CMLS, Cell. Mol. Life Sci. 54 (1998) 1102–1108
1420-682X/98/101102-07 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

Prolactin, growth hormone and the immune system in humans

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Abstract. Prolactin (PRL) and growth hormone (GH) qualify as lymphoid growth and differentiation factors. Yet, long-standing hyper- or hyposecretion of PRL or GH does not induce any significant alteration of the immune system. Subclinical changes in laboratory parameters (such as chemotaxis or phagocytosis by granulocytes or macrophages or natural killer cell activity) have been reported in some of these conditions. The GH-insulin-like growth factor (IGF)-I axis is dysregulated in ageing, in catabolic states and in critical illness. Immune parameters, such as infection rate, are being monitored during clinical trials with GH or IGF-I. Hyperprolactinaemia may play an aggravating role in systemic lupus erythematosus, in autoimmune thyroiditis and in other autoimmune diseases. The patient may benefit from increased alertness about interactions between the endocrine and immune systems.

Key words. Prolactin; growth hormone; insulin-like growth factor; AIDS; ageing; pituitary adenoma; acromegaly.

Introduction

Immune deficiencies have been demonstrated in hypophysectomized rodents and in dwarf mice (reviewed in refs 1–4). No such defects are seen in children with isolated growth hormone (GH) or even with multiple hormone deficiencies.

In humans, as in rodents, many leukocyte subsets express GH and prolactin (PRL) and receptors for these factors. Many effects of GH are mediated by the insulin-like growth factor (IGF)-I. Some leukocytes also express IGF-I or receptors for IGF-I [1–5]. Recently, effects of PRL, GH and IGF-I were demonstrated in the human immune system. The present review concentrates on clinical conditions with abnormal secretion or impaired responses to GH or PRL. We will address GH deficiencies in children and adults, GH resistance [GH receptor (GH-R) mutations or acquired resistance], and GH- or PRL-producing pituitary tumours. During ageing, the GH-IGF-I axis is impaired, and during catabolic states there is GH resistance, with normal or high GH and low IGF-I. Claims that these hormone defects relate to anergy and other immunological problems will be examined, with particular concern for possible substitution therapy. Finally, as several autoimmune diseases are more frequent in women, the possible involvement of PRL in the development and progression of specific diseases will be discussed. A separate paper deals with the role of PRL, GH and IGF-I in leukaemia and lymphoma (see paper by R. Hooghe et al. in the present issue).

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GH-deficient children

The clinical heterogeneity of growth failure in children reflects differences in molecular defects in the GH-IGF-I axis [6–9]. Careful interpretation of data on immune dysregulation necessitates a clear-cut definition of the underlying growth abnormality and the degree of GH

and IGF-I deficiency. Groups of GH-deficient children have been compared with age-matched controls with normal or short stature without GH deficiency. Important information was also derived from measurements made during GH therapy (see below). GH-deficient children do have subclinical alterations in their immune system, but laboratory data could never be clearly related to overt immunological problems, such as frequent infections, allergy or autoimmunity in these children.

Peripheral blood mononuclear cells (10^6 cells in 1 ml) from dwarf children with complete or partial GH deficiency produced significantly less interleukin (IL)-1α in vitro than cells from children with normal stature (9.5 ± 4.6 vs. 41.6 ± 3.0 fmol/ml, respectively). Normal values were reached after 2 weeks and were still normal after 3 months of treatment with recombinant human GH. This is in contrast to IL-2 production, which was also reduced (31.5 ± 4.8 vs. 57.3 ± 1.0 fmol/ml) but returned to normal only after 3 months of treatment. The situation is rather complex, as children with partial GH deficiency or constitutional short stature without GH deficiency produce intermediate amounts of IL-1α (20–30 fmol/ml) and IL-2 levels similar to those seen in total GH deficiency. Nevertheless, before the start of GH therapy, there was a good correlation between IGF-I serum levels and IL-1α production [10].

Haematological values, including lymphocyte subpopulations, were not significantly changed in children with short stature, with or without GH deficiency. Natural killer (NK) activity, however, was repeatedly found to be lower in children with GH deficiency than in children without GH deficiency (with either normal or short stature). NK activity was significantly increased after 3 months of treatment with recombinant human GH and reached normal levels after 6 or 9 months of treatment. A 24-h incubation of cells from GH-deficient or control children in the presence of either GH (0.25–50 μg/ml) or IGF-I (50–600 ng/ml) had no effect on NK activity [11–13].

Phagocytic function, mediated by both polymorphonuclear neutrophils and monocytes, was also significantly impaired in GH-deficient subjects compared with control children with short stature but no GH deficiency. A significant increase was seen in phagocytic activity of both neutrophils and monocytes during long-term replacement therapy with recombinant human GH [14].

GH-deficient children with X-linked agammaglobulinaemia (XLA)

Males from a small number of families suffer from isolated GH deficiency and humoral immunodeficiency. This very rare association may be due to different genetic defects. In most cases (Bruton's XLA), XLA results from a mutation in the *btk* gene, which codes for Bruton's agammaglobulinaemia tyrosine kinase. This defect has been documented in several families with GH deficiency and XLA. However, the *btk* gene and protein are normal in other boys with agammaglobulinaemia and GH deficiency. Clinically, these subjects have normal-size tonsils in contrast to Bruton's XLA (where tonsils fail to develop), and the GH deficiency is more severe [15, 16].

GH-IGF-I-deficient adults

Acquired chronic GH deficiency is most often related to large pituitary tumours. The GH-IGF-I axis is also impaired in ageing (see below). Adult patients with GH deficiency have increased abdominal adiposity and cardiovascular risk factors, leading to premature mortality, reduced basal metabolic rate, reduced strength and exercise capacity, reduced bone density, impaired quality of life and well-being and subnormal kidney function (reviewed in ref. 17).

In a group of 22 adults with GH deficiency resulting in most cases from irradiation or compression by large pituitary tumours (thus leading to multiple hormone defects), cell counts and percentage of lymphocyte populations were normal, except for a 50% reduction in $CD3^-CD56^+$ NK cells [18]. GH deficiency in young women was associated with reduced NK activity, which increased during short-term GH therapy [19]. The decreased NK cell activity in GH-deficient patients may be caused at least in part by low serum IFG-I as IGF-I modulates NK cell activity [20].

Immunological findings in GH-treated patients

Immunological findings in GH-treated patients have been reviewed by Rappaport [21] and by the group of Wit [11, 22]. Very few significant findings emerge from these studies covering, together, large numbers of patients over many years. The following conclusions can, however, be drawn:

1) Most laboratory values were normal before and remained so during treatment with human GH.

2) Short-term GH administration did not restore NK cell activity, but long-term treatment did.

3) During GH treatment, some patients had significantly decreased levels of circulating B cells [23]. Defects in B cell differentiation were also reported in acromegaly [24].

Children with GH insensitivity

Severe growth retardation with low IGF-I and IGF-binding protein-3 and high levels of basal and stimu-

lated GH is seen in liver disease and malnutrition. In a rare genetic disease (Laron syndrome), the GH-R is deficient as a result of a recessive mutation present in both parents [25, 26]. (A dominant form has also recently been reported [27]). The two main cohorts of patients with Laron syndrome live in Israel and in Ecuador. The Israeli patients have no haematological or immunological problems. They respond normally to vaccination (Z. Laron, personal communication). Mortality before the age of 7 in the Ecuadorian cohort is high: 19% in homozygous affected children (−/−), 11% in their unaffected siblings (+/− or +/+). Mortality was due to 'the usual childhood problems in the area (pneumonia, diarrhoea, meningitis)'. Although the Ecuadorian data suggest the genetic defect contributes to early death, Israeli data indicate that with optimal care there is no increase in mortality. Further information from Ecuador would be very important in evaluating the possible contribution of GH to immune function. In particular, data from control children in the same area would establish whether heterozygotes have increased mortality compared with children with two normal alleles. Causes of death and in particular respective contributions from metabolic and infectious causes should be reported.

The effect of IGF-I on the functional capacity of neutrophils was studied in two children with Laron syndrome and in controls. Before treatment with recombinant human IGF, neutrophils from the patients bound more antibody to the IGF-I-R than neutrophils from the controls. After 1 and 4 months of treatment, there was no significant difference between patients and controls. In untreated patients, phagocytic capacity and oxidative burst in response to formylmethionylphenylalanine were not different from controls, and remained stable during treatment. Priming with IGF-I (32.5 nM for 3 h), however, had stronger effects on both phagocytosis and oxidative burst in untreated patients than in treated patients or controls [28]. Taken together, these data show no major defect in the functional capacity of neutrophils from patients with Laron syndrome.

Acromegaly

GH-secreting adenomas lead to elevated levels of GH and IGF-I. The untreated disease carries a high morbidity and mortality, due to a higher incidence of cardiovascular disease and cancer [29]. However, in most patients haematological and immunological parameters remain within normal limits. In a small series, T lymphocytes from patients with acromegaly expressed more transferrin receptors (CD71) than T cells from controls, indicating a higher level of T cell activation. However, expression of other activation markers was not different. Also phagocytic activity of granulocytes was significantly higher in patients with acromegaly than in controls. In contrast, chemotaxis of neutrophils towards *N*-formylmethionylphenylalanine was significantly reduced in acromegaly. Spontaneous migration was also reduced [30, 31]. Although none of these changes led to abnormal defence against infectious diseases or autoimmunity, it has been suggested that the increase in cancer incidence was due to reduced immunosurveillance. Alternatively, high local production of IGF-I may also promote tumour growth.

Prolactinoma

PRL-secreting adenoma is common in young women and leads to isolated hyperprolactinaemia. Haematological parameters are normal, but some immune responses are altered. Prolactinoma has also been linked with autoimmune disease. Several authors have studied NK function in hyperprolactinaemic patients [30–35]. In some studies the numbers of large granular lymphocytes and of $CD56^+$ cells are reduced in women with puerperal hyperprolactinaemia or with prolactinoma [31, 32] compared with normal controls. The reduction of NK activity was not seen if adherent cells had been removed [33]. Treatment with bromocriptine not only corrected NK function but even made it more efficient [36]. The latter data are not easy to interpret in view of the known direct effects of bromocriptine on lymphocytes, independent of its action on PRL secretion [37]. Chemotaxis of neutrophils towards *N*-formylmethionyl-phenylalanine was significantly reduced in prolactinoma. Spontaneous migration was also reduced [31].

Ageing

With advancing age, an increasing proportion of men and women with no evidence of pituitary pathology show decline in GH secretion and serum levels of IGF-I, and in old animals and people, immune responses are reduced. The reason for this is poorly understood. In rodents, treatment with GH maintains thymus structure and function [38]. So far, there are no comparable studies in humans analysing the effects of GH therapy in elderly people based on immunological parameters. Treatment of aged female monkeys with GH, IGF-I or a combination for 7 weeks had clear-cut effects on the histology and cellular composition of lymph nodes, spleen and blood as well as responses to antigens and mitogens [39]. The observed changes were indicative of stimulation of the lymphoid compartment. Whether this

would have beneficial clinical relevance is at present not clear. These studies are important as they clearly show effects of GH and IGF-I in normal (albeit ageing) primates.

HIV infection

Immunodeficiency following infection with the human immunodeficiency virus (HIV) can lead to subsequent alterations in metabolism as a result of chronic infections. Clinical manifestations of these abnormalities are growth failure in children, which is one of the most sensitive indicators of disease progression, and a wasting syndrome in adults and children. Although there are case reports of GH deficiency in HIV-infected children, in asymptomatic HIV infection and acquired immunodeficiency syndrome (AIDS), the GH-IGF-I axis is normal [40]. In severely ill AIDS patients with wasting and anorexia, there are two reasons to consider therapy with GH or IGF-I. First, as discussed below, these hormones reverse the catabolic state. Second, GH and IGF-I could act as lymphohaematopoietic growth factors and correct some aspects of the blood picture related to the disease or to the treatment. Very recently, it was demonstrated that purified T cells from HIV-infected patients in different stages of the disease had a selective reduction in signal transducer and activator of transcription (STAT)5 [41]. GH and PRL are among the factors that signal through STAT5 (see paper by Yu-Lee et al. in the present issue) and it is therefore logical to consider that they may have therapeutic value. In vivo studies in rodents [severe combined immunodeficiency (SCID) mice and azathioprine-treated mice] were promising, as GH increased the number of granulocyte-macrophage colony forming units in SCID mice and largely prevented the haematological toxicity of azathioprine [42]. In vitro, both GH and IGF-I increased HIV replication in infected T cells, but this was not the case in the presence of azathioprine [43]. Therefore, any strategy that contemplates the administration of GH or IGF-I to HIV-infected patients must include the simultaneous use of inhibitors of HIV replication. In severe cases of AIDS, GH therapy transiently restored anabolism [44, 45]. The most promising clinical trials show positive changes in nitrogen balance and transient improvements in lean body mass with concomitant decrease in fat mass. The improvements observed in body composition are consistent with reported effects of GH in GH-deficient patients. Pharmacological doses of GH therapy seem to be maximal in most studies at 6 weeks following initiation of therapy. These changes increased strength and endurance, improving functional capacity. However, no significant changes were observed in CD4 cell counts. There was no protection against opportunistic infections and one patient (out of seven) became positive for the HIV antigen p24 [45]. In HIV-infected children with growth failure, both recombinant GH and IGF-I improved growth rate and lean body mass [46]. The therapeutic effect of GH and IGF-I in HIV-infected patients derives from anabolic effects. The possibility of contribution to immune reconstitution still remains to be demonstrated.

Acute-phase response, shock, stress

GH and PRL have been described as stress hormones. Indeed, in several animal model systems and in human volunteers infected with endotoxin or undergoing surgery a rise in GH and PRL levels has been observed [47–50]. The increase in GH and PRL secretion was considered an adaptive process in the regulation of inflammation as symptoms were worse when the rise in GH was prevented [51–53].

Catabolic states and critical illness

In critical illness and catabolic states, both endocrine and immune systems are dysregulated [54, 55]. GH levels are often normal, but as a result of resistance IGF-I levels remain low. Clinical trials with GH have resulted in transient anabolism without improvement of the final outcome [56, 57]. After major surgery or in patients with, for example, burns, the effect of IGF-I therapy is also being evaluated. Only after the results of larger trials are available will it be possible to look for correlations between hormone treatment and immunological parameters (such as anergy, infection rate). The role of PRL may become apparent from clinical reports on the use of dopamine in critical care [58]. Dopamine agonists suppress pituitary secretion of PRL. It must, however, be noted that dopamine has direct effects on lymphocytes, unrelated to PRL [37].

Autoimmunity

Autoimmune diseases result from quantitative or qualitative abnormalities in self-reactivity [59]. The incidence of several autoimmune diseases is higher in women. Therefore, a role for sex hormones in the pathogenesis of these diseases has been advocated [60]. PRL has not received the same amount of attention as oestrogens and it is not always sufficiently realized that oestrogens and PRL are members of the same network. Indeed, oestrogens are major inducers of PRL secretion, and PRL in turn modulates the expression of enzymes involved in the metabolism of steroid hormones and reduces gonadotrophin secretion, which contributes to the feedback resulting in reduced oestrogen secretion.

Much effort has been devoted to defining the possible participation of PRL in the development of diabetes, arthritis and lupus-like conditions in rodents. Women are much more prone to develop autoimmune diseases than men, but the particular hormones responsible have not been clearly identified. In particular, there is circumstantial evidence for a role of PRL in only a few conditions. Despite this lack of information, patients with uveitis or multiple sclerosis have been treated with bromocriptine with the hope that a reduction in serum PRL levels would improve their symptoms. As far as we know, results were disappointing.

Systemic lupus erythematosus (SLE)

In SLE, high levels of serum autoantibodies relate to multiorgan inflammation and injury. Lupus erythematosus is more frequent in women of child-bearing age, and flares are common during pregnancy [61]. Moderately elevated PRL levels have repeatedly been found in patients [62–64]. Recently, four cases of lupus associated with very high levels of PRL have been reported. In three of these cases, lupus developed after a prolonged period of hyperprolactinaemia, and two patients suffered from lupus exacerbations after withdrawal of bromocriptine (which results in the rise of serum PRL levels) [65].

The data suggest that sustained hyperprolactinaemia plays a deleterious role in both development and progression of the disease. In the primary antiphospholipid syndrome, an autoimmune disease that shares several features with SLE, the hormonal context is also compatible with a precipitating or aggravating role for PRL, as disease occurrence is often related to pregnancy or the puerperium [66].

Rheumatoid arthritis (RA)

RA is a chronic, recurrent, systemic inflammatory disease primarily affecting the joints. Three quarters of the cases occur in women. Evidence supporting the involvement of hormones in the pathogenesis or the progression of RA is weak, although this condition has been investigated extensively [67]. GH levels were within normal limits, but circadian fluctuations were not normal, and the total amount of GH secreted daily in young patients could be reduced. IGF-I levels were low [68]. Growth retardation is indeed a frequent problem in such patients. Girls with the juvenile form of RA and a positive antinuclear antibody (ANA) test had significantly higher PRL levels than girls with RA and a negative ANA test than age-matched controls [69].

Thyroiditis

High titres of antithyroid antibodies and autoimmune thyroid disorders occur in hyperprolactinaemic women far more frequently than in the general population [70]. In a group of 82 women with hyperprolactinaemia (idiopathic in half of these cases), 20% had antithyroglobulin antibodies, and 12% had antibodies against microsomes. Most patients were euthyroid, and a variety of diseases accounted for the cases of hypo- or hyperthyroidy. The relationship between pituitary hormones and specific thyroid diseases deserves further investigation.

Multiple sclerosis

The hypothesis that PRL plays a role in multiple sclerosis has been tested by measuring PRL levels in patients. There is no consistent increase, although some patients have high serum PRL, in particular during exacerbations of the disease [71, 72]. The clinical course is not suggestive of a strong involvement of PRL, as the frequency of relapses is not increased during pregnancy. There is, however, an increase during the postpartum. The possibility that a rise in serum PRL may result from a hypothalamic lesion should always be considered in patients with multiple sclerosis.

Conclusion

Long-standing GH or PRL hypo- or hypersecretion does not induce clinically significant immunological impairment. However, GH and PRL influence granulopoiesis, erythropoiesis and immune function in vitro and in vivo in animal models. In all the conditions examined in the present review, immunoregulatory mechanisms might be operational, and the redundancy of the system allows correct immune function. The increased incidence of autoimmune diseases and of exacerbations in women, in particular during pregnancy or the postpartum, is strong but still circumstantial evidence for the role of hormones, in particular for SLE, the antiphospholipid syndrome or lymphocytic hypophysitis [66, 73]. The complexity of the endocrine network makes it difficult to estimate the contribution of different hormones in increasing the severity of the disease. Special attention should be paid to patients with increases in PRL or oestrogen only and to animal models, such as hypopituitary dwarfs and knockout mice, where deficits are more limited than, for example, after hypophysectomy, castration or ovariectomy. So far, hormones were mostly found to have a stimulatory effect in the immune system. The other

side of the coin (effects of cytokines on hormone secretion) should be kept in mind as well [74, 75].

Acknowledgment. Thanks to Ron Kooijman for reading the manuscript.

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