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WOOD, ROGER J., EDMUND T. ROLLS, AND BARBARA J. ROLLS. *Physiological mechanisms for thirst in the nonhuman primate.* Am. J. Physiol. 242 (Regulatory Integrative Comp. Physiol. 11): R423–R428, 1982.—The relationship between body fluid deficits and drinking has been investigated in a nonhuman primate. Intravenous sodium chloride infusions (0.93–3.25 M) given to rhesus monkeys caused drinking correlated with increases in plasma osmolality and sodium concentrations. Sucrose infusions (0.3 M in 0.15 M NaCl) also caused drinking while equiosmolal urea infusions did not. It was found that the drinking threshold corresponded to a 2.3% increase in plasma osmolality. Water deprivation for 24 h caused significant cellular dehydration, as indicated by a 5.8% elevation in plasma osmolality that exceeded the threshold for thirst, and a significant hypovolemia as indicated by elevated plasma protein and hematocrit values. Intravenous water preloads decreased plasma osmolality and produced a dose-related decrease in subsequent drinking. Infusions that restored plasma osmolality to predeprivation values, reduced intake by 85%. Intravenous isotonic saline preloads which abolished the hypovolemia did not have a consistent effect and reduced mean water intakes by only 3.2%. Thus in the rhesus monkey, cellular dehydration is an effective stimulus for thirst, and it is the primary determinant of drinking after water deprivation, used as an example of a natural thirst stimulus. In contrast to findings in nonprimates, the extracellular deficit contributes very little to drinking after water deprivation.

cellular dehydration; extracellular depletion; water deprivation

DESPITE DISTURBANCES OF FLUID BALANCE in many clinical conditions and many studies on the control of drinking in nonprimates, relatively little is known about the regulation of water intake in primates, including humans. In this paper, investigations of the physiological mechanisms underlying drinking in the rhesus monkey are described.

In nonprimates, depletion of either the cellular or the extracellular fluid compartment can initiate drinking (12, 13). Depletion by 1–3% of the cellular fluid compartment, produced for example by the administration of hypertonic sodium chloride, is sufficient to induce drinking (2, 22, 23). Depletion of the extracellular fluid compartment through blood withdrawal (17) or hyperoncotic colloid injections (16) can also induce drinking. In a number of species, including the rat (10), dog (11), monkey (24), and man (14), drinking induced by a natural thirst stimulus, water deprivation, has been studied, and it has been found that depletion of both the cellular and extracellular fluid compartments is produced by the water deprivation. The suggestion that drinking after water deprivation depends on this double depletion has been investigated in the rat and dog. It was found that following 24-h water deprivation, removal of the cellular deficit using preloads of water reduced drinking by 65% in the rat (10) and by 72% in the dog (11), whereas selective removal of the extracellular deficit using preloads of isotonic saline reduced drinking by 20% in the rat (10) and by 27% in the dog (11). Thus in these species depletions in both the cellular and extracellular fluid compartments contribute significantly to the drinking following water deprivation.

Although it has been shown in man that cellular dehydration following sodium chloride infusions (22), or hypovolemia produced by sodium depletion (7), may cause thirst, the contributions of deficits in the two fluid compartments after the relatively natural stimulus of water deprivation have not been determined in a primate species. In the experiments described here, drinking by monkeys in response to different osmotically active and inactive solutions was first measured. Infusions of hypertonic sodium chloride, sucrose, and urea, were given intravenously into initially fluid-replete animals. The degree of cellular dehydration caused by the infusions was assessed from the measured increases in the osmolality and sodium concentration of plasma samples. The degree of cellular depletion required to initiate drinking during an infusion of sodium chloride was determined, and the degree of cellular dehydration produced by water deprivation was measured to determine whether this exceeded the threshold for drinking. Then the effects of repletion of either the cellular or the extracellular fluid compartment on the drinking following water deprivation were measured to determine to what extent depletions of these two compartments contribute to water deprivation-induced drinking in a primate. These investigations are basic to understanding the control of drinking in the primate.

METHODS

Subjects. All experiments were performed on three male rhesus monkeys, *Macaca mulatta*, weighing between 3.3 and 5.5 kg. As consistent results were obtained, the number of animals used was restricted to three. They were prepared under pentobarbitone sodium anesthesia with indwelling cardiac catheters implanted through the jugular vein. They were accustomed to sitting in a primate chair inside a sound-insulated cubicle and to the procedures of infusion and blood sampling via the cath-

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eter, as described in detail previously (6, 24). The monkeys were individually housed at 20–21°C, normally with free access to drinking water, and were fed once daily on laboratory diet (Dixons FPI, 40 g·kg^{-1} mixed with half this weight of water).

Effect on drinking of intravenous infusions of hypertonic solutions. Before the start of all experiments the animal was weighed. The tubes to allow sampling and infusion via the intracardiac catheter were attached, and the animal was allowed to settle with access to the drinking spout for 10 min. The drinking spout was removed, and the infusion of prewarmed solution (37°C) was made for 20 min. At the end of this period, the infusion was continued but at 10% of the preceding rate; as in pilot experiments this was found to hold the measured plasma osmolality and sodium concentration constant. The water spout was moved back in front of the animal and water intake over the following 15 min was recorded. Blood samples were drawn before the infusion, immediately before access to the drinking tube was allowed, and at 5, 10, and 15 min after water access was allowed.

A dose-response curve of the effect of sodium chloride on drinking was determined from infusions of isotonic (0.15 M) and hypertonic NaCl (0.93, 1.7, 2.47, and 3.25 M) given at a rate of 0.1 ml·kg^{-1}·min^{-1}. To measure the effects of other osmotically active or inactive substances, 1.7 M sucrose and 1.7 M urea, made up in 0.15 M NaCl, were given at the same rate. Each animal received 1 infusion/day, in a semirandom order. The two most concentrated infusions were not given on successive days to minimize any cumulative dehydration. In two animals, treatments were repeated in a different order to check the reliability of the effects.

Determination of drinking threshold. The procedure was as described above except that the animal had access to water throughout the infusion of 1.7 M NaCl given at the usual rate. The main infusion terminated at the time when the animal first drank at least 5 ml during a single drinking bout, and a blood sample was obtained at that time. Thereafter, the low-rate infusion (10% of initial) continued for another 15 min of water access. A further blood sample was taken after 10-min access to water.

Intravenous preloads of water following water deprivation. In this experiment, the dose-response relationship of the effect of intravenous preloads of water on the drinking produced by water deprivation was determined. The different preloads were ¼, ½, ¾, 1, and 1½ times the magnitude of the preload which in pilot experiments had been estimated as necessary to restore plasma osmolality to predeprivation levels. The extent of the repletion of the cellular compartment achieved by the water preloads was estimated from the measures of osmolality and sodium concentration of plasma samples taken during the experiment.

On the morning preceding the drinking test the monkey was weighed, and a resting blood sample was taken before the animal was returned to its home cage without further access to drinking water. It was given its usual quantity of food 1 h later at the normal time.

The next day, 24 h after the predeprivation blood sampling, the animal was weighed, the infusion and sampling lines were attached, and the animal was allowed to settle for 10 min before the infusion was begun. The volumes of water estimated from the pilot experiments as necessary in each animal to restore plasma osmolality to predeprivation levels (1 W in Fig. 2) were between 22 and 33 ml·kg^{-1} and were infused over a 40-min period. The infusion of smaller volumes of water (¼, ½, ¾ W) was made at the same rate, but began later in the 40-min period, while the infusion of a greater volume of water (1½ W) was at a correspondingly higher rate. At the end of the infusion, there was a 5-min delay before access to drinking water was allowed for 15 min. Blood samples were taken before starting the infusion, immediately before giving access to water, and at 10 and 15 min after access to water. In the control, no-infusion condition, the animal had to wait the same 40- plus 5-min period before being given water. At least 3 days elapsed between the treatments, which were given in randomized order. Each animal received the control (no infusion) and 1 W treatment twice, and all treatments were repeated in two of the animals to test the reliability of their effects.

Intravenous preloads of isotonic saline following water deprivation. In this experiment, the dose-response relationship of the effect of intravenous preloads of isotonic saline on the drinking produced by water deprivation was determined. The preloads were designed to produce different degrees of repletion of the extracellular fluid compartment, while leaving any cellular dehydration unchanged.

The experimental protocol was as above. The volumes of isotonic saline infused, over 40 min, were equivalent to ⅛, ¼, and ½ of the total body weight change during water deprivation (D in Fig. 2). The volume equivalent to ½ D varied between 14 and 22 ml·kg^{-1} depending on the animal. The smaller infusions were given at the same rate, but began later in the 40-min period. Blood samples were taken as above. At the conclusion of the infusion series each animal was tested again under the ¼ and ½ D conditions to determine the reliability of treatment effects.

Chemical analyses. Plasma sodium and potassium concentrations were determined by flame photometry (Instrumentation Laboratory model 343), plasma osmolality by freezing-point depression (Precision Instruments, model "Osmette S"). Plasma protein concentration was determined by refractometry (Bellingham and Stanley, immersion refractometer). Blood samples for hematocrit determination were spun in heparinized capillary tubes for 5 min at 4,000 rpm.

Statistics. An analysis of variance (ANOVA) was performed on all behavioral and physiological data, using a within-subjects, repeated-measure design. The significance of individual effects was determined from a Newman-Keuls multiple comparison test (21). Correlation coefficients (Pearson's r) were calculated, and a matched pairs t test (1) was used where appropriate. These statistical analyses were performed on data obtained in the first run of treatments in each animal.

RESULTS

Drinking following infusions of hypertonic solutions. The effects of the sodium chloride, sucrose, and urea

infusions on drinking are shown in Fig. 1. In calculating the means and SEs given in Fig. 1 for the two animals run twice, the average of the replications was used. It is clear that sodium chloride elicited drinking that was dose dependent, and that the drinking was also related to the degree of cellular dehydration produced by the infusions, as estimated by the increase in plasma osmolality and plasma sodium concentration produced by the infusion. (For statistical analysis, see below.) The infusions of sucrose, which does not cross the cell membrane and therefore produces cellular dehydration by osmosis but does not elevate plasma sodium (see Fig. 1), caused drinking ($P < 0.001$). The infusions of urea, which crosses the cell membrane and therefore does not produce cellular dehydration, did not cause drinking (see Fig. 1). Thus it is concluded that cellular dehydration causes drinking in the monkey.

The results of the statistical analyses were as follows. Infusions of the hypertonic sodium chloride (0.93–3.25 M NaCl) solutions caused significant water intake in each animal [ANOVA for treatments on intake F (6,12) = 15.55, $P < 0.001$; effect of 0.93 M NaCl significant at $P < 0.05$]; and intake was correlated with the concentration of sodium chloride infused ($r = 0.85$, $n = 15$, $P < 0.001$). The infusion of sucrose caused significant drinking ($P < 0.001$) but infusion of equiosmolar urea did not. The infusion of isotonic (0.15 M) sodium chloride did not produce a significant drinking response. Significant changes in plasma sodium and osmolality were associated with the NaCl infusions [e.g., ANOVA for treatments on plasma sodium, F (6,12) = 102.22, $P < 0.001$]. In each animal water intake was correlated with the absolute value of plasma sodium concentration following the infusion ($r = 0.96$, 0.98, and 0.94 for the three animals). The

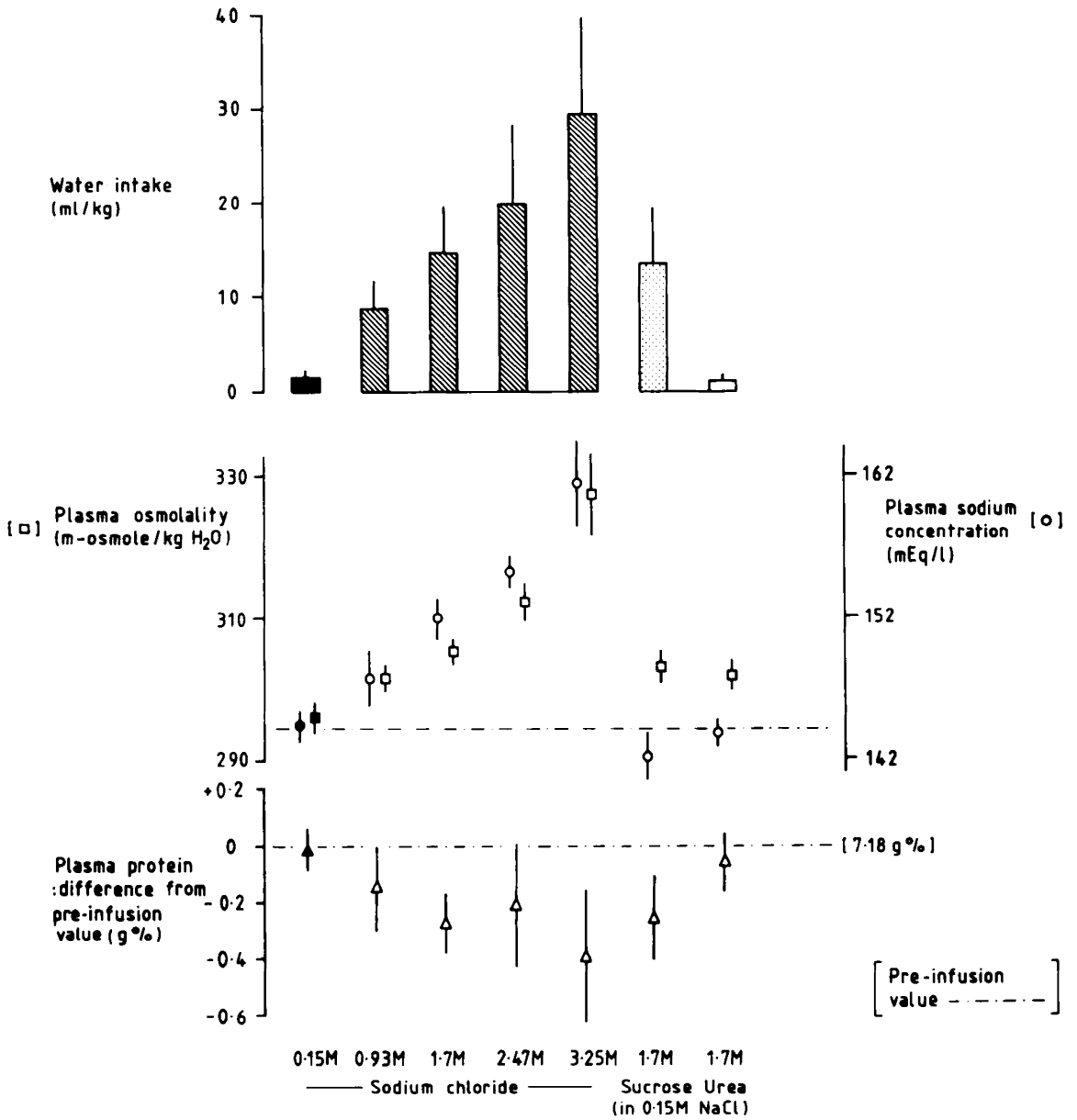

FIG. 1. Water intake and plasma composition following infusions of hypertonic solutions in 3 monkeys. Mean and SE are shown for drinking over 15 min and for plasma osmolality and sodium concentration. Plasma protein data is represented as differences in concentration from preinfusion values. Plasma samples were taken at initial access to drinking water. All infusions were given at 0.1 ml·kg^{-1}·min^{-1}. Isotonic (0.15 M) saline was given as a control.

effect of hypertonic infusions was reproducible in animals run twice under each condition (a mean difference in intake across conditions of 2.3 ± 2.0 ml·kg^{-1}: a 7.5% variation).

As in a previous study (24) some variation in resting values for plasma protein concentration was apparent, and the mean data are given as differences from preinfusion values in Fig. 1. The treatments tended to expand plasma volume by withdrawing water from the cellular fluid compartment, as indicated by the reductions in plasma protein concentration shown in Fig. 1. The treatments had significant effects on plasma protein concentration [ANOVA for treatments on protein concentration, F (6,12) = 3.22, $P < 0.05$; treatments on protein difference from predeprivation, F (6,12) = 4.36, $P < 0.05$]. The 2.47 and 3.25 M NaCl infusions significantly reduced protein concentrations ($P < 0.05$) with respect to control (0.15 M NaCl) values.

The infusion of urea increased plasma osmolality ($P < 0.05$) but not plasma sodium concentration.

Drinking threshold determination. The threshold determination experiment showed that drinking was initiated in the monkeys when plasma sodium concentration increased by 2.9 ± 0.7% (value derived from individual data) from 144.4 ± 0.9 meq/l to 148.6 ± 0.7 meq/l, and plasma osmolality increased by 2.3 ± 0.2% from 293 ± 3 to 300 ± 3 mosmol·kg^{-1}. The mean latency to start drinking was 10.5 ± 0.5 min after the start of the sodium chloride infusion (1.7 M) and the mean intake over the following 15 min was 9.8 ± 2.2 ml·kg^{-1}.

Drinking and body fluid changes produced by water deprivation. A mean volume of 32.1 ± 12.2 ml·kg^{-1} was drunk over 15 min following 24-h water deprivation (Fig. 2 no infusion condition). The mean weight loss during the deprivation period was 35 ± 7.8 g·kg^{-1}. The plasma osmolality increased from 295 ± 2 to 312 ± 3 mosmol·

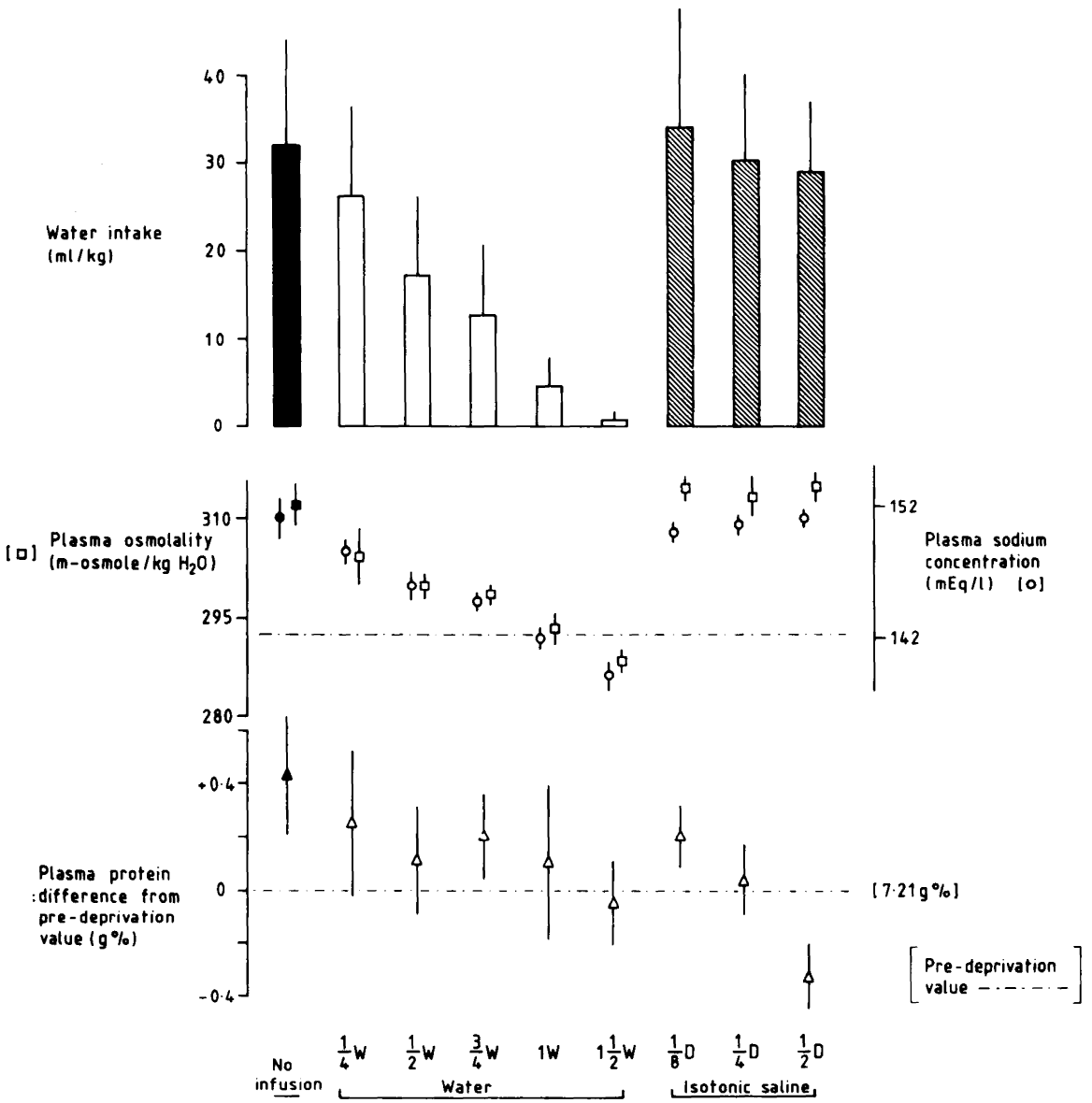

FIG. 2. Water intake over 15 min and plasma composition following preloads of water or isotonic saline in 3 monkeys previously deprived of water for 24 h. Mean and SE are shown for plasma osmolality and sodium concentration. Plasma protein data is represented as differences from preinfusion values. Plasma samples were taken at initial access to drinking water. Water infusions were in proportion to volume calculated for each animal (1 W = 22–33 ml·kg^{-1}) as sufficient to restore plasma osmolality to predeprivation values. Saline infusions were in proportion to the total fluid deficit (wt loss, D = 28–44 ml·kg^{-1}) for each animal.

kg^{-1}, and the plasma sodium concentration increased from 143 ± 0.4 to 151 ± 1.4 meq/l. The magnitude of the cellular dehydration produced by water deprivation is indicated by the increases observed in plasma osmolality (5.8 ± 0.4%) and sodium concentration (5.6 ± 1.4%), and this exceeded the threshold value of a 2.3–2.9% depletion as determined above. It is concluded that the cellular dehydration produced by 24-h water deprivation is sufficiently large to induce significant drinking. The plasma protein concentration increased from 7.3 ± 0.7 to 7.7 ± 0.5 g/100 ml, and the hematocrit increased from 36.5 ± 1.0 to 38.0 ± 1.2% during the deprivation. The depletion of plasma volume was thus approximately 5.7 ± 2.9%, estimated from the plasma protein change.

Drinking following water preloads. The effects of the different water preloads on the drinking produced by water deprivation are shown in Fig. 2. The 1 W water infusion, which restored plasma osmolality and sodium concentration to predeprivation values and thus quite accurately repleted the cellular fluid compartment, decreased the drinking following the water deprivation by 85 ± 5% (range 81–90%), with respect to the control (no infusion) condition. Therefore, a large part of the drinking produced by 24-h water deprivation in the monkey is due to cellular dehydration.

The statistical analyses showed the following. The water preloads significantly attenuated subsequent water intake with respect to the control (no infusion) condition [ANOVA for treatments on intake, F (5,10) = 15.76, $P < 0.001$] and significantly decreased plasma concentration [ANOVA for treatments on plasma sodium, F (5,10) = 58.37, $P < 0.001$; plasma osmolality, F (5,10) = 17.05, $P < 0.001$]. Each water infusion significantly decreased plasma sodium concentration (e.g., ¼ W, $P < 0.001$) and plasma osmolality (e.g., ¼ W, $P < 0.05$). Infusions (1½ W) which significantly reduced plasma sodium concentration and osmolality to below predeprivation values (t = 8.66 $P < 0.02$ for sodium; t = 9.38 $P < 0.02$ for osmolality; paired t test) virtually abolished water intake. In each animal, the water intake was highly correlated with the absolute values of plasma sodium concentration following the infusions (r = 0.98, 0.98, and 0.97 for the three animals). The reliability of the effects is indicated by the small differences in intake between the replications of the 1 W and control treatments in all three animals (difference between runs for the control water intake = 2.3 ± 1.7 $ml \cdot kg^{-1}$; for the 1 W water intake = 5.4 ± 2.6 $ml \cdot kg^{-1}$ relative to the control intake of 32.1 ± 12.2 $ml \cdot kg^{-1}$).

The ANOVAs for the effect of treatments on plasma protein and hematocrit were not significant, but Fig. 2 indicates a trend for an increase in plasma volume, as shown by the decrease in plasma protein concentration following the water infusions. This change is unlikely to make much contribution to the decrease of drinking as shown by the next experiment.

Drinking following isotonic saline preloads. The infusions of isotonic (0.15 M) sodium chloride solution had little effect on water intake following water deprivation (see Fig. 2) [ANOVA for treatments on intake, F (3,6) = 1.12, NS], despite substantial effects on measures of plasma volume [ANOVA for treatments on plasma protein concentration, F (3,6) = 4.96, $P < 0.05$; treatment on protein concentration difference from predeprivation, F (3,6) = 16.91, $P < 0.01$; on hematocrit difference from predeprivation, F (3,6) = 8.65, $P < 0.05$]. The ¼ D saline infusion successfully abolished the hypovolemia of water deprivation (protein and hematocrit returned to levels not significantly different from predeprivation values) while the ½ D saline infusion produced a significant hypervolemia, with respect to predeprivation values (e.g., plasma protein t = 5.7 $P < 0.05$, paired t test). Water intake was only slightly, and variably, reduced in the animals (−3.2 ± 7.2%) when the hypovolemia was abolished. Significant hypervolemia reduced water intake further (−9.7 ± 6.1%) but inconsistently and not significantly. Water intakes were similar between repetitions of treatments (differences of water intakes between two runs in each animal; ¼ D = 2.8 ± 2.5 $ml \cdot kg^{-1}$; ½ D = 2.7 ± 1.9 $ml \cdot kg^{-1}$; compared to control intakes of 32.1 ± 12.2 $ml \cdot kg^{-1}$). No significant increases in plasma sodium concentration or osmolality occurred during the saline infusions.

The infusion procedures were well tolerated in all experiments. The monkeys would eat if offered food during trial infusions. No significant progressive dehydration (as shown by daily plasma samples and body weights) was apparent over the course of the experiments and no hemolysis of samples occurred.

DISCUSSION

The threshold cellular dehydration necessary to elicit drinking, as determined in this experiment, was between 2.3% (from plasma osmolality) and 2.9% (from plasma sodium). This is of a similar order to that reported in other species; in the rat it is 1.6% (2), in the dog, 2.3% [e.g., Wolf (22)], and in man 1.2% (22). Because the volumes of water drunk in the experiment were highly correlated with the physiological changes over a wide range (Fig. 1), this sensitive mechanism serves to precisely regulate intake according to the magnitude of the depletion.

It was shown that the 24-h water deprivation produced a cellular dehydration between 5.8% (from plasma osmolality) and 5.6% (from plasma sodium) and was thus larger than the threshold change required to elicit drinking. Thus the drinking following this natural thirst stimulus was associated with cellular dehydration which was above the threshold for thirst.

The preloading experiments showed clearly that a substantial part of the drinking by monkeys following the water deprivation was due to cellular dehydration. Infusing a volume of water just sufficient to remove the cellular dehydration reduced the drinking following water deprivation by 85%, whereas infusing a greater volume of water caused dilution of plasma below predeprivation concentrations and virtually eliminated water intake. For comparison, in the rat 65% of total intake is due to cellular dehydration (10), whereas in the dog 72% is due to the cellular stimulus (11).

In contrast, abolishing the hypovolemia of water deprivation by infusing an appropriate volume of isotonic saline did not significantly attenuate drinking and producing a hypervolemia did not significantly inhibit drinking to the persistent cellular stimulus. The absence of a

demonstrable role for hypovolemia in thirst in the monkey contrasts with findings in other species. The hypovolemic component of thirst accounts for approximately 20 and 27% of water intake following water deprivation in the rat (10) and the dog (11), respectively. The present finding is paralleled by a reported absence of a significant effect of left atrial distension on antidiuretic hormone (ADH) release in the monkey (4). In the dog, atrial volume-receptor mechanisms are involved in the control of ADH release (5, 15) and probably in mediating hypovolemic thirst (3). Decreased sensitivity of volume-receptor mechanisms for regulating both water intake and excretion (4) may be adaptive in primate species, if postural changes during normal activity significantly influence systemic fluid distribution.

The results of the hypertonic and water-infusion experiments, and the short-latency threshold drinking response, indicate a sensitive mechanism for cellular thirst that responds rapidly to systemic changes. The location of the receptor is not known, but central osmosensitive neurons have been demonstrated in the monkey (20), as in other species (9, 23). Because hypertonic sucrose infusions, which produced cellular dehydration by osmosis but did not elevate plasma sodium, did lead to drinking, it seems likely that the effective stimulus for such drinking is withdrawal of water from the cells and not elevated sodium concentration. However, as the sensors are located centrally, it would be useful to measure CSF osmolality and sodium concentration during peripheral hypertonic infusions to determine which is most closely associated with drinking (19).

In conclusion, it has been demonstrated that drinking in rhesus monkeys is regulated according to the magnitude of cellular fluid deficits. Drinking following a natural stimulus to thirst, 24-h water deprivation, is associated with a cellular deficit that exceeds the threshold cellular dehydration for the initiation of drinking. This stimulus accounts for a substantial proportion, 85%, of total water intake. In contrast to findings in nonprimate species, the depletion of plasma volume associated with water deprivation contributes very little to drinking.

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