ADIPOSE TISSUE METABOLISM DURING HYPOBARIA

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Possible factors affecting the metabolism of adipose tissue under hypobaric conditions have been reviewed. The hormonal changes brought into play under hypoxic stress generally increase the adipose tissue lipolysis.

Studies on high altitude physiology have gained importance because of the popularity of mountaineering sports and the necessity for the defence to man our mountainous northern frontier. The comprehensive reviews by Hurtado[1], Van Liere and Stickney[2], Weihe[3], Pugh[4-6], Ward[7] and many others have covered different aspects of the biological changes due to altitude exposure and the physiological adaptive mechanism for acclimatization to hypoxic environment. In recent years large volumes of literature on different aspects of high altitude physiology have mounted at such a rate that it is no longer feasible to review the entire field in a single short paper. In this review, an attempt has been made to describe the possible factors which may affect the metabolism of 'adipose tissue' under hypobaric condition. 'Adipose tissue' has been selected as a subject for discussion because of its importance as a storage organ and for its high sensitiveness to hormonal and nutritional changes.

Loss of body weight due to mobilization of depot fat

Loss of body weight was one of the several biological changes observed in men and animals during high altitude exposure. During the first Everest expedition in 1922, Somervell[8] noticed that a person even though well acclimatized upto 23,000 ft could not stay there longer due to deterioration of health. He used the term 'high altitude deterioration' for the first time. Loss of body weight was the only objective criteria of high altitude deterioration. Poor living conditions, inadequate food and fluid intake also contributed to accentuated deterioration during earlier expeditions. The problem could be studied satisfactorily during Himalayan Scientific and Mountaineering Expedition in 1960-61, only when prefabricated hut, fully equipped with adequate shelter and cooking facilities, was made available. Although all the members of the scientific team of the expedition staying in the fabricated hut at Mingbo glacier (19,000 ft.) from December 1960 to March 1961, felt well and energetic, they lost weight at the rate of 0.5 to 1.5 kg. per week[4].

Decreased appetite and calorie intake[9-21], delayed gastric emptying and slow intestinal movement[22], inhibition of intestinal absorption of actively transported sugars[23], delayed protein absorption[24], decreased digestion and absorption of fat[11], general malabsorption[25], etc could be the effects of low oxygen atmosphere and consequent loss of body weight.

This loss of body weight during hypobaric condition had been attributed to hypohydration by several investigators[14, 26-32] but others[9, 15, 33-35] could not confirm the finding. On the other hand, many evidences were available to show that the primary cause of weight loss was due to loss of body fat during exposure to low baro-metric pressure[9, 10, 36-40]. Siri[39] reported that every member of the successfuf American Everest expedition in 1963, lost 10-15 pounds weight, most of which was due to loss of body fat. In human subjects at 14,000 ft. altitude a significant reduction of body fat was observed after determining the skin-fold thickness, body density, creatine excretion and whole body[40] K counting[9-37].

Rise of serum free fatty acid (FFA) level due to increased lipolysis of adipose tissue

As the ability of the body to store glycogen is limited, the organism depends on fat for major supply of energy. Schoenheimer & Rittenburg[41] reported a rapid turn over of lipid deposit and thus established the importance of fat as 'energy buffer of the body'. FFA derived from adipose tissue constitute the form of fat transported to the site of its utilization by the working tissue or re-esterification in the adipose tissue[42]. About 41-49 per cent of the energy required by the working muscles in human subjects is derived from FFA[43]. Elevated level of serum FFA in man was noticed on the first day of arrival at 14,000 ft. altitude and it remained high throughout the entire period of altitude exposure[46]. Lorentzen[44] also reported a rise in serum FFA level in men after 15 min. exposure to a simulated altitude of 20,000 ft. Hypoxia in dogs either acute

or chronic increased level of serum FFA[45,47]. Increased serum FFA and high lipolytic activity of liver, adipose tissue and lungs in rats exposed to hypoxic gas mixtures were reported by Upenskii & Chou-Su[48]. Alpert[49] reported an increased *in vitro* lipolysis of adipose tissue in chronically hypoxic rats. The findings indicated that hypoxic stress in men and animals caused increased lipolysis and consequent rise in serum FFA level.

Hormonal changes responsible for increased lipolysis

The neuro-hormonal changes brought into play under hypoxic stress either acute or chronic, could be responsible for the increased rate of lipolysis. Adipose tissue contains a hormone sensitive lipolytic system, which responds to epinephrine, norepinephrine, adrenocorticotrophic hormone (ACTH), glucagon and thyroid stimulating hormone (TSH) [50,51]. These hormones activate the enzyme lipase through the intermediary of a second messenger adenosine 3′5′ monophosphate (cyclic AMP), which is formed from adenosine triphosphate (ATP), by the action of cyclase [52]. Addition of cyclic AMP *in vitro* increased the rate of lipolysis in adipose tissue[52,53]. The lipolytic action of growth hormone (GH) is mediated through different mechanism[54] i.e., RNA mediated protein synthesis. On the other hand insulin[55-57] and prostaglandins[58, 119] have been shown to have a potent inhibiting action on the hormone sensitive triglyceride lipase of adipose tissue. Under hypoxic stress some of these hormones may change their level in favour of increased lipolysis as described below :

Adrenaline and ACTH :

The essentiality of the adrenal gland to withstand hypoxic stress was evident from the fact that adrenalectomized rats were less tolerant to reduced barometric pressure than normal rats and the survival period was prolonged when the adrenalectomized animals were pretreated with cortisol[59]. The ability of the animals to withstand hypoxic stress was found to increase with increase in level of cortical hormones[60,61]. During the early stages of hypoxia the activities of both the adrenal medulla and cortex increased significantly[62-69]. In man the activity of the adrenal gland returned to normal after acclimatization[70-73]. However, during the American Everest expedition in 1963, it was observed that despite the severity of hypoxia and general hostile environment, the adrenal gland functions of the climbers were essentially normal[74]. The maximal adrenal response to hypoxia usually appeared after 24-48 hours of altitude exposure[75,76]. It could be possible, that once the initial adjustment to hypoxia was made, no further intervention was required by the adrenal gland to complete the process of acclimatization. A higher level of ACTH was necessary to maintain the normal activity of the adrenal gland at high altitude[66, 67, 70]. Enlargement of adrenal gland and atrophy of the target organs such as thymus, spleen and lymph nodes were observed in rats after 24 hours of their induction at high altitude indicating thereby an increased level of ACTH. The adrenal hypertrophy was less marked after prolonged exposure and it was absent in rats born and raised at high altitude second generation[69]. Increased level of blood and pituitary ACTH was reported by Marks et al[77] in rats continuously exposed to varying hypoxic stress from 3 to 120 hours. The elevation of pituitary ACTH was the highest when the hypoxic stress was more severe.

Thus, it appears that during early stages of acclimatization to high altitude, the enhanced rate of lipolysis was due to increased secretion of adrenaline and ACTH.

Thyroxine and TSH

The response of thyroid gland to hypoxia did not appear as clear as that of the adrenal gland. Unlike adrenalectomized animals thyroidectomized animals had more tolerance to hypoxia[78]. Since oxygen consumption is reduced in hypothyroidism, it was presumed that the increased tolerance of thyroidectomized animals to hypoxia was due to less oxygen requirement and catabolism of cortical hormones. The influence of hypoxia on thyroid activity of human beings and animals has been studied by several investigators[70-89] who have reported a reduction of thyroid activity in most of the cases. However, an increase in thyroid activity of rats exposed to a simulated altitude of 282 mm Hg for 6 hours was observed by De Bias and Yen[90]. They made the measurement at specific time during the experiment without considering possible changes in the pattern of thyroidal uptake or release over extended period of time. Surks[91] reported an increase in free thyroxine concentration in human subjects due to altitude exposure and this was reflected in the elevation of basal oxygen consumption. Increase in concentration of thyroxine was observed inspite of increased level of thyroxine binding plasma protein[92]. Several investigators[79,80] claimed that hypoxia influenced the metabolism of iodine in thyroid gland at various stages. A low TSH content of blood in rats exposed to 250-280 mm Hg pressure for 2-3 weeks was observed by Gordon et al[81].

Glucagon

Picon-Reategui[100] had observed that the hyperglycemic response to intravenous injection of glucagon was lower in adults living at high altitude (4540 m above sea level) than those at sea level. It was suggested that although enzyme systems activated by glucagon might be impaired by chronic exposure to altitude, a higher utilization of glucose by extrahepatic tissues and possibly an impaired recycling were probably mainly responsible for the lower hyperglycemic response to glucagon by the high altitude residents. The same investigator also observed no significant change in the effect of glucagon on *Na* or *K* excretion under hypoxic condition in man. However, no reference on glucagon level in blood[100—102] under hypoxic condition has appeared to author's knowledge.

Growth Hormone

De Bias[59] reported that when GH was administered with a subeffective dose of cortisol it increased the tolerance of adrenalectomized rats to simulated high altitude. GH is reported to correct certain responses and augment the adaptive changes in rats exposed to simulated high altitude[99]. Although the beneficial effect of GH in the adaptive processes during altitude exposure was indicated[59,99] yet the exact measurement of GH level in blood was not made. It is well established that elevated level of GH could increase lipolysis and decrease lipogenesis[93]. It has been reported that the level of epinephrine and norepinephrine in blood and urine increase[94-97] during excercise and the level of GH increased linearly with the increase in exercise[98]. Since strenuous exercise has certain similarities with oxygen deficiency, it might be possible that hypoxic stress would increase the level of GH along with the increase in epinephrine and norepinephrine in blood. However, nothing can be said with certainty without ascertaining the level of GH under the hypoxic condition.

Insulin

In vitro experiment with adipose tissue revealed that insulin acts in two ways to inhibit the release of FFA; firstly it facilitates the entrance of glucose into the cell, resulting in the formation of glycerophosphate which is then used to re-esterify fatty acids, and secondly, it suppresses the activation of lipase by inhibiting the formation of cyclic AMP from ATP[103-107]. Inhibition of insulin release by epinephrine was reported in monkey[108], pig, dog[109-111] and rats[112]. Epinephrine, exercise and stress inhibited the release of insulin in rat[112] as well, the inhibition is mediated by the adrenergic receptors[114]. Therefore, it is very likely that under the hypoxic stress there could be an inhibition of insulin release. This is confirmed by the experiments of Baum[113] on the release of insulin in puppies subjected to hypoxia. The regulatory role of alpha adrenergic receptor in inhibiting insulin release during oxygen deficiency was also confirmed. A heightened sensitivity to insulin of rats exposed to high altitude was reported by Davidson[115]. This could be due to chronic insulin deficiency as shown by Chattopadhyay and Martin[116], in case of pancreatectomized diabetic rats. Picon-Reategui[117] was, however, unable to observe any difference in insulin response between high altitude natives and sea level residents. This could be attributed to the adaptation of the high altitude residents to hypoxic environment.

Prostaglandins

The wide spread occurrence of prostaglandins in mammalian tissues as well as their broad spectrum of biochemical and pharmacological actions has recently attracted much attention[118]. Steinburg[58] et al and Bergstrom[119] et al reported that prostaglandin E_1 (PGE_1) was able to antagonize *in vitro* and/or *in vivo* the lipolytic effect of various hormones, e.g., epinephrine, norepinephrine, ACTH, TSH and glucagon. But little is known about the role of prostaglandins in the adaptive changes during altitude exposure.

Increased fatty acid oxidation due to rise in serum FFA level

The rate of turnover of FFA increased with the increase in the level of serum FFA[120—123]. The rate of oxidation of fatty acids appeared to be a function of the plasma concentration of FFA. The limiting factor in the oxidation of fatty acids is the palmityl *Co A* carnitine acyltransferase[124-127]. An increase in the activity of long chain fatty acyl *Co A* carnitine acyltransferase was observed with the increase in the rate of lipolysis and rise of serum FFA in rats treated with GH[128]. The activity of the enzyme correlates well with their capacity to oxidise fatty acids[129,130]. Thus it is very likely that under the hypoxic stress and increased level of serum FFA there would be a concomitant rise in the activity of fatty

acyl *Co A* carnitine acyltransferase. Although no report on the rate limiting step in fatty acid oxidation under hypobaric condition has come to author's knowledge, yet indirect evidence of a shift in the metabolism from carbohydrate to noncarbohydrate has been reported by several investigators such as a low respiratory quotient (RQ) in sheep[131] chronically exposed to simulated altitude and in man[132-134] under hypoxic stress.

Decreased lipogenesis due to increased lipolysis

In the control of different metabolic processes the key rate-limiting enzymes play a crucial role in determining the direction of overall pathway. Feed back inhibition of the key rate-limiting enzymes in lipogenesis by fatty acids is well known[135-137]. The decreased rate of incorporation of glucose and acetate into lipids by rats under condition of oxygen deficiency[138,159], therefore, supports the view that lipogenesis could be inhibited under hypoxic stress as a result of increased lipolysis and rise of serum FFA level. However, further work on the key rate-limiting enzymes in fatty acid synthesis is necessary to evaluate the nature of lipogenesis under hypoxic condition.

Influence of increased lipolysis on glucose utilization

It is well known that the hormones which increased the rate of lipolysis, had a depressing effect on glucose utilization and vice versa. There is considerable evidence that the rate of FFA oxidation played a regulatory role in blood glucose homeostasis[163]. FFA as an end product of glucose metabolism inhibit selectively and in dose dependent fashion the key enzymes of glycolysis[139—142]. In the sequence of catabolism of glucose, FFA and acetyl *Co A* were able to exert 'Sequential feed back inhibition'. It was suggested by Burlington and Klain[148] that the homeostatic regulation of glycogen and gluconeogenesis, during hypoxic condition, were rather precariously maintained. The decreased rate of glycolysis under hypoxic state[143,144], decreased incorporation of ^{14}C-glucose into lipids[138] under condition of oxygen deficiency, diminished production of $^{14}CO_2$ following intraperitoneal injection of ^{14}C-glucose and diminished hexose monophosphate shunt activity[145] in rats exposed to high altitude, diminished oxidation of glucose to CO_2 in mice raised at high altitude[146], reduced tolerance to glucose in hypoxic rats[147,158], etc. therefore, are in keeping with the reported inhibition of glucose metabolism at various steps by FFA. Blume and Pace[160] also showed that the liver glycogen lebelling after glucose injection was more in altitude exposed rats compared to controls. Such a stimulation of glycogen synthetase activity by FFA was reported by Randle[161]. Although a depressed utilization of glucose under high altitude stress was indicated in these reports[138, 143, 147] there were contradictory finding[115, 149—157,160] of increased glucose utilization. The apparent discrepancies among the observations might be due to differences in the degree and duration of altitude exposure either simulated or natural along with variation of ambient temperature from experiment to experiment.

Concluding Remark

It may be conjectured that under hypoxic stress the increased secretion of catecholamines and ACTH would activate the hormone sensitive lipase in adipose tissue resulting in increased lipolysis and consequent rise in serum FFA level. The increased level of catecholamines might also inhibit the release of insulin and at the same time stimulate glucagon release through alpha-and beta-adrenergic receptors in pancreas, respectively[162], and thereby would further accelerate the rate of lipolysis under the hypoxic stress. The role of TSH in the increased lipolytic activity under oxygen deficiency is doubtful. Although GH could be beneficial for altitude acclimatization and increase the rate of lipolysis but its level in circulating blood under high altitude condition is yet to be determined. Not much is known about the participation of glucagon and prostaglandins under oxygen deficient atmosphere. However, the overall hormonal changes in hypoxic state appear to be favourable for increased lipolysis which would raise serum FFA level and alter the metabolism of glucose. Whether such a change in metabolic direction from glucose to fatty acids is beneficial for the individual's adaptive mechanism for altitude acclimatization is yet to be established. Further studies on various key rate limiting enzymes in lipogenesis, fatty acid oxidation, gluconeogenesis and glycolysis and the assay of different lipolytic and antilipolytic hormones are essential for elucidating the nature of metabolic alterations in hypobaric environment.

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