understanding of possible biological pathways to endocrine neoplasia. The hope is that this understanding may guide medical anti-tumour therapy, although the first trials of imatinib (a tyrosine kinase inhibitor, including anti-RET) in medullary thyroid carcinoma with RET activating mutations are disappointing. Another problem is how best and cost-effectively to test the many patients with familial endocrine neoplasia syndromes for tumours. Patients will need annual scans of several body parts. This represents a substantial lifetime radiation exposure if computed tomography is used. Magnetic resonance imaging is still slow, and the hope is that new magnetic imaging modalities will speed up scans without reducing diagnostic sensitivity and specificity. The finding that paragangliomas in patients with succinate dehydrogenase B subunit mutation are best identified by fluorodeoxyglucose positron emission tomography will help with the problem of imaging.[11] Such avidity for a glucose analogue potentially fits with the biology of the mutation, whereby a cellular defect in the flow sheet of Kreb's cycle respiration may lead to increased demands for glucose by alternative pathways.

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Giant leaps forward

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Introduction

A review of developments in the management of pituitary disease in the last 30 years reveals the contrasting pace of advances in treatment options between acromegaly and Cushing's disease. Both diseases have benefited from refinements in surgery and radiotherapy. The opening up of the transsphenoidal route to the fossa, the operating microscope, and more recently the endoscope, have greatly improved the results of surgery which still remains the first line of treatment. Multi-fractional, three field radiotherapy has been available for 40 years, but the accuracy afforded by computed tomography (CT) planning, and more lately superseded by magnetic resonance imaging (MRI), has reduced morbidity, while in the last decade the Gamma Knife and other forms of stereotactic radiotherapy have provided advances.

Drug treatment

The contrast in progress becomes apparent when one considers the new pharmacological agents available for acromegaly, while Cushing's syndrome is still likely to be treated with the same drugs as a generation ago, namely metyrapone, mitotane and ketoconazole. The transformation in the treatment of acromegaly can be credited to a combination of fortuitous observations and scientific endeavour. Underpinning the therapeutic advances was the 'somatomedin hypothesis' of Daughaday which postulated that the actions of growth hormone (GH) were mediated through a downstream factor initially known as somatomedin-C and latterly renamed insulin-like growth factor-1 (IGF-I), which, along with GH, can be used as a measure of disease activity.

Dopamine agonists

Prior to the introduction of bromocriptine, the first dopamine agonist, in the early 1970s, the only available medical option was oestrogen therapy which, as early as the 1930s, was shown to improve the well-being and glucose tolerance of patients with acromegaly. The paradox of the dopamine agonists is that they induce a pulse of GH secretion in normal individuals but inhibit secretion in patients with acromegaly. The recognition of the potential for treating acromegaly came from the observation of disease regression in a patient initiated on bromocriptine for Parkinson's disease. Cabergoline has become the dopamine agonist of choice because of the combination of greater efficacy and reduced side effects.

Dopamine agonists have the virtues of being orally administered, relatively inexpensive and particularly effective in GH prolactin co-secreting tumours. However, in most patients the degree of disease-control achieved is suboptimal and other pharmaceutical agents are required.

Somatostatin analogues

The somatostatin analogues are the 'gold standard' against which other agents must be judged and are a fortuitous spin-off of the search for the hypothalamic peptide responsible for stimulating pituitary GH secretion. Attempts to isolate GH releasing hormone (GHRH) from hypothalamic extracts resulted in the identification of a peptide that inhibited GH release from pituitary somatotrophs. Native somatostatin exists in two forms, SMS-14 and an amino-terminal extended SMS-28, both peptides being encoded by a common prepro-somatostatin gene located on chromosome 3q28. The various actions of somatostatin are mediated through specific cell-surface receptors expressed in the central nervous system, leptomeninges, anterior pituitary, mucosa of the gastrointestinal tract, and both the endocrine and exocrine pancreas. Five human subtypes of the somatostatin receptor have been cloned, all of which possess seven membrane-spanning domains and are functionally linked to adenylate cyclase through coupling mechanisms involving guanine nucleotide-binding (G) protein. Octreotide, a synthetic octapeptide, was the first analogue introduced into clinical practice and is 45 times more effective than native somatostatin at inhibiting GH secretion. Unlike native somatostatin, which binds with equal affinity to all five somatostatin-receptor (SSTR) subtypes, octreotide has a much longer half-life (3 min v >70 minutes) and binds with high affinity to SSTR-2 and -5, with moderate affinity for SSTR-3, but does not bind to SSTR-1 and -4. Lanreotide is the other currently available somatostatin analogue with a new generation of analogues in clinical development. The acute suppression of GH secretion in response to octreotide administration in patients with acromegaly is dependent on SSTR availability, which in turn predicts the long-term effect of octreotide therapy on serum GH and IGF-I concentrations in most patients. Somatostatin analogues suppress serum GH, with serum IGF-I normalisation in approximately 50–60% of patients and can induce significant tumour shrinkage. The inconvenience of thrice daily administration, has led to the development of long-acting intramuscular depot preparations administered monthly.

Other approaches

The glucocorticoid (and progesterone) receptor antagonist mifepristone would be an attractive treatment option for Cushing's were it not for the problem of monitoring disease activity. Mifepristone blocks cortisol action rather than lowering circulating cortisol levels, and in the absence of a downstream marker of cortisol action, the risk is that overtreatment and consequent hypoadrenalism would go undetected. The difficulty of measuring disease activity in patients receiving mifepristone has hindered its use. In contrast, circulating IGF-I, which is predominantly hepatic in origin, provides a means of measuring GH action and disease activity which, along with a serendipitous observation, led to the development of a GH receptor (GHR) antagonist. GH is a 22 kD, 191 amino acid protein with a complex tertiary structure that binds to a ubiquitously expressed cell surface receptor, a member of the cytokine receptor family. The growth promoting action of GH resides in the third of its four alpha helices and John Kopchick, in a series of experiments, substituted various amino acids in the third alpha helix with the intention of producing a GH analogue with increased biological activity. Disappointingly, all the analogues generated had the same affinity for the GH receptor as wild-type GH. It therefore came as a surprise that when expressed in transgenic mice, the analogues containing a substitution of the glycine at position 119 with arginine (equivalent to aa 120 in man) had decreased circulating IGF-I concentrations and a dwarf phenotype. The explanation for the apparent unaltered receptor binding but reduced bioactivity came only with the subsequent recognition that the GHR exists as a preformed dimer. In retrospect, it was recognised that the GH analogues bound with normal affinity to the first GHR but that the substitutions at position 120 impair the interaction with the second GHR and fail to induce the configurational change in the GHR necessary to trigger activation and the subsequent intracellular cascade. The half-life of the GH antagonist was increased from approximately 15 minutes to in excess of 70 hours by conjugation to leucine residues of polyethylene glycol moieties which increased the molecular weight from 22 to approximately 45 kD. Pegvisomant is a potent GHR antagonist that with adequate dose titration blocks GH action (due to feedback circulating levels actually rise) and lowers IGF-I levels to normal and relieves symptoms in virtually every patient with acromegaly.

Future challenges

There remain many challenges in the management of acromegaly. Firstly, the high cost of some of the treatment options, particularly pegvisomant, is prohibitive which means many NHS patients are not able to access all modalities. Finally, the phenomenal improvement in treatment choices makes it all the more frustrating that there has been no perceivable reduction in the delay of nearly a decade between the onset of symptoms and confirmation of the diagnosis with the result that, however good the treatment, some of the damage done is irreversible.