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The pathophysiology of hereditary nephrogenic diabetes insipidus and possible treatments. AnUpdate

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Abstract (600 word limit)

The posterior pituitary releases the antidiuretic hormone arginine-vasopressin (AVP) under physiological conditions to prevent excessive loss of water through urine. Several cellular responses elicited by AVP are associated with increased osmotic reabsorption of water by the kidney. Exocytosis of the water channel aquaporin 2 (AQP2) at the apical membrane of the principal cells of the collecting duct is triggered by the binding of AVP to its type-2 receptor (AVPR2). AVPR2 mutations or AQP2 mutations cause nephrogenic diabetes insipidus, characterized by the lack of response of the collecting duct to AVP's antidiuretic action. Being unable to concentrate urine, the affected individual presents marked polyuria and compensatory polydipsia, which is accompanied by severe dehydration. In addition to the genetic and clinical tests for a prompt diagnosis of the disease in newborns, the molecular basis of the disease is fully uncovered. There is no real cure for nephrogenic diabetes insipidus (NDI), and the main symptoms of the disease are managed by constant water intake, a restrictive diet, and nonspecific drugs. Currently, there are few and only partly effective therapeutic options. Combining in vitro or animal model studies with clinical trials will eventually lead to the identification of one or more targeted strategies that can replace or improve conventional therapy and provide NDI patients with a better quality of life. This article offers an updated overview of the genetic defects causing NDI, the most recent strategies under investigation for rescuing the activity of mutated AVPR2 or AQP2, or bypassing defective AVPR2 signaling and restoring AQP2 expression at the plasma membrane. During water deprivation, elevated plasma osmolality (hypernatremia) or decreased blood volume (hypovolemia) signal the kidneys to conserve water, a physiological condition known as antidiuresis. Arginine vasopressin, also known as AVP, is released into the bloodstream when the hypothalamic osmoreceptors shrink and aortic and carotid baroreceptors become inactive..

Biography (200 word limit)

Richard Smiley with a PhD in Gynecology. My experience includes managing projects, conducting research, and teaching. Obstetrics has been a focus of my expertise. In addition, I have contributed to the development of biotechnology programs in both public and private companies. Currently, I am working at Washington University, Missouri. I am studying the role of the Cardio-obstetrics: Recognizing and managing cardiovascular complications during pregnancy.

About Research Topic (200 word limit)

Congenital NDI is currently treated by limiting urine output rather than by tackling the underlying cause. In order to prevent NDIs, adequate fluid supply is essential in combination with a low-salt and low-protein diet to minimize the amount of water that has to be excreted. The standard therapy for NDI includes diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs), and can only partially reduce polyuria. When used in

conjunction with a very low sodium-restricted diet, thiazide diuretics effectively reduce urine output. Through a mechanism likely involving inhibition of potassium loss caused by thiazide diuretics, potassium sparing agents like amiloride may exert an additive effect with thiazide diuretics. By promoting reabsorption of sodium and water in the proximal tubule, diuretics in NDI patients reduce urine output by delivering less water to the collecting ducts. NSAIDs such as Ibuprofen and Indomethacin improve urinary concentration defects in NDI patients whose urine output can be reduced by 25% to 50% , and the combination with Hydrochlorothiazide has an additive effect. Choosing single-drug therapies is not recommended because of their low efficacy. Two children with NDI were given oral indomethacin (0.75 to 1.2 mg/kg/day) three times a day for a mean duration of three years by Dayal. The drug was withdrawn from one patient after two years because a normal fluid balance and body growth occurred in both patients. All patients tolerated the treatment well, and no adverse events occurred. 6.5 years of follow-up were averaged. A larger sample of patients is needed to test this observation. Selective COX2 inhibitors may be helpful in patients who cannot tolerate indomethacin. NDI patients should exercise caution when using indomethacin and selective COX-2 inhibitors since their administration can result in acute kidney damage. There is little experience with treatment with cyclooxygenase inhibitors when used as a single agent . Despite the improvement of NDI symptoms with these therapeutic approaches, the patients' quality of life is still negatively impacted by the urinary concentrating defect.

About Institution (200 word limit)

Washington University in St. Louis (WashU, or WUSTL) is a private research university in Greater St. Louis with its main campus (Danforth) mostly in unincorporated St. Louis County, Missouri, and Clayton, Missouri. It also has a West Campus in Clayton, North Campus in the West End neighborhood of St. Louis, and Medical Campus in the Central West End neighborhood of St. Louis. Founded in 1853 and named after George Washington, the university has students and faculty from all 50 U.S. states and more than 120 countries. Washington University is composed of seven graduate and undergraduate schools that encompass a broad range of academic fields. To prevent confusion over its location, the Board of Trustees added the phrase "in St. Louis" in 1976. Washington University is a member of the Association of American Universities and is classified among "R1: Doctoral Universities – Very high research activity".

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