Lithium treatment and remodeling of the collecting duct

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DIETARY LITHIUM TREATMENT in rats results in severe diabetes insipidus associated with marked, but reversible downregulation of aquaporin (AQP)-2 and -3, as well as other proteins involved in sodium and water reabsorption along the renal tubule (4–6, 8, 9). More recent studies (2, 4) revealed that this downregulation coincided with an increase in the fraction of intercalated cells relative to principal cells in the collecting duct (CD). Specifically, there was increased density of cells labeling with intercalated cell markers, i.e., apical H+-ATPase and basolateral AE1 (Cl-/HCO3- exchanger), and reduced density of cells labeling with AQP2 (marker for principal cells). This suggested several possibilities: 1) more intercalated cells were being made either through proliferation of existing cells or via stem cell recruitment and differentiation; 2) principal cells were selectively being lost either through apoptosis or sloughing off; and/or 3) principal cells were transforming into intercalated cells.

In the studies presented in the article by Christensen et al. (1) appearing in this issue of AJP-Renal Physiology, these same marker proteins were used, as well as markers of apoptosis and proliferation in an attempt to elucidate the time course and cellular mechanisms underlying this change. To achieve this, the authors treated male Wistar rats with lithium for anywhere from 4 days to 4 wk. Reversibility of these changes was also examined by removing lithium from the diet and waiting 4 wk.

As expected, the length of treatment correlated with progressively worsening diabetes insipidus, as evidenced by increased urine output, decreased urine osmolality, and decreased AQP2 abundance. These changes were apparent even at 4 days. Changes in cell type identity as determined by labeling with the marker proteins took slightly longer but were apparent by 10 days. At 10 days, relatively more cells labeled with H+-ATPase, suggesting an increased population of intercalated cells at this time. However, some cells labeling with H+-ATPase did not have AE1 staining of the basolateral membrane, indicating that they were not fully differentiated. There were other cells that had neither AQP4 nor H+-ATPase labeling. These are interesting findings and, as the authors suggest, might be evidence of a population of stem cells of either renal or extrarenal origin in different stages of differentiation into intercalated cells. Also, there was nearly an absence of cells labeling with both AQP4 and H+-ATPase, which might suggest that interconversion between intercalated cells and collecting duct cells was less likely.

In addition, the authors determined whether lithium affected proliferation of the cells by use of an antibody against the proliferating-cell nuclear antigen (PCNA), an auxiliary protein of DNA polymerase (3). Here, they found essentially increased proliferative activity of both intercalated and principal cells; however, counter to expectations, there was a greater degree of proliferation in principal cells. In addition, at 10 and 15 days, some cells that labeled with PCNA were negative for both H+-ATPase and AQP4, and occasionally cells were negative for all three proteins.

To determine the role of apoptosis in these changes, tissue sections were also probed with an antibody against apoptosis-inducing factor (AIF-1). After 10–15 days of lithium treatment, a small number of cells labeled positive for AIF-1, whereas none were found for control rats, suggesting a role for increased apoptosis in determining changes in relative cell populations. These cells were presumed to be principal cells because they showed no colabeling with H+-ATPase.

So, how can this all fit together to explain these and previous observations (2, 4) of a decrease in the fraction of principal cells to intercalated cells, especially in the early portion of the inner medulla? The authors provide us with several possible scenarios and, based on the current time course data, suggest that none can be essentially eliminated. First, it is possible that increased apoptosis of cell sloughing of selectively principal cells plays some role in these changes; however, the presence of cells without any markers or with labeling for H+-ATPase but not AE1 suggests that this is clearly not the whole story. Second, increased cell proliferation does occur, but this appears to occur at an even higher rate in principal cells and is thus, similarly, not a sole explanation. Third, do cells convert from principal cells to intercalated cells? It is possible, but one would expect cells labeled with both sets of markers in this case, which really didn’t occur to any extent. Perhaps the most intriguing possibility is that stem/progenitor cells may give rise to new intercalated cells. This might fit with the finding of cells that lack staining for all markers. The authors nicely describe this possibility and other evidence supporting stem cell recruitment in injured renal tissue (7).

Overall, this work invites fresh thinking on possible mechanisms involved in CD remodeling, not only with lithium but potentially in other models of diabetes insipidus or renal disease. The idea of physiological adaptation at the tissue rather than the cellular level is fairly novel.

REFERENCES


