Fasting downregulates renal water channel AQP2 and causes polyuria

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Fasting downregulates renal water channel AQP2 and causes polyuria. Am J Physiol Renal Physiol 280: F513–F523, 2001.—Starvation causes impairment in the urinary concentrating ability. The mechanism of this defect, however, remains unknown. We tested the possibility that food deprivation might affect the expression and activity of aquaporins (AQP1, 2), thereby impairing renal water reabsorption in the kidney. Rats fasted for 24 h exhibited severe polyuria (urine volume increased from 11 before fasting to 29 ml/24 h after fasting, P < 0.0001) along with failure to concentrate their urine (urine osmolality decreased from 1,485 before fasting to 495 mosmol/kgH2O after fasting, P < 0.0001). Refeeding for 24 h returned the urinary concentrating ability back to normal. Northern hybridization was increased significantly at both protein (P < 0.004) and mRNA levels (P < 0.003) in the outer medulla. In the cortex, fasting decreased AQP2 protein abundance by 60% (P ≤ 0.004) but did not alter its mRNA expression. During the recovery phase, AQP2 expression returned to normal level in both tissues. In the inner medulla, the expression of AQP2 was not altered in fasting, but was increased significantly at both protein (±92%) and mRNA (±43%) levels during the recovery from fasting. The proximal nephron water channel (AQP1) was not affected in response to fasting or recovery from fasting. We conclude that 1) fasting impairs the urinary concentrating ability in rats, and 2) the renal water-handling defect in fasting results specifically from the downregulation of AQP2 in the cortical and outer medullary collecting duct.

urinary concentrating mechanism; aquaporin 2; hypoglycemia

Fasting or abstaining from food has been practiced voluntarily (religious belief or dieting) or involuntarily (famine) throughout time. Food restriction induces adaptive mechanisms in the body that permit survival for prolonged periods of fasting. Indeed, human beings can endure several months of fasting (33). In humans, the first week of fasting is associated with a marked increase in water excretion, suggesting an impairment in the urinary concentrating mechanism (31). In the rat, it was reported that fasting induces a dual effect on renal function: a first phase characterized by a decline in both whole kidney glomerular filtration rate (GFR) and single nephron GFR (SNGFR), followed by an adaptive phase with normalization of both GFR and SNGFR (2). In the rabbit, it was shown that male rabbits deprived of food but having free access to water, developed a polyuric-polydipsic syndrome associated with decreased urine osmolality as early as 24 h of food deprivation (7). Despite these observations, the molecular basis of impaired urinary concentrating mechanism in response to food deprivation remains unknown.

Renal collecting duct water channels [aquaporins (AQPs)] are essential to normal urinary concentrating ability by enhancing water reabsorption along this nephron segment. The majority of water reabsorbed in the collecting duct occurs in the principal cells, via the AVP-regulated water channel AQP2 (3, 16, 34). In the outer and inner medulla, AQP2 is present in both glycosylated (~35 kDa) as well as nonglycosylated (~29 kDa) forms, whereas in the cortex only the nonglycosylated form (~29 kDa) is detected (22, 25). This water channel is predominantly expressed in the apical surface of connecting tubule and the entire collecting duct system (25). This study was undertaken to examine whether 24 h of food deprivation affects urinary concentrating ability in rats and to investigate the molecular basis of such a defect. Our results indicate that rats that fasted for 24 h demonstrated a defect in the kidney’s ability to produce a concentrated urine and exhibited a polyuria along with hypodipsia. This correlated with the downregulation of AQP2 protein expression in the cortical and outer medullary collecting duct (OMCD).

METHODS

Animal model. Male Sprague-Dawley rats were placed in metabolic cages and allowed free access to food and water. After 3–4 days of adjustment to metabolic cages, rats were divided into two groups. One group (control) had free access to food and water, whereas the second group was deprived of...

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Table 1. Blood composition

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>BUN, mg/dl</th>
<th>Creatinine, mg/dl</th>
<th>Na⁺, meq/l</th>
<th>K⁺, meq/l</th>
<th>Cl⁻, meq/l</th>
<th>CO₂, meq/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4</td>
<td>19 ± 1.75</td>
<td>0.38 ± 0.03</td>
<td>148 ± 0.25</td>
<td>5.05 ± 0.27</td>
<td>100 ± 0.29</td>
<td>24 ± 0.47</td>
</tr>
<tr>
<td>Fasting</td>
<td>4</td>
<td>16 ± 0.83</td>
<td>0.36 ± 0.03</td>
<td>148 ± 0.49</td>
<td>5.18 ± 0.14</td>
<td>102 ± 0.37</td>
<td>24 ± 0.31</td>
</tr>
<tr>
<td>Recovery</td>
<td>4</td>
<td>18 ± 1.35</td>
<td>0.57 ± 0.03</td>
<td>146 ± 0.57</td>
<td>5.10 ± 0.19</td>
<td>101 ± 0.58</td>
<td>25 ± 0.86</td>
</tr>
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Values are means ± SE. BUN, blood urea nitrogen; CO₂, total CO₂.
creasing from 113 ± 3.92 mg/dl in control rats to 46 ± 7.47 mg/dl (n = 4 rats for each group, P < 0.009). Fasting was also associated with a decrease in total body weight [from 165 ± 2.1 before to 138 ± 1.2 g after fasting (n = 8, P < 0.0001)]. However, the net body weight loss (see METHODS) was ~17.3 ± 1.1 g (P < 0.05). After 24 h of refeeding the net body weight gain was 18.5 g, and hypoglycemia was also recovered to a level of 121 ± 2.41 mg/dl, indicating that both hypoglycemia and weight loss were corrected during 24 h of recovery from fasting.

Water balance and urine osmolality in fasting. Water intake, urine output, and urine osmolality were measured every 24 h. A significant polyuria was developed in fasting rats, with urine output increasing from 11 ± 0.6 to 29 ± 4.2 ml/24 h for control and fasting, respectively, (n = 17 for each, P < 0.0001, Fig. 1B). The polyuria improved during recovery from fasting (Fig. 1B). The polyuria was associated with a significant decrease in urine osmolality [from 1,485 ± 55 to 495 ± 63 mosmol/kgH2O for control and fasting, respectively, (P < 0.0001, n = 17 for each, Fig. 1C)]. The first 24 h of the recovery phase were associated with an increase in urine osmolality above the normal levels [2,153 ± 114 (n = 8) vs. 1,485 ± 55 mosmol/kgH2O (n = 17), P < 0.001, Fig. 1C]; urine osmolality returned to baseline level after 48 h of refeeding (Fig. 1C). Interestingly, water intake decreased significantly during fasting [from 31 ± 1.6 to 21 ± 3 ml/24 h for control and fasting, respectively, (n = 17 for each, P < 0.002 Fig. 1A)], indicating that the polyuria was not secondary to polydipsia. The water intake first increased then returned to normal level during the recovery from fasting (Fig. 1A). Water intake, urine volume, and urine osmolality remained unchanged in the time control group (data not shown). These studies demonstrate that 24 h of fasting impair the urinary concentrating mechanism and results in polyuria (without polydipsia).

Molecular Regulation of AQP2 and AQP1 Expression in Fasting

Immunoblot analysis of AQP2 expression. In the next sets of experiments, the effect of fasting on AQP2 protein expression was studied. Accordingly, microsomes were prepared from the inner stripe of outer medulla (as well as superficial cortex and inner medulla) of kidneys harvested from control, fasting, and recovery from fasting groups. In the outer medulla, the AQP2 protein abundance was decreased by 80% in fasting animals compared with control group (100 ± 5% and 21 ± 4% for control and fasting, respectively, n = 82 for each, Fig. 2A)). AQP2 returned to normal levels after 24 h of recovery [100 ± 5 vs. 85 ± 5% for control (n = 8) and recovery from fasting (n = 7),

1The densitometry values reported in the RESULTS section correspond to the level of the expression on the nonglycosylated form (29 kDa) of AQP2 or AQP1 water channels, which is expressed as a percentage of pooled controls.

2The levels of AQP2 protein or mRNA expression shown in bars reflect the mean of blots from different experiments pooled together. The blots shown in the figures are representative blots only.
respectively, \( P > 0.05 \) Fig. 2A]. Comparable protein loading in various lanes was verified by gel staining (Fig. 2B). The expression of AQP2 protein in the cortex was decreased by 60\% in fasted animals compared with control group (100 ± 7 vs. 40 ± 7\% for control and fasting, respectively, \( n = 8 \) for each, \( P < 0.004 \) Fig. 2C). During the recovery from fasting, AQP2 returned to control level [100 ± 7 vs. 82 ± 8\% for control (\( n = 8 \)) and recovery (\( n = 8 \)), respectively, \( P > 0.05 \) Fig. 2C]. In the inner medulla, AQP2 abundance was not affected in response to fasting (100 ± 16 vs. 91 ± 13\% for control and fasting, respectively, \( n = 7 \) for each, \( P > 0.05 \) Fig. 2D). During the recovery period, AQP2 was, however, increased above the control level (100 ± 16 vs. 192 ± 36\% for control and recovery, respectively, \( n = 7 \) for each, \( P < 0.05 \) Fig. 2D). The equity in protein loading in the cortex and inner medulla was verified by gel staining (data not shown).

**Northern hybridization of AQP2.** Total RNA was isolated from the cortex and outer and inner medulla of kidneys harvested from control, fasting, and recovery from fasting animals. AQP2 mRNA expression was
examined by Northern hybridization. In the cortex, the expression of AQP2 mRNA was not altered in fasting (n = 7, P > 0.05, Fig. 3A) or during recovery from fasting (n = 6, P > 0.05, Fig. 3A) compared with control (n = 6). In the outer medulla, AQP2 expression significantly decreased in fasting rats, with mRNA levels decreasing by ~69% [from 100 ± 8% in control (n = 6) to 31 ± 6% in fasting group (n = 7), P < 0.003 Fig. 3B]. The recovery phase was associated with an overexpression of AQP2 mRNA above the normal levels (from 100 ± 8% in control to 196 ± 21% in recovery group, n = 6 for each, P < 0.004 Fig. 3B). In the inner medulla, total RNA was isolated from pooled tissues of three to four rats in each group (a total of seven rats was used in each group of control, fasting, and recovery), and used for Northern hybridization. AQP2 mRNA expression was not altered in response to fasting (Fig. 3C) compared with control. However, during the recovery from fasting, AQP2 mRNA levels were increased by 43% above the control levels (Fig. 3C). Taken together, these results indicate that fasting causes polyuria and urinary concentrating defect, primarily via the downregulation of AQP2 protein abundance in the outer medulla and cortex. During the recovery period, the decrease in urine volume and the increase in urine osmolality involve the recovery of AQP2 protein in the cortex and outer medulla, and an increase in its expression levels in the inner medulla.

**Immunoblot analysis of AQP1 expression.** AQP1 is the major water-absorbing channel in the proximal nephron and is expressed in both apical and basolateral membranes of proximal tubule and the entire descending limb of Henle’s loop. To examine whether the expression of AQP1 protein is also altered in fasting, immunoblot analysis of AQP1 protein was performed. The results are summarized in Fig. 4, and show that AQP1 protein abundance was not altered in fasting or during the recovery from fasting in the cortex (Fig. 4A), outer medulla (Fig. 4B), and inner medulla (Fig. 4C).

**Role of Hypoglycemia in Fasting-Induced Polyuria**

**Blood glucose level and body weight in glucose-treated and fasted rats.** Fasting in rats was associated with hypoglycemia (see above). To examine the possible role of hypoglycemia in fasting-induced polyuria, rats were supplemented with 2.5% glucose added to their drinking water and subjected to the fasting protocol. The presence of glucose in the drinking water prevented hypoglycemia during fasting, with blood sugar levels of 123 ± 17 and 130 ± 8.5 mg/dl in fasting and control, respectively (n = 4 for each, P > 0.05). The body weight was decreased in fasted rats (from 218 ± 4 before fasting to 200 ± 5.6 gm after fasting, n = 7, P < 0.00001). However, the net body weight loss (after adjusting for the gastrointestinal contents; see Methods) was only 7 ± 0.01 g (P < 0.05).

**Water balance and urine osmolality in glucose-treated and fasted rats.** Addition of 2.5% glucose alone to the drinking water was associated with a significant increase in urine osmolality in the cortex and outer medulla. During the recovery phase, AQP2 mRNA increased in inner medulla by 43% above control levels. In the cortex and outer medulla, each lane was loaded with 30 μg total RNA from a different rat. In the inner medulla, each lane was loaded with 30 μg total RNA. Of the two lanes in the inner medulla, one lane represents RNA isolated from pooled tissues of three rats, and the other lane is from four rats.
increase in fluid intake in normal animals compared with no glucose (from 27 ± 6 to 42 ± 8 ml/24 h in control to 36 ± 6 ml/24 h in the presence of glucose, n = 22 for each, P < 0.05, Fig. 5A). Interestingly, fluid intake further increased to 76 ± 9 ml/24 h in fasted rats on glucose (P < 0.005, n = 14, Fig. 5A). Urine volume paralleled fluid intake, as it was significantly increased in the presence of glucose alone compared with no glucose control (from 12 ± 2 ml/24 h for control to 24 ± 7 ml/24 h for glucose alone, n = 22 for each, Fig. 5B, P < 0.001). Urine volume further increased to 73 ± 9 ml/24 h in response to fasting (n = 14) compared with glucose alone (n = 22, P < 0.001, Fig. 5B). The presence of 2.5% glucose in the drinking water caused a significant drop in urine osmolality compared with control (from 1,387 ± 100 to 685 ± 73 mosmol/kgH2O for control and glucose alone, respectively, n = 22 for each, P < 0.0001, Fig. 5C). Urine osmolality further decreased to 100 ± 46 mosmol/kgH2O in fasted animals (n = 14) compared with glucose alone (n = 22) (P < 0.0001, Fig. 5C). During the 24 h recovery from fasting, fluid intake (Fig. 5A) and urine output returned to baseline levels (Fig. 5B). Urine osmolality was, however, increased above the normal levels and reached 1,354 ± 197 for recovery (n = 6) vs. 685 ± 73 mosmol/kgH2O for glucose alone group (n = 22, P < 0.04, Fig. 5C). Taken together, these results indicate that addition of 2.5% glucose alone to the drinking water was associated with a significant impairment of water balance and urine osmolality. Furthermore, the results show that 2.5% glucose treatment corrected hypoglycemia but did not prevent polyuria in fasting, indicating that fasting-induced polyuria is not secondary to hypoglycemia.

Molecular Regulation of AQP2 Expression in Glucose-Treated and Fasted Rats

Immunoblot analysis of AQP2. Microsomes were prepared from the cortex and outer and inner medulla of kidneys harvested from normal rats (control), 2.5% glucose-treated animals (glucose), and 2.5% glucose-
treated, fasted rats (glucose + fasting). In the cortex, the presence of glucose alone in the drinking water was associated with a significant decrease in AQP2 protein abundance (−25%) [from 100 ± 7 to 75 ± 4% in control (n = 4) and glucose alone (n = 5), respectively, P < 0.04, Fig. 6A]. In glucose-treated, fasted rats AQP2 protein abundance was decreased by 40% [from 100 ± 7% in control (n = 4) to 60 ± 6% in glucose + fasting group (n = 5), P < 0.03, Fig. 6A]. In the outer medulla, 2.5% glucose alone did not alter the expression of AQP2 protein (n = 5) compared with control (n = 4) (P > 0.05, Fig. 6B). However, in glucose + fasting group, AQP2 protein abundance was decreased by 63% [from 100 ± 3 to 37 ± 9% in control (n = 4) and glucose + fasting (n = 7), respectively, P < 0.03, Fig. 6B]. In the inner medulla, the expression of AQP2 protein did not change in glucose-treated (n = 5, P > 0.05) or in glucose + fasting animals (n = 5, P > 0.05) compared with control (n = 4) (Fig. 6C). Comparable protein loading in various lanes of these blots was verified with parallel gels stained with Coomassie brilliant blue (data not shown). These results indicate that glucose treatment alone decreased AQP2 protein in the cortex, which is likely responsible for altered water balance and decreased urine osmolality in this condition (Fig. 5). Furthermore, fasting downregulates AQP2 protein in the cortex and outer medulla despite correction of hypoglycemia.

**Northern blot analysis of AQP2 mRNA.** In a manner similar to that in the above experiments, the effect of fasting on AQP2 mRNA expression was studied in glucose-treated animals. Accordingly, total RNA was isolated from cortex and outer and inner medulla of kidneys harvested from control, 2.5% glucose-treated, or glucose + fasting groups. In the cortex, AQP2 mRNA expression was not altered in glucose-treated animals (n = 6, P > 0.05), or in glucose + fasting (n = 6, P > 0.05) compared with control (n = 6) (Fig. 7A). In the outer medulla, 2.5% glucose alone did not alter the expression of AQP2 mRNA (n = 6, P > 0.05) compared with control (n = 6) (Fig. 7B). However, in the glucose-treated and fasted group, AQP2 mRNA was decreased by 60% [from 100 ± 20 to 40 ± 7% for control (n = 6) and glucose + fasting (n = 7), respectively, P < 0.04; Fig. 7B]. Taken together, these results indicate that fasting-induced nephrogenic urinary concentrating defect is due to the downregulation of AQP2 expression in the outer medulla and cortex and that this effect is independent of blood glucose levels.

**DISCUSSION**

The studies above demonstrate that food deprivation resulted in polyuria and urinary concentrating defect (Fig. 1). Polyuria was associated with a decrease in water intake, indicating that it was not secondary to polydipsia (Fig. 1). The alterations in urine output and urine osmolality in fasting were reversed within 24 h of refeeding (Fig. 1). Examination of AQP2 water channel expression revealed that the abundance of this protein

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**Fig. 5.** Correction of hypoglycemia does not prevent fasting-induced polyuria. Rats (n = 22) were placed in metabolic cages with free access to food and water. After 3 days, at time 0, the drinking water was supplemented with 2.5% glucose. At time +72 h, 8 rats remained on food and water + glucose (Glucose), whereas the remaining 14 rats were deprived of food for 24 h but with free access to water + glucose. Eight rats were killed (glucose + fasting (G + F)), and the other 6 were switched back to normal diet for 24 h before death (Recovery). Another group of 7 rats was on food + water (control/dH2O). Fluid intake (A), urine volume (B), and urine osmolality (C) were measured daily.
was heavily suppressed in the outer medulla (Fig. 2A) and significantly decreased in the cortex (Fig. 2C). The downregulation of AQP2 protein in fasting correlated with a significant decrease in the expression of AQP2 mRNA in the outer medulla (Figs. 3B and 7B) but not in the cortex (Figs. 3A and 7A). Urine osmolality and polyuria were corrected during the recovery from fasting (Figs. 2 and 3). Furthermore, the effects of fasting or recovery from fasting were specific to AQP2, as the expression of AQP-1 was not altered in these conditions (Fig. 4).

The mechanism underlying the decrease in AQP2 protein abundance without alteration in the mRNA expression levels in the cortex is not clear. An inhibition of the translation process and/or activation of the AQP2 protein turnover are possible explanations. Alteration in the cellular distribution or trafficking of AQP2 protein is unlikely, as total cellular protein was used for the immunoblotting experiments (see METHODS). In the inner medulla, the expression of AQP2 protein/mRNA was not affected by food deprivation (Figs. 2D and 3C). However, an increase in AQP2 mRNA and protein was observed during the 24-h recovery from fasting (Figs. 2D and 3C). The increase in AQP2 expression during the recovery period without alteration in fasting may result from the fact that the effects of fasting and recovery on collecting duct AQP2 are mediated via distinct signaling pathways. It is also plausible that the cell heterogeneity along the collecting tubule [principal cells in the cortical collecting duct (CCD) and OMCD vs. inner medullary collecting duct (IMCD) cells] may play a role in the differential response of AQP2 in fasting vs. recovery from fasting.

The chemical analysis of blood composition indicated that serum electrolyte profile and osmolality were comparable in control and fasting animals (Table 1). One
would expect an increase in serum osmolality and sodium in the face of polyuria and decreased water intake in fasting. The reason for the lack of alteration in plasma osmolality and blood composition despite a significant fluid loss after 24 h of fasting is not very clear at the present. One possibility is that fasting has caused a transcellular fluid shift from intracellular to extracellular compartment, hence attenuating extracellular volume depletion due to polyuria.

Food deprivation was associated with hypoglycemia. Correction of hypoglycemia, however, did not prevent the generation of polyuria (Fig. 5B) and dilute urine (Fig. 5C) in fasted animals. Furthermore, the polyuria and urinary concentrating defect in glucose-treated, fasted animals was also associated with a significant decrease in AQP2 expression in both cortical (Fig. 6A) and OMCD (Fig. 6B). These results indicate that the downregulation of AQP2 protein and the resulting urinary concentrating defect in fasting animals is not mediated by hypoglycemia. Interestingly, there was an increase in water intake in fasted animals supplemented with glucose, which was opposite to the fasted animals on no glucose (Figs. 1A and 5A). Whether polyuria and AQP2 downregulation in fasting resulted from increased water intake (sweet taste) is unlikely. In water-loaded rats, studies by Ecelbarger et al. (10) showed a significant decrease in AQP2 protein abundance in the inner medulla along with a 46% decrease in the osmotic water permeability of IMCD of water-loaded rats. However, our studies indicate that AQP2 protein abundance was not altered in the inner medulla of glucose-supplemented and fasted rats (Fig. 6C), indicating that polyuria and decreased AQP2 in these animals is a result of fasting rather than water loading. Finally, the presence of glucose alone was associated with a significant alteration in water balance, as both fluid intake (Fig. 5A) and urine volume (Fig. 5B) were increased along with decreased urine osmolality (Fig. 5C). The increase in urine output in the presence of glucose is likely due to decreased AQP2 protein expression in the CCD (as shown in Fig. 6A).

Recent studies have demonstrated that the expression of AQP2 protein in the collecting duct is significantly decreased in several forms of acquired nephrogenic diabetes insipidus (such as lithium treatment, hypercalcemia, K+ depletion, and ureteral obstruction) (9, 21, 22) as well as models of nephrotic syndrome (puromycin aminonucleoside, adriamycin, and low protein diet) (12, 13, 21). Whereas other isoforms of water channels (i.e., AQP3 and AQP4) are expressed in the collecting duct, the urinary concentrating defect in the above conditions results mainly from the alterations in the AQP2 expression, as this transporter is the only apical water channel in the collecting ducts (8, 9, 15, 16). However, an eventual dysregulation of the basolateral AQP3 and AQP4 in response to fasting or recovery from fasting is not excluded.

The mechanism by which fasting downregulates AQP2 and, as a result, impairs urinary concentrating ability is not clear. One possibility is hormonal dysregulation in response to hypoglycemia. However, correction of hypoglycemia did not block the urinary concentrating defect in fasting animals (Figs. 5 and 6). An eventual role of alteration in the levels of circulating antidiuretic hormone (ADH) is unlikely. The plasma osmolality was not significantly affected, and BUN and serum creatinine remained unchanged in fasting, suggesting the stability of the volume status. Moreover, fasted animals have a significant negative water balance as a result of polyuria without polydipsia. Therefore, if anything, serum ADH should increase in response to the possible dehydration, and that should actually increase the expression of AQP2 water channel (8, 32).

Fasting is associated with protein deprivation, which has been shown to alter the urinary concentrating ability in both human (reviewed in Ref. 20) and experimental animals (13, 24, 29). Defective urine concentration in a low-protein diet was reversed by urea supplementation (13, 29). Whether polyuria and decreased urine osmolality in fasted animals result from decreased protein intake with subsequent reduction in urea delivery to the medullary interstitium remains speculative. Such a possibility is unlikely, as the effect of a low-protein diet requires 2-3 wk to develop (24, 29),
whereas fasting-induced urinary concentrating defect occurs within 24 h.

Several hormones, such as growth hormone, adrenal steroid, and prostanoids, have been reported to be increased in fasting (2, 15, 19, 26). Prostaglandins are known to antagonize the effect of AVP on water transport in the collecting duct (11). Adrenal gland steroids also play an important role in the process of urinary concentrating ability in both human (35) and experimental animal (18, 30). Whether these hormones play any role in fasting-induced urinary concentrating defect remains to be determined. Another interesting observation in this model is the lack of any significant alteration in serum sodium in fasted animals despite significant polyuria and negative water balance (Table 1). It is possible that food deprivation is also associated with an increase in urinary Na+ loss. It has been reported that fasted male rabbits developed a polyuric-polydipsic syndrome associated with enhanced urinary Na+ loss (6, 28). However, rats and rabbits respond differently to fasting in that rabbits develop both polyuria and polydipsia (1, 14, 17, 27), whereas rats develop polyuria and hypodipsia (Fig. 1). It is worth mentioning that animals may have not reached a steady state after 24 h of fasting. Hence, more studies are required to fully describe the renal response to fasting with respect to urinary concentrating mechanism and renal sodium handling at both short and long term.

In conclusion, fasting impairs the urinary concentrating ability and, as a result, causes polyuria. This effect is mediated via suppression of AQP2 expression in the collecting duct. The inability to concentrate urine in fasting is rapidly reversible on refeeding and is associated with a return of AQP2 expression to normal levels. Lastly, fasting-induced urinary concentrating defect is independent of glucose homeostasis.

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REFERENCES

28. Nocenti MR and Cizek LJ. Influence of estrogen on renal function and water intake in male rabbits rendered polyuric-
29. Pennell JP, Sanjana V, Frey NR, and Jamison RL. The
effect of urea infusion on the urinary concentrating mechanism
30. Schwartz MJ and Kokko JP. Urinary concentrating defect of
31. Sigler MH. The mechanism of the natriuresis of fasting. J Clin
Long-term regulation of four renal aquaporins in rats. Am J
Physiol Renal Fluid Electrolyte Physiol 271: F414–F422,
1996.
33. Thomson TJ, Runcie J, and Miller V. Treatment of obesity by
total fasting up to 249 days. Lancet 2: 992–996, 1966.
34. Verkman AS. Mechanisms and regulation of water permeabil-
C850, 1989.
35. Wilson DM and Sundermann FW. Studies in serum elec-
trolytes. XII. The effect of water restriction in a patient with
Addison's disease receiving sodium chloride. J Clin Invest 18:
35–43, 1939.