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Plasma Concentrations of Hypophyseal Hormones and Corticosterone in Male Mice Acutely Exposed to Simulated High Altitude[1,2] (40779)

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Relatively few studies have examined the plasma concentrations of hypophyseal hormones of sea level resident animals or humans exposed to natural or simulated high altitude (hypobaric hypoxia). Plasma LH and FSH concentrations in pregnant rats were not reported to be significantly affected after various durations of exposure to approximately 12,400 ft simulated altitude as compared to sea level control animals (1). Exposure of mature male mice to higher simulated altitudes (18,000 and 22,000 ft) for 1 to 28 days appears to depress plasma LH values only during the initial 24-hr period of treatment (2), and this effect may be related to hypoxia-induced anorexia and adypsia which have been observed in pregnant female mice (3). Plasma FSH concentrations in male mice are generally reduced through Day 28 of exposure at 22,000 ft (2). The profiles of plasma gonadotropins, PRL, and TSH in men have been reported to be unchanged or slightly reduced during short-term exposures to altitudes between 12,000 and 15,000 ft (4–8), whereas basal GH values may increase slightly (9). In all of the aforementioned studies, the plasma concentrations of hypophyseal hormones were determined in samples obtained over a relatively limited range of altitudes and after at least 24 hr of exposure. Furthermore, the experimental design of these studies did not always compensate for alterations in dietary intake which could potentially confound hormonal parameters. The objectives of the present investigation were to delineate and compare the plasma concentrations of LH, FSH, GH, PRL, and corticosterone (B), and systemic changes immediately following an acute exposure (4 hr of hypobaric hypoxia) to a wide range of simulated altitudes (5000–25,000 ft).

Materials and methods. Male Swiss–Webster mice (Taconic Farms, Inc., Germantown, N.Y.), 5 weeks of age, were received and held for 4 to 6 weeks prior to the initiation of an experimental replicate. The animals were housed in groups of 14 in clear plastic cages (29 × 29 × 18 cm), and were maintained at 21 ± 2° on a 12-hr light:12-hr dark photoperiod. The mice were provided access to food (formula 20-RF; Agway, Inc., Syracuse, N.Y.) and water *ad libitum*.

At the initiation of an experimental period (0800 hr), food and water were removed from one cage of mice to be treated (Fig. 1). The cage of animals was moved to the hypobaric facility (10) and was placed adjacent to the operating hypobaric chamber (mice exposed to the noise generated by the chamber; sea level colony control; 760 Torr), placed within the chamber and maintained at 760 Torr (sea level chamber control), or placed within the chamber and decompressed at a rate of 50 Torr/min to 632 Torr (5000 ft), 523 Torr (10,000 ft), 429 Torr (15,000 ft), 349 Torr (20,000 ft), or 282 Torr (25,000 ft).

The treatment period was terminated after 4 hr (1200 hr). The exposed group of mice was returned to the ambient sea level environment within 0.25–2.0 min, at which time 12 animals were decapitated within the next 3 min. The blood samples were col-

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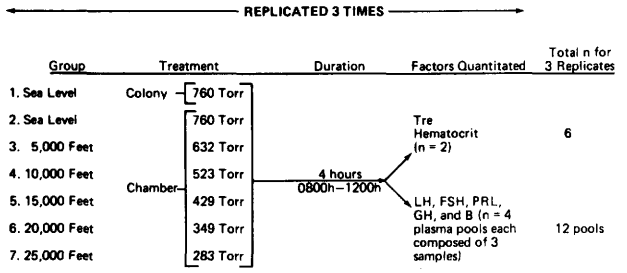

FIG. 1. Experimental design.

lected through funnels into heparinized tubes, and the plasma obtained following centrifugation was pooled (three samples/pool) and frozen at −10°. Rectal temperature (T_{re}) (thermistor probe No. 405 and telethermometer; Yellow Springs Instrument Co., Yellow Springs, Ohio) and hematocrit (microhematocrit method employing a decapitation sample) were then determined in the two remaining mice. These seven treatments were replicated three times (blocks) during consecutive weeks.

The concentrations of LH, FSH, PRL, GH, and B were determined (3, 11, 12) using plasma volumes of 150, 30, 20, 20, and 2 μl, respectively. All samples were analyzed within single radioimmunoassays. The mean coefficients of variation for duplicate determinations were 4.1% for LH, 4.8% for FSH, 3.0% for PRL, 2.9% for GH, and 4.2% for B. The radioimmunoassay data were processed using natural logarithm and logit transformations employing a weighted linear regression model (13).

This study was conducted and analyzed as a 7 × 3 randomized complete block experiment (7 treatments × 3 replications). All variables were tested for homogeneity of variance (14), and were transformed when necessary. The variables were then tested by analysis of variance and subsequently by Duncan's multiple-range test.

Results. Log-transformed LH values were significantly reduced ($P < 0.05$) at pressures below 760 Torr (Fig. 2). The mean circulating levels of FSH appeared to be reduced at pressures below 632 Torr, although the reduction was not always significant (Fig. 2). Mean log-transformed GH estimates in groups exposed to reduced pressure were consistently less than control means; however, comparisons to the sea level colony control group did not reveal any significant differences (Fig. 3). Plasma prolactin concentrations fluctuated considerably, but were not uniformly affected in a pressure-related manner (Fig. 3). Peripheral B concentrations did not differ significantly at pressures ranging from 760 to 429 Torr; however, the plasma estimates of this hormone were elevated approximately threefold ($P < 0.05$) by exposures of 349 and 282 Torr (Fig. 4).

Following the 4-hr exposure period, the hematocrit was unchanged in mice exposed

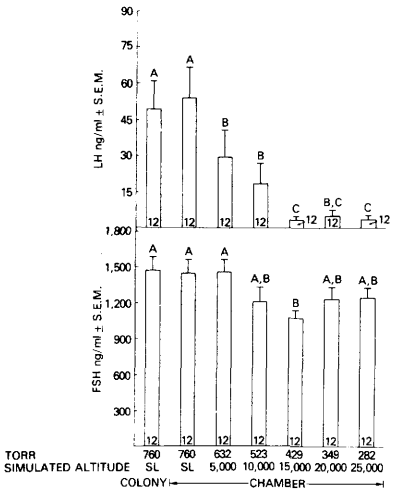

FIG. 2. Effect of a 4-hr exposure to various pressures (760–282 Torr) which simulated altitudes from sea level (SL) to 25,000 ft on the mean plasma concentrations of LH (untransformed values) and FSH (NIAMDD RP-1 standards). Bars with different letter designations are significantly different ($P < 0.05$). The number in each bar corresponds to the number of plasma pools.

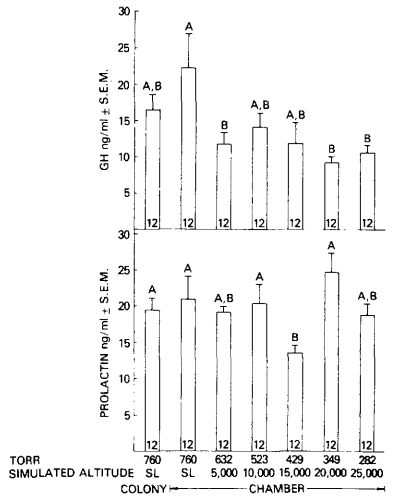

FIG. 3. Effects of a 4-hr exposure to various pressures (760–282 Torr) which simulated altitudes from sea level (SL) to 25,000 ft on the mean plasma concentrations of GH (untransformed values) and PRL. Bars with different letter designations are significantly different ($P < 0.05$). The number in each bar corresponds to the number of plasma pools.

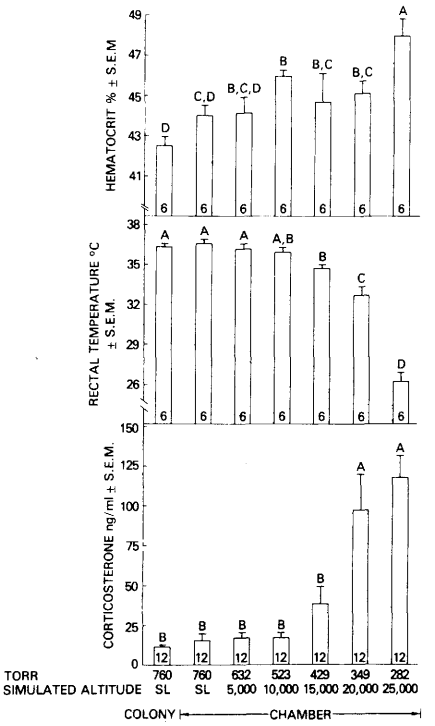

FIG. 4. Effects of a 4-hr exposure to various pressures (760–282 Torr) which simulated altitudes from sea level (SL) to 25,000 ft on the mean hematocrit, rectal temperature, and plasma corticosterone concentration in male mice. Bars with different letter designations are significantly different ($P < 0.05$). The number in each bar corresponds to the number of observations or plasma pools.

to 523, 429, and 349 Torr, and was significantly elevated ($P < 0.05$) in the 282-Torr group as compared to the sea level control groups (Fig. 4). Rectal temperature was reduced ($P < 0.05$) at pressures below 523 Torr, and extreme hypothermia was observed in mice exposed to 282 Torr (mean ± SEM of 26.1 ± 0.60° versus 36.7 ± 0.17° in the sea level colony control group; Fig. 4).

Discussion. The dramatic reduction in the plasma concentration of LH and the moderate decrease in FSH represent the direct effects of hypobaric hypoxia, per se. Previous investigations have demonstrated that plasma LH levels are reduced in pregnant mice exposed to hypoxia; however, this change was related to a reduction in dietary intake (3, 11). The animals in all groups in the present study were deprived of food and water during the treatment period, and thus, the observed effects of acute exposure to simulated high altitude on the plasma content of gonadotropins are not confounded by differential dietary consumption. Furthermore, the reduction in plasma LH levels and the slight decline in plasma FSH concentrations were not initiated by the exposure to the novel environment of the hypobaric chamber, since the concentrations of these hormones were not significantly different in the sea level colony control and sea level chamber control groups. The threshold at which plasma LH levels were depressed occurred at a relatively low altitude (i.e., 5000 ft), and these hormonal changes appeared to be independent of the stress-evoked alteration in plasma corticosterone and systemic hypothermia that are apparent at higher altitudes. This suppression of plasma LH is only transient, since the concentration of this hormone in male mice exposed to either 18,000 or 22,000 ft simulated altitude returns to sea level control values within 3 days; however, plasma FSH levels appear to remain depressed in a sustained manner

for as long as 4 weeks during exposure to 22,000 ft (2).

Prolonged exposure or exercise during acute exposure to high altitude enhances GH secretion in man (9, 15). The observations of the present study indicate that hypoxia fails to elevate GH in the blood of mice, and may actually depress GH content (3). The inability to elevate plasma GH concentration or the actual reduction in the levels of this hormone has been observed for a number of stressors (e.g., cold, exercise, and restraint) in mice and rats (16–19). This decrease in plasma GH concentration could be partially responsible for the reduced ponderal growth of mice observed during chronic altitude exposure (2).

The changes in the plasma concentrations of LH, FSH, GH, and B upon exposure to simulated high altitude are considered to be due to alterations in hormone secretion and possibly clearance. It is known that maximal activation of the hypothalamo–hypophyseal–adrenocortical system during acute hypoxia is dependent upon peripheral chemoreceptors (20–22), and central and peripheral aminergic and cholinergic function (23, 24). In the rat it has been demonstrated that hypoxia decreases brain synthesis and metabolism of norepinephrine, dopamine, and serotonin due to diminished activities of tyrosine and tryptophan hydroxylases, which is presumably the result of a reduction in oxygen substrate (25, 26). These changes in neurotransmitter turnover, and possibly the direct effect of reduced oxygen on hypothalamo–hypophyseal function, may ultimately be responsible for the observed changes in the circulating concentrations of gonadotropins and GH (27, 28).

The plasma concentrations of PRL were not consistently modified by exposure to simulated high altitude, whereas corticosterone levels increased at simulated altitudes of 20,000 and 25,000 ft. A common neuroendocrine pathway for the release of PRL and ACTH (as assessed by the rise in circulating B) during stress has been described (29–31); however, the concentrations of PRL and corticosterone following hypoxic exposure do not seem to be related in this study and another (2). This apparent discrepancy in PRL and corticosterone concentrations, and the inconsistencies in the effects of altitude and certain other noxious stimuli (i.e., a 4-hr exposure to varying degrees of hypobaric hypoxia does not uniformly affect plasma PRL concentration, whereas exposure to ether fumes, cold, restraint, or laparotomy initially elevates plasma PRL levels, which then seem to decline below control values for several hours; 17, 19, 29, 32), could be due to factors such as duration, intensity, and nature of the stressors, or biological rhythms, age, sex, and reproductive state of the animals.

The elevation of hematocrit and the reduction in body temperature constitute typical systemic responses to acute hypoxic exposure. The moderate polycythemia is probably related to the reduction in plasma volume (resulting from polyuria and respiratory loss of body water) and to an increase in circulating red blood cells (brought about by contraction of the spleen), rather than by enhanced hematopoiesis which accompanies chronic hypoxia (33). Hypoxia-induced poikilothermia has been described in rodents, and the more pronounced hypothermia observed in exposed mice as compared to rats is probably due to their relatively greater surface area which facilitates heat dissipation (33, 34). The reduction in body temperature appears to coincide with adrenocortical activation, but does not seem to be related to the plasma concentration of the hypophyseal hormones measured in this study.

Summary. The concentrations of gonadotropins, growth hormone, prolactin, and corticosterone were determined in plasma pools ($n = 12$) obtained from male mice immediately after a 4-hr exposure to 632, 523, 429, 349, or 282 Torr (simulating 5000–25,000 ft altitude). The mice in all groups were deprived of food and water during the 4-hr treatment period. The peripheral levels of LH were consistently reduced ($P < 0.05$) by exposure to an altitude as low as 5000 ft, whereas plasma FSH and GH estimates were somewhat reduced at simulated high altitude as compared to sea level controls. Plasma PRL concentration was not uniformly affected

by simulated altitude exposure, but circulating corticosterone values increased ($P < 0.05$) at altitudes above 15,000 ft. The findings of this study demonstrate that moderate hypoxia, per se, can significantly reduce the plasma concentrations of LH, and to a lesser degree FSH and GH, even in the absence of changes in dietary intake, systemic hypothermia, and the stress-related rise in plasma corticosterone.

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