ANIMAL METABOLISM AND NUTRITIONAL REQUIREMENTS UNDER PHYSIOLOGICAL STRESS—EFFECT OF HIGH ALTITUDE

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Various biochemical and physiological aspects of high altitude exposure and an integrated picture of metabolism of the organism during stress has been reviewed in this paper. This has been further utilised to point out specific nutrient requirement, if any, for survival of the organism during stress and to develop increased resistance towards high altitude exposure. Carbohydrates appear to be the best calorific food material under conditions prevailing at high altitude.

The study of biological response under the stress of high altitude, especially on human beings, has attained considerable significance in the last decade due to the onset of space age and to human urge to explore the mountainnous terrain of our planet. The studies are also of importance as the northern frontiers of our country are delimited by the mountainous terrains occasionally more than 3000 meters high and also due to the significance of air cover in modern warfare.

The biological response and subsequent adaptation to high altitude is a complex phenomenon. The influencing factors are progressive decrease of atmospheric pressure, oxygen tension, temperature, humidity, and dust particles and gradual increase in the intensity and variation in the nature of light and cosmic radiations. However, hypoxia and low temperature play more significant role as compared to other factors at high altitude in producing a strain in the living system. Besides, the combined action of these factors is not insignificant. The variation in excretory pattern of several salts and nitrogen compounds is only transiently affected by altitude stress. whereas cold and heat, when coupled with altitude, provide a more severe climatic strain on the organism and often make the strain more lasting[1,2]. At high altitude the increase in the production of energy in order to make up the heat losses due to very low ambient temperature has to be adjusted by the ventilation capacity of the organism and availability of oxygen[3,4] and so on. In this review, the studies involving high altitude flying in aeroplanes or spacecrafts have not been emphasized because of the several other complicating factors. Earlier reviews on the subject deal primarily with the physoilogical aspects of high altitude exposure and adaptation.

HORMONAL VARIATION AND CELLULAR METABOLISM AT HIGH ALTITUDE

Adrenal hyperfunction and hypertrophy[5] on exposure to high altitude reflects on anterior pituitary sensitivity and typical pituitary adrenal response during stress[6]. Adrenalectomised animals are more sensitive to reduced pressure at high altitude and their resistance increased with the administration of cortisol[5]. However, in comparison to other stressors the adrenal activity during high altitude exposure may remain high even after 3—4 months[7] though, the ACTH (Adrenocortico-traphic hormone) sensitivity of the adrenal cortex is apparently decreased as determined by the enhanced nitrogen excretion in response to exogenous ACTH[8].

The excretion of 17—ketosteroids[9—11] cortisone[12] and 17—hydroxy corticosteroids[13] increases at high altitude. Flying personnel showed a tendency to excrete larger amounts

of corticosteroids[14,15] with an increase in plasma level of free and conjugated steroids[16] if flying at high altitudes with high speed[14—16, 18]. Steroid level in urine has been suggested as an index for evaluation of stress in flying[19] personnel. The failure to detect adrenal personel personnel response at high altitude in some of the investigations[20—23] is difficult to interpret. Even in foetal stage, hypoxia equivalent to 5486 meters brings out an adrenal response[24].

The haemoglobin level in the blood appears to be under the direct control of "Erythropoietin" and "Erythropenin" (presumably secreted by kidney) detected in the urine of high altitude exposed human beings[25] and under the indirect control of several other humoral factors such as testosterone and estradiol, somatotrophic hormone, ACTH and thyrotrophic hormone. Residents of high altitude do not excrete any specific substance similar to erythropoetin in urine[26]. The equilibrium between the destruction and the formation of erythrocytes is maintained by the specific and nonspecific regulatory processes which interact and supplement each other[25]. The excretion of 3-methoxy-4-hydroxy mandelic acid[27] and uropepsin also increases during stress and excretion of uropepsin appears to be mediated through adrenal hormones[28].

A report by Hale and Meffered emphasised the role of somatotrophic hormone in augmenting resistance and adaptation changes in rats exposed to simulated altitude[29]. However, the somatotrophic hormone has a protective effect when given with subeffective doses of cortisol to adrenalectomized animals indicating further the significance of adrenals in resistance mechanism to high altitude[30]. Under simulated high altitude conditions the concentration of nor-adrenalin in a brain, and adrenalin and nor-adrenalin in the adrenals increased with duration and decrease of pressure indicating variation in circulatory system and increased mobilization of carbohydrate and fat stores[31].

Thyroidectomy as well as administration of thyroid suppressing drugs were found to enhance the survival of normal rats at high altitude[32]. However, adrenalectomized rats do not show increased resistance and higher survival rate on being thyroidectomized. On the other hand, a definite and significant increase in resistance occurred on the administration of subeffective amount of cortisol to adrenalectomized thyriodectomized rats[30]. This effect might have been due to decreased rate of steroid degradation in thyriodectomized rats[33,34]. The significance of adrenals, therefore, in augmenting the resistance to high altitude seems beyond doubt.

Increased thyroid activity appears to decrease the resistance due to limited availability of oxygen at high altitude environment. Hypoxia, in itself, seems to suppress thyroid activity[35]. Thyroid iodine content is less in swines raised and reared at high altitude as compared to those at plains. The increased muscle fat content among high altitude swines also point out a decreased thyroid activity[36].

Inspite of the freqeunt studies relating the variations in level of hormones to stress, the link between hormonal system and metabolic machinery has been investigated only in few cases[37]. These reactions are of importance from the point of view of enzymatic regulation and metabolic control *in vivo* and therefore, are of significance in studies connected with metabolic changes and adaptation in response to climatic variations.

Glucose is the immediate source of energy in emergency situations[38] especially for the survival of muscle tissues and central nervous system. Therefore, an increase in glycogenolysis, circulating glucose level and peripheral utilization of glucose is expected in response to hypoxia and high altitude. Several conflicting reports regarding variations in blood sugar level[38—45,3] and tissue glycogen concentrations[40, 41, 43, 47,] in response to hypoxia and high altitude are available. In order to evaluate these, Timiras *et. al*[48] carried out

a detailed investigation on rats. The hyperglycemia was observed in fed rats exposed to high altitude after 24 hours, and hypoglycemia after 72 hours. Long term exposure brought the sugar level to normal concentration. Well-fed rats exposed to an altitude of 3,800 meters for seven and a half hours had markedly decreased glycogen content in liver, heart and skeletal muscle. However, on fasting, rats exposed at altitude retained higher concentration of glycogen as compared to that at plains indicating a decreased glycogen mobility during starvation. Prolonged exposure from two to six months brought the glycogen level to the same concentration as that at plains but after ten months glycogen concentration decreased again.

The cardiac glycogen content, however, remained high throughout the period after two months of exposure. The rat born at high altitude had lower body weight, smaller size and decreased hepatic and skeletal muscle glycogen content[48]. Hyperglycemia observed in dogs exposed to simulated altitude of 9,754 meters was abolished during subsequent exposures but other concommitant enzymatic changes took place. Ecolid partially inhibited the hyperglycemicresponse indicating that it was connected with the neural stimulation[49]. Hyperglycemia was also observed in response to decreased pressure[50, 51]. During exhaustion the blood sugar level decreased to dangerously low levels with possibility to prove fatal[52, 53].

Exposure of guinea pigs to reduced pressure of 0·3 atmoshpere lasting twenty seconds once or repeatedly, decreased the glycogen of liver and muscle and increased the lactic acid of liver and blood without affecting glucose and pyruvic acid level[54]. Probably an equilibrium exists between utilisation and subsequent oxidation of glucose and pyruvate with the formation of glucose through glycogenolysis during high altitude exposure. Another report[55], confirmed that the glucose and pyruic acid levels of liver and blood remain unaffected in response to high altitude. Repeated hypoxic exposure induced a conditioned reflex drop in muscle glycogen and a rise in lactic acid in liver[54]. Exposure of female mice for 3—4 months at an altitude of 6096 meters brought down the tissue citric acid level by 20—30%. This effect did not appear to be mediated through cortisone as the latter, under similar conditions, did not affect the citric acid concentration in tissues except in kidney and spleen[56]. The increase in brain lactic acid in response to high altitude appears to be mediated through adrenal[57]. Hypoxic exposure of rabbits resulted in an increased anaerobic glycolysis in nerve cells and only a slight increase in glia cells[58]. The increase in aldolase concentration of skeletal muscle of high altitude acclimated rats [59] and serum aldolase of rabbits[60] indicated an increased rate of glycolysis in muscles although brain glycolytic intermediates like hexose diphosphate, glucose-l-phosphate, diphosphopyridine nucleotide and orthophosphate were not affected in rats acclimated to high altitude[61]. Heart aldolase and lactic dehydrogenase activity of blood, liver and muscle of rats [59—62] exposed to high altitude were more or less not affected.

The variation in the metabolism of carbohydrates as a result of acclimation to high altitude is interesting and more significant. Picon-Reategui[63] reported a lower blood glucose concentration and low glucose tolerance curve in subjects residing at high altitude. Increased utilisation of sugar was indicated only in first thirty minutes after glucose administration Variation in absorption rate was insignificant in persons residing at high altitude as compared to those residing at sea level. An increase in the level of pyruvate and lactic acid in residents of high altitude after 240 minutes of glucose administration was interpreted in terms of epinephrine release. Epinephrine appears to raise the blood lactic and pyruvic acid to a higher level in subjects acclimated to high altitude as compared to those living at sea level[63].

The equilibrium between protein utilisation and gluconeogenesis in response to cortisone administration at an altitude of 4,267 and 6,096 meters was 46 and 36% respectively. In contrast the control had 92·90%. At high altitude if oxygen was provided the percentage[8] resynthesised carbohydrates was 98%. At high altitude gluconeogenic capacity of mice is radically affected and oxygen restores this capacity[64]. However, excretion of nitrogen did not show a decrease when oxygen was given indicating that the protein degradation was primarily in response to reduced atmospheric pressure rather than due to hypoxia. Acclimation to high altitude results in an elevated rate of peripheral utilisation of glucose[63].

Enhanced glucose transport and phosphorylation was reported by Morgan and *et. al.*[65]. Hypoxia simulating high altitude, appears to result in changes in electron transport path way as indicated by an increase in DPNH oxidase, and transdehydrogenase activities of heart and skeletal muscle[66] and liver expressed on the basis of nitrogen content. The activity of DPNH oxidase in human muscle homogenate and TPNH cytochrome C reductase and transdehydrogenase in mitochondial fraction were higher in high altitude residents. The microsomal DPNH-Cytocrome C reductase and TPN iso-citric dehydrogenase, mitochondreal iso-citric dehydrogenase and lactic dehydrogenase in the supernatant did not differ in the activity as compared to control values[67]. The increase in DPNH oxidase activity in the thigh muscle of guinea-pigs at high altitude was shown by Renyafarje[68]. An increase in cytochrome oxidase of nerve cells was also reported[58]. The Cytochrome C reductase of liver and kidney first decreased but after two months of exposure became higher[69].

An interesting study connected with the genetic acclimation of mice to hypoxia was carried out by Verzhbinskaie. The study was extended over to eleven generations of mice. Adaptation to hypoxia took several generations to develop and consisted of an increase in metabolism of adensintriphosphate, permeability of blood brain barrier to P^{32} and subsequently an increased efficiency of oxidative phosphorylation in brain[70]. In contrast acclimatization spread over a short period did not result in an increased incorporation rate P^{32} into ATP determined with brain tissues although by a doubtful technique[61]. The P/O. ratio with heart and liver was not affected by high altitude acclimation of rats. In fact succinate, α—Ketoglutarate and β—*OH*-butyrate respiration by liver mitochondria showed a decreased rate. ADP stimulated heart mitochondria of acclimated animals to a greater extent, as compared to corresponding controls[71]. Complete anoxia even for three minutes brought a drastic variation in energy metabolism in acclimated rats resulting in spontaneous break down of Adenosine di-and tri-phosphate, phosphocreatine and glycogen stores of brain with simultaneous increase in orthophosphate, lactic acid and adenylic acid[61]. The levels of glycolytic intermediate like hexosediphosphate, glucose-6-phosphate and fructose-6-phosphate were not affected. At high altitude there is a general accumulation of high energy phosphates and DNA[72]. The cytochrome C-oxidase activity in liver was also elevated[72] though brain cytochrome oxidase was not affected[61].

A transient but sharp increase in serum transminases, lactic dehydrogenase and alkaline phosphates was reported by Highman & Altland[49] in dogs exposed for 4 hours to simulated altitude of 9, 754 meters, The glutamic-oxaloacetate transminase of myocardium,[73] liver[74] and kidney[69] were decreased during hypoxia. The glumatic pyruvic transaminase also decreased in liver and kidney. If the exposure is prolonged or repeated, it shows variations in the serum enzyme levels. Glumatic-oxaloacetic acid-transminase and lactic dehydrogenase show a steady increase over a 7 week period; glumatic-pyruvic-transminase values were stabilised at the end of second week at slightly higher values and alkaline phosphatese

and aldolase stabilised after third week at two to three times of the normal values. After cessation of stress, values attained normal level by the sixth week. In the first two weeks values fell markedly[59]. Acclimation to high altitude resulted in an elevated level of blood alkaline phosphatese and orthophosphate. The glumatic-oxaloacetate and glutamic-pyruvic transaminase activities were not affected[75]. Baranski's[76] studies connected with the incorporaton of P^{32} in brain structures indicated a wide disturbance in cellular metabolism as a result of exposure of mice to hypoxia simulating an altitude of 3,000 to 8,000 meters Protein and nucleoprotein metabolism seems to be radically affected as indicated by slow incorporation rate of P^{32}.

The DNA content of neurons increases in response to hypoxia[58]. The cholinesterase activity in blood diminished in children residing at an altitude of 2,200 m[77]; Hepatic histidine decarboxylase decreased and histamine increased indicating a very low level of histamine in the system in response to high altitude and conservation of histidine. This response was abolished if histidine was incorporated in the diet indicating its specific requirement in low oxygen atmosphere[78]. Vacca had reported earlier that succinic-oxidase and succinic dehydrogenase activities of heart, kidney, liver and skeletal muscle of rats subjected to acute and discontinuous chronic hypoxia were not affected[70]. On the other hand, hepatic succinic dehydrogenase (rats)[79,7] and succinic oxidase (guinea pigs)[72] activities were reported to be high in tissues of experimental animals exposed to high altitude. The capacity to mobilize protein resulting in increase of blood non-protein nitrogen and nitrogne excretion in response to administration of ACTH seems to diminish in high altitude adapted mice[8]. In rats, excretion of urea, uric acid, creatinine and taurine after 24 hours of fasting was suppressed during exposure to 3,658 m. The excretion of histidine, glycine, alanine, methionine, serine and aspartic acid also decreased markedly[80].

The lipid metabolism as a whole, appears to be depressed under hypoxia and at high altitude. At a simulated altitude of 5,486 m. a decreased incorporation of acetate in the total non-saponifiable lipids, cholesterol, total fatty acids and solid and liquid fatty acid was reported[79] in comparison to rat tissues not exposed to high altitude. The ratios between solid fatty acids/cholesterol, cholesterol/non-saponifiable lipids, and solid fatty acid/liquid fatty acid were decreased. Increased cholesterol and phospholipid concentration in the blood of pilots flying for a day was reported[39].

Infusion of fat at 3,658 m. results in a sharp decrease in oxygen content of the blood, the decrease is more than double the amount which takes place on ground level, indicating an enhanced utilisation of oxygen for oxidation of fat[81]. The 17-oxy-steroid excretion increased and a possible relationship between cholesterol metabolism and steroid excretion was indicated. Administration of lipo-oxidase in rats under hypoxia gave a protective action upto 3 hours. The protection might have been brought by the lipoperoxides as an accessory source of oxygen.

BASAL METABOLIC RATE, RESPIRATION AND AC DIBASE BALANCE

A study was made by Picon-Reategui to establish a standard of reference for basal metabolic rate (BMR) in order to compare the findings of other investigators and to correlate BMR with creatinine excretion and body composition among residents of high altitude[82]. The BMR of healthy adult males living at an altitude of 4,542 m. above sea level was not different from the people residing at sea level on the basis of the body surface area. When fat free body mass, cell mass or cell solids were used as standard of reference,

the BMR was reported to be higher in the high altitude residents[83] indicating an increased level of cellular activity at high altitude. Recently, Grover has indicated an increased oxygen requirement at high altitude for unacclimated human subjects, reflecting the increased energy requirement for enhanced ventilation [84]. However, Johnson and coworkers have presented the data indicating no difference in oxygen consumption at different ambient pressures[85].

Hypoxia at high altitude may not affect the BMR as determined on the basis of body surface area or the efficiency of muscular work but definitely has psychologically depressing and lethargic effect and lowers the endurance of working and the work capacity. The first symptoms of hypoxia at high altitude appear at about 1,524 m. in the form of diminished night vision; at and above 3,048 m, the blood oxygen saturation falls to 90% as compared to 95% at sea level and clinical symptoms of hypoxia begin to develop. At 4,268 m. oxygen saturation in blood falls to 84% and vision dims; hand tremor, clouding of memory and errors in judgement begin to take place at 4,877 m, the individual becomes disoriented, belligerant or euphoric and completely irrational. Between 5,486–6,096 m., neurocirculatory collapse or primary shock occurs with the loss of consciousness, the intensity of which, increases at still higher altitude and may prove fatal. The oxygen requirement, therefore, needs supplementation even at 1,524 m. and goes on increasing with elevation[86,87]. Administration of pure oxygen should be avoided. Even at a partial pressure of 192 mm of mercury, pure oxygen results in an irritation of eye and respiratory tract. These effects are removed by mixing water vapour and carbon dioxide with oxygen[88]. Incorporation of carbon dioxide may as well prevent respiratory alkalosis[89].

Respiratory and circulatory systems are the most affected ones at high altitude and cases of cerberal thrombosis, pulmonary infarcation, acute pulmonary oedema and hypertension become more common besides other respiratory and circulatory defects at high altitudes[90—94]. Even latent defects in respiratory system may prove fatal[95]. During acclimatisation, these two sytems undergo major adaptational changes as well, leading to increased efficiency in oxygen intake and subsequent distribution of oxygen to the tissues. Increased vital capacity, pulmonary ventilation, haemoglobin concentration, red blood corpuscle count, heart rate, blood volume, cardiac output, decreased alveolar carbon dioxide tension resulting in increased higher oxygen tension, all of these are adaptational changes leading to maintain oxygen tension of the blood at normal level[96—99].

With decrease in partial pressure of oxygen at high altitude oxygen tension decreases within the lung alveoli and arterial blood[100]. However, the metabolic rate is not altered appreciably since the amount of carbon dioxide produced by the body remains unaffected; there is generally no change in alveolar carbon dioxide tension below 3,048 m[101]. Above 3,048 m. along with the decrease in alveolar pO_2 alveolar pCO_2 begins to diminish allowing at the same time pO_2 to increase [100,102]. Low oxygen tension of the atmosphere is moreover compensated by the organism by increasing the intake of air per minute, resulting in hypertension[96,103]. The chemoreceptors, situated along the aorta and cartoid arteries regulate the ventilation rate along with a centrally control mechanism. They are stimulated by a fall in the oxygen tension of the blood[103]. The respiratory centre of the brain controlling breathing movement responds to the carbon dioxide tension of the arterial blood[104]. At high altitude the increased ventilation brings about a reduction in the partial pressure of carbon dioxide in lungs which in turn is reflected in a corresponding fall in the CO_2 tension of arterial blood. The respiratory centre of the brain is in consequence denied of its normal compliment of stimulus and responds instead to stimuli provided by peripheral receptor organs, sensitive to oxygen tension [103]. Even under acute anoxia, chemoreceptor drive of breathing is sufficient to increase the ventilation volume despite the

fact that in so doing the arterial pCO_2 and hence the hydrogen ions are lowered.[105]. Acclimatisation to high altitude results presumably in an increased oxygen sensitivity of the chemoreceptor[105], and perhaps the oxygen stimulus is most significant in controlling the respiratory movement at high altitude[106]. The ventilatory response at high altitude to exercise appears to be controlled by humoral mechanism as well[107] Keelog *et al*[108] were able to differentiate between the respiratory control mechanisms operting under moderate hypoxia and under acute hypoxia. The curve relating the respiratory minute volume to the inspired or alveolar carbon dioxide tension was found to shift towards left rather than upward with the human subjects acclimated to an altitude of 3,800 m., indicating thereby the increase in the carbon dioxide sensitivity of the chemoreceptors. In contrast the shifting of the carbon dioxide response curve upwards, as described by Christensen[109] and Riley *et al* [110] under acute hypoxia or under moderate hypoxia with increased muscular exertion would suggest a general elevation of the motor activity and respiratory centres of brain rather than an increase in carbon dioxide sensitivity of the chemoreceptors. This would suggest that the chemoreceptors which normally respond to oxygen tension of the blood become sensitive to variations in CO_2 tensions as well under moderate hypoxia as a result of acclimatisation. The organism, therefore, becomes more sensitive to variations in carbon dioxide tension of the blood during acclimatisation[38,50].

The muscular exertion at high altitude results in an increased oxygen requirement and respiration rate as compared to that at sea level both among acclimated and non-acclimated individuals[107,29] . Arterial oxygen saturation falls rapidly and may come down to 50% under severe exercise. Decrease in Arterial oxygen pressure takes place even when oxygen tension in lung alveoli is increased with the increase in work load, indicating limitations in diffusion capacity of the lungs.

With the decrease in oxygen tension, saturation of haemoglobin with oxygen decreases. The increased concentration of reduced haemoglobin accepts hydrogen ions more readily than oxhyaemoglobin, the plasma (H^+) falls slightly resulting in alkalosis [102,111,89,112] . The decrease of the pCO_2 in arterial blood due to hyperventilation further contributes to alkalosis[6]. The increase in leucocyte oxidase and consequently an increased rate of glycolysis and formation of lactic acid of blood in acclimatised person during flying at high altitude, may act as a deterrent to respiratory alkalosis as well as in response to hypoxia[75].

Almost identical value of cation concentration in blood were found among the residents at high altitudes and those at sea level with a significant decrease in bicarbonate and increase in chloride anions [113]. The blood *pH* depends primarily on the ratio of plasma-carbon dioxide to plasma bicarbonate concentration. The compensation for reduced CO_2. partial pressure occurred in these cases, by a reduction in plasma bicarbonate level[67] The kidney, therefore, excretes a more alkaline urine, restoring the normal plasma (H^+) —Hyperventilation in high altitude acclimated human beings appears to be due to an increase in oxygen capacity and acidity of blood, caused by the renal alkali excretion. Ammonium chloride given subjects simulate in their respiratory behaviour under hypoxia and hyperoxia to the high altitude acclimated persons[114]. Administration of hydrochloric acid increases the resistance of mice exposed to acute hypoxia, while sodium bicarbonate decreases it[115].

Even in the absence of hypoxia, low pressure at high altitude results in significant changes in respiratory activity. Breathing capacity and percent of forced vital capacity during the first second of effort is increased with simultaneous decrease in forced vital capacity. The magnitude of variation was some what proportional to altitude[116]. Minute ventilation volume appears to vary directly wth the reduced pressure[117].

BLOOD AND CIRCULATORY SYSTEM

Hypoxia in general results in an elevated level of blood haemoglobin and increased haematocrit values leading to increased oxygen capacity[7,61,118—123]. The response is so quick that at a simulated altitude of 9144 m. the haematocrit values show an increase within 30 minutes of exposure. Several workers have reported increased haemoglobin concentration and decreased arterial oxygen saturation among high altitude residents [120,121,124] and those who stayed for comparatively shorter period at high altitude[20,125,126] and among exprimental animals exposed to simulated altitude[127,128]. Carbon dioxide tension in arterial blood also decreased simultaneously especially if the exposure was prolonged or acute[127,94]. The significance of reduced carbon dioxide tension can very well be realised in view of the cerebrovasoconstrictor effect of low carbon dioxide tension resulting in an increased venous tone and cerebral venous pressure[129]. Under these conditions brain oxygenation may be drastically cut off, even if the arterial oxygen pressure is maintained. Incorporation of carbon dioxide in oxygen at high altitude, therefore, appears to be essential [130].

The increase in haemoglobin concentration in response to high altitude is curvilinear[7] and is an indication of increased capacity to capture and hold oxygen from rarified air. On descent, the haemoglobin concentration, along with several other circulatory adjustments return to normal levels [131]. The erythropoiesis is reduced and erythrolysis increases on descent, as compared to that at high altitude[132]. The biosynthesis of haemoglobin was accelerated four to five times the normal rate during first two days of exposure; subsequently the rate of synthesis became a function of the degree of hypoxia in rats exposed to simulated altitude of one to eight thousand[133] m. However, the circulating haemoglobin increased at a later stage; during the first two days erythropoietically active tissues appeared to have the increased haemoglobin. Hemolysis remained unaffected during first two days; Plasma proteins increased and presumably this increase was related to increase in haemoglobin concentration[134]. The low ambient temperature at high altitude may play some significant role in haemoglobin metabolism as heat was reported to effect haemoglobin level adversely at an altitude of 5486 m[7].

The haemoglobin of the animals native to high altitude has a higher affinity for oxygen than that of their sea level relatives [135], indicating genetic adaptation. On the other hand, haemoglobin of altitude acclimated persons, has a slightly lower affinity for oxygen thus facilitating delivery of oxygen to the tissues[136]. The residents of high altitude have a larger red blood cell (RBC) count [7,11,137]. Exposure to high altitude even for short duration increases RBC count in human beings and in experimental animals[125]. However, dogs less than two months old do not show any variation in the morphology of blood in response to hypoxia thereby reflcting a deficiency in receptor mechanism. Adult dogs show increased RBC count and haemoglobin and fluctuating leucocyte count[138]. The rats, 14-20 months old, also failed to adapt themselves to low oxygen tension and retained adaptation to a lesser degree. They, however, had the ability to synthesise haemoglobin and showed haemoglobin response to hypoxia[139]. Besides, variation in RBC mass, blood volume increases with a decrease in plasma volume. In rats the increase in RBC count is due to the activity of the bone narrow and atonic contraction of spleen[140]. The erythropoietic response to hypoxia is slow in splenectomised dogs but some increase occurs eventually. Glomectomized dogs show even greater erythropoietic response indicating hyperventilation as a deterrent to erythropoiesis[141].

It appears that the demand of iron for the synthesis of heamoglobin and RBC at bone marrow is reflected in absorption of iron in the intestine,[142, 143] the latter increases at high altitude in unacclimatised human subjects during the first week. Residents of high altitude have a decreased iron absorption compared to sea level residents[120]. Iron demand at bone narrow level rather than hypoxia appears to be the major factor affecting iron absorption at high altitude[142, 143]. Dietary iron contained in a normal high altitude diet was found to be sufficient at an altitude of 7821 m. and additional iron did not affect the heamoglobin concentration at high altitude[23]. An overall study of iron metabolism indicating increased absorption, heamoglobin and RBC synthesis in human subjects was carried out by Reynafarje[144] and co-workers.

In human subjects, the total plasma bilirubin concentration was doubled and the excretion of urobilinogen was increased to the same extent as the total circulating heamoglobin. The hemolytic index (mg. daily urobilinogen excretion per 100 gm. total heamoglobin) therefore, remained unaffected at 4542 m[120]. It appears that the rate of heamoglobin degradation relative to circulating mass remains normal in acclimated subjects at high altitude. The bilirubinaemia at altitude has been attributed primarily to the defective liver function and secondarily to hypoxemic state and other factors associated with acclimatisation[42,121]. Liver function studies were made on native subjects living in a state of chronic hypoxia. Total bilirubin in the majority of cases was more than that found at sea level; increase in total bilirubin was related to the degree of poycythemia[22].

In general, myoglobin content of muscles shows an increase at high altitude in dogs[145], rats[92], wild animals and sartorius of human subjects[67] but probably comes down on prolonged exposure [7,146]. The increase in myoglobin may also be a reflection of decreased water content[147]. Moreover, acclimatisation does not seem to have any effect on myoglobin oxygen reaction rate constants. Cardiac-myoglobin, however, showed a decreased oxygen association[148]. Oxymyglobin equilibrium constant also remained unaffected[149]. Myoglobin level seems to be more sensitive in skeletal muscle and diaphragm than heart muscles.

Significant alteration in electrophoretic pattern of blood proteins at high altitude and under hypoxia have been reported; these changes are presumably mediated through pituitary—adrenal axis[150]. Exposure of dogs to a simulated altitude of 9000 m. for two days resulted in the appearance of a new lipoprotein band[151] which disappeared within three days at normal atmospheric pressure. Total protein in rabbit blood remained unaffected at an altitude of 4000 m., but a marked increase in β-globulin occurred, resulting in lowering of albumin/globulin ratio; γ-globulin decreased at 1829 m. The variations were more marked at 3048 m[152,153]. During first week of exposure, a relative decrease in the concentration of albumin and increase in α and β-globulin took place in rabbits exposed to 3,800 m. Subsequently after 30 days, relative albumin concentration increased and α and β-globulin decreased as compared to controls[154]. In human subjects flying at 4200 m., α, β and γ-globulin increased with a decrease in albumin fraction[155]. Total protein was not affected but albumin/globulin ratio changed in residents at high altitude[75].

Total and free cholesterol, lipoproteins and phospholipides were unaffected under artificial flight conditions at high altitude[156, 39]. But prolonged exposure to hypoxia, simulating 6,500 m. brought a general increase in lipodial fractions of blood. Total lipids, free and combined β-steriods, and its esters, phosphatides, neutral fatty acid, and digitonin-non precipitable steriods increased significantly indicating a marked disturbance in lipid metabolism in response to hypoxia[157]. Coagulation mechanism seems to be radically affected in response to hypoxia[158].

The cardiac output, pulse rate and stroke volume increased in response to high altitude though mean venous pressure remained unchanged[159]. The increase in cardiac output is related to the decreased arterial oxygen saturation and declines during prolonged exposure[160,161]. Carbon dioxide content in the inspired air as well appears to control the cardiac output. The manner in which this takes place is uncertain[162], but pulmonary hypertension might be responsible for the right ventricle and septal hypertrophy observed by Hultgren and co-workers in animals residing at or above 3048 m[163]. Steers and Lambs are especially susceptible to high altitude hypoxia as they develop a severe pulmonary hypertension and show a marked rise in pulmonary arterial pressure[164]. A modest ventricular hypertension and dilatation with marked polycythemia was observed in rabbits. Cats were unable to survive at 4313 m.—the cause of the death remained unexplained. It was not due to circulatory failure[128].

Systolic pressure increased but diastolic pressure remained either unaffected or decreased on exposure to an altitude of 4572 m.[165]. The mean arterial pressure in subjects acclimatised to the same altitude is generally below sea level values. At very high altitude, there is a slight increase in mean arterial pressure[166].

WATER AND SALT RELATIONSHIP

Stress, in general, affects protein catabolism in the beginning, followed by capillary permeability and electrolyte balance and ultimately changes in water compartments of the body. During the shockphase, there is a general oedema due to movement of water into the intracellular spaces. The hemoconcentration is usually very pronounced and is accompanied by a decrease in total blood volume. During the stages of alarm and exhaustion, urine output and blood volume is reduced, while in the stage of resistance it is usually at or above normal values resulting in blood dilution and increased blood volume[12,167,168]. These effects are reversible within a period of 2-24 hours after discontinuation of exposure[169,170].

Siri *et al*[171] reported a difference of 5% in the body water, determined in young students (males) at sea level and in miners (males) living at 4999 m. or above. This is considered to suggest a slight difference in relative amount of fat and lean body mass resulting from the different occupations of the two groups rather than to high altitude. On the other hand when unacclimated subjects were exposed to a simulated altitude of 5486 m. and 10211 m. for 30 and 17 days respectively, there was a decrease in the total body water, total blood volume and plasma volume. On return to sea level, the recovery was rapid but less so for the group at 5486 m. perhaps due to more extensive changes in the body composition in response to prolonged exposure[172]. Total body water, extra cellular fluid, intracellular fluid, body fat, fat free body mass, cell solids and minerals (expressed as percentage of body weight) were determined in adult male residents at sea level and at 4542 m. Only extracellular fluid was found increased in the high altitude residents. It may indicate an increased fluid requirement for maintaining normal fluid equilibrium under hypoxia[173]. After prolonged exposure to an altitude of 4572-6096 m., the blood volume increased by about 25% presumably as a result of an increase in R.B.C. volume and number[153]. Consequently the total amount of oxygen per 100 ml. of blood remained close to the normal sea level inspite of the lower arterial oxygen tension[174].

Decrease in plasma potassium concentration in response to hypoxia and high altitude was extremely rapid and marked though it was secondary to respiratory alkalosis. Even in first 30 minutes a sudden drop took place which persisted throughout the exposure

of 90 minutes. Potassium excretion increased in response to high altitude[89, 112, 175-177] A marked decrease was reported in plasma potassium concentration in unaesthetized dogs subjected to a simulated altitude of 9144 m.[177]. Adrenalectomised dogs maintained on cortisone or deoxycortisone acetate showed a decrease of plasma potassium levels at a simulated altitude of 9,144 m. The level of potassium remained low throughout the exposure. However, sodium level remained unaffected[178]. Mountain sickness may be due to loss of potassium, though evidence in support of this hypothesis is still lacking[179].

Rats kept for 24 hours at 6400 m. showed high level of magnesium in straited muscle and liver but not in the heart or kidney[130]. Magnesium level of blood[180] and its excretion[80] was reported to be elevated under stress.

Calcium metabolism in general also appears to be disturbed at high altitude. The incidence of formation of renal and vesicular calculi is greater in flying personnel[181]. Low barometric pressure at high altitude without hypoxia being ruled out[180] as the major cause other factors like dehydration and hypoxia, therefore, assume greater significance in this connection. High altitude acclimation results in a decreased calcium, phosphorus and magnesium concentration in rat teeth. Ca/CO_4 ratio also gets lowered[182].

FOOD AND NUTRITIONAL REQUIREMENTS

A person at high altitude has to face primarily low temperature and oxygen tension. Hence, the desired food should be easily digestable, assimilable and tasty and have enough (*i*) calories and essential nutrients for survival against low temperature and (*ii*) endogenous oxidizing equivalents so as to spare ventilation effort and strain on respiratory-circulatrys system of the organism.

The caloric requirement per day has been recommended as (*i*) 4000 to 5000 K. cal. upto an altitude of 5486 m. and (*ii*) 1500 to 3000 K. cal. above 5486 m. due to lack of appetite. A high carbohydrate diet was more effective than a high protein diet as assayed with respect to thermal balance and the performance of various psychomotor tests at high altitude. On the basis of oxygen requirement, the available energy is maximum with carbohydrate diet[183] as well. Every litre of oxygen with carbohydrate oxidation yields 5·06 K. cal. as compared to 4·7 K. cal. and 4·6 K. cal. for fats and proteins respectively. There is greater craving for sugar and carbohydrates at high altitude as well[184]. Though a high fat diet represents a more concentrated form of energy than a high carbohydrate or protein diet, its oxidation demands more oxygen and, therefore, will not be suitable under hypoxiac conditions. Protein intake did not appear to influence performance capacity and in a well balanced diet the protein requirement is generally met at high altitude[183].

Vitamin C was found to increase the tolerance of animals to cold[184] but, so far, with human beings, the additional supply of ascorbic acid has been found unnecessary. Vitamin supplementation in general were found useful at high altitude.

Water is lost through respiration and sweat at high altitude especially if the exposure involves muscular work. 3-4 litres of water are required daily to replace such losses otherwise the dehydration is likely to occur even under cold climatic conditions at high altitude[184]. The extra salt is not required in any significant quantity as the water loss is mainly through respiration. The loss of potassium and magnesium may result in the deficiency symptoms and, therefore, an adequate amount of these two salts should always be present in the diet and if the stress is prolonged or involves repeated exposures, additional quantities may as well be supplied. The stimulants such as coffee, tea, or other beverages are useful but should not be consumed in large quantities.

CONCLUSION

The physiological stress at high altitude is due to several factors, low environmental temperature and oxygen tension being the most significant ones in producing a series of adaptational variations in living system under natural conditions. In this connection, the studies carried out so far have dealt with cold exposure and low oxygen tension separately. Since these factors often affect the metabolic systems in completely different directions it would be quite unjustified to arrive at any conclusion from the data so collected in connection with the metabolic adjustments under natural conditions of high altitude. For example, thyroid activity appears to be elevated during cold exposure and suppressed under hypoxia. The blood has a tendency to become acidic in cold and alkaline at high altitude. The lipogenesis appears to be depressed in cold and presumably elevated during hypoxia. It would be necessary, therefore, to combine the subzero temperature and hypoxia to simulate the natural conditions for studies connected with the biochemical and physiological adaptation to high altitude.

Besides, the biochemical studies in connection with hypoxia and low atmospheric pressure are far from complete and it is not possible, as yet to form an integrated picture of protein, lipid or even of carbohydrate metabolism under hypoxia. The investigation on biosynthetic and degradation reactions of proteins and of lipids are incomplete. The alternative pathways of carbohydrate utilization and non-mitochondrial and mitochandrol oxidation need further evaluation.

Since the oxygen requirement for complete oxidation of carbohydrates and fats with reference to available energy is not very much different, from nutritional point of view, fats and fatty acids may be considered preferable to protein or even to carbohydrates as the major source of energy at high altitude. Moreover, studies indicate an accelerated and preferential utilization of fatty reserves for thermogenic purpose in cold environment. However, higher fat content of swines reared at high altitude, depressed thyroid activity and a sudden drop in blood oxygen tension on infusion of a fat preparation in human subjects exposed to high altitude indicate a limitation on fat mobilization from reserves during hypoxia. Besides, the extent to which the dietary fat and lipids can be utilized at high altitude without producing steatorrhea is yet to be ascertained. At present, carbohydrates appear to be the best calorific food material under condition prevailing at high altitude. Regarding the specific nutrient requirements at high altitude, much remains to be done.

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