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Review

Treatment of persistent and recurrent acromegaly

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ABSTRACT

Acromegaly is a chronic insidious disease characterised by growth hormone (GH) hypersecretion, typically from a pituitary adenoma. Effective treatment of acromegaly is vital because it is associated with a mortality rate more than twice that of the general population, an increased prevalence of colonic malignancy and many significant co-morbidities. Transsphenoidal adenoma resection is still the best first-line treatment for acromegaly but persistence (43%) or recurrence (2% to 3%) of GH hypersecretion after surgery remains a problem. Treatment options for acromegaly after failed initial therapy or recurrence include further surgery, radiotherapy, radiosurgery or medical therapies, including somatostatin analogues, dopamine agonists and growth hormone receptor antagonists. There has been a progressive lowering of the accepted GH level defining cure in acromegaly. This article reviews the efficacy and safety of the various treatment options for persistent or recurrent acromegaly and the changing definition of cure.

1. Introduction

Acromegaly is characterised by hypersecretion of growth hormone (GH), almost always from a pituitary adenoma.[1] Transsphenoidal adenoma resection is still considered the best first-line treatment in acromegaly, but persistence or recurrence after surgery remains a problem.[1,2] Treatment options for acromegaly after failed initial therapy or recurrence include further surgery, radiotherapy or medical therapies. There have been numerous refinements to the definition of "cure" of acromegaly, with a progressive lowering of the accepted GH concentration over time. This article reviews the efficacy and safety of the various treatment options for persistent or recurrent acromegaly and the changing definition of cure.

With a prevalence of 5 to 6 cases per 100,000 population and an incidence of 3 to 4 cases per million, acromegaly is an uncommon disorder.[3] However, with a mortality rate more than twice that of the general population, prompt and effective treatment of acromegaly is vital. This increased mortality rate is predominantly due to cardiovascular co-morbidities such as hypertension, hypertriglyceridaemia, atherosclerosis, hypertrophic cardiomyopathy and valve disorders. Acromegaly is also associated with co-morbidities that affect quality of life such as severe arthropathy and sleep apnoea.[1,4,5] An increased risk of colonic cancer from hyperplastic polyp formation has been reported since the mid-1990s in acromegaly,[6–8] with a mortality ratio of 2.47 (confidence interval [CI] 1.31–4.22).[9]

2. Biochemistry

The main role of GH is to mediate anabolic growth by increasing the synthesis of insulin-like growth factor 1 (IGF-1), which in turn stimulates somatic growth of bone, cartilage and skeletal muscle.[2,10–12] At a cellular level, GH exerts its effects by binding to two growth hormone receptors (GHR). Phosphorylation of the intracellular domain of the GHR by tyrosine kinases then results in the creation of docking sites for a variety of cell signaling proteins (Fig. 1).[13,14] These proteins ultimately lead to transcription of target genes such as IGF-1 as well as the activation of many cellular mechanisms that affect growth (Fig. 1).[13,14] Under normal conditions GH release is regulated by the hypothalamus through GH-releasing hormone (resulting in GH secretion) and somatostatin (resulting in decreased GH release). Ghrelin, a hormone released from the stomach, also stimulates GH secretion.[2] Although GH has some direct effects such as lipolysis of fat cells, amino acid transport into muscle and bone-mineral accretion to increase bone mass, most of its major anabolic actions are mediated by IGF-1.[2]

3. Clinical features of acromegaly

Acromegaly has a slow and insidious onset that often delays diagnosis and most tumors in acromegalics are macroadenomas (>1 cm diameter) at the time of diagnosis.[2,3] The common clinical

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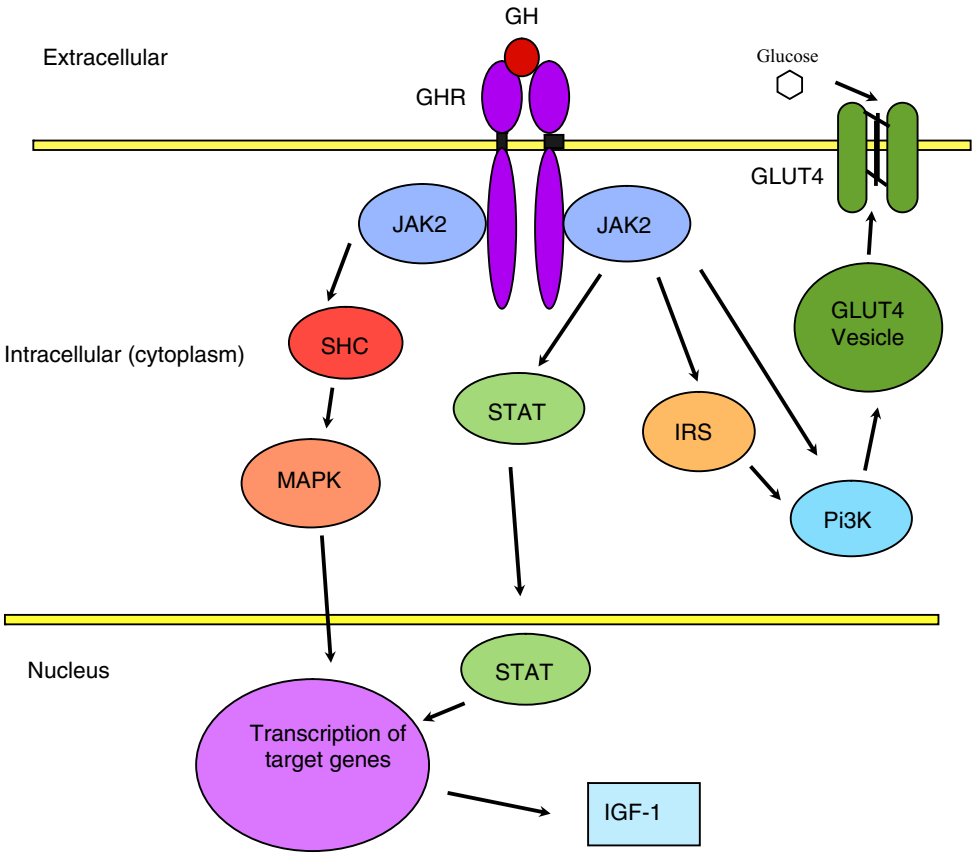

Fig. 1. Schematic showing cellular mechanisms of growth hormone (GH) action. When GH binds to two transmembrane GH receptors (GHR) it causes receptor dimerization. The GHR are then phosphorylated by tyrosine kinases such as janus kinase 2 (JAK2). Tyrosine residues on the GHR and JAK2 then provide docking sites for a variety of cell signaling proteins. For example, the signal transducer and activator of transcription (STAT) protein, which, when activated, translocates into the nucleus leading to transcription of target genes such as insulin-like growth factor-1 (IGF-1). Activation of the Src homology 2a collagen-related (SHC) protein also leads to transcription of target genes via the signaling protein mitogen-activated protein kinase (MAPK). Activation of insulin receptor substrate-1 (IRS1) and phosphoinositide 3-kinase (Pi3 K) by JAK2 causes translocation of glucose transporter protein-4 (GLUT4) from the intracellular cytoplasm to the cell surface resulting in increased glucose uptake.[14]

features of acromegaly such as acral enlargement, coarse facial features and arthropathy result from unregulated anabolic growth, although the headache frequently associated with acromegaly may be due to mass effect of the tumour on local structures or changes in the bony skull vault.[5]

Other co-morbidities that affect quality of life include: type 2 diabetes, obstructive sleep apnoea, reduced fertility and carpal tunnel syndrome.[2] Adequate control of serum GH and IGF-1 levels in acromegaly not only diminishes symptoms but also reverses sleep apnoea,[6,15] hypertrophic cardiomyopathy[4] and glucose intolerance as well as restoring normal life expectancy.[1,16,17] Accordingly, when acromegaly persists after initial treatment, so do the patients' chances of co-morbidities, and when acromegaly recurs it is often heralded by a recurrence of symptoms after their initial improvement.

4. The changing definition of cure in acromegaly

The definition of cure in acromegaly is biochemical, although alleviation of symptoms may occur without complete biochemical cure. The serum GH level used to define cure has become progressively lower over time.[2] In older series, patients were deemed cured of acromegaly with postoperative basal serum GH levels of up to 10 μg/L or even 20 μg/L in some series.[18–20] Later, the level was lowered, somewhat arbitrarily, to less than 5 μg/L. Currently normalisation of basal GH is defined at below 2.5 μg/L. This is based on compelling evidence that control of GH below 2.5 μg/L leads to a lowering of the mortality rate in acromegaly. Bates et al. reported that patients with GH levels 2.5 μg/L to 5 μg/L had mortality rates double that of age matched controls while those with GH levels less than 2.5 μg/L were not at increased risk.[21] Additionally there is evidence to suggest that IGF-1 levels do not fall into the normal range until GH levels are less than 2.5 μg/L.

More recently, IGF-1 has emerged as an important marker in reflecting disease severity in acromegaly. IGF-1, a hormone with a molecular structure similar to that of insulin, is produced by the liver and other target tissues in response to GH and works by binding to both IGF-1 and insulin receptors.[2] IGF-1 acts on nearly every cell in the body to stimulate growth especially in muscle, bone and cartilage, but also in liver, nerves, skin, lungs and kidneys.[2] Serum IGF-1 levels are an excellent diagnostic marker in acromegaly, as there is little if any overlap between IGF-1 levels in patients with established acromegaly and those of normal adult controls.[22] Therefore, the diagnosis of acromegaly can be excluded if IGF-1 levels are within normal range.[10] Teenage patients are the exception to this rule, as they have high IGF-1 levels during growth spurts. Normalization of IGF-1 levels significantly lowers the risk of morbidity and mortality in acromegaly and several studies have shown that IGF-1 is a more sensitive indicator of persistent disease activity in acromegaly than GH.[17,23–25] Therefore, normalisation of serum IGF-1 level has become part of the criteria for defining cure in acromegaly.

GH suppression after administration of oral glucose is also used to define residual disease activity in acromegaly. Under normal conditions GH secretion is notably suppressed by caloric intake,