Change in Salt Intake Affects Blood Pressure of Chimpanzees
Implications for Human Populations

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Background—Addition of up to 15.0 g/d salt to the diet of chimpanzees caused large rises in blood pressure, which reversed when the added salt was removed. Effects of more modest alterations to sodium intakes in chimpanzees, akin to current efforts to lower sodium intakes in the human population, are unknown.

Methods and Results—Sodium intakes were altered among 17 chimpanzees in Franceville, Gabon, and 110 chimpanzees in Bastrop, Tex. In Gabon, chimpanzees had a biscuit diet of constant nutrient composition except that the sodium content was changed episodically over 3 years from 75 to 35 to 120 mmol/d. In Bastrop, animals were divided into 2 groups; 1 group continued on the standard diet of 250 mmol/d sodium for 2 years, and sodium intake was halved for the other group. Lower sodium intake was associated with lower systolic, diastolic, and mean arterial blood pressures in Gabon (2-tailed $P<0.001$, unadjusted and adjusted for age, sex, and baseline weight) and Bastrop ($P<0.01$, unadjusted; $P=0.08$ to 0.10, adjusted), with no threshold down to 35 mmol/d sodium. For systolic pressure, estimates were $-12.7$ mm Hg (95% confidence interval, $-16.9$ to $-8.5$, adjusted) per 100 mmol/d lower sodium in Gabon and $-10.9$ mm Hg (95% confidence interval, $-18.9$ to $-2.9$, unadjusted) and $-5.7$ mm Hg (95% confidence interval, $-12.2$ to 0.7, adjusted) for sodium intake lower by 122 mmol/d in Bastrop. Baseline systolic pressures higher by 10 mm Hg were associated with larger falls in systolic pressure by 4.3/2.9 mm Hg in Gabon/Bastrop per 100 mmol/d lower sodium.

Conclusions—These findings from an essentially single-variable experiment in the species closest to Homo sapiens with high intakes of calcium and potassium support intensified public health efforts to lower sodium intake in the human population. (Circulation. 2007;116:000-000.)

Key Words: blood pressure ▪ diet ▪ hypertension ▪ sodium

Evidence for the role of dietary sodium in high blood pressure comes from animal and clinical studies, clinical trials, and genetic, epidemiological, and anthropological findings.1–15 In preliterate societies in which sodium excretion is low (1 to 10 mmol/d) and potassium excretion is high (80 to 200 mmol/d), blood pressure does not rise with age, and incidence of cardiovascular disease is low.1,16–19 When populations migrate to a more urbanized environment, blood pressure rises over a period of months,20 associated with an increase in dietary sodium and other dietary and lifestyle changes.21,22

National and international agencies have recommended dietary sodium intakes of no more than 100 mmol/d sodium (6 g/d salt).3,4,6 Well-conducted short-term trials have found greater blood pressure lowering for sodium reductions to 50 to 60 mmol/d.11,12 Studies of higher primates provide the opportunity to alter dietary sodium experimentally for prolonged periods in the species genetically closest to humans.

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We previously reported large increases in blood pressure among 26 chimpanzees in Gabon fed increasing amounts of salt.7 We report here the effects on blood pressure of more modest alterations of salt intake in 2 sets of chimpanzees, a cohort of 17 animals in Gabon and 110 in Bastrop, Tex.

Methods

Gabon Data
This study was performed at the Centre International de Recherches Médicales, Franceville, Gabon (CIRMF). The 17 chimpanzees (11 of which were included in the study by Denton et al7) lived in long-standing, socially stable, small groups and were on a vegetable and fruit diet with low sodium and high potassium intake supplemented by a biscuit diet (25 g/kg body weight; Mazuri Primate Chunks, SDS, Essex, UK). This provided 75 mmol/d sodium at baseline in early 1997. The study was divided into 3 periods according to sodium content of the biscuits. After 2 years at baseline, the biscuit supplement was changed to 35 mmol/d sodium in December 1999 and to 120 mmol/d sodium from August 2000 until October 2001. The 120 mmol/d period was divided into 2: measurements were taken on average 5 months apart in these final 2 periods. Calcium content of these biscuits was reported as 2.48%. Daily calcium intake from biscuits was therefore 15.5 mmol/kg (body weight). The other constituents of the biscuits were constant.

Blood pressure measurements (per Denton et al7) were taken at the end of each of the first 2 periods and, in April to May 2001 and September to October 2001 (2 of the animals were pregnant in the last period). The study was approved by the CIRMF Animal Ethics Committee and International Advisory Committee.

Bastrop Data
The study was performed at the University of Texas MD Anderson Cancer Center in Bastrop, Tex. The 138 chimpanzees at the facility (No. 7775 or 7188) lived in long-standing, socially stable, small groups and were on a vegetable and fruit diet with low sodium and high potassium intake supplemented by a biscuit diet (25 g/kg body weight; Mazuri Primate Chunks, SDS, Essex, UK). This provided 75 mmol/d sodium at baseline in early 1997. The study was divided into 3 periods according to sodium content of the biscuits. After 2 years at baseline, the biscuit supplement was changed to 35 mmol/d sodium in December 1999 and to 120 mmol/d sodium from August 2000 until October 2001. The 120 mmol/d period was divided into 2: measurements were taken on average 5 months apart in these final 2 periods. Calcium content of these biscuits was reported as 2.48%. Daily calcium intake from biscuits was therefore 15.5 mmol/kg (body weight). The other constituents of the biscuits were constant.

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Statistical Analysis
For descriptive statistics, means and percentages were compared between groups. Given the close genetic similarity between humans and chimpanzees,23 we defined hypertension as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, as in human studies. Multiple linear regression was used to assess relationships of systolic, diastolic, and MAP to sodium intake, with time period, baseline weight, sex, and attained age included in the model; for the Bastrop data, phase (first versus second period) and group assignment, ie, controls (high-high sodium) versus intervention (high-low sodium), were also included. For the Bastrop data, the age adjusted to was 19 years, and the baseline weight adjusted to was 56 kg. In the Gabon data, the age adjusted to was 21 years, and the baseline weight adjusted to was 49 kg. Supplementary analyses also included baseline blood pressure and weight change. We used data from all time periods to construct the regression models; ie, in Gabon, all 4 periods (75 mmol/d, 35 mmol/d, both periods at 120 mmol/d) were included simultaneously. In addition, we tested for interactions of the effect of sodium on blood pressure by age, sex, baseline weight, and baseline blood pressure by including all these interaction terms simultaneously. Implicitly, we are assuming the same effect of sodium on blood pressure per animal; in particular, we assume independence of normal (gaussian) measurement errors. We fitted a random-effects model to the Gabon data, taking into account the component of error in common for the measurements made for each animal;24 for the Bastrop data, such a model is not appropriate because the model we fitted—effectively looking at the difference in blood pressure differences (first versus second period) between the control and intervention groups—results in the cancellation of the within-animal errors, giving a singular design matrix. Singularities also arose in fitting the descriptive models used in Figure 1, so these analyses were conducted without the use of random effects. Parameter estimates are presented with 95% confidence intervals (CIs); probability values are 2 tailed. Analysis was performed (by M.P.L.) in S-Plus (Insightful Corp, Seattle, Wash).25

Results

Descriptive statistics at baseline are shown in the Table. Compared with Gabon, the Bastrop chimpanzees had higher body weight and blood pressure. The access to the biscuits of the control group was 2.14 years apart in the intervention group. The average, the 2 blood pressure measurements were 2.14 years apart in the control group and 2.52 years apart in the intervention group. The study was approved by the University of Texas MD Anderson Cancer Center Institutional Animal Care and Use Committee.

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The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
weight ($P=0.02$) and blood pressures ($P<0.001$); $47$ (42.7%) animals in Bastrop had hypertension compared with $2$ (11.8%) in Gabon ($P=0.02$). Among the Bastrop chimps, the controls were younger ($P=0.001$) with lower blood pressures ($P=0.05$) than the intervention group.

**Gabon Data**

With sodium reduced from $75$ to $35$ mmol/d, systolic blood pressure (without adjustment) fell by $5.3$ mm Hg (95% CI, $-0.5$ to $11.2$); with intake increased to $120$ mmol/d sodium, it rose by $10.3$ mm Hg (95% CI, $4.3$ to $16.3$) after 9 months and a further $0.7$ mm Hg (95% CI, $-5.6$ to $6.9$) after 5 more months. Results after adjustment for age, sex, and baseline weight are shown in Figure 1. In random-effects multiple regression analysis with adjustment, sodium intake lower by $100$ mmol/d was associated with systolic blood pressure lower by $12.7$ mm Hg (95% CI, $8.5$ to $16.9$), diastolic blood pressure lower by $7.5$ mm Hg (95% CI, $5.1$ to $10.0$), and MAP lower by $9.9$ mm Hg (95% CI, $6.5$ to $13.2$) ($P<0.001$).

Significant interactions existed between sodium intake and sex ($P<0.001$), baseline weight ($P=0.038$), and baseline blood pressure ($P<0.001$) for systolic blood pressure. Per sodium lower by $100$ mmol/d, estimated falls in systolic pressure were larger in females than males by $21.0$ mm Hg (95% CI, $10.5$ to $31.5$), and by $5.9$ mm Hg (95% CI, $0.3$ to $11.5$) per $10$ kg higher baseline body weight, and by $4.3$ mm Hg (95% CI, $2.7$ to $5.9$) per $10$ mm Hg higher baseline systolic pressure.

**Bastrop Data**

Over the 2 phases of the study, blood pressure fell for the control group (standard diet), but the intervention group (reduced sodium) experienced a larger fall. Without adjustment, the differences in falls between the 2 groups (intervention minus control) were $-10.9$ mm Hg (95% CI, $-18.9$ to $-2.9$) systolic, $-9.4$ mm Hg (95% CI, $-16.1$ to $-2.8$) diastolic, and $-9.3$ mm Hg (95% CI, $-15.9$ to $-2.6$) MAP for a sodium reduction of $122$ mmol/d ($P=0.007$, $P=0.005$, and $P=0.006$, respectively). Adjusted for age, sex, and baseline weight (Figure 2), the analogous numbers were $-5.7$ mm Hg (95% CI, $-12.2$ to $0.7$) systolic, $-4.4$ mm Hg (95% CI, $-9.6$ to $0.8$) diastolic, and $-4.8$ mm Hg (95% CI, $-10.2$ to $0.7$) MAP ($P=0.08$ to $0.10$).

Significant interactions existed between sodium intake and sex ($P<0.01$), baseline weight ($P<0.002$), and baseline blood pressure ($P<0.001$) for all measures of blood pressure. Per $100$ mmol/d lower sodium intake, estimated falls in systolic pressure were larger in females than in males by $9.7$ mm Hg (95% CI, $5.1$ to $14.4$), and $2.6$ mm Hg (95% CI, $1.0$ to $4.2$) per $10$ kg higher baseline body weight, and by $2.9$ mm Hg (95% CI, $2.0$ to $3.9$) per $10$ mm Hg higher baseline systolic pressure.

**Discussion**

These studies of chimpanzees, the animal species phylogenetically closest to humans, allow conclusions of relevance to...
The blood pressure problem in human populations. First, blood pressure falls were as large as or larger for sodium intakes at or below current guidelines (range, 35 to 120 mmol/d) as they were in the range of "usual" sodium intakes of humans (120 to 250 mmol/d),14,26 (ie, 12.5/7.5 mm Hg per 100 mmol versus 5.7/4.4 mm Hg for 122-mmol difference in sodium). Second, they occurred in a vegetarian "high-potassium" (≥350 mmol/d) and "high-calcium" (≥350 mmol/d) environment in contradistinction to claims that sodium intake is not relevant to blood pressure in mineral-replete states.27,28 Unlike the human studies, these were single-variable experiments uncomplicated by other lifestyle exposures such as diet change, alcohol drinking, or cigarette smoking and were prolonged over years rather than days or weeks as in most human trials.8–10,12

The chimpanzees in Bastrop were substantially heavier than the Gabon group, possibly reflecting higher daily energy intake. The large difference in baseline blood pressure might be explained by the different baseline levels of daily sodium intake, 248 versus 75 mmol/d, and the weight difference; human trial data indicate that the effects of intervention on weight and sodium intakes are additive.29 The larger association of sodium intake with blood pressure among females than males is also found in humans;30 it might relate to the hormonal milieu among females or to their smaller body and hence kidney size, with reduced ability to deal with a sodium load many times above physiological need.30 It is unlikely that the levonorgestrel implants in the Bastrop females played a role because human data indicate that contraceptives containing progestogens alone (ie, in the absence of estrogens) do not affect blood pressure.31,32

One limitation, because of logistic constraints, was that the chimpanzees in Gabon acted as their own controls, in contrast to the earlier study of Denton et al.7 By including an extended 2-year run-in period, first a fall then a rise in sodium intakes, we aimed to minimize any possible "period" effect (ie, blood pressure changes occurring over time that were unrelated to sodium). The fact that the blood pressure changes closely mirrored those of sodium (ie, a fall followed by a rise) argues against a strong period effect, unrelated to sodium, in explaining our findings.

A further limitation in Bastrop was that despite randomization of the chimps by den (ie, not individually randomized for logistic reasons because the chimps live together in social groups), they were not well matched at baseline for age, weight, and blood pressure; therefore, we adjusted for age and weight (and sex) in the analysis. The control animals had an unexplained fall in blood pressure over the course of study, a well-known phenomenon in human trials, although in that setting blood pressure measurements are made in conscious individuals. By including a control group, we were able to adjust for this trend with time, although it reduced the power of the study to detect falls in blood pressure in the intervention compared with the control group. After adjustment, the differences in blood pressure between the two groups were not statistically significant.

Our findings extend the results of the study by Denton et al,7 which considered a group of 26 chimpanzees allocated into 2 age- and sex-matched groups; baseline sodium intake was 2 to 25 mmol/d (ie, the diet of a preliterate society in which essential hypertension is rare). The treatment group was given a diet with increasing additions of salt (5, 10, and 15 g/d; ie, 85, 170, and 257 mmol/d sodium), associated with a progressive increase in blood pressure in most animals. The highest intake significantly increased mean systolic pressure by 33 mm Hg, diastolic pressure by 10 mm Hg, and MAP by 15 mm Hg. Twenty weeks after the cessation of added salt, the blood pressures of the treatment group had fallen to baseline and control group values.7

The changes in blood pressure in the Denton et al study are greater than those observed here. The highest sodium
intake in the earlier study was almost 20 times the low baseline intake. In the present Gabon study, the increase in sodium intake was only 3- to 4-fold from the lowest level of 35 to 120 mmol/d and is more relevant to present-day discussions about optimal targets for dietary sodium reduction in humans.\(^1\) In Bastrop, sodium intake was halved from 248 to 126 mmol/d (ie, a decrease from the mean sodium intake of ≥200 mmol/d found in a number of populations worldwide\(^14\) to below the mean values of ~150 mmol/d currently seen in the United States and the United Kingdom).

The results of this study are qualitatively and quantitatively consistent with results of human epidemiological studies and clinical trial data. The International Cooperative Study on the Relation of Sodium and Potassium to Blood Pressure (INTERSALT) estimated that per 100 mmol/d lower sodium intake, systolic pressure of individuals was lower by 3 to 6 mm Hg at an average of 40 years of age, and the rise in systolic pressure between 25 and 55 years of age would be smaller by 9 to 11 mm Hg.\(^1\) The Dietary Approaches to Stop Hypertension (DASH-Sodium) study was a randomized feeding trial of 412 volunteers with and without hypertension (about two thirds had blood pressure levels in the prehypertension range).\(^1,2\) For a month, participants were fed diets containing 1 of 3 levels of sodium—141, 106, and 64 mmol/d—in combination with a normal diet (one typical of the United States) or a diet rich in vegetables, fruit, and low-fat dairy products (the so-called DASH diet).\(^1\) Reducing sodium intake from the highest to the lowest level (ie, by 77 mmol/d sodium) lowered blood pressure by 3 to 7/2 to 3 mm Hg systolic/diastolic (the range depending on whether the DASH diet was used), with larger decreases among those with hypertension.\(^1,2\) In DASH, blood pressure falls were greater when sodium was reduced from 106 to 64 mmol/d than when it was reduced from 141 to 106 mmol/d, suggesting possible nonlinearity in the blood pressure response to reduced sodium. In Gabon, the fall in blood pressure from 75 to 35 mmol/d was proportionately larger than the rise from 35 to 120 mmol/d. However, we were unable to assess possible nonlinearity of response in Bastrop because we tested only 2 levels of sodium.

Our results have important policy implications for human populations. Despite the plethora of studies implicating high salt intake in the origin of high blood pressure in humans,\(^2\) some commentators have continued to question its importance.\(^27,28\) Their arguments have been strongly refuted\(^1\) but include the notion that it is dietary quality rather than dietary sodium that is important for blood pressure control, particularly the need for adequate mineral intake (calcium and potassium).\(^28\) As noted, we have shown here that in mineral-replete states, lowered dietary sodium is associated with substantial reductions in blood pressure, without threshold, down to at least 35 mmol/d sodium. It also is suggested that reducing dietary salt would be appropriate only for hypertensive people.\(^9\) Although the effects were greater for animals with higher baseline pressures, at least in Gabon, most of the animals had blood pressures in the normal or prehypertension range (<140 mm Hg systolic, <90 mm Hg diastolic), unlike the human studies, which have been carried out predominantly among hypertensive individuals.\(^8–10\) This is important in considering dietary guidelines for the millions of people with blood pressures below the clinical criterion for hypertension but who nonetheless incur increased risk of heart disease and stroke.\(^3\)

Current public health guidelines to reduce sodium intakes in human populations to 100 mmol/d (6 g/d salt) are a compromise between what might be readily achieved given the high amounts of salt added to food in manufacture and the benefits of more extensive reductions in sodium intake.\(^1\) For such policies to be effective, investment by the food industry is needed to increase consumer choice by providing a far greater range of low-sodium and sodium-free products with informative and easily understood labeling of the sodium content of foods.

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**References**

Systolic blood pressures were lower by an estimated 6 to 13 mm Hg for sodium intakes lower by 100 to 120 mmol/d. These findings from the species closest to *Homo sapiens* support intensified public health efforts to lower sodium intake in the human population.
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