Urinary UDP-Glucose as a Novel Actionable Biomarker of Dehydration-Induced Acute Kidney Injury

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Keywords

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Abstract

Background: People working in “extreme” conditions termed as sugar cane workers, firefighters and military personnel are subjected to significant dehydration. Prolonged episodes of dehydration may result in acute kidney injury (AKI). AKI is associated with inflammation and is usually diagnosed only after the kidneys have gone through significant and often irreversible damage. We showed that the P2Y₁₄ receptor mediates renal inflammation, leading to AKI following ischemia-reperfusion-injury [1]. P2Y₁₄ is activated by the danger molecule UDP-glucose (UDP-Glc). Here we hypothesized that UDP-Glc is released by cells throughout the body after dehydration-induced stress. UDP-Glc is filtered by the kidney and concentrated in collecting ducts where it activates P2Y₁₄ in intercalated cells. This would trigger renal inflammation and contribute to dehydration-associated AKI. **Objective:** The aim of this study was to characterize the participation of UDP-Glc in pro-inflammatory cell recruitment and renal dysfunction following dehydration. **Method:** Mice

were subjected to water deprivation for 24, 48, and 72 h. Kidney function was assessed via serum creatinine (SCr), blood urea nitrogen (BUN), and urine albumin. To study proximal tubule (PT) damage, aquaporin 1 (AQP1) localization was analyzed by immunofluorescence (IF). Urinary UDP-Glc concentration was measured by LC-MS, and renal recruitment of immune cells by flow cytometry and IF. **Results:** Water deprivation induced elevations in SCr and BUN after 48 h and 72 h, relative to control. Dehydration also induced albuminuria and the redistribution of AQP1 from the plasma membrane into the PT cell body indicating PT injury. An increase in urinary UDP-Glc concentration and renal recruitment of macrophages were detected at 48 h and 72 h of dehydration. **Conclusion:** This study supports the hypothesis that UDP-Glc, released by damaged cells during severe dehydration, induces the renal recruitment of inflammatory macrophages leading to PT injury and kidney dysfunction (Fig. 1). Blocking the UDP-Glc/P2Y₁₄ pathway represents, therefore, a new therapeutic avenue for the attenuation of dehydration-induced renal inflammation and injury. In this context, urinary UDP-Glc is a promising actionable biomarker for dehydration-induced AKI.

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Fig. 1. Proposed mechanism of action of UDP-Glc in mediating renal inflammation following dehydration. UDP-Glc is released by systemic damaged cells, is filtered by the kidney, and is then concentrated in the lumen of collecting duct, where it reaches higher levels due to the concentrating ability of the kidney. UDP-Glc binds to the P2Y14 receptor located on the apical surface of intercalated cells. This receptor-ligand interaction stimulates the production of chemokines, which attract macrophages into the kidney. The newly recruited immune cells aggravate renal tubular injury and kidney dysfunction. UDP-Glc, UDP-glucose; PTs, proximal tubules; BUN, blood urea nitrogen; Scr, serum creatinine.

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Statement of Ethics

All preclinical procedures were approved by the Massachusetts General Hospital (MGH) Subcommittee on Research Animal Care and were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals (National Academies Press, 2011; protocol 2018N000127).

Conflict of Interest Statement

S.B. is a cofounder of Kantum Pharma (previously “Kantum Diagnostics Inc.”), a company developing a diagnostic and therapeutic combination to prevent and treat acute kidney injury. S.B. and her spouse own equity in the privately held company. S.B. and D.B. are inventors on a patent (US Patent 10088489) covering technology that has been licensed to the company through Massachusetts General Hospital (MGH). S.B. and D.B. interests were reviewed and are managed by MGH in accordance with their conflict-of-interest policies.

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Author Contributions

M.A.B., D.B., and S.B. designed the study. M.A.B. and A.C.M. performed the experiments and analyzed the data. M.A.B., D.B., and S.B. wrote the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

Reference

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