Release of antidiuretic hormone during mass-induced elevation of intracranial pressure

LYNN GAUFIN, M.D., W. RONALD SKOWSKY, M.D., AND STANLEY J. GOODMAN, M.D.

Department of Surgery, Division of Neurosurgery, University of California at Los Angeles, and Harbor General Hospital, Torrance, and the Department of Medicine, Division of Endocrinology, Long Beach Veterans Administration Hospital, Long Beach, California

There are complex osmotic and non-osmotic factors regulating release of antidiuretic hormone (ADH). A wide variety of intracranial pathological processes may trigger ADH release sufficient to produce clinically recognizable hyponatremia, or the "inappropriate ADH syndrome." We systematically studied one non-osmotic trigger, namely mass-induced elevated intracranial pressure (ICP). Initial experiments established baseline data in normal rhesus monkeys: anesthetized animals displayed appropriate rises and falls in immunoreactive urinary ADH in response to intravenously administered hypertonic and hypotonic infusions. Next, balloon catheters were implanted subdurally over temporal lobes and the animals were allowed to recover. The final experiment consisted of anesthetizing the animals, monitoring arterial blood pressure and blood gases, and retrieving timed urinary specimens while continuously recording ICP during infusion-pump expansion of the subdural balloon. A nonlethal and a lethal series of balloon-expansion experiments were done. Control values of urinary ADH were 783 ± 125 μU/15 min, and ICP was less than 10 mm Hg. During nonlethal mass expansion ADH output rose to 3433 ± 269 μU/15 min while ICP averaged 65 mm Hg (measured at completion of mass expansion). While the mass was maintained, hypotonic infusion produced unchanged urinary ADH output of 3452 ± 277 μU/15 min. During lethal experiments, urinary ADH rose still higher to 4339 ± 1887 μU/15 min associated with ICP averaging 100 mm Hg. We concluded that there is a direct relationship between the magnitude of ICP and the amount of ADH release, and that during elevated ICP the ADH release is not suppressed by hypotonic infusion.

KEY WORDS • antidiuretic hormone • intracranial pressure • inappropriate release of ADH • mass-induced intracranial hypertension

ANTIDIURETIC hormone (ADH, arginine vasopressin, AVP) is synthesized in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of primates and released from the pars nervosa of the pituitary gland in response to osmotic and non-osmotic stimulation. Osmotic responses have been well defined in terms of accompanying electroencephalographic and electrical discharge changes, and in terms of the anatomy of the hypothalamic osmoreceptors, including the single unit discharge patterns of secretory and nonsecretory cells in the SON area of the hypothalamus.
Non-osmotic stimuli of ADH can be classified under four broad categories: volume factors (such as hemorrhage, postural changes); drugs (such as nicotine, barbiturates, morphine); hormonal mediators (such as thyroxine, angiotensin, glucocorticoids); and central nervous system (CNS) stimulation (such as pain, stress, suckling), including autonomic mediation (that is, alpha and beta adrenergic stimulation).

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) refers to a clinical condition characterized by serum hyponatremia and hypoosmolality secondary to continued (inappropriate) release of ADH, thereby decreasing renal tubular free-water clearance and further exaggerating the hyponatremia.1,2,24 Common usage of the term SIADH refers to the situation in which ADH secretion is no longer controlled by changes in plasma osmolality and volume. The terminology "inappropriate" versus "appropriate" ADH secretion obscures the fact that ADH release may be responding to some physiological trigger (except in cases of neoplastic production of ADH or an ADH-like peptide), albeit in a situation that is not physiologically beneficial to the subject. The clinically recognized etiologies of SIADH encompass a wide variety of disease entities and it is difficult to invoke a common underlying mechanism of ADH release.

In clinical practice the neurosurgeon is frequently confronted with SIADH in a number of situations. Many of the conditions causing SIADH are primary neurosurgical problems. In a patient with recent brain injury SIADH may possibly cause and/or exacerbate cerebral edema, and the symptoms of hyponatremia (lethargy, weakness, mental confusion, and ultimately convulsions and coma) may become confusingly intertwined with the signs and symptoms of the underlying brain disease.

In the current study we have systematically examined one non-osmotic trigger of ADH release, that of intracranial hypertension caused by a rapidly expanding mass. Many of the causes of neurosurgical SIADH apparently are associated with increased ICP. Our results suggest that the magnitude of ADH release can be directly related to the magnitude of the intracranial hypertension, and that under such circumstances ADH release is no longer inhibited by induced serum hypoosmolality which would decrease ADH release under conditions of normal ICP.

Materials and Methods

Four female rhesus monkeys (Macaca mulatta), weighing 4.0 to 5.5 kg, were studied sequentially over a 15-month interval while developing ADH assay methods, anesthetic techniques, and physiological maneuvers for stimulating ADH release. The final series of intracranial mass experiments terminated in death of the animals. Each animal was maintained in a single vivarium cage between experiments under controlled lighting and temperature and freely supplied with water and food. Each animal was studied twice monthly or less frequently. The animals were vigorous and healthy over the test months and maintained stable body weights.

Initially, quantitative radioimmunoassay determination of ADH in monkey serum was attempted but the existing serum extraction procedure (previously used with serum from humans, goats, sheep, and fetal monkeys) was unsuccessful. Reliable methods of assay of urinary ADH were developed and used throughout the study. All urine collections over a specified time interval were carefully quantitated. The laboratory personnel assaying urinary ADH could identify each specimen only as a numbered item and not in terms of the experimental manipulation or donor animal. Osmolality, ADH concentration (µU/cc), and total ADH (µU, total, per timed collection interval) were measured in each urine specimen. Total urinary ADH/time interval was compared between animals and during different experimental manipulations, and urine was collected every 15 minutes. Recovery of exogenous ADH added to dilute urine (that is, increased free-water clearance and low ADH) exceeded 90% in a series of preliminary studies. In addition, all urine assays were measured by comparison to urine-extracted ADH standards and corrected for recovery; thus the reported ADH urinary concentrations are not subject to misinterpretations through recovery errors.

Antisera to ADH were produced in New Zealand white female rabbits using lysine vasopressin conjugated to bovine thyroglobulin as previously described.20 Synthetic AVP was iodinated using a modification of the method of Hunter and Greenwood.20
Assay procedures were carried out as described earlier and bound and free hormones were separated by the double antibody method. Arginine vasotocin (AVT) showed negligible cross-reactivity; the ratio of AVT:AVP at 50% binding was 350:3 and oxytocin showed no significant cross-reactivity with labeled antigen. The coefficient of variation (CV) was 7.1% within assay and 14.9% between assay.

After satisfactory ADH immunoassay techniques and collection procedures were developed a series of experimental procedures were performed.

**Series 1 Studies**

Initial studies were directed toward quantitation of the effects of the anesthetic agents, pentobarbital and ketamine, upon the hypothalamic-neurohypophyseal axis and basal ADH secretion. In addition, each anesthetized animal was studied in terms of responsiveness to hypotonic (5% dextrose/water), volume-expansion (dextran 40), hypertonic (5% NaCl), and direct pharmacological (nicotine) stimulation. A 1-hour control period followed the induction of anesthesia and intubation; the bladder was catheterized with a No. 5 French pediatric feeding tube, and urine samples were collected at 15-minute intervals. A Credé maneuver was performed to assure complete bladder emptying with each sample collected. Following the 1-hour control period, each animal received a known inhibitory stimulus to ADH release: either 5% dextrose in water in graded doses of 10 to 35 cc/kg, or dextran 40 in graded doses of 15 to 35 cc/kg, each delivered over a 3- to 5-minute period via a Harvard infusion pump.* Urine for ADH determinations was collected over the next four 15-minute aliquots. At this point, each animal then received a known stimulus for ADH secretion: either 5% NaCl in a dose of 10 cc/kg or intravenous nicotine in graded doses of 0.01 to 0.2 mg/kg. Urine was collected for the next hour.

**Series 2 Studies**

In animals anesthetized with ketamine (5 mg/kg), ADH responsiveness was quantified after surgical skin incisions and electrical stimulation of dental pulp. The surgical incisions consisted of a forearm vein cutdown and scalp incision and were followed by urine collections for ADH over the ensuing 2-hour period. At this time dental pulp was stimulated for 5 minutes (30 V, 50 Hz, 0.5 msec square wave), which produced a behavioral response of facial grimacing, mouth opening, and tachypnea. After dental pulp stimulation, urine was collected for 45 minutes.

**Series 3 Studies**

Under ketamine anesthesia, a right frontotemporal craniectomy was performed for insertion of a deflated subdural balloon catheter (No. 8 French Foley catheter); the distal end of the catheter was placed in a subgaleal pouch. The cranial defect around the catheter insertion site was closed with methylmethacrylate; the scalp was sutured and the animals allowed to recover fully for at least 1 month. The following experiments were undertaken to quantitate the effect of increased ICP on ADH release. The monkey was anesthetized in the vivarium with ketamine (25 to 50 mg intramuscularly), brought to the operating room, and secured in a specially designed head-holder for position stabilization to insure reproducible ICP recording techniques. A constant infusion of Ringer's lactate (1 cc/min via a Harvard infusion pump) was continued throughout each study. In some experiments a femoral artery was catheterized, connected to a Micron arterial transducer,† and continuous arterial pressure monitored on a Beckman polygraph.‡ The animal was intubated (4.0 to 6.0 mm endotracheal tube) and placed on a Bird M-8 respirator§ using an “infant circle” and negative end-expiratory pressure. Blood gases were obtained to evaluate adequacy of ventilation throughout each study. The distal end of the subdural catheter was exposed and con-

---

*Harvard infusion pump manufactured by Harvard Apparatus Company, 150 Dover Road, Millis, Massachusetts 02054.
†Micron arterial and pressure transducers manufactured by Micron Instruments, 1519 Pontius Avenue, West Los Angeles, California 90025.
‡Beckman polygraph manufactured by Beckman Instruments, Inc., 2500 Harbor Boulevard, Fullerton, California 92634.
§Bird M-8 respirator manufactured by the Bird Corporation, Mark 3 Respirator Lane, Palm Springs, California 92262.
TABLE 1
Baseline urinary ADH values during pentobarbital and ketamine anesthesia in rhesus monkeys

<table>
<thead>
<tr>
<th>Test</th>
<th>No. Urinary ADH * Monkeys (μU/15 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pentobarbital anesthesia</td>
<td></td>
</tr>
<tr>
<td>baseline before hypotonic challenge</td>
<td>19 1339.2 ± 269.2</td>
</tr>
<tr>
<td>baseline before hypertonic/nicotine challenge</td>
<td>8 1154.6 ± 431.1</td>
</tr>
<tr>
<td>after previous D5W</td>
<td>9 374.1 ± 73.1</td>
</tr>
<tr>
<td>after previous dextran</td>
<td></td>
</tr>
<tr>
<td>ketamine anesthesia</td>
<td></td>
</tr>
<tr>
<td>baseline before hypotonic challenge</td>
<td>9 302.0 ± 67.0</td>
</tr>
<tr>
<td>baseline before hypertonic/nicotine challenge</td>
<td>6 108.2 ± 19.7</td>
</tr>
<tr>
<td>after previous D5W</td>
<td>3 60.7 ± 3.5</td>
</tr>
</tbody>
</table>

*Mean values ± standard error of the mean.

The preparation in this series was identical to Series 3 except that the subdural balloon was expanded until ICP was increased into the lethal range of 90 to 110 mm Hg terminating in death. The timing of urinary collections and of the hypotonic infusion was identical to that used in Series 3. Following each lethal experiment the brain and pituitary gland were removed and fixed in formalin. The surface of the brain was visually inspected and the anatomical site of catheter placement recorded. The pituitary gland was microscopically examined following hematoxylin and eosin staining.

Results

Series 1 Studies

Initial basal urinary ADH values under pentobarbital anesthesia averaged 1339.2 ± 269.2 μU/15 min (Table 1). Following the hypotonic challenge of D5W, there was a marked suppression of urinary ADH excretion after a 15-minute lag period, beginning in the second 15-minute collection period (−48.0 ± 9.9% of baseline values, p < 0.05) and extending into the fourth 15-minute collection period (−36.2 ± 14.4% of baseline values, p < 0.1) (Fig. 1). Acute volume expansion by dextran 40 also significantly lowered urinary ADH excretion to 68.3 ± 8.2% below control values in the second collection period (p < 0.1) and to 60.7 ± 8.7% below baseline in the third collection period (p < 0.1) (Table 1). Although various doses of D5W (10 to 30 ml/kg) and dextran 40 (15 to 35 cc/kg) were infused, no dose response effect could be observed and the results reflect averaged data utilization.

Following the D5W or dextran infusion, each animal was restudied 1 hour later. At this time period, the urinary ADH collection used as baseline values for the ensuing hypertonic/nicotine challenge differed depending on the preceding agent used (Table 1). The animals previously challenged with dextran had a significantly lower ADH excretion (374.1 ± 73.1 μU ADH/15 min) than those previously infused with D5W (1154.6 ± 431.1 μU ADH/15 min, p < 0.01), which undoubtedly reflects the longer duration of ADH suppression following the initial dextran challenge. Nevertheless, both groups of pentobarbital-anesthetized animals responded to nicotine with marked rises in urinary ADH excretion, although the dextran pretreatment appeared to blunt the nicotine
ADH and increased intracranial pressure

FIG. 1. Effects of hypotonic challenge (5% dextrose in water) and volume expansion (dextran 40) in monkey on urinary ADH, under pentobarbital anesthesia.

FIG. 2. Effects of hypertonic challenge (5% NaCl solution) and nicotine in monkey on urinary ADH, under pentobarbital anesthesia.

response (Fig. 2). In the animals previously treated with D5W, urinary ADH rose 91.6 ± 21.6% above baseline in the first 15 minutes (p < 0.1) and was 125.8 ± 74.9% in the second 15-minute collection (p < 0.1). In the animals previously treated with dextran volume expansion, significant rises in urinary ADH did not occur until the third 15-minute collection (48.7 ± 22.8% above control, p < 0.1) and the fourth collected specimen (194.9 ± 47.9% above baseline, p < 0.01). Although various doses of nicotine were administered (0.01 to 0.25 mg/kg), no significant dose response was observed. Hypertonic (5%) saline was administered only to those animals previously studied with D5W. A significant rise in urinary ADH excretion was observed both in the first and third 15-minute collection periods (Fig. 2).

Although the animals anesthetized with pentobarbital exhibited the expected alterations in ADH following osmotic, volume, and nicotine challenges, it was observed that the level of sedation was less than desirable. Also, the levels of urinary ADH exhibited marked fluctuations even during baseline collections (that is, there was a large standard error of the means), which were felt to represent an inadequate degree of anesthesia and analgesia. For this reason, another anesthetic agent with analgesic properties, ketamine, was studied.

Under ketamine anesthesia there was a significant reduction in ADH excretion, especially in the second and third collection periods (Fig. 3). As with the animals anesthetized with pentobarbital, prior dextran challenge lowered the control ADH excretion in the ketamine-anesthetized monkeys 1 hour later before the nicotine stimulation (Table 1). The long-term biological action of the previous dextran challenge also blunted any observed effect of nicotine on urinary ADH (Fig. 4). However, the prior D5W treatment did not abolish the stimulatory effects of nicotine. These animals showed increased urinary ADH above baseline values to 575.0 ± 227.6% in the first 15-minute collection period (p < 0.1), 455.7 ± 310.9% in the
bility of urinary ADH following appropriate challenges prompted us to use ketamine anesthesia throughout the remainder of the study.

**Series 2 Studies**

With the animal maintained under ketamine anesthesia, intubated and positioned in a head-holder, two surgical incisions (antecubital vein cutdown and scalp incision) did not elicit significant rises in urinary ADH over the ensuing 120 minutes (Fig. 5). Mean urinary ADH over this time period (seven 15-minute collections) averaged 396.7 ± 48.4 µU/15 min, which was not significantly higher than the previous ketamine baseline excretion (302.0 ± 67.0 µU/15 min) (Table 1). However, high intensity dental pulp stimulation for 5 minutes led to a prompt and major rise in urinary ADH to 2238.0 ± 1006.4 µU in the next 15-minute period (p < 0.1), 1758.0 ± 863.9 µU in the second 15-minute period (p < 0.1), and 3717.3 ± 1073.9 µU in the third 15-minute collection period (p < 0.1) (Fig. 5). These elevations in urinary ADH during the three 15-minute collections averaged 400.8 ± 211.6% above the preceding baseline mean (p < 0.1)

---

**Fig. 3.** Effects of hypotonic challenge (5% dextrose in water) and volume expansion (dextran 40) in monkey on urinary ADH, under ketamine anesthesia.

**Fig. 4.** Effect of nicotine in monkey on urinary ADH, under ketamine anesthesia.

**Fig. 5.** Effect of sham operation and dental pulp stimulation in monkey on urinary ADH, under ketamine anesthesia.
TABLE 2

Urinary ADH excretion and intracranial pressure during lethal and nonlethal intracranial mass expansion in rhesus monkeys under ketamine anesthesia

<table>
<thead>
<tr>
<th>Size of Expansion</th>
<th>Urinary ADH (µU/15 min)</th>
<th>Intracranial Pressure (mm Hg)</th>
<th>Urinary ADH (µU/15 min)</th>
<th>Intracranial Pressure (mm Hg)</th>
<th>Mass Expansion and Hypotonic Challenge</th>
<th>Urinary ADH (µU/15 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>667</td>
<td>10</td>
<td>3841</td>
<td>60</td>
<td>3013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 4)</td>
<td></td>
<td>(n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean SEM</td>
<td></td>
<td>884.2</td>
<td>109.3</td>
<td>3431.5</td>
<td>2967</td>
</tr>
<tr>
<td>Mass Expansion</td>
<td>1074</td>
<td>10</td>
<td>2641</td>
<td>60</td>
<td>4096</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 4)</td>
<td></td>
<td>3568</td>
<td>50</td>
<td>3730</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean SEM</td>
<td></td>
<td>725</td>
<td>90</td>
<td>2967</td>
<td></td>
</tr>
<tr>
<td>Hypotonic Challenge</td>
<td>1071</td>
<td>10</td>
<td>3676</td>
<td>90</td>
<td>3730</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 4)</td>
<td></td>
<td>1071</td>
<td>50</td>
<td>3730</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean SEM</td>
<td></td>
<td>725</td>
<td>90</td>
<td>3730</td>
<td></td>
</tr>
<tr>
<td>Series 3 Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When the mass was sufficiently expanded to raise ICP between 60 and 90 mm Hg (65.0 ± 8.7), the animals developed depressed corneal reflexes and their withdrawal to pinch was markedly diminished. Occasionally anisocoria and hemiparesis appeared. These neurological findings disappeared over a few hours following evacuation of the mass and all animals survived the nonlethal mass expansion studies without neurological deficit.

During the 2-hour control period, after all preparations were completed and before expansion of the mass, ADH excretion averaged 884.2 ± 109.3 µU/15 min (Table 2). Over the 30-minute interval of nonlethal mass expansion, urinary ADH values significantly rose to 3431.5 ± 269.4 µU/15 min (p < 0.001). The ensuing hypotonic infusion with D5W was not sufficient to inhibit these elevated urinary ADH levels which remained at 3451.5 ± 276.9 µU/15 min (Table 2, Fig. 6).

Fig. 6. Changes in urinary ADH and ICP before, during, and after nonlethal mass expansion. Graphic display of data points from experiments in four monkeys. ADH plotted as total ADH over 15-minute collection periods, and intracranial pressure plotted as mean pressure during the same time interval. Note that ADH values did not decline following hypotonic infusion (especially in Monkeys 2, 3, and 4), but did decline after mass-induced intracranial hypertension ended. White bar = mass expansion; cross-hatched bar = hypotonic infusion.
Series 4 Studies

Baseline urinary ADH excretion in the 2-hour control period in this series of lethal mass expansion averaged 782.5 ± 125.4 μU/15 min (Table 2, Fig. 7). With the mass expanded to ICP readings of 90 to 110 mm Hg (mean 99.7 ± 5.4 mm Hg), the animals lost corneal and pain responsiveness, displayed unilaterally and ultimately bilaterally dilated pupils, and eventually had deteriorating vital signs until death.

Urinary ADH release in the 30-minute period after attainment of lethal mass expansion rose to 4339.8 ± 1886.7 μU/15 min (p < 0.01). Instability of blood pressure followed, and during attempted hypotonic infusion there were marked rises in ICP precluding any analysis of the effects of hypotonic challenge during this phase of the experiment. Indeed, urinary ADH excretion rose even higher (11,079.0 ± 7199.2 μU/15 min) during this unstable period.

Vital Signs

In three separate experiments arterial pressure was monitored throughout the study and no changes in rate or mean pressure were observed until the animals were unresponsive to pain and had dilated pupils. Arterial blood gases were sampled in three separate experiments and pH, pO₂, and pCO₂ were found to be normal in each instance.

Pathological Examination

The positions of the balloon catheters were determined following death of the animals: one was at a temporal pole, one at a medial uncal surface, one on the planum sphenoidale, and one intracerebrally at the temporo-parietal junction at a depth of approximately 1.5 cm. During a lethal intracranial mass experiment, one animal rapidly developed massive pulmonary edema and died; this mass was subsequently shown to be located intracerebrally. Microscopic examination of the pituitary glands revealed normal anterior and posterior lobe architecture and morphology in all four animals.

Discussion

In the present studies we have examined the relationship between a rapidly expanding intracranial mass and ADH secretion in the anesthetized primate. Increasing ICP into either the nonlethal (60 to 90 mm Hg) or lethal (90 to 110 mm Hg) range elicited prompt and significant elevations in urinary ADH excretion (Table 2) that were not suppressed by simultaneously induced serum hypotonicity (via infusion of D5W). Although the SON osmoreceptors are believed to exert the most important control over minute-to-minute variations in ADH secretion, such “overriding” of ADH osmotic regulation as observed in the present studies has been
ADH and increased intracranial pressure

previously observed (as in severe blood loss). The nonsuppressible ADH release during intracranial mass expansion apparently supersedes physiological control of ADH via osmotic and volume stimuli.

An expanding intracranial mass produces numerous anatomical and physiological derangements, and it is possible to speculate on the link between these known derangements and the increased and nonsuppressible release of ADH observed in the present studies. Mass-induced ADH secretion may be mediated by pressure-sensitive neurons, as has been implicated in control of blood pressure. It is also possible that an expanding mass and brain-stem distortion excites specific midbrain-hypothalamic pathways leading to augmented ADH synthesis and release.

“Osmoreceptors” (outside the SON and PVN perinuclear zone) in limbic, amygdaloid, and olfactory areas are responsive to various nonspecific noxious stimuli as well as changes in blood osmolality, and these “nonspecific” osmosensitive neurons have direct anatomical connections to the SON and may induce release of ADH from the neurohypophysis. Although amygdaloid stimulation produces activity in the area of the SON, no direct monosynaptic connections have been described in the monkey or rat. Indirect neural pathways exist via multisynaptic, limbic, spinohypothalamic, and vagal inputs which may be involved in activation of the SON and ADH release during mass expansion. The decrease in cerebral blood flow and resulting hypoxia during progressive intracranial hypertension (via a number of brain-stem mechanisms), and decreased tissue perfusion (of the hypothalamus or other brain site(s)) may stimulate ADH release in a manner similar to the effect of hypoxia on carotid chemoreceptors.

Intracranial hypertension and brain-stem compression, in particular, lead to profound stimulation of the adrenergic nervous system. Beta adrenergic stimulation has been shown to have an antidiuretic effect at least partly related to a direct effect on ADH secretion, either directly upon the neurohypophysis or indirectly via baroreceptors. Monoaminergic nerve terminals ending on SON neurons can be anatomically demonstrated, and adrenergic mechanisms have been implicated in hypothalamic ADH synthetic mechanisms. The augmented ADH secretion in our study could therefore be secondary to altered sympathetic discharge.

There are some limitations and assumptions in this study. Although in our laboratories ADH has been successfully quantitated in blood of humans, goats, and sheep, we were initially unable to eliminate nonspecific binding in extractions of rhesus monkey blood (although we have subsequently overcome this difficulty) and therefore assayed urine. The assumptions made in relating urinary ADH concentration to changes in serum ADH concentration appear reasonable: glomerular filtration rate (GFR) appeared constant (arterial pressure monitoring revealed no change until preterminal major rises and falls in arterial pressure), although GFR may be altered without changes in systemic blood pressure; the fraction of ADH cleared from blood to urine remains relatively constant under physiological levels of circulating ADH and the Credé maneuver appeared to accomplish constant bladder emptying. Although measurement of urinary ADH does not reflect instantaneous intracranial events, our experimental design provides temporal averaging by virtue of the timed urinary collection every 15 minutes. We anticipated and, indeed, observed a lag time between a number of experimental manipulations and the measured change in urinary ADH. A 15-minute lag period was seen following both D5W and dextran administration in the pentobarbital-anesthetized animals (Fig. 1) before urinary ADH was suppressed. Indeed, the rise in urinary ADH observed during the initial 15-minute collection may reflect perturbations secondary to the rapid intravenous influx of fluid. This may also account for the delay in maximum ADH excretion following dental pulp stimulation (Fig. 5). Assuming stable GFR and metabolic clearance rate, it is probable that serum levels of ADH would have more closely followed the stimulatory maneuvers in time had blood levels been quantified.

If urinary excretion of ADH is a reflection of ADH in the blood perfusing the kidney, one must also assume the elevated blood ADH reflects direct alterations in ADH secretory rates. These assumptions presuppose a stable metabolic clearance rate. Since the liver and the kidney are the two main degrading organs involved in ADH
metabolism, the elevated urinary ADH levels may reflect increased removal by the renal medulla (although the stable blood pressure makes this possibility unlikely). However, the rapidity and magnitude of the changes in urinary ADH levels strongly suggest that these alterations do, indeed, reflect changes in ADH secretory rates.

The anesthetic (ketamine) used in the present study is not known to possess a direct effect on ADH release and this was also suggested by our preliminary studies. A dose of ketamine was selected that did not abolish ADH responsiveness to nicotine-induced stimulation (Fig. 4), nor hypoosmolar suppression (Fig. 3). Nonetheless, this dose of the anesthetic agent presumably exerted some inhibitory effect (possibly via higher CNS centers) as the ADH response to the stress of skin incisions was blunted (Fig. 5). This mild inhibition, however, was not sufficient to prevent the expected ADH increase following potent nociceptive (dental pulp) stimulation. In addition, the lower basal urinary ADH levels under ketamine anesthesia (302.0 ± 67.0 µU/15 min, Table 1) versus pentobarbital anesthesia (1339.2 ± 269.2 µU/15 min) are probably due to a greater degree of “CNS-sedation” (and associated ADH-blunting). Although the unanesthetized animal would presumably possess more sensitivity to physiological stimuli, the appropriateness and direction of response would be similar to that observed with ketamine. Humane and logistical considerations prompted use of anesthetized animals.

Mechanical control of respiration and alterations in end-expiratory pressure are known stimuli for ADH release. However, maintenance of normal blood gases during the depressed state with intracranial hypertension and prevention of hypoxia (another known stimulus of ADH release) necessitated using positive-negative pressure ventilation. A causal relationship between increased ICP and the clinical entity of SIADH is suggested but not proved by our study. Many patients manifesting SIADH have pathological derangements that clearly do not include increased ICP. Our observations were based on brief intracranial hypertension and short-term ADH analysis. We have no information pertaining to the duration of ADH “escape” from osmotic regulation after brief intracranial hypertension. Inappropriate secretion of ADH is seen in neurosurgical patients with diverse pathological processes (such as subarachnoid hemorrhage, meningitis, brain contusion, subdural hematoma) where multiple factors contribute to non-osmotic release of ADH. Nevertheless, since 1) there was no apparent "threshold" ICP that had to be exceeded before ADH secretion increased, 2) there appeared to be direct relationship between the magnitude of ICP and ADH release, and 3) this augmented ADH release could not be inhibited by osmotic means, we suggest that intracranial hypertension may be responsible for some of the clinical situations in which SIADH is observed.

The teleological significance of augmented ADH release during mass-induced intracranial hypertension may be related to maintenance of the vascular volume in the face of threatened brain ischemia and may, therefore, complement the observed systemic hypertension in this condition. Although the fluid retention after ADH release may be clinically treated by careful fluid restriction, the possibility exists of a direct deleterious effect on brain tissue by enhanced ADH during intracranial hypertension in a manner that would not be avoided by simple correction of peripheral hyponatremia. Since circulating ADH can be accurately measured, clinical studies need to be undertaken to assess whether a correlation exists between cerebral edema and the magnitude of plasma ADH.

References

L. Gaufin, W. R. Skowsky and S. J. Goodman
ADH and increased intracranial pressure


This paper was presented at the Annual Meeting of the American Association of Neurological Surgeons, San Francisco, California, April 4–8, 1976.

Address reprint requests to: Stanley J. Goodman, M.D., Division of Neurosurgery, Harbor General Hospital, 1000 West Carson Street, Torrance, California 90509.