We are grateful to the Medical Research Council for financial support. B. A. C. is the recipient of a Science Research Council Training Award.


Hepatic Metabolism in Pig Malignant Hyperthermia

GEORGE M. HALL

Department of Anaesthetics, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS, U.K.

JERRY N. LUCKE

Department of Veterinary Surgery, University of Bristol, Langford, Bristol BS18 7DU, U.K.

and ROGER LOVELL and DAVID LISTER

A.R.C. Meat Research Institute, Langford, Bristol BS18 7DU, U.K.

Malignant hyperthermia is a rare, but often fatal, complication of general anaesthesia. The syndrome is also found in certain breeds of pigs and these have been extensively investigated as a model of human syndrome. The primary defect in malignant hyperthermia is thought to be an increased Ca^{2+} concentration within the cytoplasm of striated muscle. The circulating metabolic changes are considered to be largely secondary to the increased muscle metabolism (Lucke et al., 1976), and the presence of a hypercarbia, lactic acidosis and hyperkalaemia confirms the diagnosis in suspected cases. In the present study we have systematically examined liver function during the hyperthermic response in pigs to determine the contribution of hepatic metabolism to the changes in circulating substrates. In particular, we considered that the progressive lactic acidosis observed in malignant hyperthermia may be due not only to the impaired hepatic uptake of lactate, but also to hepatic lactate production when the pig was grossly acidotic (Cohen & Iles, 1977).

Seven malignant hyperthermia-susceptible Pietrain pigs were investigated. A hepatic venous catheter was inserted on the day before the experiment and the position confirmed by X-ray control. A carotid artery was cannulated for sampling arterial blood. Two control samples were collected and then malignant hyperthermia was induced by ventilating the pigs with 1% halothane for 10 min together with the intravenous administration of 1 mg of suxamethonium chloride (succinylcholine chloride)/kg body wt. after 5 min of halothane. Paired arterial and hepatic venous samples were collected every 10 min during malignant hyperthermia and analysed for pH, O_2 content, glucose, potassium, lactate, pyruvate, alanine, non-esterified fatty acids and glycerol. The haematocrit and insulin concentrations of arterial samples were also determined, and hepatic blood flow was determined by the continuous infusion of the dye Indocyanine Green.

Vol. 6
The seven pigs rapidly developed malignant hyperthermia with an increase in mean muscle temperature from $37.8 \pm 0.5^\circ C$ (mean±s.e.m.) in the control period to $41.5 \pm 0.3^\circ C$ after 40min. Although mean hepatic blood flow decreased significantly with the onset of hyperthermia from $1.10 \pm 0.18$ to $0.29 \pm 0.03$ litre/min after 30min, there was a concomitant increase in $O_2$ extraction by the liver so that hepatic oxygen consumption did not change significantly. At 20min after malignant hyperthermia was induced glucose production by the liver had increased approx. 7-fold to 3.6mmol/min and was associated with an increase in arterial glucose concentration to 12.6mmol/l. There was a massive efflux of $1.1 \text{mmol of K}^+$/min early in the hyperthermic response, showing that the gross hyperkalaemia, which is characteristic of the syndrome, is mainly hepatic in origin, and not only due to potassium loss from muscle. The uptake of non-esterified fatty acids, glycerol and alanine decreased with progressive hyperthermia, but pyruvate efflux showed a small increase that appeared to be related to the massive glycogenolysis.

The mean lactate uptake by the liver increased from $0.21 \pm 0.08$mmol/min in the control period to $1.19 \pm 0.28$mmol/min after 10min of the response. Even when the pigs were grossly acidic with an arterial pH of 6.75 and an hepatic blood flow of only 25% of the control value, hepatic lactate uptake was still 3 times that recorded in the resting state. Although hepatic lactate uptake was increased in this situation it was still inadequate in the presence of gross stimulation of muscle metabolism with a mean arterial lactate concentration of $19.3 \pm 0.8$mmol/l. However, it is important to note that the liver never produced lactate despite being perfused with severely acidic arterial blood, and this is in contrast with the studies on the isolated perfused rat liver (Lloyd et al., 1973). Furthermore, the evidence in vivo for the inhibition of hepatic gluconeogenesis by a decrease in arterial pH is conflicting (Cohen & Woods, 1976) and some experiments have produced such severe physiological changes that the relevance to the intact animal must be in doubt (Berry & Scheuer, 1967; Schröder et al., 1969).

In conclusion, our results suggest that the lactic acidosis of pig malignant hyperthermia is due to the peripheral overproduction of lactate with some impairment of hepatic uptake. The gluconeogenic capacity of the liver was never completely inhibited despite the severity of the metabolic acidosis and the hyperthermia.

Berry, M. N. & Scheuer, J. (1967) *Metabolism* 16, 537–547