The Functional Significance of Individual Variation in Basal Metabolic Rate

John R. Speakman[1,2,*]
Elżbieta Król[1]
Maria S. Johnson[1]
[1]Aberdeen Centre for Energy Regulation and Obesity (ACERO), School of Biological Sciences, University of Aberdeen, Aberdeen AB24 2TZ, Scotland, United Kingdom; [2]ACERO, Division of Energy Balance and Obesity, Rowett Research Institute, Bucksburn, Aberdeen AB21 9SB, Scotland, United Kingdom

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ABSTRACT

Basal metabolic rate (BMR) was established as a common reference point allowing comparable measures across different individuals and species. BMR is often regarded as a minimal rate of metabolism compatible with basic processes necessary to sustain life. One confusing aspect, however, is that BMR is highly variable, both within and between species. A potential explanation for this variability is that while individuals with high BMRs may suffer the disadvantage of having to feed for longer to cover the extra energy demands, this may be offset by advantages that accrue because of the high metabolic rate. One suggested advantage is that high levels of BMR are a consequence of maintaining a morphology that permits high rates of the maximal sustained rate of metabolism (SusMR)—the rate of metabolism that can be sustained for days or weeks. We have been studying the energetics of MF1 laboratory mice during peak lactation to investigate this idea. In this article, we review some of our work in connection with three particular predictions that derive from the hypothesised links among morphology, basal metabolism, and sustained metabolic rate. By comparing groups of individuals, for example, lactating and nonlactating individuals, the patterns that emerge are broadly consistent with the hypothesis that BMR and SusMR are linked by morphology. Lactating mice have bigger organs connected with energy acquisition and utilisation, greater resting metabolic rates in the thermoneutral zone, called RMRt (approximately equivalent to BMR), and high sustainable rates of maximal energy intake. However, when attempts are made to establish these relationships across individuals within lactating mice, the associations that are anticipated are either absent or very weak and depend on shared variation due to body mass. At this level there is very little support for the suggestion that variation in RMRt (and thus BMR) is sustained by associations with SusMR.

* Corresponding author; e-mail: j.speakman@abdn.ac.uk.

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Introduction

Background

The idea that animals might interact with the environment in a manner reminiscent of fire had been established in the 1600s by the pioneering experiments of John Mayrow. However, it was only after the discovery of oxygen by Priestly in the early 1700s that our understanding of metabolism started to include the notion that, for as long as they are alive, most animals (and humans) continuously take up oxygen and expire carbon dioxide. The first systematic measures of the rates of oxygen consumption were made by Lavoisier and Seguin in the 1780s (Mendelsohn 1964; McNab 1992), and almost immediately it was apparent that rates of oxygen uptake are extremely variable. Lavoisier documented that the posture of his subjects had an effect on oxygen uptake, that larger individuals consumed more than smaller individuals, and also that after a meal the rate appeared greater than if the subject had been fasted. Throughout the 1800s, knowledge of the factors influencing rates of oxygen consumption continued to expand. It was not until the early 1900s, however, principally due to the efforts of Harris and Benedict (1919), that the desire to summarise the broad accumulation of literature concerning metabolic rates led to the notion that some form of standardisation of the protocols for collecting metabolic measurements would be desirable. Clearly, standardisation is best achieved by removing the variance that is associated with any particular factor. Hence, if food intake before a measurement elicited an increase in metabolic rate, it would be best to measure only fasted individuals rather than prescribe a fixed level of food intake, which could be functionally different for different individuals. Consequently, the notion of a basal metabolic rate (BMR) was conceived, which concerned the level of metabolic processes that were assumed to be the minimal rate necessary for sustaining basic physiological processes in an alert (nonsleeping) human or animal subject. The conditions of measurement required that the

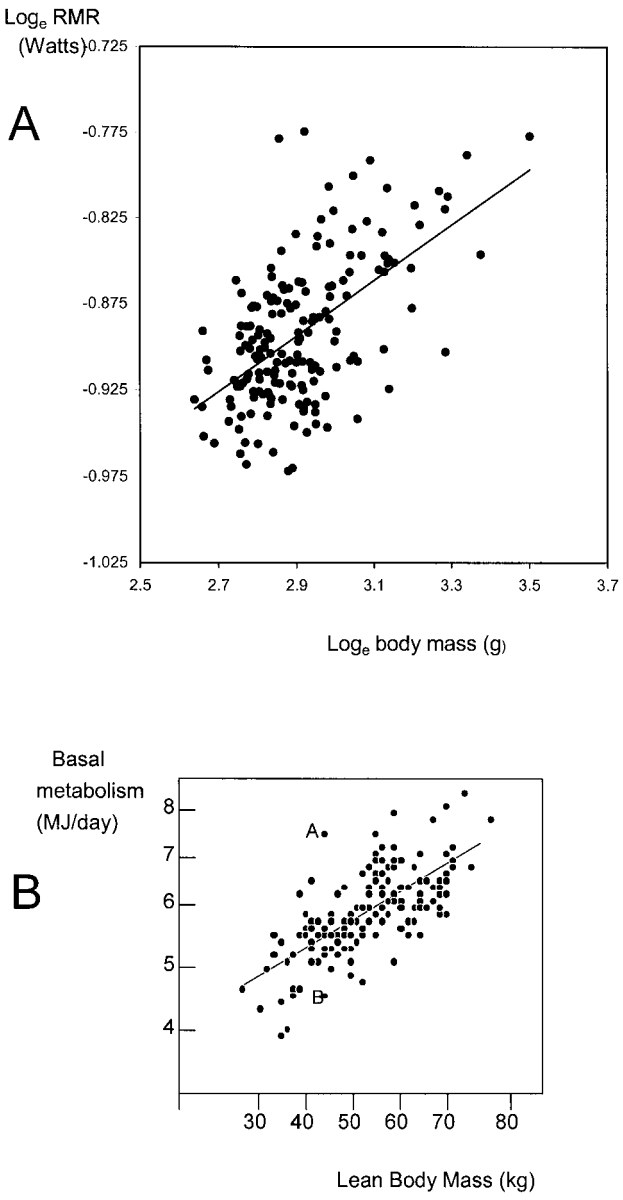

Figure 1. *A*, Resting metabolic rate in thermoneutrality plotted against body mass for 119 wild-caught field voles (*Microtus agrestis*); data from Jackson et al. (2001). *B*, Basal metabolic rate plotted against lean body mass for human subjects; data from Weyer et al. (2000). Exceptional individuals referred to in the body of the main text are denoted A and B.

subject be postabsorptive in a quiescent state (but awake), thermoregulating normally within the thermoneutral zone, and neither growing nor reproducing. Large numbers of measures of BMR accumulated over the next 30–40 yr, primarily due to the activities of several key researchers, among whom Brody (1945) and Kleiber (1961) were prominent. This period culminated in Kleiber's (1961) classic book *The Fire of Life: An Introduction to Animal Energetics* in which much of the preceding years of study are summarised, along with some discussion and analysis of interspecific variability in the basal rates of metabolism. From this analysis stemmed the familiar notion that interspecific rates of BMR scale with an exponent midway between the expectation from the surface law (0.66) and the volumetric scaling (1.0), commonly approximated to 0.75.

Most of the data summarised by Kleiber (1961) concerned domesticated animals and man. However, measurements of nondomestic species had already started to accumulate. Summaries of these latter data highlighted that between species, there was extreme variability in the trait of BMR, even among animals of the same body mass (Hemmingsen 1960; Dawson and Hulbert 1970; McNab 1980, 2002; Henneman 1983; Hayssen 1984; Hayssen and Lacy 1985; Ricklefs et al. 1996; Lovegrove 2000). This variability was unanticipated, because the standardisation of the conditions for measurement of BMR had been expected to reduce the measurement to some fundamental low level that might be anticipated to scale with mass but otherwise would be indicative of an essential basal level of subsistence processes. The fact that some species seemed capable of existing with basal rates substantially lower than in other species of the same body mass without any apparent disadvantage was perplexing. Considerable debate has ensued ever since about the nature of this interspecific variation (e.g., McNab 1980, 1983, 1986, 1987*a*, 1987*b*, 1988, 2002; Hayssen 1984; Padley 1985; Thompson and Nicoll 1986; Koteja 1987, 1991; Bennett and Harvey 1987; Trevelyan et al. 1990; Harvey et al. 1991; Haim and Izhaki 1993; Lovegrove 2000).

Individual Variability in BMR

Studies that have concerned interspecific variation in BMR have tended to perform analyses using a single datum for each species, as if BMR were fixed at an invariable rate for each species (see references above). However, closer investigation reveals that not only is BMR highly variable between species, it is also extremely variable between individuals of the same species (Fig. 1*A*). In this example we have plotted the resting metabolic rate (RMR) measured in thermoneutrality for animals that have not been previously starved against body mass. This is a slightly less rigorously defined measurement than BMR, but it is justified for small rodents because the requirement to starve individuals to get a true BMR generally elicits first a period of hyperactivity, which is incompatible with the requirement that the animals be quiescent, followed by a period where the animal drops its body temperature slightly to conserve energy, which is incompatible with the requirement that the animals be thermoregulating normally. I will call this measure RMRt to distinguish it from BMR and to indicate the RMR measure is made within thermoneutrality. Another useful aspect of RMRt is that it is functionally equivalent to BMR in reproducing animals that by definition cannot have their BMR measured.

We have made several studies of the repeatability of this trait (e.g., Król et al. 2003) in laboratory mice (*Mus musculus*, outbred MF1), and we find that in our laboratory RMRt is a repeatable measure with an error variance (coefficient of variation in repeated measurements) of about 8%.

Knowing the error connected with individual measures of RMRt is important because if the variance was extremely high, the individual variability detected in plots of BMR (or RMRt) against body mass (Fig. 1) could be entirely a consequence of this error variance. The fact that measurement error contributes only a small fraction to the total variance means that individual variability in BMR, and RMRt, is a real biological phenomenon worthy of attention. A potential source of variation in RMRt is individual differences in body composition. This is because lean body mass (LBM) has a higher metabolic rate than fat body mass (Field et al. 1939; Krebs 1950). Hence two individuals might have the same body mass, but if one consisted mostly of fat, while the other was mostly lean tissue, their BMRs (RMRts) would be expected to differ, reflecting this composition difference.

Many studies have been made of the BMRs of human subjects where not only is the measurement made under rigorous conditions but also the subjects can be instructed to be compliant with the measurement protocols (something small rodents are generally incapable of being instructed to do). These differences make the error variance lower, at about 3%. Moreover, the subjects can have their lean body mass measured using noninvasive techniques. A typical example is shown in Figure 1*B* (after Weyer et al. 2000). What is striking (but not exceptional) about these data is that in spite of the reduced error variance, and removing the effect of body composition by plotting metabolism as a function only of LBM, the individual variation in BMR is still tremendous. In fact, this study and most other studies of human BMR generate coefficients of variance in the individual residuals of about 7%–8%. In practice, this means that, even taking the effect of body composition into account, the individuals with the top 5% of residual BMRs are metabolising energy about 28%–32% faster than individuals with the lowest 5% residual BMR. Simple inspection of Figure 1*B* reveals the truth of these calculations. At a lean body mass of 43 kg, where the range of BMRs is greatest, there are two individuals with identical LBMs, yet one expended 7.5 MJ d^{-1} on BMR (marked "A" in the figure), while the other expended only 4.5 MJ d^{-1} (marked "B" in the figure). These figures hold within them the essential paradox addressed by this article. It is generally supposed that BMR (and RMRt) is a fundamental basal state of energy utilisation. Yet individual A in Figure 1*B* appears to require 3.0 MJ d^{-1} more to perform this task than individual B, who to all intents and purposes has the same lean body mass and is measured under identical conditions, using a method where the error is about 200 kJ d^{-1}. The pattern is the same in the voles depicted in Figure 1*A*. These differences in metabolic rate, at the extremes, are not small trivial differences in the context of total daily energy budgets. To illustrate this point, it is useful to consider that 3.0 MJ is about the same amount of energy that a person with 43 kg LBM might expend during a 10-km run. In effect, individual A needs to do the equivalent of a 10-km run every day to sustain the same basal processes (presumably) as individual B.

Key questions when faced with this variability in BMR (or RMRt) are why it exists and what the functional significance of the individual variation is. If the two individuals A and B depicted in Figure 1*B* lived in the wild like the voles in Figure 1*A* did, they would need to go foraging to collect food to fuel their metabolic rates. An individual with a high BMR would need to feed for longer to fuel its metabolism or, if both fed for the same time, would have less surplus available to devote to alternative activities such as reproduction (Gadgil and Bossert 1970). Put another way, if BMR is essentially a minimal state, what physiological processes require all the extra energy in those individuals that have very high metabolic rates? Consideration of the problem of the functional significance of the variability in BMR or RMRt has therefore focussed on the benefits that individuals with high RMR might derive to offset the potential disadvantages of their high rates of metabolism.

Theoretical Advantages of High BMR (RMRt)

Two similar ideas about the potential advantages that might accrue to individuals having high BMRs were published during the late 1970s and early 1980s. The first of these came about by considering the wider picture of the evolution of metabolic rates in different animal taxa. Metabolic rates differ not only between species within a given class but also between classes. In particular, endothermic animals (mammals and birds) have considerably elevated BMRs compared with ectotherms like reptiles and amphibians. These differences are much greater than the differences between individuals within a species. Bennet and Ruben (1979) suggested that endotherms maintain their systems in the basal state at such high rates of metabolism because this enables them to achieve substantially higher maximal rates of energy expenditure. This has been called the "aerobic capacity model" for the evolution of endothermy (Bennett and Ruben 1979; Taigen 1983; Bozinovic 1992; Hayes and Garland 1995). In the context of the individual differences identified in the introduction, the aerobic capacity model suggests that individuals with high BMRs sustain these rates because, despite the several identified disadvantages, they derive an advantage in situations where a maximal rate of energy metabolism is required; this might, for example, be the sustained power required for migration. To anthropomorphise, individual A in Figure 1*B* might have to eat more food than individual B every day to support the higher BMR, and that might be disadvantageous if food was in short supply. However, if food became in such short supply that both individuals had to perform a sustained feat like migration to get away from the area

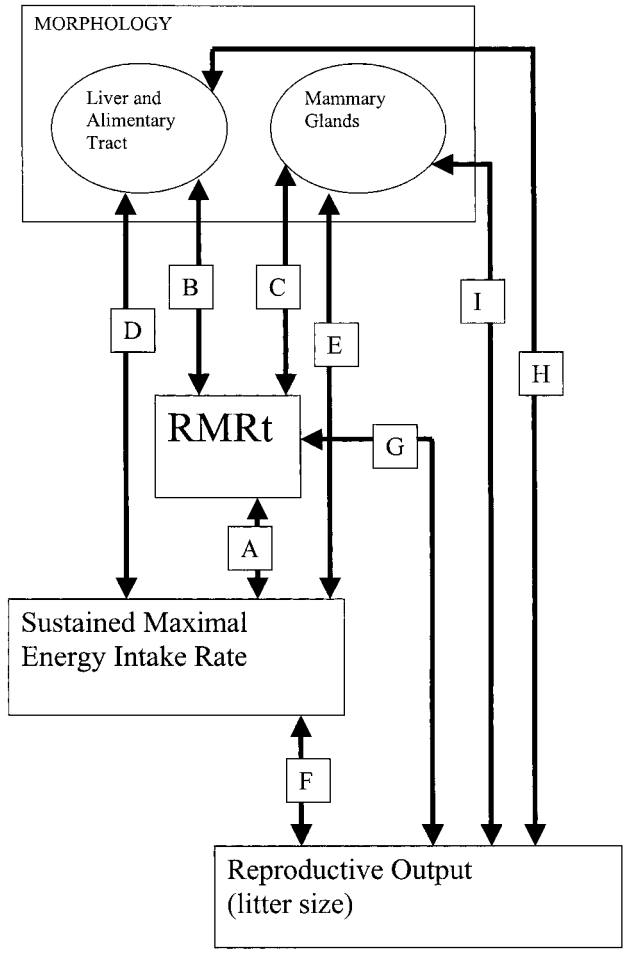

Figure 2. General model for the hypothetical links between morphology, resting metabolism in thermoneutrality (*RMRt*), maximal sustained food intake rates, and reproductive output (litter mass) based on Drent and Daan (1980), Weiner (1989, 1992), and Hammond and Diamond (1997). Anticipated associations between traits are identified by double-ended arrows. In all cases the direction of the correlation is expected to be positive. Specific interrelations referred to in the main text are identified by letters.

with poor food supply, then individual A might be much more likely to be able to perform the sustained metabolism necessary to support this activity. These contrasting benefits and costs in different situations might then sustain the observed variation in the trait in the population.

The duration for which any animal can sustain a given maximal rate of metabolism is limited. As duration increases, the maximum rate declines along a fixed pattern that is defined principally by the maximal rates of substrate utilisation under different states (McGillvery 1971). These changes are physiologically defined and explain why nobody will ever be able to run a marathon at the same speed as a 100-m sprinter (Speakman 2000). Once the duration of exercise gets very long, the need to perform competing activities (like sleeping and eating) starts to become significant. A question, however, persists over the maximal rate of metabolism that an individual could sustain for periods of many days or weeks and what the factors are that define this rate. Drent and Daan (1980) suggested that this sustained maximal metabolic rate (SusMR) is linked to the basal rate of metabolism. This "sustained maximal limit model" is a different, but evidently related, idea to the aerobic capacity model for the evolution of endothermy.

The reason underlying the supposed link between SusMR and BMR (Drent and Daan 1980) was as follows. SusMR was suggested to be ultimately limited by the capacity of the alimentary tract to absorb and process nutrients from the environment (see also Kirkwood 1983). Even under conditions of excess food, animals seldom eat continuously, and this is presumed to stem from the fact that actual ingestion rates can far exceed the capacity of the gut to process the ingested food (Tolkamp et al. 2002). However, a gut and associated organs (such as the liver) that can process energy faster make more energy available to support SusMR. What Drent and Daan (1980) suggested was that BMR is primarily the cost of maintaining the alimentary tract and its associated organs. Hence, greater capacities for SusMR would be inevitably linked to a requirement for a bigger alimentary system that would drive a higher BMR, making SusMR and BMR intimately linked. Going back to the individual variability in BMR (and RMRt) that we identified in the introduction as posing a problem, the Drent and Daan (1980) model suggests that while individual A in Figure 1*B* might have a greater BMR than individual B, at the same time, individual A would be able to extract substantially more energy from the environment, allowing it to support not only its greater BMR, but also greater rates of reproduction. So while individual A may routinely need to eat more food because of the greater BMR, there might be other benefits offsetting these costs under certain circumstances—again sustaining the trait variability in the population.

Several other authors have picked up on and developed the Drent and Daan (1980) model, in particular Weiner (1989, 1992), Peterson et al. (1990), and Hammond and Diamond (1992, 1997). It was recognised that the association between the central processing machinery for energy acquisition and BMR, and thus the link of BMR to SusMR, was only one of several possible functional linkages with a similar theme. In fact, the association could arise at the point of energy acquisition, or it could occur at the point of energy utilisation—in a similar vein to the aerobic capacity model but over an extremely extended duration. If the tissues involved in energy utilisation have high rates of energy demand in the basal state, then a similar functional linkage between tissues, BMR, and SusMR would emerge. To distinguish these two hypotheses, the acquisition model was called the "central limits theory," reflecting the fact that the limit was imposed by the central processing capacity of the alimentary system, while the utilisation

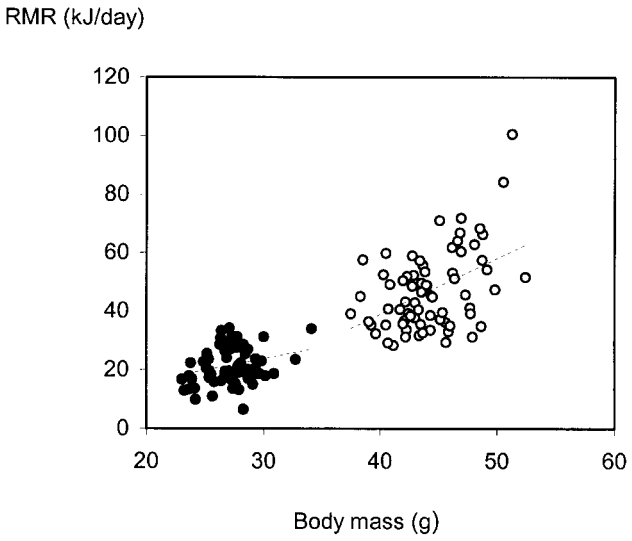

Figure 3. Relationship between resting metabolic rate at thermoneutrality (*RMRt*) and body mass for 71 MF1 mice (*Mus musculus)* measured before breeding (*filled symbols*) and at peak lactation (*open symbols*). Dotted lines are fitted curves by least squares regression for each group.

model was termed the "peripheral limits theory," reflecting the fact that limits might be imposed at the point of energy use, which would be the peripheral tissues.

A large body of work has been conducted to attempt to separate between these two different explanations for the advantage that accrues to individuals with high BMR (or RMRt). In the remainder of this article, we will summarise some work from our own laboratory that has been directed at the overall idea that morphological variability between individuals links together their BMR and SusMR. In particular, we will address three predictions, illustrated in Figure 2. The first prediction is that variations in BMR or RMRt will be linked to SusMR (link *A* in Fig. 2). The second prediction is that if the central limitations idea is correct, then individual variability in BMR (or RMRt) will be associated with variability in the sizes/capacities of the organs of the alimentary tract—including the secondary processing machinery such as the liver (*B* in Fig. 2). Alternatively, if the peripheral limits idea is correct, then this association will emerge with some other organ system, such as the skeletal muscle or, in a lactating animal, the mammary tissue (*C* in Fig. 2). Perhaps capacities of these systems are matched to whichever is the rate-limiting step—meaning associations with both would emerge as significant (the symmorphosis concept; Taylor and Wiebel 1981). These associations of morphology would also be apparent to SusMR as well (*D*, *E* in Fig. 2). The third prediction is that because of the link of BMR (and RMRt) to SusMR, these factors and aspects of morphology will also be connected to measurable differences in reproductive performance (*F* for SusMR, *G* for BMR [and RMRt], and *H*, *I* for morphology in Fig. 2).

Methods

One of the most energetically demanding periods that small mammals experience is late lactation (Thompson 1992). During the last few days of lactation, laboratory mice may increase their food intake above the prereproductive state by a factor of between 3 and 8. Actual peak levels of food intake have been shown to depend on the ambient temperature during the late lactation period (Hammond et al. 1994; Johnson and Speakman 2001; Król and Speakman 2003*a*). When mice lactate in the cold (8°C), they ingest substantially more food than when they lactate at 21°C (Hammond et al. 1994; Johnson and Speakman 2001). When they lactate in thermoneutral temperatures (30°C), they ingest substantially less (Król and Speakman 2003*a*). This effect has been considered to reflect a combination of demands being placed on the female that independently stimulate food intake (Hammond et al. 1994). This interpretation assumes that during late lactation the mammary glands are working at capacity, independent of the ambient temperature, and the thermoregulatory demand is additional to the demands of milk production. However, we have recently shown that rather than being constant, milk production increases as ambient temperature declines (Johnson and Speakman 2001; Król and Speakman 2003*b*), leading to positive effects on the growth of litters raised at cooler temperatures. This suggests that colder temperatures do not place additional demands on lactating females but rather remove a constraint on their milk production capacity. We have argued that this constraint is probably the ability of the lactating female to dissipate heat (Król and Speakman 2003*a*, 2003*b*).

Although the reasons why lactating females increase their food intake as a function of ambient temperature during late lactation may be a matter of debate, the fact that they do so is not under contention. In the strain of mouse that we have studied most intensively (the outbred MF1 strain, Harlan Laboratories, U.K.), the average food intake during the last 4–5 d of lactation for mice raising more than 10 pups averages 13 g per day at 30°C (Król and Speakman 2003*a*), at 21°C it is 23 g per day (Johnson et al. 2001*b*), and at 8°C it is 30 g per day (Johnson and Speakman 2001). By contrast, a nonlactating female MF1 mouse at 21°C consumes only 5.2 g of food per day (Johnson et al. 2001*b*). This model system, with large differences in the levels of maximal food intake between conditions, provides a rich testing ground for the ideas about why limits are imposed on sustainable metabolic rate, in particular, the three predictions introduced above.

Table 1: Seven different groups of MF1 mice studied at various ambient temperatures when not reproducing or at peak lactation

	Nonbreeding Mice			Mice at Peak Lactation			
Litter parity	…	…	…	1	1	2	1
Ambient temperature (°C)	30	21	8	30	21	21	8
Maximum food intake (g/d)	3.5	5.2	7.8	11.2	23.1	26.9	30.0
Maximum gross energy intake (kJ/d)	64.8	82.9	126.8	193.5	369.5	424.1	487.8
Maximum net energy absorption (kJ/d)	49.1	68.2	104.3	144.8	310.2	350.3	401.3
RMRt (kJ/d)	18.9	21.5	22.4	26.04	47.05	60.5	51.8
Body mass (g)	32.4	27.3	32.3	37.7	43.8	52.9	50.8
Ratio (gross/RMRt)	3.45	3.86	5.66	7.51	7.85	7.01	9.42
Ratio (net/RMRt)	2.69	2.50	3.23	5.62	7.08	6.62	7.90
Source	1, 2	3, 4	5	1, 2	3, 4	6	5

Note. Data are maximal sustained food intake, gross and net energy intake, resting metabolism at thermoneutrality (RMRt), body mass (g), and the ratios of gross and net sustained intakes to RMRt. Food intake refers to intake of CRM(P) rodent chow (Special Diet Services, BP nutrition). 1 = Król and Speakman (2003*a*), 2 = Król et al. (2003), 3 = Johnson et al. (2001*b*), 4 = Johnson et al. (2001*a*), 5 = Johnson and Speakman (2001), 6 = Johnson et al. (2001*c*).

Results

Prediction 1: Variations in BMR (or RMRt) Are Linked to Differences in SusMR

We have previously compared the resting metabolic rates in thermoneutrality (RMRt) of prebreeding mice, with the same individuals measured at peak lactation at 21°C (Speakman and McQueenie 1996; Johnson et al. 2001*b*) and have shown that on average the RMRt of mice before they breed is 21.5 kJ/d (SD = 0.72; $n = 71$). This rose significantly ($P < 0.0001$) in late lactation by a factor of 2.4 to on average 47.05 kJ/d (SD = 0.63, $n = 71$). In both groups there was a significant effect of body mass on RMRt (Fig. 3), but the relationships within each group were weak (in prebreeders, $r^2 = 0.073$, $F_{1,69} = 5.4$, $P = 0.023$; in lactation, $r^2 = 0.107$, $F_{1,69} = 8.29$, $P = 0.005$). If the data are pooled, randomly assigning individuals to one or the other group, there was a much stronger relationship between RMRt and body mass ($r^2 = 0.682$, $F_{1,69} = 148.09$, $P < 0.001$), reflecting the much greater range of body masses. However, the difference in RMRt between the prebreeding females and the lactating females was only a function of the difference in body mass between these two groups (ANCOVA, mass effect: $F_{1,68} = 10.2$, $P = 0.002$; reproductive state effect: $F_{1,68} = 0.04$, $P = 0.845$; Packard and Boardman 1999). In absolute terms, therefore, RMRt was elevated in lactation relative to prebreeding, but lactating mice are significantly heavier than prebreeding mice, and relative to body mass, there was no significant elevation in the RMRt.

We have previously compared the levels of RMRt measured during peak lactation at three different temperatures (Król et al. 2003), pooling data from our previous studies (Johnson and Speakman 2001; Johnson et al. 2001*b*; Król et al. 2003). Here we have added to these data the levels of food intake, RMRt, and body mass for the prebreeding mice detailed above (from Johnson et al. 2001*b*) and data on food intake, RMRt, and body masses for nonbreeding mice held at 30°C and 8°C (Johnson and Speakman 2001; Johnson et al. 2001*a*, 2001*b*, 2001*c*; Król et al. 2003) and mice in their second lactations (Johnson et al. 2001*c*). Overall, the pattern of increase in RMRt across these groups is mirrored in the pattern of change in maximal food and energy intake (Table 1). The association between RMRt and the sustained maximum gross energy intake across the groups (Fig. 4) was highly significant ($r^2 = 0.929$, $F_{1,5} = 62.3$, $P < 0.001$).

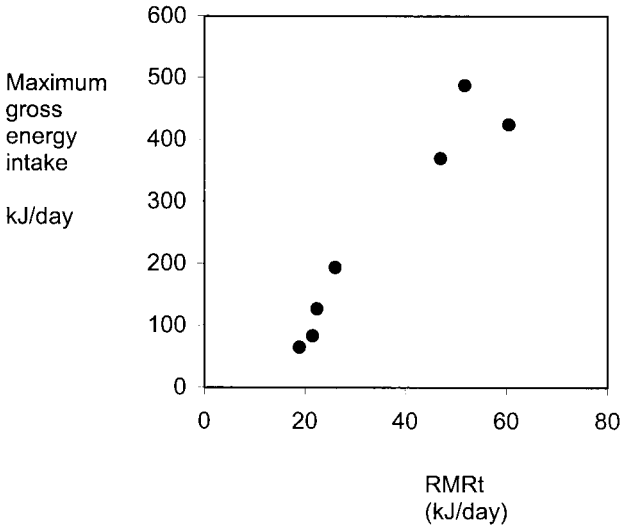

Figure 4. Maximal sustained gross intake of energy (kJ/d) plotted against resting metabolic rate in thermoneutrality (*RMRt*; kJ/d) for seven groups of MF1 mice of varying status. Source data are shown in Table 1.

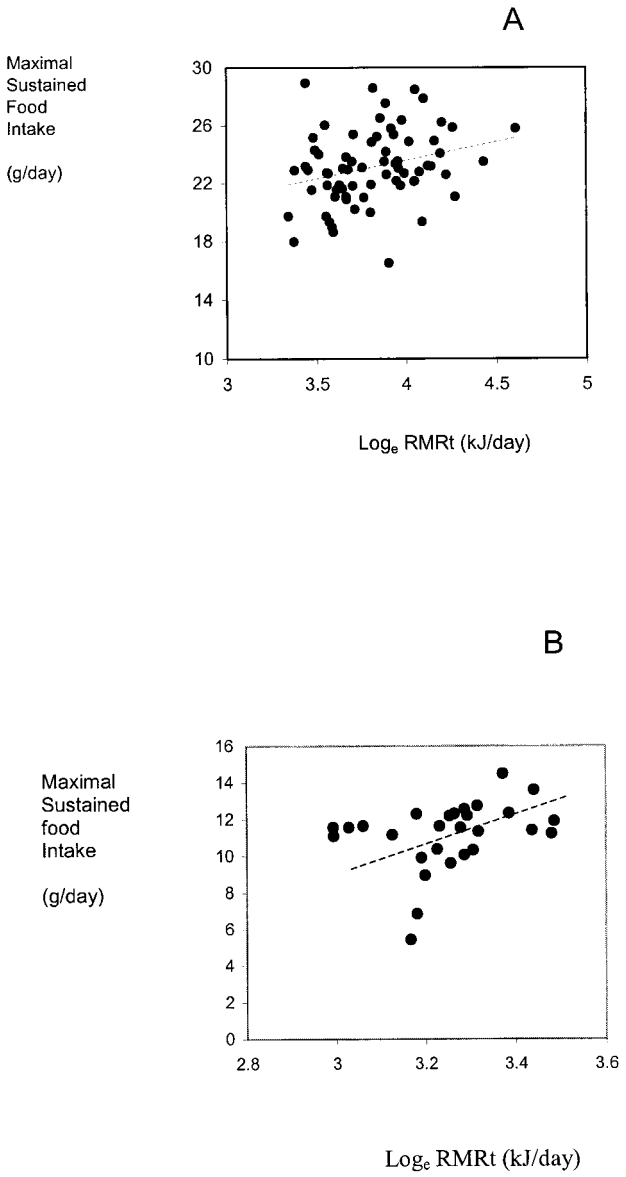

Figure 5. Relationships between maximal food intake at peak lactation (g/d) and resting metabolism at thermoneutrality (*RMRt*) for mice lactating at (*A*) 21°C and (*B*) 30°C. Both groups were feeding on CRM(P) rodent chow (Special Diet Services, BP Nutrition).

These data, however, reveal two additional facets that are not immediately obvious. First, the changes in body mass that parallel the changes in energetics parameters confirm that the responses in RMRt are a function only of the changes in body mass in response to the same manipulations (Table 1). The absence of an effect of RMRt independent of body mass is not necessarily a problem for the original prediction. The original idea was that when animals are faced with elevated demands, they would respond to these demands by hypertrophic responses in the organs either supplying the energy (central limits), utilising the energy (peripheral limits), or both (symmorphosis). The parallel changes in body mass may then reflect only the predicted response of organ hypertrophy (but see below). The fact that whole body RMRt increases in line with the increase in whole body maximal rate of gross energy intake (Fig. 4) is consistent with the original idea (Fig. 2).

Second, by expressing the intake and expenditure in common units of energy, the ratio of maximal sustained intake to RMRt can be calculated. This reveals that while the pattern of change in RMRt and maximal sustained intake across different conditions is the same, the ratio of the two differs markedly (Table 1). Nonbreeding mice seem to sustain a ratio of maximal gross energy intake to RMRt in the region of 3.5 to 5.6 × . However, during lactation the ratio increases with declining ambient temperature, until at 8°C the mice had sustained gross energy intakes that were 9.4 × RMRt. This variability in the ratio of RMRt to the maximal intake rate does not provide support for the sustained limits model, since it would be anticipated that this ratio would be maintained constant (suggested to be at around 4.0 × BMR [Drent and Daan 1980] or 7.0 × BMR [Hammond and Diamond 1997]).

The altered ratios between sustained intake and RMRt might occur for several reasons. First, the assumption of the limits model is that BMR and SusMR are linearly connected—a 20% increase in BMR precipitating a similar 20% increase in SusMR, thus maintaining the ratio constant. However, if the connection was disproportionate (e.g., a 20% increase in BMR precipitating a 40% increase in SusMR), the ratio would also increase with absolute changes in BMR. Alternatively, the ratio may vary because many other factors differ between these groups that could independently influence the two traits, leading to a broad correlation between them. In this latter case, making comparisons across groups may obscure the functional relationships between RMRt and maximal food energy intake rates at the individual level. However, if the association between RMRt and sustained maximal intake derives from the causality inferred by the model presented in the introduction, then we would also expect the link to be sustained within groups as well as between them. Data for two groups, lactating mice at 21°C and 30°C (Fig. 5), show that within these groups the relationship between maximal sustained energy intake and RMRt is less impressive than the comparison across groups (Fig. 4). In both sets of lactating mice, less than 10% of the individual variability in sustained maximal intake was explained by differences in RMRt (at 21°C, $r^2 = 0.075$, $F_{1,69} = 5.60$, $P = 0.021$; at 30°C, $r^2 = 0.094$, $F_{1,26} = 2.69$, $P = 0.113$). Moreover, maximal sustained energy intake in both groups was positively correlated with body mass (at 21°C, $r^2 = 0.097$, $F_{1,69} = 7.44$, $P = 0.008$; at 30°C, $r^2 = 0.368$, $F_{1,65} = 37.8$, $P < 0.001$). We have already noted that the association between body mass and RMRt might arise because of the processes that accompany hypertrophy of the significant organ systems that support increased sustained maximal metabolic rates. However, we might also predict that,

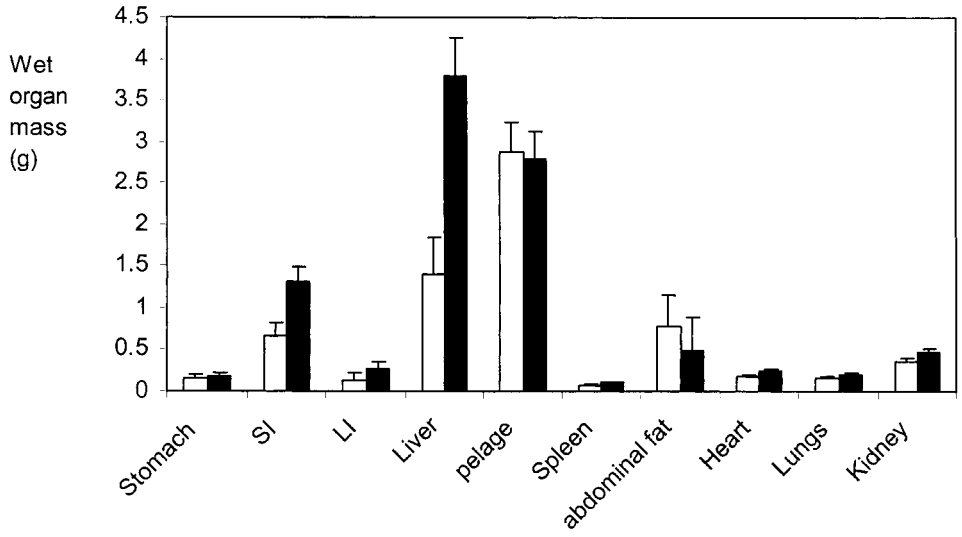

Figure 6. Wet organ masses (g) of nonreproducing mice (*open bars*, $n = 9$) and mice at peak lactation (*filled bars*, $n = 8$). Error bars show the SD (data from Speakman and McQueenie 1996). SI and LI are small and large intestines, respectively.

in addition to the link between RMRt and sustained energy intakes that arise due to covariation with body mass, there would also be an association between the residual RMRt and residual maximal intake, once the effects of body mass on both traits had been removed. We failed, however, to detect a statistically significant effect in either group (at 21°C, $r^2 = 0.022$, $F_{1,69} = 1.55$, $P = 0.217$; at 30°C, $r^2 = 0.042$, $F_{1,26} = 1.08$, $P = 0.307$).

Prediction 2: Variations in RMRt Are Associated with Differences in the Masses of Organs That Are Involved in Energy Assimilation, Energy Utilisation, or Both

During lactation, mice exhibit hyperplastic and hypertrophic responses in the organs linked to food assimilation such as the gut, pancreas, and the liver (Kennedy et al. 1958; Fell et al. 1963; Jolicoeur et al. 1980). We have demonstrated the same responses compared to nonbreeding individuals in our MF1 mouse lactation model (Speakman and McQueenie 1996; Johnson et al. 2001*b*; Król et al. 2003). Organs such as the liver, stomach, short and long intestines, kidney, and heart (all of which have high rates of metabolism) get larger during peak lactation at the expense of organs with low metabolism (such as the adipose tissue deposits), which get smaller (Fig. 6; Johnson et al. 2001*b*). Several other organs (e.g., the spleen and lungs) remain unaffected. These morphological details show that although the mice got heavier during lactation (Figs. 3, 4) and this change explained the modulations in RMRt, such effects were in fact entirely consistent with the ideas underpinning the maximal sustained limits idea.

Making comparisons across groups, however, is plagued by the problems that affect the comparisons of maximal sustained food intake and RMRt, namely that many other confounding factors differ between the groups that may lead to noncausal associations. We have therefore sought direct associations between RMRt and morphology within a group of 44 lactating mice at 21°C (Johnson et al. 2001*b*; Speakman and Johnson 2000). Simple bivariate analyses of RMRt against the sizes of the organs of suggested importance yield encouraging positive associations (Speakman and Johnson 2000; Fig. 7*A*, 7*B*). Lactating mice with higher RMRt also had larger livers ($r^2 = 0.188$, $F_{1,42} = 9.69$, $P = 0.003$; Fig. 7*A*) and larger mammary glands ($r^2 = 0.270$, $F_{1,42} = 15.52$, $P < 0.001$; Fig. 7*B*) These associations are both predicted from the sustained limits models. However, RMRt was also significantly positively associated with the masses of other organs that the model would not predict to be significantly related to RMRt, such as mesenteric fat mass ($r^2 = 0.092$, $F_{1,42} = 4.27$, $P = 0.045$; Fig. 7*C*) and masses of the carcass ($r^2 = 0.278$, $F_{1,42} = 16.19$, $P = 0.001$; Fig. 7*D*), spleen ($r^2 = 0.267$, $F_{1,42} = 15.3$, $P < 0.001$; Fig. 7*E*), and tail ($r^2 = 0.292$, $F_{1,42} = 17.28$, $P < 0.001$; Fig. 7*F*). In fact, RMRt is positively associated with the masses of almost all organs because larger mice have larger organs, and as we have seen, larger mice also have higher RMRt (Fig. 3). To remove the shared variation in both RMRt and organ masses due to variations in total body mass, we calculated the residual RMRt and residual organ masses. When these residual masses are considered, all the significant associations with particular organs disappear (e.g., for liver, $r^2 = 0.002$, $F_{1,42} = 0.07$, $P = 0.789$, Fig. 8*A*; for mammary glands, $r^2 = 0.021$, $F_{1,42} = 0.91$, $P = 0.346$, Fig. 8*B*). This analysis suggests that while larger mice have greater RMRt, tying the source of this increased metabolism down to dispro-

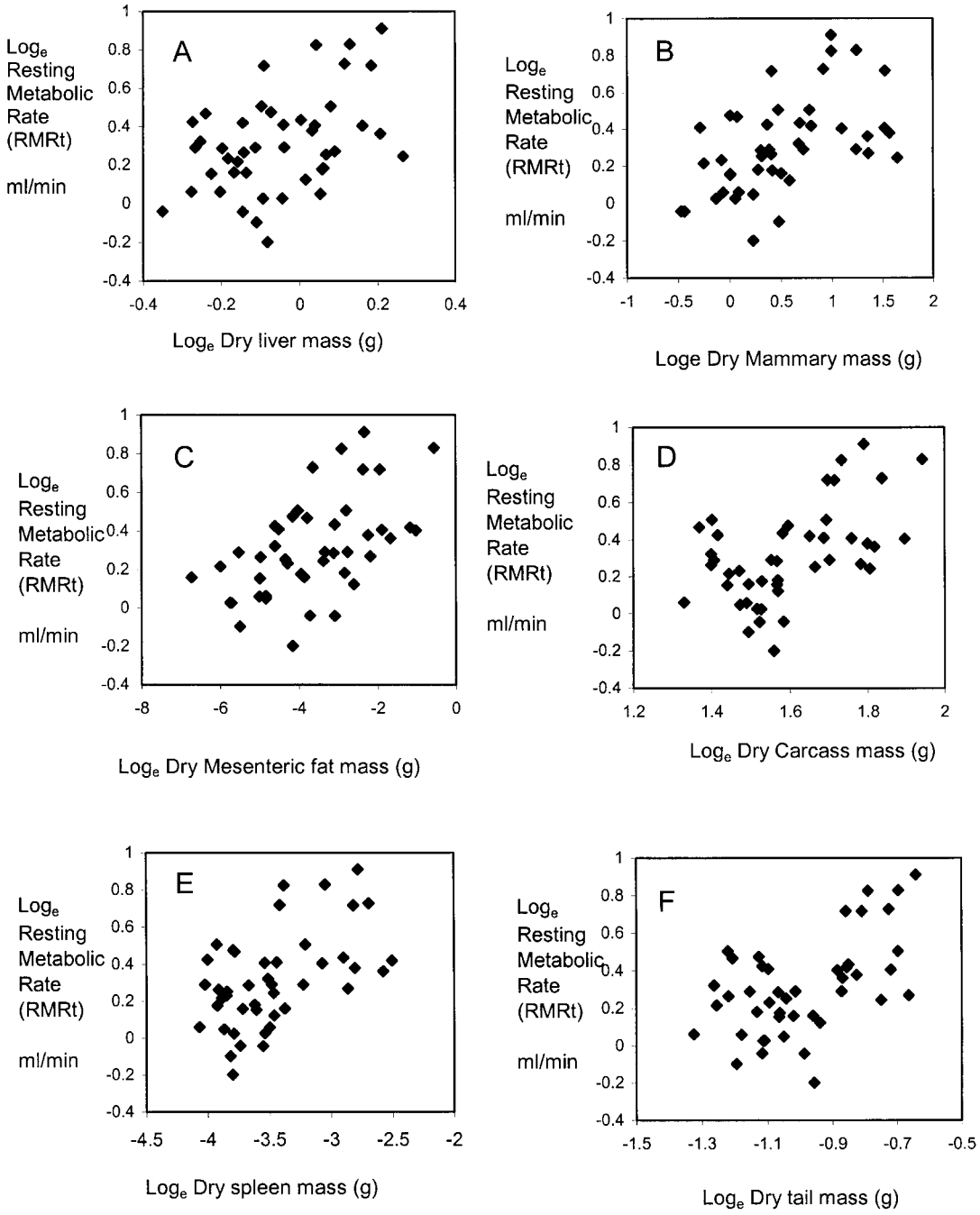

Figure 7. Relationships between the sizes of individual organs ($\log_e$ dry mass) and resting metabolism in the thermoneutral zone (*RMRt*) for a sample of 44 mice in late lactation at 21°C ambient temperature. *A*, Liver; *B*, mammary glands; *C*, abdominal fat; *D*, carcass; *E*, spleen; *F*, tail. Data from Johnson et al. (2001*b*).

portionate changes in any particular organ system was not possible in our data set. Lactating MF1 mice with relatively high RMRt do not have relatively large livers, alimentary tracts, or mammary glands. The absence of an association in these residuals (Fig. 8), combined with the lack of an association between residual RMRt and maximal sustained energy intake, does not provide support for the idea that variability in RMRt is maintained because of the links between it and organ morphology and the subsequent consequences for sustained maximal levels of energy intake.

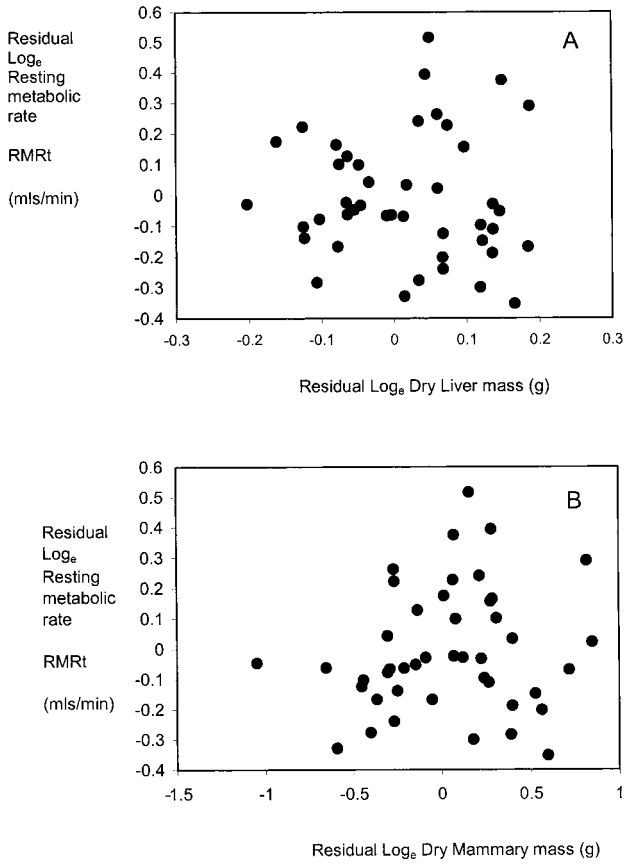

Figure 8. Relationships between the sizes of individual organs and resting metabolic rate with the shared variation due to body mass in each trait removed. *A*, Liver; *B*, mammary glands. Data from Johnson et al. (2001*b*) for a sample of 44 mice in late lactation at 21°C ambient temperature.

Prediction 3: RMRt, Sustained Maximal Intake, and Morphology Are Associated with Differences in Reproductive Performance

The primary product of lactation, in terms of fitness, is viable offspring. Offspring can be characterised in several ways. The number that are produced, their relative sex ratio, and their mean and variance in body size at weaning are some examples of possible quantifications. Relationships of these measurable traits to fitness, however, are complicated. Larger offspring may be more able to compete in competitive environments, but in noncompetitive situations a larger number of smaller offspring may be of greater fitness benefit. In addition, male offspring may generate greater fitness benefits in some situations and attract a greater share of resources, leading to elevated variance in offspring size at weaning. Females clearly have a choice in how they allocate their resources, and there is a consequent trade-off under limited resources between a large number of small offspring or a small number of larger offspring (Rogowitz 1996). Correlations between individual components of total reproductive investment (e.g., litter size) and energetics traits (e.g., RMRt) may therefore fail to pick up an association reflecting the correlation between energetics and reproductive investment because such a link is obscured by this fitness trade-off. We used total litter mass, therefore, as a measure of overall reproductive investment, which avoids the major litter size versus offspring size trade-off.

Using the same 44 mice that we analysed for the links between morphology and RMRt, there was a very strong positive relationship between the maximal sustained intake of energy during late lactation and the total litter mass at weaning ($r^2 = 0.563$, $F_{1,42} = 52.92$, $P < 0.001$; Fig. 9). This is strong evidence that high levels of sustained energy intake are translated into high levels of reproductive investment. However, the evidence linking individual variability in RMRt to variations in litter mass was far less convincing. There was no significant relationship between RMRt and litter mass ($r^2 = 0.026$, $F_{1,42} = 1.11$, $P = 0.298$) and no relationship between these traits when shared variations due to body mass were removed ($r^2 = 0.002$, $F_{1,42} = 0.07$, $P = 0.80$). When relationships between the organ masses and litter mass were considered, the masses of the liver and stomach were both not significantly related to litter mass (liver, $r^2 = 0.056$, $F_{1,42} = 2.48$, $P = 0.123$; stomach, $r^2 = 0.021$, $F_{1,42} = 0.9$, $P = 0.348$), but surprisingly the other sections of the alimentary tract did show significant associations to litter mass (small intestine, $r^2 = 0.111$, $F_{1,42} = 5.26$, $P = 0.027$; large intestine, $r^2 = 0.104$, $F_{1,42} = 4.87$, $P = 0.033$). The mass of the mammary glands was also significantly related to the litter mass ($r^2 = 0.194$, $F_{1,42} = 10.14$, $P = 0.003$; Fig. 10), but in this case the significant

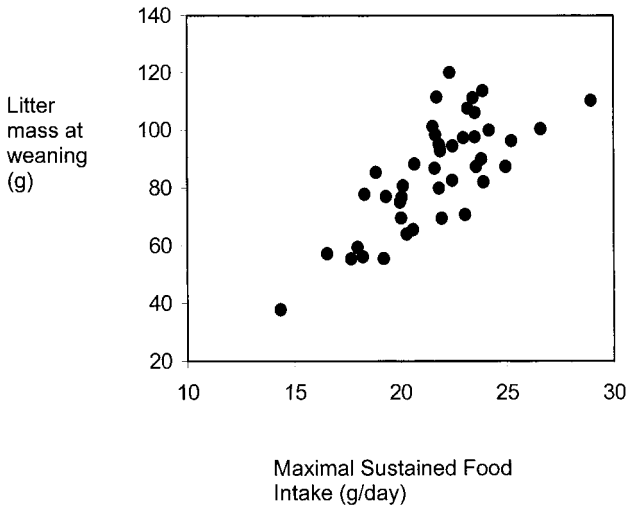

Figure 9. Litter mass (g) at weaning plotted against the maximal sustained food intake rate during late lactation (g food/d). Data from Johnson et al. (2001*b*) for a sample of 44 mice in late lactation at 21°C ambient temperature.

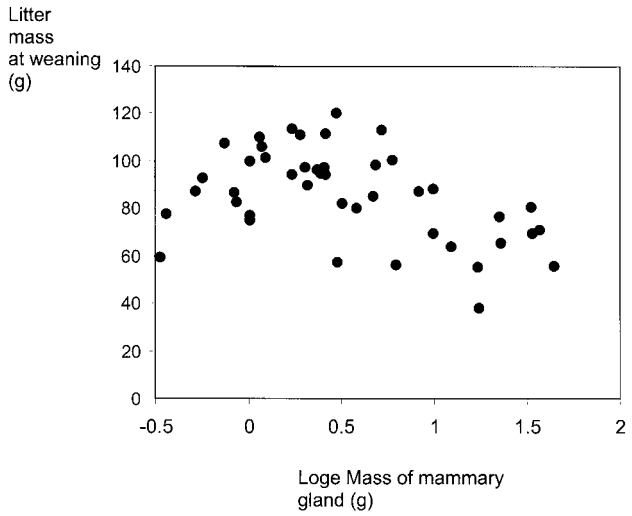

Figure 10. Litter mass (g) at weaning plotted against the mass of the mammary glands (g dry mass). Data from Johnson et al. (2001*b*) for a sample of 44 mice in late lactation at 21°C ambient temperature.

association was negative—individuals with smaller mammary glands produced heavier litters. When the shared variation in these traits due to body mass was eliminated, two of these significant associations retained their statistical significance (small intestine, $r^2 = 0.108$, $F_{1,42} = 5.1$, $P = 0.029$; mammary glands, $r^2 = 0.171$, $F_{1,42} = 18.67$, $P = 0.005$), but the relationship for large intestine did not ($r^2 = 0.062$, $F_{1,42} = 2.76$, $P = 0.104$). There was no indication that these morphology traits, whether significantly linked to litter mass or not, had any significant association with sustained energy intake (liver, $r^2 = 0.002$, $F_{1,42} = 0.06$, $P = 0.800$; small intestine, $r^2 = 0.014$, $F_{1,42} = 0.58$, $P = 0.449$; large intestine, $r^2 = 0.054$, $F_{1,42} = 2.34$, $P = 0.134$; mammary glands, $r^2 = 0.059$, $F_{1,42} = 2.58$, $P = 0.116$).

Discussion

Our work on the lactating MF1 mouse (Speakman and McQueenie 1996; Johnson and Speakman 2001; Johnson et al. 2001*a*, 2001*b*, 2001*c*; Speakman et al. 2001; Speakman and Johnson 2000; Król and Speakman 2003*a*, 2003*b*; Król et al. 2003) has shown that when comparisons are made across groups of individuals that differ in their status (e.g., between nonbreeding and lactating or between different groups of lactating mice held at different ambient temperatures), there is a broad pattern of responses that appears consistent with the ideas that BMR (here RMRt) and maximal sustainable intake rates are associated (Table 1; Fig. 4). This association was apparently mediated by their shared dependence on aspects of morphology that limit either uptake of energy or its utilisation (Fig. 6). Lactating mice have bigger alimentary tracts, bigger livers, and bigger mammary glands than nonbreeding mice. They also have greater maximal sustained intake and greater RMRt. Groups of lactating mice vary in their maximal food intake in relation to ambient temperature, and these patterns are mirrored by differences in milk production and RMRt. These patterns are predicted by the hypotheses concerning associations of BMR and sustained intake (Weiner 1989, 1992; Peterson et al. 1990; Hammond and Diamond 1992, 1997), and the data appear to provide strong support for these hypotheses. Many other studies have made similar groupwise comparisons in lactating animals and have come to the same conclusions (Hammond and Diamond 1992, 1994; Hammond et al. 1994, 1996; Konarzewski and Diamond 1995; Rogowitz and McClure 1995; Rogowitz 1998). Taken alone, these data suggest strong support for the suggestion that individual variation in RMRt is sustained by the consequences of RMRt for maximal sustained rates of energy intake.

Comparisons across groups of individuals, however, can be deceptive, and if the hypotheses are correct, we would also expect the same support to be found when comparisons are made across individuals within a group. Our data show that this support for the hypotheses at the individual level is lacking. In particular, we have found no evidence in lactating mice that individual variations in RMRt can be traced to individual differences in organ morphology. Lactating mice may have bigger livers and greater RMRs than nonbreeding mice, but the same is not true of lactating mice with big livers compared with lactating mice that have small livers. Several other studies (Koteja 1996; Corp et al. 1997; Burness et al. 1998; Geluso and Hayes 1999) making comparisons between individual variances in morphology and RMRt have failed to establish the same significant associations that emerge when comparisons are made between groups (Konarzewski and Diamond 1995; Selman et al. 2001). However, it is important to acknowledge that unlike our work, some studies have managed to successfully link morphological variation to metabolism within groups (Daan et al. 1989, 1990*a*, 1990*b*).

We also found only very weak evidence that RMRt is correlated with maximal sustained rate of food intake, and this weak association disappeared when the shared variation due to body mass was removed. Additionally, we could find no evidence that sustained energy intake at peak lactation is linked to variations in morphology of the liver, alimentary tract, or mammary tissue. Moreover, there was no evidence that RMRt at peak lactation has any relationship to litter mass, which is a composite measure of reproductive output, whether the effects of body mass on both traits are removed or not. This finding supports several other studies that have also failed to establish links between individual variations in RMR and reproductive performance at the individual level within species (Derting and McClure 1989; Earle and Lavigne 1990; Hayes et al. 1992; Stephenson and Racey 1993*a*, 1993*b*). Such failures contrast the ability to establish such links when associations are sought across species (Glazier 1985*a*, 1985*b*; Genoud 1988).

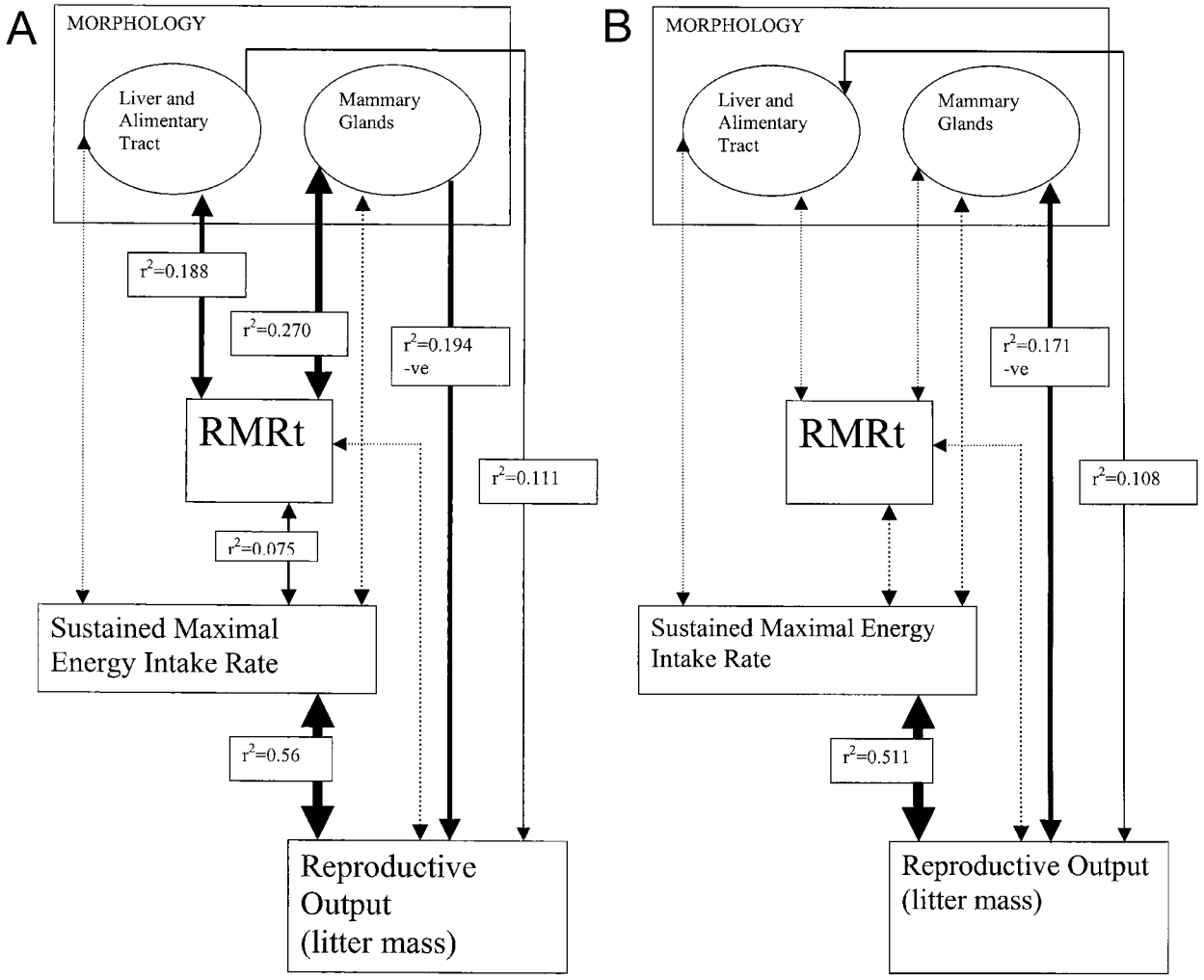

Figure 11. Relationships between morphology, resting metabolic rate at thermoneutrality (*RMRt*), and maximal food intake rates in late lactation and litter mass. Relationships between any two traits are depicted by double-ended arrows connecting their boxes. Significant associations are shown by solid lines, and the r^2 for the relationship (and direction when negative) is inserted in the line. The size of the line also reflects the strength of the relationship. Where data were available and relationships were sought but no significant relationships were found, a connecting line is shown dotted. No connecting line means no analysis was performed to find a relationship between those traits. In *A* the traits are correlated using raw data. In *B* the shared variation in each trait due to body mass effects are removed.

We did find some evidence that the masses of the alimentary tract and mammary gland were linked to litter mass at peak lactation, but this effect appears not to be mediated by any association of morphology with RMRt or sustained energy intake since these latter associations did not exist, and the correlation of mammary gland mass to litter mass, though significant, was actually negative.

However, despite the large number of expected associations that were not significant, what our studies do show is that individual variation in the maximal sustained rate of food intake at peak lactation across individuals is closely linked to reproductive output (litter mass). Individual females that invest more in reproduction eat a greater maximal sustained quantity of food in late lactation. Once the alimentary tract and associated organs and the mammary glands have grown to a certain size to support the reproductive attempt, it would appear that there is very little fine tuning of the capacities to the organ sizes. This failure to match organ sizes closely to sustained energy intake or litter mass may simply reflect the fact that organ mass is a poor measure of the capacity of a particular organ to process energy. This may also underpin the lack of association between organ sizes and RMRt (shown in our studies and elsewhere; see references above). However, there were no significant associations between RMRt and the capacity to process energy as measured by the ultimate outcomes (sustained energy intake and reproductive output), so even if organ

mass is a poor measure of morphological metabolic capacity, this does not rescue the BMR-SusMR hypothesis.

Overall, the relationships between the traits that we have detected are summarised in Figure 11*A*, including body mass as a covariate, and in Figure 11*B*, where shared effects of body mass are removed. In these figures, the r^2 values for actual relationships are presented on the lines connecting the different traits. Where a relationship was not statistically significant, the line is dotted. The thickness of a solid line also indicates the strength of the association. This is an analogous figure to Figure 2 in which the hypothetical correlative interrelationships were presented. The most striking thing about the comparison of Figures 2 and 11 is the large number of nonsignificant interrelationships between traits that are anticipated in Figure 2 but are absent in Figure 11. Even where relationships exist in Figure 11*A*, they are often only due to shared variation due to body mass, as they disappear in Figure 11*B*.

These data do not, therefore, support the notion that individual variation in RMRt is a potentiating factor for maximal sustained energy intake and hence reproductive performance. The individual variation in both maximal sustainable energy intake and RMRt therefore remains to be explained. Our recent work on MF1 mice lactating at 30°C has suggested that maximal sustained energy intake may actually be constrained by the capacities of individuals to dissipate heat generated as a by-product of processing the food (Król and Speakman 2003*a*, 2003*b*). This is a radically different hypothesis to the suggestions that limits are imposed by the capacity to either absorb or utilise energy, and it would explain our failure to establish links between maximal rates of energy utilisation and both RMRt and aspects of morphology linked to energy absorption and utilisation.

While differences in RMRt do not appear linked to maximal rates of energy intake and thus reproductive capacity, it is possible that they are linked to variability in individual survival, mediated via completely different routes to the postulated links via sustained maximal energy intake. Several lines of evidence already point in this direction. First, dog (*Canis familiaris*) breeds with higher RMR live longer than breeds with low rates of metabolism (Flurkey et al. 2002; Speakman et al. 2003), and individual variation in the RMR of voles (Fig. 1*A*) is also positively linked to their probability of surviving the winter (Jackson et al. 2001). A key factor involved in these positive associations may be the role of the uncoupling proteins UCP-2 and 3. It is already established that polymorphisms in the region of UCP-2 and 3 are linked to RMR in humans (Bouchard et al. 1997), and there is a good theoretical basis for believing that expression of UCPs might modulate production of free radicals during oxidative phosphorylation (Brand 2000; Echtay et al. 2002; Speakman 2003), perhaps providing a mechanism that joins RMRt to survival.

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