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Effect of Vanadium Administration on Coenzyme Q Metabolism in Rats. (26793)

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During studies on the *in vitro* biosynthesis of cholesterol, Curran(1) observed a marked inhibitory effect of vanadium ions on incorporation of acetate-C^{14} into cholesterol by liver homogenates. Similar observations on *in vivo* biosynthesis of cholesterol and of phospholipids in vanadium fed animals have been reported by others(2-4).

While Azarnoff and Curran(5) indicated that the inhibition occurred between the stages of mevalonic acid and β-methyl crotonate, Wright *et al.*(6) suggested that vanadium probably interfered with maintenance of adenosine triphosphate levels in the system and that this may impair the synthesis of phosphorylated intermediates from mevalonic acid. This view is further substantiated by the report that exogenous adenosine triphosphate enhances the synthesis of cholesterol from mevalonic acid(7) and that inhibitors of oxidative phosphorylation decrease it(8). A similar inhibition of acetate incorporation into phospholipids *in vitro* by fluoride, cyanide, dinitrophenol and iodoacetate has been shown earlier by Kline and De Luca(9).

That the decreased synthesis of cholesterol may be due to a lowering in tissue stores of coenzyme A is suggested by the recent work of Mascitelli-Coriandoli and Citterio(10), who have observed considerable reductions in hepatic coenzyme A in rats administered vanadium either orally or parenterally. Other workers(4,11) have suggested that the metabolism of sulfur amino acids may be interfered with by vanadium, in which case a shortage might be postulated of the sulfhydryl reserves of the cell, notably of cysteine, that are needed for biosynthesis of coenzyme A.

The well known involvement of coenzyme A in biosynthesis of isoprene units and of mevalonic acid from 2 carbon fragments and the reported incorporation(12-15) of these into the isoprenoid side chain of coenzyme Q prompted a study of the effect of vanadium administration on coenzyme Q metabolism.

Experimental. Male weanling rats (Wistar strain) 40-50 g in weight were fed a purified 10% casein diet replete in all respects (cf. 16) for a period of 8 weeks. To one group of rats, ammonium vanadate (0.6 mg/rat/week) was administered intraperitoneally while control rats received an equal amount of distilled water. At the end of 8 weeks, some animals from the vanadium ad-

TABLE I. Effect of Vanadium on Growth, Liver Content of Coenzymes A and Q and Succinoxidase Activity.

Group	Growth, g/8 wk	Coenzyme A, units/g	Coenzyme Q, μg/g	Succinoxidase activity, μl O_2/hr/g
10% casein diet	151.8 ± 12.9	164 ± 11	127 ± 7.6	1304 ± 32
Idem + intraper. admin. vanadium	106.4 ± 7.3	89 ± 17	97 ± 9.9	996 ± 51

Results are avg of 6 independent determinations ± stand. error of mean and are on fresh weight basis.

TABLE II. Intracellular Distribution of Coenzyme Q in Vanadium Administered Rat Liver.

Group	Coenzyme Q, μg/g				
	Whole liver	Nuclei	Mitochondria	Microsomes	Supernatant
10% casein diet	127 ± 7.6	37 ± 4.1	48 ± 2.7	19 ± 3.1	7 ± 1.6
Idem + intraper. admin. vanadium	97 ± 9.9	33 ± 4.3	33 ± 1.9	13 ± 1.8	6 ± .9

Results are avg of 6 independent determinations ± stand. error of mean.

ministered group were given calcium pantothenate (10 mg/rat) or l-cysteine hydrochloride (10 mg/rat) or disodium salt of adenosine triphosphate (10 mg/rat) intraperitoneally. A few rats were given all 3 simultaneously. The animals were sacrificed 24 hours after administration of these compounds by decapitation and the livers chilled, homogenised in isotonic sucrose and fractionated according to the procedures of Schneider and Hogeboom(17) and of Palade and Siekevitz(18).

Coenzyme A, coenzyme Q and succinoxidase activity of liver were determined as described earlier(16).

Results and discussion. Vanadium administration results in a lowering of liver stores of coenzyme A (CoA), coenzyme Q (CoQ) and succinoxidase (S.O. activity (Table I). The intracellular distribution of coenzyme Q shows a marked reduction in the mitochondrial fraction with no significant changes in the other fractions (Table II). These changes are similar to those obtained in pantothenic acid deficiency(16,19) and are suggestive of a primary interference by vanadium in the metabolism of either pantothenic acid or its functional form, coenzyme A.

Since a primary lowering in coenzyme A level may lead to decrease in the coenzyme Q stores in liver, the protective effects of administering calcium pantothenate, l-cysteine hydrochloride and disodium salt of adenosine triphosphate either individually or together on liver levels of coenzymes A and Q were studied. The results are presented in Table III. No significant restorative effect was observable with calcium pantothenate or ATP alone, but cysteine was partially effective. The 3 together almost completely reversed the changes due to vanadium administration. The results point to an interference by vanadium in biosynthesis of coenzyme A, possibly through its effect on tissue sulfhydryl(4) and

TABLE III. Protective Effects of Pantothenic Acid, Cysteine and Adenosine Triphosphate against Vanadium Treatment.

Compounds administered			Coenzyme A, units/g	Coenzyme Q, μg/g	Succinoxidase activity, μl O_2/hr/g
Ca-P	CSH	ATP			
+	—	—	98 ± 13	98 ± 8.4	984 ± 52
—	+	—	123 ± 9	109 ± 7.1	1144 ± 36
—	—	+	111 ± 7	106 ± 4.5	1086 ± 49
+	+	+	143 ± 12	123 ± 6.7	1361 ± 71

Calcium pantothenate (Ca-P) (10 mg/rat), l-cysteine hydrochloride (CSH) (10 mg/rat) and disodium salt of adenosine triphosphate (ATP) (10 mg/rat) were given intraper. and the animals sacrificed 24 hr later.

Results are avg of 4 independent determinations ± stand. error of mean and are expressed on fresh weight basis.

adenosine triphosphate(6) reserves.

Summary. Vanadium administration results in decreases in coenzyme A, coenzyme Q and succinoxidase activity in rat livers. A marked protection against these changes is afforded by simultaneous administration of calcium pantothenate, l-cysteine hydrochloride and disodium adenosine triphosphate. The results are discussed in relation to other reported observations on the effects of vanadium administration.

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Cytochrome Oxidase in Radiosensitive and Radioresistant Amoebae.* (26794)

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Two species of the giant amoeba *Pelomyxa* are known to differ by a factor of approximately 10 in their sensitivity to x-radiation. The x-ray LD_{50} for *P. carolinensis* is about 100 kr(1-3), whereas that for *P. illinoisensis* is about 10 kr(2,4,5). It seemed possible that there might be some fundamental metabolic difference responsible for this wide dissimilarity in radiosensitivity. Very little is known about the metabolic characteristics of *P. illinoisensis*. However, *P. carolinensis* is known to contain cytochrome pigments(6), and 70% of its respiration is cyanide-sensitive(7). Møller and Prescott(6) were unable to demonstrate absorption peaks characteristic for cytochrome *c* by direct spectrophotometric examination of ruptured cells, and several investigators have failed to detect cytochrome *c* oxidase activity (see 6). Møller and Prescott suggested that a cytochrome *e*-cytochrome *c* oxidase system was operating as the terminal oxidase in *P. carolinensis*.

It occurred to us that *P. illinoisensis* might contain cytochrome *c* oxidase, in contrast to the more radioresistant species. Thus we assayed the 2 species for this enzyme. We have found, however, that both species contained approximately the same amount of cytochrome *c* oxidase activity, although the sys-

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