

ORIGINS OF RENAL DISEASES

History of Diabetes Insipidus



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Abstract

Under physiological conditions, fluid and electrolyte homeostasis is maintained by the kidney adjusting urine volume and composition according to body needs. Diabetes Insipidus is a complex and heterogeneous clinical syndrome affecting water balance and characterized by constant diuresis, resulting in large volumes of dilute urine. With respect to the similarly named Diabetes Mellitus, a disease already known in ancient Egypt, Greece and Asia, Diabetes Insipidus has been described several thousand years later. In 1670s Thomas Willis, noted the difference in taste of urine from polyuric subjects compared with healthy individuals and started the differentiation of Diabetes Mellitus from the more rare entity of Diabetes Insipidus. In 1794, Johann Peter Frank described polyuric patients excreting 'nonsaccharine' urine and introduced the term of Diabetes Insipidus. An historical milestone was the in 1913, when Farini successfully used posterior pituitary extracts to treat Diabetes Insipidus. Until 1920s the

available evidence indicated Diabetes Insipidus as a disorder of the pituitary gland. In the early 1928, De Lange first observed that some patients with Diabetes Insipidus did not respond to posterior pituitary extracts and subsequently Forssman and Waring in 1945 established that the kidney had a critical role for these forms of Diabetes Insipidus resistant to this treatment. In 1947 Williams and Henry introduced the term "Nephrogenic Diabetes Insipidus" for the congenital syndrome characterized by polyuria and renal concentrating defect resistant to vasopressin. In 1955, du Vigneaud received the 1955 Nobel Prize in chemistry for the first synthesis of the hormone vasopressin representing a milestone for the treatment of Central Diabetes Insipidus.

Key words: Aquaporin, Central Diabetes Insipidus (DI), Nephrogenic Diabetes Insipidus (NDI), Vasopressin, Vasopressin V2 Receptor (V2R)

Introduction

Diabetes insipidus (DI) is characterized by the kidney inability to concentrate urine leading to consistent hypotonic polyuria greater than 3 liters in 24 hours in adults and persisting even during water deprivation. Three main types of DI can be defined as follows: A. Central DI (CDI) due to a defect in arginin-vasopressin (AVP) synthesis; B. nephrogenic DI (NDI) characterized by kidney resistance to the AVP action; C. gestational DI caused by accelerated AVP degradation. Besides these forms excessive fluid intake can cause DI [1] [2].

Central DI is the most frequent form and can be due to damage at the level of the hypothalamus which might affect the supraoptic or paraventricular nuclei or the osmoreceptors committed to 'sense' the alterations in blood osmolality. In rare cases (1-2%) CDI can be due to mutations of the gene coding for the AVP receptor.

On the other hand, AVP resistance due to renal defect characterizes NDI. In NDI the kidney cannot concentrate urine leading to a risk of severe volume depletion, hypernatremia, and hyperchloremia. NDI can be congenital due to mutations in the vasopressin receptor V2R gene causing X-linked NDI accounting for about 90% of congenital NDI [3] or to mutations in the gene coding for the water channel Aquaporin 2 causing autosomal-recessive or autosomal dominant DI responsible for about 10% of congenital NDI characterized by altered expression or trafficking of the AQP2 water channels [4] (full text).

Much more frequent are the forms of acquired NDI associated to a wide range of conditions such

as lithium ingestion, urinary obstructions, hypercalcemia and hypercalciuria [5].

Finally about 5% of all cases of NDI are genetically unresolved or have unidentified causative mutations [6].

The key advances in the understanding DI and NDI are shown in Figure 1.

History of Diabetes Insipidus: a disease identified about 200 years ago

DI has been described several thousand years later with respect to the similarly named Diabetes Mellitus (DM), a diseases already known in ancient Egypt, Greece and Asia. In fact, its description is date back to 1794, when Johann Peter Frank of the University of Pavia described patients characterized by "long continued abnormally increased secretion of nonsaccharine urine which is not caused by a diseased condition of the kidneys" and introduced the term "diabetes insipidus" derived from the french word "insipide" [7]. According to the historical documents, in 1841 Lancombe described a family with 8 members displaying the symptoms of DI first focusing the attention to the familial features of DI [8].

The familiarity of DI was subsequently described in a publication by McIlraith in 1892 entitled "Notes on some cases of diabetes insipidus with marked family and hereditary tendencies" [9]. In the following years it became clear that a defect in the hypothalamus was somehow responsible for the DI. In 1901 Magnus and Shaffer demonstrated that the posterior pituitary extract had a pressor and antidiuretic

activities [10]. Few years later in 1913 Fariniand van den Velden successfully used posterior pituitary extracts to treat diabetes insipidus [11][12].Subsequently Bailey and Ranson, two researchers working in Illinois, described a supraoptico-hypophyseal tract in animals that connects the hypothalamic supraoptic nuclei to the posterior pituitary and showed that an injury to this tract produced DI [13] [14]. In parallel in Europe, Camus and Roussy of the Faculté de Médecine of Paris discovered in dogs that, puncturing the hypothalamus but leaving the pituitary intact, produced polyuria [15]. In summary, the available evidence in the 1920s was conclusive enough to define DI as a disorder of the pituitary gland and actually named this disorder as ‘hypopituitary syndrome’ [16] [17].

Central Diabetes Insipidus is distinct from Nephrogenic Diabetes Insipidus

Regarding the two principal forms of diabetes, mellitus and nephrogenic, in 1670s Thomas Willis, professor of Natural Philosophy at Oxford already noted the difference in taste of urine from polyuric subjects compared with healthy individuals [18] [19] [20]. He used the term diabetes in the generic sense, meaning polyuria, however his observations led to the differentiation of diabetes mellitus from the more rare entity of diabetes insipidus a century later.

In the early 1928, a german scientist DeLange, first observed that some patients with DI did not re-

spond to posterior pituitary extracts. Moreover those families appeared not to have a male to male transmission of the disease [21]. These observations were followed by more accurate analysis by Forssman [22] [23], who established that the kidney had a critical role in those forms of DI resistant to treatment with the posterior pituitary extracts. In an original document Waring described patients with “an unusual syndrome” that presented shortly after birth, characterized by polyuria, polydipsia, fever, and constipation vomiting, high serum Na and Cl, rapid dehydration, and inability to excrete hypertonic urine. He concluded that the condition was caused by “a specific defect in tubular reabsorption of water” and appeared more frequently in boys. This description is consistent with what we know today to be the congenital form of the X-linked Nephrogenic Diabetes Insipidus. In 1947 by Williams and Henry introduced the term “nephrogenic diabetes insipidus” for the congenital syndrome characterized by polyuria and renal concentrating defect but unaffected by vasopressin [24]. They noticed the inheritance pattern realizing that the defect was transmitted by asymptomatic female to male offspring. The authors concluded that the disease was due to a congenital defect in the loop of Henle and the distal convoluted tubule.

Purification and synthesis of vasopressin

In 1955, several years later the successful treatment of diabetes insipidus using posterior pituitary ex-

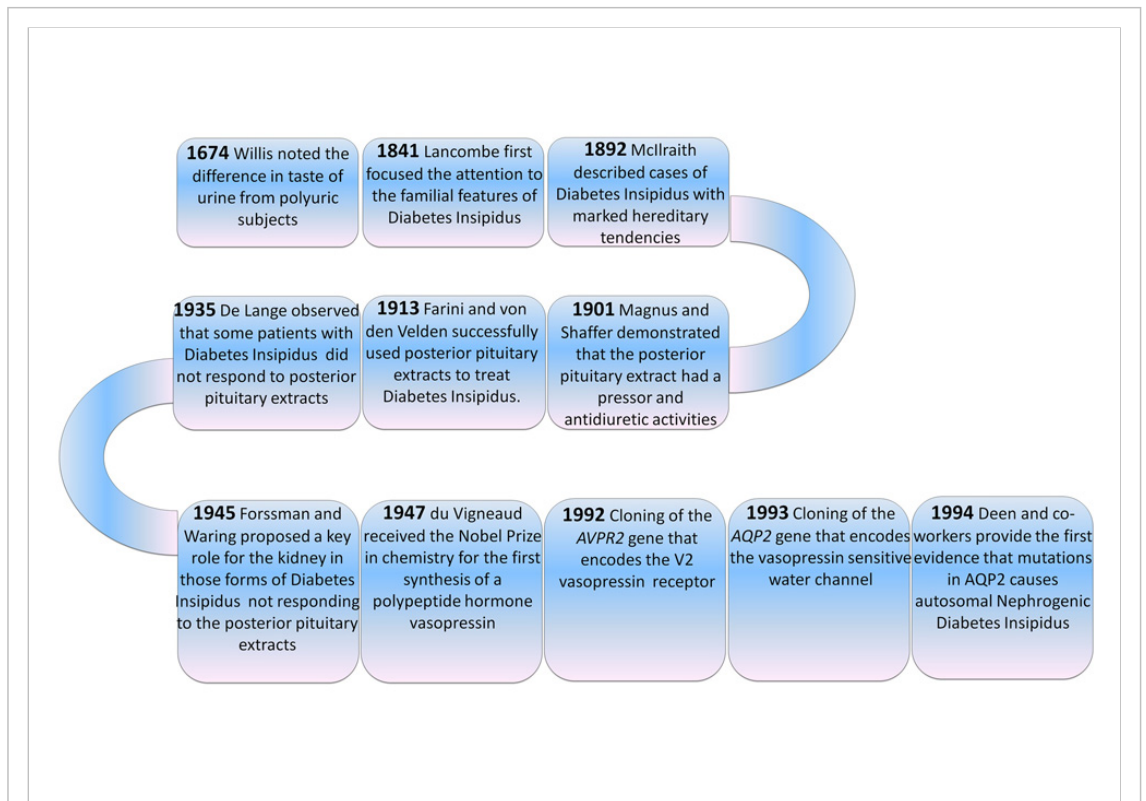


Figure 1.
The advances in the understanding Diabetes Insipidus and Nephrogenic Diabetes Insipidus

tracts in 1913, du Vigneaud of Cornell Medical College, received the 1955 Nobel Prize in chemistry for the first synthesis of a polypeptide hormone vasopressin [25]. With a seminal work, du Vigneaud purified both oxytocin and vasopressin by counter-current distribution and then chemically synthesized oxytocin in 1953 and vasopressin in 1954 [25]. Further distribution studies on the oxytocic hormone of the posterior lobe of the pituitary gland and the preparation of an active crystalline flavianate [26] (full text) [27] (full text).

Within this scenario of this series of truly landmark achievements, the 2013 marked the 100th anniversary of vasopressin treatment for DI [28].

Cloning of the V2R and identification of patients with X-linked NDI

The 1971 Nobel Prize in Physiology or Medicine was awarded to Sutherland “for his discoveries concerning the mechanisms of the action of hormones” (Sutherland EW. Studies on the mechanism of hormone action (Nobel Lecture) [29]. Sutherland promoted the idea that hormones activate the adenylyl cyclase molecule. Subsequently Pastan et al [30] introduced the concept that most hormones act at the cell surface and by binding to a finite number of molecules (receptor) on the cell surface.

In 1992 the *AVPR2* gene that encodes the V2 vasopressin receptor was cloned and mutations in this gene were identified in patients with X-linked NDI. Specifically Lolait et al from the National Institute of Mental Health, Bethesda, cloned the rat kidney V2 receptor displaying a transmembrane topography characteristic of G protein-coupled receptors. The human V2 receptor gene was localized to the long arm of the X chromosome close to the locus for nephrogenic diabetes insipidus [31].

In parallel Rosenthal and co-workers from the Baylor College of Medicine, Houston, Texas (USA) also cloned the V2 receptor and reported the case of an affected male of a family with CDI having a deletion in the open reading frame of the V2 receptor gene, causing a frame shift and premature termination of translation in the third intracellular loop of the receptor protein [32]. In parallel van den Ouweland from the University Hospital Nijmegen (The Netherlands) described 3 patients with identified point mutations *AVPR2* gene affected by NDI [33]. It became subsequently clear that mutations in *AVPR2* are responsible for about 90% of the inherited forms [2] [34]. Since this gene is located on the X-chromosome, the majority of patients with NDI are male.

To date more than 250 different *AVPR2* mutations have been described and most of these mutations are missense and based on the *in vitro* data those mutations apparently encode for functional but misfolded receptors, retained and degraded in the endoplasmic reticulum [35]. These observations opened a research field aimed at correcting those forms of NDI trying to rescue the otherwise func-

tional receptors from the endoplasmic reticulum to the plasma membrane.

Cloning of the AQP2 water channels and identification of patients with autosomal NDI

In 1993 the *AQP2* gene was cloned by Sasaki group from the University of Tokyo, Japan, and found to be expressed in the renal collecting duct [36] [37]. In 1994 Deen and co-workers showed that mutations in *AQP2* gene were found to be responsible for autosomal recessive NDI demonstrating that *AQP2* water channel is required for vasopressin-dependent concentration of urine [38].

The cloning of the vasopressin sensitive water channel *AQP2* has been obtained by homology cloning after the identification of the first water channel Aquaporin 1 by Peter Agre [39] (full text). The 2003 Nobel Prize in Chemistry was awarded jointly to Peter Agre, “for the discovery of water channels”, and to Roderick MacKinnon “for structural and mechanistic studies of ion channels”.

The discovery of Aquaporins allowed understanding the etiology of congenital NDI caused by mutation of the *AQP2* gene. Using immunogold electron microscopy, Nielsen and co-workers localized *AQP2* in intracellular vesicles in collecting duct principal cells. *AQP2* vesicles fuse to the apical membrane under vasopressin action leading to an increase in the osmotic water permeability (see schematic model in Figure 2). Removal of vasopressin caused internalization and recycling of the *AQP2* protein and markedly diminished water permeability [40] (full text). This mechanism allows water reabsorption from the lumen of collecting duct and concentration of urine. In 1994 Deen and co-workers demonstrated that aquaporin-2 water channel is required for vasopressin-dependent concentration of urine [38]. In the same year van Lieburg identified mutations of the *AQP2* gene that caused the autosomal recessive form of NDI, based on the observations that patients showed increased factor VIII responses to dDAVP, an extrarenal effect suggesting normal vasopressin receptors [41]. Subsequently, in 1998, the autosomal dominant form of NDI was identified [42]. So far 40 known mutations that cause autosomal recessive NDI have been described and 8 known mutations responsible for the autosomal dominant form of NDI [2].

Current treatment of congenital NDI focuses on dietary modification, thiazides and inhibitors of prostaglandin synthesis (see [2]). Treatment with statins have also been suggested to potentially be beneficial for ameliorate NDI [43] (full text) [44].

Novel therapies, such as mutation-specific treatment using molecular chaperones [45], have been investigated in animal models, but few data from clinical studies are currently available.

In the future, gene therapy aimed at delivering kidney-specific wild-type *AVPR2* or *AQP2* could potentially cure congenital NDI.

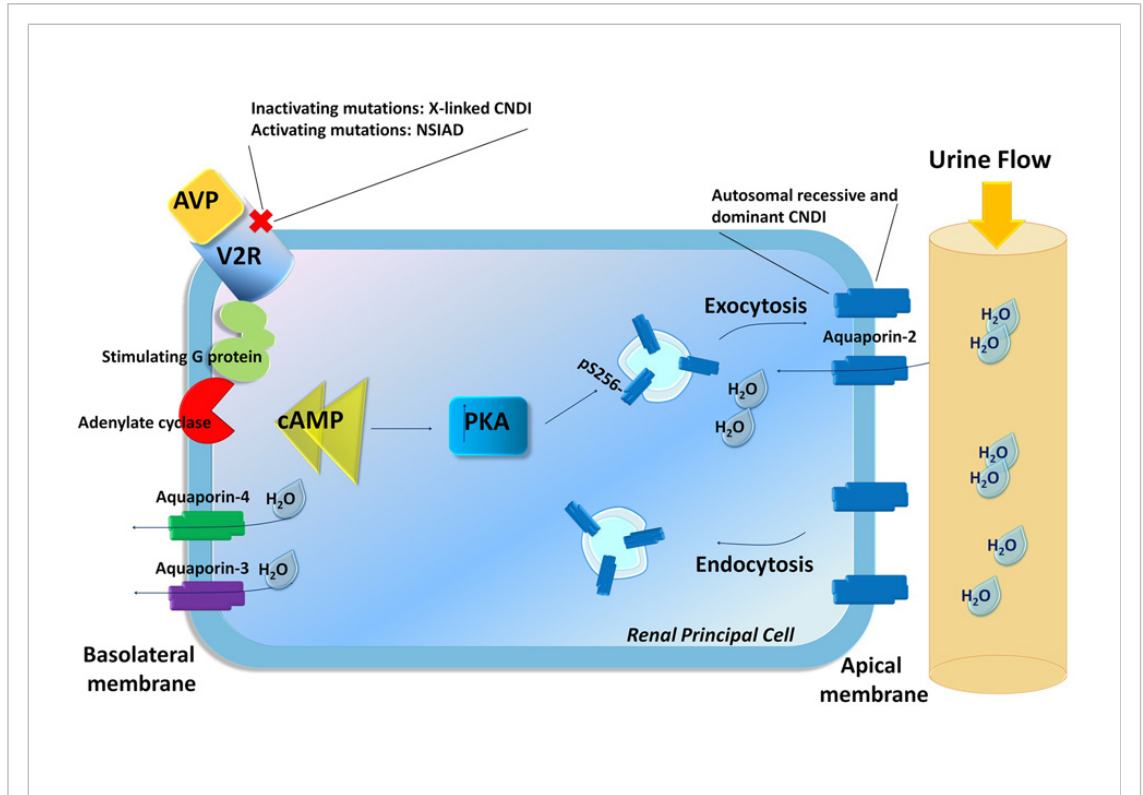


Figure 2. Schematic model of kidney collecting duct cell. Vasopressin binds to the V2 receptor located in the basolateral membrane of collecting duct principal cells. This is coupled to a heterotrimeric G protein Gs which in turn activates adenylyl cyclase. This causes increase in intracellular cAMP levels leading to activation of Protein Kinase A (PKA). PKA phosphorylates the AQP2 water channel located in intracellular vesicles and this represents a key event stimulating regulated exocytosis of AQP2. Mutation either in the V2R receptor or in AQP2 water channel have been found associated with congenital X-linked NDI and autosomal NDI respectively.

Summary and Conclusions

After 3000 years of the description of Diabetes Mellitus, a subset of polyuric patients was considered to be affected by Diabetes Insipidus. About one hundred years ago in 1913, posterior pituitary extracts (containing vasopressin and oxytocin) were used to treat Central Diabetes Insipidus and this approach represented one of the first successful therapies for a peptide hormone deficiency.

About 70 years ago, physicians recognized patients with DI who failed to respond to vasopressin and 60 years ago the Nobel Prize du Vigneaud was successful in isolation, sequencing, and chemical synthesis of oxytocin and vasopressin.

Starting 50 years ago, a multitude of cellular events at the target cell have been elucidated. An error at any step can result in defective water balance. Emerging concepts of receptors and recent genetic analysis led to the recognition of patients with mutations in the genes coding for the vasopressin receptor and for the AQP2 water channel.

The etiology of the autosomal form of Nephrogenic Diabetes Insipidus was delineated by the discovery of the first Aquaporin by Peter Agre who was awarded with the 2003 Nobel Prize for the discovery of the water channels. Our understanding of the molecular physiology of Diabetes Insipidus has greatly advanced in the past 25 years. It is known today that acquired forms of Nephrogenic Diabetes Insipidus are very common and most of those forms are associated to lithium treatment.

Today, Diabetes Insipidus includes a large series of disorders. Many of the known disorders are now susceptible to symptomatic treatments or specific interventions such as on dietary modification, thiazides and inhibitors of prostaglandin synthesis. However these treatment approaches can only ameliorate the clinical phenotype of Nephrogenic Diabetes Insipidus. In the future gene therapy to correct the deficiency of AVPR2 or AQP2 genes might potentially represent a successful approach.

References

- [1] Babey M, Kopp P, Robertson GL et al. Familial forms of diabetes insipidus: clinical and molecular characteristics. *Nature reviews. Endocrinology* 2011 Jul 5;7(12):701-14
- [2] Bockenhauer D, Bichet DG Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nature reviews. Nephrology* 2015 Oct;11(10):576-88
- [3] Kinoshita K, Miura Y, Nagasaki H et al. A novel deletion mutation in the arginine vasopressin receptor 2 gene and skewed X chromosome inactivation in a female patient with congenital nephrogenic diabetes insipidus. *Journal of endocrinological investigation* 2004 Feb;27(2):167-70
- [4] Satoh M, Ogikubo S, Yoshizawa-Ogasawara A et al. Correlation between clinical phenotypes and X-inactivation patterns in six female carriers with heterozygote vasopressin type 2 receptor gene mutations. *Endocrine journal* 2008 May;55(2):277-84 (full text)
- [5] Sands JM, Bichet DG, American College of Physicians et al. Nephrogenic diabetes insipidus. *Annals of internal medicine* 2006 Feb 7;144(3):186-94
- [6] Bockenhauer D, van't Hoff W, Dattani M et al. Secondary nephrogenic diabetes insipidus as a complication of inherited renal diseases. *Nephron. Physiology* 2010;116(4):p23-9
- [7] Frank J. *Classis V (Profluvia), Ordo I (profl. serosa). Genus II (diabetes). De Curandis Hominum Morbis.* 1832
- [8] Lacombe U. De la polydipsie *Journal of Medical Chirurgy (J Med Chir).* 1841;7:305-23.
- [9] McLraith CH. Notes on some cases of DI with marked family and hereditary tendencies. *Lancet.* 1892;2:767.
- [10] Magnus RS, E.A.. Effects of post-pituitary extracts. *Journal of Physiology.* 1901;12:32-8.
- [11] Farini F. About diabetes insipidus and hypophysiotherapy. *Wien Klin Wochenschr.* 1913;26:1867.
- [12] von den Velden R. The kidney effects of hypophysis extracts in humans. *Berl Klin Wochenschr.* 1913;50:2083.
- [13] Bailey PB, F. Experimental diabetes insipidus. *Archives of internal medicine.* 1921;28:773-803.
- [14] Ranson SW Some Functions of the Hypothalamus: Harvey Lecture, December 17, 1936. *Bulletin of the New York Academy of Medicine* 1937 May;13(5):241-71
- [15] Camus JR, G. Experimental researches on the pituitary body. *Endocrinology.* 1920;4:507-22.
- [16] Marañón. Diabetes insipidus as a hypopituitary syndrome. *Endocrinology.* 1921;5:159-73.
- [17] Motzfeldt K. Diabetes insipidus. *Endocrinology.* 1918;2:111-21.
- [18] CANNON JF Diabetes insipidus; clinical and experimental studies with consideration of genetic relationships. *A.M.A. archives of internal medicine* 1955 Aug;96(2):215-72
- [19] Eknoyan G A history of diabetes insipidus: paving the road to internal water balance. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2010 Dec;56(6):1175-83
- [20] Eknoyan G, Nagy J A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. *Advances in chronic kidney disease* 2005 Apr;12(2):223-9
- [21] de Lange C. Ueber erblichen diabetes insipidus *Jahrbuch fuer Kinderheilkunde.* 1935;145:135.
- [22] Forssman HH. On hereditary diabetes insipidus. *Acta Medica Scandinavica.* 1945;121.
- [23] Waring AJK, L. Tappan, V. A congenital defect of water metabolism. *American Journal of Diseases of Children.* 1945;69:323-4.
- [24] WILLIAMS RH, HENRY C Nephrogenic diabetes insipidus; transmitted by females and appearing during infancy in males. *Annals of internal medicine* 1947 Jul;27(1):84-95
- [25] DU VIGNEAUD V Hormones of the posterior pituitary gland: oxytocin and vasopressin. *Harvey lectures 1954-1955*;50:1-26
- [26] PIERCE JG, GORDON S, DU VIGNEAUD V et al. Further distribution studies on the oxytocic hormone of the posterior lobe of the pituitary gland and the preparation of an active crystalline flavianate. *The Journal of biological chemistry* 1952 Dec;199(2):929-40 (full text)
- [27] TURNER RA, PIERCE JG, du VIGNEAUD V et al. The purification and the amino acid content of vasopressin preparations. *The Journal of biological chemistry* 1951 Jul;191(1):21-8 (full text)
- [28] Qureshi S, Galiveeti S, Bichet DG et al. Diabetes insipidus: celebrating a century of vasopressin therapy. *Endocrinology* 2014 Dec;155(12):4605-21
- [29] Sutherland EW Studies on the mechanism of hormone action. *Science (New York, N.Y.)* 1972 Aug 4;177(4047):401-8
- [30] Pastan I, Roth J, Macchia V et al. Binding of hormone to tissue: the first step in polypeptide hormone action. *Proceedings of the National Academy of Sciences of the United States of America* 1966 Dec;56(6):1802-9
- [31] Lolait SJ, O'Carroll AM, McBride OW et al. Cloning and characterization of a vasopressin V2 receptor and possible link to nephrogenic diabetes insipidus. *Nature* 1992 May 28;357(6376):336-9
- [32] Rosenthal W, Seibold A, Antaramian A et al. Molecular identification of the gene responsible for congenital nephrogenic diabetes insipidus. *Nature* 1992 Sep 17;359(6392):233-5
- [33] van den Ouweland AM, Dreesen JC, Verdijk M et al. Mutations in the vasopressin type 2 receptor gene (AVPR2) associated with nephrogenic diabetes insipidus. *Nature genetics* 1992 Oct;2(2):99-102
- [34] Wesche D, Deen PM, Knoers NV et al. Congenital nephrogenic diabetes insipidus: the current state of affairs. *Pediatric nephrology (Berlin, Germany)* 2012 Dec;27(12):2183-204
- [35] Spanakis E, Milord E, Gragnoli C et al. AVPR2 variants and mutations in nephrogenic diabetes insipidus: review and missense mutation significance. *Journal of cellular physiology* 2008 Dec;217(3):605-17
- [36] Fushimi K, Uchida S, Hara Y et al. Cloning and expression of apical membrane water channel of rat kidney collecting tubule. *Nature* 1993 Feb 11;361(6412):549-52
- [37] Sasaki S, Fushimi K, Saito H et al. Cloning, characterization, and chromosomal mapping of human aquaporin of collecting duct. *The Journal of clinical investigation* 1994 Mar;93(3):1250-6
- [38] Deen PM, Weghuis DO, Sinke RJ et al. Assignment of the human gene for the water channel of renal collecting duct Aquaporin 2 (AQP2) to chromosome 12 region q12-->q13. *Cytogenetics and cell genetics* 1994;66(4):260-2
- [39] Preston GM, Agre P Isolation of the cDNA for erythrocyte integral membrane protein of 28 kilodaltons: member of an ancient channel family.

Proceedings of the National Academy of Sciences of the United States of America 1991 Dec 15;88(24):11110-4 (full text)

[40] Nielsen S, Chou CL, Marples D et al. Vasopressin increases water permeability of kidney collecting duct by inducing translocation of aquaporin-CD water channels to plasma membrane. Proceedings of the National Academy of Sciences of the United States of America 1995 Feb 14;92(4):1013-7 (full text)

[41] van Lieburg AF, Verdijk MA, Knoers VV et al. Patients with autosomal nephrogenic diabetes insipidus homozygous for mutations in the aquaporin 2 water-channel gene. American journal of human genetics 1994 Oct;55(4):648-52

[42] Mulders SM, Bichet DG, Rijss JP et al. An aquaporin-2 water channel mutant which causes autosomal dominant nephrogenic diabetes insipidus is

retained in the Golgi complex. The Journal of clinical investigation 1998 Jul 1;102(1):57-66

[43] Li W, Zhang Y, Bouley R et al. Simvastatin enhances aquaporin-2 surface expression and urinary concentration in vasopressin-deficient Brattleboro rats through modulation of Rho GTPase. American journal of physiology. Renal physiology 2011 Aug;301(2):F309-18 (full text)

[44] Procino G, Barbieri C, Carmosino M et al. Fluvastatin modulates renal water reabsorption in vivo through increased AQP2 availability at the apical plasma membrane of collecting duct cells. Pflugers Archiv : European journal of physiology 2011 Nov;462(5):753-66

[45] Los EL, Deen PM, Robben JH et al. Potential of nonpeptide (ant)agonists to rescue vasopressin V2 receptor mutants for the treatment of X-linked nephrogenic diabetes insipidus. Journal of neuroendocrinology 2010 May;22(5):393-9