Sodium-Selective Salt Sensitivity
Its Occurrence in Blacks

Olga Schmidlin, Alex Forman, Anthony Sebastian, R. Curtis Morris, Jr

Abstract—We tested the hypothesis that the Na\(^{+}\) component of dietary NaCl can have a pressor effect apart from its capacity to complement the extracellular osmotic activity of Cl\(^{-}\) and, thus, expand plasma volume. We studied 35 mostly normotensive blacks who ingested a low-NaCl diet, 30 mmol/d, for 3 weeks, in the first and third of which Na\(^{+}\) was loaded orally with either NaHCO\(_3\) or NaCl, in random order (250 mmol/d). In subjects adjudged to be salt sensitive (n=18; Δ mean arterial pressure: ≥5 mm Hg with NaCl load), but not in salt-resistant subjects (n=17), loading with NaHCO\(_3\) was also pressor. The pressor effect of NaHCO\(_3\) was half that of NaCl: mean arterial pressure (millimeters of mercury) increased significantly from 90 on low NaCl to 95 with NaHCO\(_3\) and to 101 with NaCl. The pressor effect of NaCl strongly predicted that of NaHCO\(_3\). As judged by hematocrit decrease, plasma volume expansion with NaCl was the same in salt-resistant and salt-sensitive subjects and twice that with NaHCO\(_3\), irrespective of the pressor effect. In salt-sensitive subjects, mean arterial pressure varied directly with plasma Na\(^{+}\) concentration attained with all Na\(^{+}\) loading. In salt-sensitive but not salt-resistant subjects, NaHCO\(_3\) and NaCl induced decreases in renal blood flow and increases in renal vascular resistance; changes in renal blood flow were not different with the 2 salts. Responses of renal blood flow and renal vascular resistance to NaHCO\(_3\) were strongly predicted by those to NaCl. In establishing the fact of “sodium-selective” salt sensitivity, the current observations demonstrate that the Na\(^{+}\) component of NaCl can have pressor and renal vasoconstrictive properties apart from its capacity to complement Cl\(^{-}\) in plasma volume expansion. (Hypertension. 2007;50:1085-1092.)

Key Words: blood pressure physiopathology • sodium • chlorides • bicarbonates • renal circulation • blacks

Blood pressure (BP) is said to be “salt sensitive” when it varies directly with the dietary intake of NaCl. Salt sensitivity characterizes “essential” human hypertension in perhaps half of those affected and confers its own cardiovascular risks, including that of the occurrence of hypertension.\(^1\) A pathophysiological mechanism for salt sensitivity has not been defined, despite recent demonstrations that human salt-sensitive hypertension can be caused by single genetic alterations that abnormally enhance the renal tubular reclamation of Na\(^{+}\) and Cl\(^{-}\).\(^-2\) These demonstrations comport with the formulation that an excessive renal retention of Na\(^{+}\) and Cl\(^{-}\) initiates all salt sensitivity and does so only by these ions’ joint osmotic expansion of extracellular fluid and thereby of plasma volume (PV).\(^2-5\) Na\(^{+}\) and Cl\(^{-}\) are the only physiological ions whose osmotic activities distribute throughout, and near exclusively to, extracellular fluid. Accordingly, in men selected only for salt-sensitive hypertension and rendered normotensive by NaCl restriction, NaCl loading induced within days both hypertension and a substantial expansion of PV, whereas Na-citrate loading induced neither.\(^6\) Such “selective” Na\(^{+}\) loading, ie, without Cl\(^{-}\), has repeatedly failed to elicit a pressor effect in NaCl-sensitive hypertension.\(^7\) Allegedly, “only NaCl causes an expansion of PV and a rise in BP.”\(^8\) However, selective Na\(^{+}\) loading appears not to have been investigated in salt-sensitive blacks. In them, compared with salt-sensitive whites, the pressor effect of dietary NaCl is, on average, greater,\(^9\) and, hence, the pressor agency of NaCl might involve more than its ions’ joint mediation of PV expansion. We find that in the more severely salt-sensitive blacks, selective Na\(^{+}\) loading (as NaHCO\(_3\)) induces an increase in BP that cannot be ascribed only to the concomitant increase in PV.

Methods
Participants and Setting
We studied 35 healthy blacks, ages 35 to 56, with screening BP <160/100 mm Hg and body weight (BW) within 30% of ideal BW, as inpatients at the General Clinical Research Center, University of California San Francisco. The study was approved by and conducted according to the guidelines of the University of California San Francisco Committee on Human Research. All of the participants gave written informed consent.

Basal Diet
Throughout the study, participants ate a eucaloric basal metabolic diet providing, per 70 kg of BW per day, 30 mmol of Na\(^{+}\) and
Intervention (Na⁺ Loading)
The study consisted of 3 consecutive 7-day periods. The 2 periods of oral Na⁺ loading were separated by a period of Na⁺ restriction. Na⁺, 250 mmol/70 kg of BW per day (but ≤300 mmol/d), was supplemented as NaCl during the first week and as NaHCO₃ during the third week, or vice versa. All of the participants received placebo tablets during the second (low-salt) week. Participants and nurses performing BP measurements were not informed about the content of the tablets.

Assessment of Na⁺-Induced Pressor Effects
With an automated oscillometric device (Dinamap, Criticon Inc) programmed to obtain 5 readings over a period of 5 minutes, BP was measured daily every 4 hours (between 6 AM and 10 PM) after 10 minutes of supine rest; an average daily BP was calculated. The first standardized BP measurements were obtained within ~2 hours of the subject’s arrival at the General Clinical Research Center, at 2 PM. The 2 PM values of day 1 are reported as “initial” (baseline) BP in Table 1 and Figure 1. To determine the pressor effects of Na⁺ salts, the average mean arterial pressure (MAP) of days 5 and 6 during Na⁺ restriction was subtracted from the average MAP of days 5 and 6 during loading of either NaCl or NaHCO₃. Salt sensitivity (SS) was defined as an NaCl-induced increase in MAP of ≥5 mm Hg and salt resistance (SR) as an increase of <5 mm Hg.

Metabolic Outcomes
We measured BW daily at 6 AM. Spontaneously voided urine was collected daily over 24-hour periods and analyzed for Na⁺, Cl⁻, and creatinine. During week 3 of the study, we measured weekly cumulative Na⁺ excretion, corrected for creatinine excretion and adjusted for 70 kg of BW. On the last day of each 7-day period, between 9 AM and noon, blood samples were obtained with participants in the supine position to determine levels of plasma renin activity (PRA), aldosterone, hematocrit, creatinine, and serum electrolytes by standard techniques.

Renal Hemodynamics
Para-aminohippurate clearance studies were performed in 31 participants (16 SS and 15 SR subjects) on the last day of each 7-day period using standard methods.

<table>
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<th>SR</th>
<th>SS</th>
<th>sNaS</th>
<th>cSS</th>
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<td>n (%)</td>
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<td>18 (51)*</td>
<td>11 (61)†</td>
<td>7 (39)†</td>
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<td>5 (28)</td>
<td>3 (27)</td>
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<td>28±2</td>
<td>29±3.5</td>
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*Initial* systolic BP and diastolic BP were obtained at 2 PM on the first day of the study, shortly after subjects were admitted, using the same standardized procedure as throughout the study. sNaS indicates “sodium-selective” SS; cSS, “classic” SS.

*Percentage of total number of subjects enrolled.
†Percentage of all SS subjects.
‡P<.005.

45 mmol of K⁺. They drank water, 20 g/kg of BW per day, during Na⁺ restriction and 35 g/kg of BW during Na⁺ loading, respectively.

Figure 1. Initial MAP and MAP with oral loading of NaCl, low Na⁺, and NaHCO₃ in SS (A) and SR (B) subjects, respectively. Na⁺ was supplemented as NaCl throughout the first week and as NaHCO₃ throughout the third week, or vice versa. Approximately half of the subjects received NaCl first. For all participants, week 2 was the low-Na⁺ period. A, MAP values grouped by supplement; B shows the 3-week time course of MAP in the same subjects. “Initial” BP was obtained at 2 PM on the first day of study, shortly after subjects were admitted, using the same standardized procedure as throughout the study. Other BP values are daily averages of days 5 and 6 of each of the 3 study periods. SR subjects had significantly lower BP than SS subjects (P<0.0001). In SR subjects, MAP did not change with changing levels of dietary Na⁺. In SS subjects, MAP was significantly lower with low Na⁺ intake compared with values both on admission and during Na⁺ loading with either NaCl or NaHCO₃. The sequence in which Na⁺ salts were loaded did not affect their pressor effects (B).
Data Analysis

We assessed the effects of Na⁺ loading as either NaCl or NaHCO₃ on BP using repeated-measures ANOVA, followed by a Newman-Keuls test. To assess whether the order in which the supplements were administered had an effect on outcome, we included “supplement order” as a between-group factor in the comparison. To rule out NaHCO₃- or NaCl-induced effects on serum K⁺ or hematocrit as a major source of between-group differences in pressor effects, we repeated between-group comparisons of pressor effects using changes in, and final concentrations of, serum K⁺ and changes in hematocrit as covariates. We assessed the effects of NaCl or NaHCO₃ on BW, hematocrit, electrolytes, and renal hemodynamics and the pressor effect in salt-sensitive subgroups using paired and unpaired t tests, respectively, for within-group and between-group comparisons. Nonparametric tests were used to assess the effect on PRA and aldosterone, as these variables were not normally distributed. Linear regression and Spearman rank correlation analyses were used to explore the relationship between variables. Data are presented as mean and 95% CI. The null hypothesis was rejected at P<0.05.

Results

Salt Sensitivity

Eighteen of 35 participants (51%; 17 males and 1 female) were SS (average NaCl-induced ΔMAP was 11±2 mm Hg), and 17 (49%; 15 males and 2 females) were SR (average NaCl-induced ΔMAP was −1±2 mm Hg; Figures 1 and 2A). In SS, but not in SR subjects, Na⁺ restriction during week 2 induced a significant hypotensive effect relative to initial BP.

Demographic Characteristics

SS subjects were slightly older than SR subjects and had a significantly higher initial BP, higher serum Na⁺ concentration, and lower body mass index (Table 1). After adjusting for age and body mass index, the difference remained significant for diastolic BP and MAP but not for systolic BP.

Pressor Effects of NaHCO₃

In SS but not in SR subjects, NaHCO₃ loading, compared with Na⁺ restriction, induced a significant pressor effect (Figures 1 and 2A and Table 2). However, this pressor effect was significantly less than that of NaCl. The sequence in which Na⁺ salts were administered did not affect their pressor effect (ANOVA, summary of effects: SS versus SR [group], P=0.004; NaCl versus low-NaCl versus NaHCO₃ [intervention], P<0.0001; sequence [of Na⁺ salt], P=0.65; interaction of intervention by group, P<0.0001; interaction of intervention by sequence, P=0.58; and interaction of sequence by group, P=0.27).

In 11 of 18 of the SS subjects, the NaHCO₃-induced increase in MAP was ≥5 mm Hg. In these 11 “sodium-selective” SS subjects (sNaS), the mean NaHCO₃-induced
increase in MAP was two thirds of that induced by equimolar amounts of NaCl (Figure 2B and Table 2). In 7 of 18 of the SS subjects, the NaHCO₃-induced increase in MAP was <5 mm Hg. In these “classic” SS subjects (cSS), the mean NaCl-induced increase in MAP was significantly lower than that in sNaS. In fact, the pressor effect of NaHCO₃ in sNaS was similar to that of NaCl in cSS (Figure 2B and Table 2). For all of the SS and SR subjects combined, changes in MAP induced by NaCl strongly predicted those induced by NaHCO₃ (Figure 3A). Mean values of ΔMAP adjusted for changes in serum K⁺ or hematocrit were not different from unadjusted means.

Effects of NaHCO₃ and NaCl on Renal Hemodynamics

In SS but not SR subjects, both NaHCO₃ and NaCl induced significant decreases in renal blood flow (RBF) and increases in renal vascular resistance (RVR; Figure 4). Changes in RBF did not differ significantly between SS subgroups. However, average changes tended to be greater in (the more salt sensitive) sNaS than in cSS. As this study was designed to compare 2 groups only, SR and SS, subgroup analysis was not expected to have sufficient power to detect relevant differences. For all of the subjects combined, NaHCO₃-induced changes in RBF and RVR, respectively, were strongly predicted by NaCl-induced changes (Figure 3B and 3C).

Metabolic Effects of NaHCO₃ and NaCl

Both NaCl and NaHCO₃ induced significant increases in BW (Figure 2C and 2D and Table 2). Increases were similar in SS and SR subjects, as well as in SS subgroups, and tended to be larger with NaCl than with NaHCO₃. Both NaCl and NaHCO₃ induced significant decreases in hematocrit values. Decreases were similar in SS and SR subjects but were significantly larger with NaCl than with NaHCO₃, in both groups (Figure 2E and 2F and Table 2). Changes in BW and hematocrit were not predictive of pressor effects for either Na⁺ salt.

Cumulative Na⁺ excretion with loading of either NaCl or NaHCO₃ did not differ between SS and SR subjects. For all of the subjects combined, cumulative Na⁺ excretion was 17% greater with NaHCO₃ than with NaCl (P=0.07). With NaCl

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<td></td>
<td>NaCl</td>
<td>0.4</td>
<td>0.2/0.3</td>
<td>&lt;0.001</td>
<td>0.3</td>
<td>0.1/0.5</td>
<td>&lt;0.001</td>
<td>0.3</td>
<td>0.2/0.4</td>
<td>&lt;0.05</td>
<td>0.3</td>
<td>0.1/0.9</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Aldo indicates aldosterone; Hct, hematocrit; PP, pulse pressure; SBP, systolic BP; DBP, diastolic BP; ns, not significant.

*Compared with a low-Na⁻ diet.
†Values are median and 25th/75th percentile.

Table 2. BP, Pulse Pressure, BW, Hematocrit, Aldosterone, and PRA During Low NaCl Intake and During Oral Na⁺ Loading With NaCl and NaHCO₃, Respectively, in SR and SS Subjects and in SS Subgroups (sNaS and cSS)
loading, cumulative Na⁺ excretion was (in millimoles per milligram of creatinine per 70 kg of BW) 0.63 ± 0.11 in SS subjects (n = 8) and 0.63 ± 0.10 in SR subjects (n = 8), and with NaHCO₃ loading it was 0.78 ± 0.16 (n = 9) and 0.69 ± 0.08 (n = 8) in SS and SR subjects, respectively.

Changes in plasma aldosterone and PRA were similar with NaCl and NaHCO₃ and were significant in both SS and SR subjects (Table 2). The NaCl-induced decrease in PRA but not in aldosterone was slightly but significantly greater in SR than in SS subjects. NaHCO₃-induced changes did not differ between SS and SR subjects.

Both Na⁺ salts induced significant increases in serum levels of Na⁺ in SS and SR subjects. In both groups, the increase was slightly larger with NaCl than with NaHCO₃, the difference being significant in SS subjects (Table 3). As expected, NaHCO₃ loading induced a small but significant decrease in serum K⁺ in both SS and SR subjects (Table 3). Serum K⁺ levels remained within the reference range in all but 1 SR subject, who developed mild hypochloremic alkalaosis with NaHCO₃ loading. The NaHCO₃-induced decrease was slightly but significantly larger in SS than in SR subjects. NaCl-loading induced a significant increase and NaHCO₃ loading a significant decrease in serum Cl⁻ in both SS and SR subjects (Table 3).

In SS but not in SR subjects, BP varied directly and highly significantly with the serum concentration of Na⁺ (R = 0.541; P < 0.0001). When sNaS only were included in the analysis, the relationship was stronger than in all of the SS subjects combined (Figure 5). For SS and SR subjects combined, the responses to NaHCO₃ of serum Na⁺, aldosterone, and PRA but not those of hematocrit or K⁺ were strongly predicted by the responses to NaCl.

Discussion

In the currently studied blacks, half were judged to be SS and half SR. In at least two thirds of the SS subjects, selective dietary Na⁺ loading with NaHCO₃ induced a pressor effect of ≥5 mm Hg, despite a sustained restriction of dietary NaCl. Thus, salt sensitivity occurs not only frequently in blacks, but in many the phenomenon is sodium-selective in that Na⁺ loading is pressor without concomitant Cl⁻ loading. In such sNaS subjects, the mean NaHCO₃-induced increase in MAP was fully two thirds of that induced by equimolar NaCl loading. To our knowledge, these observations provide the first demonstrations both that a non-Cl⁻ salt of Na⁺ can induce a pressor effect and that any salt other than NaCl can induce a pressor effect in humans.

In one third of the currently studied SS subjects, selective Na⁺ loading induced little or no pressor effect. For such salt

![Figure 3](http://hyper.ahajournals.org/)

Figure 3. Relationship between NaCl- and NaHCO₃-induced changes in MAP, RBF, and RVR in all subjects combined. NaCl-induced changes in MAP (A), RBF (B), and RVR (C) are highly predictive of NaHCO₃-induced changes. For all subjects combined, the magnitude of the NaHCO₃-induced changes amounts to approximately half that induced by NaCl. NaCl- and NaHCO₃-induced effects are presented as the percentage change from low-NaCl baseline.

![Figure 4](http://hyper.ahajournals.org/)

Figure 4. NaHCO₃- (□) and NaCl-induced (●) changes in RBF (A) and RVR (B) in SR and SS subjects. Values are the average changes from day 7 of low-NaCl to day 7 of Na⁺-loading periods. Values are means; error bars are 95% CI; P values for within-group comparisons of Na⁺-loading vs low-NaCl periods: *P < 0.05, ‡P < 0.001, respectively. In SS but not in SR subjects, NaHCO₃ and NaCl induced decreases in RBF and increases in RVR. The changes in both variables were similar with the 2 salts.

![Figure 5](http://hyper.ahajournals.org/)

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sensitivity is that induced only by Na\(^+\) and Cl\(^-\) loading combined.\(^6,10–12\) We assign the modifier “classic” (cSS). In sNaS subjects, NaHCO\(_3\) induced a pressor effect similar to that induced by NaCl in cSS subjects. For all subjects combined, the pressor response to NaHCO\(_3\) loading varied directly and highly significantly with the pressor response to NaCl loading. The pressor effect of NaHCO\(_3\) loading amounted to half that of NaCl loading. These observations would suggest that, in many salt-sensitive blacks, a selective pressor effect of dietary Na\(^+\) is a major component of the pressor effect of dietary NaCl, and the magnitude of the selective pressor effect of Na\(^+\) a major determinant of the severity of NaCl sensitivity.

In previous studies of mainly white hypertensive subjects\(^6,11\) and of animal models of salt-sensitive hyperten-

sion\(^13–15\) in which selective dietary loading of Na\(^+\) failed to elicit a pressor effect, the failure might be inferred to reflect a failure to expand PV to some critical extent.\(^2,3,5,7\) As judged by the currently observed changes in hematocrit, it appears that both NaHCO\(_3\) and NaCl induced expansion of PV. In accord with previous observations,\(^6\) the current observations would indicate that PV expansion with NaHCO\(_3\) was about half that with NaCl, not only in SS but also in SR subjects.

NaCl-induced PV expansion is formulated to be a critical event in the pathogenesis of salt-sensitive BP by entraining a transient increase in cardiac output (CO) that elicits a pressor effect in 2 phases and ways: an immediate direct pressor effect and, several days later, an indirect, sustained pressor effect that is mediated by an increase in systemic vascular resistance occurring only in autoregulatory response to the increase in CO.\(^2,3\) However, in NaCl-loaded salt-sensitive subjects,\(^16–19\) the apparent extent of neither PV expansion\(^16–19\) nor increase in CO\(^20\) induced by NaCl has predicted the extent of salt sensitivity. In a recent study comparing normotensive salt-sensitive and salt-resistant blacks with respect to the time courses of their hemodynamic and metabolic responses to NaCl loading, we observed similar increases in Na\(^+\) balance, PV, and CO. By contrast, in the 2 groups, the divergent pressor responses induced by dietary NaCl loading were attended from their outset by divergent vascular responses, systemic vascular resistance decreasing sharply and immediately in the salt-resistant but changing little in the salt-sensitive subjects.\(^20\) In all of the subjects combined, the changes in systemic vascular resistance induced by NaCl on the second day of its loading were strongly predictive of the changes induced by NaCl on MAP on the seventh day of its loading; NaCl-induced changes in PV and CO were not

**Figure 5.** Relationship between serum Na\(^+\) concentration and MAP in sNaS subjects at the end of the low-NaCl diet (●) and Na\(^+\)-loading with either NaCl (▲) or NaHCO\(_3\) (△). In sNaS, serum Na\(^+\) with and without Na\(^+\) loading is highly predictive of BP.
predictive. These observations indicate that, in the salt-sensitive subjects studied, an impaired systemic vasodilatory response to NaCl loading, but not an abnormally increased PV or CO, is critical to the pathogenesis of salt’s pressor effect.

In keeping with these observations, in the current study, the extent to which loading with either NaCl or NaHCO₃ induced PV expansion does not account for the extent of salt’s pressor effect. As judged by the decrease in hematocrit, the increase in PV induced by NaCl loading in the SS subject is indistinguishable from that induced in the SR subject. Indeed, while inducing a pressor effect only slightly less than that induced by NaCl, NaHCO₃ induced in the sNaS subjects a decrease in hematocrit only one third that induced by NaCl in the SR subject. In all SS subjects combined, as well as in the sNaS and cSS subgroups, the Na⁺-induced mean changes in MAP adjusted for changes in hematocrit were not different from unadjusted mean changes in MAP. These observations and considerations suggest that, in most SS blacks, the pressor effect of dietary NaCl involves something more than its capacity to mediate osmotic expansion of PV, the only capacity of NaCl called for in the traditionally formulated mechanism of NaCl’s pressor effect.2,3,5

In the SS subjects, and particularly in the sNaS subgroup, BP varied directly and highly significantly with the serum concentration of Na⁺, with and without Na⁺ loading, but not with changes induced in BW or hematocrit. This observation suggests that, in some salt-sensitive humans, the plasma concentration of Na⁺ attained with Na⁺ loading may critically determine the extent of the pressor effect of dietary NaCl. The observation accords with observations that Qi et al.21 reported in the NaCl-loaded Dahl SS/Jr rat, in which BP varied directly and highly significantly with plasma Na⁺ concentration, irrespective of the hydration state orally imposed. Qi et al.21 proposed, as have others,4,22,23 that “directly mediated increases in plasma Na⁺ can increase arterial BP in rats by mechanisms that are apparently not related to fluid volume changes.” An increase in plasma Na⁺ concentration may elicit a pressor effect by increasing cerebro-spinal fluid Na⁺ concentration24 and by thereby activating central sympathoexcitatory mechanisms that give rise to increased sympathetic outflow.21,25–27

In SS but not in SR subjects, NaHCO₃, as well as NaCl loading, induced a clear-cut reduction in RBF and, hence, a robust increase in RVR, a phenomenon described previously only with NaCl loading in salt-sensitive humans.28,29 including normotensive blacks.19 Clearly, the Cl⁻ component of NaCl is not required to elicit this dysfunctional renal hemodynamic response to Na⁺ loading. It has been proposed that a similar renal hemodynamic response is critically involved in the salt sensitivity of patients with “nonmodulating” essential hypertension.30 The extent of Na⁺-induced renal vasoconstrictive changes in those with salt sensitivity has been related to the extent of their pressor response.19,31

Perspectives

In establishing the fact of “sodium-selective” salt sensitivity, and its occurrence in many blacks who are salt-sensitive, the current observations extend to human relevance the consideration of ion-selective pressor phenomena, observed previously only as Cl⁻-sensitive hypertension in the spontaneously hypertensive rat32 and in the stroke-prone spontaneously hypertensive rat.33,34 In some instances of salt sensitivity, initiation of the pressor effect of dietary NaCl would appear to require something beyond, or other than, an abnormally enhanced renal retention of its ionic components and their complimentary osmotic capacities to expand PV,20,33,34 possibly an increase in plasma Na⁺ that elicits an increased central nervous system sympathetic outflow.4,21–23,25,27 Accordingly, the current observations expand the scope of possible pathogenic mechanisms of human hypertension and, hence, the scope of its potential treatment and prevention.

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Disclosures

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References

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