blood Pressure of Dahl Salt-Sensitive Rats on Low and High Salt Diet

<table>
<thead>
<tr>
<th>Age (wk)</th>
<th>Low salt</th>
<th>High salt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>All rats on normal drinking water</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>105±6</td>
<td>107±5</td>
</tr>
<tr>
<td>8</td>
<td>104±8</td>
<td>106±6</td>
</tr>
<tr>
<td>10</td>
<td>108±4</td>
<td>111±5</td>
</tr>
<tr>
<td>Rats placed on either 100% H2O or 25% D2O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>110±6</td>
<td>105±5</td>
</tr>
<tr>
<td>12</td>
<td>114±8</td>
<td>110±6</td>
</tr>
<tr>
<td>13</td>
<td>121±7</td>
<td>116±7</td>
</tr>
<tr>
<td>14</td>
<td>122±6</td>
<td>117±8</td>
</tr>
</tbody>
</table>

Values are mean±SD. n=6 in each group. Starting at 6 weeks of age, rats were given either a low (0.4% NaCl) or high (8% NaCl) salt diet for 4 weeks. At that time both groups of rats were given either 100% H2O or 25% deuterium oxide (D2O) as their drinking water for 4 weeks.

*Significantly different (p<0.01) from low salt diet group.
†Significantly different (p<0.01) from all other groups.

Effect of Oral Intake of Deuterium Oxide on Calcium Uptake by Aortas of Dahl Salt-Sensitive Rats

Mean±SD values of calcium uptake by aortas of rats on high salt diet and 100% H2O at 14 weeks of age were significantly higher than that found in all other groups (Table 3). Mean values of aortic calcium uptake in rats on low salt diet and D2O were not significantly different from rats on low salt diet and H2O. Thus, D2O treatment lowered aortic calcium uptake in hypertensive rats without affecting the uptake in normotensive rats.

TABLE 3. Effect of Oral 25% Deuterium Oxide Treatment on Calcium Uptake by Aortas of Dahl Salt-Sensitive Rats on Low and High Salt Diet

<table>
<thead>
<tr>
<th>Group</th>
<th>Calcium uptake (μmol Ca²⁺/kg tissue/20 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% H2O</td>
</tr>
<tr>
<td>Low salt</td>
<td>474±50</td>
</tr>
<tr>
<td>High salt</td>
<td>828±132*</td>
</tr>
</tbody>
</table>

Values are mean±SD. n=12 aortic rings from six rats in each group. Starting at 6 weeks of age, rats were given either a low (0.4% NaCl) or high (8% NaCl) salt diet for 4 weeks. At that time both groups of rats were given either 100% H2O or 25% deuterium oxide (D2O) as their drinking water for 4 weeks. All calcium uptake measurements were done in normal HEPES buffer (without D2O).

*Significantly different from other groups p<0.001.

Effect of Oral Intake of Deuterium Oxide on ⁸⁶Rb+ Uptake of Dahl Salt-Sensitive Rat Aortas

Ouabain-sensitive ⁸⁶Rb uptake of aortas represents its Na⁺-K⁺ pump activity. Mean±SD values for total and ouabain-sensitive ⁸⁶Rb uptake were significantly higher (p<0.01) in rats fed the high salt diet as compared with the low salt diet. D2O consumption did not affect ⁸⁶Rb uptake in rats on either low or high salt diet.

Effect of Oral Intake of Deuterium Oxide on Body Weight and Organ Weight of Rats

As shown in Table 1 and in Table 5 the mean body weights of the rats on the high salt diet was less (p<0.05) as compared with rats on the low salt diet. D2O treatment had no significant effect of body weight of rats. There was no significant difference in mean values of liver and kidney weight among the

TABLE 4. Effect of Oral 25% Deuterium Oxide Treatment on Rubidium ⁸⁶Uptake by Aortas of Dahl Salt-Sensitive Rats on Low and High Salt Diet

<table>
<thead>
<tr>
<th>⁸⁶Rb uptake (μmol/kg tissue/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% H2O</td>
</tr>
<tr>
<td>Low salt</td>
</tr>
<tr>
<td>High salt</td>
</tr>
<tr>
<td>Ouabain-sensitive</td>
</tr>
<tr>
<td>Ouabain-insensitive</td>
</tr>
</tbody>
</table>

Values are mean±SD. n=12 aortic rings from six rats in each group. Starting at 6 weeks of age, rats were given either low (0.4% NaCl) or high (8% NaCl) salt diet for 4 weeks. At that time both groups of rats were given either 100% H2O or 25% deuterium oxide (D2O) as their drinking water for 4 weeks.

*Significantly different from low salt group (p<0.01).
were significantly higher ($p<0.05$) in high salt vascular tone in peripheral resistance vessels, causes this animal model. Further-
more, D$_2$O normalized elevated aortic calcium uptake and systolic blood pressure without affecting Na+-K+ pump activity as the cause of hypertension in hypertensive animals has been shown as compared with low salt groups. D$_2$O treatment did not affect organ weights in either low salt or high salt groups.

### Discussion

The mechanism by which dietary sodium contributes to the etiology of hypertension is unclear. In recent years, attention has been focused on the possibility that the basic cellular abnormality in hypertension is an inability to maintain a normal membrane electrolyte gradient.$^{5,22,23}$ One hypothesis is that chronic excess sodium intake leads to production of a humoral hypertensinogenic factor.$^{24-26}$ One proposed candidate for this transferable factor is the putative natriuretic hormone or endogenous ouabain-like substance that, by inhibiting Na$^+$/K$^+$ pump, might have a saluretic action in the kidney and, by enhancing vascular tone in peripheral resistance vessels, causes increased blood pressure.$^{4,24-26}$ More specifically, Na$^+$/K$^+$ pump inhibitors act by increasing intracellular sodium concentration, thus leading to increased intracellular calcium concentration via the sodium-calcium exchange mechanism and hence, vasoconstriction.

Increased sodium-potassium adenosine triphosphatase (Na$^+$/K$^+$-ATPase) inhibitory activity has been shown to be present in the plasma of hypertensive$^{27,28}$ and dialysis-dependent subjects$^{29,30}$ and in some hypertensive animal models.$^{27}$ In contrast to this, the majority of other studies that have evaluated this "sodium pump" in vascular smooth muscle have found that its activity is increased in hypertension in some other animal models.$^{31,32}$ Also, in Dahl salt-sensitive rats on a high salt diet, an increase not a decrease in Na$^+$/K$^+$ pump activity measured by $^{86}$Rb uptake in arteries of these hypertensive animals has been shown as compared with normotensive animals on a low salt diet.$^{21,33,34}$ Increased vascular Na$^+$/K$^+$ pump activity in the present study also supports the earlier work. Furthermore, D$_2$O normalized elevated aortic calcium uptake and systolic blood pressure without affecting elevated $^{86}$Rb uptake thus dissociating vascular Na$^+$/K$^+$ pump activity as the cause of hypertension in this animal model.

Recently, it has been shown that plasma from patients with essential hypertension contains a substance that increases the cytosolic calcium concentration in platelets,$^{29}$ and it has been suggested that a plasma factor that acts on platelets may similarly do so on vascular smooth muscle cells. Furthermore, there is strong evidence of plasma factors causing increased calcium uptake in vascular tissue of salt-sensitive hypertensive Dahl rats on a high salt diet$^{19}$ and in spontaneously hypertensive rats.$^{36}$

We have previously shown that a high salt diet leads to an increase in systolic blood pressure in Dahl salt-sensitive rats together with an increase in cytosolic free Ca$^{2+}$. Whatever the mechanism by which high salt intake induces hypertension, increased cytosolic free Ca$^{2+}$ appears to represent the common mediating factor$^{30}$ and increased uptake seems to be responsible for this increased intracellular Ca$^{2+}$. In the present study, D$_2$O administration to salt-sensitive, salt-induced hypertensive rats normalized their elevated aortic calcium uptake and blood pressure thus further supporting the role of calcium in the etiology of hypertension.

In the present study, the hypotensive response to D$_2$O was found to be a useful tool for the assessment of in vivo cellular calcium metabolism in vascular tissue. Earlier, we have shown that D$_2$O normalized the high calcium uptake in spontaneously hypertensive rat aortas and prevented the onset of hypertension. Both antihypertensive and aortic calcium uptake effects of D$_2$O were irreversible.$^{17}$ It has also been reported that isotopic substitution of deuterium for hydrogen may, indeed, affect cell surface calcium channels.$^{16}$ This group, while studying the binding and unbinding of single protons and deuterium ion in L-type Ca$^{2+}$ channels of guinea pig ventricular myocytes found the rate constant for the unbinding of deuterium ions to be 2.5 times slower than protons. They also found that the frequency and duration of calcium channel blockage increases with increasing concentration of deuterium ions. It is suggested that the antihypertensive effects of D$_2$O may be the result of increased blockage of calcium channels by bound deuterium ions.

We gave 25% D$_2$O orally to rats in our study as our previous studies have demonstrated this dose to be effective in both normalizing blood pressure and
calcium uptake. With this dose, there was no significant effect on body weight, food intake, serum calcium, magnesium, and creatinine, suggesting that 25% D2O in drinking water for 4 weeks does not seem to be detrimental to health in these rats. D2O treatment lowered serum sodium and tended to increase serum potassium in rats on the high salt diet. Furthermore, D2O treatment significantly increased plasma renin activity as compared with rats on 100% H2O with similar salt intake. D2O also lowered serum aldosterone in rats on a high salt diet. D2O treatment also decreased water intake. Although we did not measure urine output and sodium excretion in these rats, the above observations seem to suggest that D2O treatment in the rats on the high salt diet may affect sodium and water balance. Further studies are warranted to look into this aspect.

In conclusion, high resting aortic calcium uptake in Dahl salt-sensitive rats on a high salt diet might be due to defects in calcium handling. The parallel increase in systolic blood pressure and vascular calcium uptake and normalization with D2O treatment suggests that increased uptake mechanisms are associated with hypertension. D2O appears to normalize elevated blood pressure in salt-induced hypertensive Dahl rats by normalizing higher aortic calcium uptake.

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References


**KEY WORDS** • deuterium oxide • essential hypertension • calcium • Dahl salt-sensitive rats
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