Hypertriglyceridemia in Rats at Simulated High Altitudes

Some early observations indicate that lipemia occurs in rabbits exposed for some days to low atmospheric pressure[1–5]. On the other hand, short exposures of a few hours' duration have been shown to have no increasing effect on blood lipids in cats, dogs, and rabbits[6]. To the author's knowledge, there are no reports of the effect of prolonged atmospheric hypoxia on blood lipid levels of humans, or animals other than the rabbit. The lack of this rather fundamental knowledge became apparent during recent studies on the pathogenetic mechanisms of the hemorrhagic lipemia[7,8], the main etiological factor of which is most probably the anaemic hypoxia. A study on serum lipids in the rat at low ambient pressures was thus undertaken.

Methods. Sixty male rats of the Sprague-Dawley strain, weighing initially 185–240 g, were used. The animals were divided into 10 groups of 6 rats in each. Simulated altitudes of 3000, 5000 and 7000 m were obtained by reducing the pressure by 235, 355 and 450 mm Hg, respectively, in a low pressure chamber. The chamber was opened daily for feeding and cleaning procedures, which took about $^1/_2$ h. The decompression as well as the 'descent' to sea level was accomplished in 5–10 min.

The rats were allowed to eat and drink ad libitum. The food consumption was nil during the first day of experiment and minimal up till the fourth or fifth day, increasing thereafter to normal level in all low pressure groups. The control rats kept at sea level pressure, were given only the same amount of food as the rats at 5000 m altitude actually ate. At the end of each experiment, the rats were killed under rapidly induced ether anaesthesia by withdrawing as much blood as possible by cutting the abdominal aorta. This was done within 1–2 h after bringing the animals to sea level pressure. The previously described[7] analytical methods were used except for serum free fatty acids which were determined by the method of NOVÁK[9].

Results and discussion. The rats tolerated the experiment, including the rapid decompressions, quite well. Only one rat died at 7000 m simulated altitude on the eleventh day of the experiment. The most important results appear in the Table.

A significant increase in serum triglyceride concentrations was observed at all altitudes used. No consistent changes occurred, however, in serum phospholipids or total cholesterol. A tendency to higher liver triglyceride concentrations after 6–12 days, as compared with the corresponding control groups, was observed at 3000 and 5000 m. This was not seen at 7000 m where also serum triglycerides tended to be less markedly elevated. 7000 m is indeed the upper limit of altitude that non-acclimatized rats can tolerate[10].

No significant increases occurred in serum free fatty acid (FFA) concentrations in the low pressure rats as compared with the corresponding controls. This was also true for serum total ketone bodies. This argues against increased peripheral lipid mobilization, e.g. caused by catecholamines, as being the cause of hypertriglyceridemia in hypoxia. There are no previous reports on serum FFA concentrations in prolonged hypoxia. The reports of the effect of acute hypoxia on the FFA levels, on the other hand, are contradictory[11–14].

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Results of experiments in rats at simulated high altitudes

	Sea level			3000 m	5000 m			7000 m		
	3 days n = 6	6 days n = 6	12 days n = 6	12 days n = 6	3 days n = 6	6 days n = 6	12 days n = 6	3 days n = 6	6 days n = 6	12 days n = 5
Serum triglycerides										
mg/100 ml	32.3	16.8	14.0	63.5[b]	52.5	81.4[b]	94.0[b]	53.3[a]	74.0[b]	52.0[b]
S.E.	5.2	1.5	2.0	8.9	9.1	5.1	14.6	5.9	9.8	7.9
Liver triglycerides										
mg/g of wet weight	16.1	5.9	5.9	8.9[b]	10.6	10.4[b]	7.9[a]	11.6	7.9	6.8
S.E.	2.4	1.1	0.4	0.6	1.1	0.8	0.8	1.4	1.2	1.5
Serum free fatty acids										
µEq/l	485	463	570	255[b]	595	352	475	560	453	254[b]
S.E.	68	41	50	27	22	36	26	47	58	34
Blood hemoglobin										
g/100 ml	15.2	13.7	13.9	15.1[b]	16.1[a]	17.2[b]	19.2[b]	16.5[b]	17.8[b]	20.2[b]
S.E.	0.15	0.27	0.24	0.11	0.33	0.13	0.36	0.13	0.32	0.37
Weight loss										
% from initial weight	9.4	4.5	2.7	0.4	16.3[a]	10.3[a]	8.6	19.1[b]	23.3[b]	21.7[b]
S.E.	2.2	1.7	1.9	2.3	1.2	1.1	2.7	1.0	1.2	1.0

Results are mean values of the groups. S.E., standard error; n, number of animals in the group. [a] $p < 0.05$, [b] $p < 0.01$ as compared with the respective control group kept at sea level pressure on equal amount of food as the rats at 5000 m simulated altitude actually ate.

It is well known that, in hypoxia, appetite is initially lost and body weight goes down[15]. The weight loss cannot, however, wholly be explained by the reduction in food intake, because the present high altitude groups lost more weight than the control groups in spite of equal food consumption. An additional mechanism leading to weight loss is dehydration[15]. Plasma volume decreases of up to 26% have been found in rats after at least 10 days of acclimatization to 2400–6100 m[10,16]. Thus the observed increases of blood hemoglobin and hematocrit, changes in the latter running quite parallel to the former, must be partly due to dehydration and partly to a rapid increase of erythropoiesis in hypoxia[15].

The hyperlipidemia of hypoxia in rabbits resembles that caused by repeated bleedings[3,4], all serum lipid classes being elevated. In the present rats, only serum triglycerides showed an increase. This is in contrast to the finding in hemorrhagic hyperlipidemia in rats, in which serum phospholipids and cholesterol increase as well[7]. This increase of serum phospholipids and cholesterol is, however, probably a secondary phenomen to the hypertriglyceridemia. Thus the lack of increase of serum phospholipids and cholesterol in the rats exposed to simulated high altitudes may be explained by the fact that the hypertriglyceridemia was much less marked than that seen in severe bleeding anaemia. The lack of increase of the serum FFA and ketone body concentrations, as well as the slight tendency for triglyceride to accumulate in the liver, are in accordance to findings in hemorrhagic anaemia[7].

It is generally considered that diminished partial pressure of oxygen produces the physiological effects observed at high altitudes[15]. It is interesting to note that cobalt, which is a depressor of cell respiration, also causes marked hyperlipidemia[17]. Thus any type of hypoxia, whether hypoxic, hemic or histotoxic, seems to be connected with hyperlipidemia. Whether this always arises by the same mechanism remains to be studied[18].

Zusammenfassung. Ratten, die 3–12 Tage in einer Luftverdünnung entsprechend einer Höhe von 3000, 5000 und 7000 m gehalten wurden, hatten eine signifikante Hypertriglyceridämie und eine leichte Tendenz zu erhöhten Lebertriglyceridkonzentrationen. Die freien Fettsäuren des Serums waren nicht erhöht.

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Action of Some Compounds on the Adenosine Triphosphatase Activity of *Streptococcus faecalis*

We have previously reported the action of some compounds on the metabolic swelling and glycolytic activity[1] and on the adenosine triphosphate (ATP) pool[2] in protoplasts and/or whole cells of *Streptococcus faecalis*.

The permeability changes responsible for the metabolic swelling seem to be partially dependent of a membrane-bound ATPase[3–5] whose Mg^{++} dependence[6] and sub-unit structure[7] have recently received special attention. In an attempt further to clarify the mechanism of action of those compounds, the present investigation was designed to study their action on the ATPase activity of lysed protoplast suspensions of *S. faecalis*.

Material and methods. S. faecalis ATCC 9790 was grown as reported[1]. The cells were harvested by centrifugation, washed 3 times with redistilled water and twice with 0.075 *M* potassium phosphate pH 6.2, again centrifuged and resuspended in 0.075 *M* potassium phosphate pH 6.2–0.4 *M* sucrose. Muramidase (200 µg/ml) was added, and the mixture incubated at 38 °C in a water bath for 120 min. The resulting protoplasts were harvested by centrifugation, resuspended in a convenient volume of redistilled water to give a protein content between 2.0–2.6 mg/ml, and vigorously stirred. Rapid lysis due to osmotic shock followed. The lysate was diluted 2-fold with $MgCl_2$ 0.01 *M*-*Tris*(hydroxymethyl)aminomethane 0.20 *M*, pH 7.2, and the mixture placed in a water-bath at 38 °C. Additions and sampling were as described before[2], except that glucose was replaced by ATP 2.5×10^{-3} *M*. Following addition of 50 µl of 70% perchloric acid/ml, the samples were assayed for phosphorus by the method of SUMNER[8].

Results and discussion. ATPase activity was an exponential process affected by the compounds tested as represented in the Table. The most pronounced effect was the inhibitory one observed with gramicidin and sodium azide, both of which had an opposite action on the previously studied rate of decay of the ATP in the ATP pool of whole cells metabolizing glucose[2]. Although the 2 processes do not necessarily run parallel since ATPase activity is part but not all of the ATP decay process, it is also important to remember that they were studied in quite different conditions.

Although metabolic differences between whole cells and protoplasts cannot be excluded, it seems now of interest to relate the effect of the tested compounds on the metabolic swelling, glycolytic activity, ATP pool[1,2] and ATPase activity.

The inhibitory action of sodium azide on the metabolic swelling could represent both a slower glycolysis and a

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