Sodium Sensitivity of Baroreceptors

Reflex Effects on Blood Pressure and Fluid Volume in the Cat

DIANA L. KUNZE AND ARTHUR M. BROWN

SUMMARY The sodium sensitivity of the carotid sinus baroreceptor reflex was demonstrated in anesthetized cats. Decreases in carotid perfusate sodium concentration [Na⁺], of 5% and 12.5% attenuated the depressor response to increased carotid sinus pressure. At constant sinus pressure, increases in systemic pressure and heart rate were produced when the carotid perfusate [Na⁺], was switched from 145 mm (control) to 138 or 127 mm, and this was accompanied by an increase in urine volume. The changes in [Na⁺], had no effect on the static pressure-volume relationship of the carotid sinus, indicating an action on the baroreceptors that already has been confirmed directly by studies of baroreceptor discharge. Chemoreceptor involvement, examined by recording chemoreceptor discharge, was negligible. The increase in urine volume was not dependent on intact renal sympathetic nerves, and renal denervation alone produced an increase in urine volume during control perfusion. At 87.5% carotid sinus [Na⁺], the urine volume increased from 28 ± 2.0 (SEM) to 31 ± 3.0 μl/min in innervated kidneys and decreased from 32 ± 3.1 to 27 ± 4.6 in denervated kidneys. Urine sodium excretion was higher in denervated kidneys (1.61 ± 0.21 μEq/min compared to 1.40 ± 0.14 μEq/min for innervated kidneys) and was unchanged in innervated kidneys (1.36 ± 0.18 μEq/min) as carotid perfusate sodium was decreased. However, sodium excretion from denervated kidneys was increased (1.86 ± 0.3 μEq/min) as carotid perfusate sodium was lowered. Renal sympathetic discharge also was increased as carotid sinus sodium was reduced. Thus, reducing extracellular [Na⁺], by as little as 5% produces significant baroreceptor reflexes, including a rise in blood pressure, and diuresis with no change in total sodium excretion. These studies indicate a role of the sodium sensitivity of baroreceptors in the regulation of blood pressure, body fluid volume, and body sodium.

THE PRESSURE response characteristics of arterial baroreceptors have been described in many studies of axonal discharge patterns. Attention has turned only recently to the ionic mechanisms underlying the receptor potential which initiates axonal discharge. The ionic sensitivity of aortic baroreceptors was studied by recording single fiber discharge in response to pressure changes while altering ionic composition of the fluid perfusing the isolated aortic arch. A reduction in perfusate sodium concentration increases threshold pressure and decreases sensitivity to suprathreshold pressures. The reflex consequences that might be anticipated from these results are an increase in arterial blood pressure and a decrease in the effectiveness with which baroreceptors control blood pressure. Furthermore, since the baroreceptors participate in the regulation of renal sympathetic activity and alterations in renal sympathetic nerve activity alter water and sodium reabsorption, an effect on urine volume and composition might be anticipated. The present report deals with the sodium sensitivity of the baroreceptor reflexes. We examined the reflex effects of changes in the sodium concentration [Na⁺], of the fluid perfusing carotid sinus baroreceptors and found that reductions in [Na⁺], of as little as 5% elevate arterial blood pressure, reduce the static open loop gain of the carotid sinus reflex, and increase heart rate and renal sympathetic discharge. Some preliminary results have been reported. A reflex diuresis also occurs, but Na⁺ excretion from the innervated kidney is unchanged. However, in denervated kidneys, natriuresis is elicited by the test carotid sinus solutions. Thus Na⁺-sensitive baroreceptor reflexes act to conserve Na⁺ and eliminate water. Under normal or closed loop conditions, this would restore [Na⁺]. Therefore, we propose that the arterial baroreceptors have a direct role in regulating sodium concentration and body fluid volume.

Methods

Twenty-six cats of either sex, weighing 2.5-4.5 kg, were fed Purina cat food and allowed to drink water freely for several days prior to an experiment. For the experiments, they were anesthetized with a mixture of chloralose (J.T. Baker Chemical Co.), 50 mg/kg, and urethane (Matthewson, Coleman and Bell), 200 mg/kg, injected intraperitoneally. The cervical vagi including the depressor nerves were cut bilaterally, and one carotid sinus nerve was cut. The carotid sinus with the intact sinus nerve was isolated by tying all arterial branches in the region, with the exception of the common carotid and the external carotid arteries. The common carotid then was cannulated and perfused via polyethylene tubing coupled to a constant flow pump (Holter, Inc.) which was connected to a reservoir containing Krebs-Henseleit solution gassed with 95% O₂ and 5% CO₂ and heated at 37°C. The perfusate was collected from the cannulated external carotid artery and discarded. Pressure in the perfusion circuit was non-pulsatile and was measured with a Statham P23Db strain gage manometer. The control carotid perfusate solution

From the Department of Physiology and Biophysics, University of Texas Medical Branch, Galveston, Texas. Supported by National Institutes of Health Grants HL-17601 and HL-16657. Address for reprints: Diana L. Kunze, Ph.D., Department of Physiology and Biophysics, University of Texas Medical Branch, Galveston, Texas 77550. Received June 6, 1977; accepted for publication January 16, 1978.
contained in mm: Na+, 145; K+, 6.0; Mg2+, 1.2; Ca2+, 1.1; Cl−, 127; HCO3−, 25; H2PO4−, 1.2; and dextran, 5.5. A solution containing 87.5% (127 mm) of control sodium was prepared by replacing 18.12 mm NaCl with 24.73 mm Tris [Tris-(hydroxymethyl)aminomethane], adjusting the pH to 7.4 by the addition of 18 mm HCl. A 95% sodium solution (138 mm) was made by replacing 7.25 mm sodium with 9.88 mm Tris. In five experiments, the sodium was replaced isosmotically by sucrose instead of substituting with Tris. Systemic pressure was measured through a polyethylene cannula inserted into the abdominal aorta via the femoral artery. The cannula was connected to a P23Db strain gage manometer connected to a Honeywell Accudata bridge amplifier. The pressure was recorded on tape (Hewlett Packard) and displayed on a Tektronix D10 oscilloscope and also on a Brush recorder.

The frequency response curve of the catheter manometer system was flat ±5% to 25 Hz. The heart rate was calculated from the recorded electrocardiogram or from the interval between arterial pressure pulses on the blood pressure record.

In 12 cats, carotid perfusion pressure was maintained constant while perfusate was switched from one containing 145 mm Na+ (control) to a test solution containing either 138 mm Na+ or 127 mm Na+ and then back to control and then to the other of the two test solutions, with a final return to control. The changes in heart rate (steady state) and blood pressure (maximum and steady state) from the control values were measured following introduction of each test solution.

In four additional experiments, carotid pressure was increased in step fashion from 60 to 180 mm Hg. The maximum reflex decrease in systemic pressure was plotted against carotid sinus pressure to give the characteristic curve. This was performed in control sodium (145 mm) and in 138 and 127 mm sodium solutions. Curves representing the cumulative data from the four experiments were fit by a least squares method and compared for significant differences as determined by F-test.

In five experiments, the pressure-volume (P-V) relationship of the isolated carotid sinus was examined. Flow was stopped and the sinus pressure was opened to the atmosphere or zero reference pressure. Known volumes of control and test solutions were injected using a 250-μl Hamilton syringe. The static pressures at each volume also were recorded.

In 12 cats in which urine flow was examined, an intravenous injection of Krebs-Henseleit solution equal in volume to 1.0% of body weight was given over a 20-minute period at the beginning of the dissection. This was followed by continuous infusion of Krebs-Henseleit solution at 5 ml/hr to stabilize urine flow. Urine output was measured for periods of 8-16 minutes by collecting the urine flowing from polyethylene catheters which were inserted into the ureters. Urine sodium concentration was measured using sodium glass miniature electrodes. The sodium glass was Corning NAS 11-18 and had a Nernstian response for Na+ and a selectivity of 50:1 and 100:1, respectively, over K+ and NH4+. The sodium values are reported as activities. The measurements were made on urine samples that had cleared the dead space of the catheters. This required about 2 minutes following changes in the carotid sinus test solutions. Differences in sodium and water excretion during the control and 87.5% sodium perfusion periods were tested for significance by paired t-test. In all experiments, one kidney was denervated by cutting all visible nerves entering the kidney in the vicinity of the renal artery and vein. The innervation of the other kidney was undisturbed. In four of these cats, renal nerve activity was recorded by placing the central cut end of the renal sympathetic fibers on bipolar platinum irradium recording electrodes. The activity was led to a PAR preamplifier (model 113), displayed on a Tektronix D13 storage oscilloscope and stored on tape (Hewlett Packard 3960) for subsequent analysis. The multifiber activity was summed using a Hewlett Packard Universal Counter (5325A) for 15-second periods. Total spike activity was counted for 2 minutes prior to 87.5% [Na+], and again for 2 minutes after 3 minutes in 87.5% [Na+], perfusion. Another 2-minute count was made 2 minutes after return to normal. The cats breathed spontaneously, and end tidal CO2 of the animal was recorded with a Beckman CO2 analyzer and was 4-5%. In four cats, activity of the carotid sinus nerve was recorded to determine whether chemo receptor activity was present at the flow rates used in these experiments. Perfusion with solution equilibrated with 95% N2 and 5% CO2 was used to elicit chemoreceptor discharge.

Results

A. Effect of Decreased Carotid Sinus [Na+]o, at Constant Carotid Sinus Pressure

In 12 cats, the carotid sinus was perfused with the control solution (145 mm sodium) at a mean pressure of 100 mm Hg (flow of 5 ml/min). The control solution then was switched to a test solution containing either 95% or 87.5% of the control sodium. There was an increase in arterial blood pressure which peaked in 2-4 minutes (Fig. 1). The arterial blood pressure declined slowly over the next 4-6 minutes to a steady level above the control arterial pressure. The final level was maintained for the duration of low sodium perfusion which ranged from 16 to 30 minutes (see Fig. 4). Twelve cats were tested with both 95% and 87.5% of control sodium. Mean arterial pressure rose 109 ± 2.61 SEM to a peak value of 125 ± 2.71 mm Hg and a steady state value of 120 ± 2.41 mm Hg (10% increase) as perfusate was switched from 145 to 138 mm sodium. Mean arterial pressure rose 109 ± 2.54 mm Hg to a peak value of 152 ± 2.82 mm Hg and a steady state value of 141 ± 2.38 mm Hg (29% increase) as perfusate was changed from 145 mm [Na+]o to 127 mm [Na+]o. The carotid sinus test solutions had less marked effects on heart rate. Bilateral vagotomy, section of one carotid sinus nerve, and maintenance of control pressures of 40-100 mm Hg in the innervated sinus resulted in high resting heart rates. Nevertheless, the test solutions usually elicited a further increase in heart rate. Seven of 12 cats showed an increase from 228 ± 8 beats/min to 241 ± 10 in 87.5% Na+, and 229 ± 8 to 234...
FIGURE 1  Effects on systemic blood pressure of changing carotid sinus perfusate sodium concentration, [Na+]₀, from 145 to 138 mM (A) and from 145 to 127 mM (B). Twenty minutes before trace C was taken, the carotid sinus nerve was cut. Then, 127 mM [Na+]₀ test perfusate was re-introduced. No change in pressure occurred.

± 8 in 95% Na⁺, whereas 5 of 12 cats showed no change in heart rate in response to test solutions. Section of the carotid sinus nerve eliminated the pressor response and increased heart rate, as well as the renal response to be described subsequently, indicating that the changes elicited by the test solutions were reflexly induced.

The measured osmolality of the solutions in which Tris was substituted for Na⁺ was unchanged, although an increase of 2% was calculated. The role of Tris was examined further by comparing the effects of substituting sucrose isosmotically for Na⁺. The results were identical. When NaCl was simply omitted from the 95% [Na⁺]₀ test solution, the measured osmolality was reduced by approximately 5%. However, the reflex effects were unchanged. Increasing the osmolality by 10% with sucrose also had no effect. In four experiments, we studied the effects of increasing [Na⁺]₀ by 14% to 165 min with Cl⁻ as the anion, which also increased the measured osmolality from 290 to 321 mOsm/liter. No effects were observed. Increases in [Na⁺]₀ of 20–25% had inconsistent effects on arterial pressure. Chloride ion concentration was unchanged in the Tris substitution experiments.

The pressure in the isolated carotid sinus at constant flow was unchanged by the test solutions, indicating that the resistance was unchanged and suggesting that the P-V relationships also were unaltered. This was examined directly by measuring the static P-V relationship in the five isolated sinus preparations in the control sodium, 95% sodium, and 87.5% sodium solutions. This relationship was unchanged. A similar result was obtained in the isolated rat aortic arch.6

B. Effect of Decreased Carotid Sinus [Na⁺], at Different Carotid Sinus Pressures

In eight cats, the mean carotid sinus pressure was raised in step fashion from a control value of 40 mm Hg to different values between 80 and 280 mm Hg, and the maximum decrease in systemic pressure was recorded. When the reflex change in systemic pressure was plotted against the carotid sinus pressure, a linear response range that varied from 90 to 180 mm Hg to 120 to 240 mm Hg among the preparations was found. In four cats in which the linear range fell between 80 and 180 mm Hg, the experiment was repeated over the linear range while perfusing with 87.5% or 95% [Na⁺]₀ test solutions (Fig. 2). Then the effect of the control solution was examined once more. The reflex depressor effects elicited by pressure steps above 80 mm Hg, using the control solutions, were reproducible for the two trials that bracketed the effects elicited during perfusion with the test solutions. The reflex changes in systemic pressure were decreased as [Na⁺]₀ was lowered, and the slope of the lines through points relating the carotid sinus pressure to systemic pressure also were reduced with decreasing [Na⁺]₀ values in the test solutions. The lines were fitted to the points by a linear least squares method. The slope of the line representing experiments in 95% control sodium was significantly different from that of 100% of control sodium at the P < 0.05 level; that of the line representing 87.5% of control sodium was different from control at P < 0.01.

The reduction in the static open loop gain of the carotid sinus reflex amounted to 58% in 87.5% [Na⁺]₀ and 15% in 95% [Na⁺].

C. Changes in Urine Flow due to Changes in Carotid Sinus [Na⁺]

In 12 cats, one kidney was denervated and the innervation to the other was left intact. Six of these were from the group of animals described in section A, and the other six...
Denervation caused a significant increase in urine output in the denervated kidney. The control and test solutions (P < 0.05). The Na+ test solution caused a significant increase in sodium output from the innervated kidney when 7/8 Na+ was used, whereas there was a significant increase under the same conditions in the denervated kidney (P < 0.01). Earlier studies did not contain sufficient observations to show these differences.

D. Changes in Excretion of Sodium due to Changes in Carotid Sinus [Na+]

In the same cats, the urinary sodium excretion rate was measured when the carotid sinus was perfused with control Na+ solutions and then with 87.5% Na+ solutions (Fig. 3B). In the control period, total sodium excretion was higher in the denervated kidney than in the innervated kidney. The rate of sodium excretion was not changed in the innervated kidney when the carotid sinus was perfused with 87.5% Na+, but it was increased significantly under the same conditions in the denervated kidney (P < 0.01). Earlier studies did not contain sufficient observations to show these differences.

E. Changes in Renal Sympathetic Activity due to Reductions in Carotid Sinus [Na+]

Renal sympathetic activity was recorded from the central cut end of the sympathetic fibers entering the kidney during carotid sinus perfusion with control solutions and during perfusion with 87.5% Na+ test solutions (Fig. 4). During sinus perfusion with control solutions, sympathetic activity occurred in bursts with silent intervals. This changed to a more continuous higher frequency pattern during perfusion with the test solutions. The bursting pattern returned when the sinus again was perfused with the control Na+ solution. Results of the four experiments are shown in Table 1, where spike activity was summed for three 2-minute periods, the first prior to the switch to 87.5% Na+, the second 3 minutes after switching to 87.5% Na+, and the third 2 minutes after return to control perfusion. Activity clearly was enhanced by the test solutions.

F. Chemoreceptor Activity in Carotid Sinus Nerve

The carotid sinus nerve was cut where it joined the glossopharyngeal nerve in four experiments. The nerve was desheathed and placed on bipolar recording electrodes. Baroreceptor activity was evident at constant pressures above 80 mm Hg. At 60–80 mm Hg, baroreceptor activity ceased (Fig. 5, a and b). In the four experiments, only a few spikes were present. Equilibration of the control perfusate with 95% N2-5% CO2 then was used to evoke carotid body activity (Fig. 5c). Perfusion with a lowered sodium solution equilibrated with 95% N2-5% CO2 then was used to test the effect of reduced sodium on carotid chemoreceptor discharge. Discharge was not significantly affected at 95% and 87.5% of control sodium in any of the experiments but was inhibited at 50% of control, using sucrose or Tris substitution (Fig. 5d, Tris substitution).
Discussion

The Pressor Response Elicited by Reduced Carotid Sinus [Na\(^+\)].

Small reductions in carotid sinus [Na\(^+\)], produce reflex increases in arterial pressure, heart rate, and urine flow. The effects are abolished by section of the carotid sinus nerves and in all likelihood are mediated by the carotid sinus baroreceptors. Changes in sinus distensibility do not appear to be involved, and the mechanisms underlying the [Na\(^+\)], effects are discussed in a later section. Comparable reductions in [Na\(^+\)], have been demonstrated to increase threshold and reduce the pressure sensitivity of aortic baroreceptors in the rat, probably by a direct action on the baroreceptors. The possibility that the effect is influenced by the carotid body chemoreceptors was made unlikely by the demonstration that chemoreceptor activity was not demonstrable in this preparation at flow rates producing carotid pressures of 60 mm Hg or greater. In addition, when chemoreceptor activity was evoked by perfusion with nitrogen-equilibrated solutions, this activity was unaffected by smaller changes in [Na\(^+\)], although it was eliminated by reducing sodium to 50% of control. In any event, a decrease in chemoreceptor discharge would have produced a decrease in systemic pressure, opposite to the effects of decreased baroreceptor discharge.

The effects of change in [Na\(^+\)], should not have been complicated by the Tris substitution. Tris is quite impermeable in vertebrate nerve membranes. Moreover, the same results were obtained by substitution of sucrose. Chloride is not involved, since the [Cl\(^-\)], was constant in control and test solutions. The baroreceptors also do not seem to be responsive to increases of 10% in osmolality and other baroreceptors, namely, those in the atrium, also do not respond to osmolality increases of 20%.

The increases in mean arterial pressure and heart rate elicited by reductions in sinus [Na\(^+\)], have been studied here by using static carotid sinus pressures ranging from 80 to 180 mm Hg. These effects probably are related directly to the demonstrated increase in baroreceptor threshold and reduction in suprathreshold sensitivity due to reductions in [Na\(^+\)]. There are precedents for basing

Table 1

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control, 145 mm Na(^+)</th>
<th>Test, 129 mm Na(^+)</th>
<th>Control, 145 mm Na(^+)</th>
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<td>1041</td>
<td>1299</td>
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</tr>
<tr>
<td>4</td>
<td>1305</td>
<td>1532</td>
<td>1289</td>
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</tbody>
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FIGURE 4 Renal nerve activity (bottom trace) in response to a decrease in carotid perfusate [Na\(^+\)] from 145 to 127 mm. The simultaneous increase in arterial blood pressure is shown in top trace. Note the different time bases for the two traces. The letters on both traces indicate the relationship of the renal neural discharge pattern with the arterial blood pressure.

FIGURE 5 The activity of the peripheral cut end of the carotid sinus nerve is shown when the carotid sinus perfusion pressure (CSP) is constant at 180 mm Hg (a). The pressure is dropped to 60 mm Hg and baroreceptor activity disappears (b). The perfusate is then equilibrated with 95% N\(_2\)-5% CO\(_2\) to elicit chemoreceptor activity (c). The chemoreceptor activity is inhibited (d) by perfusion with solution containing 50% of the control sodium (with sucrose or Tris substitution). Activity reappears upon return to normal sodium (e).
our interpretation on results from receptor experiments, since baroreceptor reflexes frequently are accounted for on the basis of predicted changes in baroreceptor discharge. The reduction in static open loop gain of the carotid sinus reflex (Fig. 2) also may be due to the reduced sensitivity to suprathreshold pressures shown by baroreceptors when $[\text{Na}^+]_o$ is decreased. Further evidence for reduced effectiveness of the carotid sinus pressure buffering mechanism at lowered $[\text{Na}^+]_o$ values came from experiments reported earlier in which modified periodic step changes in carotid sinus pressure were used. The modified periodic pressure steps were produced by a shaker at frequencies of 0.05 Hz and elicited inverse changes in arterial pressure that were about 180° out of phase (Fig. 1 of Ref. 15). When the test solutions were introduced, not only was mean arterial pressure increased, but the sinusoidal oscillations in mean arterial pressure were reduced. The transient maximum of the pressor response evoked by the reduction in carotid sinus $[\text{Na}^+]_o$ may be attributable to baroreceptor adaptation. However, the time course of the change in $[\text{Na}^+]_o$, as seen by the baroreceptors is unknown, so that the transient response is not interpretable in a straightforward manner. In addition, the central and efferent mechanisms may show time dependence. Thus, steps of carotid sinus pressure elicit responses with transient and static components.

The effenter mechanism underlying these sodium-induced reflex increases in blood pressure and heart rate have not been investigated in detail. However, a direct demonstration of enhanced renal sympathetic discharge has been shown, and it is likely that increased sympathetic discharge is the basis for the increase in blood pressure and heart rate. The vagi are not involved in the present experiments, since they were cut. A simple interpretation of the sodium-sensitive baroreceptor pressor reflex is that a reduction in $[\text{Na}^+]_o$ has reflex effects similar to a reduction in arterial blood pressure.

The mechanism whereby reductions in $[\text{Na}^+]_o$ reduce baroreceptor discharge is unknown. Small reductions in $[\text{Na}^+]_o$ may act directly on the baroreceptors by altering the equilibrium potential for Na⁺ as suggested in the model proposed by Saum et al. Precedents for sodium sensitivity exist from studies of other mechanoreceptors. The generator potential of crayfish stretch receptor is reduced by decreasing extracellular sodium. The Paci

The Renal Response to Reduced Carotid Sinus $[\text{Na}^+]_o$.

The diuresis due to a reduction in carotid sinus $[\text{Na}^+]_o$ is significant in both innervated and denervated kidneys. Although it is somewhat greater in the denervated kidneys, the responses are not significantly different. On the other hand, the natriuresis elicited by the test carotid sinus solutions differs significantly between innervated and denervated kidneys. Thus, the Na⁺ excretion of innervated kidneys is unchanged when carotid sinus $[\text{Na}^+]_o$ is reduced, whereas the Na⁺ excretion of denervated kidneys is enhanced significantly.

The mechanism of the diuresis has not been established. It may be due to the increase in arterial pressure alone, since increases in perfusion pressure cause a diuresis in isolated kidneys. However, the renal sympathetic nerves also may be involved. Section of these nerves produces a significant diuresis, as our experiments also demonstrate. Changes in renal blood flow and filtration fraction and redistribution of intrarenal flow have been provoked by adjusting the frequency of stimulation of the renal nerves. In the present experiments we have shown that renal sympathetic discharge is increased reflexly by the reduction in carotid sinus $[\text{Na}^+]_o$. This result was not unexpected, since reflex changes in renal sympathetic discharge resulting from changes in carotid sinus pressures have been reported. It is unlikely that changes in levels of antidiuretic hormone (ADH) are involved in the diuresis, since reductions in baroreceptor discharge increase ADH secretion and produce an antidiuresis. The absence of an accompanying natriuresis clearly depends on the presence of an intact renal innervation. Thus, natriuresis accompanies diuresis in denervated kidneys. The renal nerves have been shown to influence Na⁺ excretion from the kidneys, although the mechanisms are not understood. Stimulation of renal nerves increases reabsorption of Na⁺ and nerve section increases Na⁺ excretion. Compression of the common carotids or a decrease in carotid perfusion pressure, procedures expected to increase renal sympathetic discharge reflexly,
have been shown to decrease sodium excretion with no change in glomerular filtration rate. It is possible that the renin-angiotensin system also is involved.34

The importance of a diuresis without a change in urinary Na⁺ excretion is associated closely with the possible functional significance of the exquisitely sodium-sensitive baroreceptor reflexes we have reported presently. Thus, small reductions in extracellular [Na⁺], would, via the sodium-sensitive baroreceptor reflex, result in the excretion of a relatively hypernatriuretic urine and the restoration of extracellular [Na⁺] to control levels.

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D L Kunze and A M Brown

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