Effects of high-altitude hypoxia on the hormonal response to hypothalamic factors

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Submitted 23 July 2010; accepted in final form 5 October 2010

Rochalet JP, Letournel M, Souberbielle J. Effects of high-altitude hypoxia on the hormonal response to hypothalamic factors. Am J Physiol Regul Integr Comp Physiol 299: R1685–R1692, 2010. First published October 6, 2010; doi:10.1152/ajpregu.00484.2010.—Acute and chronic exposure to high altitude induces various physiological changes, including activation or inhibition of various hormonal systems. In response to activation processes, a desensitization of several pathways has been described, especially in the adrenergic system. In the present study, we aimed to assess whether the hypophysal hormones are also subjected to a hypoxia-induced decrease in their response to hypothalamic factors. Basal levels of hormones and the responses of TSH, thyroid hormones, prolactin, sex hormones, and growth hormone to the injection of TRH, gonadotropin-releasing hormone, and growth hormone-releasing hormone (GHRH) were studied in eight men in normoxia and on prolonged exposure (3-4 days) to an altitude of 4,350 m. Thyroid hormones were elevated at altitude (+16% to +21%), while TSH levels were unchanged, and follicle-stimulating hormone and prolactin decreased, while leutinizing hormone was unchanged. Norepinephrine and cortisol levels were elevated, while no change was observed in levels of epinephrine, dopamine, growth hormone (GH), IGF-1, and IGFBP-3. The mean response to hypothalamic factors was similar in both altitudes for all studied hormones, although total T4 was lower in hypoxia during 45 to 60 min after injection. The effect of hypoxia on the hypophysal response to hypothalamic factors was similar among subjects, except for the GH response to GHRH administration. We conclude that prolonged exposure to high-altitude hypoxia induces contrasted changes in hormonal levels, but the hypophysal response to hypothalamic factors does not appear to be blunted.

thyroid hormones; prolactin; growth hormone; leutinizing hormone; follicle-stimulating hormone; catecholamines; cortisol

HIGH ALTITUDE INDUCES VARIOUS physiological changes in sea level natives, both on acute and more prolonged exposure, including control of hormonal secretion. A substantial amount of work has been done on hormones regulating water and electrolytes handling or stress hormones at high altitude (for review, see Ref. 34). Other hormones dealing with metabolic regulations have been scarcely examined in hypoxic conditions. Thyroid hormones have been found increased at high altitude in most studies, although TSH secretion is not modified, and the mechanisms involved in this dissociation are still unclear (2). The reports on the effects of acute hypoxic exposure on sex hormones (18), prolactin (21), and growth hormone (5) are few and often contradictory. Some endocrine or neuroendocrine pathways are activated in response to the hypoxic stressor, while other pathways are blunted. For example, a cortisol release is activated while an aldosterone release is blunted by hypoxia, although these two hormones are secreted by adjoining zones in the same organ. A resistance appears to occur with certain stimuli, limiting the effects of the activated pathways. These down-regulation processes may counteract the numerous activation phenomena leading to an increase in stress hormones (cortisol, catecholamines) observed in response to hypoxia. Finally, an optimal adaptation to the stressful environment would depend on an adequate balance between activation and resistance (33). To test the hypothesis that hypophysal secretions are also subjected to a desensitization phenomenon during a prolonged (3 to 4 days) exposure to high altitude (4,350 m), the responses of thyroid hormones (TSH, T3, T4), prolactin, leutinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone (GH) to the injection of hypothalamic factors have been evaluated in eight male sea-level natives.

METHODS

Subjects

Eight healthy men with a mean age of 28 yr (range 23–34 yr), a mean weight of 74 kg (range 58–90 kg), and a mean height of 1.80 m (range 1.76–1.90 m) were included in the study. Subjects were sea-level residents, moderately trained, and nonacclimatized to high altitude.

Experimental Protocol

All subjects were examined according to the same protocol at sea level (Hôpital Avicenne, Bobigny, France, at an altitude of 50 m) and 3 or 4 days after a rapid ascent by helicopter from Chamonix (1,035 m) to 4,350 m (Observatoire Vallot, Mont Blanc, France). Subjects were allowed to perform only light physical exercise. Room temperature was about 20°C at both altitudes, but since subjects were allowed to go outdoors when residing at Observatoire Vallot, they were intermittently exposed to moderate cold. The investigations were performed in the morning after overnight fasting. A venous catheter was inserted in the cubital vein of one arm. Thereafter, the subjects rested in a supine position for 30 min before hormone administration. Blood samples to determine GH, TSH, T3, free T3 (fT3), T4, free T4 (fT4), LH, FSH, and prolactin were collected before and after a slow infusion (2 min) of a mixture of growth hormone-releasing hormone (GHRH; 1 mg/kg), TRH (0.5 mg) and gonadotropin-releasing hormone (GnRH; 0.1 mg). Times of collection were 00:00, 03:00, 06:00, 09:00, and 12:00 min with respect to infusion. For GH, +15:00- and +45:00-min sampling times were omitted. Additionally, blood was withdrawn prior to the injec-
tion for the measurement of basal plasma concentration of cortisol, norepinephrine, epinephrine, dopamine, IGF-1, and IGFBP-3. Just before drawing the blood samples, heart rate, oxygen saturation, and blood pressure were measured. At high altitude, the Lake Louise score of acute mountain sickness, a self-report questionnaire with a score from 0 to 15, was recorded daily (35a). Hypothalamic hormones were obtained from Roussel Laboratories (Paris, France) in the form of injection solutions. Blood samples were centrifuged and then stored in liquid nitrogen during the remaining days at altitude and during transport to Paris. Analyses were performed at Necker Hospital. Concentrations of TSH, T3, fT3, T4, fT4, LH, FSH, and prolactin were analyzed in each subject by automated immunoassays, using MiniVidas apparatus (BioMérieux, Marcy-l’Étoile, France). All of these assays presented an intra- and interassay coefficient of variation (CV) that was <5%, and <6%, respectively, throughout the whole range of concentrations. GH (Cis-Bio International, GIF sur Yvette, France), IGF-1 (IGF-I RIACT; Cis-Bio International), and IGFBP-3 (Diagnostic Systems Laboratories, Webster, TX) were measured in duplicate by means of immunoradiometric assays. Intra-assay CV were <5%, <5.5%, and <10% for GH, IGF-1, IGFBP-3, respectively, whereas interassay CV was <5%, 7.8%, and 11% for GH, IGF-1, and IGFBP-3, respectively. Catecholamine levels were measured by using a HPLC method with electrochemical detection. Cortisol levels were measured in duplicate with radioimmunoassay (Cis-Bio International, GIF-sur-Yvette, France) with intra- and interassay CV <6.2% and 7.4%, respectively. The study was approved by the ethical committee of Necker Hospital in Paris, and all subjects gave their written informed consent according to the Helsinki Declaration.

Statistical Analysis

Baseline values in normoxia and hypoxia were obtained by averaging the two values obtained 15 min and 2 min prior to the injection, and then compared using two-tailed paired Student’s t-test with Bessel’s correction. Values obtained after the hormonal injection were statistically analyzed using a two-way ANOVA (condition and time). A Tukey post hoc test was then applied when appropriate. Correlation between different variables was evaluated by linear regression analysis. A P value less than 0.05 was considered to be significant.

RESULTS

Baseline Concentrations of Hormones at Sea Level and After 3–4 Days at 4,350 m

Thyroid hormones. Baseline levels of both total and free forms of T3 (+16%) and T4 (+21%) were elevated at high altitude (Table 1), with a slightly greater increase in T4, as shown by a significant increase in the ratio T4/T3 (+4.4%). TSH remained unchanged.

Sex hormones. FSH decreased by 17% in hypoxia, while LH did not vary significantly (Table 1).

Stress hormones and prolactin. Norepinephrine increased by 66% in hypoxia, while epinephrine and dopamine did not vary significantly (Table 1). Cortisol increased by 26% without reaching significance. Prolactin decreased by 52% in hypoxia.

Growth hormone. GH tended to decrease, but the variability was great among subjects, and mean variation was not significant (Table 1). IGF-1 and IGFBP-3 did not change with hypoxic exposure.

Hormonal Response to Hypothalamic Factors

Thyroid hormones. Hormonal injection had no significant effect on free or total T4 (Fig. 1); however, total T4 had a tendency to decrease in hypoxia during the first 60 min. Total and free T3 showed a progressive increase during the 2 h following injection in both environments. After hormone stimulation, TSH increased quickly and reached a peak value after 30 min. This response was not modified in hypoxia. TSH and thyroid hormone patterns did not differ between subjects. T4 at high altitude were those who showed a large hypoxia-induced increase in epinephrine (Fig. 2).

Prolactin. The increase in prolactin in response to TRH was very rapid in both altitudes (P < 0.001) and reached a peak value after 15 min (Fig. 3). Thereafter, levels dropped to near normal after 2 h. The pattern and amplitude of the response were similar in hypoxia and normoxia. All subjects showed similar responses.

Sex hormones. The response after hormone injection was similar in the two environments for both LH and FSH (Fig. 3). The LH increase was significant (P < 0.001) and reached its peak after 30 min. The FSH increase was slower (P < 0.05), reaching the highest level after 30–60 min and then plateauing during the remaining test period. The pattern of response was similar in all subjects, but the amplitude was variable.

Growth hormone. The average peak and mean values of the response were not significantly different between hypoxia and normoxia, although the mean response tended to have a lower amplitude 30 min after injection in hypoxia (Fig. 3). The increase in GH after GHRH injection varied among subjects in the two environments, showing three different patterns: subjects 1 and 5 had an increased response at altitude, subjects 6, 7, and 8 had a decreased response at altitude and subjects 2, 3, and 4 showed similar responses in the two altitudes (Fig. 4).

Physiological Parameters

At the time of blood sampling for hormonal evaluation (3 to 4 days at 4,350 m), as expected, heart rate increased and oxygen saturation decreased at altitude, while no significant change was observed in blood pressure (results not shown). Symptoms of acute mountain sickness had subsided in most subjects. Subjects had total Lake Louise scores of 0 or 1 before

<table>
<thead>
<tr>
<th>Sea Level</th>
<th>High Altitude</th>
<th>P</th>
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<tbody>
<tr>
<td>Total T4, nmol/ml</td>
<td>85.1 ± 11.8</td>
<td>103.1 ± 18.5</td>
</tr>
<tr>
<td>Free T4, pmol/l</td>
<td>13.9 ± 2.4</td>
<td>16.8 ± 3.4</td>
</tr>
<tr>
<td>Total T3, nmol/l</td>
<td>1.72 ± 0.20</td>
<td>1.99 ± 0.29</td>
</tr>
<tr>
<td>Free T3, pmol/l</td>
<td>6.51 ± 0.41</td>
<td>7.54 ± 0.69</td>
</tr>
<tr>
<td>T4/T3</td>
<td>49.7 ± 5.1</td>
<td>51.9 ± 5.1</td>
</tr>
<tr>
<td>TSH, mU/ml</td>
<td>1.51 ± 0.80</td>
<td>1.37 ± 0.93</td>
</tr>
<tr>
<td>Prolactin, nmol/l</td>
<td>0.63 ± 0.30</td>
<td>0.30 ± 0.20</td>
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<tr>
<td>FSH, mU/ml</td>
<td>4.15 ± 2.44</td>
<td>3.44 ± 1.73</td>
</tr>
<tr>
<td>LH, mU/ml</td>
<td>2.79 ± 0.94</td>
<td>2.33 ± 0.99</td>
</tr>
<tr>
<td>Norepinephrine, nmol/l</td>
<td>3.13 ± 0.73</td>
<td>4.69 ± 1.05</td>
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<tr>
<td>Epinephrine, nmol/l</td>
<td>1.01 ± 0.27</td>
<td>1.00 ± 0.54</td>
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<tr>
<td>Dopamine, nmol/l</td>
<td>2.14 ± 1.04</td>
<td>2.50 ± 0.93</td>
</tr>
<tr>
<td>Cortisol, nmol/l</td>
<td>261 ± 107</td>
<td>330 ± 137</td>
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<tr>
<td>GH, ng/ml</td>
<td>1.40 ± 1.86</td>
<td>0.73 ± 1.05</td>
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<tr>
<td>IGF-1, μg/l</td>
<td>168 ± 55</td>
<td>184 ± 53</td>
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<tr>
<td>IGFBP3, mg/l</td>
<td>2.17 ± 0.28</td>
<td>2.16 ± 0.28</td>
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At high altitude, plasma concentrations were measured for 3 to 4 days at 4,350 m; n = 8. T3, T4, thyroid hormones; FSH, follicle stimulating hormone; LH, luteinizing hormone; GH, growth hormone; ns, not significant.
injection, and those values were maintained during the entire control period.

**DISCUSSION**

The present study offers, for the first time, a quite comprehensive picture of important hormonal changes induced by exposure to high altitude. These changes are not caused by modifications of the hypothalamo-hypophyseal axes. No desensitization process appears to develop in response to prolonged exposure to hypoxia, in opposition to what has been evidenced in other hormonal or neurohormonal systems. For example, in the adrenergic system, a decrease in the chronotropic response to \( \beta \)-adrenergic stimulation has been identified through a change in G protein coupling (11, 20, 35). Similarly, a decrease in adipose tissue lipolysis has been attributed to a desensitization of \( \beta \)-adrenergic, GH, and parathyroid hormone (PTH) lipolytic pathways (10). A decrease in the urinary cyclic AMP excretion has also been related to a decrease in kidney response to PTH stimulation (43). It might be hypothesized that the G protein coupling, which is not involved in the hypothalamo-hypophyseal axes explored in the present study, except for the GHRH receptor, might be a determinant element in these downregulation processes.

**Thyroid hormones.** Our findings of unaltered baseline TSH concentration, but elevated levels of both total and free fractions of T3 and T4 are consistent with most of the previous studies (8, 12, 22, 30, 31, 39, 43), suggesting that a slight hyperthyroidism may be necessary to withstand the extreme environments of high altitude (4). Thyroid hormones increase the levels of 2,3-diphosphoglyceric acid in erythrocytes, facilitating oxygen release to the tissues, by causing a shift of the oxyhemoglobin dissociation curve to the right, advantageous in hypoxia (42). Several explanations for the TSH-independent T4 rise have been proposed. A change in hormone levels can
be caused by either a modified secretion rate, a disturbed clearance, or a hemoconcentration and vascular shift. The T4 rise at high altitude cannot be explained simply by dehydration and hemoconcentration evaluated by the concentration of total plasma proteins (45). The T4 degradation rate increases during the first 3 days at altitude and thereafter remains slightly elevated, thus contradicting decreased clearance as a possible cause of T4 elevation (46). In men trekking at altitudes around 3,500 m, thyroxine-binding globulin (TBG) levels were found sufficiently elevated to explain a concomitant T4 rise (8). However, in most studies, small or no changes in TBG and thyroxine-binding prealbumin have been found (26, 31, 39, 45). Thus, a binding alteration is not likely to be the entire explanation. Unchanged (22) or increased (4) T3 uptake has been found at high altitude, suggesting a normal binding capacity, supported by the observation that free hormone levels increase in parallel with total levels (4, 22, 31). The increase in thyroid hormones at high altitude has been paralleled to an increase in basal metabolic rate (25, 46). Cold is a potential disturbing factor on the thyroid status at altitude. The low T3 values in the study by Hackney et al. (16) (but not their observation of decreased TSH and unchanged T4) may be explained by this cold influence (16). T3 and T4 were elevated on exposure to simulated hypoxia at +22 to +24°C ambient temperature, demonstrating a thyroid hormonal increase independent of cold exposure (39). The subjects in our study experienced only intermittent and moderate cold exposure, which probably did not influence their thyroid status. The T3 and T4 increase at altitude was accompanied by an increase in norepinephrine plasma concentrations, reflecting a well-documented rise in sympathetic activity (46). Thyroid hormones, particularly T4, rise during intense exercise, while no change in TSH is seen (17), possibly due to an adrenergic influence, since sympathetic branches innervate the thyroid gland. Investigations have shown a direct inhibition of the gland by β-blockers that have been used for many years to relieve symptoms of hyperthyreosis. Therefore, the augmented levels of catecholamines may be the main cause of the increased level of thyroid hormones at high altitude. The unchanged level of TSH contrasts with the increased levels of T3 and T4 and may reflect an altered feedback regulation or disturbed hypophyseal function. Our study, along with earlier ones (12, 30, 31, 39,
43), does not show any evidence of a hypophyseal malfunction, as a normal TSH response is seen after TRH administration. As TSH response to TRH was normal, T4 and T3 response to TRH-induced increase in TSH is also unaffected by hypoxia, suggesting that the thyroid gland responsiveness is also unaltered. By contrast, at the extreme altitude of 5,400 – 6,300 m, an increased TSH response to 500 μg of TRH was found, suggesting that the level of hypoxic stress or the association with other stressors (cold) could influence the hypophyseal response (26). The protective function and the role among the adaptive mechanisms to high altitude for these thyroid hormonal changes remain to be clarified.

**Prolactin.** The effect of hypoxic exposure on prolactin has been scarcely studied in sea-level native men. Our results of depressed basal prolactin levels are in accordance with previous findings (6), yet they conflict with other studies in which elevated resting levels and amplified prolactin response during exercise have been described (5, 38, 44). TRH stimulates not only a TSH response, but also a marked prolactin increase. This response was not altered in our study, which agrees with results from earlier papers (26, 30), though unchanged baseline levels of prolactin were found at altitude in both studies in contrast to our decreased values. As prolactin is under the influence of numerous regulators, many possible factors could interfere with hypoxia. Dopamine and possibly noradrenaline inhibit prolactin secretion and could provoke a prolactin depression at high altitude (3). However, while noradrenaline consistently increases in hypoxia, the dopamine changes are inconsistent, either unchanged or increased (27, 29, 41). Interestingly, the acute administration of erythropoietin (EPO) induced a fall in plasma prolactin in patients with amyotrophic lateral sclerosis (24). In a study performed on 10 normal subjects in very similar conditions as the present study (3 days at Observatoire Vallot, 4,350 m), serum EPO increased from 17.6 ± 8.7 at sea level to 97.2 ± 43.1 mU/ml (37). Therefore, the altitude-induced increase in EPO could be responsible for the decreased plasma prolactin observed in the present study. As EPO is known to have many protective effects through its receptors, present in several regions of the central nervous system, it could promote dopamine release and, therefore, inhibit prolactin secretion (24). Cold exposure may diminish the exercise-induced prolactin response (7), but it does not seem to influence baseline levels (38). Whatever the mechanism that alters prolactin baseline levels, it seems to be overridden by hypothalamic influence since prolactin response to TRH stimulation was not altered by exposure to high altitude.

**Sex hormones.** The observed decrease in basal concentrations of FSH (P < 0.02) and LH (insignificant) is consistent with earlier findings (13, 18, 38), but the reason for this decrease remains speculative. The unaltered LH and FSH responses after GnRH administration in acute hypoxia exclude an insufficient hypophyseal function as an explanation for the depressed levels at altitude. Catecholamines influence LH secretion, but opposite effects have been described for dopamine, inhibiting, and noradrenaline, probably stimulating, LH release. Intermittent exposure to moderate cold induces a decrease in LH levels, independent of hypoxia (38). Results from high-altitude expeditions may be influenced by this fac-

![Fig. 4. Individual pattern of GH response to GHRH among subjects. Two subjects have a higher GH concentration at all time points in hypoxia (#1 and #5), three subjects have a lower GH concentration at all time points in hypoxia (#6, #7, #8), three subjects have a similar response in hypoxia compared with normoxia (#2, #3, #4). Mean values for the three groups are presented on the right. ● normoxia; □ hypoxia.](http://ajpregu.physiology.org/doi/abs/10.1152/ajpregu.00021.2010)
tor, possibly explaining the observed inconsistency. As the hypophyseal response of sex hormones to hypothalamic factors is unaltered by high altitude, the reduced baseline levels of hormones remain unexplained.

**Growth hormone.** The unaltered GH baseline level that we found in prolonged hypoxia is in agreement with most earlier reports (32, 38). However, in 1993, Anand et al. (1) recorded a large increase in GH concentration, but this observation could be due to the workload of the subjects, the long duration of the exposure, and/or the stressful environment, since exercise, chronic hypoxia, and stress are all considered to induce a GH increase (1). In addition, the spontaneous secretion of GH is variable, and thus, baseline levels are very difficult to determine accurately. This is the reason why levels of IGF-1 and IGFBP-3 are considered more reliable for estimating GH activity. The unchanged levels of IGF-1 and IGFBP-3 in our study suggest a normal GH activity. GHRH pulses are important stimuli for GH release in normal conditions. Various patterns have been observed in different individuals, and no correlation with other parameters has been noted. The decreased response of GH to GHRH observed in 4 subjects in hypoxia suggests a disturbed influence of this hypothalamic regulator at high altitude. This could be caused by a desensitization of the GHRH receptor or an altered GH production. The GHRH receptor is a seven-transmembrane G protein-linked receptor and, similar to other G protein-linked systems, could be downregulated in prolonged hypoxia (20). The reason for the changes in GH at high altitude is unclear, but it could play a role in modifying the metabolism to satisfy increased needs at altitude both during short-term exercise and during long-term exposure (39). Lactic acid has been proposed to stimulate GH during exercise (49), but some studies have failed to prove any correlation between these parameters (32, 47). Hypoglycemia induces GH secretion (19), but increased plasma levels of glucose are seen in situations when GH levels are elevated, that is, in chronic hypoxia and during exercise in acute hypoxia, making hypoglycemia an unlikely cause (40).

Thyroid hormones are important for a normal secretion of GH, and severe hypothyroidism is associated with a GH deficiency (14). In hyperthyroidism, the GHRH-induced release of GH is reduced, probably by an increase in hypothalamic somatostatin tone (14). Thus, the increased level of thyroid hormones at high altitude could possibly play a role in the GH changes observed at altitude. Dopamine and norepinephrine also regulate GH secretion (28, 50). GH release, induced by exercise or falling levels of metabolites, is reduced by α-adrenergic blockade and amplified by β3-adrenergic blockade (48). This is likely to reflect the influence of catecholamines at various regulatory levels and their elevation in hypoxia might explain the varying GH responses at high altitude. The effect of dopamine on GH secretion is still debated, but it appears clearly that, in normal subjects, acute administration of dopamine agonists (l-dopa, apomorphine, dopamine itself, bromocriptine) causes GH release and stimulates the GH response to GHRH, possibly via a somatostatin withdrawal (14, 28). However, in the present study, we failed to find a significant correlation between the individual changes in GHRH-induced GH release and any other hormone change (data not shown). The amplitude of the GH response to exercise is dependent on physical fitness, as acute exposure to hypoxia (2,325 m) blunted the GH and IGFBP-3 response to submaximal physical exercise in untrained but not in trained individuals (15). $V_{O_2 max}$ in normoxia and hypoxia was measured in our subjects in a parallel protocol (36), but no correlation was found between the GH response and neither the $V_{O_2 max}$ values in normoxia nor their modification in hypoxia (data not shown). Somatostatin inhibits GH release and is an important regulator of GH baseline level (23), but its influence in hypoxia remains speculative. The feedback mechanism of GH secretion is complex and involves GH itself, besides its mediators, the somatomedins, free fatty acids, GHRH, and ghrelin, which bind to a receptor stimulating GH (9). The hypothalamic factor in small doses will decrease, rather than increase GH secretion, perhaps via a somatostatin interaction. Interindividual threshold variation might result in either increased or decreased response at altitude via this mechanism.

In conclusion, prolonged exposure to altitude hypoxia provokes important hormonal changes that are not caused by modifications of the hypothalamo-hypophyseal axes since unaltered responses to hypothalamic factors were found. Thyroid hormones increased on exposure to high altitude. TSH and the thyroid response to TRH and TSH on the other hand remained unchanged, suggesting the importance of other regulators, such as norepinephrine. Prolactin baseline level was lower at altitude. The inhibitory influence of dopamine on prolactin release could be exacerbated by altitude-induced EPO secretion. Baseline levels of FSH diminished on exposure to high altitude. This hormonal axis seemed disturbed, although LH and FSH responses to GnRH administration were similar at high altitude and at sea level. GH, IGF-1, and IGFBP-3 baseline levels and GH response to GHRH were not affected by hypoxia, although a blunted GH response to GHRH was found in some individuals.

**Perspectives and Significance**

Successful adaptation to prolonged hypoxia depends on an adequate balance between upregulation and downregulation processes. Some agonist-receptor systems involving G proteins seem to be downregulated in hypoxia, while other pathways, such as those depending on hypoxia-inducible factors, are upregulated. Response of hypophyseal hormones to hypothalamic stimulation does not seem to be altered in hypoxia, although GH may play a specific role in metabolic adaptation to hypoxia. Mechanisms behind those effects remain speculative, and further studies on the regulation of the signal transduction systems of these hormones are needed, with a special interest for the effect of hypoxia on G protein-linked pathways.

**ACKNOWLEDGMENTS**

We thank all the volunteers who participated in this study, Malin Sternby, who helped process the data; and Didier Chapelot, who participated in the discussion of the manuscript. We thank Roussel Laboratories (Paris, France) for the hypothalamic factors and BioMérieux, (Marcy-l’Etoile, France) for the use of the MiniVidas apparatus.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

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