Aquaporin 2 excretion in urine in humans

A study of urinary aquaporin 2 excretion after felodipine, furosemide, and fasting in healthy humans, and after furosemide in patients with chronic heart failure

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ABSTRACT

The PhD dissertation is based on three scientific studies, which were carried out in the Department of Medical Research, Holstebro Hospital in the period 2002-2004.

The vasopressin (AVP) sensitive water channel aquaporin-2 (AQP2) mediates water transport across the apical plasma membrane of the renal collecting ducts. Urinary AQP2 excretion (u-AQP2) reflects the action of AVP on the collecting ducts.

The aim was to investigate the effects of felodipine and furosemide on u-AQP2, urine volume, free water clearance (C_{H2O}), AVP, and the renin-angiotensin-aldosterone system in healthy humans, the effect of furosemide in patients with chronic heart failure (CHF), and the effect of 24 hours of fasting in healthy humans on the same parameters.

Three randomized, placebo-controlled, cross-over studies were carried out to investigate the effect of felodipine and furosemide in healthy humans and in patients with CHF, and a randomized, cross-over study was carried out to examine the effect of fasting and the effect of 3% saline infusion after fasting in healthy humans.

Felodipine did not induce a significant difference in u-AQP2, urine volume or C_{H2O} compared to placebo, presumably due to an increase in the renin-angiotensin system, and a masking effect of dietary sodium supplement prior to each study day.

After a single intravenous dose of furosemide in healthy humans, u-AQP2, AVP, and the activity of the renin-angiotensin-aldosterone system were increased. These changes are most likely compensatory phenomena in the ductal part of the nephron due to a furosemide-induced reduction in sodium reabsorption in the proximal part of the nephron, to prevent an excess loss of sodium and water.

In patients with CHF u-AQP2, AVP, and the activity of the renin-angiotensin-aldosterone system were increased after a single intravenous dose of furosemide like in healthy humans. Despite the increase in u-AQP2 the water reabsorption capacity was overridden as shown by increased C_{H2O} after furosemide, suggesting a reduced compensatory capacity in patients with CHF.

Twenty-four hours of fasting decreased u-AQP2 and reduced urine osmolality most likely as a result of decreased sensitivity of collecting duct cells to AVP. Fasting related insensitivity of collecting duct cells to AVP was restored by saline infusion as indicated by increased u-AQP2. In the setting of 3% saline infusion, other factors such as the increased plasma atrial natriuretic peptide levels could also contribute to the regulation of water transport and u-AQP2.

Future studies will by the use of drugs or hormones with known effect on the sodium and water regulation clarify pathophysiologic mechanisms including up- and downregulation of AQP2 in patients where water homeostasis is disturbed, and thereby in time possibly improve the treatment of these states in humans.