Brown adipose tissue activity in pyrexial cases of cot death

M E J LEAN, G JENNINGS

From the Dunn Nutrition Laboratory, Medical Research Council and University of Cambridge, Cambridge

SUMMARY Brown adipose tissue was investigated in two cases of cot death in which core temperatures were above 40°C on arrival at the mortuary. Evidence was obtained from mitochondrial (8-3H) guanosine diphosphate (GDP) binding and oxygen uptake of active thermogenesis with uncoupled mitochondrial respiration which was recoupled by GDP. Thermogenic capacity of brown adipose tissue, estimated by radioimmunoassay of the specific mitochondrial membrane "uncoupling protein" responsible for heat production, was similar to that measured in other infants or in experimental animals acclimated to moderately warm conditions (23°C).

Brown adipose tissue thermogenesis, occurring inappropriately in a warm, well insulated infant, could be a cause of some cases of cot death.

Some cot deaths, or sudden infant death syndrome (SIDS), have recently been considered to be related to problems with thermoregulation, resulting in overheating.1,2 Overinsulation with clothes or bedding may be an important factor, especially if the room temperature is kept warm, but excessive endogenous heat production could also play a part. Suggestions as to the source of excess heat production have not been made, but Naeye and coworkers reported increased amounts of brown adipose tissue in cot death infants.3

The possibility that the activity of brown adipose tissue could, in some instances, be involved in the mechanisms leading up to cot death by generating heat inappropriately is difficult to explore. We have, however, had the opportunity of investigating the properties of brown adipose tissue in two pyrexial cases of cot death from which it was possible to obtain fresh tissue. The results suggest that brown adipose tissue is thermogenically active in such cases. Although its activity may not be different from that of normal infants, thermogenesis in this situation is inappropriate and could indeed contribute to death.

Material and methods

The two infants were both male and aged 5 months: they had died at home in their cots between 7–8 am. Body weights were 7 and 8 kg, respectively. These were both typical cases of cot death: previous developmental history and health were unremarkable and no underlying cause of death was found. The rectal temperature in each case, however, was above 40°C on arrival at hospital, and postmortem examinations were carried out within two hours of death.

Adipose tissue was removed from sites of axillary, cervical, interscapular and perirenal brown adipose tissue, and cytochrome oxidase activity (E.C.1.9.3.1) was measured as an index of mitochondrial mass by a spectrophotometric method.4 For electron microscopical examination, tissue was fixed in osmium tetroxide and embedded in Spurr's resin and sections were stained with uranyl acetate and lead citrate. Mitochondrial preparations were prepared within two hours, and thermogenic activity was assessed by a (8-3H) guanosine diphosphate (GDP) binding assay, according to previously described methods.5 Mitochondrial uncoupling protein content was measured as an index of thermogenic capacity using a solid phase radioimmunoassay with a lower limit of detection of 0.8 μg/mg total mitochondrial protein, using a specific rabbit anti-human uncoupling protein antiserum.6 In case 2 direct measurements of mitochondrial respiration were made using an oxygen electrode (YSI Co, Ohio, USA) at 25°C with 10 mM α-glycerophosphate as substrate in a medium (pH 7.1) containing 100 mM sucrose, 10 mM glycyglycine, 5 μM rotenone and bovine serum albumin 2.5 mg/ml. Initial respiration rate was obtained and GDP added (1 mM final concentration) to obtain the fully coupled respiration rate. Finally, 5 μM of the uncoupling agent FCCP (Sigma Chemical Co, Poole, Dorset) was added to estimate fully uncoupled oxygen uptake.

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Biochemical results on brown adipose tissue obtained within two hours of death from two cot death infants, and comparison with published figures in infants and mice

<table>
<thead>
<tr>
<th></th>
<th>Cytochrome oxidase activity (µmol/min/g)</th>
<th>Uncoupling protein (µg/mg mitochondrial protein)</th>
<th>GDP binding activity (pmol/mg mitochondrial protein)</th>
<th>Change in O2 uptake from GDP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case 1:</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>246</td>
<td>22</td>
<td>147</td>
<td></td>
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<tr>
<td>Cervical</td>
<td>202</td>
<td>23</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>Perirenal</td>
<td>94</td>
<td>11</td>
<td>133</td>
<td></td>
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<tr>
<td>Interscapular</td>
<td>18</td>
<td>7</td>
<td>91</td>
<td></td>
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<tr>
<td><strong>Case 2:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>66</td>
<td>10</td>
<td>129</td>
<td>-23%</td>
</tr>
<tr>
<td>Perirenal</td>
<td>23</td>
<td>9</td>
<td>104</td>
<td>-9%</td>
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<tr>
<td><strong>Human infants:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>-</td>
<td>15 ± 11</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Perirenal</td>
<td>-</td>
<td>9 ± 11</td>
<td>-</td>
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<tr>
<td><strong>Mice: 3 months:</strong></td>
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<tr>
<td>33°C–22°C</td>
<td>40–178</td>
<td>9–43</td>
<td>69–200</td>
<td></td>
</tr>
</tbody>
</table>

Mean results obtained using the same methods on mitochondria:
*From 17 infants who died suddenly from a variety of causes
†From the interscapular brown adipose tissue (the principal site) of mice housed at 33°C (warm) and at 22°C (cool) room temperatures

Results

Biochemical measurements made on fresh brown adipose tissue from cases 1 and 2 are shown in the table: histological appearances were typical of active brown adipose tissue, with high vascularity, rounded nuclei, and multivesicular cytoplasm packed with mitochondria, and without evidence of necrosis (fig 1). Uncoupling protein content was significantly correlated with cytochrome oxidase (r = 0.97, n = 6, p < 0.001) and GDP binding activity (r = 0.85, p < 0.02). All were highest in axillary and cervical sites. Scatchard analyses (fig 2) at GDP concentrations of 0.5–25 µM were interpreted as indicating single site mitochondrial GDP binding characteristics with dis-
**Brown fat in cot deaths**

Active thermogenesis, such as in brown adipose tissue, involves increased oxygen uptake and would clearly be inappropriate in the setting of hypoxia. This consideration questions the recent suggestion of Stephenson and Variend that necrosis of brown adipose tissue in cot death results from continued metabolic activity in hypoxic tissue. The viral infective cause suggested by Grist and Urquhart seems more plausible, given the long known attractiveness of brown adipose tissue as a site of primary viral multiplication.

The oxygen uptake of maximally stimulated brown adipose tissue in 23°C acclimated mice is about 1.5 ml O₂/minute, equivalent to a heat production of 8–10 calories/minute/g tissue. If Hull’s figure of 30 g of brown adipose tissue in a neonate is accepted, then the heat output under maximal acute stimulation, but without any long term trophic stimulation, would be about 250 calories/minute. Thermogenesis of this order would increase the basal metabolic rate of a neonate by about 200%—more than sufficient to account for the observed metabolic response to cold temperature or noradrenaline infusion, and enough to raise core temperature by 5–6°C/hour. The lower thermogenesis of brown adipose tissue of adult rats, acclimated to a temperature of 33°C and stimulated by noradrenaline measured at 0.4 ml O₂/minute/g by Foster and Frydman, would still produce an almost 100% increase in the metabolism of an infant with 30 g brown adipose tissue. If this occurred inappropriately and suddenly in a well clothed and insulated infant, the core temperature might be raised to dangerous levels and induce apnoea. Our biochemical findings indicate that this might have occurred in our two cases of pyrexial cot death. This conclusion can be made, irrespective of a separate question, which cannot be answered at present: is brown adipose tissue equally active in infants who have died of other causes?

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Requests for reprints to: Dr M E J Lean, Diabetic Clinic, Woolmanhill Hospital, Aberdeen Royal Infirmary, Aberdeen AB9 1GS, Scotland.
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M E Lean and G Jennings

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