HORMONAL CHANGES UNDER ALTITUDE STRESS

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The separate effects of exposure for six hours to cold (8°C), hypoxia (4267 m.) and simulated altitude (8°C at 4267 m.)have been studied on ten human subjects in a decompression chamber, with respect to the changes in blood cortisol, ADH and urinary catecholamines. Changes in blood cortisol, PBI, ADH urinary excretion of 17-keto steroids and urine volume have been recorded on another ten subjects on acute exposure to high altitude (3505 m.). Changes in the same parameters alongwith urinary testosterone level, have been recorded on another 20 subjects on prolonged exposure for two years to high altitude (3505 m.). The results have been discussed.

Hormones have been reported to play a major role in the maintenance of resistance to environmental changes[1]. The adrenal hormones, both medullary and cortical appear to be the most important regulatory factors[2]. The output of adrenal cortical hormones increases in response to acute hypoxia but returns back to the sea level values within 3-21 days of stay at high altitude[3—7]. Increased secretion of epinephrine and nor-epinephrine have been reported to indirectly decrease the altitude tolerances while cortisone and ACTH secretions stimulate[9] it. Adult female rats have been reported to be much more resistant to hypoxic stress than the males, perhaps because their adrenals are larger in size[2]. In mice, resistance to anoxia is reported to be increased by administration of posterior lobe extracts[10]. ADH has been reported to regulate the water balance under hypoxic stress[11]. Diuresis has been reported to occur on exposure to actual or simulated altitude stress[12]. Thyroid activity has been reported to be depressed during stay at high altitude[13] while Surks [14] *et. al.* reported elevated PBI level under hypoxic stress, and Verzer[15] *et. al.* correlated the increased adrenocortical function with decreased thyroid activity. In rats, thyroidectomy and administration of propylthiouracil have been reported to increase while feeding of desiccated thyroid to decrease resistance to hypobaric hypoxia[16].

Brief exposure of rats to simulated altitude has been reported to cause testicular tension, impairment of spermatogenesis and degeneration of the germinal epithelium but these changes regress to normal on return to sea level conditions[17]. Decrease in sperm concentration, azoospermia, decreased sperm motility and increased abnormal forms have been reported [18,19] in sheep transported to high altitude. Human subjects on exposure to 4267 m. for four weeks have been reported[20], to show decrease in sperm count, a significant increase in the abnormal forms, decreased motility but an elevation in seminal fructose level. Seminal *pH* was also reported to have been raised but seminal citric acid remained normal until descent to sea level which led to recovery. It has been reported that sea level residents transferred to high altitude show a significant decrease in the urinary testosterone level on the third day of exposure[21]. A decreased excretion of 17-ketosteroids in human subjects at high altitude has also been noted[5]. Results of different investigations carried out by us on human subjects under various periods of stay at high latitude and on exposure to simulated high altitude conditions, hypoxia and cold, in a temperature controlled human decompression chamber are presented in this paper.

MATERIALS AND METHODS

Phase I : *Studies in the Temperature Controlled Human Decompression Chamber*

Two groups of five adult male human subjects of the age group 20-30 years were exposed for six hours in the decompression chamber, at intervals of one week between exposures, under the following stresses :—

(*i*) Cold stress only at 8°C without hypoxia.

(*ii*) Hypoxic stress only simulating an altitude of 4267 m. at 28°C (room temperature).

(*iii*) Altitude stress simulating 4267 m. at 8°C (Cold and hypoxia).

Their urinary catecholamines, plasma cortisol and blood ADH levels were determined before and immediately after six hr. exposure to the stress concerned.

Phase II : Studies Under Actual Altitude Stress (3505 m.)

(a) Short term acute exposure, to high altitude Av. temp. (10°C): A group of 10 adult male human subjects of the age group 20-30 years, who are normal residents of sea level regions, were examined at the base laboratory for their sea level (S.L.) values of blood cortisol, serum PBI, blood ADH, 24 hr. excretions of 17-Ketosteroids and 24 hr. urine volume. These subjects were then airlifted to an altitude of 3505 m. and examined periodically for the same parameters during their stay for 18 days at high altitude. They were again examined after three days of their descent, by air, to S.L. (R.S.L.)

(b) Effect of prolonged stay at high altitude : Twenty subjects similar in nature to those studied under (*a*) were initially examined at the base laboratory and their sea level (S.L.) values for serum PBI, plasma cortisol, blood ADH, 24 hr. urinary testosterone and 17-ketosteroids excretion were determined. These subjects went up to an altitude of 3505 m. by road and stayed there for a period of two years including one to two months stay each year at their sea level residence and re-entry to high altitude by road. The above parameters in these subjects were again determined within 15 days of their return to the base laboratory at sea level and these values (R.S.L.) compared with the initial (S.L.) values.

Serum PBI was determined by the method of Barker and Humphery[22], plasma cortisol by the fluorimetric method of van de vies[23], ADH by the bioassay method of Yoshida[24] *et. al.*, catecholamines by the fluorimetric method of Sobel and Henry[25] urinary 17-Ketosteroids by the method of Drekter[26] and urinary testosterone by the method of Szereday and Sacks[27].

RESULTS

Hormonal changes observed in human subjects exposed to various stresses in the temperature controlled human decompression chamber are given in Table 1.

TABLE 1

HORMONAL CHANGES ON EXPOSURE TO VARIOUS STRESSES IN DECOMPRESSION CHAMBER FOR SIX HOURS

(Mean±SE for 4 subjects)

Parameter	Basal 28°C at S.L.	Cold 8°C at S.L.	Hypoxia 28°C at 4267 m.	Altitude 8°C at 4267 m.
Urinary excretion of catecholamines μg/6 hrs	36·3± 7·30	* 58·2 ± 7·31	47·3 ± 8·06	48·3 ± 10·42
Plasma cortisol μg/100 ml.	8·63± 2·39	* 9·54± 0·20	** 12·64± 0·32	** 17·92± 0·00
Blood ADH μu/ml.	2·2± 0·39	2·23± 0·37	* 4·67± 0·75	2·88± 0·70

Significance of difference from basal value.

*P<0·05 **P<0·001

Urinary excretion of catecholamines was significantly raised on exposure to cold, plasma cortisol was raised both in hypoxia and altitude stress while blood ADH was high on hypoxic stress only.

Progressive changes in the levels of blood cortisol PBI, ADH and urine volume of lowlanders during their short stay at actual high altitude (3505 m.) are given in Table 2. Plasma cortisol began to rise within three days of arrival at high altitude, reaching the maximum level in 7– 9 days. After 13 days it appeared to stabilise for the rest of the period of stay (18 days) at high altitude. On return to the sea level it again showed a sharp rise. All these changes are statistically significant.

TABLE 2

PROGRESSIVE CHANGES IN BLOOD CORTISOL, PBI, ADH AND URINE VOLUME OF LOWLANDERS DURING SHORT STAY AT HIGH ALTITUDE (3505 m. AT 10°C AVERAGE TEMP.)

Parameter studied	Period of stay at high altitude (days)							
	S.L. at 28°C	0—3	4—6	7—9	10—12	13—15	16—18	R.S.L.
		*	***	***	***	**	**	***
Plasma Cortisol μg/100 ml.	18·0± 0·485	22·50± 1·82 ***	49·0± 3·363 ***	55·50± 3·75 ***	40·50± 2·856 ***	21·50± 1·125 ***	21·50± 1·25	32·0± 2·98
PBI (Serum) μg/100 ml.	6·9± 0·19	5·0± 0·191	5·2± 0·190	5·3± 0·215 ***	5·55± 0·203	5·55± 0·195	.. ..	7·0± 0·501 **
ADH (Blood) μ/ml.	1·95± 0·112	1·40± 0·107	2·23± 0·207 **	3·40± 0·05	.. .. ***	2·50± 0·15 ***	.. ..	1·50± 0·075
Urinary excretion of 17-ketosteroids, mg in 24 hrs.	8·00± 1·00	.. ..	17·00± 1·6	.. .. *	24·00± 2·1	23·8± 1·9	.. ..	9·5± 1·2
Urine Volume, m l/24 hrs.	1030± 60	1040± 50	1200± 55	1339± 110	1238± 70	1217± 70	.. ..	1015± 55

Significance of difference from S.L.

*P<0·05; **P<0·01; ***P<0·001

PBI level decreased within the first three days of arrival at high altitude and maintained a significantly low level during the period of stay at high altitude. On return to sea level PBI rise to the original S.L. value.

ADH level showed a decrease within the first three days followed by a rise in 4-6 days, reaching a maximum at 7-9 days which is statistically significant. At 13-15 days the level was lower than the maximum and on return to sea level it decreased further below the original S.L. value.

Twenty-four hours urinary excretion of 17-Ketosteroids progressively rose in the subjects at high altitude till 10-12 days and dropped back to S.L. value on return to S.L. Urine volume for 24 hr. gradually rose at high altitude till 7-9 days and then gradually decreased but maintained a higher level till 13-15 days. It dropped to the original S.L. value on return to S.L.

Hormonal changes in subjects after a prolonged stay of two years at high altitude are given in Table 3. Serum PBI level and 24 hr urinary excretion of testosterone were still significantly lower than the original S.L. values.

TABLE 3

HORMONAL CHANGES ON PROLONGED STAY AT HIGH ALTITUDE (3505 m).

Parameter studied	Sea Level (S.L.)	After two years' stay at High altitude (R.S.L.)	Significance of change
Serum PBI μg/100 ml.	6·9± 0·19	5·59± 0·6008	P<0·05
Plasma Cortisol μg/100 ml.	18·0± 0·485	18·43± 2·9923	NS
Blood ADH μu/ml.	2·6± 0·218	2·66± 0·6455	NS
Urinary testosterone μg/24 hrs.	30·0± 2·19	18·26± 1.8098	P<·001
Urinary 17-ketosteroids, mg/24 hrs.	10·00± 0·09	12·38± 1·30	NS

DISCUSSION

The involvement of the adrenal cortex in the mammalian response to hypoxic stress was first suggested by Rabenno[23] although he concluded that the increased cortical activity of the gland in animals exposed to high altitude was due more to the cooler ambient temperatures than to the decreased oxygen tension encountered in mountainous regions. Giragossintz and Sundstroem[29] suggested that there was a greater need by the body for adrenal cortical hormones under conditions of hypoxia. Interest in this problem during the second world war[30] stimulated research which established that hypoxia is a powerful stimulator of the adrenal cortex[31–36].

Our studies Table 1 suggest that the adrenal medulla is more stimulated than the cortex under the cold stress whereas the reverse is true, as suggested by earlier observers, for the hypoxic stress. At high altitudes, where both these stresses are involved, a mixed effect is observed, although the effect on cortisol activity is more apparent. Any sudden change of altitude has been found to bring about a rise in blood cortisol level as has been clearly observed in our subjects who showed a rise in blood cortisol level on being airlifted to 3505 m. from the sea level and again on being flown back to sea level after stabilization of the cortisol level at high altitude after 18 days stay, (Table 2). On prolonged stay at high altitude, however, adrenal cortical activity seems to return to the sea level value as is evidenced by the plasma cortisol levels at S.L. and after two years of stay at high altitude (Table 3).

The antidiuretic hormone (ADH) secretion had been postulated to be lower at high altitude leading to diuresis[3] as normal human subjects have been reported to suffer from diuresis on arrival at high altitude[37]. Our observations in the decompression chamber show that (Table 1) hypoxia has a direct effect in increasing ADH secretion whereas cold or altitude and cold exposure doesn't alter the blood ADH level significantly.

Our studies on lowlanders taken to high altitude (Table 2) have shown that the ADH level falls slightly on arrival at high altitude and shows a gradual rise after three days, reaching a maximum level in 7-9 days, while the urine output also shows a significant rise at the same time as the maximum levels of both ADH and cortisol in the blood, *i.e.*, at 7-9 days of stay at high altitude. It is apparent, therefore, that the high ADH level at nine days is not able to exert its usual antidiuretic effect, which may be due to a simultaneous rise in the plasma cortisol level, a normal adaptive phenomenon.

According to Currie and Ullmann[38], when the pituitary adrenal system is activated by stress, both vasopressin and adrenal steroids are released. In such conditions, whether a person will exhibit antidiuresis or polyurea, apparently depends upon the equilibrium between vasopressin and the adrenal steroids. For example, patients undergoing severe stress with demonstrably increased adrenocortical activity excrete large volumes of relatively dilute urine even when dehydrated. This occurs despite marked increase of ADH in plasma and urine and there is only a slight antidiuretic response to administered ADH; suggesting that the renal action of ADH is antagonised by the adrenal steroids[39]. In our studies, therefore, the raised ADH level could not exert the usual antidiuretic effect since the cortisol level had risen simultaneously to antagonise the renal action of ADH. This explains how normal subjects have been observed to exhibit diuresis at high altitude despite raised ADH levels.

It would be interesting to mention here, that persons susceptible to pulmonary oedema fail to show the normal adaptive phenomenon of rise in blood cortisol on arrival at high altitude, or they fail to maintain a raised cortisol level for sufficient period to counteract the renal effect of the raised ADH level[40]. Oliguria, as noted by Inder Singh[12] *et. al.*, in such cases may, therefore, be due to this uncompensated ADH rise related to failure of the normal cortical response. Attempts to raise the blood cortisol level in such cases should appear helpful in controlling the onset of pulmonary oedema. Moreover, cortocosteroids probably protect against hypoxia by facilitating aerobic metabolism[41].

Thyroid function at high altitude has been reported to be depressed by many workers[42–44] while increased activity has also been reported[45, 46]. Our observations on lowlanders taken to high altitude (Table 2) support decreased activity as evidenced by a low PBI level within the first three days of arrival with a slight tendency to rise till 10-12 days when it gets stabilized at a lower level. The lower level continues during the stay at altitude even after two years (Table 3). On return to sea level, however, PBI promptly returns to the initial level (Table 2). Experimental rats

subjected to high altitude hypoxia exhibit no visible pathological changes but there is nevertheless marked hypofunctioning of the gland[47, 48]. The thyroid hypofunction at high altitude has been suggested to lead to a series of complex changes like retardation of growth, fall in fertility and in severe cases even total sterility [49–53].

Timiras[5] *et. al.* reported that human subjects showed increased excretion of 17-Ketosteroids for the first three days of stay at 3800 m., urinary and plasma level of all adrenocortical hormones and their metabolites appeared to be related to the duration of exposure and the degree of acclimatisation. They rose for the first three days of each sojourn at altitude and then reduced to the sea level values. Siri[54] did not find increased excretion of 17-ketosteroids and a few of his subjects on the Himalayan expedition showed decreased excretion of 17-ketosteroids at 6096 m. Elizabeth[55] also noted a decreased excretion of 17-Ketosteroids at 20,000 ft; while there was an increase in the excretion of 17-hydroxy corticoids.

The excretion of 17-ketosteroids in our subjects at high altitude doubled in 4-6 days of stays (Table 2) and attained a maximum level in 10-12 days after which there was no further rise, and as evidenced by our observation on subjects after two years stay at high altitude (Table 3) there must have been a gradual decline in excretion bringing the level to just slightly above the sea level value. Since the 17-ketosteroids are a complex mixture of compounds which may originate from several glandular percursors, some of which are not androgens, its usefulness as an index of androgen function is limited and so it cannot be ascertained whether this initial rise of 17-ketosteroids is due to increased testicular activity or is the result of increased adrenal cortex activity as noted by us and also by previous workers (Loc-cit). Testosterone level of blood or its excretion level only can give useful indications of testicular function at high altitude. It was not possible for us, for technical reasons, to estimate gradual changes in testosterone excretion at high altitude. This was done only once at sea level before induction to high altitude and again at the end of two years stay at high altitude.

The results (Table 3) indicate a significant decline in urinary testosterone after two years stay at high altitude.

Monge[56] found that cattle and domestic cat show signs of reproductive failure, at altitudes of 3350-4500 m. The failure of the male fertility was attributed to exfoliation of the germ cells into the ducts of the epididymis before maturation. The spermatozoa were found to be outnumbered by immature cells. Azoospermia, decreased sperm motility and deviations of *pH* have also been observed[57–59]. Both follicular activity and Leydig cell activity thus appear to be suppressed at high altitude.

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