Thermogenesis in stress-susceptible pigs: a review[1]

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Stress syndromes

Malignant hyperthermia (MH) is a fulminant thermogenic syndrome occurring during anaesthesia in which a hypermetabolic condition stimulates muscle to the level that would be expected during intense exercise. MH occurs rarely in human subjects (Britt & Kalow 1970), but commonly in certain breeds of pig such as the Pietrain and some strains of Landrace and Poland China pigs. Such animals are often referred to as stress-susceptible because they succumb to a variety of stress factors, showing many of the signs that would be seen in MH (Sybesma & Eikelenboom 1969). The severe stress of slaughter, for example, induces a fast rate of post-mortem muscle glycolysis in such pigs: the rapid fall in pH before cooling denatures myofibrillar protein so that intracellular water is lost. This is an economically important condition referred to as pale, soft exudative (PSE) pork (Lister 1970).

The association between extreme sensitivity to stress and MH in pigs has been well established. There is some evidence which suggests that individual people and families susceptible to MH may also be particularly susceptible to stress, so that there may be analogous human and porcine stress syndromes (Wingard 1974).

It is only in specific breeds of pigs that MH can be reproduced with any degree of certainty, and there is little convincing evidence that the syndrome occurs during anaesthesia in other species. However, it seems likely that stress and excitement might induce a fatal hyperthermia in some wild animals and birds through increased muscle metabolism (Harthoorn *et al.* 1974, Henschel & Louw 1978). This syndrome, referred to as capture myopathy, has many biochemical features in common with MH and this suggests that a thermogenic effect of catecholamines on muscle might be widespread in nature (Lucke *et al.* 1979).

Malignant hyperthermia

Clinical signs: These are seen during induction or maintenance of anaesthesia, using a variety of drugs. Halothane with or without suxamethonium is most commonly used to induce MH experimentally in pigs. These two compounds are also most frequently implicated as triggering agents in clinical cases. The initial signs of the syndrome are stimulatory with an increase in heart and respiratory rates; an increase in muscle tone is usually but not invariably seen; signs of reduced peripheral perfusion are recognized as blotchy cyanotic mottling of the skin; and a rise in body temperature can be detected early in the course of the syndrome.

Metabolic changes occurring during MH have been investigated systematically in pigs (Lucke *et al.* 1976, Hall *et al.* 1980, 1982). It was found from the whole animal studies that there was an increase in oxygen consumption and an even greater increase in carbon dioxide production. Within 30 minutes of inducing MH, there was a fall in arterial pH (<6.8) associated with a combined metabolic and respiratory acidosis. By examination of substrate exchange across the liver (Hall *et al.* 1980) and a hind leg (Hall *et al.* 1982), it has been shown that increased hepatic glucose production and a small efflux of glucose from muscle

contributed to the hyperglycaemia. Levels of circulating non-esterified fatty acids (NEFA) fell during MH, but a rise in glycerol indicated increased lipolysis. From the leg studies it now seems likely that triglyceride breakdown continued during MH but there was local oxidation of fatty acids.

Haemoconcentration is an early feature of porcine MH and although splenic contraction would contribute, the arteriovenous differences across the leg do suggest a movement of water into the intracellular space. The major electrolyte changes in the above studies were a hyperkalaemia which seemed to be derived from liver and not muscle as expected; and a hyperphosphataemia, probably associated with increased hydrolysis of adenine nucleotides.

Body temperature: This can rise at the impressive rate of 1°C in 5 minutes. Hyperthermia is a result of excessive heat production over loss, although peripheral vasoconstriction would contribute to the temperature rise by limiting the dissipation of heat from the body. Muscle has been considered the primary source of heat because the temperature rise was detected first in muscle (Lucke *et al.* 1976), and on a hind leg preparation the femoral venous blood was 1°C higher than arterial (Clarke *et al.* 1973). From whole body oxygen consumption, it can be calculated that the enthalpy of glucose oxidation plus lactate production from anaerobic glycolysis could account for heat production in muscle (Hall *et al.* 1976).

Sympatho-adrenal stimulation: This is a major feature of MH and related conditions of stress. During porcine MH a massive rise in circulating catecholamines has been demonstrated (Lucke *et al.* 1976) and it was found that total depletion by adrenalectomy and bretylium abolished sensitivity to triggering agents completely (Lucke *et al.* 1978). Gronert & Theye (1976) held the view that the rise in catecholamines was secondary to the stress of the metabolic disturbance and hyperthermia. We have always considered sympatho-adrenal stimulation to be an integral part of MH probably potentiating sensitivity to triggering agents and, by further stimulation of muscle, contributing to the malignant nature of the syndrome (Lister *et al.* 1975, Lucke *et al.* 1977).

The precise mode of catecholamine stimulation of muscle in porcine MH has not been determined; the rise in muscle temperature is not associated with convulsive movements or shivering and an increased muscle stiffness is not always present. It is interesting to note, therefore, that noradrenaline-induced non-shivering thermogenesis in hibernating creatures and cold-adapted animals does not involve any visible increased activity of muscle either, and it has been postulated that invisible biochemical activity in cell and mitochondrial membranes might account for heat production in muscle (Himms-Hagen 1976).

In 1979 a growing interest developed in the potential role of brown adipose tissue (BAT) in non-shivering thermogenesis (Foster & Frydman 1978), diet-induced thermogenesis (Rothwell & Stock 1979), and the control of obesity in mice (Himms-Hagen & Desautels 1978) and possibly man (Rothwell & Stock 1979). This led us to consider the possibility that BAT might contribute to heat production in MH.

Thermal response to noradrenaline infusion

An 18-week-old male Pietrain pig weighing 58 kg was anaesthetized with ketamine and thiopentone and ventilated with nitrous oxide and oxygen. Anaesthesia was maintained with incremental doses of thiopentone. Arterial and venous canulae were inserted, muscle temperature was measured by a thermistor probe 10 cm deep in biceps femoris, and the skin temperature over the back was measured by infra-red thermography (AGA Thermovision 780M). Noradrenaline bitartrate was infused intravenously at 5 µg/kg/min for 30 minutes: a dose which had been shown in earlier experiments to produce a large lipolytic response in Pietrain pigs (Hall *et al.* 1977). There was a small decrease in muscle temperature (38.8–38.5°C) during the 30 minute period of infusion but a further 30 minutes later it had returned to the control level. At the same time, the noradrenaline infusion produced a rise in skin temperature, representing an increase of 0.6°C, starting midline at the thoracolumbar

junction and spreading caudally each side of the lumbar spine. Ten minutes after the period of infusion, a second area of heat was seen cranial to the interscapular region, spreading out from the midline over the neck. 'Hot spots' were also seen at the base of each ear. During the time of infusion there was a ten-fold increase in plasma NEFA from 0.13 to 1.35 mmol/l, but no change in arterial pH.

A control period of 30 minutes was allowed after completion of noradrenaline infusion before MH was induced by ventilation with 1% halothane and intravenous administration of 100 mg suxamethonium. Muscle temperature subsequently increased by 2.8°C in 20 minutes and there was a fall in arterial pH to less than 6.8; however, skin temperature over the lumbar and cervical regions decreased and there were the characteristic signs of reduced perfusion and cyanotic mottling.

Conclusions

The experiment confirmed that heat production in MH originates from muscle, not BAT, and that peripheral vasoconstriction reduced heat loss.

An infusion of noradrenaline produced a peripheral thermogenic response which, topographically, was similar to that reported in man after administration of ephedrine (Rothwell & Stock 1979). Pigs are reputed not to have BAT (Le Blanc & Mount 1968) and we have not found any macro- or microscopic evidence for BAT in Pietrain pigs. However, morphological evidence for BAT has been described in Large White pigs up to 3 months of age but not in older animals (Dauncey *et al.* 1981).

The appearance of 'hot spots' in response to noradrenaline infusion is likely to have been a result of changes in blood flow: D Stribling (personal communication) has used the labelled microsphere technique in younger pigs to demonstrate a 30-fold increase in blood flow to back fat in the same areas as the 'hot spots' in the Pietrain pig and, more specifically, a 50-fold increase in blood flow to a pad of fat at the base of each ear. Stribling did not find any convincing morphological evidence for BAT in younger Large White or Pietrain pigs and failed to demonstrate any difference in guanosine diphosphate (GPD) binding which, according to Nicholls (1977), would indicate uncoupling of respiration through a proton conductance pathway in the inner mitochondrial membrane.

Such a blood flow response suggests a considerable increase in metabolic activity in specific areas of fat even though the pig might not possess BAT; it does not, however, indicate a rise in skin temperature above that of the core as suggested by Rothwell & Stock (1981). It is possible that the source of heat production is not derived from BAT but from specialized areas of white fat which may also respond to sympathetic stimulation with a thermogenic metabolic change.

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