Patterns of Sodium Excretion During Sympathetic Nervous System Arousal

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The purpose of this study was to examine Na\(^+\) handling and regulation during 1 hour of behaviorally induced sympathetic nervous system (SNS) arousal followed by 2 hours of recovery. Two patterns of response were observed among experimental subjects, despite similar changes in blood pressure and heart rate. In one group \((n=19)\), Na\(^+\) excretion increased significantly during SNS arousal, which then decreased significantly during recovery (12.3 versus 16.0 versus 13.1 meq/hr, baseline, SNS arousal, recovery, respectively). Changes in Na\(^+\) excretion were correlated with changes in creatinine clearance from baseline to SNS arousal \((r=0.54)\) and SNS arousal to recovery \((r=0.58)\), and were accompanied by significant increases in plasma renin activity \((1.5 \text{ versus } 2.0 \text{ ng/ml/hr})\) and aldosterone \((8.5 \text{ versus } 10.3 \text{ ng/ml/hr})\) from baseline to SNS arousal. Na\(^+\) excretion decreased during SNS arousal in the other group \((n=17)\) and remained below baseline levels during recovery (16.2 versus 12.7 versus 11.9 meq/hr). These changes were associated with significant decreases in creatinine clearance from baseline to recovery \((138 \text{ versus } 121 \text{ ml/min/1.73 m}^2)\) and significant increases in plasma renin activity from baseline to SNS arousal \((1.3 \text{ versus } 2.2 \text{ ng/ml/hr})\) but not in aldosterone. Control subjects \((n=24)\) maintained baseline levels of each variable throughout the procedure. These results suggest that individuals differ in Na\(^+\) handling and regulation during behavioral arousal. Decreases in Na\(^+\) have been reported previously in humans and animals at risk for the development of hypertension. (Hypertension 1991;17:1156–1160)

Guyton\(^1\) has proposed that the renal–body fluid system is responsible for the long-term regulation of blood pressure (BP). Based on this model, increases in BP will cause the kidneys to increase the excretion of both salt (pressure natriuresis) and water (pressure diuresis), decreasing extracellular fluid volume and blood volume. This decreases cardiac output, which returns BP to previous levels. Conversely, decreases in BP increase Na\(^+\) and water reabsorption, increasing cardiac output and returning BP to previous levels. The research of DiBona\(^2\) and others\(^3\)–\(^9\) is consistent with the hypothesis that the sympathetic nervous system (SNS) can influence the renal–body fluid system through direct actions on the renal tubules, changes in renal blood flow and glomerular filtration rate, and changes in plasma renin activity (PRA). PRA controls circulating levels of angiotensin II, which directly stimulates the renal tubules, and leads to the release of aldosterone, both of which promote Na\(^+\) retention. The purpose of this study was to determine if there are different patterns of Na\(^+\) excretion \((U\text{Na}_V)\) in response to behaviorally induced SNS arousal, and to identify factors associated with the differences.

**Methods**

*Subject Characteristics and Casual Measurements*

A multiracial sample of 54 healthy, normotensive men (18–35 years of age) was recruited for this study. Health status was determined by medical history and a brief physical examination to rule out cardiovascular or other abnormalities. The subjects were randomly assigned into either a control group \((n=24)\) or an experimental group \((n=36)\).

*Testing Procedure*

The protocol was approved by the Institutional Committee on Human Research and the Clinical Research Center board. Pairs of subjects were admitted to the research center in the evening before the study and fasted with the exception of water after 10:00 PM until the completion of the study the following day. The morning of the study \((6:30 \text{ AM})\), the subjects voided and were given an oral water bolus of 50 ml/kg body wt to ensure sufficient urinary flow rate. A water volume equal to the amount voided was given after each void to maintain consis-
tent urinary flow. An indwelling venous catheter was inserted into the radial vein of the forearm for the collection of blood samples.

Experimental subjects underwent a 2-hour baseline, 1-hour SNS arousal, and 2-hour recovery period. Subjects were permitted to read, watch television, or study during the baseline and recovery periods. During the arousal period, the subjects competed in a series of computer video games, with an additional monetary award for the subject with the highest combined score. The subjects remained in a semirecumbent position throughout the baseline and recovery periods, except when it was necessary to void, and were seated in an upright position during the SNS arousal period. Control subjects underwent an identical protocol except for the SNS arousal period.

**Specimen Collection and Procedures**

Systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) were manually measured at 15-minute intervals. Urine specimens were collected at 60-minute intervals on the hour and blood specimens at 60 minutes on the half-hour. Serum and urinary creatinine concentrations were measured with a Beckman Creatinine Analyzer 2 (Beckman Instruments, Inc., Brea, Calif.). Endogenous creatinine clearance (Cc) was then calculated from the serum concentration and urine excretion values. Urinary Na\(^+\) and K\(^+\) were measured with a NOVA 13 electrolyte analyzer (NOVA Biomedical, Waltham, Mass.), and U_{Na}\(^+\) V, K\(^+\) excretion (U_{K}\(^+\) V), and fractional excretion of Na\(^+\) (FE_{Na}\(^+\)) were calculated. Plasma samples for the determination of PRA, aldosterone, and corticotropin were drawn and measured as described previously.\(^\text{10}\)

**Data Analysis**

Data analyses were performed on a Macintosh SE/30 computer with SUPERANOVA software (Abacus Concepts, Inc., Berkeley, Calif.). Analysis of variance tests were performed to determine group differences in demographic characteristics, as well as on each variable to determine group differences in baseline levels. In addition, separate analysis of variance models were performed for each group to examine the overall treatment effect on each variable. Values obtained during the second hour of the pretest period were designated as “baseline,” and during the second hour of the posttest period as “recovery.” If the treatment effect was significant, planned comparisons between the baseline, SNS arousal (hours 2 and 3 for the control group), and recovery conditions (hour 5 for the control group) were performed with the Dunn test using the Bonferroni correction to minimize the problem of multiple comparisons. A value of \(p<0.05\) was considered significant.

**Results**

**Control Versus Experimental Group**

Control and experimental subjects were similar in mean age (25 versus 24 years), body surface area (1.94 versus 1.98 m\(^2\)), and baseline levels of SBP (120 versus 118 mm Hg), DBP (76 versus 77 mm Hg), HR (61 versus 59 beats/min), U_{Na}\(^+\) V (13.4 versus 12.5 meq/hr), PRA (1.6 versus 1.6 ng/ml/hr), and aldosterone (11.9 versus 10.5 ng/ml/hr). The treatment effects for the control group were not significant for any of the variables (Table 1). The treatment effects for the experimental group were significant for SBP (118 versus 126 versus 119 mm Hg [baseline, arousal, recovery]; \(p<0.001\)), DBP (78 versus 85 versus 78 mm Hg; \(p<0.001\)), and HR (59 versus 70 versus 59 beats/min; \(p<0.001\)), with significant increases from baseline to SNS arousal and significant decreases from SNS arousal to recovery periods. The treatment effects also were significant for PRA (\(p<0.04\)) and aldosterone (\(p<0.01\)). PRA (1.4 versus 2.1 versus 1.7 ng/ml/hr) and aldosterone (9.7 versus 11.6 versus 11.1 ng/ml/hr) both increased from

| Table 1. Values During Baseline, Sympathetic Nervous System Arousal, and Recovery for Experimental and Control Subjects |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Excreters (n=19) | Retainers (n=17) | Control subjects (n=24) |
| Variable        | Baseline        | Arousal         | Recovery         | Hour 2           | Hour 3           | Hour 5           |
| SBP (mm Hg)     | 116±7           | 124±7*          | 117±6            | 117±10           | 115±9            | 119±9            |
| DBP (mm Hg)     | 77±7            | 84±5*           | 78±8             | 78±7             | 76±8             | 76±8             |
| HR (beats/min)  | 58±6            | 68±7*           | 58±7             | 60±5             | 72±10*           | 61±5             |
| U_{Na}\(^+\) V (meq/hr) | 3.7±1.3       | 5.0±2.3*        | 4.2±1.8          | 4.3±2.0          | 3.8±1.5†         | 4.8±2.3          |
| FE_{Na} (%)     | 1.4±0.7         | 1.5±0.6         | 1.5±0.8          | 1.4±0.4          | 1.2±0.5          | 1.2±0.4          |
| V (ml/min)      | 8.8±3.2         | 8.9±3.8         | 10±3.6           | 9.4±3            | 8.4±4.0          | 11.5±3.3         |
| S[Na\(^+\)] (meq/l) | 141±5          | 140±4           | 142±9            | 142±4            | 141±3            | 142±4            |
| ACTH (pg/ml)    | 35±16           | 34±11           | 36±11            | 31±14            | 29±7             | 28±10            |

Excreters are those subjects who increased sodium excretion during sympathetic nervous system (SNS) arousal; retainers are those who decreased sodium excretion during SNS arousal.

Values are mean±SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; U_{Na}\(^+\) V, K\(^+\) excretion; FE_{Na}\(^+\), fractional excretion of Na\(^+\); V, excretion rate; S[Na\(^+\)], serum Na\(^+\) concentration; ACTH, corticotropin.

\(^*p<0.001\). SNS arousal>baseline and recovery periods

\(^tp<0.05\), SNS arousal<recovery periods
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FIGURE 1. Line graphs showing patterns of sodium excretion (top panel) and creatinine clearance (bottom panel) for subjects who increased excretion during sympathetic nervous system (SNS) arousal (excreters) and decreased excretion during SNS arousal (retainers).

Patterns of Sodium Excretion

Two patterns of UNaV were identified among the experimental subjects (Figure 1). Approximately half of the subjects (n=19) increased significantly UNaV from baseline to SNS arousal (excreters), whereas the other half (n=17) decreased significantly UNaV from baseline to SNS arousal (retainers). The treatment effect for UNaV was significant for excreters (p<0.0002), who significantly increased UNaV from baseline to SNS arousal and significantly decreased UNaV from SNS arousal to recovery. The treatment effect for retainers also was significant (p<0.0001). Retainers had higher baseline levels of UNaV than excreters and a significant decrease in UNaV from baseline to SNS arousal, which remained significantly lower into the second hour of the recovery period. Excreters and retainers had similar excretion rates and serum Na⁺ concentrations at baseline, SNS arousal, and recovery periods (Table 1).

Baseline to SNS arousal but did not return to baseline levels during recovery period.

Plasma Renin Activity, Aldosterone, and Corticotropicin

Excreters and retainers had similar baseline levels of PRA, aldosterone, and corticosterone. The treatment effect for retainers was significant for PRA (p<0.006) but not for corticosterone. PRA and aldosterone both increased significantly from baseline to SNS arousal (Figure 2) and decreased from SNS arousal to recovery periods, though not significantly. For retainers, the treatment was significant for PRA (p<0.001) but not for aldosterone or corticosterone. PRA increased significantly from baseline to SNS arousal and decreased from SNS arousal to recovery periods, though not significantly.

Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate

Excreters and retainers had similar baseline levels of SBP, DBP, and HR. The treatment effect for SBP was significant for SBP (p<0.001), DBP (p<0.001), and HR (p<0.001). All three variables increased significantly from baseline to SNS arousal and decreased significantly from SNS arousal to recovery periods (Table 1).

Discussion

The results of this study indicate that 1 hour of behaviorally induced SNS arousal results in heterogeneous responses in Na⁺ handling and regulation. UNaV increased in response to SNS arousal in one group of subjects (excreters) and returned to baseline levels by the second hour of recovery. UNaV decreased in another group of subjects (retainers), remaining below baseline levels 2 hours into the median (n=19) did not show significant changes in any variable, including UNaV, throughout the study.
FIGURE 2. Line graphs showing patterns of plasma renin activity (top panel) and aldosterone (bottom panel) for subjects who increased sodium excretion during sympathetic nervous system (SNS) arousal (excreters) and decreased excretion during SNS arousal (retainers).

recovery period. Changes in $U_{Na^+}V$ for both groups were associated with changes in $C_G$.

Several factors may account for the differences in the patterns of $U_{Na^+}V$ in the present study. First, excreters and retainers may have experienced different levels of SNS arousal. However, both groups had comparable significant increases in HR, SBP, and DBP during SNS arousal and comparable significant decreases during recovery periods, suggesting that both groups experienced similar levels of SNS arousal. Second, differences may have been due to baseline levels of $U_{Na^+}V$ and $C_G$. Although not conclusive, similar analyses performed on control subjects did not support this explanation. Control subjects with higher baseline levels of $U_{Na^+}V$ than retainers and control subjects with lower baseline levels than excreters maintained baseline levels throughout the procedure. Third, differences between excreters and retainers may have been the result of differences in patterns of tubular reabsorption of Na$^+$. Contrary to this explanation were the findings that the baseline levels of FE$_{Na}$ were similar for both groups, and the levels of FE$_{Na}$ did not change during the study for either group. Fourth, differences may have been due to the activity of the renin-angiotensin-aldosterone system. Excreters and retainers had comparable significant increases in PRA during SNS arousal and nonsignificant decreases during recovery. However, excreters and retainers differed in changes in aldosterone. Specifically, excreters had significant increases in aldosterone in response to SNS arousal, with nonsignificant decreases during recovery. In contrast, retainers did not change aldosterone throughout the study. The differences in the response of aldosterone could not be attributed to differences in corticosterone, which did not change in either group throughout the study.

To our knowledge, only one previous study has examined changes in $U_{Na^+}V$ in humans in response to 1 hour of behaviorally induced SNS arousal. Light and her colleagues examined changes as a function of risk for the development of established hypertension. Risk was defined as either borderline systolic hypertension or a parental history of hypertension. Among subjects who had significant increases in HR during behaviorally induced SNS arousal, two patterns of $U_{Na^+}V$ were described. Subjects not at risk for the development of hypertension increased $U_{Na^+}V$ during SNS arousal, the pattern of response of our subjects classified as excreters. However, subjects at risk for the development of hypertension decreased $U_{Na^+}V$ during SNS arousal, which continued to decrease 1 hour into the recovery period. This is the pattern of response of our subjects classified as retainers. The factors responsible for differences in $U_{Na^+}V$ during SNS arousal were not identified.

Previous animal studies have examined the influence of SNS arousal on $U_{Na^+}V$. In a series of studies, Koepke et al measured changes in $U_{Na^+}V$ in response to aversive conditioning in dogs. In the first study, three of six conscious, saline-infused dogs decreased $U_{Na^+}V$ during SNS arousal, demonstrating individual differences in the response patterns as we found in our subjects. In a second study, nine dogs increased and 21 dogs decreased $U_{Na^+}V$ during SNS arousal. Contrary to our results, decreases in $U_{Na^+}V$ were coupled with decreases in FE$_{Na}$ in all dogs, but only 11 dogs also decreased glomerular filtration rate. In the third study, the conversion of angiotensin I to angiotensin II was blocked, which blunted the decrease in $U_{Na^+}V$ during SNS arousal. These results are consistent with our findings that decreases in $U_{Na^+}V$ during SNS arousal are associated with a failure to increase aldosterone. Anderson and his colleagues have examined the influence of behavioral arousal and Na$^+$ regulation on the development of hypertension. In these studies, dogs underwent a regimen of twice daily avoidance conditioning over a period of 12 days, increases in dietary Na$^+$ and decreases in dietary K$^+$ for 12 days, or a combination of avoidance conditioning and dietary modification. Dogs exposed to combined dietary modification and behavioral arousal developed hypertension, whereas those exposed to either dietary changes or behavioral arousal did not. Consistent with our results was the finding that changes in $U_{Na^+}V$ were associated with changes in $C_G$.

In summary, healthy, normotensive men differed in patterns of Na$^+$ handling and regulation during
and after 1 hour of SNS arousal. In one group, $U_{NaV}$ increased during SNS arousal and decreased during recovery. In the other group, $U_{NaV}$ decreased during arousal and continued to decrease 2 hours into the recovery period. This pattern has been reported previously in humans and animals at risk for the development of hypertension. This group was characterized by higher baseline levels of $U_{NaV}$ and $C_{O}$ and did not increase aldosterone during SNS arousal. Changes in $U_{NaV}$ in both groups were associated with changes in $C_{C}$. 

References


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