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Dietary Carotene and the Degree of Esterification of Vitamin A in the Milk and Blood of Cows

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In a previous paper (Chanda & Owen, 1952) the authors showed that depriving cows of carotene caused an increase of the vitamin-A alcohol in their milk and that this increase was enhanced by imposing thyroxine treatment simultaneously with the carotene deprivation. These increases were interpreted as indicating a draft by the cow from the stores of vitamin A in the liver. In the previous paper the effects of carotene deprivation on the composition of milk were studied but no analyses of blood were made. In the present experiment the β -carotene, vitamin A ester and vitamin-A alcohol were studied in both the blood and milk of a further four cows on diets which provided intakes of carotene varying from a mere trace to more than 2000 mg./cow/day.

EXPERIMENTAL

The experiment lasted 20.5 weeks and was divided into seven periods, all except the last of which are shown in Fig. 2. In periods 1, 3 and 6, each of four Ayrshire cows received diet 1, which was free from carotene and consisted of (parts by weight): oats, 6; bran, 1; field beans, 2; decorticated-earthnut meal, 1. Diet 2, which was fed during period 2, consisted of: oats, 18; beans, 12; dried grass, 9; lucerne meal, 4. In periods 4 and 5, diet 3 was fed. It consisted of: oats, 18; beans, 12; dried grass, 7; lucerne meal, 5. Diet 1 contained no carotene, whilst diets 2 and 3 contained carotene as a natural constituent of the dried grass and lucerne meals. The concentrate ration for each period was prepared in a single batch. On all diets, straw and beet pulp

were fed as roughage. As in a previous experiment (Chanda, Clapham, McNaught & Owen, 1952), analyses showed that faecal carotene became negligible after 7 to 8 days of carotene deprivation.

In 24 hr. representative samples of Sunday's and Wednesday's milk, the partition of vitamin A between alcohol and ester and the content of carotene were determined. On the last day of each period and also in the middle of period 6 these same determinations were made on the blood of each

Table 1. Carotene intake and carotene content of production rations

Cow no.	Period	Food intake* (kg./day)	Carotene (mg./100 g. food)	Carotene intake (mg./day)
1	2	9.05	2.96	268
	4	10.50	5.26	552
	5	10.50	6.28	659
	7†	9.00	22.61	2035
2	2	9.07	2.96	269
	4	10.29	5.26	541
	5	10.50	6.28	659
	7†	9.50	22.61	2148
3	2	9.04	2.96	268
	4	10.50	5.26	552
	5	10.50	6.28	659
	7†	8.70	22.61	1967
4	2	8.13	2.96	241
	4	8.77	5.26	461
	5	8.47	6.28	532
	7†	8.30	22.61	1877

* Not including oat straw and beet pulp fed according to appetite.

† Grazing.

of the animals. During each of the carotene periods, 2, 4 and 5, samples of food were analysed every 4 days for carotene, and from the known weight of food eaten the carotene intake was calculated. At the conclusion of the experiment, in period 7, the four cows were used by the Animal Husbandry Department of this Institute for a grazing trial. From the intake of grass computed by them and from its carotene content the carotene intake during period 7 was calculated. It will be seen that the cows were allowed intakes of carotene which increased as the experiment progressed (Table 1). Carotene intakes varied from a mere trace in periods 1, 3 and 6 to about 2000 mg./day in period 7. The intake in periods 4 and 5 (about 550 mg./day) was twice as great as during period 2.

Methods of analysis

These were as described in earlier papers (Chanda, Owen & Cramond, 1951; Chanda & Owen, 1952). The procedure of Morton & Stubbs (1946) was used to correct both the milk and blood vitamin A for irrelevant absorption. Fig. 1 shows the extent of this irrelevant absorption for blood. The fat was extracted from the blood serum by the method of Yudkin (1941) but hexane was used as the solvent. The method of separation of vitamin-A ester in blood from vitamin-A alcohol and the method of separation of β -carotene from total carotenoids by chromatography on alumina were as described by Chanda & Owen (1952) for milk.

Fig. 1. The absorption spectrum of vitamin A in cow blood. Upper curve uncorrected, lower curve corrected for irrelevant absorption.

RESULTS

Composition of milk

The effects on the milk of the dietary treatments are shown in Tables 2 and 3 and in Fig. 2. As was expected, the amount of β -carotene in the milk

Table 2. Average milk yield and average percentage of fat in the milk of each period, together with the concentration of β -carotene in the fat
(β -Carotene is given as $\mu\text{g./g. fat.}$)

Period no.	Cow no.	1. Carotene-free			2. Carotene			3. Carotene-free			4. Carotene			5. Carotene			6. Carotene-free		
		Milk yield (kg./day)	Fat (%)	Carotene ($\mu\text{g./g. fat.}$)	Milk yield (kg./day)	Fat (%)	Carotene ($\mu\text{g./g. fat.}$)	Milk yield (kg./day)	Fat (%)	Carotene ($\mu\text{g./g. fat.}$)	Milk yield (kg./day)	Fat (%)	Carotene ($\mu\text{g./g. fat.}$)	Milk yield (kg./day)	Fat (%)	Carotene ($\mu\text{g./g. fat.}$)	Milk yield (kg./day)	Fat (%)	Carotene ($\mu\text{g./g. fat.}$)
1	1	14.07	3.41	2.54	11.28	3.53	4.42	9.26	3.22	3.32	8.34	3.24	5.90	7.85	2.88	8.80	6.19	3.16	3.42
2	2	13.44	3.43	2.35	13.22	3.72	4.62	13.40	3.70	3.00	13.88	3.42	5.44	12.40	3.58	7.12	11.47	3.60	2.68
3	3	15.46	3.69	2.25	14.18	3.90	4.16	13.76	3.72	2.86	14.12	3.66	5.04	13.65	3.53	7.26	11.74	3.78	2.78
4	4	16.27	3.04	2.87	16.65	3.18	5.79	16.04	2.90	3.23	15.75	3.15	5.73	13.23	3.63	8.07	12.12	3.19	3.08

Table 3. Minimum vitamin-A ester and corresponding β -carotene and vitamin-A alcohol during deprivation of β -carotene (periods 1, 3 and 6) and maximum vitamin-A ester and corresponding β -carotene and vitamin-A alcohol during re-alimentation with β -carotene

(β-Carotene is given as μg./100 ml. milk and vitamin A as i.u./100 ml. milk.)																								
Cow no.	Period 1				Period 2 (carotene)				Period 3				Period 4 (carotene)				Period 5 (carotene)				Period 6			
	Vitamin A				Vitamin A				Vitamin A				Vitamin A				Vitamin A				Vitamin A			
	β-Caro- tene	Ester	Alcohol		β-Caro- tene	Ester	Alcohol		β-Caro- tene	Ester	Alcohol		β-Caro- tene	Ester	Alcohol		β-Caro- tene	Ester	Alcohol		β-Caro- tene	Ester	Alcohol	
1	6	54	12	16	86	6	7	46	12	12	43	25	25	97	5	25	25	97	7	6	40	13		
2	6	50	13	17	80	7	6	43	12	12	56	25	25	106	5	26	26	104	5	5	42	13		
3	6	50	13	19	80	8	5	56	15	15	8	24	25	99	7	25	25	100	6	5	41	15		
4	6	47	15	20	75	7	5	40	15	15	7	25	25	97	8	26	26	103	6	4	34	15

Fig. 2. Yields of milk, of carotene, vitamin-A ester and vitamin-A alcohol in milk, and percentage of fat in milk of cow no. 1.

reflected the β -carotene intake. On the carotene-free diet the β -carotene in the milk decreased gradually in period 1 and more rapidly in periods 3 and 6. In periods 2 and 4, re-alimentation with carotene caused rapid increases of β -carotene in the milk. Fig. 2 shows the milk yield, the percentage of fat in the milk and the outputs in the milk of vitamin-A ester, vitamin-A alcohol and β -carotene for cow no. 1, which in this and all other respects was typical. For brevity, therefore, the graphs for the other three cows have been omitted. Data in Tables 1-5 show that the behaviour of all four cows was uniform. The general decline (Fig. 2) of the outputs of vitamin-A ester and β -carotene is a reflexion of the natural decline of the milk yield. Throughout the experiments and for all the milk samples examined from all four cows, the percentage of β -carotene in the total milk carotenoids ranged from 76 to 92 averaging 82.4 ± 1.9 s.e. The non-carotene carotenoids were 13, 28, 14, 10, 10 and 11 $\mu\text{g./100 ml. milk}$ for periods 1-6, respectively, each figure being the average of four concordant averages for each of the four cows. In Table 2, the average milk yield, the average percentage of fat in the milk and the average concentration of β -carotene in the milk fat are recorded for the four cows. In Table 3, the minima of vitamin-A ester in the milk during deprivation of carotene in periods 1, 3 and 6 and maxima of vitamin-A ester during re-alimentation with β -carotene are recorded, together with the values of β -carotene, vitamin-A alcohol and

fat in the samples of milk which showed these maximum and minimum values. It was noticed that, when vitamin-A ester was maximal, β -carotene was also maximal, and that minima of these two substances in the milk also coincided. In contrast, minima of vitamin A-alcohol in the milk coincided with maxima of vitamin-A ester and vice versa (Fig. 2).

Vitamin-A ester in milk. The amount of vitamin-A ester in the milk changed with diet in much the same way as did β -carotene (Fig. 2 and Table 3), decreasing markedly in periods 1, 3 and 6 when carotene was withheld from the diet, and increasing markedly on re-alimentation with carotene in periods 2 and 4. These changes were of similar magnitude in all four cows and were obvious, whether the results were expressed as yields per cow or as percentages of the milk or as percentages of the milk fat. Indeed this last statement was true of the changes of β -carotene and of vitamin-A alcohol also.

Relationships between vitamin-A ester and β -carotene and between vitamin-A ester and vitamin-A alcohol in milk. Comparison of the figures for successive periods in Table 3 and a reference at the same time to the trends in Fig. 2 show the dependence of both β -carotene and vitamin-A ester in the milk upon dietary β -carotene. Fig. 2 also shows that trends of vitamin-A alcohol were the reverse of those of β -carotene and vitamin-A ester. In confirmation of a previous finding of Chanda & Owen (1952), Fig. 2 shows that vitamin-A alcohol increased as β -carotene intake diminished, and decreased as β -carotene intake increased, thus producing the relationships between their maxima and minima already mentioned and illustrated in Fig. 2 and Table 3. The changes of vitamin-A ester in the milk were in the same direction as those of β -carotene, but the changes of vitamin-A alcohol were in the opposite direction from those of β -carotene. Thus, correlations between vitamin-A ester and β -carotene in the milk were large and positive, whilst, in contrast, correlations between vitamin-A ester and vitamin-A alcohol were almost equally large and were negative. The coefficients of these correlations, recorded in Table 4, are statistically very significant.

Table 4. *Correlations between vitamin-A ester and β -carotene and between vitamin-A ester and vitamin-A alcohol*

(Values are determined as i.u. (vitamin-A ester or alcohol) or μg . (β -carotene)/100 ml. whole milk.)

Cow no.	No. of paired observations	Coefficients of correlation	
		Vitamin-A ester $\times$ β -carotene	Vitamin-A ester $\times$ vitamin-A alcohol
1	35	+0.930	-0.862
2	35	+0.902	-0.829
3	35	+0.891	-0.783
4	33	+0.926	-0.821

Composition of blood serum

β -Carotene in blood serum. Table 5 shows how sensitive the blood serum was to changes of intake of β -carotene. For all four cows, blood carotene increased approximately in proportion to intake, and all of them showed the lowest carotene figures when they were eating the carotene-free diet (in periods 1, 3 and 6) so that in all the cows β -carotene in the blood was a fair indication of the carotene intake. Nevertheless, it is noteworthy that even after 3 weeks of depletion there was still an easily measurable amount of β -carotene in the blood.

Non-carotene carotenoids were present in the blood as some 10–20% of the total carotenoids. They were present in the blood serum in smallest concentration in periods 1, 3 and 6. In periods 2, 4, 5 and 7 their concentrations, like those of β -carotene, reflected the intake of greenstuff. In periods 1, 3 and 6 the blood serum contained 8, 12 and 10 units, respectively, of non-carotene carotenoids. In periods 2, 4, 5 and 7 it contained 23, 44, 53 and 100 units, respectively, each figure being the average of four concordant figures given by the four cows in each period. The figures were calculated on the same basis as was used for true β -carotene. These figures show that the passage of non-carotene carotenoids into the blood did not increase as rapidly with increasing intake of greenstuff as did the passage of true β -carotene into the blood (Table 5). Differences between periods in the non-carotene carotenoids in the blood were greater than the corresponding differences in the milk. This disparity between the blood and the milk probably indicates limitations of the permeability of both the intestinal and mammary epithelia to non-carotene carotenoids. Comparison of milk and blood β -carotene values in Tables 3 and 5 shows that similar considerations apply to β -carotene also.

Vitamin A in blood serum. Table 5 shows the concentrations of vitamin-A ester, of vitamin-A alcohol and of β -carotene in the blood of four cows in each of the experimental periods. It shows clearly the dependence of vitamin-A ester in the blood on the carotene intake. When the intake of β -carotene was zero, the blood vitamin-A ester was zero also. As the carotene intake increased so did the blood vitamin-A ester. The table shows that in respect of vitamin-A ester all four cows behaved similarly. As already mentioned, the effect of β -carotene intake on blood β -carotene was equally marked but, in contrast to vitamin-A ester, blood β -carotene did not become zero on zero intake. Blood vitamin-A alcohol behaved quite differently from either vitamin-A ester or β -carotene. The small changes which it showed bore no relation at all to the intake of β -carotene. Thus, although subjection of the cows to periods of deprivation of dietary carotene had

Table 5. Carotene deprivation and the concentrations of β -carotene, vitamin-A ester and vitamin-A alcohol in blood serum of the lactating cow

Period no.	Duration (days)	Carotene* intake (mg./day)	β -Carotene (μ g./100 ml. serum)				Vitamin-A ester (i.u./100 ml. serum)				Vitamin-A alcohol (i.u./100 ml. serum)								
			Cow no. 1	Cow no. 2	Cow no. 3	Cow no. 4	Cow no. 1	Cow no. 2	Cow no. 3	Cow no. 4	Cow no. 1	Cow no. 2	Cow no. 3	Cow no. 4					
1	21	Trace	48	45	64	38	0	0	0	0	87.8	96.1	103.7	84.0	86.6	99.6	107.9	86.6	87.4
2	20	262	136	131	151	168	11.4	9.7	12.5	10.5	82.1	93.1	98.4	87.4	95.8	111.7	114.0	105.6	100.3
3	18	Trace	70	57	80	89	0	0	0	0	107.9	115.5	117.0	113.2	96.5	113.2	127.7	111.7	111.7
4	17	527	411	339	446	424	21.2	25.1	26.5	27.1	99.6	107.9	113.2	96.5	99.6	107.9	127.7	111.7	111.7
5	15	627	555	443	614	552	27.8	25.5	29.6	27.8	31.6	36.8	31.0	34.4	31.0	36.8	31.0	34.4	34.4
6a	13	Trace	93	92	119	101	0	0	0	0	31.6	36.8	31.0	34.4	31.0	36.8	31.0	34.4	34.4
6b	10	Trace	38	40	47	47	0	0	0	0	31.6	36.8	31.0	34.4	31.0	36.8	31.0	34.4	34.4
7	29	2007	867	822	944	1117	31.6	36.8	31.0	34.4	31.6	36.8	31.0	34.4	31.0	36.8	31.0	34.4	34.4

* Average for all four cows.

no effect on vitamin-A alcohol in the blood serum, it nevertheless caused a marked diminution of circulating β -carotene and caused vitamin-A ester to disappear altogether from the blood serum. At the conclusion of period 7, during which access to pasture enhanced the intakes of carotene from an average of 635 mg./cow/day in period 5 to an average of more than 2000 mg., the largest concentrations of vitamin-A ester and β -carotene in the blood occurred. These large changes of carotene intake had, however, no demonstrable effect on the vitamin-A alcohol in the blood serum (Table 5). Inspection of Table 5 shows that blood β -carotene increased much more with increasing intake of greenstuff than did vitamin-A ester. This was doubtless due to the efficient removal of vitamin A from the blood by the mammary gland or the liver or both.

DISCUSSION

These experiments confirm the earlier observation of Chanda & Owen (1952) that the metabolism of vitamin-A ester is distinct from that of vitamin-A alcohol and that as they exist in the blood serum these two substances are not in equilibrium with one another. Thus, Chanda & Owen (1952) found that deprivation of carotene caused a marked increase of both the concentration and the yield of vitamin-A alcohol in the milk. Such deprivation also caused simultaneous reductions of the concentrations of carotene and vitamin-A ester in the milk. These observations are confirmed by the present experiments. In the blood, the vitamin-A alcohol was unaffected by the large changes of intake of carotene. Since most of the vitamin A in the blood is in the form of the alcohol, it is not surprising that attempts to change the total vitamin A in the blood by means of dietary carotene are not successful (Klosterman, Bolin & Ford, 1951; Thomas & Moore, 1952; others quoted in a review by Owen, 1954). Chronic deprivation of carotene decreases the concentration of vitamin A in the blood (Eaton, Helmbolt, Jungherr, Carpenter & Moore, 1951; Eveleth, Bolin & Goldsby, 1949), but larger intakes of carotene do not necessarily increase it (Klosterman *et al.* 1951; Thomas & Moore, 1952). Apparently the stores of vitamin A in the liver need to be severely depleted for the cow to lose its ability to maintain the normal concentration of vitamin-A alcohol in the blood. By analogy with work from other laboratories on the metabolism of β -carotene and vitamin A in the rat, it is extremely probable that the action of thyroxine in the experiments of Chanda & Owen (1952) was to mobilize the reserves of vitamin A in the liver and to release them into the blood as vitamin-A alcohol. It is necessary to suppose that the power of the mammary gland to re-esterify vitamin A is limited. Without such

a hypothesis it is difficult to account for the increase of the free form of the vitamin in the milk, when, owing to deprivation of carotene, the cow is forced to use its liver reserves. When thyroxine causes these liver reserves to be mobilized at an enhanced rate, the limited power of the mammary gland to esterify vitamin A is placed even more in evidence (Chanda & Owen, 1952). Nevertheless, it must be supposed that the gland does esterify the vitamin, since the present experiments show that the ester form is absent from the blood of cows which are deprived of carotene, while the bulk of the vitamin A in the milk is still in the ester form (Table 5).

The present experiments confirm the observation of Chanda (1953) that vitamin-A ester occurs in cattle blood, and show that it reflects the intake of β -carotene, as indeed the experiments of Thompson, Ganguly & Kon (1949) would lead one to expect. In the absence of evidence as to the relative rates at which the mammary epithelium can take up vitamin-A alcohol and vitamin-A ester, it is not possible to say in which form the major part of the vitamin A originating from dietary carotene is absorbed by the mammary gland. β -Carotene is absorbed from the gut into the intestinal lymphatics (Thompson *et al.* 1949; Glover, Goodwin & Morton, 1948; Eden & Sellers, 1950) chiefly as vitamin-A ester. From these lymphatics the vitamin-A ester will pass to the venous system, to the lungs and then to the general body circulation, so that the liver will have no better chance of intercepting it than will the mammary gland.

SUMMARY

1. Lactating cows were fed, in alternate periods, carotene-free diets and diets containing carotene; the intakes of carotene in the successive carotene periods increased as the experiment progressed.

2. In confirmation of the authors' previous results, carotene deprivation caused the amount of vitamin-A alcohol in the milk to increase.

3. The concentration of vitamin-A alcohol in the blood serum was not affected by the removal of carotene from the diet.

4. Carotene deprivation caused vitamin-A ester to disappear completely from the blood serum. The ester reappeared when carotene was again fed.

5. It is concluded from these results and from earlier results with thyroxine-treated animals that increases in vitamin-A alcohol in the milk of cows indicate a transfer of reserves of vitamin A from the cow's liver to the milk.

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The Excretion of Kynurenine and 3-Hydroxykynurenine by Man

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3-Hydroxykynurenine was first shown to be a tryptophan metabolite in animals in experiments with pyridoxine-deficient rats (Dalgliesh, Knox & Neuberger, 1951; Dalgliesh, 1952*b*). Later, Makino, Satoh, Fujiki & Kawaguchi (1952) claimed that 3-hydroxykynurenine is responsible for the diazo

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reaction and Weiss urochromogen reaction shown by the urine of patients suffering from acute tuberculosis. This suggested that in acute tuberculosis the function of pyridoxine-deficient enzymes might be deranged, and the purpose of this work was to investigate this possibility. It was found that the excretion of hydroxykynurenine by man is unrelated to tuberculosis and occurs in many cases