Hormonal replacement therapy has been very successful in the treatment of the major syndromes of endocrine insufficiency. However, endocrine substitution does not reproduce the normal plasma hormone profiles of healthy individuals. Moreover, the effects of hormones in general are difficult to quantify at the tissue level. Consequently, titration of endocrine replacement therapy is possible only with certain limits. Also, many patients treated for endocrine deficiencies still suffer from more or less vague complaints and a decreased quality of life. It is likely that these complaints are, at least in part, caused by intrinsic imperfections of hormone replacement strategies in mimicking normal hormone secretion. We do not have the tools to discover and follow-up on subtle physiological derangements, while we also do not have methods to objectively assess the clinical situation against the subjective complaints by the individual patient. Still, recognition of these intrinsic shortcomings of endocrine treatment is of great importance for appreciation of the complaints of some of these patients and to prevent incorrect labeling of these complaints [4].

There is increasing evidence that there are genetically determined differences in hormone secretion and hormone sensitivity. For instance, early studies into the relationships between serum TSH and free thyroxine concentrations have indicated that a certain reproducible, genetically determined individual set-point exists in normal persons at which the feedback control of the pituitary-thyroid axis is set [5]. In addition, glucocorticoid sensitivity, as measured by the dexamethasone-mediated suppression of early morning cortisol concentrations, is quite variable between, but highly reproducible within, individuals [3]. Interestingly, a number of frequently occurring polymorphisms in and around exon 2 of the glucocorticoid receptor gene are associated with an increased [2,9] or decreased [10] sensitivity to glucocorticoids. Presence of a high number of CAG repeats within the androgen receptor gene attenuates the effects of testosterone on bone density and bone metabolism [11], whereas a decreased number of CA repeats in the IGF-I gene is associated with a lower birth weight, lower body height and serum IGF-I concentrations at the lowest quartile of normal [6,7]. A polymorphism in the LH gene and the ensuing variant serum concentrations of LH reflect androgen bioactivity in elderly men in a different manner than in individuals with wild-type LH [8]. Oestrogen receptor polymorphisms considerably modify the effects of hormone replacement therapy on concentrations of high-density lipoprotein cholesterol and other outcomes related to oestrogen treatment in postmenopausal women [1].

These recently obtained new insights into the genetic variations (polymorphisms) of hormones and their receptors have provided important new insights into the individual set-points of activity of the hormonal axes involved, and into the mechanisms of the respective differences of hormone sensitivity at the level of the target tissues. The challenge of clinical endocrinology in the coming years will be to apply this knowledge to the treatment of individual patients in order to optimize the dose and frequency of hormone replacement.

References


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