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EDITORIAL

Impaired growth hormone secretion associated with low glucocorticoid levels: an experimental model for the Giustina effect

Andrea Giustina · Gherardo Mazziotti

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Hattori et al. [1] in this issue of Endocrine report on an interesting experimental model of dioxin-induced fetal growth retardation. This study found that oral administration of dioxin to pregnant rats reduced both the pituitary expression and serum levels of growth hormone (GH) in perinatal pups [1]. Concomitantly, dioxin decreased serum concentration of corticosterone in the studied model. Administration of physiological doses of corticosterone to dioxin-exposed mothers restored or tended to restore the dioxin-induced reduction of both GH expression and fetal body weight [1]. Taken together, these observations suggest that dioxin-induced fetal growth disorders are due, at least in part, to impaired GH expression and secretion in the presence of low circulating glucocorticoids [1].

GH is secreted in pulses by the pituitary gland. It is regulated by the hypothalamus via the stimulating factor GH-releasing hormone (GHRH) and the inhibitory hormone somatostatin [2]. In addition to classic hypothalamic peptides, many other neuropeptides (ghrelin and galanin), neurotransmitters (acetylcholine), metabolic substances (glucose and amino acids), and circulating hormones (thyroid and sex hormones) modulate GH production [2–6]. Regulation of GH secretion is deranged in many human diseases including Cushing syndrome [7–9]. In fact, glucocorticoids are among the most relevant circulating hormones acting as GH regulators with multiple effects at hypothalamic (increase somatostatin tone), pituitary (expression of GH and GHRH receptor), and peripheral level (decreased production of insulin-like growth factor 1, IGF-I, which is the peripheral mediator of GH action) [10, 11].

Interestingly, findings of Hattori et al. [1] are in agreement with data suggesting that glucocorticoids may be crucial for differentiation and maturation of somatotropes [12, 13]. Glucocorticoids can also enhance the GH response of somatotropes to GHRH and ghrelin as effect of enhanced expression of their receptors on pituitary cells [14–16].

In vivo studies suggest that glucocorticoids may both stimulate and inhibit GH secretion with the net biological effect related to hormonal levels and duration of exposure [10, 11]. In fact, as authors of the Endocrine paper correctly pointed out [1] although maternal co-treatment with corticosterone at low dose (1 mg/kg) restored defects produced by dioxin, higher doses such as 10 mg/kg corticosterone failed to produce beneficial effects on dioxin-exposed fetuses. In the adrenalectomized rat a blunted GH secretion in response to GHRH was observed while glucocorticoid replacement restored GH secretion to normal [17]. The work by Hattori confirmed that glucocorticoids may in vivo, as well as in vitro, directly stimulate GH secretion with a non-hypothalamic action. In fact, in the rats, administration of supraphysiological doses of glucocorticoids resulted in a decreased GH secretion and this effect appeared to be determined by an increase of somatostatin and decrease of GHRH in hypothalamus [18–20]. In vivo, long-term administration of glucocorticoids in the rats resulted in a decrease in body growth and/or weight and a profound catabolic state which was restored by passive immunization with somatostatin antibodies and somatostatin type 2 receptor antagonists [21, 22].

The study by Hattori et al. constitutes an interesting and innovative in vivo model for the evaluation of physiological effects of glucocorticoids on GH secretion which in

A. Giustina (✉) · G. Mazziotti
University of Brescia, Poliambulatori di Via Biseo,Via Biseo 17, 25123 Brescia, Italy
e-mail: a.giustina@libero.it

humans can only be derived from studies involving patients exposed to glucocorticoid deprivation due to idiopathic ACTH deficiency or familiar resistance to ACTH. In fact, patients with isolated ACTH deficiency had impaired GH response to the stimuli with GH reserve restored to normal after glucocorticoid supplementation [23]. The occurrence of functional hypoadrenalism-induced GH deficiency reversible during glucocorticoid replacement, i.e., the Giustina effect [7, 11], has been also shown in children with isolated ACTH deficiency or ACTH resistance [24, 25] in whom GH deficiency was transient since corticosteroid therapy normalized GH secretion. Indeed, GH deficit even if transient was prolonged and consistent with the hypothesis formulated by Hattori et al. that glucocorticoid deficiency may have impacted on physiological development of somatotropes.

The Giustina effect is experimentally supported by the data of Hattori et al. [1] showing impaired GH secretion in the presence of low circulating glucocorticoids, likely due to dioxin-mediated accelerated corticosterone metabolism, while it was reversible after corticosterone supplementation. The evidence that this effect originally described in humans is highly preserved among species confirms that glucocorticoids are essential for a physiological development of somatotropes and for preserving a physiological GH secretion and, as a consequence, for a normal body growth. In clinical practice, the Giustina effect implies that in hypopituitary patients with glucocorticoid deficiency pituitary GH reserve should be re-tested after adequately replacing glucocorticoids and GH treatment should not be given unless retesting confirms deficient GH secretion [11].

Consistently with what reported by Hattori et al. [1], high-dose short- and long-term administration of glucocorticoids suppressed GH in humans with a somatostatin-dependent mechanism [26], since it was reverted by functional antagonists of somatostatin, such as the acetylcholinesterase inhibitor pyridostigmine and arginine [27–30]. An inhibited GH secretion was also observed in subjects chronically exposed to slight degree of glucocorticoid excess, as determined by inhaled corticosteroids or in patients with adrenal incidentaloma [31, 32].

Therefore, in children even slight glucocorticoid excess, as well as glucocorticoid deficiency, could cause growth retardation [33]. In adults, excess glucocorticoid-mediated GH suppression impacts on bone and energy metabolism [34]. Coexistent GH deficiency and glucocorticoid excess may pose the subjects at high risk of bone loss and fragility fractures [35, 36] Short-term (7 days) GH administration was able to significantly increase bone turnover in adults chronically treated with glucocorticoids [37]. Moreover, glucocorticoid-induced proteolysis and protein wasting could be counteracted by concomitant administration of recombinant GH [38].

In conclusion, article by Hattori et al. [1] highlights the positive "physiological" role of glucocorticoids in the stimulation of maturation and function of somatotropes in experimental conditions further supporting the concept behind the Giustina effect which identifies a functional impairment of GH secretion in the presence of a low glucocorticoid milieu which is reversible after adequate cortisol replacement. The Giustina effect also identifies the opposite situation in which excess glucocorticoids may suppress endogenous GH secretion. Therefore, extrapolating the Hattori findings to humans may suggest the notion that both hypo- and hyper-cortisolism can cause impaired GH secretion with relevant diagnostic and therapeutic implications. In fact, correction of hypoadrenalism may restore GH reserve to normal whereas clinical but even subclinical hypercortisolism almost invariably suppress GH secretion.

In perspective, future studies should be performed to better define the Giustina effect in humans with the objective to investigate the time needed to observe the blunting effect of GH secretion in the presence of low glucocorticoids across the life span as well as the timing to recovered GH secretion after starting glucocorticoid substitution. Moreover, not only the dose–response curve [39] but also possibly low and high threshold cortisol levels below and above which the effect can be observed are still to be defined.

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