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DIHYDROXYACETONE STUDIES

I. Its Respiratory and Carbohydrate Metabolism in Normal Men[1]

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INTRODUCTION

The triose, dihydroxyacetone, has been known for many years, but its experimental study has been restricted due to difficulty in obtaining the chemical in sufficient quantity. Fischer (1) prepared dihydroxyacetone synthetically, the first step being the formation of α acrose by condensation from formaldehyde which by oxidation with bromine was changed into a mixture of glyceric aldehyde and dihydroxyacetone. He further suggested that by treatment with alkalies condensation would take place to hexoses. Another and the commoner method of preparation was by bacterial action upon glycerol.

Theoretical considerations have been advanced by Buchner and Meisenheimer (2), and by Embden, Schmitz, and Wittenberg (3) to the effect that dihydroxyacetone is probably a normal product in the intermediary metabolism of carbohydrate. The former think that it is a product formed early in the fermentation of glucose, while the latter believe that fructose (levulose) is normally split into d-glyceric aldehyde and dihydroxyacetone. More recently Woodyatt (4) has stated that the trioses are probably normal intermediates in carbohydrate metabolism.

[1] The dihydroxyacetone employed in this work was made by Farbwerke v. Meister Lucius and Brüning, Hoechst a Main, and was supplied gratis by the Mallinckrodt Chemical Works, Ltd., Montreal.

That dihydroxyacetone is promptly absorbed and under certain circumstances readily converted into glucose is well known. Lusk (5) has shown that all the trioses are quantitatively converted into glucose in a phlorhizinized dog, and Ringer and Frankel (6)confirmed these findings using a nine gram dose of dihydroxyacetone administered subcutaneously. Carbon determinations in their experiments also confirmed its complete conversion into glucose. Embden (3) has further shown its conversion into glucose by liver perfusion. That the trioses, including dihydroxyacetone, are glycogen formers has been shown by Mostkowski (7). Isaac and Adler (8) stated that in rats and mice after dihydroxyacetone feeding there is more glycogen in the liver than after similar feeding with glucose.

The relation of dihydroxyacetone to lactic acid formation is not clear. Apparently the muscles, muscle juice, and red blood cells can convert dihydroxyacetone into lactic acid (Embden, Baldes, and Schmitz (9), Woodyatt (4)). Isaac and Adler (8) have shown that in cases with a disturbance of liver function after the ingestion of dihydroxyacetone the blood lactic acid rises to a higher level than in individuals with a normal liver function. This might indicate difficulty in forming glycogen and is supported by the fact that with liver disease the blood sugar rises after the ingestion of dihydroxyacetone, a finding which is absent in normal individuals. They have also noted after giving dihydroxyacetone and insulin that the blood lactic acid and its urinary excretion increase much more than after a like dose of glucose and insulin, and that there is an associated fall in the blood sugar. These findings have been obtained in both normal and diabetic individuals. From this they argue that dihydroxyacetone, under the influence of insulin, is not completely changed into glucose but that it is involved in the process of formation of lactic acid by the liver.

That dihydroxyacetone is antiketogenic would appear from the paper of Ringer and Frankel (6) in which phlorhizinized dogs were used. More recently Rabinowitch (10) has reported a case of diabetic ketosis treated with dihydroxyacetone where an antiketogenic action was observed.

The chemical dihydroxyacetone is a white crystalline substance with a slightly tart taste. It dissolves readily in water. Apparently it is absorbed promptly after being taken by mouth, fails to cause any

gastro-intestinal disturbance, and even when taken in large doses (150 grams per day) has shown no evidence of renal irritation. Experiments indicate that it is absorbed slowly by the rectum, and that when given intravenously up to 25 grams it is well tolerated.

In 1924 Isaac and Adler (8) published a communication showing blood sugar curves in normal and diabetic individuals after the administration of 25 to 50 gram doses of dihydroxyacetone by mouth. These were compared with curves obtained in the same patients after equal quantities of glucose. The results were uniform and showed that in normal people there was no rise in the blood sugar after such doses, while in diabetics the rise was of a much less degree than after a similar dose of glucose. This was confirmed by Rabinowitch (11), who also reported one respiratory quotient curve in a mild diabetic after 100 grams of dihydroxyacetone by mouth. A rise of the R.Q. from the basal level of 0.706 to 0.817 was obtained in two hours.

The work reported in this paper was undertaken to determine the effect of dihydroxyacetone upon the respiratory metabolism of normal individuals. A series of five normal patients were chosen from the general medical wards who had an undisturbed carbohydrate tolerance. Four of the five dihydroxyacetone experiments were controlled by a similar one using the same quantity of glucose.

EXPERIMENTAL METHODS

The respiratory experiments were all conducted under like circumstances with the patient in the basal state during the morning hours. A preliminary basal hour was obtained as a base line, at the end of which the glucose or dihydroxyacetone were given in one dose unless otherwise stated, this being followed by hourly observations for the next three to four hours. The fluid intake amounted to 200 cc. per hour. Expired air was collected for ten minute periods in a Douglas bag, during the last ten minutes of the basal hour, and, after the ingestion of the glucose or dihydroxyacetone, during the final ten minutes of the thirty-minute, one-hour, two-hour, and three-hour periods. After a preliminary emptying of the bladder at the start of the basal hour, urines were collected hourly and the urinary nitrogen determined in duplicate by the Günning modification of the original

Kjehdahl technique. A blood sample was taken at the end of the basal hour, again in one-half hour, one hour, two hours, etc., and the blood sugar determined by the method of Folin and Wu. The expired air was measured in a wet meter and samples were analysed in duplicate by a modified Henderson-Haldane gas analysis apparatus. For the qualitative determination of the presence of dihydroxyacetone in the blood and urine the observation that dihydroxyacetone will reduce an alkaline copper solution in the cold was employed. In addition a test that Pinoff developed for determining the presence of levulose was used as well. It is based on the reduction of ammonium molybdate to an oxide in an acid solution when a blue color is produced (Miller and Taylor (12)). The calculation of the non-protein respiratory quotient was made by subtracting from the total respiratory carbon dioxide and oxygen the protein carbon dioxide and oxygen. In the production of one gram of urinary nitrogen 5.91 liters of oxygen are consumed and 4.76 liters of carbon dioxide are given off. The non-protein respiratory quotients based on the gas collection of the first thirty minutes of the test period were corrected as for the urinary nitrogen of the complete hour. The estimation of the non-protein calories was made according to the tables of Zuntz and Schumberg as modified by Lusk (13). The factor used for the conversion of carbohydrate calories into grams was 3.74, thereby expressing combustion in terms of glucose. In the experiments where dihydroxyacetone was present in the urines the amount is expressed in terms of glucose.

EXPERIMENTAL FINDINGS

A study of the data obtained in five normal individuals, as summarized in table 1, and depicted graphically in figure 1 shows that there is a material difference in the respiratory and carbohydrate metabolism after like doses of glucose and dihydroxyacetone.

The respiratory quotient. After the ingestion of 25 or 50 grams of dihydroxyacetone there is a rapid rise in the non-protein respiratory quotient which reaches unity or slightly above in one-half to one hour. This rise is followed by a rapid drop to or slightly below the basal level. In no case was this rise preceded by a fall in the respiratory quotient. In one case, experiment 3, the ingestion of 2 grams of dihy-

droxyacetone every fifteen minutes for two hours produced a slightly delayed rise, the maximum respiratory quotient being attained at the end of the first hour. The subsequent drop was of the same character

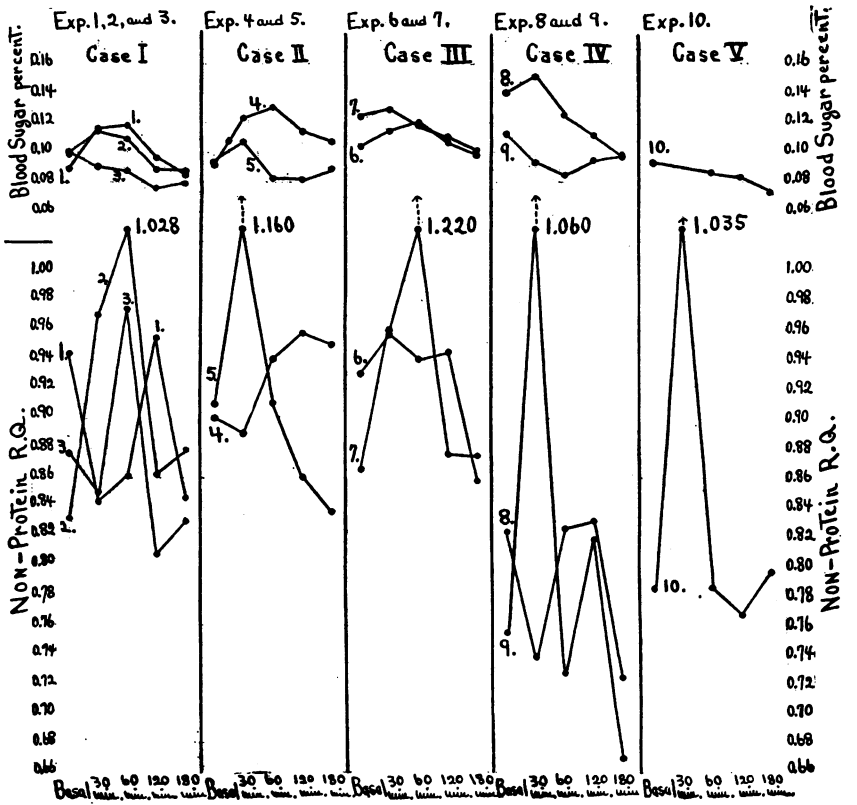

FIG. 1. REPRESENTING GRAPHICALLY THE NON-PROTEIN RESPIRATORY QUOTIENT AND BLOOD SUGAR TIME CURVES IN THE EXPERIMENTS RECORDED IN TABLE 1

Experiments 1, 6, and 8 are after 25 grams of glucose; experiment 4 is after 50 grams of glucose. Experiments 2, 7, 9 and 10 are following 25 grams of dihydroxyacetone; experiment 5 is after 50 grams of dihydroxyacetone.

with the same increment decrease as in the case of experiment 2, when 25 grams of dihydroxyacetone were given. In four of the cases the observations were controlled by the ingestion of a like dose of glucose,

TABLE 1

Simultaneous respiratory exchange and blood sugar time curves in normals

Time	CO_2 per hour	O_2 per hour	Total R.Q.	Nitrogen per hour	Non-protein R.Q.	Calories per hour	Carbohydrate per hour	Blood sugar	Dihydroxyacetone in blood	Dihydroxyacetone in urine	Remarks
minutes	*liters*	*liters*		*grams*			*grams*	*per cent*		*per cent*	
Basal	11.23	12.37	0.904	0.551	0.944	59.95	9.95	0.089	—	—	Case I. Experiment 1. May 12, 1925.
30	10.69	12.83	0.833	—	0.843	61.20	6.12	0.116	—	—	Male. Age 15. Surface area 1.43
60	11.02	12.98	0.849	0.517	0.861	62.00	7.03	0.118	—	—	sq. m. Glucose: 25 grams
120	11.68	12.40	0.939	0.200	0.955	61.30	13.50	0.096	—	—	
180	10.23	12.29	0.832	0.691	0.846	58.15	5.25	0.084	—	—	
Basal	10.42	12.60	0.827	0.389	0.832	60.10	5.92	0.098	0	0	Case I. Experiment 2. May 13, 1925.
30	12.78	13.53	0.945	—	0.970	66.75	13.82	0.115	0	—	Dihydroxyacetone: 25 grams
60	12.61	12.73	0.991	0.360	1.028	62.95	14.30	0.109	0	0	
120	10.41	12.17	0.856	0.240	0.862	58.76	7.66	0.088	0	0	
180	10.60	12.23	0.866	0.334	0.879	59.05	8.11	0.087	0	0	
Basal	10.89	12.67	0.859	0.505	0.876	60.72	7.52	0.100	0	0	Case I. Experiment 3. May 15, 1925.
30	10.80	12.89	0.838	—	0.850	61.45	6.32	0.090	0	—	Dihydroxyacetone: 2 grams every 15
60	12.63	13.54	0.934	0.560	0.974	66.25	12.60	0.088	0	0	minutes for 2 hours
120	10.28	12.73	0.809	0.594	0.808	60.03	4.29	0.076	0	0	
180	10.43	12.76	0.817	1.115	0.830	59.38	3.49	0.079	0	0	
Basal	9.89	11.28	0.877	0.464	0.900	54.33	7.44	0.091	—	—	Case II. Experiment 4. April 21, 1925
30	11.22	12.84	0.875	—	0.890	62.09	8.45	0.123	—	—	Male. Age 26. Surface Area 1.525
60	11.50	12.60	0.913	0.441	0.940	61.42	10.59	0.130	—	—	sq. m. Glucose: 50 grams
120	11.28	12.17	0.926	0.429	0.958	59.51	11.02	0.114	—	—	
180	11.16	11.77	0.948	0.035	0.951	58.59	12.84	0.107	—	—	
240	10.47	11.61	0.900	0.048	0.904	57.08	12.68	0.097	—	—	

Basal	10.78	12.12	0.888	0.380	0.910	58.73	9.04	0.092	0	0	Case II. Experiment 5. April 23, 1925.
30	14.91	13.61	1.090	—	1.160	67.23	14.94	0.107	0	—	Dihydroxyacetone: 50 grams
60	11.28	12.67	0.890	0.424	0.911	61.38	9.30	0.082	0	0.1	
120	10.58	12.47	0.848	0.419	0.860	59.76	6.84	0.082	0	0	
180	9.27	11.13	0.834	0.332	0.837	53.21	5.31	0.089	0	0	
240	9.43	11.09	0.847	0.316	0.860	53.38	6.30	0.089	0	0	
Basal	11.55	12.64	0.914	0.275	0.930	61.98	11.32	0.104	—	—	Case III. Experiment 6. February 3,
30	12.01	12.85	0.933	—	0.957	63.23	13.60	0.114	—	—	1926. Male. Age 18. Surface area
60	11.95	12.98	0.920	0.316	0.940	63.63	11.90	0.120	—	—	1.625 sq. m. Glucose: 25 grams
120	12.06	13.08	0.921	0.336	0.945	64.16	12.40	0.106	—	—	
180	10.95	12.82	0.854	0.262	0.858	61.99	7.85	0.098	—	—	
Basal	10.24	11.94	0.858	0.282	0.866	57.67	7.54	0.124	0	0	Case III. Experiment 7. February 4,
30	11.42	12.20	0.937	—	0.960	59.93	12.00	0.129	0	—	1926. Dihydroxyacetone: 25 grams
60	15.95	13.77	1.160	0.322	1.220	68.33	16.00	0.118	0	0	
120	10.36	11.95	0.867	0.306	0.876	57.91	7.92	0.110	0	0	
180	10.07	11.68	0.862	0.393	0.875	56.21	7.25	0.101	0	0	
Basal	9.42	11.46	0.822	0.574	0.823	54.20	4.32	0.140	—	—	Case IV. Experiment 8. January 11,
30	8.93	11.87	0.753	—	0.738	55.43	1.32	0.152	—	—	1926. Male. Age 32. Surface area
60	10.30	12.58	0.819	0.439	0.823	59.83	5.32	0.125	—	—	1.67 sq. m. Glucose: 25 grams
120	9.85	11.95	0.824	0.487	0.830	56.70	5.14	0.111	—	—	
180	8.88	11.93	0.744	0.499	0.724	55.52	0.71	0.096	—	—	
Basal	8.80	11.41	0.771	0.668	0.754	53.10	1.61	0.112	0	0	Case IV. Experiment 9. January 14,
30	12.48	12.51	0.997	—	1.060	61.40	12.71	0.093	0	—	1926. Dihydroxyacetone: 25 grams
60	11.10	12.48	0.889	0.552	0.727	60.40	9.52	0.084	0	0	
120	9.23	11.32	0.815	0.442	0.818	53.70	4.34	0.094	0	0	
180	7.90	11.19	0.706	0.520	0.669	51.48	0	0.097	0	0	

TABLE 1—*Continued*

Time	CO_2 per hour	O_2 per hour	Total R.Q.	Nitrogen per hour	Non-protein R.Q.	Calories per hour	Carbo-hydrate per hour	Blood sugar	Dihy-droxy-acetone in blood	Dihy-droxy-acetone in urine	Remarks
minutes	*liters*	*liters*		*grams*			*grams*	*per cent*		*per cent*	
Basal	10.72	13.55	0.790	0.582	0.785	63.77	3.63	0.093	0	0	Case V. Experiment 10. June 18, 1925.
30	15.42	15.56	0.998	—	1.035	76.85	17.05	—	0	—	Male. Age 39. Surface area 1.65
60	11.28	14.28	0.789	0.498	0.785	67.40	4.07	0.086	0	0.17	sq. m. Dihydroxyacetone: 25 grams
120	10.85	13.98	0.778	0.515	0.767	65.83	3.03	0.083	0	0	
180	10.37	12.99	0.798	0.461	0.796	61.28	4.20	0.073	0	0	

experiments 1, 4, 6, and 8. In three of these experiments, 1, 4, and 8 the respiratory quotients showed a decrease during the first one-half hour, as originally noted by Zuntz and Mering (14). This early fall in the respiratory quotient after the administration of glucose is considered to have a relation to the degree of saturation of the glycogen depots. Subsequently, the maximum increment increase was attained at the end of the first or second hour, but in no case was the rise as great as after a like dose of dihydroxyacetone. In the four experiments with glucose the average maximum increment increase

TABLE 2

Normals: Increase in heat production over basal level

Experiment Number	Dose	Increase calories per hour		Time attained
		Glucose	Dihydroxyacetone	
	grams	*per cent*	*per cent*	*minutes*
1	25	3.6	—	60
2	25	—	11.2	30
3	*	—	9.0	60
4	50	14.0	—	30
5	50	—	14.5	30
6	25	3.4	—	120
7	25	—	18.3	60
8	25	10.8	—	60
9	25	—	16.0	30
10	25	—	20.5	30
Average.....		10.6	16.1	

* Dihydroxyacetone: 2 grams every 15 minutes for 2 hours.

in the non-protein respiratory quotient was 0.026, while in the five dihydroxyacetone experiments it was 0.271. The fact that the non-protein respiratory quotients rose above unity after administration of single large doses, 25 to 50 grams of dihydroxyacetone, would suggest change of dihydroxyacetone or its conversion product to fat as shown by Lusk (15) to follow the "metabolism of carbohydrate plethora." The fall of the non-protein respiratory quotient to 0.669 in the third hour in experiment 9 may possibly be explained by the storage of glucose derived from protein.

The total metabolism. The increase in total metabolism is more

marked and usually occurs more rapidly after dihydroxyacetone than after a like dose of glucose. From table 2 it can be seen that in all instances except experiments 4, and 5, comparable experiments upon the same case gave a greater and earlier rise in heat production with dihydroxyacetone than after the same dose of glucose. In experiments 4 and 5, both after a dose of 50 grams, the increase in heat production was practically the same 14.0 and 14.5 per cent, and in both instances the maximum level was reached in thirty minutes. The average maximum increase of heat production in the case of glucose was 10.6 per cent as against 16.1 per cent after dihydroxyacetone. In experiment 3 when dihydroxyacetone was given at the rate of 2 grams every fifteen minutes for 2 hours the rise in total metabolism was delayed, its peak being reached at the end of sixty minutes, and again with a percentage increase of 9 per cent, appreciably greater than after the single dose of 25 grams of glucose in the same case, experiment 1. In experiment 4 (50 grams glucose) the rise in total metabolism took place coincidently with a slight fall in the respiratory quotient, subsequently declining as the respiratory quotient rose.

The blood sugar. The blood sugar curves obtained synchronously with the respiratory data show a consistently lower level after the dihydroxyacetone than after a like dose of glucose. In two instances experiments 5 and 10, a trace of dihydroxyacetone was detected in the urine of the first test hour, a demonstration of its probable low renal threshold.

DISCUSSION

From the above data it would appear that dihydroxyacetone when ingested by normal men in doses of 25 or 50 grams results in a fundamentally different metabolism from that of glucose. The immediate and marked rise of the respiratory quotient would suggest rapid carbohydrate combustion, or combustion of a conversion product such as lactic acid. That combustion takes place is further supported by the accelerated increase in heat production which parallels the rise in the respiratory quotient.

These studies indicate that at least the greater part of the dihydroxyacetone escapes conversion into glucose in the alkaline duodenum.

Otherwise there would not be such a difference between the parallel experiments.

The impossibility of detecting the dihydroxyacetone qualitatively in the blood stream would argue for its prompt conversion or removal. Also, the fact that the blood sugar shows a very slight increment increase, and in some cases a progressive fall, would also indicate its rapid removal or conversion.

The similarity of these results with those as reported by Benedict and Carpenter (16) after levulose is striking. In seven experiments on seven normal subjects using 100 grams of levulose they found an average increase of heat production of 15 per cent as against our 16 per cent in six experiments with dihydroxyacetone (table 2). The total respiratory quotient in their cases had an average maximum increase of 18 points, as compared with a similar increase of 22 points after dihydroxyacetone. Their highest total respiratory quotient was 1.11 and values of 1.07 to 1.09 were of frequent occurrence. Following dihydroxyacetone the maximum total respiratory quotient was 1.16 (experiment 7) and in one other instance (experiment 5) a value of 1.09 was obtained.

CONCLUSIONS

1. In normal men dihydroxyacetone when given in 25 or 50 gram doses causes a more rapid and a greater carbohydrate combustion than does the same dose of glucose.

2. The total metabolism is usually elevated more rapidly and to a higher level of heat production after dihydroxyacetone than after a like dose of glucose.

3. The blood sugar presents less increment increase after dihydroxyacetone than after a like dose of glucose.

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