70-kD protein. Intriguingly, 56% of sera derived from patients with AH, but none of the control sera, reacted with both the 60-kD and the 70-kD variants, but not with the 46-kD variant. In contrast, all three species were recognized by rabbit anti-human CaSR antibody. Moreover, autoantibodies reacting with CaSR were detected in 13/18 (72%) female patients, but only in 1/7 (14%) male patients. Thus, only portions of the extracellular domain of CaSR, both in its glycosylated and non-glycosylated form, may act as antigenic epitopes in patients with AH, and this reactivity reveals marked female preponderance (8).

Despite these intriguing observations, AH still harbors numerous mysteries. Detection of antibodies directed against the extracellular CaSR does not prove that this is the initial event and is the cause rather than a consequence of AH. Furthermore, what mechanisms may be at work in patients with AH in whom CaSR antibodies are not detected? Do these (predominantly male) patients present a unique pathogenetic entity? What role do T cells play in the pathogenesis of AH?

Various parathyroid disorders now appear to be associated with abnormalities in calcium-sensing mechanisms exerted by the parathyroid glands (6–8). Characterization of the structure–function relationship of the CaSR is likely to reveal more detailed insight into receptor–ligand interactions and signal transduction pathways in parathyroid cells. Moreover, exposure of autoimmune-prone animals to CaSR antigenic epitopes could provide an experimental model of AH for studying the natural course of the disease, and for the design of novel therapeutic strategies. Finally, development of CaSR immunoassays will provide clinicians with novel tools to establish the diagnosis of AH. With further secrets of the CaSR being unraveled step by step, parathyroidologists may soon have to revise their concepts of AH, and adjust their terminology.

References

Ectopic expression of the pituitary V3 vasopressin receptor reveals new aspects of the ectopic ACTH syndrome

Jérôme Bertherat
Service d’Endocrinologie and INSERM CJF 92-08, CHU Cochin, Paris, France

Specific pituitary vasopressin receptors involved in stress-induced ACTH secretion have been postulated for a long time. This hypothesis was recently confirmed by the cloning of a cDNA coding for a new subtype of vasopressin receptor, termed V3 or V1b (1, 2). This receptor belongs to the superfamily of seven transmembrane domain receptors coupled to G proteins. It is coupled to a Gq-like protein and activates phospholipase C. The pharmacological characteristics of the V3 receptor are different from the characteristics of the V1a and V2 receptors. In humans, this receptor seems mainly expressed in the pituitary corticotrophs.

Various neuroendocrine tumors expressing the proopiomelanocortin (POMC) gene, such as bronchial carcinoids, small cell carcinomas of the lung (SCCL), pheochromocytomas, pancreatic carcinoids, medullary thyroid cancer and others are known to secrete ectopic ACTH and induce Cushing’s syndrome. The bronchial carcinoids are usually highly differentiated and have a rather benign course. On the other hand, other types of ectopic ACTH-secreting tumors, like the SCCL, are poorly differentiated and are highly malignant. The mechanisms of ectopic POMC gene expression are not extensively known. Furthermore, the carcinoids tumors often have a particular clinical presentation and give rise to diagnostic pitfalls because they can mimic Cushing’s disease of a pituitary origin.
De Keyzer et al. (3) have studied in various human ACTH-secreting endocrine tumors the expression of the V3 vasopressin receptor, as a potential marker of the “corticotroph phenotype”. The V3 vasopressin receptor is expressed in almost all pituitary corticotroph adenomas as well as in normal human pituitary. By contrast, V3 vasopressin receptor expression in GH- and PRL-secreting pituitary adenomas is inconstant and very low. Interestingly, V3 vasopressin receptor expression was observed in six out of eight bronchial carcinoid ACTH-secreting tumors. Indeed, the level of V3 vasopressin receptor expression is similar in bronchial carcinoid tumors and in corticotroph adenomas. Nevertheless, this expression is restricted to ACTH-secreting tumors, because it was not observed in carcinoid tumors that did not express the POMC gene. Furthermore, V3 vasopressin receptor expression in other types of ectopic ACTH-secreting tumors (i.e. neuroendocrine tumors metastasis and pheochromocytomas) was much lower than in pituitary or bronchial carcinoids tumors expressing the POMC gene.

Therefore, the expression of the V3 vasopressin receptor seems to be a good marker of the corticotroph cells. It defines from a molecular point of view a new subgroup of ectopic ACTH-secreting tumors (i.e. the bronchial carcinoid tumors) that behave like pituitary tumors. It is tempting to speculate that the molecular mechanisms involved in POMC gene expression and V3 vasopressin receptor expression are the same in corticotroph pituitary adenomas and in bronchial carcinoid tumors. Furthermore, one would expect that different mechanisms trigger POMC gene expression in non-carcinoid ectopic ACTH-secreting tumors. Finally, it is worthwhile noting that the corticotropin-releasing hormone (CRH) receptor expression did not correlate with POMC gene expression in the neuroendocrine tumors studied. Indeed, expression of the CRH receptor gene was detected in most of the non ACTH-secreting tumors studied. This suggests that the V3 vasopressin receptor is more specific to “corticotroph phenotype” than CRH receptor.

The V3 vasopressin receptor expressed in bronchial carcinoid tumors seems to be functional. Northern blots and S1 nuclelease protection assays of V3 vasopressin receptor mRNA gave the same results in normal and adenomatous pituitary as in bronchial carcinoid tumors. Furthermore, retrospective analysis in two patients with ACTH-secreting bronchial carcinoid tumors expressing the V3 vasopressin receptor showed that in both cases in vivo administration of vasopressin had induced an ACTH and cortisol response. This last finding is likely to explain the difficulties for diagnosing the origin of ACTH secretion in patients with ACTH-secreting carcinoid tumors. Finally, the authors suggest that the presence of the V3 receptor in ACTH-secreting tumors will offer a new diagnostic tool and may offer new therapeutic approaches using specific V3 receptor ligands.

References

Jérôme Bertherat Service d’Endocrinologie and INSERM CJF 92-08, CHU Cochin, 27 rue du Faubourg-St Jacques, 75014, Paris, France