URACIL INCORPORATION IN LIVER RNA OF YOUNG AND PREGNANT RATS AND IN RNA OF FETAL TISSUES AND CERTAIN TUMORS*

A.Cantarow, T.L.Williams, and K.E.Paschkis

Departments of Biochemistry and Medicine, and Division of Endocrine and Cancer Research, Jefferson Medical College, Philadelphia, Pa.

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Previous observations have given rise to the view that utilization of uracil for nucleic acid synthesis in the rat may be a metabolic characteristic of rapid growth or stimulated protein anabolism in non-neoplastic as well as neoplastic tissues. We are adding here observations in this connection on the livers of young (4 weeks) and pregnant rats, fetal tissues, and three transplantable tumors not previously reported on (Walker 256; Murphy lymphosarcoma; Furth pituitary "mammogenic" tumor).

MATERIALS AND METHODS

Rats of three strains were used in different experimental groups, as follows: normal adults (Wistar, Fisher, AxC); Furth "mammogenic" tumor (Fisher); hepatoma (AxC); pregnancy (Wistar); young rats (Wistar); Walker tumor (Wistar, Fisher). All animals were obtained from Barkbridge Farms, N.J., and were maintained on a stock diet of Purina Chow.

Studies involving the transplanted tumors were performed at a time when the tumor was observed to be growing actively. The pregnant rats were sacrificed on the 17th day. Three fetuses were pooled for each analysis, minced, and homogenized.

Animals in all experimental groups received 20 mg. of uracil-2-C^{14} (500 μc/mmole)** in 10 ml of 0.85% NaCl solution intraperitoneally 18 hours prior to sacrifice by cervical fracture and decapitation; previous studies

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showed maximum incorporation in liver nucleic acids at about this time (Rutman et al., 1954). After exsanguination, the livers were perfused in situ with cold 0.25M sucrose solution and (also subcutaneous tumors) were excised and placed on cracked ice.

The livers and tumors were blotted dry, minced with scissors, and homogenized at 0°C. in 0.25M sucrose (1:10) in a Potter-Elvehjem homogenizer. Analyses were performed in duplicate on individual livers and tumors. RNA was isolated (Herbert et al., 1957) and analyzed (Allen, 1940) in conventional manner. Samples were plated by evaporation and counted in a gas-flow counter to ±5 per cent accuracy.

RESULTS AND DISCUSSION

The pertinent data are presented in the table, which includes, for purposes of comparison, findings reported previously for normal adult, preneoplastic, and regenerating liver, and hepatoma (Rutman et al., 1954; Cantarow et al., 1958). No significant difference was found between male and female Wistar rats, nor between male Wistar, Fisher, and AxC rats in either normal or regenerating liver.

Specific Activity of RNA after intraperitoneal Injection of 20 mg. Uracil-2-C^{14} (3.3×10^6 counts/min./mg.)

	SPECIFIC ACTIVITY RNA (c/min/mg)	
	LIVER	TUMOR
NORMAL ADULT (26)*	206±38#	
NORMAL 4 WEEKS (6)	1628±460	
PRENEOPLASTIC (14)	1464±246	
PARTIAL HEPATECTOMY (16)	1545±284	
PREGNANCY 17 DAYS (2)	576;684	
FETUS 17 DAYS (6)	1823±248 (whole fetus)	
TRANSPLANTED TUMORS		
Lymphosarcoma (9)	738±317	2258±491
Walker 256 (12)	559±249	1894±446
Hepatoma (16)	698±120	1856±344
Mammogenic (9)	350±48	359±62

*Figures in parenthesis indicate numbers of animals
#Specific activity values are means, with mean deviations

The activity of uracil incorporation in fetal tissues and in the Walker 256 tumor and Murphy lymphosarcoma was of the same order of magni-

tude as had been found for preneoplastic liver, regenerating liver, and hepatoma. Increased incorporation occurred also in the livers of rats bearing these tumors and of pregnant rats. These findings are in accord with the concept that activity of this pathway is related to states of increased protein anabolism and/or accelerated turnover of RNA. They are in accord, too, with the recent reports of high thymidylate kinase (Hiatt and Bojarski, 1960) and low uracil and thymine catabolic (Stevens and Stocken, 1960) activity in fetal and young rat liver.

However, the values obtained for the "mammogenic" tumor and the livers of rats bearing this tumor, although higher than those for normal adult liver, were lower than those for other tumors and livers of other tumor-bearing animals. This is the first instance that we have encountered of comparatively limited incorporation of uracil into RNA of an actively growing tumor. The relatively low values obtained with the livers of rats bearing this tumor are particularly striking in view of the markedly stimulated growth of these animals (body wt. up to 500g; liver wt. up to 24g.), due presumably to active production of growth hormone (?) by the tumor.

This suggests the possibility that growth hormone, which stimulates incorporation of uracil into RNA in the livers of normal adult rats (Cantarow et al., 1958), may act differently under different experimental conditions. This possibility is being investigated.

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