There remains considerable controversy about the exact mechanisms that determine the increase in sodium excretion following either an oral or an intravenous sodium load. Several lines of evidence suggest that suppression of the renin-angiotensin-aldosterone system is one important mechanism for both the immediate and the longer-term increase in sodium excretion following an oral sodium load (3, 27). More recently, we have shown the importance of the suppression of renin and thereby angiotensin II (30) and aldosterone (31) in the increase in sodium excretion following a sodium load given intravenously. An intriguing aspect of the response to both oral and intravenous sodium loads is that Lennane and colleagues (19, 20) found that the increase in sodium excretion is greater following an oral load than an intravenous load. They suggested that there might be a gastrointestinal monitor of sodium intake, which would be important in stimulating excretion of sodium when given orally, but that this monitor did not act to the same extent when sodium was given intravenously.

Contrasting endocrine responses to acute oral compared with intravenous sodium loading in normal humans. Am. J. Physiol. 274 (Renal Physiol. 43): F111–F119, 1998.—There is evidence in animals and in humans for accelerated natriuresis after oral compared with intravenous sodium loading. To assess the role of atrial natriuretic peptide (ANP) as a contributory mechanism, we compared the hormonal responses to an intravenous sodium load and to the same sodium load taken orally in three separate groups of healthy subjects in balance on low, normal, or high sodium intake. On each diet, there was a trend for an early delay in sodium excretion, followed by increased natriuresis after the oral compared with intravenous sodium load. On all levels of dietary sodium intake, there was a significant (−2-fold) increase in plasma ANP levels after intravenous saline infusion. There was a significant suppression of the renin system both after oral and intravenous sodium loading. However, there was no acute increase in plasma ANP levels after the oral sodium load, except on the very low sodium intake. This striking and unexpected observation suggests that changes in plasma ANP levels appear to play little role in the early response to an acute oral sodium load in subjects with sodium intake in the range of 150–350 mmol/day. Endocrine mechanisms for the accelerated increase in sodium excretion after oral compared with intravenous sodium loading remain to be elucidated.

natriuresis; kidney; gastrointestinal hormones; sodium chloride

informed consent to the study, which was approved by the local ethical committee.

Paired 24 h urine samples were obtained for measurement of volume, sodium, potassium, and creatinine on the 4th and 5th day of each fixed sodium intake. On the 5th day of each dietary period, a cannula was inserted into an antecubital vein under local anaesthesia. An initial water load of 5 ml/kg was given followed by 2 ml/kg hourly throughout the study. After 2 h of sitting, each subject then received a 300 mmol sodium chloride load, either as 1) a 60-min infusion of 2 liters of 0.9% sodium chloride or 2) an 800-ml soup meal along with 1,200 ml of tap water given over 1 h. The order of receiving intravenous infusion or oral sodium loading was randomized. Subjects remained sitting throughout the study, except for blood pressure measurements or, for men, for micturition. After the intravenous or oral sodium loading subjects were then observed for an additional 4 h. Urine was collected every 30 min throughout the study from 2 h before until 5 h after the sodium load. Measurements were made of urinary volume and electrolytes. Blood samples were taken before and at 90, 150, and 270 min after the start of the sodium load for measurement of hematocrit and hormones. Plasma ANP after Sep-Pak extraction (26), renin activity (24), and aldosterone (17) were measured by radioimmunoassay.

Results are reported as means ± SE. For each level of sodium intake, statistical analysis was performed, after log transformation of results, if appropriate, by two-way analysis of variance (ANOVA) for repeated measurements, unless otherwise stated. Where significant differences were found using ANOVA, paired measurements were then compared by t-tests using the pooled variance from the ANOVA.

RESULTS

Responses to Oral vs. Intravenous Load: Normal Initial Sodium Intake

Urinary electrolyte excretion and urine flow rate. Initial urinary sodium excretion after 5 days on low-sodium diet and 10 Slow Sodium tablets/day was similar before oral compared with intravenous sodium loading (Table 1). As expected, there was a significant increase in urinary sodium excretion with sodium loading (ANOVA, F = 38.5, P < 0.001; Fig. 1) with a small and nonsignificant excess in cumulative increase in sodium excretion at 5 h (46 ± vs. 40 ± mmol) after oral compared with intravenous sodium loading. However, there was a significant difference in the pattern of urinary sodium excretion after the oral compared with the intravenous 2-liter load with 300 mmol sodium chloride (ANOVA treatment/time interaction, F = 5.36, P < 0.001). The increase in urinary sodium excretion after the high-sodium meal was initially lower than after saline infusion. However, from 2 h after the start of sodium loading, urinary sodium excretion was greater after oral than intravenous sodium loading (5 h post start of intravenous load, 82.4 ± 22.1 µmol/min; oral sodium load, 124.4 ± 18.9 µmol/min; Fig. 1). There were no significant changes in blood pressure with acute sodium loading.

ANP, plasma renin activity, aldosterone, and hematocrit. Initial plasma ANP on the 2 study days was not significantly different (Fig. 1). With infusion of saline, there was a significant increase in plasma ANP from 3.1 ± 0.6 to 6.7 ± 2.3 pmol/l 15 min after the end of infusion (Fig. 2; ANOVA time effect, F = 4.8, P < 0.01). Plasma ANP then returned to initial values by 150 min after the start of infusion. With oral administration of sodium, there was no significant change in plasma ANP levels (Fig. 1).

Plasma renin activity before sodium loading was not significantly different on the 2 study days (Fig. 2). Plasma renin activity was significantly suppressed both by intravenous and by oral sodium loading (Fig. 2). There was a trend for delayed suppression of plasma renin activity after the oral sodium load (ANOVA interaction term, F = 2.4, P = 0.085), and plasma renin activity was significantly lower 15 min after the end of intravenous compared with the oral sodium load (P < 0.05). Plasma renin activity then remained similarly suppressed on each study day from 150 min after the start of the sodium load (Fig. 2).

Initial plasma aldosterone was similar before sodium loading on both study days (Fig. 2). There was similar sustained suppression of plasma aldosterone from 90 until at least 270 min after the start of oral and intravenous sodium loading (Fig. 2). There were sustained decreases in hematocrit with both oral and intravenous sodium loading (Fig. 2). However, the pattern differed significantly (ANOVA interaction term, F = 3.9, P < 0.02) with a more gradual decrease in hematocrit after the oral sodium load.

Responses to Oral vs. Intravenous Load: Low Initial Sodium Intake

Urinary sodium excretion, urine flow, and endocrine effects. Initial urinary sodium excretion on the low-sodium diet was 16 ± 3 mmol/24 h on the day of the oral sodium load and 7 ± 2 mmol/24 h on the day of the intravenous sodium load (Table 1). There was no significant difference in urinary sodium excretion after intravenous compared with oral sodium loading (cumulative 5-h increase in sodium excretion: oral sodium, 11.9 ±

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Values are means ± SE. U_Na, urinary sodium excretion; U_K, urinary potassium excretion; UV, urinary volume.
There were increases in plasma ANP levels with both oral and intravenous sodium loading (ANOVA time interaction term, F = 5.03, P > 0.9). Fig. 2. Plasma renin activity (F = 33.2, P < 0.001), aldosterone (F = 26.7, P < 0.001), and hematocrit (F > 114, P < 0.001) after an oral or intravenous 300 mmol sodium and 2-liter volume load over 60 min (normal sodium intake of 150 mmol/day, n = 8). Results are for two-way ANOVA for time effect after intravenous or oral sodium load. *P < 0.05, oral vs. intravenous load.

4.2 mmol; intravenous sodium load, 13.1 ± 4.3 mmol; ANOVA interaction term, F = 0.03, P > 0.9).

There were increases in plasma ANP levels with both oral and intravenous sodium loading (ANOVA time interaction term, F = 5.03, P > 0.9). Fig. 2. Plasma renin activity (F = 33.2, P < 0.001), aldosterone (F = 26.7, P < 0.001), and hematocrit (F > 114, P < 0.001) after an oral or intravenous 300 mmol sodium and 2-liter volume load over 60 min (normal sodium intake of 150 mmol/day, n = 8). Results are for two-way ANOVA for time effect after intravenous or oral sodium load. *P < 0.05, oral vs. intravenous load.
effect, F = 8.0, P < 0.001; Fig. 3). However, the pattern of increase in ANP levels differed with each route of sodium administration (ANOVA interaction term, F = 3.5, P < 0.025). Plasma ANP increased significantly by 75 min after the start of the intravenous sodium load (P < 0.05, Fig. 3). However, with the oral sodium load, there was a lag in the rise in plasma ANP levels that did not increase significantly until 150 min after the start of the sodium load (P < 0.05, Fig. 3).

There was a sustained decrease in hematocrit, plasma renin activity, and aldosterone levels with oral and with intravenous sodium loading (Fig. 4). There were no significant changes in blood pressure with acute sodium loading.

Responses to Oral vs. Intravenous Load: High Initial Sodium Intake

Urinary sodium excretion, urine flow, and endocrine effects. Initial urinary sodium excretion on the high-sodium diet was 429 ± 34 mmol/24 h on the day of the oral sodium load and 362 ± 30 mmol/24 h on the day of the intravenous sodium load. Unlike in subjects on low or normal sodium intake at the time of study, in subjects on a high sodium intake, there was no longer a clear difference in the pattern of natriuresis after an oral compared with an intravenous sodium load (Fig. 5). In the 5 h after the oral load, there was no significant difference in the cumulative increase in sodium excretion (38 ± 8 mmol) compared with the same period after the intravenous sodium load (45 ± 17 mmol, Fig. 5).

Initial plasma ANP levels were similar on the two high-sodium study days (Fig. 5). As for subjects on a normal sodium intake, there was no significant change in plasma ANP levels after the oral sodium load. However, after the intravenous sodium load, there was a significant increase in plasma ANP (ANOVA time effect, F = 4.4; P < 0.01), which was more sustained than in subjects given an intravenous sodium load on a low (Fig. 5) or on a normal sodium intake.

There was a sustained decrease in hematocrit, plasma renin activity, and aldosterone levels with oral and intravenous sodium loading (Fig. 6).

Later plasma ANP response to sodium loading. On the high sodium intake, plasma ANP levels had returned to initial values by 24 h after both oral and intravenous sodium loading (Fig. 7). In contrast, on the low-sodium diet, plasma ANP levels were still significantly elevated above initial values 24 h after both oral and intravenous sodium loads (Fig. 7).

DISCUSSION

General Comment

The main and unexpected new finding of this study was the major difference in the plasma ANP response when the same sodium and volume load was given orally compared with intravenously. When subjects were in sodium balance, at the end of each 5-day period of constant dietary sodium intake, plasma ANP levels
reflected steady-state dietary sodium intake, so that the higher the salt intake, the greater the initial plasma ANP level. There was a consistent response of plasma ANP to a standard intravenous sodium load on each level of dietary sodium intake studied. However, changes in plasma ANP levels appear to play little role in the early response to an acute oral sodium load in the usual range of dietary sodium intake.

Response to Intravenous Sodium Load

For intravenous isotonic sodium loading, plasma ANP increased with the volume load, returning to initial values within 5 h. This increase in plasma ANP...
levels with intravenous sodium loading occurred regardless of the level of steady-state sodium intake across a range of sodium intakes reflecting the usual range, as well as the extremes of low and high sodium intake consumed by humans. The absolute increase in plasma ANP was greater the higher the initial sodium intake. However, the relative increase in plasma ANP with intravenous sodium loading was similar at around twofold in each group of subjects. This order of increase in plasma ANP levels, when achieved by infusion of ANP or by elevation of endogenous ANP levels after neutral endopeptidase inhibition, is associated with physiologically significant increases in renal sodium and water excretion (2, 18).

With the intravenous sodium load, the pattern of increase in plasma ANP differed, depending on the sodium intake at the time. In subjects on a low or on a normal sodium intake, plasma ANP increased transiently, returning to initial values by 150 min after the start of the sodium load. In contrast, in subjects on a high sodium intake, the increase in plasma ANP level persisted for about twice as long as in subjects on a normal or on a low sodium intake receiving the same intravenous sodium load. There are three obvious explanations for this difference in kinetics of ANP response. It is now clear that a major mechanism for ANP release is increased atrial stretch (8, 21). Thus one explanation for the above observation is that the increase in right atrial pressure and stretch with saline infusion may be both greater and more prolonged on a high than on a low sodium intake. The greater plasma

Fig. 6. Plasma renin activity (F = 19.5, P < 0.001), aldosterone (F = 6.8, P = 0.001), and hematocrit (F = 19.5, P < 0.001) after an oral or intravenous 300 mmol sodium and 2-liter volume load over 60 min (high sodium intake of 350 mmol sodium/day, n = 8). Results are for two-way ANOVA for time effect after intravenous or oral sodium load.

Fig. 7. Plasma ANP levels for up to 24 h after an oral (bottom) or intravenous (top) 300 mmol sodium and 2-liter volume load over 60 min (n = 8 for separate groups of subjects on low sodium or high sodium intake). *P < 0.05 vs. initial values.
ANP response to intravenous volume expansion with increasing initial dietary sodium intake is also consistent with the observation by Anderson et al. (1) that increased atrial stretch, mediated by increased central venous pressure, is a major mechanism for the cardiac secretion of ANP in response to an acute intravenous sodium load. Second, there may be less rapid redistribution and clearance of the volume load on the high-sodium diet. This seems unlikely as there was a similar increase in urine flow and decrease in hematocrit to that observed in subjects on a normal or low sodium intake. Third, there may be suppression by the high-sodium diet of factors that would normally act to limit the degree and duration of a stimulated increase in expression of ANP and/or stimulation by the high-sodium diet of factors that enhance ANP expression.

Plasma ANP and Response to Oral Sodium Loading

From previous studies, it was unclear whether increased ANP secretion is important in the short-term, hour-to-hour, hormonal regulation of oral sodium intake. One study attempted to address this by measurement of plasma ANP levels before and then 30 min after a meal (rolls and casserole with free fluid intake) in subjects in balance on a low (13 mmol/day), normal, or high sodium intake (271 mmol/day) (32). The authors reported a significant change in plasma ANP level only in subjects on a high-sodium diet (32). Even in this group, there was only a moderate 25% postprandial increase in plasma ANP. No data on dietary sodium content or urinary sodium excretion after the meal were reported. That study was very unusual in being unable to detect any difference in fasting plasma ANP levels between subjects in balance on a low or normal compared with high sodium intake (32). Furthermore, the study was confounded by use of a complex meal, high in protein, which is a stimulus for increased sodium excretion, in part mediated by a rise in glomerular filtration rate and associated with a transitory increase in plasma ANP levels (33).

In the present study, with oral sodium loading, there was no significant increase in plasma ANP levels, except in subjects on a very low sodium intake. This suggests that for sodium intake in the usual mid- or upper range for most societies (16), stimulation of ANP secretion does not appear to be important in the initial natriuretic response to an acute dietary sodium load. This finding also indicates that any gastrointestinal or portal sensing of increased dietary sodium intake (19, 20) does not overtly act acutely by stimulating ANP release, except possibly in subjects on a very low sodium intake.

Plasma ANP and Sustained Changes in Oral Sodium Intake

Although unexpected, these observations remain consistent with reports of increased plasma ANP levels in response to dietary sodium loading (25, 26, 29). Those studies examined the plasma ANP response to sustained rather than the acute changes in dietary sodium intake in the present study, in which subjects then continued on their initial level of dietary sodium intake. One explanation for these striking contrasts in the pattern of ANP response after oral compared with intravenous sodium loading is the differences in the degree and kinetics of volume expansion, depending on the route of sodium administration. There was evidence for this mechanism from the reduced rate and degree of volume expansion in the subjects with normal initial sodium intake, in whom there was a significant delay in fall in hematocrit after the oral compared with intravenous sodium load. On the normal sodium intake, there was also a trend for delayed suppression of plasma renin activity in response to the oral compared with the intravenous sodium load.

Other Mechanisms for Natriuresis After Acute Oral Sodium Loading

The above findings clearly suggest that factors other than increases in plasma ANP secretion determine the renal response to acute changes in dietary sodium intake in subjects on a usual or high-range sodium intake. The natriuretic response to oral sodium intake may be mediated in several ways. There could be a neural reflex that either suppresses release of antinatriuretic hormones or inhibits sympathetic nervous actions in the kidney, analogous to the cardiorenal neural reflex (12). Evidence is emerging for a specific hepatorenal reflex involved in the regulation of oral sodium loading. Studies in the cat, dog, and rabbit suggest the presence of sodium receptors in the portal vein, stimulation of which increases hepatic afferent nerve activity, resulting in increased renal sodium excretion and reduced intestinal sodium absorption (14). Hepatic denervation results in a marked blunting of the decrease in renal sympathetic nerve activity associated with oral sodium loading (14). It is clear from the present study, as well as from previous reports, that acute and sustained suppression of the renin-angiotensin-aldosterone system appears to play a role in the initial response to both oral (19) and intravenous sodium loads (26, 30, 31) across a wide range of initial levels of dietary sodium intake from very low to high. Other mechanisms may include differences in physical factors. Blood sodium concentration (10, 11), oncotic pressure (15), and changes in hematocrit (28) have all been implicated in renal sodium handling. Within the observation period of our study, changes in hematocrit could thus have contributed to natriuresis after both the oral and the intravenous sodium loads.

Other members of the natriuretic peptide family could be involved in excretion of an oral sodium load. Candidates include brain natriuretic peptide, which is natriuretic on infusion in the physiological range (5), and urodilatin, urinary excretion of which increases after oral sodium loading (7).

A further candidate mechanism is modulation of gut hormone release, as there is increasing evidence that several gastrointestinal hormones may have direct or indirect actions on renal sodium handling. For example, vasoactive intestinal peptide appears to have a
complex role in sodium balance, with antinatriuretic effects in vivo (4) and in vitro inhibition of renin and aldosterone secretion. Guanylin and uroguanylin are peptides that are secreted by the jejunum and are natriuretic as well as stimulating secretion of salt and water into the intestinal lumen (9).

Insulin may also have important effects on sodium excretion. However, a role for insulin in explaining natriuresis of an oral sodium load would be complex: insulin secretion is stimulated by diet, but insulin has antinatriuretic effects through actions on receptors present throughout the nephron, most densely in the thick ascending limb of the loop of Henle and in the distal convoluted tubule (22). Insulin administration results in reduced sodium, potassium, phosphate, and water excretion, even under experimental conditions in which glucose levels are clamped and glomerular filtration rate and renal blood flow remain unchanged (6). Most interestingly, a previously undefined natriuretic hormonal system could be involved.

Accelerated Natriuresis After Oral vs. Intravenous Sodium Loading

Based on studies in animals and humans on very low sodium intake, Lennane et al. (19, 20) postulated the existence of gastrointestinal and/or portal system sodium or osmoreceptors to account for the differences they observed in the response to oral compared with intravenous sodium loading. We did not set out to repeat Lennane’s study design, and our protocol used different amounts of sodium and a different time period. In the present study, a short-term difference was noted in the pattern of excretion of a standard sodium chloride and water load in subjects on low or on mid-normal range dietary sodium intakes but not on the high sodium intake.

In contrast to the study of Lennane and colleagues (19), which was confined to normal subjects on a low-sodium diet, in our study, there was no significant difference with route of administration in cumulative increase in sodium excretion in the 5 h after the start of the sodium load in subjects on a low, normal, or high sodium intake. We did, however, observe a delay in increase in sodium excretion after the oral compared with the intravenous sodium load, followed by greater short-term natriuresis of an oral sodium load in subjects on a low or on a normal sodium intake. This finding would be consistent with a physiological lag due to delayed absorption of the oral load, in contrast to direct delivery by the intravenous infusion of sodium and water load to the circulation, with a greater volume expansion after the intravenous load as evidenced by a greater early decrease in hematocrit on each sodium intake.

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Present address of M. G. Buckley: NHIL Heart Science Centre, Imperial College, Harfield UB9 6H, UK.

Address for reprint requests: D. R. J. Singer, Clinical Pharmacology Unit, Dept. of Pharmacology & Clinical Pharmacology, St. George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK.

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