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Carbohydrate Metabolism in *Pasteurella multocida.* I. Mechanism of Glucose Oxidation.* (28943)

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In the genus *Pasteurella,* studies on carbohydrate metabolism have been concerned mostly with *Past. pestis.* Resting cells of *Past. pestis* (strain Tjiwidej) oxidize glucose through the combined action of the Embden-Meyerhof pathway and the Krebs cycle(1,2) while proliferating cells oxidize glucose almost exclusively through the pentose pathway(3). The present study deals with the mechanism of carbohydrate oxidation in *Past. multocida.* This organism oxidizes easily hexoses, pentoses and Krebs cycle intermediates(4,5) and the operation of the pentose pathway is suggested by the presence of aldoheptose in the cellular lipopolysaccharide (6). A preliminary account has been published(7).

Materials and methods. Suspensions of *Past. multocida* (resting or proliferating) were obtained as described previously(8). *Preparations of cell-free extracts.* The acetone-dried(9) bacteria (5 g) were homogenized with 30 ml 92 mM K_2HPO_4. The suspension was left at 22-25° (room temperature) for 2 hours and then at 3° for 24 hours. The pH was maintained at 7.0 ± 0.5 by addition of 0.1 N NH_4OH. The suspension was then centrifuged at 25000 *g* and the sediment resuspended in 10 ml 90 mM pH 7.0 phosphate buffer, kept at 3° for 24 hours and centrifuged as above. Supernatants of the first and second centrifugation were joined and kept at —18°. Protein concentration was measured at 280 mμ(10).

Reagents. Xylulose and ribulose were a gift of Prof. M. Calvin; glucose-6-phosphate, fructose-1,6-diphosphate, ribose-5-phosphate, Polidase Type S and DL-glyceraldehyde-3-phosphate(diethylacetal) from Schwarz Bio-Research Inc.; glucose-1-phosphate, DL-

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glyceraldehyde, sedoheptulose, 6-phosphogluconate, ATP,† NAD and NADP from Sigma Chemical Co. and Dowex AG 501-X8 (D), 20-50 mesh from BioRad Laboratories, Calif. Other reagents were of analytical grade. Glucose-1-C^{14} (4.6 mC/mmole), glucose-6-C^{14} (2.24 mC/mmole) and sodium bicarbonate (22.8 mC/mmole) were from the Radiochemical Centre, Amersham, England. *Analysis of cell constituents.* After incubation in culture medium the cell suspensions were centrifuged at 4°, washed twice in the centrifuge with the original volume of 0.85% NaCl and resuspended in distilled water. These suspensions as well as those of resting cells incubated with radioactive substrates, were mixed with 9 vol. of methanol. After centrifugation, the supernatants (soluble cell fraction) were concentrated at low temperature(11) and chromatographed with phenol-water and *n*-butanol-propionic acid(12). For separation of sugar phosphates, a further sample of each extract was chromatographed for 24 hours with phenol-water and 20 hours with *n*-butanol-propionic acid(13). Radioautography and counting of the radioactive compounds were as described previously(11). The radioactive compounds were identified by cochromatography and radioautography with pure specimens. The sugar phosphates (*a*) were rechromatographed with ethanol-acetic acid(14) and revealed with perchloric acid-molybdate(15), quinine sulfate(16) or ferric chloride-sulfosalicylic acid(17), and (*b*) after hydrolysis with Polidase(18), the free sugars were rechromatographed with phenol-water(12). Aldoses were revealed with aniline-hydrogen oxalate(19), ketoses with orcinol-TCA(20) or naphthoresorcinol-TCA (21) and heptoses with *p*-anisidine(22). Carboxylic and amino acids were rechromatographed with *n*-butanol-propionic acid(12). Carboxylic acids were revealed with bromophenol-blue(23) and amino acids with ninhydrine(24). Sugars(25), pentose(26), triosephosphate(27), sedoheptulose phosphate (28) and hexosephosphate(28) were determined as indicated in the respective methods. Dehydrogenases were measured by reduction of NAD or NADP followed spectrophotometrically at 340 mμ. Transaldolase(28), transketolase(27,28), hexokinase(29), gluconate kinase(29), ribose kinase(30) and aldolase(27,31) were demonstrated in cell-free extracts as indicated. *Preparation and assay of radioactive samples and expression of results* were as described before(11).

Results and discussion. Resting *Past. multocida* oxidized with significant velocity glucose, fructose, gluconate and ribose but not arabinose and xylose; gluconate oxidation involved carboxylation as shown by selective fixation of $C^{14}O_2$ (Table I). Comparison of the oxidation of glucose-1-C^{14} and of glucose-6-C^{14} revealed an unequal distribution in respiratory $C^{14}O_2$ (Table II); thus with resting cells the specific activity of $C^{14}O_2$ from glucose-6-C^{14} was only 12% of the produced from glucose-1-C^{14}. In the growth experiment competition with other carbon sources reduced the oxidation of labeled glucose and simultaneously diluted the specific activity of $C^{14}O_2$.

After 30 minutes' incubation (at 37°) of resting *Past. multocida* (119 mg of cells in 10 ml of mM phosphate buffer, pH 7.2) with glucose-1-C^{14} (1 μmole; 5.9 × 10^5 c.p.m) distribution (%) of C^{14} in the soluble cell

TABLE I. Carbohydrate Oxidation by *Past. multocida.* Fixation of $C^{14}O_2$. *Respiration exp.* Incubation in Warburg manometers, at 37° for 60 min. 2.85 ml mM phosphate buffer, pH 7.2; 0.15 ml 3.3 N KOH in center well of manometric flask. *$C^{14}O_2$ fixation exp.* $NaHC^{14}O_3$, 0.40 μmole (9.4 × 10^5 cpm); other conditions as above (KOH omitted). Organism (mg): 27 (Exp *A* and *B*) and 24 (*C*).

Exp	Substrate	Q_{O_2}	C^{14} in cells (cpm/mg)
A	D-Glucose	23.0	135
A	D-Gluconate	19.6	622
A	D-Ribose	12.8	189
A	None	2.2	175
B	D-Fructose	21.6	—
B	None	2.6	—
C	L-Arabinose	2.6	82
C	D-Xylose	2.9	80
C	None	3.6	99

† Abbreviations used are: ATP, adenosinetriphosphate; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; TCA, trichloracetic acid; Tris-buffer, tris(hydroxymethyl)aminomethane buffer; IA, iodoacetate (sodium salt); Q_{O_2}, μl oxygen uptake/mg of cells (dry weight)/hr.

TABLE II. Distribution of C^{14} in $C^{14}O_2$ Formed from Glucose-1-C^{14} and Glucose-6-C^{14} by *Past. multocida*. Incubation in double side-arm Warburg flasks. 2.65 ml of mM phosphate buffer, pH 7.2 (exp with resting cells (11.9 mg)) or culture medium(8) (exp with growing cells (7.1 mg)). Glucose-1-C^{14}, 0.35 μmole and glucose-6-C^{14}, 0.83 μmole. C^{14}: 9.4 × 10^5 cpm. 0.15 ml 3.3 N KOH in the center well and 0.2 ml 3 N H_2SO_4 in one side bulb of manometric flask. After 2 hr incubation at 37° the acid was mixed with reaction mixture and agitation continued for 15 min. Carbonate fixed in KOH was precipitated as $BaCO_3$ and counted for C^{14}.

Organism	Labeled glucose	Total glucose (mM)	C^{14} activity in $BaCO_3$	
			cpm	cpm/mg
Resting	G-1-C^{14}	5.0	19600	4800
"	G-6-C^{14}	5.0	1740	580
Growing	G-1-C^{14}	11.1	550	20.6
"	G-6-C^{14}	11.1	338	13.2

fraction was: glucose, 18.4; glucose-6-phosphate, 3.8; fructose-1,6-diphosphate, 2.9; 6-phosphogluconate, 1.8; ribose-5-phosphate, 3.7; sedoheptulose-phosphate, 1.8; lactic acid, 6.6; malic acid, 1.8; succinic acid 1.4; glutamic acid, 2.7; alanine, 8.4; threonine, 5.3; leucine, 6.3; tyrosine, 2.0; and tryptophane-valine, 8.4. A certain number of weak radioactive areas remained unidentified. Labeling of sedoheptulose phosphate (identified as free sugar), 6-phosphogluconate and ribose-5-phosphate supported the operation of the pentose pathway. The radioactivity of lactic acid, alanine and glutamic acid demonstrated the formation of pyruvic and α-ketoglutaric acids respectively. The labeling of malic and succinic acids confirmed the operation of the Krebs cycle and accordingly, threonine should arise from oxalacetate. Radioactivity of leucine, tyrosine and eventually, tryptophan demonstrated the ability of *Past. multocida* to synthesize *de novo* these amino acids from glucose carbon. In a similar experiment aspartic acid appeared also radioactive. The kinetics of C^{14} incorporation into the sugar phosphates after short term oxidation of glucose-1-C^{14} by resting *Past. multocida* (Fig. 1) showed the following order: 1) glucose-6-phosphate, 2) 6-phosphogluconate, and 3) ribose-5-phosphate, sedoheptulose-7-phosphate and fructose-1,6-diphosphate. The radioactivity in glucose decreased rapidly simultaneously with the increase in the other substances. With proliferating cells similar results were obtained.

Several essential enzymes of the pentose pathway and glycolysis were demonstrated in cell-free extracts of *Past. multocida*. Hexokinase and gluconate kinase were detected indirectly by the reduction of NADP in the presence of ATP, Mg^{++} and the respective substrate (Table III, Exp. *A* and *B*). The product of each reaction was the substrate of glucose-6-phosphate or 6-phosphogluconate

TABLE III. Enzymes Related to Glucose Degradation in *Past. multocida*. 3.0 ml reaction mixture. 1.3 mM Tris buffer pH 7.5 and 16 mM $MgCl_2$ (Exp *A* and *B*); 25 mM phosphate buffer, pH 6.9 (*C* and *D*); and 10 mM phosphate buffer, pH 8.0 (*E-G*). Cell-free extract (mg of protein): 1.80 (Exp *A-D*); 0.4 (*E*) and 1.2 (*F* and *G*). 6.6 mM cysteine and 16 mM arsenate in Exp *E-G*. *Substrates:* 1.6 mM glucose (Exp *A*) or gluconate (*B*); 3.3 mM glucose-6-phosphate (*C*) or 6-phosphogluconate (*D*); 4.2 mM fructose-1,6-diphosphate (*E*); 1.6 (*F*) or 0.8 (*G*) mM glyceraldehyde-3-phosphate.

Additions	Enzyme activity (△A340 × 10^3/min)
Exp A: Hexokinase assay	
5 mM ATP + .16 mM NADP	27
Idem (without glucose)	5
.16 mM NADP	1
Exp B: Gluconate kinase assay	
5 mM ATP + .16 mM NADP	10
Idem	5
.16 mM NADP	1
Exp C: Glucose-6-phosphate dehydrogenase assay	
.16 mM NADP	58
.16 mM NAD	2
None	3
Exp D: 6-phosphogluconate dehydrogenase assay	
.16 mM NADP	40
.16 mM NAD	4
None	2
Exp E: Aldolase assay	
.33 mM NAD	400
None	20
Exp F: Glyceraldehyde-3-phosphate dehydrogenase assay	
.33 mM NAD	325
.33 mM NADP	55
.33 mM NAD (without substrate)	60
None	10
Exp G: Same as Exp F	
.33 mM NAD	78
.33 mM NAD + 1.0 mM IA	50
.33 mM NAD + 3.0 mM IA	35

dehydrogenase, both specific for NADP (Table III, Exp. *C* and *D*). Aldolase was shown by the reduction of NAD with fructose-1,6-diphosphate as substrate (Table III, Exp. *E*) and by direct determination of triose-phosphate with the hydrazone method (Table IV). The former reaction implied the presence of glyceraldehyde-3-phosphate de-

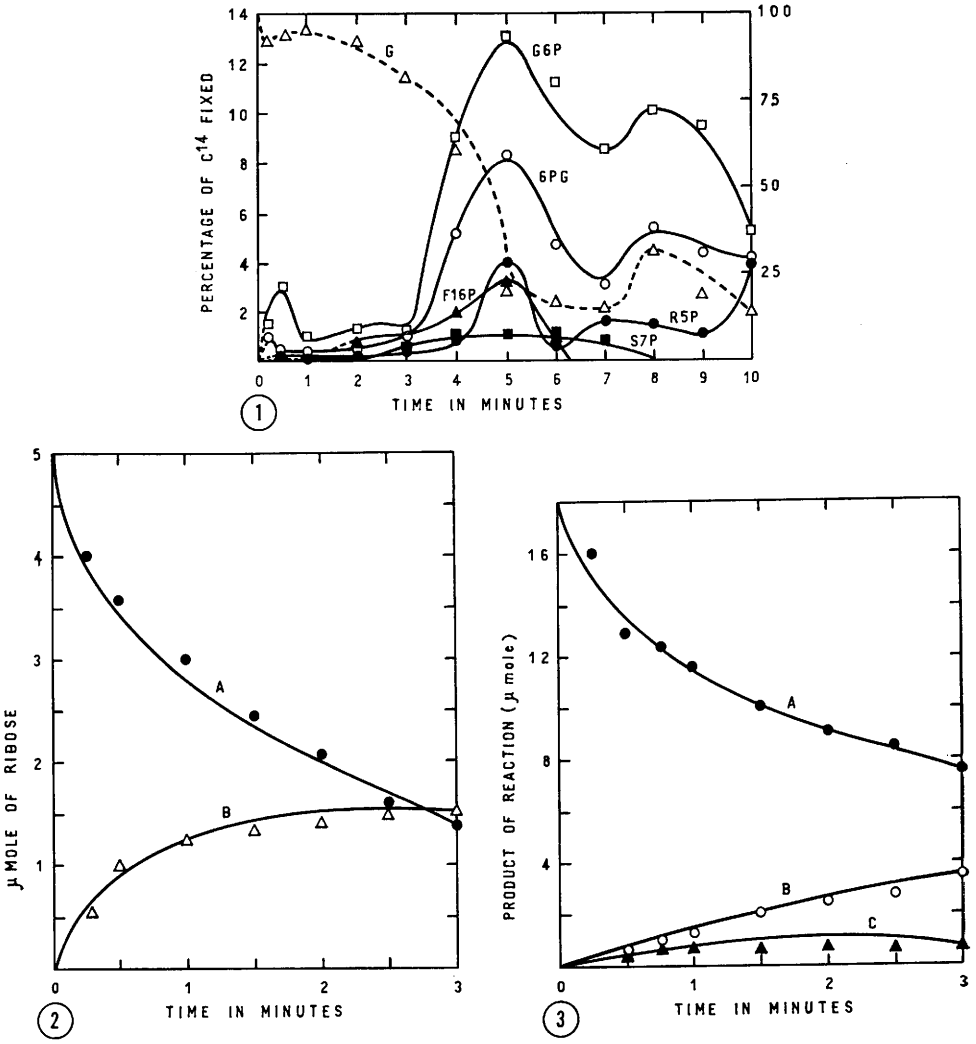

FIG. 1. Kinetics of C^{14} distribution after oxidation of glucose-1-C^{14} by resting *Past. multocida*. 148 mg of cells suspended in 10 ml of mM phosphate buffer pH 7.2 containing glucose-1-C^{14} (10 μmole); C^{14}, 1.18 × 10^7 cpm. Incubation at 24°. G (△), glucose; G6P (□), glucose-6-phosphate; 6PG (○), 6-phosphogluconate; R5P (●), ribose-5-phosphate; F16P (▲), fructose-1,6-diphosphate and S7P (■), sedoheptulose-7-phosphate. Line G refers to right-hand ordinate and the other lines to left-hand ordinate.

FIG. 2. Ribose kinase in *Past. multocida*. Tris-buffer (pH 7.5), 20 μmole; ATP, 5 μmole; $MgCl_2$, 10 μmole; cysteine (neutralized), 5 μmole; ribose, 5 μmole and cell-free extract (0.80 mg of protein). Total vol.: 1.75 ml. Temp.: 30°. 0.2ml of reaction mixture were added ethanol (1 ml) and saturated barium acetate solution (0.01 ml). After centrifugation, pentose was measured in precipitate and supernatant. The figures show control values without substrate and enzyme, respectively. Line A, ribose, and B, pentose phosphate.

FIG. 3. Transketolase and transaldolase in *Past. multocida*. Tris buffer (pH 7.5), 400 μmole; ribose-5-phosphate, 17.5 μmole and cell-free extract (20 mg of protein). Total vol.: 7.60 ml. Temp.: 30°. After addition of 1 ml 10% TCA to 1 ml of reaction mixture and centrifugation, pentose (line A), hexose (B) and sedoheptulose (C) were measured in the supernatant. The figures show control values without substrate and enzyme, respectively.

TABLE IV. Aldolase and Transketolase Activities in *Past. multocida*. *Aldolase assay*: 8.9 mM Tris buffer pH 8.6; 31 mM hydrazine sulfate and cell-free extract (16 mg of protein). Total vol: 4.5 ml. *Transketolase assay*: 22 mM phosphate buffer, pH 7.0; cell-free extract (20 mg of protein) and other conditions as above. Temp: 30°. 1 ml samples of reaction mixture were taken at 30 sec intervals, for 2 min and added 1 ml of 10% (w/v) TCA. After centrifugation, triosephosphate was measured(27) in the supernatant. Formation of triosephosphate was determined by subtracting initial value.

Additions	Triosephosphate (μmole/min)
Assay: Aldolase	
2.8 mM Fructose-1,6-diphosphate	1.02
Idem, enzyme omitted	0
None	0
Assay: Transketolase	
3.1 mM Ribose-1-phosphate	1.00
Idem, enzyme omitted	0
None	0

hydrogenase which was demonstrated by Exp. *F* (Table III). This enzyme was sensitive to IA, like the muscle dehydrogenase (Table III, Exp. *G*). Ribose kinase was demonstrated by disappearance of ribose and formation of ribose-5-phosphate (Fig. 2). The ester values are relatively low because of the incomplete precipitation of barium pentose-5-phosphate with ethanol. Transketolase was demonstrated by triosephosphate formation (Table IV) and transaldolase plus transketolase activities are shown in Fig. 3. The action of these enzymes as well as phosphoribose isomerase and phosphoribulose epimerase is also inferred from the experiment described in Table V where transformation of ribose-5-phosphate in heptulose, fructose, xylulose and ribulose was established.

The evidence summarized above demonstrates that the pentose pathway is the main mechanism for glucose oxidation in *Past. multocida* (resting and proliferating cells). The conclusion is supported by (*a*) relatively fast oxidation of gluconate and ribose; (*b*) preferential conversion of carbon-one of glucose to CO_2; (*c*) formation of 6-phosphogluconate, ribose-5-phosphate and sedoheptulose-7-phosphate after oxidation of glucose-1-C^{14} (and 6-C^{14}); (*d*) presence of glucose-6-phosphate and 6-phosphogluconate dehydrogenases, transaldolase and transketolase, and (*e*) formation of fructose, sedoheptulose, xylulose and ribulose from ribose-5-phosphate with cell-free extracts. The activity of aldolase and glyceraldehyde-3-phosphate dehydrogenase, as well as the formation of fructose-1,6-diphosphate and lactic acid from glucose agree well with the operation of both the pentose pathway and the Embden-Meyerhoff cycle. The pattern of C^{14} distribution after oxidation of glucose-1-C^{14} can be easily explained according to the pentose pathway model(32) by a rearrangement of glucose carbon atoms based on the already demonstrated(33) reversibility of the transaldolase and transketolase reactions.

At variance with *Past. pestis* (strain Tjiwidei) where only proliferating cells oxidize glucose through the pentose pathway(2,3), in resting *Past. multocida* the pentose pathway seems to be the main route of glucose degradation. However, the difference between *Past. multocida* and *pestis* must not be exaggerated since in *Pasteurella* the metabolic

TABLE V. Transformation of Ribose-5-phosphate by Extracts of *Past. multocida*. 15 ml of reaction mixture containing ribose-5-phosphate (140 μmole), Tris-buffer (80 μmole; pH 7.5) and extract (66 mg of protein) were incubated at 30° for 30 min. 1 ml of 60% (w/v) $HClO_4$ was added and after centrifugation, excess of $HClO_4$ removed with KOH and further centrifugation. Sugar phosphates in the supernatant were hydrolyzed at 30° with Polidase, for 24 hr and the solution deproteinized with $HClO_4$ as above. The solution was passed through a 1 × 12 cm column of Dowex 501 (H^+, OH^- cycles) and the sugars eluted with distilled water (elution controlled with the sulfuric acid-phenol test(25)). The combined eluates were concentrated, residual $KClO_4$ eliminated and the sugars chromatographed with the phenol-water system(12) simultaneously with control specimens.

Substance	Color developed with orcinol(20) in chromatogram	R_f
Sedoheptulose		
Control	Light blue	.70
Unknown	Same	.69
Xylulose		
Control	Green-gray	.59
Unknown	Grayish	.56
Ribulose		
Control	Violet	.66
Unknown	Pink-violet	.65
Fructose		
Control	Green	.58
Unknown	"	.55

patterns differ considerably even from one strain to the other of the same specie(2,3, 34).

Summary. The pentose pathway is the main route for carbohydrate oxidation in *Past. multocida* as demonstrated by C^{14} distribution after oxidation of labeled glucose, and the activity of the respective enzymes in cell free extracts from the organism. The Krebs cycle operates as a supplementary oxidative mechanism. Glucose carbon is also utilized for synthesis of amino acids.

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Susceptibility of a Strain or Rat Virus to Statolon and Other Virus Inhibitors.* (28944)

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Antiviral substances vary in relative breadth of activity from interferon, whose scope encompasses agents as small as the enterovirus group(1) and as large as psitta-

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