Pathway of Ethanol Metabolism in the Rat[1] (34141)

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(Introduced by R. L. McGeachin)

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The pathway of ethanol metabolism via acetaldehyde and acetyl coenzyme A is well documented (1). However, considerable effort has been made to answer the question as to whether or not this is the only pathway of ethanol metabolism in the mammal.

Bloom and Westerfeld (2) and Bloom *et al.* (3) demonstrated 5-hydroxy-4-ketohexanoic acid (HKH) as a metabolite of ethanol and acetaldehyde in various rat tissue homogenates. They reported that HKH is formed but not degraded by rat tissue homogenates. If HKH-5-^{14}C (formed from ethanol-1-^{14}C) were oxidatively metabolized, acetyl-1-^{14}C coenzyme A would be a logical intermediate.

Russell and Van Bruggen (4, 5) noted that a number of enzymes capable of utilizing acetaldehyde substrate have been identified in mammalian tissues. Products from acetaldehyde by these systems include methyl tetrose phosphate, deoxyribose-5-phosphate, threonine or allothreonine, and acetoin (6–8). If ethanol-1-^{14}C is metabolized via acetaldehyde-1-^{14}C to one of the above mentioned compounds, further metabolism of ethanol-1-^{14}C via acetyl-1-^{14}C coenzyme A, will yield only carboxyl-labeled TCA cycle intermediates. Glutamic and aspartic acids are in rapid equilibrium with the cycle intermediates; hence labeling patterns in these two amino acids reflect the pattern of the

TABLE I. Labeling Patterns in Liver Free Glutamate and Aspartate of Fed and Fasted Rats 12 min after Intraperitoneal Injection of Ethanol-1-^{14}C.[a]

					Glutamic acid			Aspartic acid		
						Percentage in			Percentage in	
Rat no.	Conditions	Body wt (g)	Dose (μCi)	$^{14}CO_2$ expired (%)	Total sp act (μCi /mmole)	C-1	C-5	Total sp act (μCi /mmole)	Carboxyl	Carbons
333	Fed	174	23	5.6	4.7	18	78	14.3	100	
334	Fasted 48 hr	140	23	18.5	6.2	30	69	16.2	96	
337	Fasted 48 hr	168	23	9	3.2	30	70	9.4	102	

[a] From New England Nuclear (5 mCi/mmole); permanganate oxidation (9) gave acetate-1-^{14}C; Schmidt decarboxylation of the latter released all the ^{14}C as carbon dioxide (9).

[1] Supported in part by Research Grant GM-06765 from the National Institutes of Health, United States Public Health Service.

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corresponding keto acid of the TCA cycle. After injection of suitably labeled metabolites, the labeling patterns of glutamate and aspartate readily distinguish between metabolism via a carboxyl group and that proceeding via the noncarboxyl portion of a molecule (9–11).

In view of the considerable interest in possible other pathways of ethanol metabolism, we have administered ethanol-1-^{14}C intraperitoneally to fed and fasted rats. Twelve min later the animals were killed by decapitation and the free glutamate and asparate of liver was isolated, degraded, and assayed for radioactivity (10, 12, 13). The results are presented in Table I.

Within experimental error all the radioactivity found in aspartate or glutamate was located in the carboxyl positions. Moreover, the percentage of label in carbon-5 of glutamate as compared to carbon-1 is exactly as expected for the metabolism of acetate-1-^{14}C or its precursors (9). These results support the concept that ethanol metabolism proceeds primarily via acetaldehyde and acetyl coenzyme A. They further suggest that if another pathway(s) of ethanol metabolism exists, it is very slow or it accomplishes the conversion of carbon-1 of ethanol to carbon-1 of acetate rather than to a noncarboxyl portion of a TCA cycle intermediate or its precursor.

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Received April 25, 1969. P.S.E.B.M., 1969, Vol. 132.