Attenuated Arteriolar Dilator Responses to Calcium in Genetically Hypertensive Rats

HENRY W. OVERBECK

SUMMARY Vascular responses to calcium were studied in 14 genetically hypertensive (GH) rats of the New Zealand strain and 16 weight- and age-matched normotensive parent strain control rats under chloralose-pentobarbital anesthesia. Calcium (chloride or gluconate) in an isosmolar solution was infused intraarterially into the hindlimb vascular bed which was vascularly isolated, innervated, and pump-perfused (blood, 1 ml/min). Increases in limb plasma calcium concentrations up to 30 mEq/liter decreased limb vascular resistance, with no evidence for vasoconstriction. In GH rats decreases in limb vascular resistance in response to increments in limb plasma calcium concentrations of 3.6 to 10.8 mEq/liter were significantly ($p < 0.02$) attenuated compared to age-matched controls. When responses in GH were compared to weight-matched controls, similar trends toward attenuation reached significance ($p < 0.02$) at Ca$^{2+}$ increments of 10.8 mEq/liter. In eight other GH rats, we measured total serum calcium concentrations and found them reduced (4.94 ± 0.08 mEq/liter), especially as compared to values in eight rats of an unrelated Wistar strain (5.42 ± 0.04 mEq/liter; $p < 0.05$). These experiments provide evidence that, over physiological ranges, calcium relaxes arteriolar smooth muscle in rats and that this vasodilation is attenuated in genetically hypertensive rats. Thus, both the lower serum levels of calcium and the attenuated responses to calcium may contribute to the elevated peripheral vascular resistance and hypertension in these rats.

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KEY WORDS • vascular smooth muscle • cell membrane ion transport • serum magnesium • serum calcium • serum proteins

RECENT evidence suggests abnormalities in calcium metabolism in spontaneously hypertensive rats of the Aoki-Okamoto strain (SHR), in rats with steroid hypertension, and also in patients with essential hypertension. Serum total and/or ionized calcium is reported to be reduced,1,2 perhaps secondary to altered calcium binding to plasma proteins, decreased calcium intake, and/or increased renal calcium excretion. High calcium diets attenuate the hypertension while low calcium diets exacerbate it.1,4 It has been suggested that the elevated vascular resistance may result in part from membrane abnormalities in vascular smooth muscle cells associated with the lowered levels of extracellular Ca$^{2+}$.5,7 According to this concept, increases in extracellular Ca$^{2+}$ should relax arteriolar smooth muscle, hence evoking vasodilation and reducing blood pressure. However, local intraarterial infusions of calcium evoke vasoconstriction, rather than vasodilation, in vascular beds of dogs and humans,8,9 and the in vivo effects on arterioles of increases in extracellular calcium have never been studied in rats.

Thus, we designed the present study to investigate local responses to elevations in calcium in the intact, blood-perfused limb vascular bed of rats. Additionally, we compared responses in normotensive and genetically hypertensive strains to test the possibility that responses might be abnormal in the hypertensive rats. Because we had previously demonstrated normal vascular responses to another vasoactive ion (K$^+$) in New Zealand genetically hypertensive rats,10 we elected to study rats of this strain. We also measured the serum levels of calcium, magnesium, and proteins.

Methods

Included in this study were 65 male Wistar rats: 33 rats of the New Zealand genetically hypertensive strain (GH), 24 age- or weight-matched normotensive control rats (N) from the parent New Zealand colony,11 and eight unrelated 16-week-old Wistar rats (W) obtained from a commercial supplier (Charles River...
Breeding Laboratories). All rats drank tap water and were fed a standard diet that contained 0.37% total sodium, 0.62% total potassium, 1.2% total calcium, and 0.22% total magnesium.

A systolic blood pressure greater than 140 mm Hg, sustained for at least 4 weeks in GH rats, was assessed in rats under light ether anesthesia by the tail plethysmographic method. Systolic blood pressures in N and W rats remained below 140 mm Hg. All rats were in good health at the time of the experiment.

Hindlimb vascular responses were studied in 25 GH and 16 N rats. These rats were initially anesthetized with intravenous (i.v.) chloralose (100 mg/kg) and pentobarbital (6 mg/kg). Respiration was natural. Using methods we have previously described,10 we isolated one hindlimb from the body by severing and ligating skin and muscle connections and by dislocating the hip from the pelvis with a tourniquet. Under these conditions, vascular isolation was virtually complete. The major nerve connections in the limb were left intact, and the femoral vein was undisturbed.

The rat was given 400 USP units of heparin and a supplemental dose (1.5 mg/kg, i.v.) of pentobarbital. Then blood was pumped13 from the contralateral femoral artery at a constant rate of 1 ml/min into the femoral artery of the isolated limb. Pump and tubing held a maximum of 1.5 ml of the rat's blood.

We monitored pump perfusion pressure in the pump outflow tubing, and we also monitored the rat's systemic blood pressure in the pump inflow tubing with Statham P23Gb pressure transducers and a Hewlett Packard recorder. At least 15 minutes after perfusion of the limb was begun, when a steady-state perfusion was established, vascular responses were studied.

In five rats (two GH and three N) we studied dose-response relationships for infusions of isosmolar (297 mOsm/liter) NaCl solution and for infusions of isosmolar calcium (calcium chloride or calcium gluconate) solution. These infusions, which lasted up to 20 minutes, were administered into the pump tubing upstream to the pump at rates up to 0.2 ml/minute. The infusions of calcium solutions increased calcium concentration in limb arterial plasma by 0.003 to 72 mEq/liter.

In 11 GH rats, we studied the effects of various pharmacological blocking agents on the limb vascular response to infusions of calcium at 0.010 mEq/min, which increased limb plasma calcium concentration by 18 mEq/liter. In three rats, atropine 1.5–3 mg/kg was administered i.v.; this completely blocked the limb vasodilator response to acetylcholine 20 μg injected intraarterially into the limb. In four rats, pyrribenzamine 10 mg/kg was given subcutaneously (s.c.); this completely blocked the limb vasodilator response to histamine 0.001 μg/min infused intraarterially into the limb. In four rats, propranolol 1.5 mg/kg was given i.v.; this completely blocked the limb vasodilator response to isuprel 0.0015 μg injected intraarterially into the limb.

In the other 25 rats (13 N and 12 GH), three sets of paired infusions were made into the tubing upstream to the pump, and vascular responses were monitored. The N rats were either weight-matched or age-matched to GH rats. Each pair of infusions included a 4-minute infusion of isosmolar NaCl solution (control) followed by a 4- to 5-minute infusion of isosmolar CaCl₂ solution. The isosmolar CaCl₂ solution was diluted to the appropriate volume with isosmolar NaCl solution, so that all infusions could be made at a rate of 0.05 ml/min. The NaCl and CaCl₂ infusions were separated by a 3-minute pause, and the pairs of infusions were separated by 5-minute pauses. Three dose levels of isosmolar CaCl₂, that delivered 0.002, 0.004, or 0.006 mEq calcium/min were infused in order of increasing dosage. Calculated increments produced in calcium concentrations in limb arterial plasma were 3.6, 7.2, or 10.8 mEq/liter, respectively.

At the end of the final CaCl₂ infusion, supplemental pentobarbital (3 mg/kg, i.v.) was administered. In all rats, the femoral and sciatic nerves were then severed to reduce limb vascular resistance. After a 10-minute pause, the last pair of infusions was repeated. Arterial blood was then taken for measurement of hematocrit. All rats were autopsied.

The perfusion pressure gradient across the outflow tubing and cannula (measured in each rat) was subtracted from the perfusion pressures used to calculate limb resistances. Limit resistances were calculated as the ratio of perfusion pressure to limb blood flow and expressed in terms of hindlimb wet weight.

The paired Student's t test was used to compare steady-state responses to isosmolar NaCl solution with those to the paired isosmolar CaCl₂ solution. As previously described,10 responses to the NaCl solution were then subtracted from responses to the paired calcium solution in each rat before data were further analyzed. Analysis of variance (ANOVA) was used to compare limb initial resistance (IR) and magnitude of response to CaCl₂ (ΔR) in hypertensive and control rats. A separate analysis was done for age-matched and weight-matched groups of rats. For each dose level of CaCl₂, linear correlation coefficients were calculated to determine if there were significant relationships between IR and ΔR. Analysis of covariance was then used to compare responses adjusted for regression on IR in the groups of rats.

From an additional eight GH, eight N, and eight W (unrelated Wistar) age-matched rats under light ether anesthesia, blood was obtained by puncture of the abdominal aorta for measurement of serum concentrations of calcium, magnesium, proteins, and creatinine. Calcium and magnesium were measured by autoanalyzer, proteins by electrophoresis, and creatinine by Creatinine Assay (Sigma Chemical Company, St. Louis, Missouri). ANOVA followed by treatment contrasts13 were used to compare results in the three groups of rats. The null hypothesis was rejected at p < 0.05.

**Results**

Systolic blood pressures (by tail plethysmography), mean arterial pressure directly measured, body weights, ages, and hematocrits of the perfused GH and
N rats are presented in Table 1. Similar values plus chemistries of the three groups of rats from which serum was obtained (GH, N, and W) are presented in Table 2. Blood pressure was significantly elevated in the GH rats. In the rats from which serum was obtained, systolic blood pressure in the N rats was higher than that in the W rats, although in N rats it did not exceed 140 mm Hg. Matching of age or weight of the perfused N and GH rats was documented. There was no evidence for significant differences in hematocrits in the groups of rats. Ventricular weight/body weight was elevated in GH rats (Table 2). Serum creatinine did not significantly differ among the three groups of rats. ANOVA revealed significant differences in serum electrolytes and proteins among the three groups of rats. Serum calcium concentrations in GH rats were higher than those in the W rats, although in N rats it did not exceed 32 mEq/liter. Osmolar calcium solutions evoked greater drops in limb resistance than did osmolar NaCl solutions. At infusion rates greater than 0.10 ml/min (n = 2), the calcium solutions evoked highly variable responses, which suggested net rises in limb resistance. At equal infusion rates of calcium we detected no differences in responses evoked by calcium chloride (n = 3) and calcium gluconate (n = 2) solutions.

To determine the mechanism of the reduction in resistance evoked by isosmolar calcium infusions, we blocked cholinergic, histaminergic, and beta-adrenergic vasodilation in the limbs of 11 other rats. Such blockade did not attenuate the reductions in limb resistance evoked by isosmolar calcium infusions at 0.010 mEq/min (0.05 ml/min), which elevated plasma calcium by 18 mEq/liter.

In the other 25 rats, isosmolar CaCl$_2$ was infused at rates up to 0.03 ml/min (0.006 mEq/min), which elevated plasma calcium up to 10.8 mEq/liter. Systemic arterial pressure was not changed by these infusions. In most of these rats, limb vascular responses to the NaCl and CaCl$_2$ infusions became stable by the 3rd minute of the infusions. These steady-state responses were recorded. Compared to the response to isosmolar NaCl solution, limb resistance decreased in response to these infusions of CaCl$_2$. Table 3 presents means ± SEM of these responses to CaCl$_2$ (ΔR); responses to the paired NaCl infusions had been subtracted. The magnitude of initial limb resistance (IR) in GH rats tended to be greater than that in N rats. By ANOVA there were no
Infusion rate (mL/min) 0.04 0.08 0.12 0.16 0.20

Infusion rate (mEq Ca^{2+}/min) 0.008 0.016 0.024 0.032 0.040

Ca^{2+} Increment arterial plasma (mEq/l) +14.4 +28.8 +43.2 +57.6 +72.0

**Figure 1.** Dose-response curve from pooled data from two genetically hypertensive (GH) and from three normotensive (N) rats. • = limb vascular responses (means ± SEM) to intrabrachial arterial infusions of isosmolar NaCl solution at rates up to 0.20 mL/min. ○ = responses to infusions of isosmolar calcium chloride (n = 3) or calcium gluconate (n = 2).

**Figure 2.** Changes in limb vascular resistance (ΔR, vertical axis) in response to infusions of isosmolar calcium chloride solutions at 0.006 mEq calcium/min (which increased limb plasma Ca^{2+} by 10.8 mEq/liter) as a function of initial limb vascular resistance (IR, horizontal axis) in 10 genetically hypertensive (GH) rats (○) and 10 age-matched normotensive (N) rats (●). Regression line and 95% confidence intervals for predicted values are drawn for responses in N rats.

Statistically significant differences in responses of GH and N rats, although there were consistent trends for greater responses in the N rats. At the two higher dose levels and especially if we included responses after nerve section, which reduced IR to levels lower than 1500 mm Hg/mL/min/100 g, there were statistically significant positive linear correlations between IR and ΔR. This significant relationship between IR and ΔR is seen in Figure 2, which presents individual responses (ΔR) to calcium 0.006 mEq/liter plotted against IR. Inspection of this figure suggests a trend for lesser responses in the GH rats.

Thus, we also used analysis of covariance to compare responses in the groups adjusted for their significant regression on IR, as we have done with our previous response studies in hypertensive animals. In most cases (six of eight), analysis of covariance provided evidence for significant decreases in the responses of the GH rats to the calcium infusions.

Figure 3 is a log dose-response curve drawn from the means ± SEM of regression-adjusted responses from Table 3 (age-matched rats). There is a linear relationship between log dose and response in each group of rats. Figure 3 further illustrates the reduced responsiveness in the GH rats.
TABLE 3. Initial Resistances (IR) and Evoked Changes in Resistance (ΔR)

<table>
<thead>
<tr>
<th>Rat group</th>
<th>No.</th>
<th>IR ± SEM*</th>
<th>ΔR ± SEM*</th>
<th>p (AoV)</th>
<th>p (correl coeff)†</th>
<th>Regression adjusted ΔR ± SEM‡</th>
<th>p (AoCV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N&lt;sub&gt;A&lt;/sub&gt;</td>
<td>10</td>
<td>2367 ± 169</td>
<td>-13.5 ± 25.0</td>
<td>0.32</td>
<td>0.35</td>
<td>-34.0 ± 19.6</td>
<td>0.02</td>
</tr>
<tr>
<td>GH</td>
<td>10</td>
<td>2958 ± 250</td>
<td>20.2 ± 21.7</td>
<td>0.39</td>
<td>0.44</td>
<td>40.7 ± 19.6</td>
<td>0.07</td>
</tr>
<tr>
<td>N&lt;sub&gt;W&lt;/sub&gt;</td>
<td>10</td>
<td>2311 ± 183</td>
<td>6.7 ± 25.8</td>
<td>0.18</td>
<td>0.03</td>
<td>-8.7 ± 20.8</td>
<td>0.21</td>
</tr>
<tr>
<td>GH</td>
<td>10</td>
<td>2876 ± 169</td>
<td>36.3 ± 15.3</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N&lt;sub&gt;A&lt;/sub&gt;</td>
<td>10</td>
<td>2551 ± 173</td>
<td>-99.2 ± 37.2</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
<td></td>
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</tr>
<tr>
<td>GH</td>
<td>10</td>
<td>3041 ± 303</td>
<td>-40.5 ± 18.8</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
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<tr>
<td>N&lt;sub&gt;W&lt;/sub&gt;</td>
<td>10</td>
<td>2477 ± 174</td>
<td>-46.5 ± 37.9</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
<td></td>
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<tr>
<td>GH</td>
<td>10</td>
<td>3036 ± 270</td>
<td>-29.0 ± 20.5</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
<td></td>
<td></td>
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<tr>
<td>N&lt;sub&gt;A&lt;/sub&gt;</td>
<td>10</td>
<td>2660 ± 198</td>
<td>-207.1 ± 49.0</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
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<tr>
<td>GH</td>
<td>10</td>
<td>3118 ± 333</td>
<td>-91.9 ± 41.4</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N&lt;sub&gt;W&lt;/sub&gt;</td>
<td>10</td>
<td>2605 ± 196</td>
<td>-162.7 ± 48.2</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
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<td></td>
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<tr>
<td>GH</td>
<td>10</td>
<td>3215 ± 320</td>
<td>-108.9 ± 38.3</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
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<tr>
<td>N&lt;sub&gt;A&lt;/sub&gt;</td>
<td>10</td>
<td>2024 ± 184</td>
<td>-96.2 ± 36.8</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
<td></td>
<td></td>
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<tr>
<td>GH</td>
<td>20</td>
<td>2353 ± 242</td>
<td>-51.0 ± 22.9</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
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<td></td>
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<tr>
<td>N&lt;sub&gt;W&lt;/sub&gt;</td>
<td>20</td>
<td>1994 ± 178</td>
<td>-92.1 ± 28.9</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
<td></td>
<td></td>
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<tr>
<td>GH</td>
<td>20</td>
<td>2407 ± 244</td>
<td>-55.9 ± 23.8</td>
<td>0.006</td>
<td>0.004 mEq calcium/min</td>
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<tr>
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*mm Hg/ml/min/100 g limb weight.
†Correlation coefficient for relationship between IR and ΔR within each group.
‡Adjusted for regression on IR.
§Extra response points after nerve section added.

Discussion
The new information provided by this study includes evidence that: 1) local increases in extracellular calcium concentrations up to about 30 mEq/liter reduce arteriolar resistance in the limb vascular bed of the rat with no evidence for vasoconstrictor responses; 2) this arteriolar dilatory response to calcium may be attenuated in rats with genetic hypertension; and 3) the serum levels of calcium are lower in genetically hypertensive rats of the New Zealand strain.

Dose-response relationships suggest that the maximal decrease in limb arteriolar resistance evoked by calcium infusions occurs at increments in arterial plas-
ma calcium of about 20 mEq/liter. At infusion rates above this level, these effects on resistance wane, and then vascular resistance rises (in part due to observed precipitation of calcium in the pump tubing). We noted no differences in responses to calcium chloride and calcium gluconate, which suggests that these vascular responses were mediated by the cation rather than the anion. Although it is possible that these effects of calcium resulted from induced changes in blood viscosity, we know of no evidence for such a mechanism. Thus, we feel that the decreases in resistance we observed represented arteriolar vasodilation.

This arteriolar vasodilation evoked by increases in extracellular calcium in the rat contrasts with vascular responses to calcium in the dog and humans. In an almost identical preparation, we observed limb vasocostriction in response to infusions of CaCl₂ into the brachial artery of the dog, which increased calcium concentrations in the limb arterial plasma by 4–8 mEq/liter. In humans, intrabrachial arterial infusions of CaCl₂ that elevated measured calcium concentrations in the limb venous plasma by 2 to 15 mEq/liter also increased limb vascular resistance, with no evidence found for vasodilation. Thus, it appears that the response of rat arteriolar smooth muscle to increases in concentrations of extracellular calcium qualitatively differs from that in dogs and humans. We did not measure resulting levels of intracellular Ca²⁺, so we cannot comment on the role of that variable in the responses we observed.

Although we believe that this is the first study of in vivo vascular effects of calcium in the rat, there have been several studies of the effect of calcium on isometric tension of rat conduit arteries studied in vitro. Results of those studies indicate that increases in bath concentrations of calcium up to approximately 10 mEq/liter contract the vascular strips. However, elevations above that concentration produce relaxation, especially in strips previously contracted with KCl. It is noteworthy that in the present in vivo experiments we found no evidence for constrictr responses of arterioles to increases in serum calcium up to 10 mEq/liter. This may reflect differences between conduit and resistance vessels in their dependency on external calcium for vasoactivity.

In vitro studies at bath calcium levels greater than 10 mEq/liter, which evoked vascular relaxation, have suggested that increases in extracellular calcium concentrations may have a "membrane stabilizing effect" in vascular smooth muscle, possibly related to hyperpolarization of the membrane by incompletely understood mechanisms, or possibly related to decreased membrane permeability to monovalent ions, and/or to specific inhibition of Ca²⁺ membrane entry via slow membrane channels. This membrane-stabilizing effect is felt to account for the vascular relaxation induced by calcium in vitro. It is likely that similar mechanisms account for calcium-induced vascular relaxation in vivo. In this regard, the present study provided no evidence for cholinergic, histaminergic, or beta-adrenergic mechanisms.

In the present experiments we also compared the vasodilatory responses to calcium in normotensive and genetically hypertensive rats. Conceivably, an attenuated vasodilatory response to calcium might play a role in the increased vascular resistance of the hypertensive rats. Vascular responses are a function of the initial baseline state of resistance of the vascular bed, and initial resistance is higher in hypertensive rats. Therefore, with evidence for a significant linear correlation between initial resistance (IR) and the magnitude of response (ΔR), we used analysis of covariance to compare responses of normotensive and hypertensive groups, as we have done in the past. This comparison provided evidence at all three dose levels of calcium studied for significant attenuation of the vasodilatory response in the rats with genetic hypertension (Table 3, Figure 3).

It is possible that such attenuated vasodilation in the hypertensive rats represents a nonspecific abnormality. There is evidence in other forms of hypertension for impaired vasodilation. However, in a previous study we used similar techniques to study the limb vascular response to local infusions of K⁺ in GH and N rats. We found no evidence for attenuated vasodilatory responses in the genetically hypertensive rats. These previous findings allow us to argue that the attenuated vasodilatory responses to calcium in the genetically hypertensive rats which we observed in the present study are not nonspecific.

To our knowledge these are the first studies to provide in vivo evidence for an attenuation of calcium-induced relaxation of vascular smooth muscle in hypertensive animals. However, there is previous in vitro evidence for such an attenuation in vascular muscle from conduit vessels excised from rats with spontaneous, DOCA-salt, and two-kidney, one clip hypertension, and from pigs with DOCA hypertension. These findings suggested to the investigators that the plasma membrane in vascular smooth muscle in the hypertensive animals is more labile, and therefore a higher concentration of external calcium is necessary to stabilize cell responsiveness. The present studies reveal similar changes in vivo in arterioles and suggest that the increased membrane lability may also be present in arterioles of genetic hypertensive rats of the New Zealand strain. The attenuated responses to calcium we observed in the genetically hypertensive rats might also be related to alteration in intracellular stores of Ca²⁺, changes in membrane permeability to Ca²⁺, or a greater norepinephrine-activated calcium sensitivity of their vascular smooth muscle cells.

Serum concentrations of Na⁺ and K⁺ have been reported to be similar in GH and N rats. However, our data suggest that levels of serum total calcium and magnesium may be reduced in this strain. Compared to the unrelated Wistar normotensive strain, the GH rats showed decreases in serum calcium that averaged about 9% and that were accompanied by 33% reductions in serum albumin concentrations. Ionized calcium levels were not measured. Clearly, these chemi-
VASCULAR RESPONSES TO CALCIUM IN RATS/Overbeck


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References


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