Studies on Parathyroid Hormone, Vitamin D and Pseudohypoparathyroidism : An Example of Trail from Basic Science to Clinical Practice

Pseudohypoparathyroidism is a pathological condition first described by F. Albright in 1942 as an example of Seabright-Bantam syndrome in man (1). Major features of this condition are 1) metabolic abnormalities consistent with hypoparathyroidism, namely hypocalcemia and hyperphosphatemia; 2) refractoriness to the action of parathyroid hormone (PTH) administered externally, and 3) unique developmental abnormalities, now termed as Albright's hereditary osteodystrophy. At that time, Seabright bantam, a species of chick, was considered to be resistant to the actions of hormone, androgen in this particular case, and Albright concluded that the central abnormality of patients with pseudohypoparathyroidism was resistance to the action of another hormone, parathyroid hormone. The ensuing 40 years have witnessed a remarkable expansion of the knowledge on mechanisms of hormone action and deepened the understanding of the pathogenesis of hormone resistance. If we limit our discussion to polypeptide hormones, many new hormones were discovered. Most of their structures and the structure - function relationships were elucidated. In the majority of the cases, their receptor proteins in plasma membrane were identified and their transmembrane signal transduction systems were being elucidated. In case of parathyroid hormone (PTH), the receptor is not completely defined yet. However, interaction between PTH and the receptor was shown to stimulate second messenger (cyclic AMP) production through a mechanism where a GTP binding protein, G_s , exerts a pivotal function in the signal transduction occurring in the membrane. In pseudohypoparathyroidism (type 1), PTH cannot produce the cyclic AMP response, and defect in the G_s protein was discovered at least in a subset of the patients with this disorder (2). Therefore it is widely believed that the principal defect in this condition is that of the G_s protein, and PTH cannot exert its effects because it is allegedly implied that all of the effects develop through cyclic AMP produced by the function of the G_s protein.

In an independent series of studies, M. Yamamoto and myself have conducted basic experiments on regulation of calcium metabolism, and found that calcemic action of PTH requires the collaboration of an active metabolite of vitamin D, $1,25(\text{OH})_2\text{D}_3$ (3). N. Horiuchi, T. Suda and myself also showed that the production of the active vitamin D is stimulated by PTH through a mechanism involving cyclic AMP (4). Then we entertained a hypothesis that, from a functional point of view at least, the defect in pseudohypoparathyroidism (type 1) resides only in proximal renal tubule where the PTH-sensitive production of active vitamin D takes place, and that the deficiency in calcemic action of PTH in pseudohypoparathyroidism is not the primary but the secondary event of the failure in production of the active vitamin D. Both of these premises were proved to be the case by careful clinical studies (5). With these conceptual considerations and the results from basic studies, we could now construct quite an easy and almost infallible method for the control of the abnormality of calcium metabolism in patients with pseudohypoparathyroidism; just replacing them with physiological doses of the active metabolite(s) of vitamin D. Thus, this is one of the examples where developments of basic science led through a trail with some detour to the establishment of a new and thus far unexpected therapeutic modality.

REFERENCES

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Etsuro OGATA

Professor of Medicine

The Fourth Department of Internal Medicine

University of Tokyo Faculty of Medicine, Tokyo