Biochemical Pharmacology, Vol. 16, pp. 721–724. Pergamon Press Ltd. 1967. Printed in Great Britain

THE RESPIRATION OF HUMAN LIVER TISSUE

J. BOOTH, E. BOYLAND and C. COOLING

Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital and the Royal Marsden Hospital, Fulham Road, London, S.W.3

(*Received* 19 *December* 1966)

Abstract—The rate of respiration of liver from various species decreases with increase in body weight so that the respiratory rate is approximately inversely proportional to the logarithm of the body weight. The rate of respiration of human liver has been measured in various media to give values that agree with this relationship.

EARLY workers reported that the respiration of animal tissues *in vitro* was approximately equal in different species.[1, 2] However, Kleiber[3] found that the rate of respiration of liver slices from different species, in the presence of glucose, decreased with increasing body weight. Krebs[4] considered that these differences may have been due to variation in conditions of measuring oxygen uptake, and devised a saline-phosphate medium (medium II type A,[4]) which also contained fumarate, glutamate and pyruvate. Using this medium Krebs[4] found that the rate of respiration of tissues from larger animals was lower than the corresponding values from smaller species. In this paper, measurements of the rate of O_2 uptake by rat and human liver slices in various media show that the values for rat liver are comparable with results published in the literature, and that the correlation between the rate of O_2 uptake and body weight is similar for man and the other animals studied.

METHODS

Specimens of human liver, removed when tissue was required for other investigations, were chilled and sliced by hand with a razor blade. Rat livers, treated in the same way, were from adult Chester Beatty strain rats (wt. approx. 200 g). The rate of O_2 uptake was measured in standard Warburg vessels at 37°. Incubation media were (1), Krebs–Ringer phosphate;[5] (2), Krebs medium II, type A which contains pyruvate (4·9 mM), fumarate (5·4 mM) and glutamate (4·9 mM;[4] (3), Krebs–Ringer phosphate containing succinate (20 mM). All media contained glucose (11·5 mM).

RESULTS AND DISCUSSION

All the human liver specimens examined in this work were taken from subjects under anaesthesia but it is unlikely that the respiration rate was influenced by the anaesthetic which, if present, would be largely washed out by the suspending medium. The rate of O_2 consumption was constant for 1 hr except in a few experiments in Krebs medium II. In these cases the initial rate, which was always constant for at least 0·5 hr, was used to calculate the rate of O_2 uptake and the results are shown in Table 1.

The results show that the oxygen uptake was higher in rat liver than in human liver in all the media used and that the difference was largest, when glucose was the only added substrate. Under these conditions the ratio of the mean values for the respiration of rat liver and human liver is 3·9 (9·0/2·3). This is similar to the metabolic rate factor of rat to man (4·6) which has been determined by Drabkin.[6] Drabkin (personal communication) found the oxygen consumption of isolated perfused rat liver to be 0·1285 ml/g liver/min and the oxygen consumption of catheterized human liver with portacavel shunts to be 0·0295 ml/g liver/min. The ratio of these values Rat/Man is 4·36 which is close to the corresponding metabolic rate factor. There is a correlation between metabolic rate and body weight in various animals ranging from mice to cattle and including man. The decrease in the rate of respiration of liver slices *in vitro* with increasing body weight is similar to that which occurs in the metabolic rate of the living animal.[3, 7]

When the mean values for the rate of oxygen consumption by liver slices, measured in medium II, 4 are plotted on a linear-logarithmic scale with the body weight (Fig. 1)

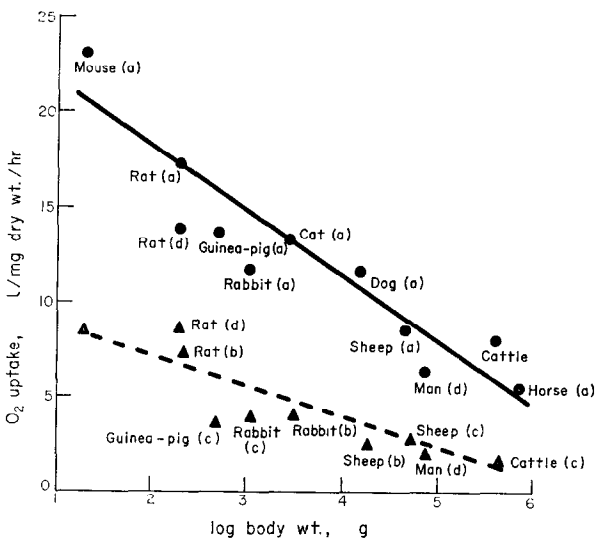

FIG. 1. Relationship between rate of respiration of liver slices and body wt. in various species. O_2 uptake measured in ▲——▲, Krebs–Ringer phosphate; ●—●, Krebs medium II, type A. The average body wt. of man is taken as 67 kg.[16] References (a), Krebs[4]; (b), Kleiber[3]; (c), Kratzing[17] (body wts. taken from Krebs[4]); (d), this paper.

the values for animals examined by Krebs[4] and for man (this paper) are reasonably close to a line drawn between those of the mouse and horse. A similar plot of published values of oxygen uptake, with glucose as substrate, by liver of various species and by rat and man (this paper) also shows a correlation between rate of respiration and body weight. With both types of media the value for products of the rate of respiration and the logarithm of the body weight are reasonably constant so that the respiratory rate varies inversely with the logarithm of the body weight.

The decrease in metabolic rate which occurs with increase in body size may be due to relatively fewer cells being present in the larger organs of heavier animals.

With larger organs the space taken up by supporting connective tissue, blood vessels and other noncellular material becomes larger.

The increase in O_2 consumption which occurs on the addition of succinate has been used as an indication of the activity of the cytochrome system. In the presence of glucose the respiration of normal tissues is increased considerably by addition of succinate but that of neoplastic tissues is not.[8–11] However, Rosenthal and Drabkin[12] considered these comparisons should be made in the absence of glucose and found that under these conditions the respiration of normal tissues such as liver, kidney cortex, brain cortex and probably muscle was increased considerably on addition of succinate, but that of gastric mucosa, lung, skin and tumours was not. Table 1 shows

TABLE 1. RESPIRATION OF HUMAN AND RAT LIVER IN VARIOUS MEDIA

Incubation medium and substrate	O_2 consumption (μl/mg dry wt./hr)	
	Man	Rat
Krebs–Ringer phosphate + glucose (11·5 mM)	2·3 ± 0·3	9·0 ± 0·9
Krebs Medium II + glucose (11·5 mM) + pyruvate (4·9 mM) + fumarate (5·4 mM) + glutamate (4·9 mM)	6·3 ± 0·7	13·8 ± 1·6
Krebs–Ringer phosphate + glucose (11.5 mM) + succinate (20 mM)	24·9 ± 3·9	27·7 ± 4·8

Liver slices (5–20 mg dry wt.) were incubated at 37° in 3 ml medium in Warburg vessels and the rate of oxygen consumption recorded over a period of 1 hr. Results are expressed as the mean value of six experiments ± standard deviation.

that the rates of O_2 consumption in the presence of succinate by liver of man (24·9) and rat (27·7) are similar and consistent with other observations such as rates of 25·2 for mouse liver slices,[10] and 27·4 rat liver homogenate,[9] suggesting that the rate of succinate oxidation is independent of the size of the animal.

The respiration of human liver is less than that of human cancer tissue. Warburg *et al.*[13] measured the respiration of eleven different human carcinomata and the Q_{O_2} ranged from 2 to 8 with a mean value of 5·1. This value is twice that for human liver and indicates that human malignant tissues have a higher respiration than most normal tissues. Roskelley, Mayer, Norwitt and Salter[14] gave Q_{O_2} values for twenty-one different human tumours which varied from 3·0 to 13·3 with a mean of 8·7. This was higher than the corresponding values of normal tissues—skin (4·0), rectum (4·2), thyroid (5·6), testicle (6·4) and prostate (6·5)—with the exception of kidney (9·2). This means that the Warburg concept of a "cancer metabolism" with defective respiration does not apply to human tissues which is in contrast to smaller animals such as chickens, rabbits, mice and rats where the respiration of the liver is greater than that of tumour tissues.

The relatively small variation in the respiration of cancer tissues from animal species of different body size may be considered as an example of dedifferentiation of tumours. It may be analogous to the observations of Greenstein[15] that the enzyme activities of malignant tissues vary less than those of other tissues.

The metabolism of toxic substances by animals is to a large extent dependent upon the activity of the liver, which inactivates foreign compounds mainly by oxidative processes or processes which use energy derived from respiration. As the respiration

of rat liver is approximately four times as great as that of human liver, and the liver forms the same proportion of the body weight in both species, it follows that rats should inactivate toxic substances by metabolism much more rapidly than men. Many compounds are therefore likely to be more toxic to men than to rats when given in a single dose (expressed in mg/kg). On the other hand, if the substance is given as an ingredient of the diet, then the toxicity (e.g. expressed as ppm of diet) will not be so different, because rats eat much more food (expressed in g/kg body weight) than do men.

Acknowledgements—The authors wish to thank Sir Hans Krebs for his helpful comments on this work. This investigation has been supported by grants to the Chester Beatty Research Institute (Institute of Cancer Research: Royal Cancer Hospital) from the Medical Research Council and the British Empire Cancer Campaign for Research, and by the Public Health Service Research Grant No. CA-03188-09 from the National Cancer Institute, U.S. Public Health Service.

REFERENCES

1. E. GRAFE, H. REINWEIN and V. SINGER, *Biochem. Z.* **165**, 102 (1935).
2. F. TERROINE and J. ROCHE, *C. r. hebd. Séanc. Acad. Sci., Paris* **180**, 225 (1925).
3. M. KLEIBER, *Proc. Soc. exp. Biol. Med.* **48**, 419 (1941).
4. H. A. KREBS, *Biochim. biophys. Acta* **4**, 249 (1950).
5. H. A. KREBS and K. HENSELEIT, *Hoppe-Seyler's Z. physiol. Chem.* **210**, 33 (1932).
6. D. L. DRABKIN, *Perspect Biol. Med.* **2**, 473 (1959).
7. M. KLEIBER, *Physiol. Rev.* **27**, 511 (1947).
8. E. BOYLAND and M. E. BOYLAND, *Biochem. J.* **30**, 224 (1936).
9. N. MAYER, *Cancer Res.* **4**, 345 (1944).
10. F. N. CRAIG, A. M. BASSETT and W. T. SLATER, *Cancer Res.* **1**, 869 (1941).
11. J. G. KIDD, R. J. WINZLER and D. BURK, *Cancer Res.* **4**, 547 (1944).
12. O. ROSENTHAL and D. L. DRABKIN, *Cancer Res.* **4**, 487 (1944).
13. O. WARBURG, K. POSENERK and E. NEGELEIN, *Biochem. Z.* **152**, 309 (1924).
14. R. C. ROSKELLEY, N. MAYER, B. N. NORWITT and W. T. SALTER, *J. clin. Invest.* **22**, 743 (1943).
15. J. P. GREENSTEIN, in *Biochemistry of Cancer*, 2nd ed., p. 361. Academic Press, New York (1954).
16. G. F. HUMPHREY, in *Biochemist's Handbook* (Ed. C. LONG), p. 639. Spon, London (1961).
17. C. C. KRATZING, in *Biochemist's Handbook* (Ed. C. Long), p. 801. Spon, London (1961).