

Overall research theme:

Integrative studies of cardiovascular function and salt and water metabolism in cardiovascular and renal diseases. Pathophysiological mechanisms and pharmacological approaches

Latest update:

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Characteristics of the research group:

The research group combines competences in basic research and clinical medicine. An unique feature is the combination of integrative research in whole animal models with methods in cellular and molecular biology. The group has developed and refined a rat model with permanent catheters which allows repeated experiments to be performed in the same animal for up to 6 weeks. Animal models includes congestive heart failure, liver cirrhosis, chronic renal failure, hypertension and diabetes insipidus. Methods for assessment of cardiac function, systemic and renal hemodynamics and tubular function in conscious animals are combined with morphometric and biochemical methods, primarily localization and quantitation of receptors, sodium transporters and aquaporins.

Running projects: Titles and abstracts:

Vasopressin escape in experimental heart failure and liver cirrhosis

Decompensated states of congestive heart failure and liver cirrhosis are characterized by high plasma levels of vasopressin and excessive water retention, and the resulting hyponatremia is a predictor for poor prognosis. The normal kidney is able to excrete a water load despite high levels of vasopressin, and this phenomenon termed "Vasopressin escape" is associated with down-regulation of aquaporin 2 in the collecting duct cells. We have demonstrated that the vasopressin escape phenomenon is intact in our rat model with experimental liver cirrhosis, whereas not in our rat model with congestive heart failure. The project aims to elucidate the intracellular signal transduction mechanisms involved in the normal vasopressin escape phenomenon, and further to define the intracellular site for the tubular dysfunction observed in rats with congestive heart failure. The studies may disclose important new targets in the treatment of hyponatremia.

Salt reabsorption in the thick ascending limb of Henle's loop in experimental liver cirrhosis and heart failure

We have demonstrated that the early sodium retention in a rat model with liver cirrhosis induced by ligation of the bile duct is associated with increased NaCl-reabsorption in the thick ascending limb of Henle's loop and hypertrophy of the corresponding renal zone (inner stripe of the outer medulla). The natriuretic response to loop-diuretics is enhanced by 60% in this model, and similar observations have been made in rat models with congestive heart failure and hypertension. The project aims to elucidate the factors which regulate salt reabsorption in the medullary thick ascending limb (mTAL) in normal and pathophysiological states, and to assess the physiological consequences of increased mTAL NaCl-reabsorption. In rats with liver cirrhosis it has been demonstrated that the cortico-medullary osmotic gradient is enhanced, facilitating tubular water reabsorption, and that the response to thiazide diuretics is impaired. The studies may disclose new regulatory sites for sodium homeostasis and define new targets for treatment of sodium retaining states.

Renal mechanism of action of nociceptin analogues - potential new aquaretic drugs

Nociceptin, a peptide discovered in 1995 as a ligand to the orphan receptor ORL-1, affects the CNS as well as the cardiovascular/renal system. ORL-1 is a 7-TM receptor which inhibits cAMP formation through interaction with an inhibitory G-protein. In the kidney nociceptin exerts a marked aquaretic

effect and we have shown that ORL-1 is co-localized with aquaporin 2 in principal cells from the inner medullary collecting duct. Our studies aim to elucidate the mechanism underlying this aquaretic action, using a new peptide analogue without effects on the CNS. This potential new aquaretic can be of therapeutic value in the treatment of water retention and hyponatremia associated with congestive heart failure

Sodium transporters, aquaporins, and pulmonary edema

Drainage of fluid from the pulmonary alveoli to the lymphatic system depends on the epithelial sodium channel (ENaC) in the alveolar epithelium as well as on aquaporins in the capillary endothelial cells (AQP1) and the alveoles (AQP5). These transporters are important for the postnatal drainage as well as for the capacity to drain pulmonary edema in response to an increase in pulmonary capillary pressure. Thus, ENaC(-/-) knock-out mice die within 40 hours after birth with water filled lungs. The study examines pulmonary osmotic water permeability and the pulmonary expression of ENaC and AQP1 and 5 in a rat model of congestive heart failure, both in the early compensated state and in the late decompensated state, where the drainage capacity becomes insufficient to compensate for the rise in capillary hydrostatic pressure. The project may identify new targets for pharmacological or genomic treatment of life-threatening pulmonary edema.

Mechanisms of thiazide-induced antidiuresis in diabetes insipidus

Thiazide diuretics exert a specific ("paradoxical") antidiuretic action in diabetes insipidus (DI) and are presently the only available therapy for nephrogenic DI including lithium-induced polyuria. We have studied the mechanism of thiazide-induced antidiuresis both in Central and Nephrogenic DI. In both states the major mechanism seems to be a reduction in the delivery of tubular fluid from the proximal tubules, which is due to a compensatory increase in proximal tubular fluid reabsorption. However, in CDI thiazides in addition stimulate distal water reabsorption through an unknown mechanism. The studies aim to elucidate the tubular mechanisms underlying the stimulation of proximal reabsorption during thiazide treatment, and further to define the effect of thiazides on water transport in the distal nephron.

Basic studies on synergism between diuretic drugs

Diuretics inhibit specific sodium transporters in different nephron segments and when different classes of diuretics are combined they exert synergistic diuretic/natriuretic actions. We have demonstrated that when bendroflumethiazide is added to chronic furosemide administration the natriuretic response is increased, so-called supra-additive synergism. Current studies focus on the question whether the tubular profile of a thiazide (in terms of effects on the proximal tubules) modifies its synergistic properties when co-administered with loop diuretics, as has been repeatedly suggested in the literature.

Novel treatment concepts against ischemia/reperfusion induced organ damage

Recent publications related to the projects described above:

- Staahtoft, D., S. Nielsen, N. Janjua, S. Christensen, O. Skøtt, Marcussen N. & T.E.N. Jonassen: Chronic losartan treatment normalizes renal water handling in rats with congestive heart failure. *Am. J. Physiol.* 282, F307-315, 2002.
- Janjua, N.R., Jonassen, T.E.N., Johansson S., Thomsen, K. & S. Christensen: Role of sodium depletion for the acute antidiuretic effect of bendroflumethiazide in rats with nephrogenic diabetes insipidus. *J. Pharmacol. Exp. Ther.* 299, 307-313, 2001.
- Jonassen, T.E.N., S. Christensen, T.-H. Kwon, S. Johansson, N. Salling & Søren Nielsen: Renal water handling in rats with decompensated liver cirrhosis. *Am. J. Physiol.*, 279, F1101-F1109, 2000
- Jonassen, T.E.N., A.-M. Sørensen, J.S. Petersen, F. Andreasen & S. Christensen: Increased natriuretic efficiency of furosemide in rats with carbon tetrachloride induced liver cirrhosis. *Hepatology* 31, 1224-1230, 2000
- Jonassen, T.E.N., D. Promeneur, S. Christensen, J.S. Petersen & S. Nielsen: Decreased vasopressin-mediated renal water reabsorption in rats with chronic aldosterone-receptor blockade. *Am. J. Physiol.* 278, F246-F256, 2000.
- Jonassen, T.E.N., S. Christensen, A.-M. Sørensen, N. Marcussen, A. Flyvbjerg, F. Andreasen & J.S. Petersen: Effects of chronic octreotide treatment on renal changes during liver cirrhosis in rats. *Hepatology*, 29, 1387-1395, 1999.
- Jonassen, T.E.N., J.S. Petersen, A.-M. Sørensen, F. Andreasen & S. Christensen: Aldosterone receptor-blockade inhibits furosemide sensitive sodium transport in rats with liver cirrhosis. *J. Pharmacol. Exp. Ther.* 287, 931-936, 1998.
- Jonassen, T.E.N., S. Nielsen, S. Christensen & J.S. Petersen: Decreased vasopressin-mediated renal water reabsorption in rats with compensated liver cirrhosis. *Am. J. Physiol.*, 275, F216-F225, 1998.
- Shalmi, M., T.E.N. Jonassen, K. Thomsen, J.D. Kibble P. Bie & S. Christensen: Model explaining the relation between distal nephron Li^+ reabsorption and urinary Na^+ excretion in the rat. *Am. J.*

Physiol. 274, F445-F452, 1998.

Grønbeck, L., D. Marples, S. Nielsen & S. Christensen: Mechanism of antidiuresis caused by bendroflumethiazide in rats with diabetes insipidus. *Brit. J. Pharmacol.* 123, 737-745, 1998.

Spannow, J., K. Thomsen, J.S. Petersen, K. Haugan & S. Christensen: Influence of renal nerves and sodium balance on the acute antidiuretic effect of bendroflumethiazide diuretics in rats with diabetes insipidus. *J. Pharmacol. Exp. Ther.* 282, 1155-1162, 1997.

Jonassen, T.E.N., N. Marcussen, K. Haugan, H. Skyum, S. Christensen, F. Andreassen & J.S. Petersen: Functional and structural changes in the thick ascending limb of Henle's loop during liver cirrhosis. *Am. J. Physiol.* 273, R568-R577, 1997.

Christensen, S., M. Shalmi, A. K. Hansen & N. Marcussen: Effects of perindopril and hydrochlorothiazide on the long-term progression of lithium-induced chronic renal failure in rats. *Pharmacology & Toxicology* 80, 132-141, 1997.

Jonassen, T.E.N., L. Grønbeck, M. Shalmi, J.S. Petersen, F. Andreassen & S. Christensen: Supra-additive synergism of bendroflumethiazide and furosemide in rats. *J. Pharmacol. Exp. Ther.* 275, 558-565, 1995.

Marples, D., S. Christensen, E.I. Christensen, P.D. Ottosen & S. Nielsen: Lithium-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla. *J. Clin. Invest.* 95, 1838-1843, 1995.

Lunau, H.E., M. Bak, J.S. Petersen, M. Shalmi, N. Marcussen & S. Christensen: Renal adaptations to constant administration of furosemide and bendroflumethiazide in rats. *Pharmacology & Toxicology* 74, 216-222, 1994.