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Chapter 14. Hereditary Neurohypophyseal Diabetes Insipidus

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Abstract
Neurohypophyseal diabetes insipidus (DI) is most often caused by trauma, including operations, and infiltrating processes in the hypothalamic-pituitary region. Irradiation, ischemia, infections, or autoimmunity can also underlie the disease. Since the middle of the 19th century, familial forms of neurohypophyseal DI have been described. Most commonly, the disease is transmitted in an autosomal-dominant fashion; very rarely, autosomal-recessive inheritance has been observed. Hereditary neurohypophyseal DI is caused by mutations in the gene encoding the antidiuretic hormone vasopressin (AVP) and its carrier protein neurophysin II (NPII). Symptoms result from the lack of hormone, or from the inability of mutant AVP to activate its renal receptor, and respond to treatment with desmopressin (DDAVP). Dominant mutations cause retention of the hormone precursor in the endoplasmic reticulum (ER) of vasopressinergic neurons in the hypothalamus, resulting in cellular dysfunction and eventually neuronal death. This so-called "neurotoxicity hypothesis" was initially established on the basis of autopsy studies in affected humans and has been supported by heterologous cell-culture expression experiments and murine knock-in models. Current data show that retained mutants fail to be eliminated by the cell's quality control system and accumulate in fibrillar aggregations within the ER. Autosomal-dominant neurohypophyseal DI may thus be viewed as a neurodegenerative disease confined to vasopressinergic neurons.

Keywords (5-10): diabetes insipidus; neurohypophyseal; vasopressin; neurophysin; hereditary; endoplasmic reticulum; aggregation; Wolfram

List of abbreviations:

DI	diabetes insipidus
AVP	vasopressin; antidiuretic hormone
OT	oxytocin
NPII	neurophysin II
DDAVP	desmopressin
ER	endoplasmic reticulum
OMIM	Online Mendelian Inheritance In Men database
AVPR2	vasopressin V2 receptor
aa	amino acid
SP	signal peptide
UPR	unfolded protein response
ERAD	endoplasmic reticulum - associated degradation
DIDMOAD	diabetes insipidus, diabetes mellitus, optic atrophy, sensorineural deafness
AQP	aquaporin
cAMP	cyclic adenosine monophosphate
ATP	adenosine triphosphate
PKA	protein kinase A

14.1. Introduction

The term "diabetes insipidus" (DI) refers to the excretion of copious amounts of diluted urine (*diabetes*: flow, *insipidus*: tasteless), setting the disorder apart from diabetes mellitus (*mellitus*: sweet) and exemplifying the former practice of evaluating a differential diagnosis by tasting the patients' urine. Polydipsia (excessive thirst) ensues as a consequence of polyuria. Under physiological circumstances, the antidiuretic hormone arginine-vasopressin, AVP, is synthesized in specialized hypothalamic neurons that extend to the posterior pituitary, from where it is secreted when plasma osmolality rises or circulating blood volume falls. AVP promotes free water reabsorption from the tubular lumen across renal collecting duct cells into the interstitial and intravasal spaces (**Fig. 14.1**). If this antidiuretic axis is disturbed, DI results.

Hereditary DI is a monogenetic disorder and usually follows a clear pattern of inheritance, reflecting either autosomal-dominant, autosomal-recessive, or X-linked transmission. Rarely, additional signs and symptoms are present. In these patients, DI thus constitutes a component of a syndromic disorder.

In this chapter, we will discuss the features of hereditary neurohypophyseal DI , focusing on both clinical and pathophysiological aspects.

14.2. Evolution of research on hereditary neurohypophyseal DI

Hereditary DI has been described as early as 1841 (Lacombe 1841). In the late 19th and early 20th century, large autosomal-dominant pedigrees were reported in the German literature (Weil 1884, 1908; Gänsslen and Fritz 1924). While the molecular basis of the disorder was still unknown, important etiological insight came from *post mortem* studies in patients with hereditary or "idiopathic" neurogenic DI (Gaupp 1941; Blotner 1958; Braverman et al. 1965; Green et al. 1967; Bergeron et al. 1991; Nagai et al. 1984). These investigations showed loss of vasopressinergic magnocellular neurons and mild gliosis in supraoptic and paraventricular hypothalamic nuclei, suggesting that neuronal damage had occurred specifically to AVP-producing cells and establishing the basis of the so-called neurotoxicity hypothesis. If a cell type-specific toxic effect, conferred e.g. by a mutant protein, could lead to cell death and eliminate AVP secretion, this would explain the autosomal dominant transmission observed in inherited neurogenic DI. In addition, a neurotoxic agent typically leads to progressive cell damage over a prolonged period of time, which would be in accordance with the clinical observation that the disease develops gradually after the initial manifestation several months to years after birth, albeit with high penetrance.

The gene encoding the precursor of AVP was an obvious candidate to cause hereditary neurogenic DI. The human genes for prepro-AVP and its homolog prepro-oxytocin (OT) were cloned over 30 years ago (Sausville et al. 1985). In 1991, the first paper reporting a heterozygous mutation in the AVP gene was published (Ito et al. 1991). Currently, 71 mutations are listed in the public domain of the Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk).

Several animal models for neurohypophyseal DI have been described (Bernal et al. 2016). In the Brattleboro rat, studied since the 1960s (Valtin and Schroeder 1964), DI is transmitted in an autosomal recessive manner and results from a single base deletion in the *AVP* gene, which causes a frame shift and leads to inefficient translation of the mutant mRNA (Schmale et al. 1984). The first mouse model to reproduce many facets of human autosomal-dominant neurohypophyseal DI was reported in 2003 (Russell et al. 2003). In these animals, a naturally occurring heterozygous human truncation mutation of the AVP precursor protein was introduced, resulting in a clear DI

phenotype. Since then, additional rat (Si-Hoe et al. 2000; Davies and Murphy 2002; Castino et al. 2005) and mouse (Hayashi et al. 2009; Hagiwara et al. 2014) models have been published, with varying results regarding recapitulation of clinical polyuria/polydipsia and histological evidence of cytotoxicity in vasopressinergic neurons.
Since the 1990s, numerous expression studies have analyzed intracellular trafficking of mutant vs. wild-type AVP hormone precursors (Olias et al. 1996; Beuret et al. 1999; Siggaard et al. 2005). In autosomal dominant neurogenic DI, retention of pathogenic AVP mutants in the endoplasmic reticulum (ER) has uniformly been found. Recent work has focused on aggregation of misfolded precursors in the ER and on ER-associated degradation, suggesting that insoluble fibrillar aggregates may contribute to or even cause cell death in dominant neurogenic DI (Rutishauser et al. 2016).

14.3. Differential diagnosis of hereditary diabetes insipidus (OMIM 192340; 125700)

In adults with *ad libitum* access to fluids, polyuria is defined as a 24-hour urinary output of >45-50 ml/kg body weight (Robertson 2001). Polyuria should be quantified, as estimations by patients tend to be imprecise. Uncontrolled diabetes mellitus resulting in glucosuria and thus solute diuresis must be excluded. The differential diagnosis between neurohypophyseal DI, nephrogenic DI, and primary polydipsia can be facilitated by measuring copeptin concentrations at baseline and after sufficient stimulation (i.e. serum [Na] ≥ 150 mM) by water deprivation and/or hypertonic saline infusion (Timper et al. 2015; Fenske et al. 2018).
Although *de novo* mutations in previously unaffected families can occur (Rutishauser et al. 2002; Bourdet et al. 2016; Joshi et al. 2017), a positive family history of polyuria and polydipsia is usually present in hereditary forms (Babey et al. 2011). The mode of transmission and consideration of clinical characteristics often allow to make a presumptive diagnosis, but confirmatory genetic analysis is advocated for both nephrogenic and neurogenic familial DI (Bichet and Bockenhauer 2016; Rutishauser et al. 2016; Joshi et al. 2018). The majority of patients with hereditary nephrogenic DI have mutations in the vasopressin V2 receptor (*AVPR2*) gene, which is encoded on the X chromosome. Autosomal recessive or, less common, dominant transmission is associated with mutations in the gene encoding aquaporin 2 water channels. Hereditary nephrogenic DI, particularly the X-linked and recessive types, is present at birth and characterized by potentially life-threatening dehydration. Conversely, symptoms of familial neurohypophyseal DI typically develop gradually, manifesting months or even years after birth.
In hereditary neurohypophyseal DI, both autosomal recessive and, much more commonly, dominant transmission occur. Since these disorders have distinct pathophysiologies, they will be considered separately.

14.4. The vasopressin gene and its product

The homologous genes encoding prepro-vasopressin (*AVP* gene) and prepro-oxytocin (*OT* gene) are located in a head-to-head orientation on chromosome 20p13, separated by a ~12 kilobase intervening sequence. The *AVP* gene (**Fig. 14.2**) consists of three exons, encoding the 19-amino acid (aa) N-terminal signal peptide (SP), the AVP nonapeptide hormone, a 93-aa neurophysin II (NPII) moiety, and a C-terminal 39-aa glycoprotein. The latter, called copeptin, represents the main distinctive feature between the *AVP* and *OT* genes, as it is present only in the AVP precursor protein. After

directing the nascent polypeptide chain to the ER, the SP is cleaved during cotranslational translocation. Prohormone folding in the ER implies AVP binding into a binding pocket of NPII (Wu et al. 2001; De Bree et al. 2003) and stabilization by eight disulfide bonds. After ER exit, the prohormone is transported through the Golgi apparatus to the trans-Golgi network, where it is sorted into neurosecretory granules and cleaved into AVP, NPII and copeptin. In addition, AVP is C-terminally amidated. The three proteins are secreted into the circulation from nerve endings in the posterior pituitary by regulated exocytosis. Upon secretion, NPII and copeptin have no clinically appreciated function.
The majority of mutations in hereditary neurogenic DI are missense or nonsense point mutations, but deletions (Christensen et al. 2013; Luo et al. 2012) and indels have also been found (see http://www.hgmd.cf.ac.uk), as well as mutations altering splice sites (see below). No mutations have been described in the copeptin moiety.

14.5. Autosomal recessive neurohypophyseal DI

Compared to the much more common dominant type, this mode of inheritance in hereditary neurogenic DI is exceedingly rare. A recurrent recessive point mutation has been reported in two apparently unrelated Palestinian families originating from Texas (Willcutts et al. 1999) and Israel (Abu Libdeh et al. 2010). The mutation, passed on to the affected offspring by each of the heterozygous consanguineous parents, replaces proline at position 7 of the AVP moiety by leucin (P7L). Polyuria and polydipsia developed by the age of 15 to 24 months in affected children of one family and in the neonatal period in the other, but the reason for this discrepancy is unclear. Symptoms were successfully treated with desmopressin (DDAVP). At the cellular level, it was shown that the mutation caused a ~30 fold decrease in binding of AVP to its renal receptor. Conversely, when the P7L mutant was later expressed in cultured cells, its intracellular trafficking and secretion was normal (Birk et al. 2009).
Another child with very early-onset recessive neurogenic DI, born to consanguineous parents, was reported in 2013 (Christensen et al. 2013). Hypernatremia and urinary hypoosmolality were correctable by the administration of DDAVP, suggesting that the disorder was not caused by a defective AVPR2. Rather, a chromosomal deletion of ~10 kilobases in the *AVP* gene was identified on both alleles, assumedly abolishing gene transcription.
More recently, Canadian pediatricians reported on a child of Lebanese descent, born to asymptomatic parents and presenting with neurohypophyseal DI. Polyuria and polydipsia responded to DDAVP treatment, as did growth retardation. Sequence analysis of the *AVP* gene in the patient revealed a compound heterozygous state, with one allele carrying the known P7L mutation and the other a novel variant in the splice acceptor site of intron 1 (Bourdet et al. 2016). This case underscores the importance of genetic testing, even in the absence of a suggestive family history, in childhood-onset DI of uncertain origin.

14.6. Autosomal dominant neurohypophyseal DI

In the vast majority of published families with hereditary central DI, disease transmission follows a dominant pattern. Affected individuals gradually develop polyuria and polydipsia due to progressive AVP deficiency. Symptoms and signs typically start to manifest in infancy to early childhood. Disease penetrance is complete and symptoms are usually severe, although signal peptide mutations causing inefficient signal cleavage have been associated with later manifestation and a partial phenotype

(McLeod et al. 1993; Siggaard et al. 2005; Toustrup et al. 2018). If children are deprived of adequate access to fluids, failure to thrive may occur, which is reversible by treatment with DDAVP (Brachet et al. 2011). Interestingly, the same mutation may result in variable disease severity, even among affected members of the same family (Repaske et al. 1997). Another peculiarity is partial recovery of polyuria in elderly males with familial neurohypophyseal DI (Rutishauser et al. 1996; Babey et al. 2011). The physiological basis of these observations is unclear.

14.6.1. *ER retention and possible links to neuronal cell loss.*

Much insight has emerged from heterologous expression studies in cell culture experiments. The common denominator of all dominant neurogenic DI variants is that the mutant prohormone is retained in the ER by the ER quality control system, a machinery that ensures that only correctly folded proteins exit the ER (Araki and Nagata 2011). ER retention is common to the large group of "ER storage diseases", such as cystic fibrosis (retention of the mutant CFTR chloride channel), LDL receptor defect, or nephrogenic DI (retention of mutant AVPR2 or aquaporin 2) (Rutishauser and Spiess 2002). However, as opposed to the majority of these disorders, in autosomal dominant neurohypophyseal DI the disease does not result from the mere lack of functional protein, which should be compensated by the wild type allele, but from a dominant-negative effect of the mutant over the wild type counterpart.

ER retention can be demonstrated by pulse-chase and immunoprecipitation experiments using cells expressing mutant or wild type (control) provasopressin (**Fig. 14.3**). ER-retained proteins produce a typical reticular or more densely packed aggregate pattern when visualized by immunofluorescence, co-localizing with ER-resident marker proteins (**Fig. 14.4**).

Disruption of ER homeostasis, i.e. the mismatch between the load of proteins populating the ER and the ER folding and secretory capacity, activates a program of pathways signaling from the ER lumen to the cytoplasm and the nucleus (Chapman et al. 1998; Mori 2000). This program, termed ER stress response or unfolded protein response (UPR), is made up of several distinct components; e.g. upregulation of ER-resident chaperones and folding enzymes occurs, or programmed cell death pathways may become activated (Oyadomari and Mori 2004). In autosomal dominant neurohypophyseal DI, while the mechanism of neurotoxicity appears to be different from apoptosis (Ito and Jameson 1997), a heterozygous knock-in mouse model, carrying a human truncation provasopressin mutant, reproduced not only the clinical phenotype of AVP-deficient DI, but also demonstrated by immunostaining an apparent reduction in vasopressinergic neurons in the hypothalamus (Russell et al. 2003). This seemingly direct evidence for the neurotoxicity hypothesis has been questioned, however, in later experiments with mice carrying the same heterozygous truncation mutant. By *in situ* hybridization for AVP mRNA, vasopressinergic neurons were detectable despite the presence of polyuria in the mutant mice (Hayashi et al. 2009). The polyuria phenotype thus preceded neuronal loss. In the ER and nuclei of vasopressinergic cells, large aggregations were detected which contained markers of autophagy, a lysosomal clearance mechanism of intracellular protein waste (Hagiwara et al. 2014). Thus, in the pathophysiology of autosomal dominant neurogenic DI, the autophagy pathway may be involved, but the exact nature of the link between ER retention and toxic impact on neurons remains unclear.

14.6.2. *Degradation and fibrillar aggregation of pathogenic provasopressin mutants*

ER-retained misfolded proteins are retrotranslocated from the ER lumen into the cytosol and targeted for ER-associated degradation (ERAD) by the proteasome (Ciechanover and Schwartz 1998; Hershko et al. 2000). This process has been demonstrated in the case of pathogenic provasopressin mutants in cell culture experiments where proteasome inhibitors were used (Friberg et al. 2004) (**Fig. 14.5**). Interestingly, it was found that not only mutant, but also a portion of wild type precursors were degraded by the proteasome pathway. Indirect evidence for a "system overload" came from the early observation that a dominant AVP mutant associated with severe DI formed disulfide-linked oligomers (Beuret et al. 1999). It was later confirmed that these homo-oligomers accumulated in cells transfected with pathogenic AVP mutants (Birk et al. 2009). Further analysis of transfected cells by immunofluorescence staining and immunogold electron microscopy revealed that large aggregations with a fibrillar substructure gradually accumulated in the ER lumen (Birk et al. 2009; Beuret et al. 2017) (**Fig. 14.6**). These findings indicated that autosomal dominant neurohypophyseal DI shares essential characteristics with neurodegenerative disorders such as Huntington's, Alzheimer's or Parkinson's disease associated with fibrillar (amyloid) aggregation.

Recent studies have shown that two sequences within the provasopressin prohormone independently confer the ability to form fibrils, namely the AVP nonapeptide and the C-terminal copeptin (Beuret et al. 2017). Interestingly, the same two sequences also mediate physiological aggregation and sorting of the prohormone into neurosecretory granules (Beuret et al. 2017), lending support to the proposal that secretory granules are "functional amyloids" (Maji et al. 2009).

The current hypothesis thus states that the amount of mutant AVP precursor molecules exceeds the capacity of the degradation machinery, leading to accumulation and deposition of large fibrillar aggregations in the ER and, potentially, to neuronal damage by undefined mechanisms. Recent experimental work has addressed the role of the ER quality control and degradation system in the context of vasopressin physiology. Remarkably, mice with an intact *AVP* gene, but deficient in Sel1L protein, a component of the ERAD complex, develop AVP-deficient DI without showing evidence of damage in magnocellular neurons (Shi et al. 2017). In a mouse neuroblastoma cell line deficient in Sel1L, wild type and mutant vasopressin precursors accumulate in amyloid-like fibrillar aggregations (Shi et al. 2017). These data show that a functional ERAD is essential for maintaining the antidiuretic system in the wild type context already, and support the pathophysiological concepts outlined above which underlie autosomal dominant neurohypophyseal DI.

14.7. X-linked neurohypophyseal DI

Only one family tree with apparent X-linked transmission of neurogenic DI has been reported in abstract form (Habiby et al. 1996). Females are unaffected, and males show desmopressin-responsive DI of varying severity, manifesting months to years after birth (Babey et al. 2011). The phenotype has been linked to a region on chromosome Xq28. Importantly, both the *AVP* and *AVPR2* genes in affected males are normal. The gene causing this form of hereditary DI has not been identified so far.

2.3.2.1.8. Desmopressin-responsive diabetes insipidus in the context of the Wolfram syndrome 1 (DIDMOAD syndrome)

Patients affected with this rare autosomal-recessive syndrome, first described in 1938 (Wolfram and Wagener 1938), carry homozygous or compound heterozygous

mutations in the *WFS1* gene (Inoue et al. 1998; Strom et al. 1998) (OMIM 222300). Diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness (DIDMOAD) are the components of the complex disorder, with DI manifesting in up to 70% of affected individuals (Barrett et al. 1995). Insulin-dependent diabetes mellitus and bilateral optic atrophy are the two features requested to make a diagnosis, but besides DI and deafness, psychiatric illness associated with a high risk of suicide (Swift et al. 1991; Swift et al. 1998) and brain stem and cerebellar disease (Chaussenot et al. 2011) have also been observed. Prognosis is poor when patients develop neurological dysfunction.

The *WFS1* gene, located in chromosome 4p16.1, encodes wolframin, an ER-resident transmembrane protein which is believed to control ER calcium levels and attenuate ER stress in pancreatic beta cells (Fonseca et al. 2005; Rigoli et al. 2018). Heterozygous mutations in *WFS1*, resulting in deficiency in wolframin, may trigger the ER stress response and eventually activation of pro-apoptotic pathways (Delprat et al. 2018).

Conclusions

The clinical presentation, along with a careful medical history, will often allow a correct differential diagnosis in hereditary DI, which is confirmed by functional tests and genetic analysis. The neurogenic form is most often transmitted in an autosomal dominant fashion, and symptoms develop gradually, rarely endangering affected individuals. In abrupt neonatal onset, much more often caused by nephrogenic than neurogenic DI, rapid hydration treatment is key. Mutational analysis is recommended in all patients with suspected hereditary DI; importantly, a genetic basis should be considered in idiopathic childhood DI even in the absence of a family history, because *de novo* mutations in the responsible gene may occur.

References

Abu Libdeh A, Levy-Khademi F, Abdulhadi-Atwan M, Bosin E, Korner M, White PC, Zangen DH (2010) Autosomal recessive familial neurohypophyseal diabetes insipidus: onset in early infancy. European Journal of Endocrinology 162 (2):221-226

Araki K, Nagata K (2011) Protein folding and quality control in the ER. Cold Spring Harb Perspect Biol 3 (11):a007526

Babey M, Kopp P, Robertson GL (2011) Familial forms of diabetes insipidus: clinical and molecular characteristics. Nat Rev Endocrinol 7 (12):701-714. doi:10.1038/nrendo.2011.100

Barrett TG, Bundey SE, Macleod AF (1995) Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet 346 (8988):1458-1463

Bergeron C, Kovacs K, Ezrin C, Mizzen C (1991) Hereditary diabetes insipidus: an immunohistochemical study of the hypothalamus and pituitary gland. Acta Neuropathologica 81 (3):345-348

Bernal A, Mahía J, Puerto A (2016) Animal models of Central Diabetes Insipidus: Human relevance of acquired beyond hereditary syndromes and the role of oxytocin. Neurosci Biobehav Rev, vol 66.

Beuret N, Hasler F, Prescianotto-Baschong C, Birk J, Rutishauser J, Spiess M (2017) Amyloid-like aggregation of provasopressin in diabetes insipidus and secretory granule sorting. BMC Biology:1-14

Beuret N, Rutishauser J, Bider MD, Spiess M (1999) Mechanism of endoplasmic reticulum retention of mutant vasopressin precursor caused by a signal peptide truncation associated with diabetes insipidus. Journal of Biological Chemistry 274 (27):18965-18972

Bichet DG, Bockenhauer D (2016) Genetic forms of nephrogenic diabetes insipidus (NDI): Vasopressin receptor defect (X-linked) and aquaporin defect (autosomal recessive and dominant). Best Pract Res Clin Endocrinol Metab, vol 30.

Birk J, Friberg MA, Prescianotto-Baschong C, Spiess M, Rutishauser J (2009) Dominant pro-vasopressin mutants that cause diabetes insipidus form disulfide-linked fibrillar aggregates in the endoplasmic reticulum. Journal of Cell Science 122 (Pt 21):3994-4002

Blotner H (1958) Primary or idiopathic diabetes insipidus: a system disease. Metabolism 7 (3):191-200

Bourdet K, Vallette S, Deladoëy J, Van Vliet G (2016) Early-onset central diabetes insipidus due to compound heterozygosity for AVP mutations. Hormone Research in Pediatrics 85 (4):283-287

Brachet C, Birk J, Christophe C, Tenoutasse S, Velkeniers B, Heinrichs C, Rutishauser J (2011) Growth retardation in untreated autosomal dominant familial neurohypophyseal diabetes insipidus caused by one recurring and two novel mutations in the vasopressin-neurophysin II gene. European Journal of Endocrinology 164 (2):179-187

Braverman LE, Mancini JP, Mc Goldrick DM (1965) Hereditary idiopathic diabetes insipidus. A case report with autopsy findings. Annals of Internal Medicine 63:503-508

Castino R, Davies J, Beaucourt S, Isidoro C, Murphy D (2005) Autophagy is a prosurvival mechanism in cells expressing an autosomal dominant familial

neurohypophyseal diabetes insipidus mutant vasopressin transgene. FASEB Journal 19 (8):1021-1023

Chapman R, Sidrauski C, Walter P (1998) Intracellular signaling from the endoplasmic reticulum to the nucleus. Annu. Rev. Cell Dev. Biol., vol 14.

Chaussenot A, Bannwarth S, Rouzier C, Vialettes B, Mkadem SA, Chabrol B, Cano A, Labauge P, Paquis-Flucklinger V (2011) Neurologic features and genotype-phenotype correlation in Wolfram syndrome. Ann Neurol 69:501-508

Christensen JH, Kvistgaard H, Knudsen J, Shaikh G, Tolmie J, Cooke S, Pedersen S, Corydon TJ, Gregersen N, Rittig S (2013) A novel deletion partly removing the AVP gene causes autosomal recessive inheritance of early-onset neurohypophyseal diabetes insipidus. Clinal Genetics 83 (1):44-52

Ciechanover A, Schwartz AL (1998) The ubiquitin-proteasome pathway: the complexity and myriad functions of proteins death. Proc Natl Acad Sci USA 95 (6):2727-2730

Davies J, Murphy D (2002) Autophagy in hypothalamic neurones of rats expressing a familial neurohypophysial diabetes insipidus transgene. Journal of Neuroendocrinology 14 (8):629-637

De Bree FM, Van der Kleij AAM, Nijenhuis M, Zalm R, Murphy D, Burbach JPH (2003) The hormone domain of the vasopressin prohormone is required for the correct prohormone trafficking through the secretory pathway. Neuroendocrinology 15:1156-1163

Delprat B, Maurice T, Delettre C (2018) Wolfram syndrome: MAMs' connection? Cell Death Dis 9 (3):364

Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro-Oliveira A, Drescher T, Bilz S, Vogt DR, Malzahn U, Kroiss M, Christ E, Henzen C, Fischli S, Tönjes A, Mueller B, Schopohl J, Flitsch J, Brabant G, Fassnacht M, Christ-Crain M (2018) A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. N Engl J Med, vol 379.

Fonseca SG, Fukuma M, Lipson KL, Nguyen LX, Allen JR, Oka Y, Urano F (2005) WFS1 is a novel component of the unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic beta-cells. Journal of Biological Chemistry 280 (47):39609-39615

Friberg MA, Spiess M, Rutishauser J (2004) Degradation of wild-type vasopressin precursor and pathogenic mutants by the proteasome. Journal of Biological Chemistry 279 (19):19441-19447

Gänsslen, Fritz (1924) Über Diabetes insipidus. Klin Wochenschr 3 (1):22-23

Gaupp R (1941) Über den diabetes insipidus. Zeitschr für die gesamte Neurologie und Psychiatrie 171:514-546

Green JR, Buchan GC, Alvorg EC, Swanson AG (1967) Hereditary and idiopathic types of diabetes insipidus. Brain 90:707-714

Habiby R, Robertson GL, Kaplowitz PB, Rittig S (1996) A novel X-linked form of familial neurohypophyseal diabetes insipidus [abstract]. Journal of Investigative Medicine 44:341A

Hagiwara D, Arima H, Morishita Y, Wenjun L, Azuma Y, Ito Y, Suga H, Goto M, Banno R, Sugimura Y, Shiota A, Asai N, Takahashi M, Oiso Y (2014) Arginine vasopressin neuronal loss results from autophagy-associated cell death in a mouse model for familial neurohypophysial diabetes insipidus. Cell Death Disease 5:e1148. doi:10.1038/cddis.2014.124

Hayashi M, Arima H, Ozaki N, Morishita Y, Hiroi M, Ozaki N, Nagasaki H, Kinoshita N, Ueda M, Shiota A, Oiso Y (2009) Progressive polyuria without vasopressin neuron loss in a mouse model for familial neurohypophysial diabetes insipidus. American Journal of Physiology (Regulatory, Integrative and Comparative Physiology) 296 (5):R1641-1649

Hershko A, Ciechanover A, Varshavsky A (2000) Basic Medical Research Award. The ubiquitin system. Nat Med 6 (10):1073-1081

Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E, Mueckler M, Marshall H, Donis-Keller H, Crock P, Rogers D, Mikuni M, Kumashiro H, Higashi K, Sobue G, Oka Y, Permutt MA (1998) A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nature Genetics 20 (2):143-148

Ito M, Jameson JL (1997) Molecular basis of autosomal dominant neurohypophyseal diabetes insipidus. Cellular toxicity caused by the accumulation of mutant vasopressin precursors within the endoplasmic reticulum. Journal of Clinical Investigation 99 (8):1897-1905

Ito M, Mori Y, Oiso Y, Saito H (1991) A single base substitution in the coding region for neurophysin II associated with familial central diabetes insipidus. Journal of Clinical Investigation 87 (2):725-728

Joshi S, Brandstrom P, Gregersen N, Rittig S, Christensen JH (2017) Novel de novo AVPR2 Variant in a Patient with Congenital Nephrogenic Diabetes Insipidus. Case Rep Nephrol Dial 7 (3):130-137

Joshi S, Kvistgaard H, Kamperis K, Færch M, Hagstrøm S, Gregersen N, Rittig S, Christensen JH (2018) Novel and recurrent variants in AVPR2 in 19 families with X-linked congenital nephrogenic diabetes insipidus. Eur J Pediatr 177 (9):1399-1405

Lacombe LU (1841) De la polydipsie. L'Expérience 203-208:305-391

Luo Y, Wang B, Qiu Y, Zhang C, Jin C, Zhao Y, Zhu Q, Ma X (2012) Clinical and molecular analysis of a Chinese family with autosomal dominant neurohypophyseal diabetes insipidus associated with a novel missense mutation in the vasopressin–neurophysin II gene. Endocrine.

Maji SK, Perrin MH, Sawaya MR, Jessberger S, Vadodaria K, Rissman RA, Singru PS, Nilsson KPR, Simon R, Schubert D, Eisenberg D, Rivier J, Sawchenko P, Vale W, Riek R (2009) Functional amyloids as natural storage of peptide hormones in pituitary secretory granules. Science 325 (5938):328-332

McLeod JF, Kovács L, Gaskill MB, Rittig S, Bradley GS, Robertson GL (1993) Familial neurohypophyseal diabetes insipidus associated with a signal peptide mutation. Journal of Clinical Endocrinology & Metabolism 77 (3):599A-599G

Mori K (2000) Tripartite management of unfolded proteins in the endoplasmic reticulum. Cell 101 (5):451-454

Nagai I, Li CH, Hsieh SM, Kizaki T, Urano Y (1984) Two cases of hereditary diabetes insioidus, with an autopsy finding in one. Acta Endocrinologica 105:318-323

Olias G, Richter D, Schmale H (1996) Heterologous expression of human vasopressin-neurophysin precursors in a pituitary cell line: defective transport of a mutant protein from patients with familial diabetes insipidus. DNA Cell Biol., vol 15.

Oyadomari S, Mori M (2004) Roles of CHOP/GADD153 in endoplasmic reticulum stress. Cell Death And Differentiation, vol 11. Nature Publishing Group SN -,

Repaske DR, Medlej R, Gültekin EK, Krishnamani MR, Halaby G, Findling JW, Phillips JA (1997) Heterogeneity in clinical manifestation of autosomal dominant neurohypophyseal diabetes insipidus caused by a mutation encoding Ala-1-->Val in the signal peptide of the arginine vasopressin/neurophysin II/copeptin precursor. Journal of Clinical Endocrinology and Metabolism 82 (1):51-56

Rigoli L, Bramanti P, Di Bella C, De Luca F (2018) Correction: Genetic and clinical aspects of Wolfram syndrome 1, a severe neurodegenerative disease. Pediatr Res, vol 84. Nature Publishing Group,

Robertson GL (2001) Antidiuretic hormone. Normal and disordered function. Endocrinol Metab Clin North Am 30 (3):671-694, vii

Russell TA, Ito M, Ito M, Yu RN, Martinson FA, Weiss J, Jameson JL (2003) A murine model of autosomal dominant neurohypophyseal diabetes insipidus reveals progressive loss of vasopressin-producing neurons. Journal of Clinical Investigation 112 (11):1697-1706

Rutishauser J, Böni-Schnetzler M, Böni J, Wichmann W, Huisman T, Vallotton MB, Froesch ER (1996) A novel point mutation in the translation initiation codon of the pre-pro-vasopressin-neurophysin II gene: cosegregation with morphological abnormalities and clinical symptoms in autosomal dominant neurohypophyseal diabetes insipidus. Journal of Clinical Endocrinology and Metabolism 81 (1):192-198

Rutishauser J, Kopp P, Gaskill MB, Kotlar TJ, Robertson GL (2002) Clinical and molecular analysis of three families with autosomal dominant neurohypophyseal diabetes insipidus associated with a novel and recurrent mutations in the vasopressin-neurophysin II gene. European Journal of Endocrinology 146 (5):649-656

Rutishauser J, Spiess M (2002) Endoplasmic reticulum storage diseases. Swiss Medical Weekly 132 (17-18):211-222

Rutishauser J, Spiess M, Kopp P (2016) Genetic forms of neurohypophyseal diabetes insipidus. Best Pract Res Clin Endocrinol Metab 30 (2):249-262

Sausville E, Carney D, Battey J (1985) The human vasopressin gene is linked to the oxytocin gene and is selectively expressed in a cultured lung cancer cell line. Journal of Biological Chemistry 260 (18):10236-10241

Schmale H, Ivell R, Breindl M, Darmer D, Richter D (1984) The mutant vasopressin gene from diabetes insipidus (Brattleboro) rats is transcribed but the message is not efficiently translated. EMBO Journal 3 (13):3289-3293

Shi G, Somlo DRM, Kim GH, Prescianotto-Baschong C, Sun S, Beuret N, Long Q, Rutishauser J, Arvan P, Spiess M, Qi L (2017) ER-associated degradation is required for vasopressin prohormone processing and systemic water homeostasis. Journal of Clinical Investigation 127 (10):3897-3912

Si-Hoe SL, De Bree FM, Nijenhuis M, Davies JE, Howell LM, Tinley H, Waller SJ, Zeng Q, Zalm R, Sonnemans M, Van Leeuwen FW, Burbach JP, Murphy D (2000) Endoplasmic reticulum derangement in hypothalamic neurons of rats expressing a familial neurohypophyseal diabetes insipidus mutant vasopressin transgene. FASEB Journal 14 (12):1680-1684

Siggaard C, Christensen JH, Corydon TJ, Rittig S, Robertson GL, Gregersen N, Bolund L, Pedersen EB (2005) Expression of three different mutations in the arginine vasopressin gene suggests genotype-phenotype correlation in familial

neurohypophyseal diabetes insipidus kindreds. Clinical Endocrinology 63 (2):207-216

Strom TM, Hörtnagel K, Hofmann S, Gekeler F, Scharfe C, Rabl W, Gerbitz KD, Meitinger T (1998) Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. Human Molecular Genetics 7 (13):2021-2028

Swift RG, Perkins DO, Chase CL, Sadler DB, Swift M (1991) Psychiatric disorders in 36 families with Wolfram syndrome. Am J Psychiat 148:775-779

Swift RG, Polymeropoulos MH, Torres R, Swift M (1998) Predisposition of Wolfram syndrome heterozygotes to psychiatric illness. Molec Psychiat 3:86-91

Timper K, Fenske W, Kühn F, Frech N, Arici B, Rutishauser J, Kopp P, Allolio B, Stettler C, Müller B, Katan M, Christ-Crain M (2015) Diagnostic Accuracy of Copeptin in the Differential Diagnosis of the Polyuria-polydipsia Syndrome: A Prospective Multicenter Study. Journal of Clinical Endocrinology and Metabolism 100 (6):2268-2274

Toustrup LB, Kvistgaard H, Palmfeldt J, Bjerre CK, Gregersen N, Rittig S, Corydon TJ, Christensen JH (2018) The Novel Ser18del AVP Variant Causes Inherited Neurohypophyseal Diabetes Insipidus by Mechanisms Shared with Other Signal Peptide Variants. Neuroendocrinology 106 (2):167-186

Valtin H, Schroeder H (1964) Familial hypothalamic diabetes insipidus in rats (Brattleboro strain). Am J Physiol, vol 206.

Weil A (1884) Über die hereditäre Form des Diabetes insipidus. Virchows Arch 90:70-95

Weil A (1908) Über die hereditäre Form des Diabetes insipidus. Archiv für klinische Medizin 93:180-200

Willcutts MD, Felner E, White PC (1999) Autosomal recessive familial neurohypophyseal diabetes insipidus with continued secretion of mutant weakly active vasopressin. Human Molecular Genetics 8 (7):1303-1307

Wolfram DJ, Wagener HP (1938) Diabetes mellitus and simple optic atrophy among siblings: report of four cases. Mayo Clin Proc 13:715-718

Wu CK, Hu B, Rose JP, Liu ZJ, Nguyen TL, Zheng C, Breslow E, Wang BC (2001) Structures of an unliganded neurophysin and its vasopressin complex: Implications for binding and allosteric mechanisms. Protein Sci 10:1869-1880

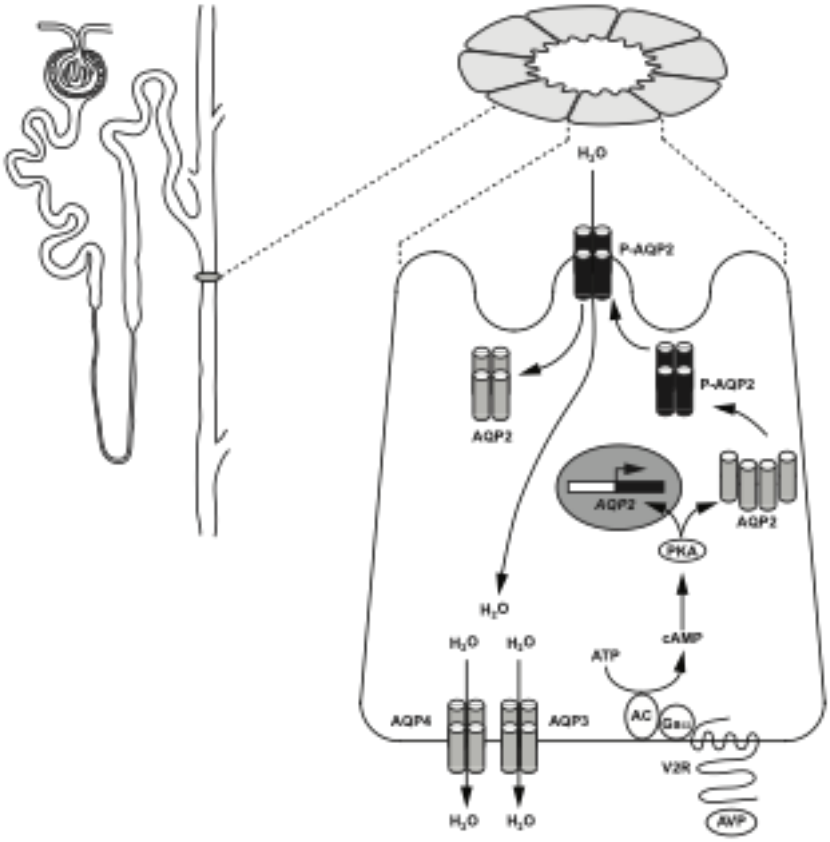

Figure 14.1
Schematic of the AVP-mediated antidiuretic mechanism. A polarized principal cell of the renal collecting duct is shown on the right. Circulating AVP binds to its renal receptor (V2R), a G protein-coupled seven transmembrane domain receptor, which is located at the basolateral membrane. Coupling of the receptor to the stimulatory G protein α (Gsα) activates adenylyl cyclase (AC), which in turn converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP then activates the protein kinase A (PKA) pathway, which exerts two effects. PKA activates nuclear factors, which increases the transcription of the aquaporin 2(AQP2) water channel gene. PKA phosphorylates AQP2, which leads to the formation of homo tetramers (P-AQP2), the functional water channel unit, which is inserted into the apical membrane and allows free water flow from the collecting duct lumen into the cell. Water molecules exit the cell into the interstitial space through aquaporin 3 and 4 water channels (AQP3, AQP4), located at the basolateral membrane. Dephosphorylation of the P-AQP2 homotetramers is followed by their internalization and dissociation. (Reproduced, with permission, from (Rutishauser et al. 2016)).

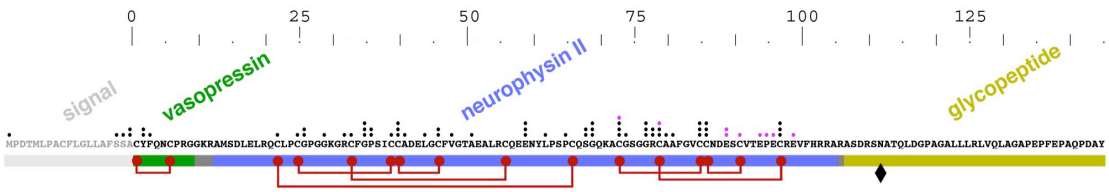

Figure 14.2
Domain organization of prepro-vasopressin neurophysin II. The hormone precursor consists of the 19-amino acid (aa) signal peptide (grey), the vasopressin nonapeptide (green), the 93-aa carrier protein neurophysin II, and the C-terminal glycopeptide, copeptin (yellow). The glycosylation site is indicated by a black diamond. There are a total of eight disulfide bridges, seven in the neurophysin II and one in the vasopressin moieties, respectively, indicated by red lines. Dots indicate heterozygous mutations associated with autosomal-dominant neurohypophyseal diabetes insipidus; missense or deletion in black, nonsense or frameshift in pink.
(Reproduced, with permission, from (Beuret et al. 2017)).

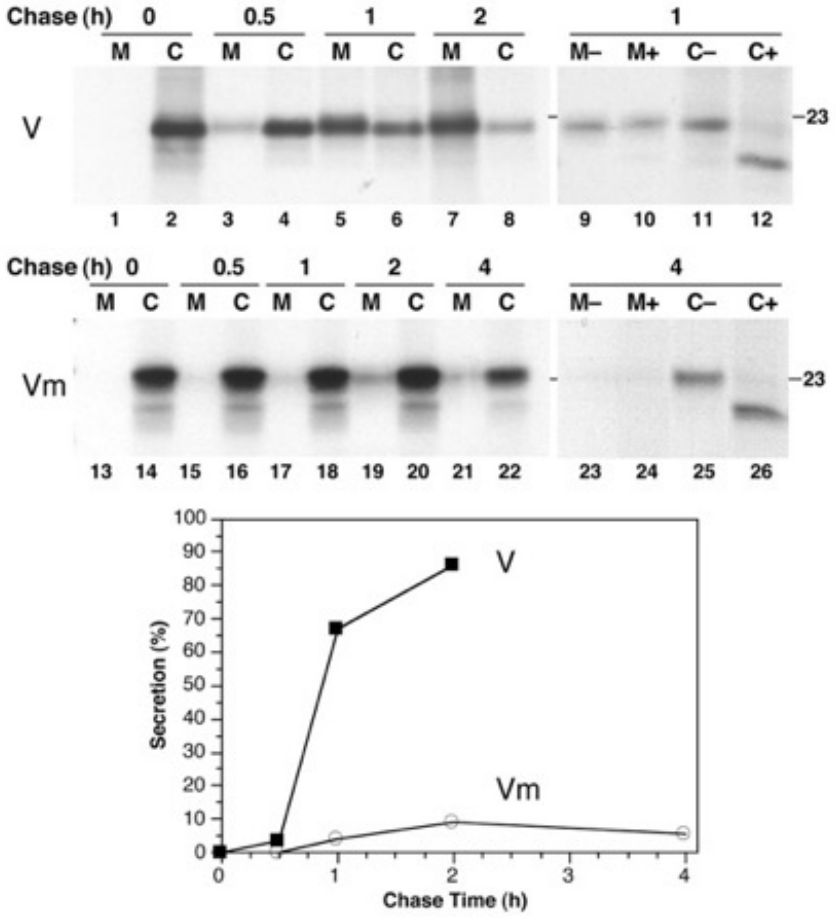

Figure 14.3
ER retention of a dominant DI mutation. Wild type vasopressin precursor (V) and the pathogenic signal peptide mutant ΔG227 (Vm; see (Rutishauser et al. 1996)) were expressed in transiently transfected COS-7 fibroblast cells. After pulse-labeling for 30 min. with [^{35}S]methionine, cells were chased for the indicated durations with excess unlabeled methionine. Media (M) and cell lysates (C) were immunoprecipitated and subjected to gel electrophoresis and autoradiography. The wild type protein was rapidly secreted into the medium (lanes 1-8), while the mutant was retained quantitatively in the cells even after a chase of 4 hrs (lanes 13-22). Some samples were incubated with (+) or without (-) endoglycosidase H. Cell lysates (lanes 11,12 and 25, 26) were sensitive to this treatment, indicating high-mannose glycosylation typical for the ER. In contrast, wild type protein found in the media (lanes 9,10) was endoglycosidase H-resistant, indicating that it had adopted complex glycosylation in the Golgi apparatus.
(Reproduced with permission. This research was originally published in the Journal of Biological Chemistry. Beuret N., Rutishauser J., Bider M.D., Spiess M. Mechanism of endoplasmic reticulum retention of mutant vasopressin precursor caused by a signal peptide truncation associated with diabetes insipidus. J. Biol. Chem. 1999; 274(27): 18965-18972. © The American Society for Biochemistry and Molecular Biology.)

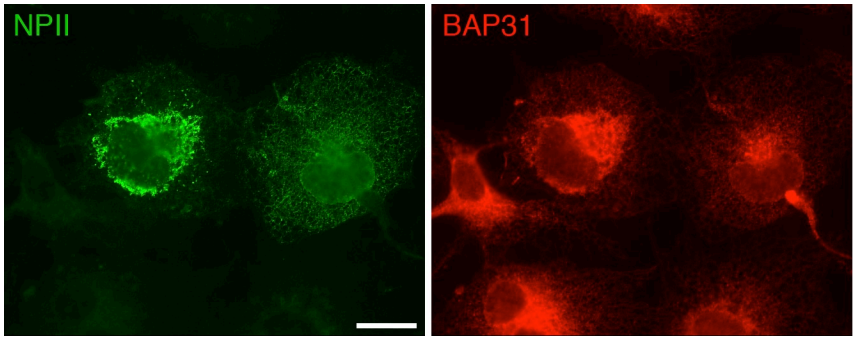

Figure 14.4
ER localization of a dominant DI mutant by immunofluorescence. COS-1 fibroblast cells were transiently transfected with the dominant mutant C28Y. Cells were stained with antibodies against NP II (left panel) or the ER resident protein BAP31 (right panel). The mutant protein produces a reticular staining pattern typical for the ER (NPII staining, right cell). Some cells show a more aggregate pattern (NPII staining, left cell). Anti BAP31 staining shows co-localization with the C28Y mutant.
Size bar: 20 µm.
(Adapted, with permission, from (Rutishauser et al. 2016)).

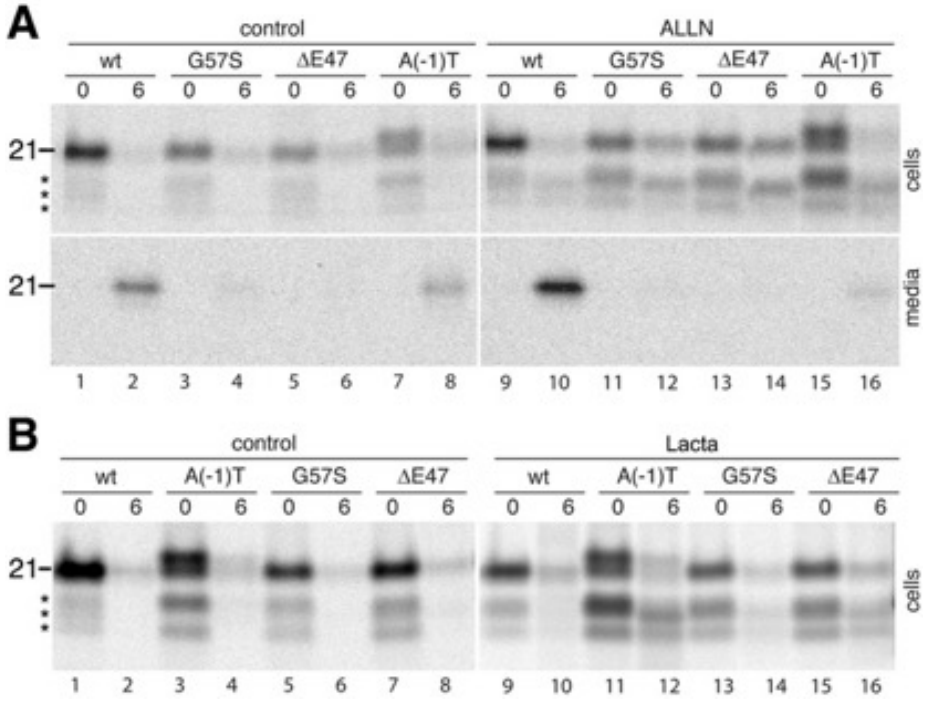

Figure 14.5
Degradation of provasopressin by the proteasome. Wild type (wt) and three different dominant DI mutants were expressed in transiently transfected COS-1 cells. G57S and ΔE47are two mutations in the NPII moiety of the precursor. The signal peptide mutant A(-1)T) causes partial signal cleavage deficiency. Cells were pulse-labeled with [^{35}S]methionine and chased for 0 or 6 hrs. in the absence (control; lanes 1-8) or presence (lanes 9-16) of proteasomal inhibitors, 250 μM ALLN (panel A) or 25 μM Lactacystin (panel B). Cell lysates (panel A, top; panel B) and media (panel A, bottom) were subjected to immunoprecipitation, gel electrophoresis and autoradiography After labeling, the precursor was detected as a major cytosolic ~21 kDa species, corresponding to glycosylated provasopressin. In the case of the A(-1)T mutant, a slightly larger band was also visible, representing uncleaved prepro-vasopressin. After 6 hrs. of chase, wild type and the signal-cleaved fraction of the A(-1)T mutant were detected in the media. Hardly any secretion-deficient mutants were detectable in the cells after 6 h, suggesting that they had been almost completely degraded. The addition of the proteasome inhibitors ALLN and Lactacystin, but not the lysosomal inhibitors Leupeptin and Pepstatin (not shown) stabilized the cytosolic 21 kDa mutant and wild type proteins. In addition to the full-length precursor, three cytosolic degradation intermediates of ~17-19 kDa (asterisks; panel A top and panel B) were also produced after labeling. These bands were equally stabilized by ALLN and Lactacystin. These results indicate that retained dominant DI mutants – and to a smaller degree also wild type – provasopressin is degraded by proteasomes.
(Reproduced with permission. This research was originally published in the Journal of Biological Chemistry. Friberg M.A., Spiess M., Rutishauser J. Degradation of Wild-type Vasopressin Precursor and Pathogenic Mutants by the Proteasome. J. Biol. Chem. 2004; 279(29): 19441-19447. © The American Society for Biochemistry and Molecular Biology.)

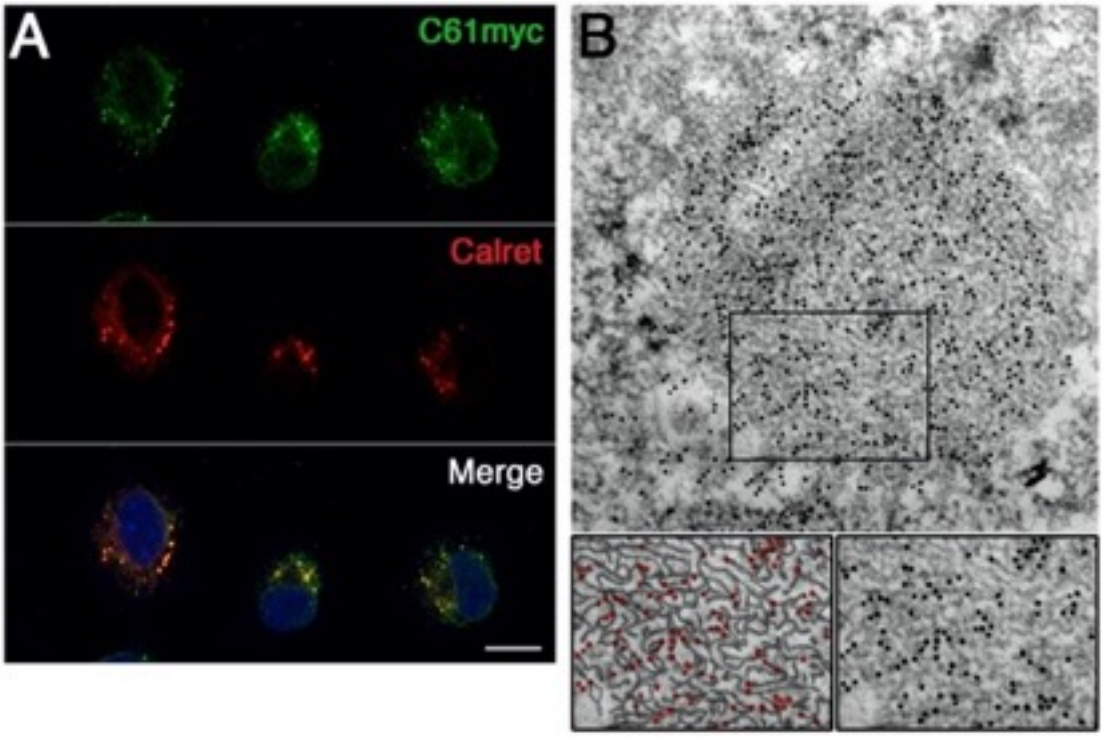

Figure 14.6
ER aggregation of a C-terminally truncated DI mutant. In the shortest known naturally occurring dominant DI mutant, C61X, the codon for cysteine at position 61 is altered to a stop codon. This truncation mutant is not recognized by anti-provasopressin antibody raised against the C-terminal portion of NPII and copeptin and was myc-tagged for detection by anti-myc antibody. The C61myc mutant was expressed in transiently transfected mouse hippocampal HN10 neuroblastoma cells and analyzed by immunofluorescence microscopy after co-staining for myc and the ER chaperone calreticulin (panel A, top and middle). Nuclei were stained with DAPI (blue). The two proteins co-localized in aggregations (panel A, bottom), indicating that the mutant was retained in the ER. Immunogold electron microscopy demonstrated that the provasopressin aggregates consisted of a network of fibrils, decorated by gold particles seen as black dots (panel B, top and bottom right). To enhance clarity, the fibrils were manually highlighted and the black dots colored in red (panel B, bottom left). Size bar: 200 nm.
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