The effect of atenolol on the growth hormone response to growth hormone-releasing hormone in obese children

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We have evaluated the effect of acute administration of atenolol, a selective β-adrenergic antagonist, on the GH response to GHRH in nine obese children and in eight age-matched controls. The GH response to GHRH (1–29, 1 μg/kg iv), evaluated both as the GH peak and as integrated area under the curve, was significantly lower in the obese children than in the controls. Pretreatment with atenolol (50 or 100 mg orally in subjects with body weight < or > 40 kg, respectively, administered 120 min before the GHRH injection) significantly increased the GH response to GHRH in the obese subjects, such that their mean peak GH levels and mean integrated area under the curve after atenolol plus GHRH were similar to those of the control children after GHRH. Also in control children, atenolol caused a significant augmentation of the GH response to GHRH. Mean peak GH levels and mean integrated area under the curve after atenolol plus GHRH were significantly higher in the controls than in the obese children given the same treatment. These data show that inhibition of central β-adrenergic receptors counteracts the blunted GH response to GHRH present in the obese children. In view of the alleged mechanism of action of β-adrenergic blockade (inhibition of endogenous SRIH release), our data suggest that the somatostatinergic system is intact in obesity, and that the suppressed GH secretion is due to other causes.

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Reduced GH response to a wide variety of stimuli (see 1 for review), including GHRH (2–6), are characteristic features of obese subjects. Although the cause(s) of this reduced GH secretion is not fully understood, a number of findings indicate that an increased release of SRIH may be at least partly responsible for this phenomenon. In fact, administration of cholinergic agonist drugs (7) or galanin (8) restores GH responsiveness in obese children, an effect likely due to the ability of these drugs to inhibit endogenous SRIH release (9–11).

Catecholamines play a key role in the physiologic control of GH secretion by influencing the pattern of GHRH and somatostatin release from the hypothalamus (12). Stimulation of α-adrenergic receptors (13–15) causes GH release in man, while administration of β-adrenergic blocking drugs, though incapable per se of stimulating GH secretion, enhances its release in response to a variety of central nervous system-mediated stimuli (16–18), and also augments the GHRH-induced GH release in normal adults (19), normal and short children (20, 21) and in children with GH deficiency during long-term GHRH therapy (22). Several findings indicate that the ability of β-adrenergic blocking agents to enhance GH release is due to inhibition of endogenous SRIH release (23–25).

It has been previously shown that propranolol administration enhances the GH response to l-dopa in obese adult subjects (26), but it is still unknown whether β-adrenergic blockade can also increase the GHRH-induced GH release in obesity. In this study we have investigated the effect of atenolol, a selective β-adrenergic antagonist, on the GH response to acute GHRH administration in a group of normal and obese children.

Materials and methods

Nine obese prepubertal children (5 males and 4 females, age 5.3–10.7 years, height sds -0.68 to 0.92, mean 0.36 ± 0.21 sds) with excess body weight ranging from 48 to 100%, for their stature were studied. Eight age-matched short normal children (5 males and 3 females aged 6.8–11.3 years) with body weight within ±10% of their ideal weight served as controls. All control children were referred to our department for short stature (height sds -2.9 to -0.67 sds, mean -1.9 ± 0.25 sds) and were asked to participate in the study. The non-existence of other endocrine abnormalities was carefully checked in all obese children by means of clinical and laboratory investigation. In particular, thyroid and adrenal function, and skull X-ray were normal. The study was approved by the Ad Hoc Ethics Committee of the Department of Pediatrics of the University of Cagliari.
and informed consent was obtained from each subject or from their legal guardians prior to the study. After an overnight fast, two basal samples were taken 30 min apart. The first drawn 30 to 60 min after an indwelling catheter was inserted into the forearm vein. GHRH (GRF 1-29, kindly provided by Pierrel, Milan) was then injected in a dose of 1 μg/kg iv over 30 sec. Blood samples were obtained after 15, 30, 60, 90 and 120 min. On separate occasions, all subjects underwent a second GHRH test after previous treatment with atenolol (50 mg in patients with body weight <40 kg and 100 mg in subjects with body weight >40 kg) administrated orally 60 min before GHRH. Blood pressure, pulse and respiratory rate, body temperature and neurological status were monitored throughout the test. Subjective and objective symptoms were recorded every 20 to 30 min during the tests and for 3 h after the tests were completed. GH was measured using an IRMA method using reagents provided by Sorin (Saluggia, Italy). The limit of detection of the assay was 0.2 μg/l with intra- and interassay cvs of 2.7 and 4.5%, respectively.

The statistical significance of the differences was calculated using a paired or unpaired t-test preceded by ANOVA. Non-parametric analysis of variance was also performed where appropriate (Kruskal-Wallis test). Plasma GH integrated areas under the curve after GHRH were calculated by means of trapezoidal integration. A p-value of less than 0.05 (two-tailed) was considered as indicating a significant difference. All data are given as the mean ± SEM.

Results

Baseline GH values were 0.5 ± 0.1 and 1.0 ± 0.2 μg/l (p<0.05) in the obese and short normal children, respectively. Administration of GHRH evoked a prompt increase in plasma GH in all short normal subjects. GH rising from basal values to peak values of 39.1 ± 8.2 μg/l (Fig. 1) between 30 and 60 min. In all the obese children GHRH stimulated GH secretion, but mean peak GH levels (between 30 and 60 min) after GHRH (14.0 ± 2.8 μg/l) were significantly lower (p<0.01) than in the short normal subjects (Fig. 1). Evaluation of area under the curve—GH also showed a significantly lower (p<0.05) GH response to GHRH in the obese children (98.8 ± 19.1 μg·min·l⁻¹) than in the short normal group (204.7 ± 46.3 μg·min·l⁻¹) (Fig. 2). Pretreatment with atenolol caused a significant increase in GHRH-stimulated GH secretion in the obese subjects (26.2 ± 4.3 μg/l, p<0.0001), such that mean peak GH levels after atenolol + GHRH were no different from those of the short normal group after GHRH alone (Fig. 1). Peak GH levels occurred in both groups between 30 and 60 min after GHRH administration. Neither was mean area under the curve—GH of the obese children after atenolol + GHRH (185.7 ± 37.8 μg·min·l⁻¹) significantly different from area under the curve—GH observed in the short normal children after GHRH alone (Fig. 2). In addition, in short normal children, pretreatment with atenolol caused a significant augmentation of the GHRH-induced GH rise (mean peak GH levels = 65.8 ± 12.1 μg/l, p<0.02 vs GHRH (Fig. 1) (mean area under the curve—GH = 429.3 ± 77.3 μg·min·l⁻¹, p<0.005 vs GHRH) (Fig. 2). Mean peak GH levels (Fig. 1) and mean area under the curve—GH (Fig. 2) after atenolol + GHRH were significantly higher in the short normal than in the obese children. Atenolol administration caused no significant changes (paired t-test) in baseline GH concentration (3.8 ± 1.6 and 1.3 ± 0.5 μg/l in short normal and obese children, respectively). No adverse effects were recorded in any of the subjects after GHRH alone or after pretreatment with atenolol.

Discussion

As previously shown (20, 21), atenolol enhanced the GH response to GHRH in our short normal children. Furthermore, atenolol also increased the GHRH-induced GH release in the group of obese children to levels similar

![Fig. 1. Mean ± SEM of peak GH levels after GHRH, and atenolol + GHRH in obese children (shaded bars) and controls (closed bars).](image-url)
to those observed in the control group after GHRH alone. This type of response is strikingly similar to that observed after administration of pyridostigmine, a cholinergic agonist (7), or galanin (8) to obese children, and might indicate that obese children have an increased endogenous SRIH tone which would be counteracted by agents capable of inhibiting SRIH release. An impaired endogenous GHRH release/action has also been suggested by Cziszmadia et al. (27), based on the finding that repeated GHRH injections increased both the peak and the integrated GH response to GHRH. However, spontaneous GH secretion is also reduced in obesity (28, 29) and, interestingly, Veldhuis et al. (29) found normal GH intersecretory burst intervals in some obese subjects (particularly at night), suggesting that GHRH neuronal firing rates could be normal at this time. As these authors pointed out, GHRH may fail to evoke detectable amounts of GH secretion because of high somatostatinergic inhibitory tone. Furthermore, normal baseline as well as 1-dopa-stimulated plasma immunoreactive GHRH levels have been found in obese children (Loche et al., unpubl. obs.).

As already observed with pyridostigmine (7) and with galanin (8), atenolol administration enhanced the GH response to GHRH to a significantly greater extent in short normal children than in the obese, indicating that there is some chronic background suppression of GH secretion in obese subjects which does not involve SRIH. In fact, if the reduced GH secretion seen in obesity was solely due to increased somatostatinergic tone, one would expect a normalization of the GH response to GHRH once the SRIH inhibitory tone had been removed. In this regard it is worth noting that obese subjects tend to have elevated IGF-I levels (5, 7, 28, 30) and that IGF-I negative feedback on GH secretion is exerted on both the hypothalamus and the pituitary (31), and therefore the possibility of an IGF-I-mediated inhibition of GH synthesis (32, 33) cannot be ruled out. In addition, other hormonal and/or metabolic factors such as insulin (32) and FFA (34), which are known to be increased in obese subjects (35, 36), or other unknown factors may also contribute to the pathophysiology of the reduced GH secretion, as indicated by the increased GH responsiveness to GHRH after acute nutrient deprivation in obesity (37).

Several data have accumulated indicating the reversibility of the defect after weight reduction (2, 27, 37, 38) or fasting (37, 39), strengthening the view that the obesity-associated impairment in GH secretion is a metabolic consequence of obesity rather than a primary defect. Whatever factor/s may be involved as the cause/s of the reduced GH secretion in obesity, the ability of atenolol (as shown in this study) and of pyridostigmine (7) and galanin (8) to partially restore GH secretion, in view of their alleged mechanism of action, is consistent with the view that the somatostatinergic system is intact in obesity, and that suppression of GH secretion is due to other factors. Whether manipulation of brain neurotransmitters would eventually restore a normal spontaneous GH secretion in obese children deserves further investigation. The potential clinical implications of such an effect do not escape attention, inasmuch as normalized GH secretion may help promote lipid mobilization and limit protein breakdown during diet programs.

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