Original Paper

HORMONE RESEARCH

Horm Res 260
DOI: 10.1159/000XXXXXX

Received: February 11, 2009
Accepted: July 9, 2009
Published online: ■■■

Functional Characterization of Vasopressin Receptor 2 Mutations Causing Partial and Complete Congenital Nephrogenic Diabetes Insipidus in Thai Families

Taninee Sahakitrungruang[a, c] Meng Kian Tee[c] Natthakorn Rattanachartnarong[b]
Vorasuk Shotelersuk[b] Kanya Suphapeetiporn[b] Walter L. Miller[c]

[a]Division of Pediatric Endocrinology and [b]Division of Medical Genetics and Metabolism, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [c]Division of Endocrinology, Department of Pediatrics, University of California at San Francisco, San Francisco, Calif., USA

Key Words
Mutation analysis · *AVPR2* · G-protein · Polyuria

Abstract
Background: *AVPR2* mutations cause nephrogenic diabetes insipidus (NDI); 211 *AVPR2* mutations have been described, but only 7 are described causing partial NDI. ***Methods:*** Two unrelated Thai boys had polyuria and polydipsia in infancy but had normal electrolytes and serum osmolality at 2 years of age. Patient 1 could not concentrate his urine in response to water deprivation or 1-desamino-8-D-arginine vasopressin (DDAVP); patient 2 could concentrate to ~600 mosm/l. The patients' *AVPR2* genes were sequenced and the identified mutations were re-created in AVPR2 cDNA expression vectors. AVPR2 activities were measured by stimulating transfected HEK293T cells with arginine vasopressin (AVP) or DDAVP, and assessing the resulting cAMP production by the activation of a luciferase reporter. ***Results:*** Patient 1 carried the previously described missense mutation R181C; patient 2 carried the novel missense mutation M311V. When transiently transfected into HEK293T cells, 6.8×10^{-12} M AVP induced the half-maximal response (EC50) of the wild-type, whereas the EC50 value for R181C was 5.9×10^{-9} M and for M311V was 2.6×10^{-10} M. Responses to DDAVP were qualitatively similar but required 10-fold higher concentrations. ***Conclusion:*** The novel AVPR2 mutation M311V retains partial activity and results in a milder form of NDI.

Nephrogenic diabetes insipidus (NDI), wherein renal collecting ducts cannot concentrate urine in response to arginine vasopressin (AVP), can be inherited or acquired. NDI is characterized by vomiting, anorexia, failure to thrive, fever and constipation, usually within the first year of life [1]. About 90% of NDI is X-linked (XNDI) (OMIM 304800) [2], caused by loss-of-function mutations in the *AVPR2* gene on chromosome Xq28 [3]. About 10% of NDI patients have autosomal-recessive mutations in the gene for aquaporin 2 *(AQP2)* [4] (OMIM 125800); a very rare autosomal-dominant form has also been reported [5]. *AVPR2* encodes the G protein-coupled, seven-transmembrane arginine vasopressin receptor 2 (AVPR2) consisting of 371 amino acids. Vasopressin binds to AVPR2 on the basolateral membrane of principal cells in renal collecting ducts, which then stimulates adenylyl cyclase to produce cAMP and activate protein kinase A.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0301–0163/10/0000–0000$26.00/0

Accessible online at:
www.karger.com/hre

Walter L. Miller, MD
HSE 1427, University of California at San Francisco
San Francisco, CA 94143-0978 (USA)
Tel. +1 415 476 2598, Fax +1 415 476 8214
E-Mail wlmlab@ucsf.edu

The resulting protein phosphorylation translocates AQP2 water channels from an intracellular reservoir to the apical membrane. This mechanism is essential for reabsorption of water from the collecting ducts to concentrate the urine [5].

At least 211 different mutations in *AVPR2* causing NDI have been described [6]. Of these, only 7 mutations causing partial NDI have been previously reported [7–13]. Most *AVPR2* mutations are missense mutations that disrupt receptor function at various levels, such as intracellular receptor retention, defects in ligand binding or defects in G protein coupling and activation [14]. Rare gain-of-function mutations in *AVPR2* cause the nephrogenic syndrome of inappropriate antidiuresis (OMIM 300539) [15].

Case Reports

Patient 1

A 2-year-old Thai boy was referred for polydipsia, polyuria, frequent vomiting and recurrent fever since infancy. Prenatal history was unremarkable; birth weight was 3,455 g. He was the only child of healthy, nonconsanguineous parents. His 70-year-old maternal grandfather had a history of polydipsia and polyuria since infancy, but had not sought medical attention. His mother had no polydipsia and polyuria. Physical examination was unremarkable; height was 91 cm (75th percentile) and weight was 12 kg (25th–50th percentile). Initial laboratory evaluation included serum Na 143 mmol/l, K 3.7 mmol/l, Ca 2.5 mmol/l, blood urea nitrogen of 2.5 mmol/l, and creatinine of 35.4 μmol/l. Serum and urine osmolalities were 300 and 54 mosm/l, respectively. After 4 h of water deprivation, urine volume did not decrease significantly, and serum osmolality (306 mosm/l) and Na (148 mmol/l) rose despite a low urinary osmolality (59 mosm/l), hence the test was stopped. Urine osmolality did not increase after administration of nasal 1-desamino-8-D-arginine vasopressin (DDAVP) at the end of water deprivation (table 1). Urinary tract ultrasonography was normal. Treatment with hydrochlorothiazide (2 mg/kg/day) improved his polyuria from 3.1–5.5 to 2.7–3.5 liters/m^2/day, although nocturnal enuresis persisted. No clinical dehydration was observed during a 1-year follow-up. His serum creatinine and electrolytes remained normal, and neurodevelopmental status remained appropriate for age.

Patient 2

A 2.5-year-old Thai boy was referred for polydipsia and polyuria since infancy. None of his family members had polydipsia and polyuria. Physical examination was unremarkable; height was 88.5 cm (25th percentile) and weight was 12.9 kg (50th percentile). Initial investigation included Na 140 mmol/l, K 4 mmol/l, Ca 2.45 mmol/l, blood urea nitrogen 2.86 mmol/l, and creatinine 44.2 μmol/l. Serum and urine osmolalities were 287 and 75 mosm/l, respectively. Water deprivation for 8 h showed elevated serum osmolality (299 mosm/l), submaximally concentrated urine (634 mosm/l) and no increase in urine osmolality after administration of DDAVP (table 1). Urinary tract ultrasonography was normal. Treatment with hydrochlorothiazide (2 mg/kg/day) decreased 24-hour urine volumes from 3.9–6.3 to 2.9–3.0 liters/m^2/day. At follow-up, the patient had appropriate growth and developmental milestones with normal serum electrolytes.

Table 1. Results of water deprivation tests

	Patient 1	Patient 2
AVPR2 mutation	R181C	M311V
Baseline		
Serum sodium, mmol/l	136	140
Serum osmolality, mosm/l	294	287
Urine osmolality, mosm/l	54	75
After water deprivation		
Serum sodium, mmol/l	148	143
Serum osmolality, mosm/l	306	299
Urine osmolality, mosm/l	59	634
After DDAVP, 0.025 μg/kg, subcutaneous		
Urine osmolality, mosm/l	70	593

Fluids were withheld after 8 a.m.; body weight and serum and urine sodium and osmolality were measured hourly. DDAVP was given when weight fell by 5% or serum osmolality exceeded 300 mosm/l.

Materials and Methods

DNA Sequencing

With informed consent, leukocyte genomic DNA was extracted and the three exons of the *AVPR2* gene were amplified by polymerase chain reaction (PCR). Exon 1 was amplified with forward primer 5′-TCTATAAGGGCTCCAGTCCA-3′ and reverse primer 5′-CTCATGCAGTCCAGAAGGAA-3′ at 56 C; and exons 2 and 3 were amplified with forward primer 5′-TGGGGTGTGTATCCCTCATA-3′ and reverse primer 5′-TACAGCTGGGGATGTGGAGA-3′ at 63 C. We used 100 ng of genomic DNA, PCR buffer (Promega, Madison, Wisc., USA), 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 0.2 μM of each primer and 0.5 U Taq DNA polymerase (Promega) in a volume of 20 μl. The sizes of the PCR products were confirmed by electrophoresis in 1.5% agarose gel. The PCR products were treated with exonuclease I and shrimp alkaline phosphatase (ExoSAP-IT, USP Corporation, Cleveland, Ohio, USA), and sequenced commercially (Macrogen Inc., Seoul, Korea). Sequence data were analyzed using Sequencher (version 4.2; Gene Codes Corporation, Ann Arbor, Mich., USA).

Construction of AVPR2 Expression Vectors

The R181C mutant was recreated in the human *AVPR2* cDNA bearing a *myc* tag at its NH_2 end and cloned in pcDNA3.1 (Invitrogen, Carlsbad, Calif., USA) [16] by PCR-based, site-directed mutagenesis using the primers 5′-CATCTTCGCCCAGTGCAACGTGGAAGG-3′ and 5′-CCTTCCACGTTGCACTGGGC-

GAAGATG-3′. The M311V mutant was created similarly using 5′-CCTTTGTGCTACTCGTGTTGCTGGCCAGC-3′ and 5′-GCTGGCCAGCAACACGAGTAGCACAAAGG-3′. The methylated parental wild-type cDNA was digested with 10U *Dpn*I at 37°C for 180 min, and the remaining unmethylated mutagenized cDNA plasmid was used to transform *Escherichia coli* DH5α cells. The mutagenized *AVPR2* cDNAs were verified by sequencing.

Cell Culture and Transient Transfection

HEK293T cells were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum and antibiotics at 37°C in a humidified 5% CO_2 incubator. Cells were divided into 6-well plates (Falcon 3046, BD Biosciences, Lincoln Park, N.J., USA) 24 h before transfection at ~50% confluence using Effectene (Qiagen, Valencia, Calif., USA). Each well received 400 ng of plasmid DNA and 50 ng of a cAMP-responsive luciferase reporter plasmid (pCREluc) containing 16 copies of the consensus cAMP response element [17]. To control for transfection efficiency, cells were cotransfected with 5 ng of *Renilla* luciferase reporter plasmid (pRL-CMV) (Promega) per well.

AVP and DDAVP Stimulation and Dual Luciferase Assay

Cells were split 24 h after transfection into 96-well plates and incubated overnight. After washing in DMEM with 0.1 mg/ml bovine serum albumin, cells were incubated in the fresh medium containing 0.25 mM isobutylmethylxanthine, 0–10^{-5} M AVP (Sigma, St. Louis, Mo., USA), 0–10^{-7} M DDAVP (Sigma) or 1 mM 8Br-cAMP for 6 h at 37°C in 5% CO_2. Cells were lysed and assayed using the Dual Luciferase Reporter Assay System (Promega). Luciferase activity was normalized to *Renilla* luciferase activity and the results were expressed as relative luciferase activity. The sigmoid concentration-response curve and the calculation of its 50% effective concentration (EC50) were analyzed using PRISM 3.02 (GraphPad Software, Inc., San Diego, Calif., USA). Statistical significance was determined by an unpaired t test.

Results

Mutation Analysis

Both patients were seen at 2 years of age with polydipsia and polyuria. At the end of their water deprivation tests, both had serum hyperosmolality with dilute urine and did not respond to DDAVP, suggesting nephrogenic diabetes insipidus. Sequencing of *AVPR2* showed that patient 1 had the mutation 1132C>T (NCBI reference sequence NC_000023), changing arginine 181 to cysteine (R181C) (fig. 1a). Patient 2 had the mutation 1628A>G changing methionine 311 to valine (M311V) (fig. 1b). This novel missense alteration was not detected in 100 unaffected control Thai chromosomes (data not shown).

Activities of the AVPR2 Mutants

Binding of AVP or DDAVP to AVPR2 elicits production of intracellular cAMP. To evaluate the activities of the AVPR2 mutants, we expressed the wild-type and mutant AVPR2 in HEK293T cells and assessed production of cAMP in response to AVP by measuring the activity of a cAMP-dependent luciferase reporter fused to 16 copies of the consensus cAMP response element. In response to varying concentrations of AVP, the half-maximal response (EC_{50}) of the wild-type AVPR2 was 6.8×10^{-12} M; by contrast the R181C mutant required an 860-fold higher concentration of AVP (5.9×10^{-9} M) ($p < 0.001$), and of the M311V mutant required a 40-fold higher concentration of AVP (2.6×10^{-10} M) ($p < 0.03$) (fig. 1c).

Although neither of our patients responded to DDAVP after water deprivation, some patients with partial NDI have been treated with high doses of DDAVP [13], and some AVPR2 mutants respond differently to DDAVP than they do to AVP [18–20]. Therefore, we also characterized the responses of the AVPR2 mutants to DDAVP (fig. 1d). The EC_{50} of the wild-type AVPR2 was 6×10^{-11} M DDAVP, a concentration about 9-fold higher than the EC_{50} for AVP. This is consistent with other studies showing about a 10-fold difference in the potency of these two agents [21, 22]. The EC50 of R181C and M311V could not be calculated for DDAVP as a maximum response could not be obtained. Nevertheless, AVP and DDAVP yielded qualitatively similar dose-response curves, showing about a 10-fold higher potency for AVP with all three forms of AVPR2.

Discussion

Two unrelated Thai boys had XNDI caused by hemizygous missense mutations in the *AVPR2* gene; these mutations reduced AVP-induced cAMP production in transiently transfected HEK293T cells. This assay is highly sensitive for assessing the effects of *AVPR2* mutations; Western blotting, indirect immunofluorescence, and saturation experiments are less reliable [23].

Previous work showed that R181C is properly targeted to the plasma membrane, but had dramatically reduced vasopressin-binding capacity, elicited reduced amounts of cAMP and resulted in a 1,000-fold increased EC_{50} for AVP [24]. Consistent with this, our data showed an 860-fold increase in the EC_{50} for this mutation, and the patient harboring R181C could concentrate his urine to only 70 mosm/l. R181 is located in extracellular loop II, near the membrane. Most GPCRs, including AVPR2, contain a conserved pair of extracellular cysteine residues linking the first and second extracellular loops via a disulfide bond; substitutions of cysteine for various residues in

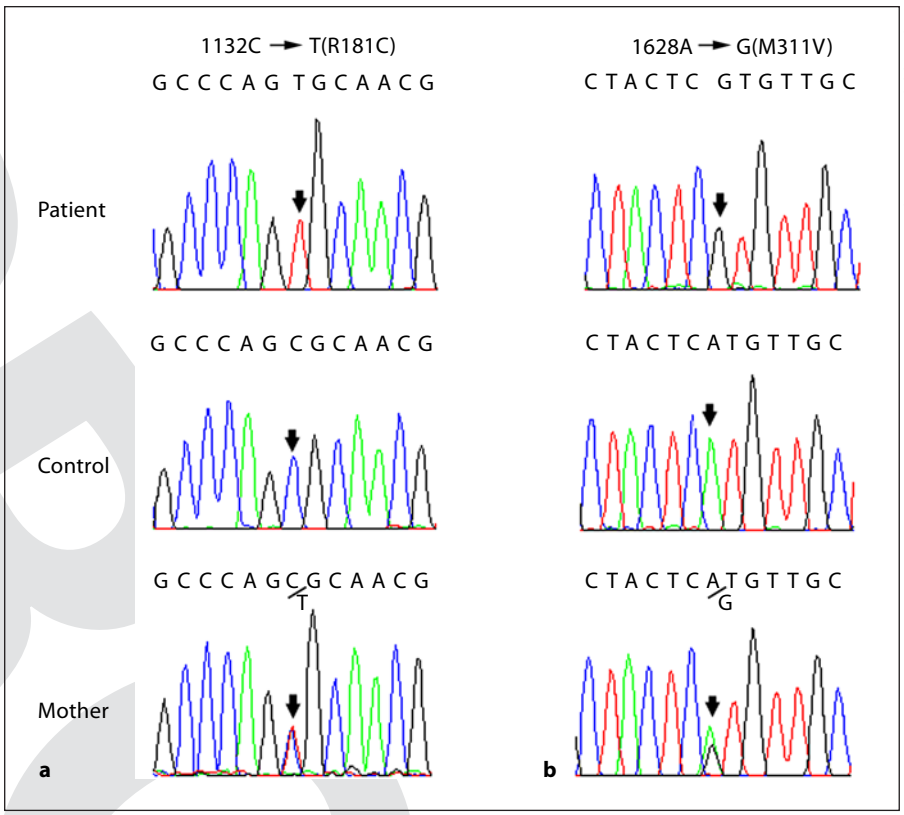
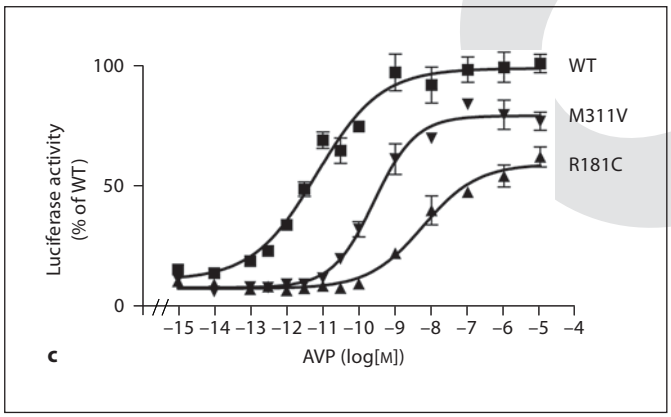
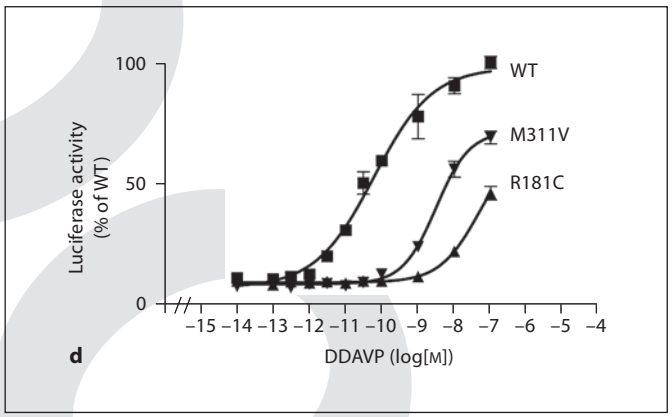


Fig. 1. Mutation analysis. **a** Patient 1 carrying R181C. **b** Patient 2 carrying M311V. The upper, middle and lower panels show the patient, control and patient's mother; each mutation is indicated by an arrow. **c** Concentration-response curve to AVP. **d** Concentration-response curve to DDAVP. Normalized luciferase activity is expressed as percentage of maximum WT V2R activity, plotted versus the concentration of AVP or DDAVP. Data are the mean ± SEM of three independent experiments, each performed in triplicate.





these loops (R181C, G185C, R202C, R203C, Y205C) cause loss-of-function mutations and XNDI [25]. The presence of an additional cysteine in these loops may cause incorrect disulfide bond formation resulting in receptor dysfunction by interfering with ligand binding [26].

The novel M311V mutant retained partial activity in vitro: its EC_{50} for AVP was only 40-fold higher than wild type, suggesting that M311V could bind AVP partially. Consistent with this, patient 2 had a partial response to his endogenous AVP when he was somewhat dehydrated, concentrating his urine to 634 mosm/l during water deprivation, but without further concentration in response to DDAVP. It is possible that if the patient were tested while normally hydrated, the urine osmolality might increase after DDAVP. Thus, our assays of receptor activity in vitro correlated with the urine-concentrating ability and the clinical phenotype. The M311V mutation is located in the seventh transmembrane domain; substitution of Val for Met typically elicits minor effects on protein folding. The homologous residue M297 in the sev-

enth transmembrane segment of the NK2 tachykinin receptor participates in binding peptide agonists [27], suggesting that AVPR2 residue M311 may play a similar role. Nevertheless, because M311V retains partial activity, it appears that it must reach the plasma membrane, but may bind ligands less avidly, although this has not been tested. Some other AVPR2 mutants that retain partial activity have reduced ligand-binding affinity and adenylyl cyclase activation [7, 8, 11] or decreased cell surface expression [7, 10].

Although treatment of partial NDI with large doses of DDAVP has been reported [13], DDAVP is not formulated in sufficiently high concentrations, and its safety in such doses has not been established. The long-term management of patients with congenital NDI remains sodium restriction, thiazide or amiloride diuretics and prostaglandin synthetase inhibitors, but they usually do not reduce urine output completely to normal. Therefore, increased water intake is generally still needed, especially in hot climates. Other therapeutic modalities may be possible. Inhibitors of cGMP phosphodiesterase, which activates a cGMP-mediated signal transduction pathway, can induce AQP2 phosphorylation and membrane insertion independently of the V2R signaling pathway [28]. Also, pharmacologic chaperones may facilitate the cell surface insertion and functional activity of some misfolded mutant V2R that would otherwise remain trapped in the endoplasmic reticulum [16, 29, 30]. Therefore, understanding the mechanism of specific mutations may facilitate the therapy of individual patients.

Acknowledgements

We thank Drs. Sayali Ranadive and Christian Vaisse (University of California, San Francisco, Calif., USA) for the myc-tagged AVPR2 expression vector. This study was supported by the Thailand Research Fund, and by funds from the UCSF Division of Pediatric Endocrinology.

References

1 van Lieburg AF, Knoers NV, Monnens LA: Clinical presentation and follow-up of 30 patients with congenital nephrogenic diabetes insipidus. J Am Soc Nephrol 1999;10:1958–1964.

2 Morello JP, Bichet DG: Nephrogenic diabetes insipidus. Annu Rev Physiol 2001;63:607–630.

3 Birnbaumer M, Seibold A, Gilbert S, Ishido M, Barberis C, Antaramian A, Brabet P, Rosenthal W: Molecular cloning of the receptor for human antidiuretic hormone. Nature 1992;357:333–335.

4 Fushimi K, Uchida S, Hara Y, Hirata Y, Marumo F, Sasaki S: Cloning and expression of apical membrane water channel of rat kidney collecting tubule. Nature 1993;361:549–552.

5 Robben JH, Knoers NV, Deen PM: Cell biological aspects of the vasopressin type-2 receptor and aquaporin 2 water channel in nephrogenic diabetes insipidus. Am J Physiol Renal Physiol 2006;291:F257–F270.

6 Spanakis E, Milord E, Gragnoli C: AVPR2 variants and mutations in nephrogenic diabetes insipidus: review and missense mutation significance. J Cell Physiol 2008;217:605–617.

7 Sadeghi H, Robertson GL, Bichet DG, Innamorati G, Birnbaumer M: Biochemical basis of partial nephrogenic diabetes insipidus phenotypes. Mol Endocrinol 1997;11:1806–1813.

8 Ala Y, Morin D, Mouillac B, Sabatier N, Vargas R, Cotte N, Dechaux M, Antignac C, Arthus MF, Lonergan M, Turner MS, Balestre MN, Alonso G, Hibert M, Barberis C, Hendy GN, Bichet DG, Jard S: Functional studies of twelve mutant V2 vasopressin receptors related to nephrogenic diabetes insipidus: molecular basis of a mild clinical phenotype. J Am Soc Nephrol 1998;9:1861–1872.

9 Vargas-Poussou R, Forestier L, Dautzenberg MD, Niaudet P, Dechaux M, Antignac C: Mutations in the vasopressin V2 receptor and aquaporin-2 genes in 12 families with congenital nephrogenic diabetes insipidus. J Am Soc Nephrol 1997;8:1855–1862.

10 Pasel K, Schulz A, Timmermann K, Linnemann K, Hoeltzenbein M, Jaaskelainen J, Gruters A, Filler G, Schoneberg T: Functional characterization of the molecular defects causing nephrogenic diabetes insipidus in eight families. J Clin Endocrinol Metab 2000;85:1703–1710.

11 Inaba S, Hatakeyama H, Taniguchi N, Miyamori I: The property of a novel V2 receptor mutant in a patient with nephrogenic diabetes insipidus. J Clin Endocrinol Metab 2001;86:381–385.

12 Chen CH, Chen WY, Liu HL, Liu TT, Tsou AP, Lin CY, Chao T, Qi Y, Hsiao KJ: Identification of mutations in the arginine vasopressin receptor 2 gene causing nephrogenic diabetes insipidus in Chinese patients. J Hum Genet 2002;47:66–73.

13 Faerch M, Christensen JH, Corydon TJ, Kamperis K, de Zegher F, Gregersen N, Robertson GL, Rittig S: Partial nephrogenic diabetes insipidus caused by a novel mutation in the AVPR2 gene. Clin Endocrinol (Oxf) 2008;68:395–403.

14 Robben JH, Knoers NV, Deen PM: Characterization of vasopressin V2 receptor mutants in nephrogenic diabetes insipidus in a polarized cell model. Am J Physiol Renal Physiol 2005;289:F265–F272.

15 Feldman BJ, Rosenthal SM, Vargas GA, Fenwick RG, Huang EA, Matsuda-Abedini M, Lustig RH, Mathias RS, Portale AA, Miller WL, Gitelman SE: Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med 2005;352:1884–1890.

16 Ranadive SA, Ersoy B, Favre H, Cheung CC, Rosenthal SM, Miller WL, Vaisse C: Identification, characterization and rescue of a novel vasopressin-2 receptor mutation causing nephrogenic diabetes insipidus. Clin Endocrinol (Oxf) 2009;71:388–393.

17 Vaisse C, Clement K, Durand E, Hercberg S, Guy-Grand B, Froguel P: Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity. J Clin Invest 2000;106:253–262.

18 Mouillac B, Chini B, Balestre MN, Elands J, Trumpp-Kallmeyer S, Hoflack J, Hibert M, Jard S, Barberis C: The binding site of neuropeptide vasopressin V1a receptor. Evidence for a major localization within transmembrane regions. J Biol Chem 1995;270:25771–25777.

19 Derick S, Pena A, Durroux T, Wagnon J, Serradeil-Le Gal C, Hibert M, Rognan D, Guillon G: Key amino acids located within the transmembrane domains 5 and 7 account for the pharmacological specificity of the human V1b vasopressin receptor. Mol Endocrinol 2004;18:2777–2789.
20 Rodrigo J, Pena A, Murat B, Trueba M, Durroux T, Guillon G, Rognan D: Mapping the binding site of arginine vasopressin to V1a and V1b vasopressin receptors. Mol Endocrinol 2007;21:512–523.
21 Saito M, Tahara A, Sugimoto T: 1-Desamino-8-D-arginine vasopressin (dDAVP) as an agonist on V1b vasopressin receptor. Biochem Pharmacol 1997;53:1711–1717.
22 Del Tredici AL, Vanover KE, Knapp AE, Bertozzi SM, Nash NR, Burstein ES, Lameh J, Currier EA, Davis RE, Brann MR, Mohell N, Olsson R, Piu F: Identification of novel selective V2 receptor non-peptide agonists. Biochem Pharmacol 2008;76:1134–1141.
23 Albertazzi E, Zanchetta D, Barbier P, Faranda S, Frattini A, Vezzoni P, Procaccio M, Bettinelli A, Guzzi F, Parenti M, Chini B: Nephrogenic diabetes insipidus: Functional analysis of new AVPR2 mutations identified in Italian families. J Am Soc Nephrol 2000; 11:1033–1043.
24 Pan Y, Wilson P, Gitschier J: The effect of eight V2 vasopressin receptor mutations on stimulation of adenylyl cyclase and binding to vasopressin. J Biol Chem 1994;269:31933–31937.
25 Fujiwara TM, Morgan K, Bichet DG: Molecular biology of diabetes insipidus. Annu Rev Med 1995;46:331–343.
26 Schulz A, Grosse R, Schultz G, Gudermann T, Schoneberg T: Structural implication for receptor oligomerization from functional reconstitution studies of mutant V2 vasopressin receptors. J Biol Chem 2000;275: 2381–2389.
27 Labrou NE, Bhogal N, Hurrell CR, Findlay JB: Interaction of Met297 in the seventh transmembrane segment of the tachykinin NK2 receptor with neurokinin A. J Biol Chem 2001;276:37944–37949.
28 Bouley R, Pastor-Soler N, Cohen O, McLaughlin M, Breton S, Brown D: Stimulation of AQP2 membrane insertion in renal epithelial cells in vitro and in vivo by the cGMP phosphodiesterase inhibitor sildenafil citrate (viagra). Am J Physiol Renal Physiol 2005;288:F1103–F1112.
29 Robben JH, Sze M, Knoers NV, Deen PM: Functional rescue of vasopressin V2 receptor mutants in MDCK cells by pharmacochaperones: relevance to therapy of nephrogenic diabetes insipidus. Am J Physiol Renal Physiol 2007;292:F253–F260.
30 Morello JP, Salahpour A, Laperriere A, Bernier V, Arthus MF, Lonergan M, Petaja-Repo U, Angers S, Morin D, Bichet DG, Bouvier M: Pharmacological chaperones rescue cell-surface expression and function of misfolded V2 vasopressin receptor mutants. J Clin Invest 2000;105:887–895.