Chronic Activation of Endothelin B Receptors
New Model of Experimental Hypertension

Gregory Fink, Melissa Li, Yanny Lau, John Osborn, Stephanie Watts

Abstract—Endothelin (ET) exerts powerful pressor actions primarily through activation of the ETA receptor subtype. The ETB receptor (ETBR) subtype, on the other hand, is generally thought to initiate physiological actions that decrease arterial pressure. Such actions include clearing ET from the bloodstream, initiating endothelium-mediated vasodilation, and facilitating renal sodium and water excretion. The effect of long-term activation of the ETBR on arterial pressure, however, never has been directly tested. In this study we evaluated cardiovascular responses to chronic (5-day) activation of ETBR in male rats using continuous intravenous infusion of the selective agonist sarafotoxin 6c. Surprisingly, we found that sarafotoxin 6c caused a sustained increase in arterial pressure that rapidly reversed on termination of infusion. The hypertension was associated with increased renal excretion of sodium and water and decreased plasma volume. Alterations in daily sodium intake did not affect the magnitude of the hypertension. Hemodynamic studies revealed a decreased cardiac output and increased total peripheral resistance during sarafotoxin 6c infusion. Infusion of sarafotoxin 6c caused a small increase in plasma ET levels. Nevertheless, the hypertension was not affected by coadministration of a selective ETA receptor antagonist (atrasentan) but was completely prevented by treatment with a combined ETA receptor and ETBR antagonist (A186280). These experiments reveal for the first time that chronic activation of ETBR in rats causes sustained hypertension. (Hypertension. 2007;50:000-000.)

Key Words: endothelin | ETB receptor | salt | hemodynamics

Endothelins (ETs) have powerful effects on arterial blood pressure regulation and contribute to the genesis of human and experimental hypertension.1 Most ET-mediated pressor actions result from stimulation of the ETA receptor (ETAR) found in vascular smooth muscle, kidney, heart, adrenal gland, and other tissues.1 The influence of ETB receptor (ETBR) on arterial pressure (AP) regulation has been more controversial, but the bulk of evidence supports an antihypertensive function. Knockout of the ETBR gene causes salt-sensitive hypertension in rats2 and mice,3,4 as does chronic pharmacological blockade of ETBR in a variety of species.5–8 One important antihypertensive mechanism associated with ETBR activation may be enhanced renal sodium and water excretion, because renal-collecting, duct-specific knockout of ETBR causes hypertension.9 Other studies, however, do not support a critical role for renal ETBR in controlling AP.3 ETBRs on endothelial cells act as plasma ET clearance receptors,10 and their absence or blockade produces increased plasma ET levels that can activate ETAR to cause hypertension.6 In addition, ETBRs located on endothelial cells promote vasodilation by releasing NO and prostanoids. Nevertheless, endothelial cell ETBRs do not seem necessary for chronic AP regulation, because their selective deletion does not cause hypertension.11 The failure to observe hypertension in ETBR knockout animals, however, could be a consequence of compensatory mechanisms engaged by the chronic loss of ETBR functions12,13 and, thus, may not reflect the true importance of ETBR in long-term pressure regulation.

Another approach to understanding how ETBRs influence AP regulation is to observe the effects of ETBR activation. Up to now, this has only been achieved using acute infusion of pharmacological agonists. For example, the snake venom peptide sarafotoxin 6c (S6c) is known to be a highly selective ETBR agonist.14 Soon after the discovery of ET peptides, Clozel et al15 showed that acute infusion of S6c into rats elicits a biphasic blood pressure response, a transient depressor followed by a longer pressor phase. The depressor response was shown to depend on the release of endothelial cell vasodilators. The mechanism of the pressor response was not established but did not seem to result from direct contraction of arteries, central effects of S6c, or the release of catecholamines or ET itself. Many subsequent studies using acute infusion of agonists (0 to 60 minutes) have confirmed these basic findings, although ETBR activation has been suggested by some to contract systemic arteries directly.16,17 Responses to acute activation of a receptor with relatively high doses of an agonist, however, may not accurately reflect its role in long-term physiological regulation. Furthermore,
blood pressure changes secondary to altered renal function generally take considerably longer to be expressed than those caused by vasoconstriction or vasodilation. Therefore, in the experiments reported here, we attempted for the first time to characterize the cardiovascular effects of chronic activation of ET\(_{A}\)R in conscious rats. This was accomplished using 5 days of continuous intravenous infusion of S6c into conscious rats instrumented for direct recording of AP and other cardiovascular variables. Our main new finding was that chronic stimulation of ET\(_ {A}\)R causes sustained hypertension.

**Methods**

**Animals**

All of the protocols were approved by the Michigan State University All University Committee on Animal Use and Care. Male Sprague-Dawley rats (Charles River Laboratories), weighing 275 to 300 g at the beginning of the study, were allowed free access to standard rat chow and distilled water for ≥5 days before surgery. During this time, rats were housed 3 per cage in a temperature- and humidity-controlled room with a 12-hour light/dark cycle.

**Surgical Methods: Standard Vascular Catheterization**

Rats under sodium pentobarbital anesthesia (50 mg/kg IP) were instrumented with permanent indwelling arterial and venous catheters as described previously.\(^{18}\) Antimicrobial prophylaxis and post-operative analgesia were achieved by administration of ticarcillin-clavulanate (200 mg/kg IP) and enrofloxacin (5 mg/kg IP) and buprenorphine (0.05 mg/kg SC), respectively. Rats recovered from anesthesia, under close observation, on a heating pad. Rats were then housed in standard stainless steel metabolic cages for the duration of the study. Free ends of the catheters exited the cage through a stainless steel tether connected to the rat by a plastic harness around the thorax. Meloxicam (1 mg/kg PO) was administered daily for 3 days for additional analgesia.

**Surgical Methods: Systemic Hemodynamic Measurements**

Studies on systemic hemodynamics were performed at the University of Minnesota. To allow continuous measurement of cardiac output (CO) in conscious animals, rats were instrumented with a flow probe on the ascending aorta as described previously.\(^{19}\) The rats were individually housed in plastic cages on recovery from anesthesia. A lightweight steel spring and custom-made polyester jacket secured and protected the venous catheter and flow probe cable. The spring and cable were connected to an electrical swivel (model SL6C, Kent Scientific) above the cage. The rats were given 10 days to recover after surgery. For the first 3 postoperative days, they were treated with 15 mg of ampicillin sodium and 1 mg of tobramycin sulfate IV for antibiotic prophylaxis. They also received 0.015 mg of buprenorphine hydrochloride IV for 5 days for analgesia.

**Cardiovascular Measurements: Standard Protocol**

Cardiovascular measurements were obtained according to our previously published methods.\(^{20}\) Briefly, systolic, diastolic, and mean APs (MAPs) and heart rate (HR) were recorded each morning between 8 and 11 AM. The transducers were connected to digital pressure monitors (Digi-Med blood pressure analyzer, Micro-Med) that provided input directly to a computerized digital pressure monitoring system. Data were collected once every second for 15 to 30 minutes. The daily value recorded was the average of the recordings taken over the last 5 minutes of the recording session.

**Cardiovascular Measurements: Hemodynamics Protocol**

The pressure transmitter signal was monitored by a Data Sciences receiver (model RPC-1) mounted behind the cage and connected to a data exchange matrix. The CO signal was transmitted via the flow probe cable to a flowmeter (model T-206, Transonic Systems); the output was digitized with a Data Sciences analog-to-digital converter (model C11V) and then sent to the data exchange matrix. Data acquisition and analysis were performed using Dataquest ART version 2.2 software on a Dell XPS B866 computer. AP, CO, and HR were sampled for 10 seconds every 5 minutes throughout the entire protocol. Total peripheral resistance (TPR) was calculated from the measured AP and CO (TPR=AP/CO).

**Experimental Protocols**

In the standard protocol, the rats were located in a climate-controlled room with a 12:12-hour light/dark cycle. They had free access to distilled water and sodium-deficient rat chow (170950, Teklad) ad libitum. All of the sodium chloride was delivered by continuous (24 hours per day) intravenous infusion in a volume of 5 mL/d. Sodium intake was controlled by adding different amounts of sodium chloride to the infusate. After 2 control days of measurements, S6c (American Peptide) was continuously infused intravenously at a rate of 5 pmol kg\(^{-1}\) min\(^{-1}\) for 5 consecutive days, then an additional 3 days of recovery measurements were collected. Rats in the control group received only saline vehicle. For the systemic hemodynamic protocol, rats consumed normal rodent chow, and there were 4 control days and 5 recovery days bracketing the S6c infusion period. In 1 group of rats studied using the standard protocol, ET\(_ {A}\)Rs were blocked throughout the experiment by administering atrasentan (also known as ABT-627) in the drinking water at a rate calculated to deliver 2 mg/kg per day. In a separate group of rats, both ET\(_ {A}\)R and ET\(_ {B}\)R were blocked throughout the protocol by administering A-182086 by intra-arterial injection twice daily at a dose of 12 mg/kg. Both atrasentan and A-182086 were generous gifts from Abbott Laboratories (Abbott Park, Ill).

**Additional Measurements**

Water drinking, water balance, sodium balance, plasma electrolytes, plasma volume (10 minute dilution volume of Evans’ Blue), hematocrit, and other plasma measures (requiring a 1.3-mL blood sample) were determined in some rats in the standard protocol according to our methods published previously.\(^{20}\) A separate group of rats received either S6c infusion (n=9) or saline vehicle infusion (n=8) using the standard protocol, and venous blood samples (1.2 mL) were drawn on control day 2, S6c infusion days 1 and 5, and on recovery day 2 for measurement of plasma ET-1 levels. The plasma was assayed using a commercial ELISA (ET-1 QuantiGlo chemiluminescent assay kit; R&D Systems), as described previously.\(^{21}\)

**Statistical Analyses**

Changes in variables measured over time within groups were evaluated using repeated-measures ANOVA followed by Tukey’s test to compare infusion period values with those on the final control period day. Between-group differences in variables measured over time were first assessed by a 2-way mixed-design ANOVA. If significant interactions or between-group differences were found, posthoc testing at each time point was performed using 1-way ANOVA and Bonferroni’s procedure to correct for multiple comparisons. Analyses were performed with SPSS (version 10). A P<0.05 was considered statistically significant.

**Results**

**Standard Protocol**

Figure 1 summarizes the changes in MAP in 6 separate groups of rats that received 5-day infusions of S6c or saline vehicle. Two groups of rats were maintained on fixed intakes of ≈0.02, 2.00, or 6.00 mEq/d of sodium, respectively,
throughout the protocol. In the 3 groups receiving S6c infusion, a significant increase in MAP (compared with control period values) was observed. The magnitude of increase in MAP was not significantly different in rats on different sodium intakes, although rats on a low-salt diet had the smallest overall response to S6c infusion. Rats receiving only vehicle exhibited a stable MAP throughout the protocol. Figure 2 illustrates changes in water intake, urine output, and sodium balance (intake − urinary excretion) in rats on 2.0-mEq/d sodium intake (data from rats on other sodium intakes were qualitatively very similar and are not shown). S6c infusion caused significant urinary losses of water and sodium during the first day or 2 before balance was restored during continued S6c infusion. Transient water and sodium retention occurred when S6c infusion was stopped. No significant changes in urine volume or sodium excretion were seen in vehicle-infused rats. The Table lists changes in plasma volume and electrolyte measures during S6c infusion in rats on 2.0-mEq/d sodium intake. Plasma volume decreased and hematocrit increased significantly in rats in the S6c group compared with the control group during the infusion period. Both measures declined during the study, likely as a result of repeated blood sampling over a relatively short period of time. There were no significant differences between the 2 groups for plasma sodium, potassium, osmolality, or urea nitrogen levels.

**Hemodynamic Protocol**

Figure 3 shows the results of continuous measurements of systemic hemodynamics in rats (n=8) receiving S6c infusion for 5 days. AP was significantly increased within 12 to 24 hours of starting S6c infusion. Hypertension was associated with significant decreases in CO and stroke volume (with a tendency for decreased HR) and a sustained increase in TPR. All of the hemodynamic indices returned to preinfusion values within 12 to 24 hours after S6c infusion was terminated.
Plasma ET Levels

The effects of S6c or vehicle infusion on plasma concentrations of ET-1 are shown in Figure 4. A small but statistically significant increase (on day 5) in plasma ET-1 occurred in rats receiving S6c. No significant change occurred in control rats.

ETAR and ETA/BR Blockade

The effects on S6c-induced hypertension of pharmacological antagonism of ET receptors are shown in Figure 5. Preinfusion AP values during blockade of ETAR with atrasentan were consistently lower (5 to 10 mm Hg) than in untreated rats. Infusion of S6c in atrasentan-treated rats, however, still produced an 20-mm Hg increase in AP relative to rats not receiving S6c. Furthermore, changes in urinary sodium and water excretion were similar to those observed in normal rats receiving S6c (data not shown).

Preinfusion AP values during combined blockade of ETAR and ETBR receptors with A-182086 also were consistently lower (5 to 10 mm Hg) than in untreated rats. Infusion of S6c in these rats, however, produced no statistically significant change in AP. There also were no significant changes in urinary sodium or water excretion during S6c infusion (data not shown).

**Changes in Plasma Volume and Electrolyte Measures During S6c Infusion in Rats on 2.0-mEq/d Sodium Intake**

<table>
<thead>
<tr>
<th>Measured Variable</th>
<th>Treatment</th>
<th>Control Day 2</th>
<th>Experiment Day 3</th>
<th>Experiment Day 5</th>
<th>Recovery Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume, mL</td>
<td>Control S6c</td>
<td>14.9±0.7</td>
<td>...</td>
<td>13.4±1.4</td>
<td>13.0±1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.6±0.4</td>
<td>...</td>
<td>10.3±0.8*</td>
<td>11.5±0.6</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>Control S6c</td>
<td>34.8±1.3</td>
<td>33.6±1.3</td>
<td>28.7±2.5</td>
<td>27.7±2.4</td>
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<tr>
<td></td>
<td></td>
<td>33.3±2.4</td>
<td>39.4±0.8*</td>
<td>37.2±2.0*</td>
<td>27.3±1.3</td>
</tr>
<tr>
<td>Plasma sodium, mEq/L</td>
<td>Control S6c</td>
<td>143.1±0.1</td>
<td>143.9±0.6</td>
<td>143.9±0.4</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>143.0±0.5</td>
<td>145.0±0.6</td>
<td>144.0±0.5</td>
<td>142.4±0.7</td>
</tr>
<tr>
<td>Plasma potassium, mEq/L</td>
<td>Control S6c</td>
<td>4.2±0.1</td>
<td>4.6±0.2</td>
<td>4.6±0.1</td>
<td>5.1±0.1</td>
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<td></td>
<td></td>
<td>4.3±0.1</td>
<td>4.5±0.1</td>
<td>4.8±0.1</td>
<td>5.0±0.2</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg%</td>
<td>Control S6c</td>
<td>14.1±1.2</td>
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<td>11.3±0.4</td>
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<td></td>
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<td>12.7±0.9</td>
<td>11.7±0.9</td>
</tr>
<tr>
<td>Plasma osmolality, milliosmol/L</td>
<td>Control S6c</td>
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<td>288.4±0.5</td>
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<td>286.6±1.1</td>
<td>289.5±1.4</td>
<td>288.0±0.7</td>
<td>285.8±0.9</td>
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</tbody>
</table>

*P<0.05 vs value in control group.

**Figure 3.** Twelve-hour average values (±SEM) of MAP, HR, CO, stroke volume (SV), and TPR in rats (n=8) receiving continuous (24 hours per day) intravenous infusion of S6c (5 pmol/kg per minute) bracketed by 4 control period days and 5 days of recovery. *Statistically significant difference (P<0.05) from the last 2 control period values.

**Figure 4.** Average (±SEM) plasma concentrations of ET-1 in rats receiving continuous intravenous infusion of S6c (5 pmol/kg per minute) or vehicle according to the same protocol shown in Figures 1 and 2. Plasma samples were obtained on control period day 2 (C), infusion period days 1 and 5 (A1 and A5), and recovery day 3 (R). Other symbols and abbreviations are the same as in Figure 1. *Statistically significant difference (P<0.05) from control period values.
The main objective of this study was to test the effects of chronic activation of the ET\textsubscript{B}R on AP. Based on the known physiological effects mediated by ET\textsubscript{B}R (see the Introduction), we hypothesized that S6c infusion would result in hypotension. Surprisingly, however, 5-day continuous infusion of S6c caused a sustained increase in AP, an effect similar to that observed previously using acute S6c injection or infusions. Other experiments were, therefore, conducted to gain insight into how S6c infusion leads to hypertension.

We showed previously that chronic infusion of ET-1 causes hypertension. This was the basis, in fact, for our choice of S6c infusion rate in the current study. Although ET-1 activates both ET\textsubscript{A}R and ET\textsubscript{B}R, there is general agreement that ET-1 increases AP by activating ET\textsubscript{A}R in the vasculature, kidney, and perhaps other organs. Although S6c seems to be a very selective ET\textsubscript{B}R agonist, it nevertheless could produce hypertension via the same mechanism as ET-1. There is some evidence to support this idea. For example, chronic infusion of ET-1\textsuperscript{22} or S6c (this study, Figure 3) increases AP by a similar hemodynamic mechanism: an elevation in TPR. Furthermore, S6c infusion caused a small elevation in plasma ET levels (Figure 4), probably by impairing the plasma clearance of ET. A similar effect occurs with ET\textsubscript{A}R antagonists\textsuperscript{7,10} and was shown to lead to hypertension by indirect activation of ET\textsubscript{A}R.\textsuperscript{6,7} It is possible then that S6c raises AP in a similar way, although the increase in plasma ET-1 levels with S6c was much smaller than that observed with ET\textsubscript{A}R antagonists, likely because S6c occupies fewer ET\textsubscript{A}Rs (and with lower affinity) than do the antagonists. Nevertheless, much additional evidence (including some from the current study) indicates that fundamentally different mechanisms account for the hypertension observed during chronic infusion of ET-1 versus S6c.

We showed previously that hypertension produced by exogenous ET-1 in rats is very salt sensitive.\textsuperscript{23} Thus, we tested whether the AP response to S6c infusion also is affected by salt intake. Unlike with ET-1, increments in pressure during S6c administration were not significantly different in rats on 3 widely different levels of daily salt intake (Figure 1). In addition, hypertension with ET-1 infusion occurred without any significant changes in sodium and water balance.\textsuperscript{22,23} In marked contrast, infusion of S6c caused large, though transient, decreases in sodium and water balance (Figure 2) associated with an increase in hematocrit and decline in plasma volume without measurable changes in plasma electrolyte values (Table 1). This disparity in effects on fluid balance also may explain subtle differences in the systemic hemodynamic responses to ET-1 and S6c, ie, S6c caused a significant decline in stroke volume and CO (Figure 3) not seen with ET-1.\textsuperscript{22,23} On a purely descriptive level then, the evidence indicates that S6c infusion is unlikely to cause hypertension by mechanisms identical to those activated by ET-1. Additional experiments were conducted, however, to confirm that stimulation of ET\textsubscript{A}R was not critical to S6c-induced hypertension.

Atrasentan is a potent and specific antagonist at ET\textsubscript{A}R\textsuperscript{24} that has been used previously to uncover ET\textsubscript{A}R-mediated cardiovascular effects.\textsuperscript{6,7,25} Here we examined the response to S6c infusion in rats treated with atrasentan throughout the duration of the experiment. The results were clear: blockade of ET\textsubscript{A}R decreased resting AP as expected but did not significantly affect S6c-induced hypertension (Figure 5). Thus, activation of ET\textsubscript{A}R is not a necessary component of hypertension caused by S6c.

Some studies indicate that the acute pressor response to S6c may be mediated by receptors that are neither ET\textsubscript{A}R nor ET\textsubscript{B}R subtypes.\textsuperscript{26,27} We performed a final experiment to test this possibility in chronic S6c-induced hypertension. Rats were treated throughout the standard S6c infusion protocol with the combined ET\textsubscript{A}R and ET\textsubscript{B}R blocking drug A-182086.\textsuperscript{24} A selective ET\textsubscript{A}R was not used, because such agents are known to increase resting AP when administered chronically to rats.\textsuperscript{20,28} Unlike treatment with atrasentan, A-182086 completely prevented hypertension (Figure 5) and body fluid changes during S6c infusion. We conclude that chronic S6c infusion in rats causes hypertension by stimulation of ET\textsubscript{B}R.

How does ET\textsubscript{B}R activation produce increased AP? A primary shift in the renal pressure-natriuresis mechanism, as demonstrated for ET-1-induced hypertension,\textsuperscript{29} does not seem plausible. Unlike with ET-1, S6c infusion caused significant sodium and water loss, in keeping with the known functions of ET\textsubscript{A}R in the renal tubules.\textsuperscript{9,30} Alternatively, the
salt and water loss caused by S6c may be because of a pressure-natriuretic effect consistent with a nonrenal mechanism of S6c-induced hypertension.

In rats, ET₄R activation causes reduced renal blood flow through constriction of afferent arterioles,¹⁵,³¹ although the response is complicated by other actions mediated by ET₄R.³² Primary renal vasoconstriction, therefore, cannot be ruled out as a mechanism of S6c-induced hypertension.

Arteries in most hemodynamically significant systemic (nonpulmonary) vascular beds show little or no contractile response to ET₄R agonists in vitro.³³–³⁵ It is reasonable to presume then that the increase in TPR observed during acute and chronic stimulation of ET₄R in vivo results, at least in part, from indirect mechanisms of arterial constriction, as was proposed soon after the discovery of the ET system.¹⁵ This postulate is supported also by findings in humans that S6c is a very weak constrictor of arteries in vitro but causes arterial vasoconstriction in vivo.³⁶ How might this occur?

One possibility is that ET₄R activation induces the release of an endogenous vasoconstrictor substance from a nonvascular tissue that affects arteries. This idea cannot be ruled out at this time, although we find no supporting evidence in the literature. Activation of the sympathetic nervous system is another possibility. We showed recently that infusion of S6c into rats causes increased concentrations of reactive oxygen species in sympathetic ganglia, which might serve to facilitate ganglionic transmission and thereby sympathetic arterial vasoconstrictor activity.¹⁸ The possibility of sympathetically mediated blood pressure responses via ET₄R stimulation is supported by earlier work from Pollock et al.³⁷ They demonstrated that acute infusion of S6c still causes pressor responses in rats lacking functional ET₄R in all tissues except those containing dopamine-β-hydroxylase (such as sympathetic neurons).

A final possibility is that venoconstriction contributes to S6c-induced hypertension. Approximately 50% of blood stored in veins is hemodynamically inactive but can be readily mobilized by active (venoconstriction) and passive changes in venous capacitance,³⁸ especially in the splanchnic circulation. Although S6c has minimal direct effects on arteries, it constricts most veins in vitro³⁹,⁴⁰ and causes venoconstriction in vivo.³⁶ Although no drugs with “pure” venoconstrictor properties are known, other relatively selective venoconstrictors have been shown to increase AP acutely and chronically.⁴¹–⁴⁴ Furthermore, experimentally induced reductions in splanchnic vascular capacitance elevate blood pressure via an increase in TPR.⁴⁵,⁴⁶ Net transfer of even a small quantity of blood from veins into the arterial system could elicit an increase in vascular resistance through myogenic arterial contraction caused by activation and/or upregulation of voltage-sensitive calcium channels.⁴⁷

Perspectives

Most studies published to date on ET₄R focus on tissue responses that would be expected to decrease AP. Although this is very likely the role of ET₄R under physiological conditions, the findings here demonstrate that chronic activation of ET₄R can increase AP. Further work is required to characterize fully the mechanisms of S6c-induced hypertension. However, a better understanding of this phenomenon could reveal novel mechanisms of hypertension development.

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References


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