Imperfect Homeothermia in the Hereditary Obese-Hyperglycemic Syndrome of Mice

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The general traits of a Mendelian-recessive syndrome characterised by obesity, hyperglycemia (either spontaneous, or immediately elicited by growth hormone or high protein diets), atrophic changes and ulceration of the skin, hypertrophy of the islets of Langerhans and by other metabolic, nutritional, and endocrine disturbances, have already been described in two general reviews (1, 2). It has since been shown that the animals show hypercholesterolemia (3) and that the increased lipogenesis from acetate is particularly marked in young animals even under paired-fed and constant weight conditions (4). A probable etiology involving primary hypersecretion of pancreatic hyperglycemic factor with a secondary hypersecretion of insulin has also received experimental support (2, 5).

In a previous report on the effect of cold on this type of obese animals (6), it was shown that they are extremely sensitive to cold and die in a few hours when exposed to an environmental temperature which their non-obese siblings withstand indefinitely. It was demonstrated that the sensitivity to cold was only partially corrected by certain thermogenic agents and, if anything, enhanced by cortisone and ACTH. When the results were discussed, it was pointed out that this lack of resistance can represent a priori either a failure of the mechanism regulating heat loss or a failure of the mechanisms responsible for heat production. It was further pointed out that a number of facts argued in favor of ascribing the sensitivity to cold of these obese mice to a failure of additional thermogenesis rather than to a failure of the mechanisms regulating heat loss. Young obese mice with a near normal surface area already show a decreased resistance to cold. Non-obese mice which carry the 'fuzzy' gene and have a very light fur, display a much greater resistance to cold than the obese-hyperglycemic animals. Hypothalamic obese animals (1) and non-obese siblings made obese by goldthioglucose (1) show adequate resistance to cold, an observation that demonstrates both the specific association of sensitivity to cold in this syndrome and the fact that increased body surface without a corresponding increase in the number of hairs is not a major factor in the sensitivity (6). However, no precise records were obtained on pilo-erection, shivering, body temperature changes, or oxygen consumption, data which are indispensable before definite failure of chemical thermogenesis could be established as the basis for the sensitivity to cold.

The present report supplies this evidence. It establishes that the animals with the obese-hyperglycemic syndrome exhibit imperfect homeothermia and indicates that this is a result of inability to respond to the cold stimulus by increased thermogenesis even though the subjects show apparently normal pilo-erection and shivering with increased respiratory rate. On the other hand no difference to a high environmental temperature between obese and non-obese siblings could be ascertained.

METHODS

The animals of mixed sexes used in the experiments were obtained from the Jackson Memorial Laboratory at Bar Harbor, Maine. The obese animals had a mean weight of 40.65 ± 4.70 gm and their thin siblings of 20.44 ± 2.03 gm. All except those used for the survival experiments were fasted for at least 16 hours prior to
being used for the purposes of this study. A cold room at a mean temperature of 3°C was a necessary adjunct to the experiments. The survival experiments were carried out in the cold room at a temperature of 3°C and the animals were kept in cages containing one animal to a cage. They were fed and watered in the normal manner. Oxygen consumptions were determined by the Haldane open circuit gravimetric method. A detailed description of this method used with mice has appeared in a previous publication (7). Owing to difficulties imposed by the cold where condensation became a problem, only the carbon dioxide produced was measured and the oxygen consumption was obtained from this by assuming the respiratory quotient of the fasting animals to be .72. The reliability of this assumption was checked during the determinations of the thin siblings in the cold where the difference between the directly obtained oxygen consumption and the indirect method was less than 1%. Furthermore it has been previously shown that there is no difference between the R.Q. of fasting obese mice and the R.Q. of their fasting thin siblings (8). As long as fasting animals were used, there is no reason to believe that this condition would be altered in the cold. Colonic temperatures were measured by use of the thermocouple principle and pilo-erection was observed visually. Respiratory rates were determined by the use of a counter manually operated in accordance with the respiratory rhythm rather than by attempting to count each respiration. This method was checked and rechecked and comparable results were obtainable. An incubator at 40°C was used to determine body temperature differences between the non-obese and the obese hyperglycemic mice in a high environmental temperature.

RESULTS

Table 1 and figure 1 demonstrate that non-obese siblings of the obese-hyperglycemic mice can endure low environmental temperatures with adequate response to the cold stimulus, by increased oxygen consumption, increased respiration, maintenance of body temperature and survival. During these experiments, although pilo-erection occurred, shivering was not observed. These observations also hold true in the case of non-obese siblings made obese by goldthioglucose treatment. It can be seen in figure 1 that there appears to be a time lag between increase of respiratory rate and increase of oxygen consumption. By contrast, as indicated in table 1, mice with the hereditary obese-hyperglycemic syndrome do not survive on exposure to cold.

Figure 2 shows the typical responses when obese-hyperglycemic mice are exposed to a low environmental temperature as it affects the colonic temperature, the oxygen consumption and respiration. Also indicated are the responses of shivering and pilo-erection.

Shivering was usually accompanied by increased activity of the animals with frequent attempts to escape, a characteristic not usually exhibited by obese mice under normal conditions. No abnormal vasomotor responses could be detected by simple observation. On exposure to cold, the acute change in tailskin temperature was normal (immediate 10° drop). After 2½ hours of exposure this voluntary and purposeful activity diminished and the response to stimulation by simple disturbance was one of violent, coarse and uncontrollable shivering which after 3 hours subsided into a state of inertia and increasingly low respiratory rates.

<table>
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<tr>
<th>Table 1. Effect of Exposure to Cold on Duration of Survival in Hereditary Obese-Hyperglycemic Mice and Controls</th>
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<tbody>
<tr>
<td>No. of animals</td>
</tr>
<tr>
<td>Duration of survival</td>
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<td>Range</td>
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This was soon followed by Cheyne-Stokes respiration accompanied by collapse leading to slow, shallow and almost imperceptible respirations, and finally, with a colonic temperature of near 14°C, to death. If the animal is removed from the cold room while any life remains, even though the central body temperature is near 14°C and simple warming treatment is applied, it recovers with no apparent damage and may be used for further experimentation. It will be noted that although the respirations show a marked initial increase in rate, there is no significant concurrent rise in oxygen consumption. The over-all effect of exposure to cold on oxygen consumption is given in table 2. The mean temperature of the animal chamber for the non-obese mice was 10.29 ± 1.5°C and for the obese mice 9.71 ± 3.4°C. The lower equilibrium chamber temperature of the obese mice would seem to correlate with the inability of the obese mice to maintain their body temperature. The difference between the oxygen consumption of the non-obese and the obese mice in the cold is highly significant.

In the course of the oxygen consumption determinations of the obese mice in the cold,
considerable variations were seen and it was noted that the obese mice with low oxygen consumptions appeared to be particularly sensitive to cold, as was indicated by their sluggish behavior after removal from the animal chamber of the Haldane apparatus.

On exposure to 40°C for 80 minutes no significant difference in the colonic temperature changes of the non-obese and the obese mice was observed. Six animals were used in each group and the results are summarized in table 3.

**DISCUSSION**

These results seem to demonstrate that in the obese-hyperglycemic syndrome, extreme sensitivity to cold is directly related to the inability of these animals to raise their oxygen consumption for the requirements of thermogenesis. Obesity per se is eliminated as a cause of increased sensitivity by the observation of normal survival of goldthioglucose obese animals. Possible decreased pelage is eliminated by previously reported observations on the survival of thin animals with the ‘fuzzy’ gene. A direct effect of the decreased spontaneous activity of the obese-hyperglycemic mice (6, 9) is eliminated by the fact that in most of the experiments reported here the animals, whether thin or obese, were confined in an animal chamber too small to permit significant activity. Failure of pilo-erection and shivering was eliminated by clear cut observations of apparently normal reactions in the obese-hyperglycemic mice. It has been shown previously that primary abnormalities of thyroid function (6, 9, 10) and adrenal function (6, 8) were not present in this syndrome.

The response of respiratory rate of the obese mice to exposure to the cold stimulus was also normal. There was an immediate increase even though an increase in oxygen consumption did not follow as it did after a few minutes in the non-obese mice. It is, of course, a classic physiologic observation (11, 12) that an increase in respiratory rate is not of necessity

![FIG. 1 (left). Colonic temperature, respiratory rate and oxygen consumption of control mice exposed to cold.](image1)

![FIG. 2 (right). Colonic temperature, respiratory rate and oxygen consumption of obese hyperglycemic mice exposed to cold.](image2)
correlated with an increase in carbon dioxide production or oxygen consumption. Pflüger (13) observed that "metabolism regulates respiration but respiration stimulated by external means does not regulate metabolism." It is therefore established that the failure of the obese mice to resist cold is not due to a failure of any of the physical responses (piloerection, shivering, exercise, increased respiratory rate and presumably vasomotor reactions).

On the other hand the universal finding of steadily decreasing metabolic rate on continued exposure to cold (as indicated by decreased oxygen intake and a falling respiratory rate after an initial rise) provides sufficient immediate explanation for the lack of resistance to cold: hypothermia occurs as a result of the failure of increased thermogenesis. In turn, it probably decreases the rate of oxidation; hence, there occurs further reduced thermogenesis and decreased body temperature, etc., until death finally supervenes. It has been demonstrated that, even under conditions of strict paired feeding, the obese-hyperglycemic syndrome is characterised by a shift toward lipogenesis and in the case of these animals a much higher proportion of administered doses of radioactive acetate is retained as fat.

Conversely, it appears that when, as in exposure to cold, the animal has suddenly to increase its oxidation of fat, it is completely unable to do so, a fact which emphasizes the relative character of any criterion for the existence or absence of 'lipophilia' (6, 14). From the point of view of the general mechanism of resistance to cold, these observations constitute significant evidence as to the primary necessity of a proper capacity for increased fat oxidation in fasted animals. In effect such animals are reacting normally to cold in all but one respect. The obese animals respond to the cold stimulus by piloerection and increased respiration which later fails. Shivering is not only present but, as thermogenesis fails, is striking in intensity. However, all these homeostatic changes do not coincide with increased metabolism as indicated by oxygen consumption. For all intents and purposes the animals are simply unable to draw upon their fuel reserves.

The observation of survival by heat treatment of animals, the central temperature of which had decreased to about 10°C, is of interest. Mice with the hereditary obese-hyperglycemic syndrome are imperfect homeotherms as they cannot maintain their body temperature in a cold environment endured easily by their non-obese siblings. They are also imperfect poikilotherms because they die in the cold.

It may be pertinent to recall the experiments of Chevillard, Hamon, and A. Mayer (15) demonstrating that decreasing the oxygen tension rendered normal mice unable to maintain their body temperature in the cold. As the oxygen tension was reduced, polypnea was the early response, followed by a gradually falling respiratory rate to Cheyne-Stokes respiration and finally death. If suitable precautions were observed, partial oxygen pressure could be reduced to below 7% and the mice could be maintained in an atmosphere of 3.5% oxygen. Under these conditions a semipoikilo-thermal state prevailed with a low central temperature strongly influenced by fluctuations of environmental temperature. Whether this failure is the converse situation (i.e., normal mobilization of fuel but unavailability

![Table 2](image-url)

<table>
<thead>
<tr>
<th>Duration of Exposure, min</th>
<th>Colonic Temp., °C</th>
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<tbody>
<tr>
<td></td>
<td>Non-obese</td>
</tr>
<tr>
<td>0</td>
<td>37.66</td>
</tr>
<tr>
<td>30</td>
<td>38.01</td>
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<tr>
<td>60</td>
<td>38.19</td>
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<td>80</td>
<td>39.33</td>
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* Gas volume recalculated for standard conditions of temperature and pressure. † ± Values represent S.D.
of oxygen) or is due to the breakdown of an altogether different mechanism is a matter for further investigation.

**SUMMARY**

The obese-hyperglycemic syndrome had been previously reported to be associated with extreme sensitivity to cold leading to death on exposure to temperatures normally endured by the non-obese siblings. Thyroid and cortical failure were ruled out. A systematic attempt to elucidate the cause of this failure has been presented.

Non-obese siblings made obese by gold-thioglucose treatment are resistant to cold. This, with previous observations on 'fuzzy' animals eliminates obesity per se and decreased thickness of pelage as causative factors. Shivering and pilo-erection do take place in the obese animals, eliminating another possible cause for failure of thermogenesis. Decreased spontaneous exercise was likewise eliminated by comparing obese and non-obese animals kept in small chambers where movement was impossible. Resistance to high environmental temperatures appears normal in obese animals. The mice with the hereditary obese-hyperglycemic syndrome are unable to raise their metabolic rate in the cold: oxygen consumption normally doubled in thin animals under the experimental conditions described here is not increased in the obese animals; this leads to a drop in body temperature, decreased respiratory rate and Cheyne-Stokes respiration, and eventually death. The obese mice recovered from exposure to cold as long as their central temperature had not dropped below 14–16°C. A discussion of this failure to resist cold in terms of the known metabolic abnormality in these obese animals is presented.

**REFERENCES**