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

Jean-Paul Richelet,1,2 Murielle Letournel,2 and Jean-Claude Souberbielle3

1Université Paris 13, Unité de Formation et de Recherche Santé Médecine Biologie Humaine, Laboratoire “Réponses Cellulaires et Fonctionnelles à l’Hypoxie,” Bobigny, France; 2Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpital Avicenne, Service de Physiologie, Explorations Fonctionnelles et Médecine du Sport, Bobigny, France; and 3AP-HP, Hôpital Necker-Enfants Malades, Laboratoire d’Explorations Fonctionnelles, Paris, France

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Richelet 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. —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 hypothalamic 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 T4 was lower in hypoxia during 45 to 60 min after injection. The effect of hypoxia on the hypothalamic 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 hypothalamic 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 hypothalamic 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 0:00, +15:00, +30:00, +45:00, +60:00, +90:00, and +120:00 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, T4, T4, LH, FSH, and prolactin were analyzed in each subject by automated immunoassays, using MiniVidas apparatus (BioMerieux, Marcy-l’Etoile, 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-1 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 was correlated to the hypoxia-induced changes in basal epinephrine; the subjects who had the highest values of 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 1. Basal plasma concentrations of hormones at sea level and at high altitude

<table>
<thead>
<tr>
<th></th>
<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>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free T4, pmol/l</td>
<td>13.9 ± 2.4</td>
<td>16.6 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total T3, nmol/l</td>
<td>1.72 ± 0.20</td>
<td>1.90 ± 0.29</td>
<td>0.006</td>
</tr>
<tr>
<td>Free T3, pmol/l</td>
<td>6.51 ± 0.41</td>
<td>7.54 ± 0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T4/T3</td>
<td>49.7 ± 5.1</td>
<td>51.9 ± 5.1</td>
<td>0.04</td>
</tr>
<tr>
<td>TSH, mU/ml</td>
<td>1.51 ± 0.80</td>
<td>1.37 ± 0.93</td>
<td>ns</td>
</tr>
<tr>
<td>Prolactin, nmol/l</td>
<td>0.63 ± 0.30</td>
<td>0.30 ± 0.20</td>
<td>0.006</td>
</tr>
<tr>
<td>FSH, nmol/l</td>
<td>4.15 ± 2.44</td>
<td>3.44 ± 1.73</td>
<td>0.02</td>
</tr>
<tr>
<td>LH, nmol/l</td>
<td>2.79 ± 0.94</td>
<td>2.33 ± 0.99</td>
<td>ns</td>
</tr>
<tr>
<td>Norepinephrine, nmol/l</td>
<td>3.13 ± 0.73</td>
<td>4.69 ± 1.05</td>
<td>0.012</td>
</tr>
<tr>
<td>Epinephrine, nmol/l</td>
<td>1.01 ± 0.27</td>
<td>1.00 ± 0.54</td>
<td>ns</td>
</tr>
<tr>
<td>Dopamine, nmol/l</td>
<td>2.14 ± 1.04</td>
<td>2.50 ± 0.93</td>
<td>ns</td>
</tr>
<tr>
<td>Cortisol, nmol/l</td>
<td>261 ± 107</td>
<td>330 ± 137</td>
<td>(0.07)</td>
</tr>
<tr>
<td>GH, ng/ml</td>
<td>1.40 ± 1.86</td>
<td>0.73 ± 1.05</td>
<td>ns</td>
</tr>
<tr>
<td>IGF-1, μg/l</td>
<td>168 ± 55</td>
<td>184 ± 53</td>
<td>ns</td>
</tr>
<tr>
<td>IGFBP-3, mg/l</td>
<td>2.17 ± 0.28</td>
<td>2.16 ± 0.28</td>
<td>ns</td>
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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

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**Fig. 1.** Concentrations of total T4, free T4, total T3, free T3, TSH, and ratio T4/T3 before and after injection of hypothalamic factors growth hormone-releasing hormone (GHRH; 1 mg/kg), TRH (0.5 mg), and gonadotropin-releasing hormone (GnRH; 0.1 mg). •, normoxia; □, hypoxia. Significant difference between normoxia and hypoxia, *P < 0.01 and +P < 0.001. Significant difference from time 0, #P < 0.05 or better.

**Fig. 2.** Relationship between the individual values of T4 in hypoxia vs. the variation between normoxia and hypoxia of basal plasma epinephrine concentration (▲ Epinephrine).
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,
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-
secretion is still debated, but it appears clearly that, in normal
GH responses at high altitude. The effect of dopamine on GH
levels and their elevation in hypoxia might explain the varying
amplified by
GH response to exercise is dependent on physical fitness, as
study, we failed to find a significant correlation between the
lease and stimulates the GH response to GHRH, possibly via a
apomorphine, dopamine itself, bromocriptine) causes GH re-
secretion (28, 50). GH release, induced by exercise or falling
altitude could possibly play a role in the GH changes observed
(14). Thus, the increased level of thyroid hormones at high
Thyroid hormones are important for a normal secretion of GH,
acute hypoxia, making hypoglycemia an unlikely cause (40).
plasma levels of glucose are seen in situations when GH levels
are elevated, that is, in chronic hypoxia and during exercise in
hypoxia suggests a disturbed influence of this hypothalamic
regulator at high altitude. This could be caused by a desensi-
tization of the GHRH receptor or an altered GH production.
The GHRH receptor is a seven-transmembrane G protein-
linked receptor and, 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 re-
lease 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 IGF-1
response to submaximal physical exercise in untrained but not
in trained individuals (15). VO_{2max} 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
VO_{2max} 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 in-
creased or decreased response at altitude via this mechanism.

In conclusion, prolonged exposure to altitude hypoxia pro-
vides important hormonal changes that are not caused by
modifications of the hypothalamo-hypophyseal axes since un-
altered 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 alti-
tude. The inhibitory influence of dopamine on prolactin release
could be exacerbated by altitude-induced EPO secretion. Base-
line 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 individ-
uals.

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 hypotha-
lamic 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 specula-
tive, and further studies on the regulation of the signal trans-
duction systems of these hormones are needed, with a special
interest for the effect of hypoxia on G protein-linked pathways.

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

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