Neither Dorsal Root nor Baroreceptor Afferents are Necessary for Eliciting the Renal Responses to Acute Intravascular Volume Expansion in the Primate *Macaca fascicularis*

JOSEPH P. GILMORE, THOMAS V. PETERSON, AND IRVING H. ZUCKER

**SUMMARY** We determined the contribution of the dorsal roots, vagi, and sino-aortic nerves to the renal responses to acute isotonic, isooncotic intravascular volume expansion in the nonhuman primate, *Macaca fascicularis*. Expansion of the estimated blood volume by 15% produced a significant natriuresis and diuresis. There was no significant difference between the time to peak response for either. Neither dorsal rhizotomy (C₈-T₇) nor vagotomy and sino-aortic denervation had a significant effect on these responses. We conclude that these pathways are not necessary for eliciting the renal responses to hypervolemia in the nonhuman primate. *Circ Res 45: 95-99, 1979*

ALTHOUGH there has been a number of studies concerning the contribution of neural pathways to salt and water homeostasis in the dog, little data are available for the primate. However, even in the dog, there is disagreement as to whether cardiopulmonary and/or spinal pathways are necessary for, or contribute to, the renal responses observed when blood volume is altered (Gauer and Henry, 1976; Goetz et al., 1975).

Our previous studies on the nonhuman primate have questioned the importance of atrial receptors in modulating renal function in this species. Stimulation of atrial receptors in either *Macaca fascicularis* or *Macaca mullata* had no consistent influence on renal function although, at the same time, we could demonstrate a diuretic effect in the dog (Gilmore and Zucker, 1978a). In addition, we found that in the same species of monkey the diuretic and natriuretic responses to the central hypervolemia induced by head-out vertical water immersion were not influenced by bilateral cervical vagotomy (Gilmore and Zucker, 1978b), the latter an intervention which interrupts atrial receptor input to the central nervous system (CNS) (Gauer and Henry, 1976). The present study was undertaken to determine the extent to which baroreceptor deafferentation or thoracic dorsal rhizotomy alters the renal responses to acute isooncotic, isotonic intravascular volume expansion.

**Methods**

The experiments were performed on male *M. fascicularis* monkeys weighing 3.3–5.4 kg, maintained on monkey chow containing 0.35% sodium, and allowed water ad libitum. The monkeys were sedated with ketamine HCl (5 mg/kg, im), followed by pentobarbital sodium (30 mg/kg, iv), and supplemented as needed during the experiment. One femoral vein was cannulated for administering solutions and the other for measuring central venous pressure (CVP) via a transducer-tipped catheter (Millar Instruments) inserted to the level of the thorax. One femoral artery was cannulated to obtain blood samples and the other for the introduction of a second transducer-tipped catheter to measure arterial pressure at the level of the thoracic aorta. In the control animals, this catheter was advanced periodically into the left ventricle to measure left ventricular end-diastolic pressure (LVEDP); CVP was not measured. The ureters were approached via flank incisions and cannulated with polyethylene tubing. A tracheostomy was performed through a midline neck incision. All incisions were closed with surgical clips.

The study involved the following three groups of animals.

1. **Controls (n = 6)**

Monkeys in this group underwent only the surgical procedures noted above.

2. **Vagotomy and Sinoaortic Denervation (Vag-SAD) (n = 6)**

In this group, the midline neck incision for the tracheostomy was extended to permit isolation of both carotid sinuses. Each sinus was stripped completely of nerve fibers and connective tissue and
then painted with 1% phenol. Adequacy of sinus denervation was determined by the absence of a pressor response to carotid occlusion. The cervical vagi and aortic nerves also were sectioned bilaterally in the neck.

3. Dorsal Rhizotomy (C₈-T₇) (DR) (n = 5)

In this group of monkeys, a midline incision was made through the back and the vertebrae were exposed from C₈ through T₇. The laminae were removed, the dura and arachnoid opened, and the spinal cord exposed. The dorsal nerve roots from C₈ through T₇ were completely sectioned close to the cord bilaterally. The dura was left open and all muscle layers and the skin closed with sutures. During the rhizotomy, the monkeys received an intravenous infusion of lactated Ringer's solution (Travenol). After the surgery, the estimated blood loss was replaced with an equivalent volume of 6% dextran in isotonic saline.

After the surgery was completed in each group, the monkeys were placed in the recumbent position and a priming dose of creatinine (33 mg/kg) and paraaminobipurrate (PAH) (8 mg/kg) was given, followed by a sustaining infusion (0.75 ml/min) containing 1.6 g/L of both creatinine and of PAH in 0.6% NaCl solution. An hour later, urine collections during continuous 10-minute periods were started. Four-milliliter arterial blood samples were obtained at the midpoint of alternate urine collections and, after the plasma had been separated, the red cells were reconstituted in 6% dextran in isotonic saline and returned to the monkey intravenously. After 3-4 periods of relatively constant urine flow, the monkeys were volume-expanded with 6% dextran in isotonic saline (6% Gentran 75, Travenol), the volume given being equal to 15% of blood volume (blood volume estimated as 8% body weight). The dextran has an average molecular weight of 75,000 and was infused at a rate of 11.5 ml/min. The experiment was continued until urine flow declined to one-half its peak diuretic value.

All pressures were monitored continuously throughout the experiment with a Hewlett-Packard eight-channel recorder. Creatinine and PAH concentrations were determined with a Technicon Autoanalyzer, sodium and potassium by flame photometry, and osmolality by freezing point depression. These data were used to compute basic renal functions with an IBM 1800 computer.

Statistical analysis used the paired t-test for comparisons within groups and an analysis of variance and Newman-Keuls test for comparisons among groups. Probability values of less than 0.05 were considered statistically significant.

Results

Six control, six Vag-SAD, and five DR monkeys were studied. However, in one control monkey the clearances of creatinine and PAH were not determined. Table 1 shows the control values and those found at the time of peak diuresis for the three groups.

Renal Function

Except for a higher potassium excretion in the DR group, the control renal function was not significantly different among the three groups. In all groups, volume expansion was associated with significant increases in urine flow, sodium excretion, and osmolar clearance, with no differences in the magnitude of the peak responses. The percent of filtered sodium excreted (FLE) increased in all three groups but was of only borderline significance in the DR group. Free water clearance increased significantly only in the control group. Potassium excretion increased in the Vag-SAD monkeys but was unchanged in the DR and control groups. However, in four of the six control monkeys, potassium excretion decreased from a mean of 5.9 μEq/min to 0.0 μEq/min.

The times to peak diuresis or natriuresis were not significantly different amongst the three groups of monkeys.

Figure 1 shows the typical time course of the hemodynamic and renal responses to volume expansion in control animals.

Discussion

The renal responses of our control monkeys to an isooncotic, isotonic dextran infusion are, in most instances, qualitatively similar to those reported for man. In man, the intravenous infusion of isooncotic, isotonic dextran has been reported to increase urine flow (Bergström et al., 1959; Ulrych et al., 1964), sodium excretion (Bergström et al., 1959; Ulrych et al., 1964), the filtered load of sodium excreted (Ulrych et al., 1964), and C₄PAH at a time when PAH extraction remains unchanged (Bergström, et al., 1959). C₄PAH and potassium excretion have been reported either to increase (Ulrych et al., 1964) or not change (Bergström et al., 1959). Thus, it would appear that the monkey is a suitable model for...
Table 1 Hemodynamic and Renal Parameters Measured in Control and Volume-Expanded Monkeys in the Control and Neural Ablated State

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Vag-SAD</th>
<th>Rhizotomy (Ct-T 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>D</td>
<td>C</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>95±6.4</td>
<td>106±4.2</td>
<td>108±10.0</td>
</tr>
<tr>
<td>LVEDP (cm H2O)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CVP (cm H2O)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>167±7.4</td>
<td>179±2.9</td>
<td>231†±16.0</td>
</tr>
<tr>
<td>Ccr (ml/min per g)</td>
<td>0.90±0.06</td>
<td>0.91*±0.06</td>
<td>0.64±0.06</td>
</tr>
<tr>
<td>Cpar (ml/min per g)</td>
<td>2.36±0.36</td>
<td>5.29*±0.93</td>
<td>1.68±0.19</td>
</tr>
<tr>
<td>FF (%)</td>
<td>0.27±0.03</td>
<td>0.20</td>
<td>0.40±0.03</td>
</tr>
<tr>
<td>V (ml/min)</td>
<td>0.13±0.02</td>
<td>1.0†±0.16</td>
<td>0.19±0.02</td>
</tr>
<tr>
<td>Cmax (ml/min)</td>
<td>0.25±0.03</td>
<td>0.78*±0.08</td>
<td>0.29±0.07</td>
</tr>
<tr>
<td>Cmax (ml/min)</td>
<td>−0.12±0.02</td>
<td>±0.22*</td>
<td>−0.11±0.01</td>
</tr>
<tr>
<td>UvaV (μEq/min)</td>
<td>7.0±2.1</td>
<td>69.4*±12.5</td>
<td>12.5±6.8</td>
</tr>
<tr>
<td>FLE (%)</td>
<td>0.47±0.12</td>
<td>2.79*±0.53</td>
<td>0.76±0.34</td>
</tr>
<tr>
<td>UvaV (μEq/min)</td>
<td>5.7±1.5</td>
<td>3.3±3.2</td>
<td>6.6±2.1</td>
</tr>
<tr>
<td>Time to peak V (V) (min)</td>
<td>72±6.4</td>
<td>56±8.9</td>
<td>76±8.9</td>
</tr>
<tr>
<td>Time to peak UvaV (min)</td>
<td>72±6.4</td>
<td>76±18.9</td>
<td>70±20.0</td>
</tr>
</tbody>
</table>

Abbreviations: C = control; D = peak diuresis.
*Significantly different from control (P < 0.05).
†Significantly different from intact group (P < 0.05).

studying the effects of selective neural ablation on the renal responses to acute intravascular volume expansion. The present experiments clearly demonstrate that neural pathways traversing the vagus, aortic, and carotid sinus nerves and the thoracic dorsal roots are not necessary for the renal responses to acute isoosmotic, isotonic volume expansion.

A number of workers have reached conflicting conclusions regarding the contribution of various neural pathways to the renal responses resulting from acute volume expansion. Gilmore and Weisfeldt (1965) found that either bilateral vagotomy or carotid sinus denervation attenuated the diuretic but not the natriuretic response to acute intravascular volume expansion, whereas Pearce (1959) concluded that neither vagal nor carotid sinus pathways are necessary to elicit a natriuretic or diuretic response to the same stimulus. Atkins and Pearce (1959) later found that bilateral vagotomy significantly attenuated both the diuretic and natriuretic responses to acute intravascular volume expansion if the animals had not previously been hydrated. Although Pearce (1968) found that the chronic spinal dog (C7) showed no diuresis or natriuresis in response to acute volume expansion, Michaelis and Gilmore (1969) still observed diuretic and natriuretic responses to volume expansion in the acute spinal animal (C7), as did McDonald et al. (1970) in the chronic animal (C7).
Our failure to show a significant effect of DR on the renal responses to volume expansion is consistent with the results of McDonald et al. (1970) in the dog. Since spinal section at the C8 level substantially blunted the renal responses to volume expansion whereas section at the T8 level or DR (C8 to T6) plus bilateral cervical vagotomy did not, McDonald et al. (1970) concluded that thoracic efferent fibers are importantly involved in the renal responses to volume expansion. However, their conclusion that sympathetic efferents mediate the renal responses to volume expansion assumes the applicability of the law of Bell and Magendie that all ventral root axons are motor. In this regard, several workers have shown that the ventral roots receive a significant number of afferent axons. Both Clifton et al. (1974) and Applebaum et al. (1976) found that approximately 15% of the ventral root axons are sensory. Of further interest was the observation of Clifton et al. (1974) that none of the unmyelinated afferents studied had cutaneous receptor fields, suggesting that significant visceral information enters the CNS via ventral roots. Thus, if cardiopulmonary afferents contribute to the renal responses to volume expansion, they may enter the cord via the ventral roots so that the current study and the work of McDonald et al. (1970) would not rule out the possible involvement of all spinal afferent nerves.

The present experiments provide no information concerning the possible role of renal efferent nerves in modulating the renal responses to volume expansion. However, in a separate series of acute experiments in which sodium excretion was not measured, we determined the influence of acute volume expansion in monkeys in which efferent renal nerve activity was recorded using a flank approach. We found that, although volume expansion inhibited renal nerve activity when all reflex pathways were intact, volume expansion had no effect on renal nerve activity following vagotomy and sino-aortic denervation (Echtenkamp et al., 1978). Thus, if ventral root afferents are part of a reflex pathway which contributes to the renal responses to hypervolemia, the efferent limb of the reflex does not appear to involve renal efferent nerves and raises...
the possibility that a hormonal efferent mechanism(s) is involved.

We therefore conclude from the present experiments that baroreceptor or dorsal nerve root input to the CNS are not necessary for the renal responses to acute intravascular volume expansion in the primate. If, indeed, cardiopulmonary receptors are importantly involved in salt and water homeostasis, their afferents would appear to enter ventral roots.

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References


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