COMMENTARY

Endocrinology: the next 60 years – the helix and the chip

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Abstract

In the 60 years since C H Li reported the isolation of bovine growth hormone (GH), endocrinologists have seen the widespread use of human GH for statural disorders, the measurement of plasma GH as a diagnostic test, the full development of the somatomedin hypothesis and the molecular details of the function of the GH receptor responsible for regulating somatic growth and metabolism.

In diabetes, we have passed from administration of animal insulin to formulations with different release rates, insulin pumps and inhalers, insulin sensitizers and a greater understanding of insulin signalling and insulin resistance through genetically engineered murine models. What might we expect over the next few decades?

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The next 60 years

We can expect comprehensive diagnosis of the causes of individual growth disorders, so that idiopathic short stature is no longer a diagnosis. Mass spectrograph analysis of individuals responding to GH therapy will provide a range of diagnostics to identify those likely to respond to GH therapy, whereas other growth disorders will be defined by genomics. All the signalling elements in the GH–insulin-like growth factor axis will be known, and mutations involving key transcription factors in this pathway, such as STAT5b (signal transducer and activator of transcription), will be identified by automated sequencing. The complete genome sequence for each individual will be attainable at birth, and the prognostic significance of variants in any of the 25 000 coding genes will have been assessed and will be used to assist in counselling and gene therapy, targeted individually. Minaturized analysers may be implanted to give instant radiofrequency monitoring of physiological status, initially in regard to blood glucose for diabetics (linked to an insulin pump), but later for blood chemistries using analyser chips. Automated analysis of biomarkers using such chips, combined with strides in high-resolution whole-body imaging (e.g. position emission tomography scans), will provide a complete and instantaneous record of body function. This, coupled with the individual's genomic sequence, will allow 'Dr Computer' to provide a reliable diagnosis of all forms of endocrine as well as malignant, infectious and inflammatory disease. In addition, physical measurements using miniature transducers with radiofrequency transmission could be used

to monitor, for example, micron changes at the growth plate, providing responses to growth promoting agents over periods of less than a week. These advances will permit a new era in evidence-based medicine.

We should have the three-dimensional structures of all hormone receptors (at least the ligand-binding domain), allowing for the design and synthesis of orally active small agonists and antagonists in combinations tailored for maximum individual effect. These will be supplemented with selective modulators of hormone action with tissue-specific footprints (selective estrogen receptor modulator (SERM) variants). Usage of these new pharmaceuticals will be controlled by the individual, based on readouts from the implanted microanalyzers. This will minimize hospital visits for most people. Patterned delivery of drugs will optimize responses. Individual responses to hormones and xenobiotics will be predicted based on the level of expression or genetic polymorphisms in aryl hydrocarbon or nuclear hormone receptors such as constitutive androstane receptor and pregnane X receptor.

We can expect beta-oxidation enhancing drugs to target individual fat depots or myogenesis-enhancing drugs to target muscles, for example, allowing the individual to sculpt body shape and minimize risk of type 2 diabetes. Metabolic diseases such as the current epidemic of obesity and dyslipidemia will no longer present a problem. There will also be new metabolic and other drugs based on as yet undiscovered hormones and paracrine agents. This can reasonably be predicted on the basis of the recent demonstration that adipose tissue is an endocrine organ, as are the gut, kidney and

cardiac muscle. Current searches of the human genome will facilitate such discoveries, while proteomics and nuclear magnetic resonance-based metabonomics (i.e. the study of quantitative metabolic responses to drugs and diseases) will lead to the identification of bioactive molecules that are not currently evident from genome sequences.

The current high level of funding for stem cell research will probably result in the ability to grow and replace damaged endocrine tissues such as the beta islets or individual pituitary secretory cell types, overcoming the need for hormone injections. This may apply to oocytes, and these may be held in stasis to allow conception into a woman's sixth decade. Alternatively, with appropriate hormonal regimes, it may be possible to conserve oocytes, prolonging the period of fertility for many years.

Aging will be a major feature of the future demographic and, based on the current progress in the genetics of longevity in mice and invertebrates, genes prolonging a healthy life (health span) will have been identified and utilized. These and other advances will be based on a (hopefully) complete understanding of signalling pathways and their crosstalk in regulating metabolic pathways and cell differentiation (systems biology). Treatments to extend the health span and lifespan may be by pharmacologic approaches, or by control of gene expression through targeting particular methylation sites in gene promoters, or relevant transcription factors through small interfering RNA, antisense or other technologies. In the near future, we can anticipate that hormone replacement therapy will be used to alleviate osteoporosis without side effect, through activation of estrogen receptor

co-activators or co-repressors. Health and lifespan will also be extended by public education, reducing the incidence of smoking and obesity, and hopefully increasing the exercise level or a surrogate for this. We will learn more about the elements of the endocrine-immune-brain axis in the regulation of stress, and find better pharmacologic or other means of dealing with this health problem.

A comprehensive understanding of the developmental process and the role of hormones and hormone-like substances in development will result in benefits not only for humans (e.g. in the consequences of the Barker hypothesis), but also for the manipulation of the growth and development of farm animals for human consumption. Intensively housed animals such as chickens and pigs may be able to free-range if suitably genetically engineered to have optimum feed conversion efficiency and growth, for example.

In relation to our rapidly changing environment, we will understand more about endocrine disruptors, and be able to control or abolish their effects, not only for humans, but also for wild species. In this regard, improved understanding of reproductive biology in other species will facilitate the breeding of endangered species.

It will be a very different world, this brave new world of the double helix and the silicon chip; but not, one hopes, the world of GATTAGA. Conversely, one hopes that with global warming we will not need to grow gills and rely on prolactin!

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