PORCINE MALIGNANT HYPERTHERMIA. II: HEAT PRODUCTION

G. M. HALL, J. R. BENDALL, J. N. LUCRE AND D. LISTER

SUMMARY

The contributions of aerobic and anaerobic muscle metabolism to the heat produced in porcine malignant hyperthermia were studied in seven Pietrain pigs. Oxygen consumption measurements were used to calculate the increase in muscle temperature as a result of aerobic metabolism and this was compared with the observed muscle temperature. The results show that in the initial stages of porcine malignant hyperthermia heat production is largely aerobic in origin. Terminally, aerobic metabolism can account only for about half the observed temperature increase.

There is now little doubt that the primary site of heat production in porcine malignant hyperthermia (MH) is skeletal muscle (Britt and Kalow, 1970; Britt, 1972; Relton, Britt and Steward, 1973). An increase in muscle temperature is one of the early signs of the onset of MH, together with the metabolic changes indicative of severe muscle stimulation (Lucke, Hall and Lister, 1976). Clark and colleagues (1973) noted that, in hyperthermic Poland China pigs, the temperature of the femoral venous blood was up to 2°C greater than that of the femoral arterial blood. This study emphasized further the importance of skeletal muscle metabolism in the heat production in porcine MH.

The relative contributions of aerobic and anaerobic muscle metabolism to the thermogenesis in MH were investigated by Berman and colleagues (1970). On the basis of oxygen consumption and oesophageal temperature measurements, in two hyperthermic Landrace pigs, these workers concluded that anaerobic metabolism was the major source of heat production. Gatz (1973) argued, on theoretical grounds, that the thermogenesis in MH was largely aerobic in origin. The authors have analysed the data on oxygen consumption and muscle temperature recorded in seven hyperthermic Pietrain pigs (Lucke, Hall and Lister, 1976) to assess the relative contributions of aerobic and anaerobic muscle metabolism to the heat produced in porcine MH.

METHODS

The experimental protocol and methods used for the determination of oxygen consumption and muscle temperature have been described previously (Lucke, Hall and Lister, 1976).

In an analysis of the data the following methods were adopted. As the development of MH was particularly rapid in the two animals triggered with suxamethonium alone, these results were treated separately from the five pigs in which halothane also was administered. The mean overall oxygen consumption (ml/min STPD) for the suxamethonium pigs and the suxamethonium and halothane pigs was calculated. From these results the total amount of oxygen consumed above basal requirements (expressed as m mol oxygen/kg muscle) was obtained by integrating the mean overall oxygen consumption rate over time intervals during which the rate did not change too rapidly. Muscle weight in the Pietrain pigs was taken as 46% of body weight for 55-kg pigs (based upon complete anatomical dissection of Pietrain pigs of this weight, Meat Research Institute, unpublished results).

It was assumed that all the oxygen consumed above basal levels was used by the muscles to oxidize glucose and that the heat produced was not significantly dissipated. Thus:

heat produced = muscle weight × specific heat × temp. increase;

therefore:

\[ \text{Temp. inc.} = \frac{\text{heat produced}}{\text{muscle weight} \times \text{specific heat}} \]

and

\[ \text{Temp. inc.} = \frac{(O_2 \text{ used} > \text{basal}) \times \text{enthalpy of glucose oxidn.}}{\text{muscle weight} \times \text{specific heat}} \]

As the enthalpy of glucose oxidation is 113.3 kcal/mol O₂ (Lehninger, 1970) and the specific heat of
muscle is 0.85 cal/g°C, the temperature increase in muscle as a result of oxidation is given by:

\[
\text{Temp. inc.} = \frac{O_2 \text{ consumed above basal} \times 113.3}{\text{muscle weight} \times 0.85}
\]

Temp. inc. =

\[
\frac{O_2 \text{ consumed above basal (mol)} \times 133.3}{\text{muscle weight}} \quad (1)
\]

From equation (1) the calculated value of muscle temperature increase was then compared with the observed temperature increase recorded by the muscle thermistor.

RESULTS

The mean overall rates of oxygen consumption (ml/min STPD) and the observed muscle temperatures are shown in figures 1A (for suxamethonium and halothane) and 1B (suxamethonium alone). When the hyperthermic response was well established, oxygen consumption rates over 800 ml/min were recorded. Terminally there was a marked reduction in oxygen consumption, although the rate of muscle temperature increase did not decline.

![Graph 1A](image1a.png)

**Fig. 1.** The mean rates of oxygen consumption and the mean muscle temperatures are shown for five pigs triggered with suxamethonium and halothane (A) and for two pigs triggered with suxamethonium alone (B). Suxamethonium 50 mg was administered at times SI and SII and halothane commenced at time H.

In figure 3 the observed increase in muscle temperature is plotted against the calculated value derived from equation (1). The observed and calculated values agree well in the early stages of the response, but above a muscle temperature of 40 °C the observed muscle temperature increased more quickly than expected from consideration of the oxygen consumption alone. In the terminal stages the difference between the observed muscle temperature and the calculated muscle temperature was 2.6 °C for the pigs anaesthetized with suxamethonium and halothane and 2.25 °C for the pigs anaesthetized with suxamethonium alone.
HEAT PRODUCTION IN PORCINE MH

DISCUSSION

Figure 3 shows that at a muscle temperature greater than 40°C, aerobic glycolysis is unable to supply sufficient heat to account for the observed rate of increase in temperature. The discrepancy between the observed and calculated muscle temperatures was most marked in the terminal stages of the hyperthermic response when systemic arterial hypotension and a further increase in the plasma lactate concentration were found (Lucke, Hall and Lister, 1976). A massive stimulation of anaerobic glycolysis would be expected terminally and it is possible to calculate the lactate production in muscle necessary to account for the additional heat produced.

In the case of the five pigs triggered with suxamethonium and halothane, the difference between the observed and calculated muscle temperatures was 2.6°C in the terminal stage. This is equivalent to an additional heat production in the pig equal to 55 kcal (muscle weight (kg) x specific heat x temperature increase). As the production of lactate in muscle yields 20 kcal/mol (Wilkie, 1960), the additional heat production of 55 kcal requires the production of: 2.75 mol lactate divided by total muscle weight = 108 m mol lactate/kg muscle. For the two pigs triggered with suxamethonium alone, the additional heat produced requires a terminal lactate concentration of 94 m mol/kg muscle. Berman and Kench (1973) reported muscle lactate values of 100 m mol/kg in the terminal stages of a hyperthermic response in Landrace pigs.

Thus, most of the extra oxygen is used initially to oxidize glucose in muscle, but in the terminal stages lactate production increases and can account for the extra increase in temperature in excess of that resulting from glucose oxidation. These results appear to offer a satisfactory explanation for the source of heat in porcine MH but it must be emphasized that there are several assumptions in the calculations. For example, (a) all the oxygen consumed above basal requirements was assumed to be required for glucose oxidation in muscle; (b) the muscle temperature recorded was assumed to be representative of the total musculature; (c) heat loss was ignored. Examination of the biochemical data reported from these seven pigs by Lucke, Hall and Lister (1976) indicates an increase in plasma lactate values after the first dose of suxamethonium to concentrations in excess of 10 m mol/litre. Thus some anaerobic metabolism must have been present in muscle following this severe initial stimulation, although the plasma lactate concentration thereafter showed little change until the terminal stages. It is of interest that, in the established hyperthermic response, similar oxygen consumption rates were recorded in those pigs triggered with suxamethonium and halothane (fig. 2a) and suxamethonium alone (fig. 2b). The method of stimulating muscle metabolism seems to have little effect on the proportion of aerobic to anaerobic metabolism.

Heat production in the liver has not been considered in this analysis, although Berman and colleagues (1970) recorded a rapid increase in hepatic temperature in porcine MH. Gluconeogenesis from the circulating lactate, and a small amount of lactate oxidation, will contribute to heat production. The exact value of this hepatic contribution is difficult to assess without an accurate estimation of hepatic lactate clearance in the pig. Furthermore, Evans and colleagues (1975) found a gross impairment in gluconeogenesis and lactate oxidation in the liver of MH susceptible pigs.

Berman and colleagues (1970) concluded that less than 10% of the heat production in hyperthermic Landrace pigs could be accounted for by aerobic metabolism and that 25% was a result of anaerobic metabolism. In a further estimate of heat production utilizing direct measurement of muscle metabolites, Berman and Kench (1973) reported that anaerobic metabolism could account for 50% of the heat produced. On the basis of the calculations presented in this paper, the authors conclude that aerobic muscle metabolism is responsible for nearly all the heat produced in the initial stages of porcine MH, but this decreases to about 50% of the total heat production in the terminal stages.

ACKNOWLEDGEMENTS

G. M. Hall received generous financial support from the Wellcome Trust and the Muscular Dystrophy Group of Great Britain. G. M. Hall and J. N. Lucke are visiting research workers at the A.R.C. Meat Research Institute and thank the Director, Professor Norris, for the use of the Institute's facilities. Miss Karen Gorman provided skilled technical assistance.

REFERENCES


**HYPERTHERMIE MALIGNE DES PORCS II: PRODUCTION DE CHALEUR**

**RESUME**

Les contributions apportées par le métabolisme aérobie et anaérobie du muscle à la chaleur produite dans l’hypertémie maligne des porcs ont été étudiées sur sept porcs piétrains. Les mesures de la consommation d’oxygène ont servi à calculer l’augmentation de la température du muscle résultant du métabolisme aérobie, résultat que l’on a comparé à la température du muscle observée. Les résultats obtenus montrent qu’au cours des premiers stades de l’hypertémie maligne des porcs la production de chaleur est en grande partie d’origine aérobie. Aux stades finals, le métabolisme aérobie n’entre en ligne de compte que pour à peu près la moitié de l’augmentation de température observée.

**MALIGNE HYPERTHERMIE BEIM SCHWEIN II: HITZEERZEUGUNG**

**ZUSAMMENFASSUNG**

Die Möglichkeit aerobischen und anaerobischen Muskelstoffwechsels als mitwirkende Faktoren bezüglich der Hitzeerzeugung bei maligner Hyperthermie beim Schwein wurde ermess. Sauerstoffverbrauchsmasse wurden benützt, um die Erhöhung der Muskeltemperatur als Folgerung aerobischen Stoffwechsels zu berechnen; die Werte wurden daraufhin mit den ermessenen Muskeltemperaturen verglichen. Die Ergebnisse zeigten, dass während der Anfangsstadien der malignen Hyperthermie beim Schwein, die Hitzeerzeugung zum grossen Teil aerobisch bedingt ist. Beim Endstadium erwies sich der aerobische Stoffwechsel nur für ungefähr die Hälfte der beobachteten Temperaturanstiege erklärbär.

**HIPERTERMIA PORCINA MALIGNA. II: PRODUCCION DE CALOR**

**SUMARIO**

Se estudió en siete cerdos Pietrain la aportación del metabolismo aeróbico y anaeróbico en el músculo al calor producido en la hipertermia porcina maligna. Se utilizaron mediciones de consumo de oxígeno para estudiar el incremento en la temperatura del músculo como un resultado del metabolismo aeróbico y se comparó esto con la temperatura del músculo observada. Los resultados muestran que en las fases iniciales de la hipertermia porcina la producción del calor es en gran parte de origen aeróbico. Terminalmente el metabolismo aeróbico puede responder nada más por cerca de la mitad del aumento de temperatura observado.