Oxygen availability and liver metabolism

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The liver experiences wide variations in oxygenation, owing to changes in both the blood haematocrit and PO2, but the accompanying alterations in metabolism have received little attention. Anaemia is common, and therapeutic usefulness of O2 is limited by its toxicity. Abraham et al. (1968) have reported lysosomal damage in the rat liver perfused at a PO2 of 200–450 mmHg (27–60 kPa). In previous work (Mayes & Felts, 1976), we showed that small changes in haematocrit and PO2, within the physiological range, profoundly alter hepatic carbohydrate and lipid metabolism and the rate of secretion of very-low-density lipoproteins. The present work investigated the metabolism of the liver when perfused under an extended range of PO2 and haematocrit.

Male Wistar rats were kept at 25°C with a 12 h day-length (either 09:00–21:00 h or 12:00–24:00 h). Defibrinated blood was collected and dialysed for 24 h (Laker & Mayes, 1979). After centrifugation and separation of erythrocytes from serum, half of the blood was reconstituted to give a haematocrit of 45% at a PO2 of 35 mmHg, and progressively less as the PO2 increased above 35 mmHg, above which there was neither net release nor uptake of glucose. This equilibrium was achieved with an O2 consumption less than that of the livers which released glucose when perfused with a full haematocrit at a PO2 of 35 mmHg.

Livers perfused at a haematocrit of 45% and at every selected PO2 above 35 mmHg took up approx. 534 μmol of lactate, whereas at 35 mmHg approx. 127 μmol of lactate was released. At a haematocrit of 22.5%, either more lactate was released (at a PO2 of 35 mmHg) or less was taken up (at a PO2 of 70–400 mmHg). Glycogenolysis was probably responsible for the output of both glucose and lactate by livers at the lesser PO2 values, as their glycogen content was depleted to 2% compared with 4% in livers perfused at increased PO2. Livers perfused at a PO2 of 130–400 mmHg, but with half the haematocrit, contained glycogen in excess of 4%. However, the glycogen content of livers perfused at a haematocrit of 45 became progressively depleted (from 3.5 to 2.0%) as the PO2 was increased from 130 to 400 mmHg. The fate of this glycogen is uncertain, since neither lactate uptake nor glucose production was altered. It was probably converted into acetyl-CoA, resulting in increased fatty acid synthesis or increased oxidation in the citric acid cycle, with consequent sparing of fatty acid oxidation.

All livers perfused at a PO2 of 130–400 mmHg had similar perfusate [lactate/pyruvate] ratios (mean 9.9:1), which increased slightly at a PO2 of 70 and 96 mmHg but very significantly at a PO2 of 35 mmHg, giving a ratio of 23 at a haematocrit of 45%, and 60 at half haematocrit. Total ketone-body production was 6.5 μmol/h per g by all livers perfused at a PO2 of 130–400 mmHg; it was similar at a PO2 of 95 mmHg when the haematocrit was 45%, but at a haematocrit of 22.5% production increased at this PO2, as it did in all perfusions carried out at a PO2 of 35–70 mmHg. The ratio [3-hydroxybutyrate]/[acetoacetate] paralleled the ketone-body production rate, being always less in the perfusions at the normal haematocrit, i.e. approx. 1.25 and 1.45 respectively, over the range of PO2, 95–400 mmHg. Thus, major changes in metabolism are caused by variations in both PO2 and haematocrit. It is clear that perfusates carried out at a PO2 greater than normal do not fully compensate for changes brought about by the use of anaemic perfusates.

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