Molecular pathology of familial central diabetes insipidus

Christoph A Meier
Endocrine Division, Massachusetts General Hospital, Boston, USA

Diabetes insipidus is caused by either the lack of arginine–vasopressin (AVP) in central diabetes insipidus (CDI) or the resistance to the action of this hormone in nephrogenic diabetes insipidus (NDI). While the causes of CDI and NDI are mostly acquired, a small percentage is hereditary in either a dominant (CDI) or recessive manner (NDI). Familial CDI is typically of late onset and slowly progressive during the first few years of life, in contrast to the frequently severe dehydration seen soon after birth in patients with NDI. These differences in the clinical presentation and the genetic mode of transmission have become at least partly explicable with the characterization of the molecular defects in patients with CDI and NDI.

Over the past 4 years several mutations in the gene encoding the hypothalamic pre-pro-AVP–neurophysin II (AVP–NPII) precursor protein have been described (1–3). Both AVP and NPII are encoded by the same gene. The protein is cleaved into AVP and NPII while being transported along the axon towards the nerve endings in the posterior pituitary. Neurophysin II is able to form tetramers while binding AVP, and is thought to be important for the axonal transport and targeting of AVP. Intriguingly, none of the known mutations in kindreds with CDI affect the nine amino acids coding for the nonapeptide AVP, but they are rather located in either the amino-terminus or the carboxy-terminus of NPII. These mis- or nonsense mutations alter either the binding of AVP to its NPII transport protein or, when located in the leader sequence, they reduce the proteolytic cleavage of the immature protein (4). A novel mutation reported by Rutishauser et al. has now been found in the translation initiation codon of the pre-pro-AVP–NPII gene of another family with CDI (5). The authors provide convincing clinical correlations to suggest strongly that this mutation also causes CDI. How then do heterozygous mutations in this gene lead to clinical manifestations, since lack-of-function mutations are usually recessive and the posterior pituitary is known to have a functional reserve of 80–90% before symptomatic polyuria occurs. Given the locations of the mutations in the pre-pro-AVP–NPII gene, it is currently thought that these changes lead to the progressive accumulation of mutant protein in either the endoplasmatic reticulum (leader peptide mutants) or along the axon end nerve ending (NPII mutations), resulting in toxicity and slowly progressive neuronal cell loss. This scenario would be compatible with the observation in autopsy studies of a markedly decreased cellularity in the hypothalamic nuclei involved in AVP synthesis in patients with long-standing familial CDI. The molecular pathogenesis of NPII mutants may hence be comparable to the dominant inheritance of familial hypothyroic cardiomyopathy or osteogenesis imperfecta, where one mutant allele (β-myosin heavy chain, type I procollagen) is thought to be sufficient to disrupt the formation of most of the oligomeric structures derived from the normal allele. An important corollary of this hypothesis is that the mutant allele must be expressed to result in a phenotype. A direct proof of this being the case would be particularly interesting in the family with the mutation in the first ATG initiation codon, where the authors speculate that a second ATG located four codons downstream might be used as an alternative initiation site in the mutant gene.

In contrast to familial CDI, the mutations in the type 2 receptor for vasopressin (X-linked recessive) or aquaporin-2 water-channel (autosomal recessive) are classical loss-of-function mutations causing familial NDI (6–8). Hence, their deficiency is already present at birth and results in potentially serious neonatal dehydration if undiagnosed. The development of genetic tests for familial NDI may therefore prove clinically useful for making an early diagnosis of this disorder.

References
Growth hormone-releasing hormone (GHRH) receptor mutation and dwarfism: after the mouse, the human

Jérôme Bererat

Service d’Endocrinologie & INSERM C1F 92-08, CHU Cochin, Paris, France

Synthesis and secretion of growth hormone by the anterior pituitary gland is mainly controlled by two antagonist hypothalamic neuropeptides: the stimulatory hormone GHRH and the inhibitory hormone somatostatin. The GHRH receptor (GHRH-R) is a member of the seven-transmembrane G-protein-coupled receptor superfamily. It interacts with Gs protein to stimulate adenylyl cyclase activity and cyclic AMP (cAMP) production. Both GHRH and cAMP are known to be involved in somatotroph proliferation and differentiation. Growth hormone-releasing hormone was purified for the first time in 1982 from a pancreatic tumor responsible for acromegaly and pituitary hyperplasia. In transgenic mice, overexpression of GHRH causes also gigantism and somatotroph hyperplasia or tumor.

Growth hormone (GH) deficiency leading to growth failure might result from alterations of the hypothalamic control of the anterior pituitary, abnormal development of the somatotroph cell or GH synthesis and alterations of secretion. Some familial cases of GH deficiency have been explained by mutations of the GH gene. To date, no mutation of the GHRH gene has been reported in patients with GH deficiency. Cloning of the GHRH-R in 1992 and its mapping to chromosome 6 in mice have been rapidly followed by the report of a recessively inherited missense mutation in the extracellular domain (Asp60Gly) of this GHRH-R in little mice. This mutation causes a profound GH deficiency and pituitary hypoplasia. The pituitary of little mice is unresponsive to GHRH in vitro, as well as in vivo, and the mutant GHRH-R is unable to stimulate cAMP production in response to GHRH.

Three years later, Wajnrajch et al. report on the first cases of a human GHRH-R (hGHRH-R) mutation causing profound GH deficiency (3). They have previously mapped the GHRH-R gene to human chromosome 7p15 (4). The hGHRH-R cDNA contains an open reading frame of 1269 base pairs encoding a 423 amino acid protein. It has a strong homology to the mouse gene. Wajnrajch et al. have evaluated two children who are members of one consanguineous family. Both, the proband (a 3.5-year-old girl) and her 16-year-old male first cousin had severe growth failure. Their phenotype was typical of severe GH deficiency and they were, respectively, 4.2 and 7.4 standard deviations below the mean stature for age and sex. They did not have a GH response to clonidine, insulin hypoglycaemia or acute or prolonged GHRH treatment. Both presented a very good response to recombinant human GH treatment. Their TSH and prolactin response to TRH were normal. This differs from what is observed in patients with an inheritable Pit-1 gene mutation who usually present, along with GH deficiency, a thyrotroph and lactotroph deficiency. The proband did not have a mutation in the GH gene. Wajnrajch et al. therefore screened for mutations in the extracellular domain of the GHRH receptor. A G → T transversion at position 265 was found in both patients, resulting in a non-sense mutation (Glu72Stop). This Glu72Stop mutation predicts a severely truncated GHRH-R, lacking any of the transmembrane domains or the G-protein binding site. The Glu72Stop mutation is close to the mutation observed in the little mice (Asp60Gly) and is located in a region highly conserved between species. However, the murine mutation causes a complete but dysfunctional receptor, resulting in the loss of function. The human nonsense mutation introduces a Bsil restriction site. The restriction pattern in the family members showed that both patients were homozygous for the mutation, and confirmed heterozygosity in the unaffected parents of the proband. It would be interesting to evaluate by magnetic resonance imaging the size of the pituitary of the patients harboring the GHRH-R mutation, because pituitary hypoplasia is observed in little mice. In this regard it should be noted that the little mice exhibit partial prolactin deficiency, whether the patients studied by Wajnrajch et al. have normal basal or stimulated prolactin levels. Further study of the phenotype of the patients homozygotes for the GHRH-R mutation and the determination of the prevalence of this mutation in patients presenting with