Osmoregulation and volume regulation in rats: inhibition of hypovolemic thirst by water

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Stricker, Edward M. Osmoregulation and volume regulation in rats: inhibition of hypovolemic thirst by water. Am. J. Physiol. 217(1): 98-105. 1969.—Subcutaneous injections of hyperoncotic polyethylene glycol (PG) solutions produced hypovolemia in rats by withdrawing isosmotic plasma fluid into the local interstitium. All animals showed increased thirst, but stopped drinking water well before plasma deficits were restored. Concurrent hyperosmolality (produced by injection of hypertonic NaCl solutions) increased the water intakes of PG-treated rats in proportion to both intracellular and intravascular dehydrations, yet continued hypovolemia was again evident when drinking discontinued. Similarly, water preloads almost usually eliminated drinking in PG-treated rats but had little effect on plasma volumes. Inhibition of drinking was accompanied by significant osmotic dilution in all three experiments. In contrast, ingestion or preloads of isotonic NaCl solutions, which did not affect plasma osmolality, did not eliminate thirst in PG-treated rats unless plasma deficits were repaired. These findings indicate that an inhibitory mechanism, apparently stimulated by osmotic dilution of body fluids, is involved in the regulation of water intake during hypovolemia. This mechanism, perhaps represented in the supraoptic hypothalamus, may be functionally similar to the ventromedial hypothalamic "satiety center" involved in the regulation of food intake.

TWO DISTINCT PHYSIOLOGICAL STATES of dehydration induce thirst in rats: intracellular dehydration, usually associated with hyperosmolality of body fluids (20), and intravascular fluid volume depletion (hypovolemia) (18, 38). In brief, thirst stimulated by dehydration is believed to be mediated by a central thirst mechanism and to be satiated by negative feedback resulting from the physiological effects of fluid intake and retention (14). A schematic representation of these factors is presented in Fig. 1. That these mechanisms regulate osmoregulatory drinking is supported by considerable evidence that: (a) drinking is elicited by direct lateral hypothalamic stimulation in the absence of systemic dehydration (5, 40) and is abolished by lateral hypothalamic lesions in the presence of osmotic dehydration (15), (b) water intake is directly proportional to the dehydrating stimulus and is usually sufficient to restore normal osmolality (2, 20), and (c) thirst is not satiated unless fluid intake reduces body fluid osmolality (9, 31). Although less is known about hypovolemic thirst, recent findings have suggested that comparable mechanisms are also involved since drinking is abolished by lateral hypothalamic lesions (43), is proportional to plasma volume deficit (39), and disappears when plasma deficits are restored (42).

The schema for the regulation of water intake presented in Fig. 1 is more parsimonious than the analogous system proposed for the regulation of food intake since it omits a central inhibitory mechanism activated by postgestional factors acting directly on the "drinking center" (36). However, recent evidence that hypovolemic rats stop drinking water despite continued plasma deficits (39) suggests that inhibition may, in fact, occur. Although this inhibition of drinking seems inappropriate for volume regulation, it is possible that it instead subserves osmoregulation by preventing further increases in body-fluid dilution. The present series of investigations examines in detail this interaction between the osmo- and volume-regulatory systems, and specifically determines the behavioral and physiological effects of osmotic dilution in hypovolemic rats.

METHODS

Subjects and Pretreatment Maintenance

The animals used were adult male albino rats, weighing between 300 and 400 g, of the Sprague-Dawley and Wistar strains. There were no apparent behavioral or physiological differences between experimentally treated rats of the two strains and data from them have been combined. Animals were housed individually in wire mesh metabolism cages in a well-illuminated temperature-controlled room (75-77 F).

During each of the 3 days prior to experimental testing, the rats were deprived of food (Purina chow) and distilled water for 8 hr (9 AM-5 PM) and were then given access to water for 1 hr (5 PM-6 PM). Water intakes during this period were generally less than 1 ml. Food and water were available ad libitum from 6 PM until 9 AM on the following day. Urine was collected during the deprivation periods and its volume measured in a graduated vessel to the nearest 0.1 ml.

Procedure

Hypovolemia was produced in rats by the subcutaneous injection of 5.0 ml of 10, 20, or 30 % solutions of polyethylene glycol (Carbowax, compound 20-M; Union Carbide Corporation) dissolved in 0.15 M NaCl. These polyethylene glycol (PG) treatments produce plasma deficits of approximately 15, 22, and 30 %, respectively, in
rats 8 hr after injection by withdrawing increasing amounts of isosmotic protein-free plasma fluid into the local interstitium (18, 38, 39). Additional fluid from the general interstitium, drawn into the intravascular space by rising plasma oncotic pressure, is also drained into the injection area. As a result of these processes, administered or ingested fluids are not completely retained in the circulation but (by lowering the plasma oncotic pressure) may also enter the general interstitium. Consequently, fluid volumes considerably larger than the net plasma deficits are necessary to restore the plasma losses (39).

Osmotic dilution. The effects of acute osmotic dilution on drinking during hypovolemia were determined in 109 rats. At 9 AM of the 4th deprivation day, all rats were injected subcutaneously, in the middle of the back, with 5 ml of either 10%, 20%, or 30% PG solution (N = 42, 44, 23, respectively). Five or seven hours after these treatments (at 2 or 4 PM), rats from each group were stomach-loaded with 15 ml of water or 0.15 M NaCl through an orally inserted catheter (all fluids used for stomach loads were prewarmed to body temperature). To promote increased water retention in the 10% PG-treated rats, six animals received two 15-ml intubations of water (at 2:30 and 4 PM), whereas six other rats received an intraperitoneal injection of 8 milliunits Pitressin (Parke, Davis & Co.) in 0.2 ml isotonic saline together with a single 15-ml water intubation (at 2:30 and 4 PM). At 3 PM, all rats were permitted access to distilled water, presented in graduated drinking tubes (±0.2 ml), for 1 hr. This treatment schedule is summarized in Table 1.

Since extravascular injections of hyperoncotic colloids are known to have some antidiuretic effect (13, 18, 38, 42), the specific effects of the present PG treatments on retention of water loads were determined in 54 rats. At 9 AM on the 4th deprivation day, 42 rats were injected subcutaneously with 5 ml of 10%, 20%, or 30% PG solutions (N = 26, 8, 8, respectively). The remaining 12 rats were not injected. All rats received a 15-ml stomach load of distilled water 7 hr after PG treatment; 9 rats given 10% PG also received an intraperitoneal injection of 8 milliunits Pitressin, as above. Nine other rats given 10% PG received two 15-ml water loads, 5.5 and 7 hr after injection. Urine volumes subsequent to the water loads were measured every 30 min for 3 hr, the bladder being emptied by suprapubic pressure only at the start and finish of this interval. No food or drinking water was available during this time.

The effects of the preloads on blood volume and osmolality were determined in 63 rats. At 9 AM on the 4th deprivation day, rats were injected subcutaneously with 5 ml of either 10%, 20%, or 30% PG solution (N = 16, 20, 12, respectively). In each group, some rats were stomach loaded with 15 ml of distilled water or 0.15 M NaCl (as above) while others received no preload. The treatment schedule is summarized in the first three columns of Table 2. Between 8 and 8.5 hr after PG treatment, rats were anesthetized with Nembutal (ca. 50 mg/kg) and 5–6 ml of blood were withdrawn from the abdominal aorta for analysis (38). Determinations of hematocrit and plasma protein concentration were used to estimate plasma volume changes (39), while changes in plasma osmolality were measured directly or were assessed by changes in plasma sodium concentration (24).

No osmotic changes. If hypovolemic rats stop drinking water before their plasma deficits are repaired because osmotic dilution inhibited thirst, then ingestion of isotonic saline should proceed without inhibition since it would not affect body-fluid osmolality. To test this, each of 24 rats placed on the same deprivation schedule as above was injected subcutaneously with 5.0 ml of either 10%, 20%, or 30% PG solution (N = 8 in each group). Immediately following the injections, a graduated tube containing 0.15 M NaCl was made available for drinking and intakes were monitored for 9 hr. Blood samples were then obtained from four rats in each group and hematocrits, plasma protein, and plasma sodium concentrations were determined to assess the effects of isotonic saline ingestion on plasma volume in these animals. These data were compared with previously reported results from identically treated rats permitted 9 hr continuous access to drinking water (39).

Osmotic concentration. The effects of concurrent hyperosmolality and hypovolemia on thirst were determined in 56

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**TABLE 1. PG treatment schedule**

<table>
<thead>
<tr>
<th>Treatment, t = 0 hr</th>
<th>N</th>
<th>5 hr</th>
<th>7 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% PG</td>
<td>10</td>
<td>W</td>
<td>W†</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>W†</td>
<td>W</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>W</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>20% PG</td>
<td>7</td>
<td>W</td>
<td>W</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>30% PG</td>
<td>7</td>
<td>W</td>
<td>S</td>
</tr>
</tbody>
</table>

* Intragastric preloads were 15 ml of either water (W) or 0.15 M NaCl (S). 1-hr drinking test began 8 hr after treatment. † Rats also received an intraperitoneal injection of 8 milliunits Pitressin.
E. M. STRICKER

Fig. 2. Effect of intragastric preloads of water or 0.15 M NaCl on mean water intakes of 10% PG-, 20% PG-, and 30% PG-treated rats (N = 6-18 in each group, see Table 1). Vertical lines represent standard error of the mean.

RESULTS AND DISCUSSION

Drinking tests: All nonloaded rats showed significant increases in water intake after 10%, 20%, or 30% treatments (all P values < .001; the statistical significance of these and all other results were determined using a two-tailed t test). Figure 2 shows the effects of intragastric water and saline preloads on the subsequent water intakes of other PG-treated rats. In 10% PG-treated rats, preloading with 15 ml of isotonic saline caused a significantly greater reduction in subsequent water intake than did preloading with 15 ml of water (P < .001), which had no significant effect. In contrast, preloading with 15 ml of isotonic saline had no noticeable effect on drinking in 20% PG-treated rats, whereas 15-ml water preloads significantly reduced subsequent water intakes (P < .001). These results were obtained whether the preloads were administered 1 or 3 hr before the drinking test. However, a substantial decrease in intake was obtained when 30 ml of saline were administered in two preloads (P < .001). Finally, like 20% PG-treated rats, 30% PG-treated rats were not affected by 15-ml saline loads but showed significant decreases in water intake after 15-ml water loads (P < .001).

It is interesting to note that only the 10% PG-treated rats drank after receiving a 15 ml water load. This may have resulted from their relatively slight antidiuresis during

above and, at 9 AM on the 4th deprivation day, was injected intraperitoneally with 2% body wt of either 0.5 or 1.0 M NaCl solution (N = 28, 28). When the saline diureses were virtually completed 2 hr later, 21 rats in each group were injected subcutaneously with 5.0 ml of either 10%, 20%, or 30% PG solution (N = 7 in each subgroup). The remaining 14 rats did not receive PG treatment (N = 7, 7). Drinking water was made available 8 hr later (at 7 PM) and intakes were recorded for 1 hr. Blood samples were then obtained from four rats in each of the PG-treated groups given 1 M NaCl, and hematocrits, plasma protein, and plasma sodium concentrations were determined.

Osmotic Dilution

Drinking tests: All nonloaded rats showed significant increases in water intake after 10%, 20%, or 30% treatments (all P values < .001; the statistical significance of these and all other results were determined using a two-tailed t test). Figure 2 shows the effects of intragastric water and saline preloads on the subsequent water intakes of other PG-treated rats. In 10% PG-treated rats, preloading with 15 ml of isotonic saline caused a significantly greater reduction in subsequent water intake than did preloading with 15 ml of water (P < .001), which had no significant effect. In contrast, preloading with 15 ml of isotonic saline had no noticeable effect on drinking in 20% PG-treated rats, whereas 15-ml water preloads significantly reduced subsequent water intakes (P < .001). These results were obtained whether the preloads were administered 1 or 3 hr before the drinking test. However, a substantial decrease in intake was obtained when 30 ml of saline were administered in two preloads (P < .001). Finally, like 20% PG-treated rats, 30% PG-treated rats were not affected by 15-ml saline loads but showed significant decreases in water intake after 15-ml water loads (P < .001).

It is interesting to note that only the 10% PG-treated rats drank after receiving a 15 ml water load. This may have resulted from their relatively slight antidiuresis during

additional rats. Initial hyperosmolality should increase the water consumption necessary to achieve osmotic dilution if such dilution limits the water intake of hypovolemic rats. Each rat was placed on the same deprivation schedule as

Fig. 3. Effect of intragastric water loads on mean urine outputs of rats after control (N = 12) or PG treatments (N = 8 in each group). Vertical lines represent standard error of the mean.
INHIBITION OF HYPOVOLEMIC THIRST BY WATER

FIG. 4. Effect of intragastric water loads and intraperitoneal Pitressin on mean urine outputs of rats after control or 10% PG treatments (N = 8-12 in each group). Drinking water was not available. Stippled area represents time and duration of drinking test given to identically treated rats in Fig. 5.

the 1-hr drinking test; they retained less than 60% of the water preload, whereas 20% PG- and 30% PG-treated rats retained more than 95% of it. A more systematic investigation of the water diureses of PC-treated rats confirmed this observation (Fig. 3) and demonstrated the marked differences between the groups (at 2 hr, all P values < .001), with water retention being proportional to level of hypovolemia. Thus, it appears that the net water retentions closely paralleled their effects on water intake in the PG-treated rats. Nevertheless, it remains curious that 10% PG-treated rats stopped drinking after consuming 6-7 ml of water but not after receiving 15 ml of water by intragastric intubation. Since water consumed normally is more satiating than an equal volume administered by stomach tube (28), a water retention in excess of 6-7 ml would probably be needed to inhibit their drinking. In fact, the seven water-loaded 10% PG-treated rats drank 5.7 ± 1.3 ml and excreted 6.5 ± 1.2 ml during their drinking tests, for a net water retention of 14-15 ml. Since this approximates the volumes that were effective in the 20% PG- and 30% PG-treated rats, perhaps it represents the net water retention necessary to inhibit hypovolemic thirst in animals of this size.

This hypothesis was supported when the effects of increased retention of the intragastric water preloads on drinking by 10% PG-treated rats were determined. When 8 milliunits Pitressin were administered concurrently with a 15-ml preload, urine excretion was significantly reduced (P < .01, Fig. 4) and drinking was almost totally eliminated (P < .001, Fig. 5). This effect is probably due to some consequence of the increased water retention since Pitressin does not influence thirst directly (1, 2). In addition, a comparable inhibition of thirst was obtained in 10% PG-treated rats given two 15-ml water loads (P < .001, Fig. 5) in which endogenous ADH production was probably decreased because of the added dilution. The net water retentions (during the drinking test) following these two treatments were almost identical to one another (Fig. 4) and to that seen in 20% PG- or 30% PG-treated rats given one 15-ml water preload (Fig. 3).

Blood analyses. In untreated nondeprived rats, hematocrit is approximately 46.1 and plasma protein concentration is approximately 5.9 g/100 ml (38). Subcutaneous injection of 10%, 20%, or 30% PG solutions produced increasing intravascular dehydration, as indicated by increasing hematocrit and plasma protein concentration (all P values < .001), but caused little change in plasma osmolality or sodium concentration (Table 2). Preloads of 15 ml isotonic saline administered to the 10% PG group effectively restored plasma volume to normal, whereas identical preloads had less effect on plasma volume in the 20% and 30% PG groups. Larger (30 ml) saline preloads were needed to restore plasma volume in the 20% PG group. These effects reflect the varying ability of the saline preloads to satiate
volume deficits that require approximately 15, 30, and 45 ml, respectively, of isotonic fluid for repleniement (unpublished observations). These findings demonstrate that some consequences of water ingestion inhibit drinking in all PG-treated rats despite continued hypovolemia and clearly dispute the general theoretical formulation presented in Fig. 1.

Direct measurements of plasma osmolalities and sodium concentrations in the water-loaded 20% PG- and 30% PG-treated rats indicated a 3–6% reduction from control values (Table 2), approximating the 5–7% dilution estimated to result from the retention of 13–15 ml of pure water in 350-g rats. This hypoosmolality represents only a few milliliters more water retained and 1–2% more osmotic dilution than was observed in the 10% PG-treated rats given 15 ml-water loads, despite the significant differences in their drinking behaviors. Thus, it appears that small differences in osmotic dilution may have substantial effects on drinking behavior in hypovolemic rats. This is reminiscent of the marked effects on ADH secretion and thirst which result from 1–2% increases in osmotic concentration (46, 47).

Although the level of osmotic dilution associated with the inhibition of hypovolemic thirst is substantial, it does not even approach the extreme hyponatremia characteristic of water intoxication (21). Moreover, it should be noted that the water-loaded PG-treated rats appeared normal and ate readily when food was made available in their cages. Thus, it seems likely that the cessation of drinking in these animals was stimulated by a specific physiological stimulus and was not related to some general interruption of normal behavior.

### Table 2. Effect of preloads on various blood measures in PG-treated rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Preload</th>
<th>N</th>
<th>Hematocrit</th>
<th>Protein, g/100 ml</th>
<th>Sodium, mEq/liter</th>
<th>(Na)p</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>6</td>
<td>46.1±0.95</td>
<td>9.1±0.1</td>
<td>305.0±1.2</td>
<td>147.4±1.0</td>
</tr>
<tr>
<td>10% PG</td>
<td>None</td>
<td>8</td>
<td>53.0±0.57</td>
<td>7.1±0.1</td>
<td>306.8±0.8</td>
<td>150.9±1.8</td>
</tr>
<tr>
<td></td>
<td>S-7</td>
<td>4</td>
<td>46.9±1.25</td>
<td>5.5±0.2</td>
<td>304.2±1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>W-7</td>
<td>4</td>
<td>50.8±0.96</td>
<td>6.2±0.1</td>
<td>294.1±1.6</td>
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</tr>
<tr>
<td>20% PG</td>
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<td>35.7±0.27</td>
<td>7.5±0.1</td>
<td>304.8±1.4</td>
<td>132.8±0.9</td>
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<td></td>
<td>S-7</td>
<td>4</td>
<td>48.4±0.65</td>
<td>7.8±0.1</td>
<td>305.9±0.4</td>
<td>147.5±0.8</td>
</tr>
<tr>
<td></td>
<td>W-7</td>
<td>4</td>
<td>50.0±0.65</td>
<td>6.6±0.1</td>
<td>291.3±1.3</td>
<td>142.3±1.6</td>
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<td>S-5</td>
<td>4</td>
<td>50.5±1.86</td>
<td>4.4±0.2</td>
<td>292.9±2.2</td>
<td>150.7±1.4</td>
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<td></td>
<td>W-5</td>
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<td>51.8±0.96</td>
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<td>298.1±1.6</td>
<td>146.1±1.8</td>
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<td></td>
<td>S-5, 7</td>
<td>4</td>
<td>47.4±0.75</td>
<td>3.4±0.2</td>
<td>305.0±1.8</td>
<td>153.3±0.6</td>
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<td>30% PG</td>
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<td>51.1±0.38</td>
<td>8.5±0.1</td>
<td>303.7±2.3</td>
<td>151.9±0.6</td>
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<tr>
<td></td>
<td>S-7</td>
<td>4</td>
<td>51.8±0.26</td>
<td>6.4±0.1</td>
<td>130.8±1.8</td>
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<td></td>
<td>W-7</td>
<td>4</td>
<td>60.2±0.68</td>
<td>8.2±0.2</td>
<td>142.9±1.2</td>
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</tbody>
</table>

Values are means ± se. Rats not permitted drinking water. Preloads were 15 ml of 0.15 m NaCl (S) or water (W) administered intragastrically 5 or 7 hr after treatment. (Na)p = mEq Na/liter plasma water.

No Osmotic Changes

Rats injected with 10%, 20%, or 30% PG solutions and permitted ad libitum access to drinking water consumed 6.8, 10.4, and 13.8 ml, respectively, in the first 9 hr after treatment (39). These intakes had little effect on hematocrits and plasma protein concentrations and thus the rats remained significantly hypovolemic (Table 3; compare with nonloaded PG-treated rats in Table 2). Note that the osmotic dilution in these rats was comparable to that observed in water-loaded PG-treated rats that did not drink (Table 1). In contrast, when 0.15 m NaCl solution was

### Table 3. Effect of fluid intake on various blood measures in dehydrated rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Fluid</th>
<th>Ingested</th>
<th>Hematocrit</th>
<th>Protein, g/100 ml</th>
<th>(Na)p</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% PG</td>
<td>Water</td>
<td>49.2±1.6</td>
<td>6.7±0.1</td>
<td>143.8±1.6</td>
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</tr>
<tr>
<td>20% PG</td>
<td>Water</td>
<td>53.3±1.6</td>
<td>7.3±0.1</td>
<td>140.2±1.9</td>
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</tr>
<tr>
<td>30% PG</td>
<td>Water</td>
<td>57.4±0.9</td>
<td>7.9±0.4</td>
<td>143.1±2.0</td>
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</tr>
<tr>
<td>10% PG</td>
<td>Saline</td>
<td>46.8±1.0</td>
<td>5.7±0.1</td>
<td>148.9±0.8</td>
<td></td>
</tr>
<tr>
<td>20% PG</td>
<td>Saline</td>
<td>44.7±0.8</td>
<td>3.7±0.1</td>
<td>148.8±0.7</td>
<td></td>
</tr>
<tr>
<td>30% PG</td>
<td>Saline</td>
<td>44.1±1.1</td>
<td>5.6±0.1</td>
<td>140.7±0.6</td>
<td></td>
</tr>
<tr>
<td>10% PG + 1 m NaCl</td>
<td>Water</td>
<td>50.3±1.1</td>
<td>6.5±0.1</td>
<td>142.3±1.3</td>
<td></td>
</tr>
<tr>
<td>20% PG + 1 m NaCl</td>
<td>Water</td>
<td>52.7±0.7</td>
<td>7.1±0.1</td>
<td>142.5±0.7</td>
<td></td>
</tr>
<tr>
<td>30% PG + 1 m NaCl</td>
<td>Water</td>
<td>37.2±3.1</td>
<td>8.8±0.3</td>
<td>141.7±0.6</td>
<td></td>
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</tbody>
</table>

Values are means ± se. (Na)p = mEq Na/liter plasma water. Each group contained four rats.
available as drinking fluid, rats consumed 19.7, 29.4, and 37.6 ml, respectively (all P values < .001 when compared with water intakes). These intakes approximated the volumes of isotonic fluid required to replete plasma volumes and, since virtually all of the ingested fluid was retained, the hematocrits and plasma protein values reflect the intravascular restoration (Table 3).

These results are consistent with the hypothesis that water inhibits hypovolemic thirst by osmotic dilution. They indicate that hypovolemic rats could ingest sufficient fluid to restore plasma volume deficits, and further emphasize the inadequacy of the low water consumption. The large intakes of isotonic saline also demonstrate that premature cessation of water intake was not due to local oral or gastric effects (29). It is not likely that palatability factors influenced fluid consumption in these one-bottle drinking tests (30).

Osmotic Concentration

The water intakes of rats suffering concurrent hyperosmolarity and hypovolemia were clearly proportional to both intravascular and intracellular dehydrations (Fig. 6) and approximated the arithmetic sums of the intakes obtained when the PG and hypertonic NaCl treatments were administered separately. Table 3 indicates that these water intakes were more than sufficient to restore osmotic balance, yet had little effect on plasma volumes. Significantly, the levels of osmotic dilution in these rats were again comparable to those observed in adipsic water-loaded PG-treated rats (Table 1).

These findings suggest that the water ingestion at first satiated hyperosmotic thirst by diluting body fluids to normal, and then continued, due to hypovolemia, until sufficient osmotic dilution occurred to inhibit further intake. In addition, they indicate that hyperosmolality and hypovolemia can act independently as stimuli of thirst, and demonstrate that the satiation of hyperosmotic thirst does not inhibit further drinking by the rat if hypovolemia continues. The additive effects of hyperosmolality and hypovolemia on thirst have recently been observed in other laboratories (personal communication from J. D. Corbit and J. T. Fitzsimons). This complements previous findings that isotonic plasma volume expansion does not inhibit hyperosmotic thirst (e.g., 42).

GENERAL DISCUSSION

Osmotic Dilution as a Stimulus for Thirst Inhibition

Hypovolemic thirst is considerably more complex than thirst elicited by intracellular fluid (ICF) dehydration since it involves a relative deficit of both water and sodium (44). Since water alone cannot repair intravascular fluid (IVF) volume deficits, hypovolemic rats might be expected to consume huge quantities of water without obtaining satiety (26). Instead, although they drank in direct proportion to their needs (39), their water intakes were far short of the fluid volumes necessary to repair the deficits (Table 3).

Why do they stop drinking? The present experiments suggest that hypovolemic thirst was inhibited by osmotic dilution or concomitant ICF expansion since: a) in 20% PG- and 30% PG-treated rats drinking is also inhibited by 15-ml water preloads (indicating that inhibition was not due to oral effects of water ingestion) but not by 15-ml preloads of isotonic saline (indicating that this inhibition is not due to gastric distention), b) water preloads only inhibit hypovolemic thirst when water retention is excessive, c) drinking continues in hypovolemic rats until plasma deficits are re-paired when osmotic dilution is prevented, and d) drinking is augmented in hypovolemic rats when concurrent hyperosmolality delays osmotic dilution.

In addition to the present findings, other evidence also suggests that osmotic dilution can inhibit drinking despite the continued presence of a thirst stimulus. These studies found that overhydration produced by water preloads or excessive water ingestion noticeably impaired the drinking response of rats to intrahypothalamic injections of carbachol (32) and of goats to electrical or osmotic stimulation of the hypothalamic drinking center (3, 5). Conversely, it has also been observed that minute intraventricular injections of water or hypotonic NaCl solutions reduce thirst produced by systemic dehydration in rats (21) and cats (27).

Hypothalamic Thirst Satiety Center

The present experiments demonstrate an inhibition of thirst and suggest that the inhibitory mechanism involves osmotic dilution, but they do not deal directly with the representation of this mechanism in the central nervous system. Previous discussions of a central satiety mechanism for thirst, usually considered in the context of hypothalamic regulatory systems and in apposition to the dual excitatory-inhibitory mechanisms which appear to control food intake (4, 11, 36, 37, 48), have often rejected this concept because of the lack of accepted evidence that primary polydipsia

![Figure 6](http://ajplegacy.physiology.org/DownloadedFrom/10.23336/cv246.png)
can result from brain lesions. Presumably, ablation of a thirst satiety center should lead to excessive drinking comparable to the hyperphagia which follows ventromedial hypothalamic lesions (45). In this regard, the well-known polydipsia of diabetes insipidus (DI) resulting from lesions in or near the supraoptic nuclei traditionally has been considered secondary to a primary polyuria and dehydration resulting from the disruption of ADH secretion (4, 16). This view is strongly supported by evidence that the polyuria precedes the polydipsia in onset (16, 17, 19), and that antidiuresis resulting from renal occlusion or Pitressin administration inhibits the polydipsia (22, 33). Nevertheless, there is considerable evidence suggesting that polydipsia may be primary in some instances since: a) DI dogs with esophageal fistulas develop a marked polydipsia but only a slight and transitory polyuria (10), b) DI animals often can be maintained on limited water intake without evidence of dehydration (6, 10, 17, 25), c) polydipsia sometimes precedes polyuria in onset (6, 10), and d) an antidiuresis sometimes does not interrupt polydipsia (6, 8, 34) and may lead to water intoxication (35). A reasonable resolution of these conflicting arguments might note that a primary polydipsia or polyuria need not preclude the other, and that both may occur (6, 10, 25, 34).

In conclusion, the theoretical representation of thirst regulation that was presented in Fig. 1 considered satiety to result from the restoration of intravascular fluid volume and osmolality. Whereas previous reports are consistent with this view of osmoregulatory drinking (42), the present findings clearly demonstrate that drinking may be inhibited after water ingestion despite the continued presence of an effective antidiuresis (12, 23). Finally, this hypothesis could still recognize that other structures in the limbic system might also be involved in mediating satiety (37).

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A reformulation of the body-fluid parameters which might influence thirst and satiety appears in schematic form in Fig. 7. Proceeding from right to left, intracellular dehydration of osmoreceptors elicits increased drinking which lowers plasma osmolality to normal and thereby reduces the stimulus for further drinking (cf. Fig. 1). Clearly, a satiety center is irrelevant to considerations of hyperosmotic thirst since drinking in response to hyperosmolality would stop before osmotic dilution could occur. On the other hand, drinking elicited by intravascular dehydration progressively lowers body fluid osmolality below normal and might eventually activate a thirst satiety center, inhibiting further water intake. It should be noted that additional mechanisms involving the regulation of sodium intake and excretion might also be activated by these physiological conditions. Indeed, hyponatremia (osmotic dilution) and hypovolemia both stimulate sodium appetite in rats (11, 19) which, if ingestion of concentrated NaCl solutions were permitted, would remove the inhibition of thirst and thereby permit the increased fluid ingestion necessary for repairing plasma volume deficits.

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REFERENCES


INHIBITION OF HYPOVOLEMIC THIRST BY WATER


