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Fractionation of stable chlorine isotopes in the kidneys of mice

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Anion transport across cell membranes is crucial for a variety of physiological functions, including control of electrical excitability of muscles and nerves, salt and water homeostasis, and regulation of cell volume or acidification. Pathogenic mutations in genes encoding chloride ion (Cl^-) transporters lead to a wide range of pathologies including myotonia, cystic fibrosis, renal salt loss in Bartter's, Gitelman's or HELIX syndromes, kidney stones, deafness and osteopetrosis. We are carrying out a pilot study of chloride isotope fractionation ($^{37}Cl/^{35}Cl$) in plasma and urine from mice in order to understand if chloride stable isotopes can be used to better understand their (patho)physiology. Starting from a 200 µl fluid sample, we are able to measure the $d^{37}Cl$ of chloride dissolved in urine or plasma with a sensitivity below 4 µmoles of Cl^- and an accuracy of ± 0.03 ‰ (1s). These preliminary measurements show that plasma is systematically (n=5) depleted in ^{37}Cl compared to urine by about 0.5‰. This difference is caused by an isotopic fractionation of Cl^- in the kidney, the process of which remains to be elucidated. Simple mass balance modeling of chloride isotopes suggests that the different steps of renal reabsorption of chloride are at the origin of this fractionation. If these data are confirmed, plasma-urine ^{37}Cl fractionation could be a biomarker of the efficiency of renal chlorine reabsorption. We are planning to (i) increase our mice Cl-isotope dataset and extend it to include human plasma and urine; (ii) carry out experiments with genetically modified mice by modulating the activity of specific Cl^--transporters (NKCC2, NCC, pendrine and claudine-10). If we succeed in demonstrating variations in Cl-isotope fractionation associated to specific renal pathologies, chloride isotopes could become a new tool to investigate the (patho)physiology of epithelial chloride transport.