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The Oxidation of Various Precursors in Normal and Tumour-Bearing Mice *in vivo*

By J. KABARA

Biochemistry Research Department, University of Detroit, Detroit 21, Mich., U.S.A.

AND G. OKITA

Argonne Cancer Research Hospital, University of Chicago, Chicago, Ill., U.S.A.

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As a preliminary to studies of the incorporation of various precursors into cholesterol in normal and tumour-bearing mice, the oxidative fate of these metabolites was studied by measuring expiratory $^{14}\text{CO}_2$. Although expired CO_2 reflects an important end product of ingested carbon, it is not specifically related to any single biochemical event. Despite this lack of specificity, such tests as measurements of basal metabolism and determinations of respiratory quotient, which depend in part on measurements of CO_2 , have in the past been of great value. These same measurements can now be made more important when the relative contribution of various carbon sources to expired CO_2 are determined with the use of ^{14}C -labelled compounds. It is possible that a progressively growing tumour may cause subtle changes in the normal excretion pattern of CO_2 shown by the host before clinical signs are evident. The present studies were initiated in order to determine whether changes caused by a tumour would be reflected by a change in the rate of appearance of ^{14}C -labelled metabolites in expired air. A preliminary report of our work has been presented (Kabara, Okita & LeRoy, 1957).

MATERIALS AND METHODS

Animals and tumours. Female CF-1 or DBA/2 mice (10–12 weeks of age) weighing 20–25 g. were used as normal controls. The CF-1 mice, inoculated intraperitoneally or subcutaneously with Ehrlich ascites carcinoma cells, were used for the initial respiratory studies. Because experiments with mice bearing ascites tumours were complicated by the added factor of a change in the surface area of the mouse, the major part of the study was carried out with mice that had a solid tumour mass. Similar experiments were also carried out with the DBA/2 mice, inoculated with a lymphatic leukaemia (P-1534). All mice were bred and raised at the Argonne Cancer Research Hospital.

Radioactive metabolites. The doses of ^{14}C -labelled compounds injected into mice were all considered to be trace quantities, i.e. the normal physiology of the animal was not upset by the amount of injected material. The following doses were given either intraperitoneally or intravenously in 0.5 ml. of 0.85% NaCl: $\text{NaH}^{14}\text{CO}_3$ (1.0 mc/m-mole), 0.05 μC ; $[1\text{-}^{14}\text{C}]\text{acetate}$ (2.8 mc/m-mole), 0.5 μC ; $[2\text{-}^{14}\text{C}]\text{acetate}$ (2.0 mc/m-mole), 1.0 μC ; $[2\text{-}^{14}\text{C}]\text{leucine}$ (0.6 mc/m-mole), 1.25 μC ; $[1\text{-}^{14}\text{C}]\text{glucose}$ (0.65 mc/m-mole), 1.0 μC ; $[6\text{-}^{14}\text{C}]\text{glucose}$ (0.83 mc/m-mole), 1.0 μC ; uniformly labelled $[^{14}\text{C}]\text{glucose}$ ($[\text{U-}^{14}\text{C}]\text{glucose}$) (1.00 mc/m-mole), 1.0 μC . All the radioactive compounds were purchased from Volk Radiochemical Co., 8260 Elmwood Avenue, Skokie, Ill., U.S.A.

Apparatus for the measurement of expiratory $^{14}\text{CO}_2$. The apparatus used in these experiments was a slight modification of a prototype model adaptable to experiments *in vivo* (human or animal) and *in vitro* (LeRoy, Okita, Tocus & Charleston, 1960). In the experiments reported below the animal was injected with a specifically ^{14}C -labelled metabolite and placed in a Roth (1956) metabolism cage.

The results from the recording sheets were transposed to graph paper and the areas of the resulting curves were measured with the aid of a planimeter. The integrated areas for each 15 min. interval were measured and the cumulative results recorded. The efficiency of the counting tube was determined for the conditions of the experiment by reference to a standard area obtained by using a National Bureau of Standards solution of $\text{NaH}^{14}\text{CO}_3$.

RESULTS

The quantity of metabolite oxidized to CO_2 can be designated by the symbol q with the appropriate subscripts. Thus $q_{\text{CO}_2\text{H}}$ and q_{M} respectively refer to the amounts of $[1\text{-}^{14}\text{C}]$ - and $[2\text{-}^{14}\text{C}]$ -acetate oxidized to $^{14}\text{CO}_2$; similarly $q_{\text{G-U}}$, $q_{\text{G-1}}$ and $q_{\text{G-6}}$ refer respectively to the amounts of $[\text{U-}^{14}\text{C}]$ -, $[1\text{-}^{14}\text{C}]$ - and $[6\text{-}^{14}\text{C}]$ -glucose oxidized to $^{14}\text{CO}_2$. Since q , as measured by $^{14}\text{CO}_2$, is a function of the specific activity of the metabolite as well as its rate of oxidation, differences between normal and tumour-bearing animals may be due to differences in dilution of the injected tracer or differences in metabolic rates, or both. The shapes of curves for the expired $^{14}\text{CO}_2$ that are measured in our animal studies had no necessary physiological relationships, since the curves are functions of the physical characteristic of the instrument used to measure respiratory gases. To obtain reliable measurements, it was necessary to control such variables as air flow and dead-air space of the equipment (LeRoy *et al.* 1960).

Preliminary experiments on the effect of various routes of tracer administration were carried out. Of the various procedures attempted, the oral and subcutaneous routes gave results that were too

variable. The intravenous route was impractical where multiple injections on the same mouse were required. Since comparison of intravenous and intraperitoneal injection by using $[1\text{-}^{14}\text{C}]\text{acetate}$ showed only slight quantitative differences (Table 1), the less tedious intraperitoneal route of injection was used throughout the following series of experiments.

Before normal and pathological animals were compared, the standard deviation (s.d.) of the measurements of expiratory $^{14}\text{CO}_2$ was determined. With five normal DBA/2 mice, the s.d. was measured for each of the radioactive metabolites used in the experiments. The results of these trials showed that the s.d. of the areas obtained between experiments was not greater than $\pm 10\%$.

With the ascites form of the tumour, experiments were conducted at various daily intervals before and after the inoculation of the tumour. Pre-inoculation values for acetate oxidation were established 1 and 2 days before the inoculation of the ascites cells. As early as 48 hr. after the injection of the tumour cells an abnormal oxidation pattern was evident as measured by continuous recording of the expired $^{14}\text{CO}_2$. With increasing growth of the tumour a gradual decrease in oxidation rate was evident. A separate control used at the end of the experiment agreed with the pre-inoculation normal values. Although the deviation from normal values was significant, the interpretation of these measured changes was not obvious, since the mouse bearing the ascites tumour undergoes a great increase of surface area. Because of the uncertainty that the ascites tumour introduces in calculations of expiratory values in subsequent experiments only the solid form of the tumour was used.

To examine the oxidation of the metabolites, animals with Ehrlich solid tumour (masses of 0.1, 0.5 and 2.0 g. respectively) were examined with appropriate controls. The results calculated from the oxidation curves of either $[1\text{-}^{14}\text{C}]$ - or $[2\text{-}^{14}\text{C}]$ -

Table 1. *Effect of the route of administration of $[^{14}\text{C}]\text{acetate}$ to normal and tumour-bearing mice on the release of $^{14}\text{CO}_2$*

Experimental details are given in the text. EST₂, mouse bearing an Ehrlich solid tumour of size 1.4 cm. $\times$ 0.5 cm.

Metabolite	Mouse	Route of administration	Accumulation of $^{14}\text{CO}_2$ (%)					
			15 min.	30 min.	45 min.	60 min.	75 min.	90 min.
$[1\text{-}^{14}\text{C}]\text{Acetate}$	Control	Intraperitoneal	17.9	54.6	71.7	78.5	80.3	80.3
	EST ₂	Intraperitoneal	15.6	47.6	63.2	69.4	72.1	80.3
	Control	Intravenous	25.7	60.0	71.9	76.5	78.0	78.0
	EST ₂	Intravenous	16.9	45.9	58.9	66.0	68.6	68.8
$[2\text{-}^{14}\text{C}]\text{Acetate}$	Control	Intraperitoneal	8.5	29.5	46.0	54.4	59.2	62.2
	EST ₂	Intraperitoneal	7.8	29.0	43.4	52.4	56.1	58.5
	Normal	Intravenous	10.5	35.2	47.8	54.2	57.2	57.8
	EST ₂	Intravenous	6.8	27.0	41.5	50.1	54.6	54.8

Table 2. *Expiratory $^{14}\text{CO}_2$ from normal and tumour-bearing mice given [^{14}C]acetate*

Experimental details are given in the text. EST_1 , EST_2 and EST_3 denote mice bearing Ehrlich solid tumours of sizes 2.5 cm. $\times$ 1.8 cm., 1.4 cm. $\times$ 0.5 cm. and 0.1 cm. $\times$ 0.1 cm. respectively.

Metabolite	Mouse	Accumulation of $^{14}\text{CO}_2$ (%)					
		15 min.	30 min.	45 min.	60 min.	75 min.	90 min.
[^{14}C]Acetate	Control	17.9	54.6	71.7	78.5	80.3	80.3
	EST_3	16.4	45.2	56.3	59.5	60.8	60.8
	EST_2	15.6	47.6	63.2	69.4	72.1	72.1
	EST_1	11.3	33.4	44.6	49.4	50.7	50.7
[^{2-14}C]Acetate	Control	8.5	29.5	46.0	54.4	59.2	62.2
	EST_3	11.6	35.8	50.1	57.1	60.9	63.1
	EST_2	7.8	29.0	43.4	52.4	56.1	58.5
	EST_1	9.4	31.0	47.0	56.4	62.2	65.7

Table 3. *Expiratory $^{14}\text{CO}_2$ from normal and tumour-bearing mice given [^{14}C]glucose*

Experimental details are given in the text. EST_1 , EST_2 and EST_3 denote mice bearing Ehrlich solid tumours of sizes 2.5 cm. $\times$ 1.8 cm., 1.4 cm. $\times$ 0.5 cm. and 0.1 cm. $\times$ 0.1 cm. respectively.

Metabolite	Mice	Accumulation of $^{14}\text{CO}_2$ (%)							
		15 min.	30 min.	45 min.	60 min.	75 min.	90 min.	105 min.	120 min.
[U- ^{14}C]Glucose	Control	2.8	20.5	35.4	43.3	47.7	50.5	52.3	53.7
	EST_3	2.3	14.6	24.9	30.6	33.4	36.6	36.9	38.0
	EST_2	1.8	15.2	28.7	37.7	43.8	46.9	48.1	48.9
	EST_1	2.0	17.1	30.3	38.5	43.5	47.1	49.3	50.5
[1- ^{14}C]Glucose	Control	3.2	17.1	28.0	34.9	39.4	42.0	43.4	44.2
	EST_3	1.4	19.2	35.5	47.0	56.1	62.4	65.6	68.5
	EST_2	0.8	14.1	33.2	48.9	57.2	62.5	68.0	71.8
	EST_1	5.1	26.5	43.1	54.6	61.3	65.2	67.2	68.6
[6- ^{14}C]Glucose	Control	1.9	18.3	29.5	48.6	54.3	57.5	59.6	60.9
	EST_3	1.9	20.7	40.8	53.2	61.9	65.7	69.4	71.3
	EST_2	1.7	16.0	29.2	41.2	48.5	52.8	55.4	57.7
	EST_1	0.8	10.0	22.0	30.9	37.4	42.0	44.9	47.5

acetate are summarized in Table 2. Though the areas obtained from $q_{\text{CO}_2\text{H}}$ show differences between the normal animals and those bearing the largest tumour, the q_{Me} was the same. Control experiments with $\text{NaH}^{14}\text{CO}_3$ in the same animals showed no deviation in respiratory $^{14}\text{CO}_2$.

Experiments on the same animals were conducted with [U- ^{14}C]-, [1- ^{14}C]- and [6- ^{14}C]-glucose (Table 3). Except for the group with the smallest tumour, the areas for $q_{\text{G}-\text{U}}$ do not seem to indicate any special deviation from normal oxidation. Both [1- ^{14}C]- and [6- ^{14}C]-glucose gave patterns of oxidation that were unique for the normal and tumour-bearing animals. The injection of [1- ^{14}C]glucose into tumour-bearing mice caused a greater amount of expiratory $^{14}\text{CO}_2$ than was obtained with the normal animal. Except for animals with the smallest tumour (EST_3), the opposite was true when [6- ^{14}C]glucose was used.

The respiratory pattern for [2- ^{14}C]leucine is also markedly affected by tumour growth and mimics that found for [1- ^{14}C]acetate. This was not sur-

prising, since the metabolism of [2- ^{14}C]leucine can yield a [1- ^{14}C]acetyl derivative.

The abnormal oxidation patterns given by female CF-1 mice bearing Ehrlich carcinomas were not noted in experiments with leukaemic animals. Experiments on DBA/2 mice with a lymphatic leukaemia (P-1534) did not show any of the early changes characteristic of the mice bearing Ehrlich solid tumours until 2-3 days before death. In this morbid or pre-morbid condition, the formation of CO_2 from hydrogen carbonate, acetate and glucose was decreased to very low levels. It was therefore not possible to demonstrate the same kind of oxidative changes *in vivo* in the leukaemic DBA/2 mice as were measured with the tumour-bearing CF-1 animals.

DISCUSSION

The ability to follow the oxidative fate of exogenous ^{14}C -labelled metabolites in animals by continuously monitoring expiratory $^{14}\text{CO}_2$ has an

advantage over periodic individual collections of CO_2 . Not only is the assay of radioactivity easier, but also the whole curve rather than integrated areas can be plotted. This point-by-point assay enables the investigator immediately to notice small changes that may be missed when total areas are compared. Instruments designed to perform similar functions but based on the use of a vibrating-reed electrometer have been reported by Tolbert (1956), Domingues, Gildner, Baldwin & Lowry (1959) and Luick, Kleiver & Kaneko (1960). The instrument used in the present work was the prototype of that reported by Kabara *et al.* (1957).

The oxidation of acetate carbon atoms presumably takes place through the Krebs cycle. Normally the q_{Me} from acetate is less than q_{CO_2} since the methyl carbon atoms of acetate are utilized to a greater extent than the carboxyl carbon atoms for synthetic reactions (Weinman, Stisower & Chaikoff, 1957). Our results suggested that the production of $^{14}\text{CO}_2$ from $[1-^{14}\text{C}]\text{acetate}$ in tumour-bearing animals was less than normal, whereas that from $[2-^{14}\text{C}]\text{acetate}$ showed a difference from control values. Harmon, Kirk & Tolbert (1959) also demonstrated that there was no difference in the oxidation of $[2-^{14}\text{C}]\text{acetate}$ to $^{14}\text{CO}_2$ in normal and tumour-bearing animals. Reports by Pardee, Heidelberg & Potter (1950) and Olson (1951) also indicate a somewhat lower capacity for the oxidation of fatty acids by tumour tissue. An extensive study by Weinhouse, Millington & Wenner (1951) and Weinhouse, Allen & Millington (1953) confirmed and extended these conclusions. Their findings and the present results suggest that in tumour-bearing animals there is a decrease in the production of $^{14}\text{CO}_2$ from $[1-^{14}\text{C}]\text{acetate}$ and that the 'normal' q_{Me} found under certain conditions may reflect a decrease in utilization of the methyl carbon atoms with a consequent increased entry of the ^{14}C into oxidative pathways, as measured by expired $^{14}\text{CO}_2$.

A significant finding from the study with acetate was the observation that a tumour mass as small as 0.5% of the total body weight has a marked effect on the oxidative patterns of $[^{14}\text{C}]\text{acetate}$ in comparison with control mice. This suggests that the tumour may exert a systemic effect (toxohormone) on general body metabolism (Nakahara & Fukuoka, 1949; Greenstein, 1954; Nakahara & Fukuoka, 1958).

$[2-^{14}\text{C}]\text{Leucine}$, when metabolized, can eventually yield $[1-^{14}\text{C}]\text{acetate}$. Because of this it was not surprising that the oxidative pattern for this amino acid was similar to that found for exogenous $[1-^{14}\text{C}]\text{acetate}$. Apparently the reactions between leucine and acetate are not rate-limiting.

Glucose was used as an intermediate for oxid-

ation studies because of the prime importance of glycolysis in the metabolism of tumours (Weinhouse, 1955). It was of interest to determine whether the fraction of expiratory CO_2 that reflects glucose metabolism would be changed in the presence of a neoplasm in the host. Independently, Harmon *et al.* (1959) reported no differences in the oxidation of $[\text{U}-^{14}\text{C}]\text{glucose}$. Our results of similar rates of production of $^{14}\text{CO}_2$ for both normal and tumour-bearing mice agree with their findings. In contrast with reports on the production of $^{14}\text{CO}_2$ from $[\text{U}-^{14}\text{C}]\text{glucose}$, a distinct difference was noticed when $[1-^{14}\text{C}]$ - and $[6-^{14}\text{C}]\text{-glucose}$ were oxidized (Table 3). The extent of glucose breakdown through the hexose monophosphate oxidative route, as compared with that via the Embden-Meyerhof glycolytic pathway, is believed to be reflected by the oxidation of C-1 and C-6 respectively. Although this procedure can provide circumstantial evidence on the relative importance of the two pathways, the shortcomings in this approach have been criticized (Wood, 1955).

Several investigators have studied the pathway of glucose metabolism by tissue slices and the intact rat (Abraham, Hill & Chaikoff, 1955; Agnahoff, Brady & Colodge, 1955; Bloom & Stetten, 1955; Kit, 1956). From these studies it was calculated that nearly all of the glucose metabolized by the diaphragm and kidney was by way of the Embden-Meyerhof glycolytic pathway, whereas in liver and in hepatoma part of the glucose was metabolized through the hexose monophosphate oxidative route. Our measurements of $^{14}\text{CO}_2$ obtained from the intact animal agree with the finding that the Embden-Meyerhof pathway operates in the catabolism of glucose in normal mice, though not exclusively (Kit, 1956). In mice bearing Ehrlich solid tumours there was a significant shift in the relative importance of these two pathways. The greater release of $^{14}\text{CO}_2$ through the oxidation of $[1-^{14}\text{C}]\text{glucose}$ by the tumour-bearing animals is presumptive evidence for active participation of hexose monophosphate oxidation. This finding, together with those of Abraham *et al.* (1955), Kit (1956), Emmelot, Bosch & Van Vals (1955), Ashmore, Weber, Banerjee & Love (1961) and Van Vals, Van Hoven, Bosch & Emmelot (1958), suggests that not only does the hexose monophosphate pathway gain importance in the metabolism of a tumour cell but also that the tumour-bearing host may reflect these changes.

The results on the oxidative fate of ^{14}C -labelled metabolites indicate that animals with carcinomas show differences in oxidative patterns reflected in expired $^{14}\text{CO}_2$, whereas the mice with lymphatic leukaemia do not. Whether the results for the mice

with the Ehrlich solid tumours were specific for this mouse tumour alone, or are representative for all types of sarcomas and carcinomas, is not known. There may be some factor besides the presence of the tumour, in animals with Ehrlich solid tumours, that is responsible for the measured results. It should not be concluded that neoplasms other than the one studied would also give the same pattern of metabolite oxidation.

SUMMARY

1. The extent to which a developing neoplasm such as Ehrlich solid tumour affects the oxidation of selected precursors to CO_2 was studied. Studies of expiratory $^{14}\text{CO}_2$ *in vivo* demonstrated that a tumour mass as small as 0.5 % of the total body weight has an effect on the oxidative patterns of [^{14}C]acetate in comparison with control mice. This suggests that the tumour may exert a systematic effect on general body metabolism.

2. The decreased rate of production of $^{14}\text{CO}_2$ from [^{14}C]acetate and of [^{14}C]leucine was inversely proportional to the increase in tumour size in mice bearing Ehrlich solid tumours. [^{14}C]Acetate did not show the same difference in the production of $^{14}\text{CO}_2$.

3. The importance of the hexose monophosphate oxidative pathway in mice bearing Ehrlich solid tumours was demonstrated by the greater rate of release of $^{14}\text{CO}_2$ from [^{14}C]glucose than from [^{14}C]glucose.

4. Comparable studies of patterns of expired $^{14}\text{CO}_2$ on mice with lymphatic leukaemia failed to show similar changes.

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