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THE RELATIONSHIP BETWEEN ENERGY EXPENDITURE AND ENVIRONMENTAL TEMPERATURE IN CONGENITALLY OBESE AND NON-OBESE ZUCKER RATS

BY G. ARMITAGE, RUTH B. S. HARRIS*, G. R. HERVEY AND G. TOBIN
From the Department of Physiology, The University, Leeds LS2 9JT

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SUMMARY

1. The energy expenditure of normal and congenitally obese adult female Zucker rats has been measured by continuous indirect calorimetry for periods of 3–10 days at ambient temperatures varied from 30 to 5 °C. Rectal temperatures were also recorded.

2. Exposure to cold caused no ill-effects in normal or obese rats.

3. The rectal temperatures of obese rats were about 1 °C lower than those of normal rats. The rectal temperatures of normal rats did not change measurably with ambient temperature; in obese rats rectal temperature rose slightly as ambient temperature fell.

4. In normal and obese rats, energy expenditure showed a smooth, steeply sloping, negative relationship to ambient temperature. Energy expenditure per rat was higher in obese than in normal rats at all temperatures. The two slightly curvilinear regressions were nearly 'parallel', with a separation of about 40 kJ/day per rat at the mid-point.

5. This study therefore does not confirm suggestions that obese Zucker rats suffer from a defect in the level of energy expenditure, or in their capacity to increase it when exposed to cold.

6. It is suggested that in both normal and obese rats the level of energy expenditure was determined by thermoregulatory control. The greater heat production of obese rats may have been a response to their lower core temperature.

7. A steady state in which greater heat production is associated with lower core temperature implies lower insulation between body core and surface. This could be due to greater blood flow.

INTRODUCTION

It has been reported that mice of the *ob/ob* congenitally obese strain are more sensitive to cold than the non-obese phenotype and that this is due to inadequate increase in heat production in the cold (Davis & Mayer, 1954; Trayhurn & James, 1978). James & Trayhurn (1976) and Thurlby & Trayhurn (1979) suggested that reduced capacity to increase metabolism also causes the obesity. Rothwell & Stock

* Present address: Department of Foods and Nutrition, College of Home Economics, The University of Georgia, Dawson Hall, GA 30602, U.S.A.

(1979), Thurlby & Trayhurn (1980) and James & Trayhurn (1981) suggested that the defective component of metabolism is that contributed by brown adipose tissue.

Trayhurn, Thurlby & James (1976) and later, in a more detailed paper, Levin, Triscari & Sullivan (1980) reported that rats of the congenitally obese *fa/fa* Zucker strain also respond inadequately to cold. Trayhurn *et al.* (1976), James & Trayhurn (1976) and Trayhurn, Thurlby, Woodward & James (1979) speculated that low energy expenditure may be characteristic of congenitally obese rodents in general, and the cause of both susceptibility to cold and obesity. Wickler, Horwitz & Stern (1982) argued that measurements of blood flow with radioactively labelled microspheres demonstrated low energy expenditure in brown fat in obese Zucker rats. Reports that obese Zucker rats have lower rectal temperatures than normal controls (York, Hersham, Utiger & Bray, 1972; Godbole, York & Bloxham, 1978) and that when pair-fed with normal rats they store a larger proportion of the energy supplied (Pullar & Webster, 1974) could also be consistent with obese rats having a lower metabolic rate.

Only measurements of energy expenditure can test reliably the proposition that heat production is defective in obese Zucker rats. Few measurements have been reported; these have been short sample measurements, and the conclusions depend considerably upon the basis of comparison. Bray (1969) and Kaplan (1981) both reported that oxygen consumption, measured at normal room temperature for replicated 3–5 min periods and expressed per gram body weight, was lower in young obese Zucker rats than in non-obese controls. Bray pointed out that this was not the case if the values were 'corrected for surface area'. A lower value per unit body weight could arise simply because obese bodies contain more fat, which consumes less oxygen per unit weight than lean tissue. Since our experiments were completed Bertin, Razanamaniraka, De Marco & Portei (1983) have reported that young obese and non-obese Zucker rats showed similar increases in oxygen consumption, measured over 10 h periods and expressed on a 'surface area' basis, when the rats were acclimated for a month to 10 °C.

We report continuous measurements of the oxygen consumption of groups of obese and non-obese Zucker rats maintained for 4–11 days at each of a range of environmental temperatures from 5 to 30 °C. A preliminary communication has been made (Armitage, Harris, Hervey & Tobin, 1981).

METHODS

Animals

Twelve obese and twelve non-obese female rats were obtained from a single breeding batch of a colony of Zucker rats maintained in this Department, originally derived from stock supplied by Queen Elizabeth College, London. The rats had been weaned when 21 days old. They were 4 months old at the start of the experiment and 6 months at the end.

Environment

The rats were kept in a room with accurate control of temperature and humidity. Room temperature was 22 °C until they were 90 days old. Thereafter it was 24 °C, until the sequence of changes described below was begun. Relative humidity was approximately 55 % throughout. The temperature and humidity of the air leaving the calorimeter cages were measured by wet and dry thermistors in the air extraction tube. Lighting was on from 08.00 to 20.00 h. The rats had continuous free access to water and food (Oxoid Breeders' diet, H. C. Styles Ltd., Bewdley, Worcs.).

Body temperature

Body temperature was measured daily between 09.00 and 10.00 h by a rectal thermistor (Yellow Springs Instruments, Yellow Springs, U.S.A.), calibrated regularly against a high-quality mercury thermometer reading to 0·005 °C (Gallenkamp, London, Type THP 070C). Readings were taken 30 s after insertion of the probe. The temperatures of individual rats were measured in a standard order. Our previous experience has shown that recorded rectal temperature varies with the position of an individual rat in the sequence of measurements; this seems to be due to increased activity in all rats in the room from the time when measurements are started. In an animal the size of the rat a modest level of activity can cause short-term rises in temperature at rates such as 0·1 °C/min.

Energy expenditure

Energy expenditure was measured as oxygen consumption, using the five-channel continuous-running calorimeter described by Armitage, Hervey, Rolls, Rowe & Tobin (1983). Each cage, containing three rats, was connected in turn to the analysis line for 10 min in each hour. Measurements were interrupted from 09.00 to 10.00 h daily.

Experimental plan

The rats' body weights were measured twice weekly from 90 to 130 days of age. The rats were then allocated to groups of three, matched for body weight and rate of weight gain by the method of Armitage *et al.* (1983), put into the calorimeter cages, and recording of oxygen consumption begun. Thereafter body weights, rectal temperatures and the weight of food taken from the hopper were measured daily. Scattered food and excreta were collected and metabolizable energy intake calculated by the methods of Armitage *et al.* (1983).

Ten days were allowed for the rats to settle in the new groups and cages. At this time the rats were 140 days old. Measurements at the initial room temperature were then started, and continued for 7 days. The first of a series of changes of room temperature was then made, 1 day was allowed for energy expenditure to stabilize, and measurements made at the new temperature for 3–10 days. The sequence of room temperatures was: 24, 26, 29, 24, 18, 14, 20, 10, 6, 8 and 4 °C. Temperatures in the cages were a little above room temperature, by 0·5–1 °C in cages containing non-obese rats, and by 1–1·5 °C in cages of obese rats.

In view of the obese rats' expected sensitivity to cold the Home Office initially required that room temperature be lowered in steps. Rectal temperature was measured at half and then one hour intervals after each downward change, for several hours. Since in the event the obese rats maintained their body temperatures, groups of non-obese and obese rats were later exposed to a change from 26 to 5 °C.

RESULTS

Tolerance of cold

Over the range of temperatures studied obese rats appeared to tolerate exposure to a cold environment as well as non-obese rats. Neither showed visible evidence of harmful effects. Obese rats were always less active than non-obese, and they remained so when the room temperature had been reduced. Their ventilation rate, however, could be seen to be increased.

Non-obese rats showed an almost constant body weight throughout the experiment while room temperature was changed in steps from 29 to 4 °C. The obese rats were initially gaining weight; when the temperature was reduced below 20 °C they ceased to do so; and when it was reduced to 10 °C they began to lose weight. By the end of the experiment, however, their weight curves were flattening out. The loss of weight was then about 50 g compared with their weight at 20 or 10 °C.

Energy intake

As Fig. 1 shows, the non-obese rats' metabolizable energy intake showed an inverse relationship to environmental temperature, varying from about 265 kJ/day per rat

at 5 °C to about 160 kJ/day per rat at 29 °C. The obese rats' metabolizable energy intake appeared to be uninfluenced by environmental temperature, and was about 265 kJ/day per rat at all temperatures.

Rectal temperature and change in environmental temperature

When environmental temperature was abruptly lowered the rectal temperatures of both non-obese and obese rats typically rose by about 1 °C over the first 1–2 h after the change; they then fell over the next 2–3 h, to remain steady from *ca.* 5 h onwards. Fig. 2 illustrates this for the extreme case of the later experiment in which room temperature was changed from 26 to 5 °C.

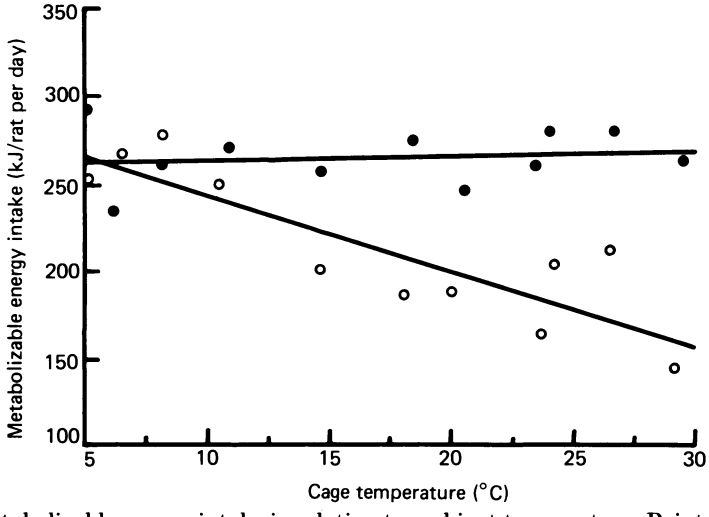

Fig. 1. Metabolizable energy intake in relation to ambient temperature. Points are means of daily intakes for two cages (each holding three rats) over 3–10 days at each temperature (beginning 1 day after changing temperature): ○, non-obese; ●, obese rats. Lines are first-order regressions (fitted to the means). Coefficients of correlation: non-obese, $r = 0{\cdot}195$; obese, $r = 0{\cdot}856$.

Steady-state rectal temperature

In Fig. 3 the means of the morning readings of rectal temperature, each for six rats and for 3–10 days, starting one day after a change of environmental temperature, have been regressed against the ambient temperature in the cages. Within measurable limits the mean body temperature of non-obese rats was unaffected by environmental temperature. Their mean rectal temperature at 22 °C, read from the regression, was 38·9 °C (S.E. of mean, ±0·1 °C); the slope of the regression was zero, with 95% confidence limits −0·01 to +0·01 °C/°C. In obese rats the mean rectal temperature at 22 °C was 37·7 °C. The difference between non-obese and obese rats was highly significant. In the obese rats the coefficient of regression of rectal temperature on cage temperature was −0·02 °C/°C, significant at the $P < 0{\cdot}005$ level, and with 95% confidence limits −0·03 to −0·01 °C/°C. Thus, while the rectal temperatures of obese rats were always of the order of 1 °C lower than those of non-obese rats, they actually became slightly but significantly higher as ambient temperature was lowered.

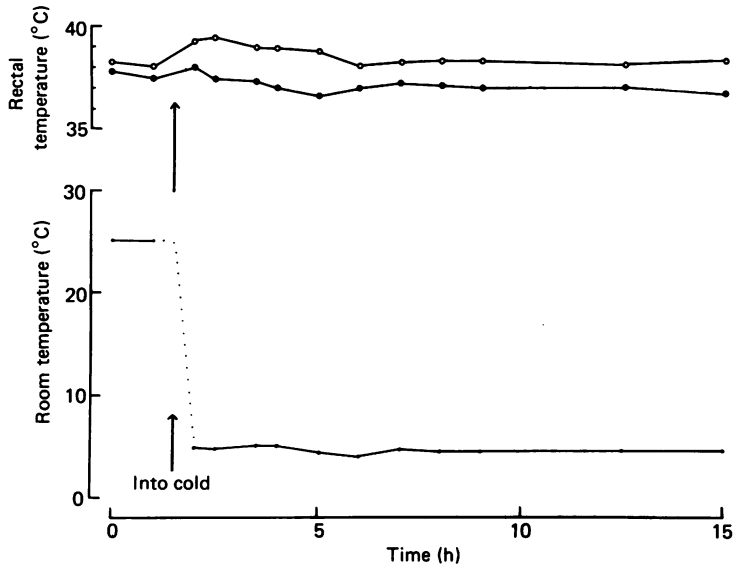

Fig. 2. Course of rectal temperature when rats were moved from a room at 29 °C to one at 5 °C. Points are means of three rats: ○, non-obese; ●, obese. Readings initially taken at approximately half-hour intervals. Lower graph: room temperature.

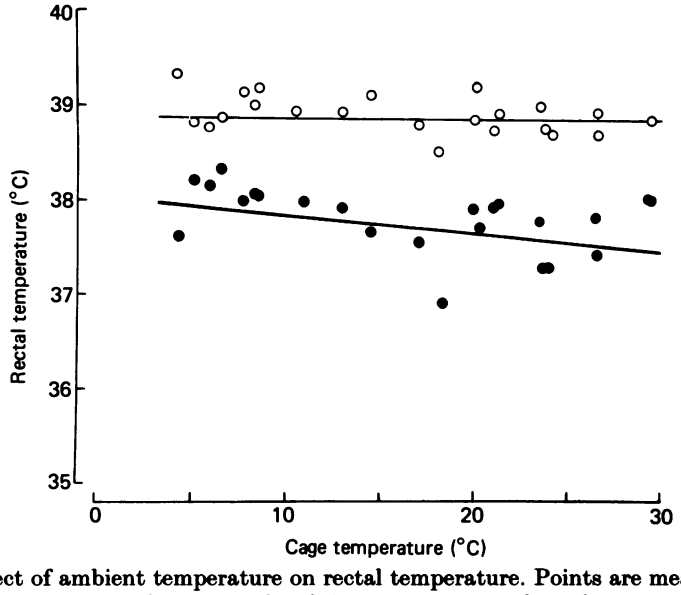

Fig. 3. Effect of ambient temperature on rectal temperature. Points are means of rectal temperatures, taken at about 09.00 h, of six rats over 3–10 days (beginning 1 day after changing room temperature). ○, non-obese; ●, obese rats. Lines are first-order regressions (for the individual data). Coefficients of correlation: non-obese, $r = 0{\cdot}071$; obese, $r = 0{\cdot}356$.

Energy expenditure

Fig. 4 shows the hourly pattern of energy expenditure over the 24 h at 29 and 5 °C. The initially raised level of expenditure, seen in both phenotypes but more conspicuous at 29 °C than at 5 °C, probably reflects the effect of opening the cages between 09.00 and 10.00 h and carrying out daily routines. The arousing effect evidently lasted for 3 h. At 29 °C both phenotypes showed a light/dark cycle with expenditure lower in the hours of daylight than during the dark hours, but the cycle was less marked in obese rats. At 5 °C the light/dark cycle was much less evident in both phenotypes.

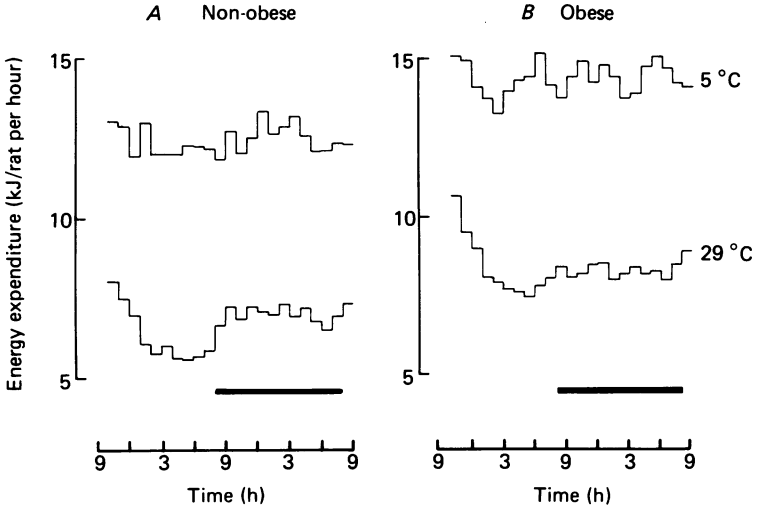

Fig. 4. Hourly patterns of energy expenditure during the day. Each hourly value is the mean of two cages (each holding three rats) over 5 days. The horizontal bars show hours of darkness. From about 09.00 to 10.00 h the calorimeter was not running and daily procedures such as weighing the rats, measuring rectal temperatures, replenishing food etc. were carried out.

Fig. 5*A* shows the relationships between ambient temperature and energy expenditure in normal and obese rats. Each point plots the mean daily energy expenditure in the two cages, each containing three rats, over the period of maintenance at each ambient temperature, excluding the first day, against the mean temperature in the cage. The bars show the standard errors of these means, i.e. of the set of daily measurements for each temperature considered. Fig. 5*B* shows, superimposed on the same means, the best fitting second-order regressions. The regressions were calculated from the individual data; the bars show the standard errors of the regressions at their mean values.

Normal and obese rats both showed similar, steeply sloping, slightly curved, negative relationships between ambient temperature and daily energy expenditure. The mean daily energy expenditures of obese rats were approximately 40 kJ/day per rat higher than those of non-obese rats at temperatures in the middle of the range.

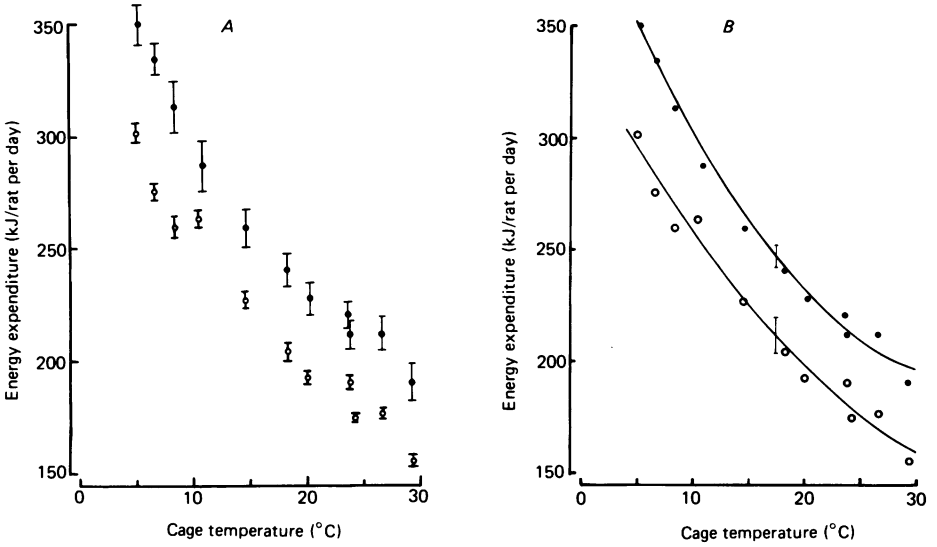

Fig. 5. Effect of ambient temperature upon energy expenditure. *A*, means, with their standard errors, of energy expenditures over 24 h (extrapolated from measurements over 23 h), each for two cages (each holding three rats) and 3–10 days (beginning 1 day after changing room temperature) at each temperature. ○, non-obese; ●, obese rats. *B*, second-order regressions fitted to these means. Vertical bars are standard errors for prediction of Y from X at the mean values. Coefficients of correlation: non-obese, $r = 0{\cdot}997$; obese, $r = 0{\cdot}989$.

DISCUSSION

Our results do not confirm suggestions in the literature that obese Zucker rats are in general less tolerant of low ambient temperatures than normal rats, have lower metabolic rates, or suffer from deficient ability to increase heat production in the cold. The smaller diurnal cycle in energy expenditure, seen in obese rats at all environmental temperatures and in non-obese rats at low environmental temperature, could be a secondary consequence of feeding having extended into the daytime (Becker & Grinker, 1977). The energy intake of obese rats did not rise as environmental temperature fell as it did in non-obese rats; this will be considered further in another paper.

Trayhurn *et al.* (1976) stated that obese Zucker rats became hypothermic in a room at 4 °C and died after 28 h with body temperatures of 12 °C. Levin *et al.* (1980) reported that, of eight obese rats previously kept at 22 °C and abruptly exposed to 2 °C, five had died from hypothermia within 24 h, and the body temperatures of the remaining three were falling (interestingly, the graphs in this paper show an initial rise in rectal temperature similar to that shown in our Fig. 2). On the other hand York *et al.* (1972) found that when obese Zucker rats were moved from 18 to 3 °C they showed a fall in rectal temperature by only about 1 °C followed by return to normal. Godbole *et al.* (1978) separated Zucker rats aged 16–35 days from the mothers for 15 min and found the rectal temperatures, which they considered stable, to be

1–2 °C lower in rats which became obese than in those which did not, but none fell below 34 °C. Bray & York (1972), Bertin *et al.* (1983), Triandafillou & Himms-Hagen (1983) and Holt & York (1983), like ourselves, appear to have experienced no difficulties due to hypothermia in exposing obese Zucker rats to cold.

The reason why the obese rats should display undue sensitivity to cold only in some experimenters' hands is not clear: possible factors are previous environment, acuteness and severity of exposure to cold, sex and age at exposure. Age, suggested by Triandafillou & Himms-Hagen (1983) seems an unlikely cause since those studies not reporting undue sensitivity include young and adult rats. Genetic differences seem unlikely within a supposedly homogeneous strain of rat. Since obese Zucker rats exposed to cold apparently cannot respond by increasing their energy intake (Harris, 1982), they must depend on mobilizing energy from body stores; they may suffer from limitations to their ability to do this (Bray, York & Swerdloff, 1972), and possibly the effect of these varies. In any case obesity seems to occur uniformly, irrespective of sensitivity to cold. It therefore seems unlikely that the factors responsible for undue susceptibility to cold play any part in causing obesity.

The steady-state rectal temperature of our adult obese rats was about 1 °C below that of non-obese rats. Godbole *et al.* (1978) reported that this was the case in *fa/fa* rats from 16 days of age, and claimed it was diagnostic of the obesity syndrome. The implications for the thermoregulatory state of obese Zucker rats will be discussed below.

Discussion of levels of energy expenditure in rodents is meaningless unless environmental temperature is taken into account. Although Herrington (1940) made comprehensive measurements and described the relationship between environmental temperature and energy expenditure clearly, many later authors have failed to appreciate that, in animals such as the rat, energy expenditure varies steeply and continuously with environmental temperature over the whole range of temperatures the animals can tolerate, and provides the principal effector of thermoregulation. There is no thermoneutral temperature such as exists for man, at which a 'basal' metabolic rate can be defined and below which regulation by increasing heat production begins. There is only an upper critical temperature, above which the animals become pyrexic and metabolic rate consequently rises.

Full data such as those of Fig. 5 are therefore necessary to make useful comparisons between metabolic rates. The data from the present experiment establish clearly that the obese rats had a higher energy expenditure than non-obese controls. This was so at all environmental temperatures, and the difference was largely independent of environmental temperature. At mid-range it was almost exactly 40 kJ/day per rat. These findings are clearly at variance with the proposition that obese Zucker rats suffer from defective heat production.

In accounting for the difference in energy expenditure, two obvious factors are the greater body size of obese rats, and the energy costs of dealing with a larger intake of food. Applying a factor such as weight$^{0.75}$ to predict the effect of body size, though frequently done, assumes a relationship for which there is actually little evidence within single species, and in this instance would overlook a gross difference in body composition. Analyses we have made of non-obese and obese female rats of similar weight to the initial weight of those used in the present experiment show that the

obese rats contained about 30 g more lean tissue and 200 g more fat than non-obese rats. Metabolism in the extra lean tissue might account for 20 kJ/day per rat. Fat has a relatively low metabolism but imposes a weight penalty: Armitage *et al.* (1983) concluded that this was about 0·1 kJ/day per gram additional body weight, which would predict an extra cost for obese Zucker rats also of the order of 20 kJ/day per rat. In this experiment the obese rats had lost about 50 g by the end of the experiment, which would reduce these differences somewhat. At the highest environmental temperature energy costs arising from food intake and weight gain (i.e. the costs of digestion and absorption and of fat synthesis) might amount to 20–30 kJ/day per rat above the energy expenditure of the non-obese rats (Armitage *et al.* 1983). This would not apply at low environmental temperatures, since food intake was then no greater and weight was being lost.

Although energy costs in these categories appear to be roughly of the right order to account for the greater energy expenditure observed in the obese rats, the smooth relationship between environmental temperature and energy expenditure in both non-obese and obese rats and the constancy of the difference between them suggest that in both the level of energy expenditure may have been determined in relation to environmental temperature. That is to say, energy expenditure was being controlled (by mechanisms at present unknown in detail) as an effector of thermoregulation. On this view expenditure would be expected to be adjusted to achieve an appropriate total heat production, irrespective of variations in components within it such as energy costs of feeding and synthesis (Mount, 1979).

Since environmental temperature was fixed, the lower core temperature and greater heat loss of the obese rats imply that the thermal insulation between body core and the outside world must have been less in them than in non-obese rats. This is surprising, for they are obviously fatter, and subcutaneous fat in general confers insulation (Pugh & Edholm, 1955; Keatinge, 1960; Quaade, 1963; Golden, 1979). The insulation provided by subcutaneous fat, however, can only be effective if the fat is not bypassed by convective transfer of heat by the circulation. There is evidence from the cold-survival field, for man and the pig, that variation in peripheral blood flow is an important cause of differences in insulation (Golden, 1979).

In a negative feed-back control system, a change in the level of the controlled quantity leads to activity by effector mechanisms that oppose the change: on a cold day the fall in temperature of a thermostatically controlled water bath calls for more heat input; a new steady state is then reached in which the temperature of the bath remains lower and the heat input greater than before. If non-obese and obese Zucker rats have similar thermoregulatory systems, and bearing in mind that in rats heat production is the principal effector of thermoregulation, one possible explanation for the lower body temperature and greater heat production of the obese rats is a relationship of this kind. This would interpret the lower body temperature of the obese rats as a 'load error' of thermoregulation.

It must be admitted that in this experiment 'load error' was not seen within either group of rats, since body temperature did not fall when ambient temperature was lowered. Benzinger (1969) suggests that in human thermoregulation the temperature gradient between body core and surface is a major input (Fig. 9 of his review). This could possibly explain how within either group of rats lower environmental

temperature led to increased heat production without rectal temperature falling. The lower insulation of obese rats would be expected to lead to higher surface temperature, and the consequently diminished peripheral input to thermoregulatory centres could result in a situation in which core temperature would have to fall to produce sufficient drive to maintain heat balance. If some vasoconstriction occurred as environmental temperature fell, this could account for the rise in core temperature with falling environmental temperature.

It is thus possible to construct an argument, admittedly theoretical, based on the properties of control systems, which can account for the findings as to body temperature and energy expenditure in obese Zucker rats. This hinges on the unexpected prediction that the thermoregulatory abnormality of the obese Zucker rat arises from abnormally low thermal insulation, which could be caused by increased blood flow from body core to surface. The brief abstract of Klinis-Tavantzis, Mendez, Kollias & Martin (1978) contains a hint that blood flow to the skin may be greater in obese than in non-obese Zucker rats. It will be of great interest to see whether further work confirms this.

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