Aldosterone Responses to Hyperkalemia in Healthy Elderly Humans

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ABSTRACT
Plasma aldosterone levels are reported to be lower in healthy elderly individuals compared with young individuals, a difference exaggerated by sodium depletion or upright posture. The aim of this study was to determine the aldosterone response to increases in serum potassium with advancing age. In the Clinical Research Center, six healthy young (20 to 35 yr of age) and six healthy elderly (65 to 85 yr of age) subjects underwent evaluation of their aldosterone responses to potassium infusion (0.5 mEq/kg over 45 min). Both young and elderly subjects had similar basal serum potassium levels (4.3 ± 0.2 versus 4.4 ± 0.1 mEq/L), similar sodium and potassium excretion amounts and similar increase in serum potassium levels during infusion (to 5.0 ± 0.2 versus 5.1 ± 0.1 mEq/L). However, elderly subjects had lower basal levels of plasma aldosterone and a blunted aldosterone response to potassium infusion (P < 0.05, analysis of variance). Advancing age is characterized by relative hypoaldosteronism in the basal state as well as in response to hyperkalemia. This may contribute to an increased susceptibility to hyperkalemia if other potassium regulatory systems fail.

Key Words: Potassium, aging, aldosterone

It has been recognized for some time that plasma levels of renin and aldosterone decline with increasing age (1,2). Aging is also associated with a decrease in distal renal tubular functions (3,4). The ability to conserve sodium in response to low salt intake is impaired (3), and the potential for disposal of potassium and acid loads declines with aging (4). The distal tubule constitutes the major site for excretion of potassium (5). At this site, sodium is reabsorbed from the tubular lumen in exchange for potassium secreted from the tubular interstitium. This exchange is enhanced in the presence of aldosterone (6,7). Because renin secretion declines with age (1,2), hyporeninemic aldosteronism is predominantly a syndrome of the elderly (8–10). The frequent occurrence of hyperkalemia in elderly patients (9) is often attributed to a defective response of the renin/aldosterone system to potassium, although direct evidence for this is sparse. The aim of this study was to assess the aldosterone response to potassium infusion in a group of healthy elderly subjects and to compare the response with that of a young group.

METHODS
The study was approved by the Beth Israel Hospital Committee on Clinical Investigation. Six young (20 to 35 yr of age) and six elderly (65 to 85 yr of age) volunteers were recruited. Volunteers gave written informed consent before their inclusion in the study. Volunteers were screened clinically (by history and physical examination), hematologically (by complete blood cell count) and biochemically (by BUN, serum creatinine, serum sodium, potassium, chloride, and bicarbonate levels). Subjects were all normotensive, with normal laboratory blood work results, and normal electrocardiogram and chest radiograph results. Volunteers were not taking any medications. Only men were studied, to avoid the variability in baseline aldosterone levels that occurs in women with fluctuation in the menstrual cycle.

The subjects were admitted to the Clinical Research Center of the Beth Israel Hospital on the evening before the study, and fasted overnight. The next morning, an intravenous cannula was inserted into each forearm of each subject: one for infusion of potassium and one for blood sampling. Three hundred mL of water was given by mouth for comfort and to initiate urine flow. Samples were drawn through an indwelling catheter, without the use of a tourniquet. No heparin flushes were used. Two basal samples of all parameters were taken 30 min apart before potassium infusion. The basal data for urinary sodium and potassium levels were obtained from a 2-h timed sample collected before initiation of the infusion. Each subject then received an infusion of potassium chloride (0.5 mEq/kg in 250 mL of normal saline over 45 min). This dose had been demonstrated previously in our laboratory to increase plasma potassium by approximately 0.6 mEq/L. Blood samples were drawn at 15- to 30-min intervals during and after the infusion. The last samples were drawn 1 h 15 min after the infusion ended.

Serum potassium levels were measured with an ion electrode analyzer (Labyte, Beckman Instruments, Brea, CA). Creatinine clearance was calculated from a pretest, 12-h overnight urine collection obtained at the time of initial screening. Aldosterone was assayed by the use of a standard double-antibody RIA (Diagnostics Products Corp., Los Angeles, CA). PRA was determined by RIA of the generation of angiotensin I (Diagnostics Products Corp., Los Angeles, CA). Atrial natriuretic peptide levels were measured by the use of a standard double-antibody RIA on extracted, lyophilized plasma collected and processed as previously described, with

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RESULTS

Baseline serum levels and urinary potassium and sodium levels were similar in both young and elderly subjects (Table 1). The elderly subjects had lower basal creatinine clearance, lower plasma levels of aldosterone, lower PRA, and higher atrial natriuretic peptide levels than the young subjects. Mean arterial blood pressure tended to be higher in the elderly subjects, but did not reach the level of statistical significance. During potassium infusion, both and young and elderly subjects had similar incremental increases in serum potassium levels, with peaks of 5.0 \( \pm \) 0.2 versus 5.1 \( \pm \) 0.1 mEq/L, respectively (see Figure 1). However, it took longer for potassium levels to return to baseline in the elderly (Figure 1).

The response of plasma aldosterone to potassium infusion was greatly blunted in elderly subjects, compared with that of the young subjects (Figure 1) \((P < 0.05,\) analysis of variance). In young subjects, plasma aldosterone rose from 94 \( \pm \) 11 pg/mL before the infusion to 216 \( \pm \) 19 pg/mL at the end of the infusion, an increase of 130%. Aldosterone rose from 64 \( \pm \) 13 pg/mL to only 117 \( \pm \) 25 pg/mL in the elderly subjects, an increase of 80\% \((P < 0.01,\) young versus elderly).

DISCUSSION

The elderly individuals in this study had lower plasma levels of aldosterone than the young subjects, both at baseline and in response to hyperkalemia. It should be emphasized that these were healthy elderly subjects without any features suggesting the syndrome of acquired hypoaldosteronism. That syndrome (with or without hyporeninemia) is more prevalent in the elderly (8–10) and is characterized by hyperkalemia associated with metabolic acidosis, mild to moderate renal failure, and decreased plasma aldosterone levels. It is likely that this clinical syndrome represents an exaggeration of the blunted aldosterone response to hyperkalemia that appears to be characteristic of normal aging.

It has been well documented that PRA and aldosterone levels decline with increasing age (1,2). Factors that regulate the renin-angiotensin-aldosterone system include systemic blood pressure and intravascular volume. Serum potassium is also a physiologically important regulator of aldosterone. Increased levels of serum potassium directly stimulate aldosterone release from adrenal glands both in vivo (6,7) and in vitro (12), by a pathway that does not involve renin/angiotensin II. Aldosterone in turn facilitates \(Na^+\)-\(K^+\) exchange in the distal tubule, resulting in a return of the serum potassium level to normal (6,7).

The reasons for the diminished aldosterone response to potassium infusion in the elderly subjects in our study remain unclear. Although potassium regulates aldosterone release from the adrenal zona glomerulosa directly, without the mediation of angiotensin II (12), potassium and angiotensin II seem to act synergistically to increase aldosterone secretion. The response of adrenal cells to potassium is conditioned by the simultaneous presence of angiotensin II (13,14). When angiotensin II levels are depressed, as in the elderly, higher levels of serum potassium should be required to elicit an increase in aldosterone secretion.

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**TABLE 1. Baseline data**

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33 (\pm) 2</td>
<td>78 (\pm) 3(^b)</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>88 (\pm) 3</td>
<td>96 (\pm) 4</td>
</tr>
<tr>
<td>Cor (mL/min)</td>
<td>120 (\pm) 8</td>
<td>95 (\pm) 9(^p)</td>
</tr>
<tr>
<td>UNa (\cdot) V ((\mu)Eq/min)</td>
<td>115 (\pm) 35</td>
<td>140 (\pm) 30</td>
</tr>
<tr>
<td>UK (\cdot) V ((\mu)Eq/min)</td>
<td>56 (\pm) 10</td>
<td>53 (\pm) 13</td>
</tr>
<tr>
<td>Aldosterone (pg/mL)</td>
<td>94 (\pm) 11</td>
<td>64 (\pm) 13(^b)</td>
</tr>
<tr>
<td>PRA (ng/L (\cdot) s)</td>
<td>1.5 (\pm) 0.4</td>
<td>0.8 (\pm) 0.2(^b)</td>
</tr>
<tr>
<td>ANP (pg/mL)</td>
<td>8 (\pm) 1</td>
<td>33 (\pm) 5(^p)</td>
</tr>
</tbody>
</table>

\(^a\) Elderly subjects had slightly higher mean arterial blood pressure (MABP), lower creatinine clearance (Cor), lower aldosterone, lower PRA, and higher atrial natriuretic peptide (ANP) levels than young subjects. Prestudy rates of sodium (UNa \(\cdot\) V) and potassium (UK \(\cdot\) V) excretion were similar in young and elderly subjects.

\(^b\) \(P < 0.05,\) values are mean \(\pm\) SE.
In addition to a progressive decrease in levels of renin and angiotensin II, aging is associated with a rise in circulating levels of atrial natriuretic hormone (ANH) (15). ANH is a powerful suppressor of aldosterone secretion both in vivo and in vitro (16,17). Furthermore, infusion of ANH in healthy young subjects has been shown to suppress the response of aldosterone to hyperkalemia (18). It seems reasonable, therefore, to hypothesize that the diminished aldosterone response to hyperkalemia observed in elderly subjects, compared with younger controls, is explained at least in part both by the reduction in plasma renin and the rise in plasma levels of ANH that are characteristic of aging.

The main effect of aldosterone is on the renal excretion of potassium, rather than its extrarenal uptake (19). Despite the blunted response of aldosterone to a standard potassium infusion in elderly subjects, the rise in serum potassium levels produced by the infusion was the same in the elderly subjects as in the young. This is consistent with the observation that early renal excretion of potassium accounts for only 15% of an administered load, so that the peak serum potassium level is governed largely by extrarenal mechanisms for potassium disposal (20). However, the elderly subjects studied here had a delayed decrease in serum potassium levels after the infusion, consistent with the delayed renal excretion of potassium in the elderly.

The relatively impaired aldosterone response to potassium infusion of the elderly subjects in this study suggests that elderly patients may be especially prone to hyperkalemia if other potassium regulatory systems are impaired. For instance, many medications commonly prescribed to older patients are inhibitors of the renin-angiotensin-aldosterone system. Angiotensin-converting enzyme (ACE) inhibitors suppress aldosterone release (7) by inhibiting the conversion of angiotensin I to angiotensin II. β-blockers (21) and nonsteroidal anti-inflammatory agents (22,23) also suppress this system. β-blockers additionally interfere with intracellular potassium uptake (19). Spironolactone (an aldosterone antagonist) and other potassium-sparing diuretics interfere with potassium excretion. Heparin may suppress aldosterone secretion by directly inhibiting its adrenal synthesis (24). Trimethoprim interferes with secretion of potassium in the distal tubule (25). Careful monitoring of plasma potassium levels is therefore indicated when prescribing agents that may interfere with potassium regulation.

In summary, the increase in plasma aldosterone, normally elicited by potassium administration, is clearly blunted in otherwise healthy elderly persons. This feature of normal aging presumably predisposes to hyperkalemia, particularly in elderly patients receiving commonly prescribed drugs, which often interfere with the disposal of potassium loads.

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REFERENCES


