Lactate Dehydrogenase Subunits in Normal and Neoplastic Tissues of the Rat

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SUMMARY

A kinetic procedure, based on differences in affinity of lactate dehydrogenase (LDH) subunits for L(+)-lactate, was employed to measure the M and H subunit activities of this enzyme in a variety of normal and neoplastic tissues of the rat. Total LDH activity was highest in liver (both normal and regenerating) at about 150 units per gm fresh tissue and somewhat lower in heart and femoral muscle at about 100 units per gm. All other tissues had less than 50 units per gm and decreased in the order: uterus during pregnancy, spleen, kidney, lactating mammary gland, brain, diaphragm, uterus, thymus, lung, testes, and mammary gland during pregnancy. The proportion of the M form was highest in both normal and regenerating liver at >90% and was also predominant in femoral muscle, spleen, uterus, diaphragm, thymus, and lung. The lactating mammary gland had about 10 times as much M form but the same H form activity as the gland of pregnancy; the uterus of pregnancy had about 3 times the M form but about the same H form activity as the normal uterus. The H form was predominant in heart, kidney, brain, and testes but made up no more than about 60% of the total. Highly differentiated, slow-growing, transplantable hepatomas had relatively low total LDH activities, at about 50 units per gm, whereas poorly differentiated, rapid-growing tumors had activities between 125 and 160 units per gm. Well-differentiated tumors of intermediate growth rates had intermediate total LDH levels. Although all hepatic tumors displayed predominant M form activity, ranging from 69 to 100%, there was no consistent pattern in relation to growth rate or degree of differentiation. Three transplantable kidney tumors had two to four times as much M form activity but about the same H form activity as normal kidney; 2,6-dimethyl-

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INTRODUCTION

Recent studies from our own and other laboratories have shown that, in the neoplastic transformation of the liver cell, there are variable degrees of loss and retention of enzymes which play a functional role in hepatic metabolism, depending on growth rate of the tumors and their degree of dedifferentiation (21, 26, 39, 40, 42). In those instances in which multiple forms of enzymes are present, as, for example, glucose-ATP phosphotransferase (31, 32, 40), aldolase (1, 23), and pyruvate kinase (6, 37), loss of differentiation in hepatomas results not only in the loss of that isozyme which is normally preponderant in liver and is associated with hepatic function, but also results in a marked increase in the activity of the isozyme that is normally low in activity in liver.

The role of isozymes in tissue function is now a subject of growing significance, and since the most deeply and thoroughly studied have been the isozymes of lactate dehydrogenase (LDH) (4, 7, 8, 12, 35), we were prompted to explore their alterations in experimental liver tumors. Normal tissues contain variable quantities of two subunits, M and H, distributed randomly among the five possible tetramers, which are the enzymatically active forms. It is now well established that the two subunits act as individual catalytic entities in the tetramers (8, 35), and a number of experimental procedures are now available for reliable assays of the subunits, for example, by differences in their thermal stability and their variable affinities for pyruvate, nicotinamide adenine dinucleotide, and its analogs, and lactate (8, 35). By use of the assay procedure developed in our laboratory by Stambaugh and Post (34) based on differing affinities toward L-lactate, the LDH subunits were assayed in a number of rat tissues and in a series of chemically induced primary and transplanted liver tumors ranging widely in growth rate and degree of differentiation, and the results form the basis of this report.
MATERIALS AND METHODS

Animals

Normal rats were obtained from Carworth Farms, New City, New York, and were of the CFN (pathogen-free) strain. They were maintained on a commercial stock diet of Purina Laboratory Chow. In general, full grown rats weighing about 300 gm were used for control studies although no significant differences in liver LDH activity were observed among rats in the range of 200 to 350 gm body weight. In view of the wide ranges in various enzyme activities displayed by rat liver under a variety of nutritional and hormonal conditions, it was anticipated that significant changes in LDH or in the proportions of subunits would have been observed. However, such changes were minimal, and these data, therefore, are omitted from this study.

Tumors

The transplantable rat hepatomas, with the exception of the Novikoff, were transplanted in Bethesda by subcutaneous, intramuscular, or intraperitoneal injection as described previously (21) into rats of the Buffalo or A/C strain. The rats were then shipped to Philadelphia and were maintained on the stock diet until the tumors reached a sufficiently large size for assay, usually from 2 to 10 gm. The Novikoff hepatoma was regularly transplanted in Philadelphia into male Sprague-Dawley rats. Primary rat hepatomas were induced in Philadelphia by feeding a diet containing 3'-methyl-4-dimethylaminoazobenzene (31), and primary rat mammary tumors were produced either by feeding 3-methylcholanthrene (MCA) or 2,6-dimethylbenzanthracene (DMBA) (32). Kidney tumors were also transplanted in Bethesda and rats were shipped to Philadelphia.

Preparation of Tissue

Rats were killed by decapitation, and after exsanguination tissues were quickly excised, washed with ice-cold water, and placed in ice-cold 0.07 M Tris buffer, pH 8.6, or 0.25 M sucrose containing 1.8 mM CaCl2. The tumors were freed of any grossly visible necrotic tissue, cut into pieces, and washed free of most of the blood with the same ice-cold solutions. Samples were placed in formalin for histopathologic examination. After blotting free of excess liquid, the tissues were weighed and homogenized with somewhat less than 10 volumes of the same solution in a coaxial homogenizer with a Teflon pestle. About 15 passes over a 1-min period was sufficient for complete disruption. The concentration of the homogenate thus obtained was adjusted finally to 10% w/v.

To prepare Novikoff ascites hepatoma cells, the fluid was withdrawn by syringe, cooled, and allowed to sediment by standing. By drawing off the supernatant most of the erythrocytes were removed. The remainder was removed as follows. The cells were washed twice with 5 volumes of 0.15 M NaCl, each time followed by sedimentation at 2,000 rpm and decantation of the supernatant fluid. The residue was then suspended in 5 volumes of distilled water and allowed to stand at 0–4°C for two minutes. Osmotic disruption of essentially all the red cells yielded on centrifugation a packed, yellowish-white cell suspension. These were again diluted 5-fold with water, allowed to stand in the cold for 3 minutes, then homogenized as described above and made to a 10% w/v suspension with sufficient Tris buffer to give the same concentration as for the solid tumor homogenates.

Homogenates were centrifuged at 25,000 X g for 15 minutes, and the supernatant was employed for the enzyme assays. When dilution was necessary, this was done with the same Tris buffer immediately before the assay. Determination of the subcellular distribution of LDH, using various modifications of the fractionation procedures of Hogeboom (13) and Schneider (30) revealed that essentially all of the activity in normal and regenerating liver, and in three representative tumors, was in the supernatant fraction. Although small amounts were found in the mitochondrial and microsomal fractions, these could largely be removed by washing with 0.15 M sodium chloride and can therefore be regarded as a contaminant. However, the low activity associated with the nuclear fraction could not be removed by repeated washing. It was predominantly or entirely the M form. These findings are in agreement with those of Hultin and Westort (14), who also found LDH activity in nuclei from skeletal muscle.

LDH Assay

L (+)-Lactate used as the substrate was obtained from Sigma. It was standardized by titration, after heating momentarily and diluting. For routine determination of LDH subunits, solutions of 0.015 M and 0.25 M lactate were made up in 46 mM sodium pyrophosphate and 5.53 mM reduced NAD (NADH) at pH 8.8, the optimum for the forward reaction. These solutions were made up in batches of about 300 ml, and 2-ml samples were pipetted into vials, then frozen and stored at −20°C. The reagents are preserved indefinitely under these conditions, and when required, the vials are thawed at 25°C. The contents are transferred to quartz cuvettes with 1-cm light paths and diluted appropriately with water and enzyme preparation to a final volume of 3 ml. Readings were made at 340 mp in a Gilford model 2000 multiple sample absorbance recording system equipped with a water-jacketed cuvette compartment maintained at 25 ± 0.5°C. With a sample size chosen to give a
The absorbances are converted to international units (µmoles Tris buffer, pH 7.5, and submitted to sonic vibration at 20,000 cycles per sec for 5 periods of 60 seconds each interspersed by 1-min intervals while cooling in ice. The resulting suspension was dialyzed overnight against two successive 5-liter batches of the same Tris buffer, then centrifuged at 8,000 rpm and the supernatant was placed on a column of DEAE-cellulose, 15 x 1 cm, equilibrated with the Tris buffer, and eluted with the same buffer; the eluate was collected in 5-m1 fractions. Under these conditions the M₄ isozyme is not bound and comes off in Fractions 3 to 5. These were combined, assayed, dialyzed again overnight, and again fractionated exactly as above on DEAE-cellulose. The resultant fraction exhibited only the M₄ band on polyacrylamide gel electrophoresis.

The M₄ isozyme was isolated from rat liver by chromatography on diethylaminoethyl (DEAE)-cellulose. Liver was homogenized in 5 volumes of 5 mM Tris buffer, pH 7.5, and, as described above for the H₄ isozyme, submitted to sonic vibration, followed by dialysis and centrifugation. The supernatant was placed on a column of DEAE-cellulose, 15 x 1 cm, equilibrated with the Tris buffer, and eluted with the same buffer; the eluate was collected in 5-m1 fractions. Under these conditions the M₄ isozyme is not bound and comes off in Fractions 3 to 5. These were combined, assayed, dialyzed again overnight, and again fractionated exactly as above on DEAE-cellulose. The resultant fraction exhibited only the M₄ band on polyacrylamide gel electrophoresis.

Electrophoresis

For routine electrophoresis of liver and tumor supernatants, a Shandon electrophoresis apparatus was employed, with 17 x 2.5 cm strips of cellulose acetate paper (Sepharose III, Gelman), essentially as described by Kohn (17) for plasma proteins. The strips were wetted overnight at 4°C in 25 mM Tris buffer containing 10 mM borate and 10 mM ethylenediamine-

\[ \Delta A_{15} = \Delta A_H + 0.63 \Delta A_M \\ 
\Delta A_H = \text{absorbance due to H}_4 \\ 
\Delta A_M = \text{absorbance due to M}_4. \]

At 250 mM lactate, M₄ is optimally active, whereas H₄ is 40% of optimal activity. Therefore,

\[ \Delta A_{250} = \Delta A_M + 0.40 \Delta A_H \\ 
\Delta A_{250} = \text{observed absorbance at 250 mM lactate}. \]

By solving equations 1 and 2 for \( \Delta A_H \) and \( \Delta A_M \) respectively, we obtain the following:

\[ \Delta A_H = 1.33 \Delta A_{15} - 0.87 \Delta A_{250} \]
\[ \Delta A_M = 1.37 \Delta A_{250} - 0.55 \Delta A_{15} \]

The absorbances are converted to international units (µmoles per min) by dividing the calculated absorbances by 0.0207, on the basis of an \( A_M \) for NADH of 6.21 x 10³.

\[ Lactate Dehydrogenase in Neoplastic Tissues \]

![Chart 1. Relationships of L(+)-lactate concentration to lactate dehydrogenase activity. * M₄ isozyme, o H₄ isozyme, from rat liver and heart. act., activity.](chart.png)
In order to provide a background for proper appreciation of the tumor data, it was desirable to assay a wide variety of normal tissues of the rat, and these data are displayed in Chart 2. Highest levels of total LDH were found in liver and were somewhat lower in heart and skeletal muscle. Other tissues had markedly lower levels, the lowest being lung, testes, and mammary glands of pregnant rats. As expected from previous reports (7), highest values for the M subunit were seen in liver; at 150 units/gm the average was 50% higher than that for femoral muscle and about 3 times that in the next highest tissues, namely, heart and spleen. They were considerably lower in skeletal muscle and still much lower in all of the other tissues that were examined. Heart had by far the highest level of H subunit; skeletal muscle, kidney, and brain had about half as much, and other tissues had much lower levels. High ratios of M to H forms were observed in liver, thigh muscle, spleen, the lactating mammary gland, and the uterus of pregnancy, whereas, as particularly low ratios of M to H were found in heart, kidney, brain, and testes. It is of interest that a comparison of the mammary glands of pregnancy and lactation and the uteri of nonpregnant and pregnant rats suggests that increased size and proliferation of the organ are associated with large increases in the M form, without any appreciable change in the H form. However, proliferation per se does not necessarily lead to alterations in the subunit composition since regenerating liver at any time after partial hepatectomy had the same levels and ratio of the M and H subunits as normal, adult liver.

In most instances, the isozyme patterns obtained by electrophoresis were in good agreement with the expected binomial distribution of the subunits. However, in kidney and probably also in diaphragm, most of the activity appeared in the H₄ and M₄ forms. This would suggest that the respective subunits may be segregated in different cell types.

Two other observations worthy of note are that high total LDH is characteristic only of liver, heart, and femoral muscle and that, with the exception of heart, the level of the H form in the rat tissues studied is in a relatively narrow range of between 5 and 25 units per gm.

**RESULTS**

**LDH Subunits in Liver Tumors**

As shown in Chart 3, total LDH in a series of primary and transplanted hepatomas ranged from about 25 to 150 units per gm tissue. In a study of glycolytic enzymes in some of the same hepatomas, Shonk et al. (33) found an average value for normal liver of 162 units per gm and a range of tumor values from 41 to 199 units per gm. Thus the overall agreement is excellent. Shonk et al. (33) found that the rapidly growing tumors had on the average a much higher LDH activity than the slower growing tumors, and in general our values are in good agreement. For example, the three slowest growing tumors, 9611B, 9618A, and 7787, had the lowest LDH activities, ranging from 17 to 53 units per gm, whereas the four fastest growing tumors, namely, the Novikoff and the Morris Hepatomas 7233C, 3924A, and 3683, all of which had transplant generation times of less than a month, had the highest total LDH levels, ranging from 120 to 150 units per gm, and averaged about 140 units per gm. Likewise, the poorly differentiated primary hepatomas, induced by feeding 3'-methyl-dimethylaminoazobenzene (DAB), also had an average of 123 units per gm. All of the well-differentiated tumors of intermediate growth rate had total LDH levels between those of the slowest and fastest growing tumors.

**Ratio of M to H Subunits**

Despite the marked variations in total tumor LDH, there was a rather constant proportion of the two subunits, which did
not differ greatly from that of normal liver. In liver the M subunits made up 92% of the total LDH activity. In the tumors the proportions ranged from 64 to 100%, and there were no marked differences between the slowest and fastest growing tumors. For example, the three slowest growing tumors had proportions from 69 to 100%, and the four fastest growing tumors had proportions ranging from 64 to 91%. Thus growth rate per se or the degree of differentiation does not influence appreciably the relative proportions of the LDH subunits.

LDH Subunits in Kidney and Mammary Tumors

Data in Chart 4 show that three transplantable kidney tumors had LDH levels ranging from that of kidney to about double the kidney level. Most of the increase occurred in the M form. The mammary tumors had about the same activity as the normal lactating gland but had much higher activity than the mammary glands of pregnant animals.

Striking differences in these proportions were observed between kidney and kidney tumors and particularly between the mammary gland and its tumors. The M/H ratio in kidney was 35%, whereas in the three kidney tumors it ranged from 53 to 80%. Although the DMBA- and MCA-induced mammary tumors had almost identical subunit patterns, which were very close to that of the lactating normal gland, they differed greatly from the pattern of the gland of pregnancy, which had a very low total activity and an extremely low level of the M subunit.

DISCUSSION

M and H Subunits in Liver and Other Normal Tissues

Although this study was oriented towards LDH activities in liver tumors, some findings may be of interest with regard to normal tissue metabolism. Our data, shown in Chart 2, reveal that 92% of the LDH of rat liver is in the form of M subunits. Fine et al. (7), using an entirely different assay procedure based on differences in the activity of the subunits toward NADH and its analogs, found 95% of the activity in the M form. The good agreement attests to the reliability of our procedure for determination of tissue LDH subunits. Our finding of a preponderance of the H subunit in kidney is also in good accord with results of Fine et al. (7).
Much has been said with regard to the physiologic significance of the LDH subunits, and most of the current discussions emphasize the ratio of the two forms in relation to tissue function (7, 8, 12, 38). It is obvious, however, that one must consider the absolute magnitudes as well as the ratios of sub-unit activity in assessing their metabolic significance. It is evident from Chart 2 that in the rat a typical M-type tissue, such as femoral muscle, has as much of the H form as any tissue except heart; and the liver, which is assumed to have essentially only the M form, has as much of the H form as every other tissue studied except heart, femoral muscle, and kidney. Similarly, heart muscle, which is typically an H-type tissue, has as much of the M form as every other tissue except liver and femoral muscle. Obviously generalizations based on subunit or isozyme ratios alone are not likely to be illuminating.

In assessing the significance of the high activity of the H type in heart and the M type in skeletal muscle, Fonda et al. (8) suggested that muscles which require sustained and continuous activity, such as the heart, have predominantly the H form, whereas in tissues in which glycolysis occurs sporadically in response to specific needs, such as the working skeletal muscle, the M form is predominant. However, no clear explanation has yet been given for the high predominance of the M form in rodent liver. It is plausible to assume that the high level of the M form may play an important regulatory role in a major liver function, namely, gluconeogenesis. Among the several major sources of carbon for glucose production are the LDH substrates; lactate, which is continuously produced by peripheral glycolysis and reaches high physiologic levels in the blood during exercise; and pyruvate, which is derived from many of the gluconeic amino acids. It is conceivable that physiologic advantage might be derived by having lactate uptake by liver for gluconeogenesis regulated by an LDH with a high $K_m$ for L(+)-lactate. According to Stambaugh and Post (35) the M₄ and H₄ isozymes at pH 7.4 have $K_m$'s for L(+)-lactate of 23 mM and 9 mM respectively, and our data in Chart 1 indicate similar values for the rat LDH subunits. Since the blood lactate concentrations never reach the $K_m$ values for either LDH isozyme, lactate metabolism by liver should be proportional to its concentration in the blood. Exton and Park (5) measured effects of lactate concentration on glucose production in the perfused rat liver and obtained a $V_{max}$ of about 1 $\mu$moles per gm tissue per min. This rate is less than 1% of our observed LDH activity of rat liver of 150 $\mu$moles per gm per min. Presumably, therefore, it is unnecessary to have liver LDH operating at anywhere near maximal activity to take care of the lactate flux for gluconeogenesis. On the other hand, our observed activities, measured at pH 8.8, are probably considerably higher than they would be if measured at a physiologic pH of 7.4. Moreover, since the M₄ and H₄ isozymes have $K_m$'s for pyruvate of 0.3 and 0.2 mM respectively, some inhibition of LDH activity might be expected. However, the reported pyruvate concentrations in rat liver, which are of the order of 0.1 mM (41) indicate that product inhibition would be minor. The LDH levels of normal liver thus point to control of hepatic gluconeogenesis from lactate by lactate concentration rather than by LDH activity; but a better understanding of the possible role of the M subunit in hepatic gluconeogenesis will require a detailed study of the properties and kinetics of this enzyme.

Comparison between the quiescent normal uterus and the uterus of pregnancy, and between the mammary gland of pregnancy and the lactating mammary gland, supports the suggestion of Goodfriend and Kaplan (12) that increases of the M subunit are associated with increased metabolic activity. However, this correlation was not strikingly evident by comparison of the normal liver with regenerating liver; the latter displayed total activities and subunit ratios characteristic of the former. Interpretations of differences between tissues under differing endocrine conditions, however, are uncertain because of possible changes in the proportions of the various cell types composing the tissue.

M and H Subunits in Tumors

Although a causal relationship is often assumed between the high aerobic and anaerobic glycolysis of tumor cells and their LDH activities, two well-established observations argue against such an association. (a) No sharp distinction in LDH activity has been observed in tumors. In the first study in which modern spectrophotometric assays of LDH were performed in tumor tissues, Meister (20) found that LDH activities in 19 tumors of the rat and mouse fell within the range of activities displayed by 20 normal tissues. His values for rat liver and primary azo dye-induced rat liver tumors, when recalculated to international units, coincide closely with our values, ranging from 110 to 160 units per gm. More recent data by Shonk et al. (33) also agree closely with our figures; they reported average values of 162, 72, and 153 units per gm respectively for normal rat liver and for slowly growing and rapidly growing Morris hepatomas. (b) LDH values in all tumors are very high in relation to glycolysis. Values of LDH fall in the range of 100 units per gm tissue, corresponding to $Q_{lactate}$ of approximately 700. These levels are so high that they exceed by at least an order of magnitude the highest levels of anaerobic glycolysis ever observed. Both Beck (3) and Racker (27) pointed out that all of the enzymes of glycolysis in various cell types are considerably higher in optimal activity than the rates of glycolysis. Recent findings suggest that the low glycolysis of the well-differentiated Morris hepatomas may be due in part to lowered glucose-ATP phosphotransferase activities (31), but an additional factor involved in the high glycolytic activity of the fast growing, poorly differentiated hepatomas may be a very high pyruvate kinase activity, which promotes glycolysis by competing successfully for ADP with the respiratory system of the mitochondria (19).

Weber and Lea (39) in a comprehensive comparison of a large number of Morris tumors reported that LDH is one of the enzymes whose level in tumors could not be correlated with their growth rate. Our data on the whole are compatible with this view; however, when one examines the extremes of the data in Chart 3, it may be seen that the fast growing, poorly differentiated tumors had much higher activities of both H and M subunits than did the slowest growing, highly differentiated tumors. However, growth rate per se is apparently not a crucial factor in the LDH subunit pattern, nor is it in the normal tissues since the liver had as high total activity as any of the tumors, and neither the total nor the ratio of sub-
units was significantly changed in the rapidly proliferating regenerating liver.

Although very few studies of LDH subunits have been conducted in tumors by the use of kinetic assays, there is a host of reports in which LDH isozymes have been explored in normal and neoplastic tissues by electrophoresis (10, 11, 18, 19, 24, 29, 36). All of these studies indicate that neoplasia is associated with a shift toward higher levels of the M subunit-containing isozymes. In contrast, however, Gerhardt et al. (9) calculated subunit ratios in human brain and brain tumors by estimation from electrophoretic zymograms and reported that brain had an H/M ratio of 1.5 to 2.6, whereas brain tumors of various types had ratios ranging from below 1 to above 4.6.

Obviously, in our study a marked trend to higher M type in hepatomas would not be expected in view of the already high proportion of M type subunit in the tissue of origin. It is notable, however, that every tumor studied, whether fast or slow growing, had predominantly the M type, and two, the 7787 and 8999 hepatomas, had no detectable H subunit. It is of further interest that three of the four fast-growing, poorly differentiated tumors had considerably higher levels of the H subunit than liver. On the other hand, the kidney and mammary tumors did follow the trend observed by previous investigators in exhibiting higher M subunit levels than their tissues of origin.

In a study of human tumors using a quantitative assay method for LDH subunit composition based on NAD analog ratios, Goldman et al. (10, 11) also found a shift to predominance of the M subunit. They suggested a functional significance to this shift, based on a previous hypothesis (8) that the M form plays a specific role in pyruvate reduction in tissues such as skeletal muscle, which are geared for anaerobic reduction of pyruvate. One may cite against this hypothesis the fact that in our studies poorly differentiated, highly glycolyzing tumors had not only an increased activity of the M subunit over the low glycolyzing tumors, but also had much higher H subunit levels. Using starch gel electrophoresis both Kline and Clayton (16) and Johnson and Kampschmidt (15) found that liver of rats fed 3'-methyl-DAB and tumors derived therefrom had higher levels of the H subunit than normal liver, and our data also indicate a higher content of H form in the 3'-methyl-DAB tumors than liver. In view of the lack of any consistency among the large body of LDH isozyme and subunit data for tumors, it would be difficult at present to formulate any clear-cut association between the LDH subunit levels in tumors and their chemical composition or their glycolytic or other functional activities. This conclusion is necessitated not only from the examination of the subunit data, but follows logically also from the generally high LDH levels in tumors and the growing realization that glycolysis is tightly controlled by numerous environmental factors at multiple sites along the glycolytic sequence (19, 27).

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