Enalapril Induces Regression of Cardiac Hypertrophy and Normalization of pHᵢ Regulatory Mechanisms

Irene L. Ennis, Bernardo V. Alvarez, María C. Camilión de Hurtado, Horacio E. Cingolani

Abstract—Intracellular pH is under strict control in myocardium; H⁺ are extruded from the cells by sodium-dependent mechanisms, mainly Na⁺/H⁺ exchanger and Na⁺/HCO₃⁻ symport, whereas Na⁺-independent Cl⁻/HCO₃⁻ exchanger extrudes bases on intracellular alkalinization. Hypertrophic myocardium from spontaneously hypertensive rats (SHR) exhibits increased Na⁺/H⁺ exchange activity that is accompanied by enhanced extrusion of bases through Na⁺-independent Cl⁻/HCO₃⁻ exchange. The present experiments were designed to investigate the effect of enalapril-induced regression of cardiac hypertrophy on the activity of these exchangers. Male SHR and normotensive Wistar-Kyoto rats (WKY) received enalapril maleate (20 mg/kg per day) in the drinking water for 5 weeks. Gender- and age-matched SHR and WKY were used as untreated controls. Enalapril treatment significantly reduced systolic blood pressure in SHR and completely regressed cardiac hypertrophy. Na⁺/H⁺ activity was estimated in terms of both steady pHᵢ value in HEPES buffer and the rate of pHᵢ recovery from CO₂-induced acid load. Na⁺-independent Cl⁻/HCO₃⁻ activity was assessed by measuring the rate of pHᵢ recovery from intracellular alkalinization produced by trimethylamine exposure. Regression of cardiac hypertrophy was accompanied by normalization of Na⁺/H⁺ and Na⁺-independent Cl⁻/HCO₃⁻ exchange activities. Inhibition of protein kinase C (PKC) activity with chelerythrine (10 mmol/L) or calphostin C (50 nmol/L) returned both exchange activities to normal values. These results show that angiotensin-converting enzyme inhibition normalizes the enhanced activity of both exchangers while regressing cardiac hypertrophy. Because normalization of exchange activities could be also achieved by PKC inhibition, the data would suggest that PKC-dependent mechanisms play a significant role in the increased ion exchange activities of hypertrophic myocardium and in their normalization by angiotensin-converting enzyme inhibition. (Hypertension. 1998;31:961-967.)

Key Words: ion transport ■ hypertrophy, cardiac ■ angiotensin-converting enzyme inhibitors ■ protein kinase C ■ intracellular pH

We have recently reported that NHE activity is increased in the hypertrophic myocardium of SHR. The blockade of angiotensin II production by ACE inhibitors is proven to be potent and effective for blood pressure reduction and cardiac hypertrophy regression.

The enhancement of NHE activity has been described in various other cell types obtained both from hypertensive individuals and genetic animal models (for detailed review, see Reference 4), and it might result from an increased expression of exchanger protein units and/or an increased turnover rate of each unit. The question as to whether increased activity of NHE relates to increased turnover rate or increased mRNA and protein expression of the exchanger has been explored in different cell types, and it is still controversial. However, experiments in membranes from SHR cardiac tissue suggested a posttranslational processing mechanism involving phosphorylation as responsible for NHE hyperactivity. Activation of NHE by growth-promoting factors apparently involves an alkaline shift in the pHᵢ dependency of NHE due to phosphorylation of the exchanger protein itself and/or of a putative regulatory protein.

An increased activity of the AE in SHR myocardium has been reported by us. The parallel increase of AE activity induces net bicarbonate efflux and blunts the increase in myocardial pH, that would be induced by the NHE. It was therefore tempting to investigate whether enalapril-induced regression of cardiac hypertrophy had an influence on NHE and AE activities in SHR myocardium. In an attempt to further examine possible underlying mechanism(s), the effect of PKC inhibition was also studied.

Methods

Experiments were conducted in age-matched SHR and WKY male rats, which were originally derived from Charles River Breeding Farms, Wilmington, Mass. All animals were identically housed under controlled lighting and temperature conditions with free access to standard rat chow and tap water. All the experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (US Department of Health and Human Services). Beginning at 12 weeks of age, SBP was measured weekly in all animals by the standard tail-cuff method. By 16 weeks of age, SBP was significantly elevated in SHR (overall mean, 175±3 mm Hg; n=42) compared with WKY (118±2 mm Hg;...
n=27). By this time, rats from each breed were respectively divided at random into two groups. One group of each rat strain was treated with enalapril maleate (SHR-E and WKY-E) by inclusion of the drug in the drinking water. Concentration was adjusted every 2 days to ensure a dosage of 20 mg/kg per day. The second group of each strain served as untreated controls. Treatment lasted 5 weeks, and at the end of this period animals were deeply anesthetized with ether and their hearts were removed. From each heart, a papillary muscle was dissected free and mounted, as previously described, in an organ bath on the stage of an Olympus CK2 inverted microscope (Olympus Optical Co). Muscles were superfused with one of the following solutions: (1) HEPES-buffered solution containing (in mmol/L) 133.8 NaCl, 4.5 KCl, 1.35 CaCl2, 0.5 MgSO4, 11 glucose, and 25 HEPES (pH of the buffer solution was adjusted to 7.38) and the solution was gassed with 100% O2 or (2) HCO3-/CO2-buffered solution containing (in mmol/L): 128.3 NaCl, 4.5 KCl, 1.35 CaCl2, 20.23 NaHCO3, 0.35 NaH2PO4, 1.05 MgSO4, and 11 glucose. The solution was equilibrated with CO2/O2 gas mixture to ensure a P CO2 value of 35 mm Hg at the chamber atmosphere, and 5-nm filter every 20 seconds. To limit photobleaching, a neutral-density filter (1% transmittance) was placed in the excitation light path. At the end of each experiment, fluorescence emission was calibrated by the high K+ method.17 The calibration solution contained (in mmol/L) KCl 150.0, MgCl2 1.0, CaCl2 1.0, HEPES 5.0, nigericin 0.01, sodium cyanide 4.0, and 2.3-butanedione mono-oxime 20.0. Buffer pH was adjusted to four different values ranging from 6.7 to 7.37 at 0.1 increment at 30°C. The intrinsic buffer capacity and JH+, during the recovery from intracellular acidification, Acid loads were induced by switching from HEPES-buffered superfuse to CO2/HCO3− buffer. Recoveries of pH after acid loads were analyzed by fitting the pH versus time records to an exponential curve of the form ΔpH = ΔpH, (1−e−t/τ), where ΔpH and ΔH+ are the changes in pH from the initial value at time t and after steady state has been reached, respectively, and τ is the rate coefficient. The rate of change of pH at any selected pH value was obtained by calculating the derivative of the exponential fit at that selected pH, and thus, intracellular buffer capacity×dpH/dt represents JH+, the buffering power due to intracellular CO2/HCO3−. The latter was considered to be 2.3×[HCO3−], assuming an open system for CO2, and that its solubility and pK value are the same at either side of the cell membrane. [HCO3−] at any given pH was calculated from the Henderson-Hasselbach equation to be [HCO3−]=[H2CO3]×(pH−pK)/[H2CO3]. β was calculated as the ratio between Δ[HCO3−]/ΔpH observed when the superfusing solution was switched from HEPES to CO2/HCO3− buffer. Δ[HCO3−] was considered to equal the value of [HCO3−] immediately after CO2/HCO3− buffer introduction because in the absence of external CO2 the value of [HCO3−] is very low, ~50 μmol/L.9 The main problem for estimating β is that acid extrusion during the loading period may blunt the acidosis, thus leading to overestimation of β, value (see Reference 18 for details). Back-extrapolation of pH recovery to a point where it intersected the line defining the maximum initial rate of acid loading was used to reduce errors in β calculation, as previously shown.1,20,21

Assessment of AE Activity

The velocity of pH recovery from imposed intracellular alkalinization was used to estimate AE activity. Exposure to TMACl (Sigma Chemical Co) has been previously demonstrated as a valid technique for investigating the activity of the AE based on the fact that no recovery from TMACl-induced intracellular alkalosis is detected in HEPES buffer. Chemical Co) has been previously demonstrated as a valid technique for investigating the activity of the AE based on the fact that no recovery from TMACl-induced intracellular alkalosis is detected in HEPES buffer. The velocity of pH recovery (dpH/dt), assuming an open system for CO2, and that the solubility and pK value are the same at either side of the cell membrane. [HCO3−] at any given pH was calculated from the Henderson-Hasselbach equation to be [HCO3−]=[H2CO3]×(pH−pK)/[H2CO3]. β was calculated as the ratio between Δ[HCO3−]/ΔpH observed when the superfusing solution was switched from HEPES to CO2/HCO3− buffer. Δ[HCO3−] was considered to equal the value of [HCO3−] immediately after CO2/HCO3− buffer introduction because in the absence of external CO2 the value of [HCO3−] is very low, ~50 μmol/L.9 The main problem for estimating β is that acid extrusion during the loading period may blunt the acidosis, thus leading to overestimation of β, value (see Reference 18 for details). Back-extrapolation of pH recovery to a point where it intersected the line defining the maximum initial rate of acid loading was used to reduce errors in β calculation, as previously shown.1,20,21

Assessment of NHE Activity

The activity of the antipporter was estimated in terms of both steady pH values in the absence of external bicarbonate (HEPES buffer) and JH+, during the recovery from intracellular acidification. Acid loads were induced by switching from HEPES-buffered superfuse to CO2/HCO3− buffer. Recoveries of pH after acid loads were analyzed by fitting the pH versus time records to an exponential curve of the form ΔpH = ΔpH, (1−e−t/τ), where ΔpH and ΔH+ are the changes in pH from the initial value at time t and after steady state has been reached, respectively, and τ is the rate coefficient. The rate of change of pH at any selected pH value was obtained by calculating the derivative of the exponential fit at that selected pH, and thus, intracellular buffer capacity×dpH/dt represents JH+, the buffering power due to intracellular CO2/HCO3−. The latter was considered to be 2.3×[HCO3−], assuming an open system for CO2, and that its solubility and pK value are the same at either side of the cell membrane. [HCO3−] at any given pH was calculated from the Henderson-Hasselbach equation to be [HCO3−]=[H2CO3]×(pH−pK)/[H2CO3]. β was calculated as the ratio between Δ[HCO3−]/ΔpH observed when the superfusing solution was switched from HEPES to CO2/HCO3− buffer. Δ[HCO3−] was considered to equal the value of [HCO3−] immediately after CO2/HCO3− buffer introduction because in the absence of external CO2 the value of [HCO3−] is very low, ~50 μmol/L.9 The main problem for estimating β is that acid extrusion during the loading period may blunt the acidosis, thus leading to overestimation of β, value (see Reference 18 for details). Back-extrapolation of pH recovery to a point where it intersected the line defining the maximum initial rate of acid loading was used to reduce errors in β calculation, as previously shown.1,20,21

Assessment of AE Activity

The velocity of pH recovery from imposed intracellular alkalinization was used to estimate AE activity. Exposure to TMACl (Sigma Chemical Co) has been previously demonstrated as a valid technique for investigating the activity of the AE based on the fact that no recovery from TMACl-induced intracellular alkalosis is detected in HEPES−free solutions.9,10 Ten-minute pulses of different TMACl concentrations (10, 20, or 30 mmol/L) were applied without osmotic compensation and pH values recorded during the first minute after peak alkalosis were fitted to a straight line to estimate the initial velocity of pH recovery (dpH/dt).22

Statistics

Data are expressed as mean±SEM. Statistical analysis of results was performed using either Student’s t test or ANOVA followed by Bonferroni’s test, as appropriate. Values of P<.05 were considered significant.

Results

General characteristics for the various rat groups at the time of death are shown in Table 1. SBP remained elevated at hypertensive levels in untreated SHR throughout the 5-week experimental period but significantly decreased in the SHR-E group. Enalapril treatment completely regressed cardiac hypertrophy as shown by HW/BW and LVW/BW ratios.
Steady Myocardial pH

Fig 1 shows steady pH values determined in papillary muscles superfused with HEPES-buffered medium. In the absence of bicarbonate, steady pH is solely controlled by NHE activity. As a reflection of increased NHE activity in hypertrophic myocardium, steady pH value was more alkaline in SHR-C than in WKY-C. These data confirm previous results from our laboratory and are probably the result of an alkaline shift of the antiporter “set point.” In the same study, we also showed that the inhibition of NHE activity with the amiloride derivative EIPA normalized myocardial pH value in SHR. Enalapril treatment returned myocardial pH of SHR to values not different from those found in myocardium of normotensive rats (Fig 1). No significant changes in pH values were detected after the treatment of normotensive rats with enalapril.

With HEPES used as extracellular buffer, NHE is the only mechanism regulating pH; therefore, the steady pH values can be directly correlated to NHE activity. However, antihypertensive treatment could have changed the ability of cells to buffer protons. No significant difference between groups was detected when β values were determined (Table 2). Consequently, the reduction in steady myocardial pH value in the SHR-E group can be interpreted as the result of normalization of NHE activity.

When hypertrophic myocardium of SHR-C was exposed to a specific inhibitor of PKC activity, chelerythrine, pH value in HEPES buffer gradually decreased (Fig 2). By contrast, no significant effect of PKC inhibition on myocardial pH was observed in WKY-C. The different effect of PKC inhibition on SHR-C and WKY-C resulted in cancellation, after 25 minutes of drug administration, of the difference between pH values in hypertrophic and control myocardium. The best fit of chelerythrine-induced decrease in pH followed an exponential function that asymptotically approached a pH value of 7.07±0.04 (n=6). Interestingly, this value was close to the steady pH determined in WKY control-matched experiments (7.03±0.03, n=5) and not different from the overall mean value of steady pH values in WKY rats (7.12±0.03, n=20). The time constant of chelerythrine-induced pH decay was found to be 12.5±2.01 minutes. Essentially the same results were obtained when a structurally and mechanistically different PKC inhibitor, calphostin C, was used. In these experiments, pH in hypertrophic myocardium reached values not different from WKY-C (7.10±0.02, n=4) with a time constant of 16.1±4.1 minute after exposure to calphostin C. Therefore, the results suggest that the hyperactivity of NHE in hypertrophic myocardium is mediated by a PKC-dependent mechanism.

Fig 3 shows steady pH values in myocardium from control and enalapril-treated rats in CO₂/HCO₃⁻ buffer. In the presence of the physiological buffer, no significant differences in pH values were found between SHR-C and WKY-C or between enalapril-treated rats compared with their respective strain-matched untreated controls (ANOVA). We have previously reported the lack of pH difference between normal and hypertrophic myocardium under bicarbonate. In the same article we also demonstrated that if anion exchangers were blocked by SITS, pH value increased in hypertrophic myocardium bathed with bicarbonate buffer but not in WKY. The present results confirm therefore that NHE hyperactivity in hypertrophic myocardium is masked by a parallel enhancement of AE activity in the presence of bicarbonate.

Imposed Intracellular Acidification

When tissues are suddenly exposed to CO₂/HCO₃⁻-buffered media, CO₂ easily permeates the cell membrane, causing rapid and transitory intracellular acidification. During the pH recovery from CO₂-induced acid load, at least 50% of proton extrusion is carried by NHE in cardiac muscle. The changes in pH brought about on switching from HEPES to CO₂/HCO₃⁻-buffered superfuse were analyzed to appreciate the effect of enalapril treatment (Fig 4). The initial fall in pH was similar in all groups (Table 2), a fact consistent with the lack of difference in β values. However (and due to more alkaline steady pH values in SHR superfused with HEPES buffer), pH values of peak acidosis were higher in this group than in the remaining ones. For this reason, the rates of pH recoveries (dpH/dt) at a common pH value of 6.98 were compared. Fig 5 shows that in SHR the rate of myocardial pH recovery was about three times faster than in any other group and that chronic treatment with enalapril decreased its value to normal.

Acid-extruding mechanisms are modulated by pH; therefore, values of J,H values during the recovery from CO₂-induced intracellular acid load were estimated as a function of pH, in each experimental group. Fig 6 shows that a rather linear relationship was observed between β and ΔpH values. However, due to more alkaline steady pH values in SHR superfused with HEPES buffer, pH values of peak acidosis were higher in this group than in the remaining ones. For this reason, the rates of pH recoveries (dpH/dt) at a common pH value of 6.98 were compared. Fig 5 shows that in SHR the rate of myocardial pH recovery was about three times faster than in any other group and that chronic treatment with enalapril decreased its value to normal.

![Figure 1. Myocardial steady pH values in HEPES buffer.](image)

**TABLE 2. Cellular Buffer Capacity**

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>SHR-C</th>
<th>SHR-E</th>
<th>WKY-C</th>
<th>WKY-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>β</td>
<td>20.7±5.9</td>
<td>23.2±5.1</td>
<td>22.9±4.2</td>
<td>23.1±5.2</td>
</tr>
<tr>
<td>ΔpH</td>
<td>0.35±0.05</td>
<td>0.35±0.05</td>
<td>0.27±0.06</td>
<td>0.29±0.04</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

Values are mean±SEM. β (mmol/L per pH unit) was calculated as the ratio between Δ[HCO₃⁻]/ΔpH observed after switching from HEPES to CO₂/HCO₃⁻ buffer. ΔpH was estimated from pH immediately before the switch, and the lowest pH value was determined by back-extrapolation, as explained in "Methods." n indicates number of determinations. No significant difference between groups was detected (ANOVA).
relationship between $J_{H^+}$ and $pH_i$ was obtained in every case. However, for any given $pH_i$ value, $J_{H^+}$ values were larger in SHR compared with any other group, with the difference being larger for more acidic $pH_i$ values. The enhanced acid extrusion in SHR was reduced to values close to those seen in normotensive rats after enalapril-induced regression of cardiac hypertrophy. No significant difference was detected between WKY-C and SHR-E groups or between WKY-C and WKY-E. Thus, the enhancement of NHE activity detected after acid load in SHR was blunted by chronic treatment with enalapril. No significant difference was detected among groups. Values of intercepts were $7.17 \pm 0.02$, $7.14 \pm 0.02$, $7.10 \pm 0.01$, and $7.13 \pm 0.03$ in SHR-C, SHR-E, WKY-C, and WKY-E, respectively (NS, ANOVA). The intercepts usually reflect the value of the "set point" for the NHE when the experiments are performed in the absence of bicarbonate. However, we should keep in mind that in our experiments the acid load was induced by introducing CO$_2$/$HCO_3^-$ buffer. The contribution of bicarbonate-dependent mechanisms to $pH_i$ regulation takes place along with the recovery in $pH_i$.

**Imposed Intracellular Alkalization**

To explore AE activity, and due to the anion exchanger’s sensitivity to increases in $pH_i$, papillary muscles isolated from enalapril-treated and from untreated rat hearts were exposed to TMACl. TMACl-induced intracellular alkalinization has been previously demonstrated to be a valid technique for investigating the activity of the AE based on the fact that no $pH_i$ recovery is detected in HCO$_3^-$-free solutions. Fig 7 (top) shows the results of representative experiments in which similar peak $pH_i$ values were attained during TMACl pulses carried out on papillary muscles obtained from SHR-C and SHR-E superfused with CO$_2$/$HCO_3^-$ buffer. The initial velocity of $pH_i$ recovery was used as indicative of AE activity, and it was estimated from the linear fits of $pH_i$ records during the first minute after peak TMACl-induced alkalinization.

Using the same experimental approach, we have previously shown that recovery from alkaline loads was faster in SHR than in WKY and that lower $pH_i$ values were necessary to drive AE activity in hypertrophic myocardium. It can be appreciated now that enalapril treatment reduced the velocity of $pH_i$ recovery as well as it regressed cardiac hypertrophy (Fig 7, top). Bars in Fig 7 (bottom) depict the mean initial rate of $pH_i$ recovery in the overall experiments of both groups. A significant decrease in the rate of $pH_i$ recovery was observed after chronic treatment with enalapril. The initial rate of $pH_i$ recovery in SHR-E (0.019$ \pm 0.005$ pH unit/min, $n=10$) was not different from the values measured in WKY-E and WKY-C (0.024$ \pm 0.01$, $n=8$, and 0.021$ \pm 0.009$, $n=10$, respectively).

The rate of $pH_i$ recovery from TMACl-induced intracellular alkalinization was also measured after the inhibition of PKC activity in hypertrophic myocardium. Two structurally different PKC inhibitors, chelerythrine and calphostin C,
were used. Exposure to TMACl increased pH to a similar value in both the absence and presence of PKC inhibitors. However, the rate of pH recovery was significantly reduced by both PKC inhibitors (Fig 8). After PKC inhibition with either chelerythrine or calphostin C, the rate of pH recovery in hypertrophic myocardium was not different from the value measured in myocardium from normotensive rats at a comparable pH value. The results therefore suggest that enhanced AE activity in hypertrophic myocardium from SHR is mediated by a PKC-dependent mechanism(s).

**Discussion**

Increased NHE activity is one of the most common phenotypic differences found in hypertension. NHE is a member of a multigene family, and four NHE isoforms (NHE-1 through NHE-4) have recently been cloned. The NHE-1 isoform is expressed in virtually all tissues and species; it controls cytosolic pH and may also participate in cell growth. Evidence of enhanced NHE activity in hypertension is provided by observations in skeletal muscle of SHR and of hypertensive patients, in circulating blood cells such as platelets, leukocytes, erythrocytes; and in immortalized lymphoblasts derived from individuals with essential hypertension. The vascular smooth muscle from SHR also seems to exhibit enhanced antiport activity. In addition, we have reported an increased NHE activity in hypertrophic myocardium of SHR. However, the data presented here and our previous results show that no difference in myocardial pH between hypertrophic and normal myocardium can be detected in the presence of bicarbonate, despite enhanced NHE activity. This is due to the simultaneous hyperactivity of an acidifying (AE) and an alkalinizing (NHE) mechanism.

The question of whether antihypertensive therapy could affect the enhanced NHE activity was investigated before by Rosskopf et al in experiments conducted on platelets of hypertensive patients. These authors were unable to detect any normalization of NHE activity after 6 weeks of antihypertensive treatment with enalapril. They claimed that NHE hyperactivity was refractory to antihypertensive treatment and therefore appeared to be a relatively fixed parameter. Whether these contradictory results are a matter of difference in tissues, species, or the relative duration of treatments is not apparent at this time and requires further study. While this manuscript was in preparation, Sánchez et al reported that Na"/Li" countertransport (a mode of operation of NHE) in erythrocytes from hypertensive individuals was normalized after 6 months of enalapril treatment.

The major finding of this study was that the enhancement of NHE and AE activities in hypertrophic myocardium of SHR normalized after PKC inhibition. The C terminal of the rat NHE-1 possesses a putative PKC phosphorylation site, and many agonists promote phosphoinositide hydrolysis generating inositol triphosphate and diacylglycerol, the latter then stimulating PKC activity. In connection with this, it was demonstrated that inhibitors of PKC were able to relax aortic tone in vitro and lower blood pressure of SHR in vivo. Recent experiments from our laboratory showed that PKC inhibition decreased NHE activity in platelets from SHR but not in WKY. These present and previous data are consistent with a “PKC syndrome” that was suggested to play a central pathogenic role in hypertension. Kimura et al and Aviv et al have also presented several lines of evidence supporting a connection between [Ca"+]i, PKC, and NHE in the increased peripheral vascular resistance, cardiovascular hypertrophy, salt sensitivity, and insulin resistance of established hypertension. Moreover, stimulation of cell hypertrophy and activation of PKC by stretching isolated cardiomyocytes have been described and seem to be linked to autocrine-paracrine secretion of angiotensin II and/or endothelin-1. Significantly, both of these agonists are well known to stimulate PKC activity in the myocardium.

The regulation of the AE has been less investigated than that of NHE, but evidence for PKC involvement in its regulation in Vero cells was presented by Ludt et al. The amino acid sequences of the cardiac-specific AE3 isoform has been recently examined in rats and compared with that of mice and humans. In all three species, potential consensus
that its pharmacological effect was linked to a common PKC-related pathway. Whereas the link between PKC and NHE activity in hypertension is not new, the participation of the AE and its link with PKC in hypertension is novel and significant. Many questions related to the data presented herein need to be addressed. For example, which does enalapril treatment change first: hypertrophy, NHE activity, or AE activity? What is the temporal relationship between structural changes and exchanger activities? Is the increase in intracellular Ca\(^{2+}\) level found in hypertension the result or the cause of the hyperactivity of the exchangers? And finally, which PKC isoform is involved in determining the hyperactivity of the exchangers? All these questions should be addressed in future investigations.

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References


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Regulatory Mechanisms

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