Multiple hormonal resistances: Diagnosis, evaluation and therapy

Résistances aux hormones dont les récepteurs sont couplés aux protéines G : diagnostic et traitement

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Abstract

Molecular alterations of cAMP-mediated signaling affect primarily the signaling of the PTH/PTHrp receptor, and, with different severities the signaling of other hormones, including TSH. The identification of PTH and other hormonal resistances implies to look for the genetic disorder supporting the metabolic disorder.

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Keywords: PTH resistance; Pseudohypoparathyroidism; Acrodysostosis; G-protein coupled receptor

Résumé

Les résistances multiples aux hormones dont les récepteurs sont couplés aux protéines G (RCPG) se manifestent essentiellement par une résistance à la parathormone (PTH). Les résistances aux autres hormones sont généralement moins sévères et incluent la résistance à la TSH et à la calcitonine. L’identification de ces résistances multiples implique de chercher un défaut moléculaire dans la voie de signalisation des RCPGs induisant la production d’AMPc comme second messager intracellulaire et la stimulation de la protéine G.

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Mots clés : Résistance à la PTH ; Pseudohypoparathyroidie ; Acrodysostose ; Récepteur couplé aux protéines G

Resistances to hormones that bind to 7-transmembrane domain receptors are the consequence of the lack of the downstream, cAMP-mediated signaling activated via the ligand receptor interaction. Molecular alterations of this pathway affect primarily the signaling of the PTH/PTHrp receptor (PTH1), and, with different severities, or at various times of development, the signaling of other hormones, including TSH, epinephrin and calcitonin, that signal through GPCRs and the same Gsa/cAMP/PKA pathway. This explains why multiple hormonal resistances have been described so far only as pseudohyoparathyroidism (PHP) or pseudopseudohypoparathyroidism (PPHP).

1. Resistance to PTH

It is defined by a low (or normal-low) serum calcium, elevated serum phosphate and elevated serum PTH in absence of vitamin D deficiency and renal disease. Absent at birth, PTH resistance gradually develops during the first months or years of life [1]. PTH and serum phosphate increase; if untreated, a decrease in calcemia appears. The cause of the serum calcium decrease is not completely elucidated as:

- measured levels of 1,25OH vitamin D are not dramatically low in patients (and mice) with PTH resistance [1,2];
• the tubular reabsorption of calcium in the distal tubule is usually maintained in patients.

In the renal proximal tubule, the defect in PTH signaling likely increases the tubular phosphate reabsorption. In certain circumstances, the diagnosis of PTH resistance may be a challenge as:

• in prolonged vitamin D deficiency (a situation formerly referred as PHP type 2) [3];
• when PTH levels are mildly elevated and serum calcium are in the low normal range;
• when the etiology of the PTH resistance is unclear.

In these cases, the kidney response to the exogenous infusion of PTH (formerly Ellsworth-Howard test, which has been replaced by the infusion of recombinant PTH1-34 [4]) may be used to document the impairment of the cAMP-signaling pathway in vivo. In healthy children, the urinary phosphate and cAMP over creatinine ratios rise within the first hour by a factor 2 to 3 and 10 to 40, respectively. An expected response to PTH of the distal tubule is a decrement of the urinary calcium excretion, a condition difficult to judge as patients with PTH resistance often present with low urinary calcium at baseline [3].

2. Other hormonal resistances

Resistance to TSH is characterized by an elevated TSH (typically between 5 and 50 mIU/L [N 0–5]), low-normal free T4 with no goiter and no antibodies [2,5]. The association with the PTH resistance will raise attention and exclude the usual diagnoses of TSH receptor mutations. Usually present at birth, the TSH resistance may be revealed through neonatal screening programs. Resistances to TRH and calcitonin without symptoms have been described in patients with PHP and defects in the cAMP signaling pathway [5,6]. From our experience, PTH, TSH and calcitonin resistance are associated in almost all types of PHP, although the severity of the resistances varies amongst the disorders.

Differently, the deficient endochondral bone formation that results from the PTHrp resistance also designed as Albright hereditary osteodystrophy (AHO) [7], the epinephrine, the gonadotrophin and the GHRH resistance occur only in specific molecular alterations [8–10].

3. Integration of clinical features, hormones and diseases

The identification of PTH resistance implies to look for the genetic disorder supporting the metabolic disorder. The identification of other hormonal resistances, and additional clinical features, will greatly orientate the search. The physician will however keep in mind that PHP encompasses now a wide spectrum of diseases with different causes and mechanisms (defects in genes involved in the Gsa/cAMP/PKA pathway), different prognoses, and different risks of recurrence. It requires an integrated view of the patient’s phenotype to deliver the most appropriate care and counsel.

The diagnosis of PHP type 1A (OMIM 103580) due to maternal heterozygous loss-of-function mutations of Gsa, the alpha-stimulatory subunit of the G protein is first suggested in patients with PTH resistance, multiple hormonal resistances including AHO, GHRH resistance and obesity. Besides PTH resistance, any of these features might be the first symptom referring the patient to the physician. Other molecular defects present as phenocopies of PHP1A, including broad methylation defects (see below) encompassing the GNAS locus (encoding Gsa) and mutations in PRKAR1A, encoding the regulatory subunit of PKA.

Patients with mild resistances to PTH and other hormones signaling through GPCRs, although presenting with a severe chondrodysplasia (acro dysostosis) are highly suspect of homozygous mutations of PRKAR1A (ACRDYS1, OMIM 101800).

The diagnosis of PHP type 1B (OMIM 603233) is usually more challenging because:

• the PTH resistance is often the unique symptom, under-recognized;
• the molecular defect is an epigenetic mechanism not affecting the DNA sequence therefore not appraised through classical sequencing strategies; in fact, all patients affected with PHP1B share the loss of methylation at the A/B promoter of GNAS, the hallmark of the disease.

It is then mandatory to explore the molecular mechanism of the loss of imprinting (copy number variation, uniparental disomy or epigenetic event).

4. Management of hormonal resistances

The objectives of the treatment of the PTH-resistance are to maintain calcemia within the low-normal range (2.0 to 2.5 mM), to prevent hypercalcuria and to prevent bone resorption due to elevated PTH. In children, the major treatment is 1-a-OH-vitamin-D (calcitriol or alfacalcidol) adjusted on growth velocity rather than weight (highest doses during infancy and puberty). Treatment with vitamin D analogs rarely leads to hypercalciuria. There is no specific recommendation for vitamin D therapy; however 25 OH vitamin D level within normal range may help disease management. Calcium supplements are recommended during the year following the diagnosis of PTH resistance. Only in patients with PHP1A, TSH resistance is usually treated by L-thyroxin to reach normal free T4. Except during pregnancy, patients with PHP1B do not require treatment for their TSH resistance. Encouraging preliminary results of an ongoing trial of growth hormone in patients with PHP1A and short stature have been presented at the 2014 Endocrine Society meeting.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


