Effects of sex steroids on growth hormone responses to clonidine and GHRH in reserpine pretreated rats

E. Eriksson¹, K. Modigh¹, and J.-O. Jansson²

Departments of ¹ Pharmacology and of ² Physiology, University of Göteborg, Sweden

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Summary. Administration of reserpine in a dose causing depletion of brain monoamines led to a complete suppression of the pulsatile secretory pattern of growth hormone (GH) in gonadectomized (GX) as well as in sham-operated male and female rats. In GX animals of both sexes treated with estradiol, but not in those treated with testosterone or dihydrotestosterone (DHT), the reserpine induced inhibition of GH release was partially antagonized. Administration of the alpha2-adrenoceptor agonist clonidine caused secretion of GH in reserpine pretreated, sham-operated rats. In GX male rats GH responses to clonidine were blunted, while in GX males treated with testosterone or estradiol, but not in those treated with DHT, the responses were restored. In female rats gonadectomy did not significantly affect the GH releasing effect of clonidine. However, administration of estradiol to GX females led to enhanced responses to the alpha2-agonist. Administration of the GH releasing hormone (GHRH) induced pronounced GH secretion in reserpine pretreated animals of both sexes; this effect was not significantly affected by gonadectomy. In GX males, however, GH responses to GHRH were enhanced by replacement with estradiol or testosterone, while in GX females, estradiol, but not testosterone, had the same effect.

Keywords: Growth hormone, sex steroids, estrogens, estradiol, testosterone, gonadectomy, reserpine, clonidine, growth hormone releasing hormone (GHRH), rat

Introduction

In several species noradrenaline (or adrenaline) in brain exerts an important stimulatory influence on the release of growth hormone (GH) from the pituitary. A large number of experiments in the rat indicate that this influence is exerted by postsynaptic alpha2-adrenergic receptors located in the hypothalamus and acting by release of the GH releasing factor (GHRH) into the median eminence (Arnold and Fernstrom, 1980; Eden et al., 1981; Katakami et al., 1984; Miki
Pharmacological agents causing brain noradrenaline (and adrenaline) depletion (Eden and Modigh, 1977; Durand et al., 1977; Eden et al., 1979; Nigro-Vilar et al., 1979; Terry and Martin, 1981; Willoughby and Day, 1981) or alpha2-receptor blockade (Arnold and Fernstrom, 1980) effectively suppress rat GH secretion, while the alpha2-receptor agonist clonidine is a potent GH releaser in both rat (Eden and Modigh, 1977; Durand et al., 1977; Eriksson et al., 1982; Krulich et al., 1982) and man (Lal et al., 1975).

In psychiatric research, clonidine induced GH release is frequently used as a neuroendocrine test putatively reflecting central alpha2-receptor responsiveness. A blunted GH response to clonidine is an established finding in depressed patients (Matussek et al., 1980; Checkley et al., 1981; Siever et al., 1982; Charney et al., 1982) and has been taken as support for an involvement of alpha2-adrenergic receptors in the pathophysiology of affective disorders. However, a blunted GH response to clonidine may also reflect a pituitary dysfunction; in clinical endocrinology the clonidine/GH test has been suggested as useful in the diagnosis of GH deficiency (Keller et al., 1983; Laron et al., 1983).

Sex steroids appear to influence GH release induced by clonidine. The response is blunted in menopausal women (Matussek et al., 1980; Siever et al., 1982), and in fertile women it may be cycle dependent (Matussek et al., 1984). Furthermore, GH responses to insulin induced hypoglycemia, arginine infusion or exercise, all GH releasing stimuli that have been shown to involve alpha-receptor activation (see Martin et al., 1978), are increased in men treated with estrogens (Frantz and Rabkin, 1965; Merimee and Fineberg, 1971).

In a previous communication we reported that in castrated male rats the GH response to clonidine is drastically reduced and that this effect of gonadectomy is prevented by testosterone replacement (Jansson et al., 1982). We hypothesized the altered responses to clonidine in gonadectomized (GX) animals being due to an influence of testosterone on the responsiveness of central alpha2-receptors; an influence of the steroid on the responsiveness of GH producing cells to GHRH could, however, not be excluded. The frequent clinical use of the clonidine/GH test warrants further basic research on the influence of peripheral hormones, as well as other factors, on alpha-adrenergic regulation of GH release. In the present study we have compared the influence of testosterone and its active metabolites estradiol and dihydrotestosterone (DHT) on GH responses to clonidine and GHRH in the male rat. Similar experiments have been undertaken also in females.

**Materials and methods**

*Animals*

Male and female Sprague-Dawley rats at the age of 50–60 days (Anticimex, Stockholm, Sweden) were adapted to individual cages and housed under controlled conditions (temperature 24–26 °C, humidity 50–60%, light on from 5 a.m. to 7 p.m.). Standard laboratory chow and water were given ad libitum.