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The effects of 6 hours of hypoxia on protein synthesis in rat tissues *in vivo* and *in vitro*

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Rates of protein synthesis were measured *in vivo* in several tissues (heart, skeletal muscles, liver, tibia, skin, brain, kidney, lung) of fed rats exposed to O_2/N_2 (1:9) for 6h starting at 08:00–11:00h. Protein synthesis rates were depressed by 15–35% compared with normoxic controls in all of the tissues studied. The decreases were greatest in the brain and the skin. Although hypoxia inhibited gastric emptying, its effects on protein synthesis could probably not be attributed to its induction of a starved state, because protein-synthesis rates in brain and skin were not decreased by a 15–18h period of starvation initiated at 23:00h. Furthermore, we showed that protein synthesis was inhibited by hypoxia in the rat heart perfused *in vitro*, suggesting a direct effect. The role of hypoxia in perturbing tissue nitrogen balance in various physiological and pathological states is discussed.

Exposure of animals to hypoxic conditions results in marked changes in nitrogen metabolism. Thus experimental animals exhibit anorexia and decreased rates of growth (Schnakenberg & Burlington, 1970; Gloster *et al.*, 1972; Schnakenberg *et al.*, 1972; Koob *et al.*, 1974), increased nitrogen excretion (Berry & Smythe, 1962) and impaired nitrogen utilization (Chinn & Hannon, 1969). A limited number of reports have suggested that hypoxia may decrease rates of protein synthesis *in vivo* in brain and certain visceral tissues (Sanders *et al.*, 1965; Klain & Hannon, 1970; Metter & Yanagihara, 1979; Serra *et al.*, 1981). However, most of these studies were less than adequate methodologically (see the Discussion section). *In vitro*, there is general agreement that hypoxia or anoxia inhibits protein synthesis in rat diaphragm (Borsook *et al.*, 1950; Manchester & Young, 1959), in rat atria, papillary muscles and perfused hearts (Cohen *et al.*, 1969; Jefferson *et al.*, 1971; Lesch & Peterson, 1975; Kao *et al.*, 1976; Chua *et al.*, 1979), in perfused skeletal muscle (Preedy *et al.*, 1984*a*) and in Ehrlich ascites-tumour cells (Rabinovitz *et al.*, 1955; Quastel & Bickis, 1959; Riggs & Walker, 1963; Jarett & Kipnis, 1967). At least in studies on cardiac muscle, inhibition of protein synthesis by hypoxia was not the result of inhibition of amino acid uptake (Cohen *et al.*, 1969; Lesch *et al.*, 1970; Jefferson *et al.*, 1971). Because there has been little work on the effects of hypoxia on protein synthesis *in vivo*, we therefore carried out an extensive study.

Abbreviations used: k_s, fractional rate of protein synthesis; S_p, S_i and S_B, specific radioactivities of [4-^{3}H]-phenylalanine unbound in the plasma, unbound in the tissue and bound in tissue protein respectively.

Experimental

Materials and animals

Sources have been given previously (Preedy *et al.*, 1984*b*). Male rats were housed and fed as described in Preedy *et al.* (1984*b*). Additionally, all gas mixtures were obtained from B.O.C. Ltd.

Induction of hypoxia in vivo

Conscious, unrestrained, fed rats were individually exposed to air or O_2/N_2 (1:9) for 6h in airtight plastic chambers (volume 4.4 litres) fitted with a gas inlet and outlet. The gas flow rate was 0.25 litre/min. Control and experimental rats were treated concurrently. Experiments were started at 08:00–11:00h, and injections of [4-^{3}H]phenylalanine were performed at 14:00–17:00h. During experiments, food and water were withdrawn.

Measurement of protein-synthesis rates in vivo

Protein synthesis was measured over a 10min period by the 'flooding dose' method of Garlick *et al.* (1980). The rat's tail was pulled gently through the gas outlet of the chambers, and [4-^{3}H]-phenylalanine (sp. radioactivity 0.17–0.35Ci/mol;

150mM; 1.5 μmol/g body wt.) injected via a lateral tail vein. Rats were conscious, unrestrained and exposed to the normoxic or hypoxic environment during injections and until they were killed. At 10min after injection, rats were removed from the chambers, decapitated as quickly as possible, and tissues were rapidly removed into ice/water for subsequent dissection. The heart was dissected into the right-ventricular free wall and the left-ventricular wall plus interventricular septum. The entire diaphragm was removed, and the costal and sternal sections were dissected away from the lumbar section by cutting the central tendon. The lumbar section was discarded. Skin was obtained from the hind leg. Samples were stored and processed as described previously (Preedy *et al.*, 1984*b*). The k_s values given in Table 1 are for protein soluble in 0.1M-NaOH, except for skin, for which protein was dissolved in 0.3M-NaOH. The synthesis of mature insoluble proteins such as collagen or keratin was thus not measured. Since brain contains numerous decarboxylases involved in neurotransmitter synthesis, 2-phenethylamine content was assayed fluorimetrically in extracts used to determine S_i before the phenylalanine decarboxylation procedure. Endogenous 2-phenethylamine could only have accounted for at most 0.1% of the 2-phenethylamine present after decarboxylation.

Measurement of cardiac protein-synthesis rates in vitro

Hearts were perfused anterogradely as in Taegtmeyer *et al.* (1980) as described previously (Preedy *et al.*, 1984*b*), with Krebs & Henseleit (1932) bicarbonate-buffered saline containing 10mM-sodium acetate and 10mM-sodium lactate as fuels (the concentration of NaCl was decreased accordingly). In the initial retrograde perfusion (10kPa pressure), the medium was equilibrated with O_2/CO_2 (19:1). In the anterograde perfusion, the medium was the same as above but contained additionally 0.4mM-[U-^{14}C]phenylalanine (sp. radioactivity 0.04Ci/mol) with the concentration of each of the other amino acids at 0.2mM. The left-atrial filling pressure was 0.5kPa and the aortic pressure was 7kPa. The perfusate was initially equilibrated with O_2/CO_2 (19:1). In experiments designed to investigate effects of hypoxia, the gas mixture was altered 5min after initiation of retrograde perfusion to $N_2/O_2/CO_2$ (9:10:1). Control and hypoxic hearts were perfused concurrently. In hypoxic hearts, the aortic flow declined with time, whereas it was stable at the higher O_2 partial pressure. When hypoxic hearts would no longer pump perfusate over the aortic overflow (usually after about 70min hypoxia), perfusions were terminated and control hearts removed from the cannulae after matched periods of perfusion. Hearts were processed as described previously (Smith & Sugden, 1983*a*,*b*) to determine the rates of protein synthesis in atria and ventricles in terms of pmol of [U-^{14}C]phenylalanine incorporated/day per mg of protein, and these were converted into k_s values by using the cardiac mixed-protein phenylalanine contents determined previously (Preedy *et al.*, 1984*b*).

Other methods

Stomach contents were dried to constant weight over P_2O_5 *in vacuo*. Protein was measured by the method of Lowry *et al.* (1951) or Gornall *et al.* (1949) with rat heart mixed protein as standard (Smith & Sugden, 1983*a*). RNA was measured by the method of Munro & Fleck (1969).

Statistical methods

Results are presented as means $\pm$ S.E.M. The significance of differences between groups *in vivo* was tested by a two-tailed unpaired Student's *t* test, whereas results *in vitro* were analysed on a paired basis (pairing concurrently perfused control and hypoxic hearts). Values of $P<0.05$ were taken as being statistically significant.

Results

Effects of hypoxia on protein-synthesis rates in vivo

Results are shown in Table 1. For the control group, S_p on decapitation was 748 $\pm$ 8d.p.m./nmol, whereas for the hypoxic group it was 729 $\pm$ 4d.p.m./nmol (six observations for each group). Thus in most tissues the value of S_i on decapitation at 10min approximated to S_p. The exceptions were liver and kidney. In the former, S_i was greater in the hypoxic group than in the control group, but this was the only instance where S_i was different in the two groups. We used S_i values at 10min to calculate k_s. Because of the uncertainty of the relationship of S_i to S_p in the liver and kidney, and because of the uncertainty of the effects of hypoxia on this relationship, the results from these tissues should be viewed circumspectly. Although, in contrast with our results, Garlick *et al.* (1980) reported rapid equilibration of S_i with S_p in the liver, their k_s values for liver are similar to ours. The k_s values for mixed protein refer to protein that was soluble in 0.1M-NaOH (0.3M-NaOH for skin). Thus proteins such as mature collagen or keratin are excluded from the analysis. It has been shown, however, that there is no incorporation of [4-^{3}H]phenylalanine into those proteins over the 10min of the experiments (Preedy *et al.*, 1983). However, there is presumably incorporation of label into the soluble precursors of these insoluble proteins. In most

Table 1. *Effect of hypoxia on protein synthesis in various tissues in vivo*

Protein synthesis was measured as described in the Experimental section. The body weights of rats immediately before the experimental period were 160 ± 1 g for the control group and 161 ± 2 g for the hypoxic group. There were six rats in each group. Statistical significance for the hypoxic group versus the control group is: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

	S_i (d.p.m./nmol)		S_B (d.p.m./μmol)			k_s (%/day)		
Tissue	Control	Hypoxic	Control	Hypoxic	Decrease (%)	Control	Hypoxic	Decrease (%)
Left ventricle	659 ± 4	646 ± 7	767 ± 38	606 ± 36*	21	14.57 ± 0.78	11.74 ± 0.66*	19
Right ventricle	656 ± 9	655 ± 4	772 ± 38	614 ± 40*	20	14.75 ± 0.87	11.76 ± 0.75*	20
Diaphragm	687 ± 6	677 ± 6	662 ± 43	541 ± 30*	18	11.34 ± 0.81	9.41 ± 0.55	17
Gastrocnemius	718 ± 10	711 ± 6	506 ± 56	418 ± 20	18	9.54 ± 1.06	7.89 ± 0.38	17
Soleus	734 ± 14	730 ± 12	699 ± 42	583 ± 36	17	12.89 ± 0.92	10.71 ± 0.62	17
Plantaris	740 ± 9	724 ± 9	546 ± 49	466 ± 15	15	10.00 ± 0.97	8.65 ± 0.32	14
Liver	368 ± 19	424 ± 5*	2839 ± 151	2499 ± 215	12	104.0 ± 7.62	78.43 ± 7.02**	25
Tibia	607 ± 4	609 ± 13	2419 ± 142	1857 ± 51**	23	53.72 ± 3.25	40.98 ± 1.33**	24
Skin	587 ± 13	611 ± 11	1903 ± 111	1321 ± 116**	31	43.63 ± 2.04	28.97 ± 2.30**	34
Brain	523 ± 16	521 ± 9	608 ± 19	413 ± 23**	32	16.75 ± 0.73	11.35 ± 0.49**	32
Kidney	270 ± 12	283 ± 16	1521 ± 96	1129 ± 55**	26	65.64 ± 3.91	46.43 ± 1.74**	29
Lung	712 ± 12	695 ± 9	1401 ± 74	1077 ± 83*	23	24.69 ± 1.59	19.45 ± 1.48*	21

	RNA/protein ratio (μg/mg)		Efficiency of protein synthesis (g of protein synthesized/day per g of RNA)		
Tissue	Control	Hypoxic	Control	Hypoxic	Decrease (%)
Left ventricle	9.54 ± 0.24	9.74 ± 0.28	15.26 ± 0.60	12.13 ± 0.84*	21
Right ventricle	12.44 ± 0.24	12.62 ± 0.16	11.85 ± 0.63	9.34 ± 0.66*	21
Diaphragm	11.16 ± 0.41	10.73 ± 0.21	10.38 ± 0.62	8.75 ± 0.43	16
Gastrocnemius	8.96 ± 0.29	8.46 ± 0.19	10.59 ± 0.98	9.35 ± 0.11	12
Soleus	12.25 ± 0.30	11.66 ± 0.54	10.58 ± 0.85	9.22 ± 0.47	13
Plantaris	8.65 ± 0.27	8.37 ± 0.18	11.60 ± 1.08	10.36 ± 0.46	11
Liver	31.23 ± 0.99	30.87 ± 0.69	33.41 ± 2.66	25.47 ± 2.33*	24
Tibia	40.90 ± 2.51	40.69 ± 3.23	13.23 ± 0.66	9.94 ± 1.17*	25
Skin	18.33 ± 1.25	16.58 ± 1.06	24.21 ± 1.56	17.65 ± 1.80*	27
Brain	15.18 ± 0.48	15.48 ± 0.49	11.04 ± 0.43	7.34 ± 0.25***	34
Kidney	24.09 ± 0.64	24.60 ± 0.67	27.32 ± 1.73	18.95 ± 0.91**	31
Lung	20.54 ± 0.74	20.65 ± 1.15	12.01 ± 0.62	9.50 ± 0.67*	21

tissues examined, k_s was significantly decreased by hypoxia, by 20–35%. In the liver, k_s was decreased, but this result was dependent on the 15% difference in S_i between the control and hypoxic groups, since there was no significant difference in S_B between groups. Whether hypoxia really decreases liver protein synthesis is thus uncertain. In skeletal muscles, results are suggestive of a 14–17% decrease in k_s with hypoxia, but they did not attain significance. However, S_B values show statistically significant decreases in diaphragm during hypoxia, although S_i values are the same. Thus there is suggestive evidence that hypoxia decreases protein synthesis in skeletal muscle. Perhaps a more prolonged exposure to hypoxia would reveal significant differences. It is interesting that protein synthesis in both aerobic muscles (heart, diaphragm) and anaerobic muscles (plantaris) is inhibited by hypoxia to a similar extent. The S_i value was not necessarily related to the rate of protein synthesis. For example, although tibia and kidney have roughly similar k_s values, their S_i values differ markedly. It is unlikely also that the difference in S_i is the consequence of a low blood flow to the kidney, which is known to take a large proportion of the cardiac output for its weight. RNA/protein ratios were not altered by hypoxia. Thus, in all tissues except skeletal muscles, hypoxia significantly decreases the efficiency of protein synthesis (protein-synthesis rate relative to RNA) by 20–35%.

Effect of hypoxia on gastric emptying

Hypoxia *in vivo* is known to decrease gastric emptying (Crisler *et al.*, 1932; Van Liere *et al.*, 1933). We confirmed that 6 h of hypoxia decreased

the rate of gastric emptying. The wet weight of the stomach contents of the hypoxic group was 4.77 ± 0.37g and of the control group was 1.75 ± 0.30g (six animals in each group; $P < 0.001$). Similarly the dry weights of the stomach contents were 2.07 ± 0.20g in the hypoxic group and 0.56 ± 0.13g in the control group ($P < 0.001$).

Protein synthesis in the skin and brain in post-absorptive rats

Because starvation decreases rates of protein synthesis *in vivo* (Garlick *et al.*, 1975), it is possible that the decreases in protein-synthesis rates induced by hypoxia could have resulted from nutrient deprivation as a result of the decreased rate of gastric emptying. We therefore tested the effect of a 15–18h period of starvation beginning at 23:00h on protein synthesis in the two tissues most severely affected by hypoxia, namely skin and brain (Table 1). The k_s values and efficiencies of protein synthesis were unaffected by this period of starvation, as were values of S_p, S_i and S_B (Table 2). On decapitation, stomachs of the post-absorptive group of rats were empty of food, whereas stomachs of the fed group contained similar amounts of food to animals used in the control group for the effects of hypoxia (see above).

Effects of hypoxia on cardiac protein synthesis in vitro

Hearts were perfused with lactate and acetate as fuels in order to stimulate protein synthesis (Rannels *et al.*, 1974; Kochel *et al.*, 1984; D. M. Smith & P. H. Sugden, unpublished work) and also to prevent the formation of lactate, which occurs when glucose-perfused hearts are made hypoxic (otherwise it is possible that the lactate produced would have stimulated protein synthesis). Results are shown in Table 3. Protein synthesis in both atria and ventricles was inhibited by hypoxia by about 20–30%. The inhibition was less in atria than in ventricles, suggesting that atrial protein synthesis is less sensitive to hypoxia than is ventricular synthesis. We have previously shown that atrial protein synthesis is less sensitive to insulin or starvation than is ventricular synthesis (Preedy *et al.*, 1985).

Table 2. *Effect of overnight starvation on protein synthesis in skin and brain*

Rates of protein synthesis were measured *in vivo* between 14:00h and 17:00h in fed animals and in post-absorptive animals which had their food removed at 23:00h on the previous night. The body weight of the five fed rats was 153 ± 6g on the day before experimentation and 157 ± 6g on injection of [4-^{3}H]phenylalanine, an increase of 2.6 ± 0.5%. The body weight of the six post-absorptive rats was 152 ± 6g on the day before experimentation and 135 ± 5g on injection of radiolabel, a decrease of 10.9 ± 0.7%. S_p values in the fed and post-absorptive groups were 436 ± 3 and 436 ± 7d.p.m./nmol respectively. There were no significant differences between the fed and post-absorptive groups.

Tissue	Skin		Brain	
Nutritional state	Fed	Post-absorptive	Fed	Post-absorptive
S_i (d.p.m./nmol)	392 ± 9	379 ± 9	326 ± 3	317 ± 4
S_B (d.p.m./μmol)	1553 ± 83	1527 ± 79	430 ± 6	416 ± 6
RNA/protein ratio (μg/mg)	15.36 ± 0.67	14.24 ± 1.05	12.66 ± 0.15	12.81 ± 0.13
k_s (%/day)	51.0 ± 3.9	51.6 ± 3.0	18.8 ± 0.3	18.6 ± 0.4
Efficiency of protein synthesis (g of protein/day per g of RNA)	33.3 ± 2.3	37.0 ± 3.2	14.9 ± 0.2	14.5 ± 0.4

Table 3. *Effects of hypoxia on protein synthesis in the atrium and ventricle of the heart perfused in vitro*

Hearts were taken from rats of approx. 300g body wt. and perfused as described in the Experimental section. Four perfusions were carried out for each group. Values in parentheses show the percentage changes from the control perfusions. Statistical significance of control versus hypoxic perfusions was $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Compartment	Ventricle		Atrium	
	Control	Hypoxic	Control	Hypoxic
k_s (%/day)	8.17 ± 0.25	5.68 ± 0.09 (−30)**	11.88 ± 0.97	9.35 ± 0.56 (−21)*
RNA/protein ratio (μg/mg)	6.69 ± 0.05	6.54 ± 0.29 (−2)	11.84 ± 0.42	11.98 ± 0.22 (+1)
Efficiency of protein synthesis (g of protein/day per g of RNA)	12.21 ± 0.30	8.73 ± 0.35 (−29)***	10.00 ± 0.58	7.82 ± 0.51 (−22)**

Discussion

General methodological considerations

Previous studies of the effects of hypoxia on protein synthesis *in vivo* have been methodologically imperfect for four reasons. Firstly, radiolabelled amino acids have not always been administered directly into the bloodstream (Klain & Hannon, 1970; Metter & Yanagihara, 1979; Serra *et al.*, 1981). Secondly, only trace amounts of radiolabel have been administered (Sanders *et al.*, 1965; Klain & Hannon, 1970; Metter & Yanagihara, 1979; Serra *et al.*, 1981). Thirdly, in none of these studies was the specific radioactivity of tissue unbound radiolabelled amino acid measured. Fourthly, inappropriate radiolabelled amino acids have been used. For example, the alanine and glutamate carbon used by Klain & Hannon (1970) may enter other amino acids. In the absence of purification of the protein-bound label, this approach is not reliable. The result of all these problems is that S_i values over the course of the experiment are unknown and are likely to vary widely. Consequently, results may be influenced by the possible effect of hypoxia on processes that might affect S_i values. In our studies, we have used the 'flooding dose' method of Garlick *et al.* (1980), which obviates the above problems and in addition allows calculation of fractional rates of protein synthesis rather than rates in units of c.p.m./mg of protein.

Acute effects of hypoxia on protein synthesis

We have established that hypoxia inhibits protein synthesis by 20–35% in most tissues. This inhibition is rapidly expressed (rats were exposed to hypoxic conditions for only 6h). The inhibition was greatest in the brain and skin. The contribution of skin to whole-body protein turnover in the rat is considerable and has until recently been relatively ignored. Thus the k_s for skin is 4 times greater than for skeletal muscle, and skin constitutes about 30% of body protein (Waterlow & Stephen, 1966), of which about 15% is soluble in 0.1M-NaOH. Preedy *et al.* (1983) have shown that skin contributes about 18% of whole-body protein synthesis, compared with 25% for muscle, 15% for liver and 8% for bone, whereas the other tissues studied here (brain, heart, lung and kidney) contribute about 4% (from data in Table 1). The large inhibition of skin protein synthesis by hypoxia may therefore be of considerable significance in relation to whole-body nitrogen balance.

We do not know the mechanism by which hypoxia inhibits protein synthesis. The finding that hypoxia inhibited protein synthesis in the heart *in vitro* may be taken as evidence that the effects of hypoxia are direct and not mediated by some other change in the physiological state of the animal. Induction of the post-absorptive state by inhibition of gastric emptying does not seem to be important, because protein-synthesis rates in brain and skin were not inhibited by 15–18h of starvation. This study serves to emphasize that, when investigating turnover of proteins or nucleic acids *in vivo*, investigators should carefully consider the effects of interventions on the nutritional state of the animal, a factor that we consider is often ignored.

There are several possible mechanisms by which hypoxia might inhibit protein synthesis. *In vivo*, 105min of hypoxia lowered ATP concentrations in brain and liver, but not in the kidney (Sanders *et al.*, 1965). *In vitro*, hypoxia or anoxia is known to lower concentrations of phosphocreatine, ATP and GTP (see, e.g., Jefferson *et al.*, 1971; Chua *et al.*, 1979; Preedy *et al.*, 1984*a*). These changes may cause an inhibition of protein synthesis.

In vivo, there are additional effects of hypoxia. Body temperature, heat production and heat loss are decreased (Hayashi & Nagasaka, 1981). The decrease in body temperature is thought to be caused by a decreased ability to oxidize fuels, in shivering thermogenesis or inappropriate sympathetic tone. Of course, all these phenomena could be inter-related. Colonic temperature decreased by about 2°C over 2h in an atmosphere of 9.5% O_2 in N_2 and an ambient temperature of 25°C (Hayashi & Nagasaka, 1981). Consideration of the Maxwell–Boltzmann equation would suggest that this decrease could be sufficient to account for the observed inhibition of protein synthesis by hypoxia. However, were this the case, the inhibition of protein synthesis might be expected to be of a similar magnitude in all tissues, unless the internal temperatures of tissues are differentially affected by hypoxia.

Hypoxia causes a redistribution of blood flow, with a dilatation of coronary and cerebral vessels and a vasoconstriction in the splanchnic bed and skeletal muscles (Heistad & Abboud, 1980) and in the skin (Hayashi & Nagasaka, 1981). [Hayashi & Nagasaka (1981) suggest that hypoxia increases skeletal-muscle blood flow, however.] Since hypoxia inhibits brain and skin protein synthesis to a greater extent than in all other tissues studied (Table 1), it seems unlikely that a redistribution of blood flow could explain the observations simply.

There are also endocrine changes in hypoxia. Plasma corticosteroid concentrations are increased (MacKinnon *et al.*, 1963; Mlekusch *et al.*, 1981) which, in pretreated rats, would inhibit gastrocnemius-muscle protein synthesis both *in vivo* (Odedra & Millward, 1982) and *in vitro* (Rannels & Jefferson, 1980). However, in contrast with the effects of hypoxia, protein synthesis in liver and

cardiac and aerobic skeletal muscles is perhaps less affected by corticosteroids (Rannels *et al.*, 1978; Rannels & Jefferson, 1980; Odedra *et al.*, 1983). Thus one or more of the alterations in physiological and metabolic states induced by hypoxia could be of relevance to the inhibition of protein synthesis.

Other effects of hypoxia

Hypoxia causes right-ventricular hypertrophy in the heart, with the left ventricle being relatively unaffected (Gloster *et al.*, 1972), and polycythaemia (for a review, see Heath & Williams, 1977, pp. 39–53). The right-ventricular hypertrophy results mainly from the increase in pulmonary arterial pressure resulting from hypoxic pulmonary vasoconstriction (Heath & Williams, 1977, pp. 75–88). These findings are of relevance to our studies, since one would expect a stimulation of protein synthesis in the right ventricle and in the tibia (a site of erythrocyte maturation). The fact that we were unable to detect such changes suggests that either the necessary adaptive period is greater than 6 h or, less likely, the control mechanisms are exerted by altering the rate of protein degradation or, in the case of erythrocytes, extending their lifespan. Thus the acute inhibitory effects of hypoxia on protein synthesis probably initially over-ride any longer-term stimulatory effects in these tissues.

Possible implications of this study

A number of clinical conditions are potentially able to induce tissue hypoxia. These include conditions where cardiovascular or pulmonary performance is impaired. As mentioned above, ascent to high altitude may also induce tissue hypoxia. There is frequently wasting in all these groups of individuals. It is tempting to suggest that the inhibition of protein synthesis by hypoxia may be at least in part responsible for the loss of weight. Furthermore, if this were true, it would be unlikely that increasing the nourishment of such individuals by, e.g., hyperalimentation or parenteral nutrition would ameliorate the wasting. It could be argued that weight loss is merely a result of the anorectic effects of hypoxia. However, it could equally be argued that the anorectic effect of hypoxia is in some way initiated by the inhibition of protein synthesis by hypoxia.

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