The energy cost of reproduction in small rodents

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Abstract：Reproduction is the mechanism by which animals perpetuate their genetic contribution to future generations. Reproduction therefore has clear advantages, but it also has costs. Principal among these are elevated energy demands. Studies of energy demands in small domesticated mice have revealed that food intake increases only slightly during pregnancy, but much more dramatically during lactation. Although the increase during pregnancy are small, this may reflect competition for space in the abdomen between the alimentary tract and the developing foetal mass and intake may be limited in this situation and impose constraints on the reproductive event. During lactation energy intake increase enormously, reaching an asymptote in late lactation. Studies in wild rodents generally show the same pattern of intake between pregnancy and lactation lending hope that our work in domestic mice may provide more generally applicable insights. Studies aiming to discover the nature of the limit on intake in late lactation have been performed for at least the past 15 years. The suggestion that the limits are imposed by capacities of the alimentary tract to digest food, or the of the mammary gland to secrete milk, do not adequately explain the available data. A novel hypothesis is that the limits may be imposed by the capacity of small rodents to dissipate heat. Heat loss capacity has long been known as a constraint on lactation in large mammals. Its significance in small rodents remains uncertain, but adjustments in the level of thermogenesis from brown adipose tissue that have been classically interpreted as releasing energy to support lactation may actually reflect a reduction in obligatory heat production to avoid hyperthermia. In spite of our advances in understanding in these areas we are still far from using this knowledge to understand even simple life history trade-offs.

Key words：Energy cost; Energy intake; Reproduction; Small rodent; Thermogenesis

小型啮齿动物的繁殖能量代价

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摘要：繁殖是动物向后代传递和保持遗传信息的方式。因此繁殖的意义是显而易见的，但也需要付出代价。主要代价是能量需求增加。在对小家鼠繁殖能量需求的研究中发现，能量摄入在妊娠期只是稍微增加，而在哺乳期则急剧增加。尽管在妊娠期增加的幅度很小，但这可能反映了消化道和发育的胎儿之间在动物腹中的空间竞争，从而可能使能量摄入受到限制进而影响到繁殖过程。哺乳期间，能量摄入急剧增加，在哺乳后期达到高峰并趋于稳定。对野生鼠的研究也表明，野生鼠妊娠期和哺乳期的能量摄入模式与小家鼠是基本相同的，这样我们在小家鼠研究工作中的发现就具有更普遍的适应意义。对哺乳后期能量摄入的限制机制研究至少已经进行了15年。能量摄入受消化道消化能力的限制（中心限制假说）或者受乳腺泌乳能力限制（外周限制假说）的假说，都不能合理地解释一些现有的结果。我们提出了一个新的假说，即能量摄入可能受啮齿动物散热能力的限制（热耗散限制假说）。很久以来，一直认为散热能力是对大型哺乳动物哺乳的一个限制因素，但它在小型啮齿动物中的意义尚不清楚。传统观点认为，啮齿动物哺乳期对褐色脂肪组织产热水平的调节是为了重新分配能量以满足哺乳所需；但现在看来，实际上可能是动物为了避免体温过高而降低其基本的产热水平。我们在这个领域已经有了一些进展，但要利用这些知识来理解即使很简单的生活史权衡等问题也还有很多的工作需要做。

关键词：能量代价；能量摄入；繁殖；啮齿动物；产热

1　Introduction

The life history of an organism is a reflection of how the animal combines together different components that influence fitness into an integrated 'strategy'. A fundamental assumption of our understanding of the evolution of life history strategies is that trade-offs exist between the various components (Fisher, 1930). For example, an increase in current reproductive output by maximizing fecundity might occur only at the expense of future survival of the reproducing adult (Williams, 1966; Stearns, 1992; Charnov, 1993; Charlesworth, 1994). We assume that animals cannot combine

together the fitness components in a strategy that simultaneously maximises them all, and must therefore trade-off the components against each other (but see Johnston *et al.*, 2006).

This fundamental idea, that there must be trade-offs in fitness components, stems from the recognition that reproductive events generate fitness benefits in terms of offspring, but that reproduction also entails costs. The details of these costs drive the nature of the trade-off between the fitness components (Stearns, 1992; Roff, 1992). Despite the fact that it is widely recognised that physiology contributes to the costs of all life history trade-offs (e. g. Stearns, 1992; Ricklefs and Wikelski, 2002), the physiological contribution to most trade-offs remains poorly studied. In this paper I review our understanding of one of the best known physiological costs that is attached to the process of reproduction its energy cost in small rodents (see also reviews in Millar, 1977; Gittleman and Thompson, 1988; Loudon and Racey, 1987; Thompson, 1992).

2 Energy costs of reproduction in small domesticated rodents

Probably the most detailed data available for the energy demands of reproduction are derived from small domesticated mice. This is primarily because these animals are easily kept, and even quite invasive measurements can be made on them without the risk that they will desert their offspring (Myrcha *et al.*, 1969; Gandelman and Simon, 1978; Studier, 1979; Konig *et al.*, 1988; Hayes *et al.*, 1992). The time-course of food intake, at 21℃, throughout reproduction in a strain of laboratory mouse (MF1) that we have been studying is shown in Fig. 1 (Johnson *et al.*, 2001a). Food intake increased during pregnancy compared with

the baseline period prior to mating. During the baseline period the intake averaged 5. 5 g per day, but at its peak in pregnancy it was about 50% higher at 8 g per day. Although the pattern of foetal growth is essentially exponential between conception and birth, the pattern of food intake does not mirror this, but rather rises to a peak about 2 – 3 days earlier and then declines slightly before the day of parturition. The reason for this pattern is uncertain, but one hypothesis is that the expanding foetal mass competes for space with the alimentary tract in the abdomen, limiting the food intake. This may suggest that resources to support the gestation become limited in late pregnancy. Under such limitation competing demands may have detrimental effects on the success of the pregnancy. One such competing demand may be the level of basal energy requirements (Basal metabolic rate, BMR). We have recently shown in another strain of mouse (the C57BL/6 black mouse) that mice with higher BMR have a greater likelihood of mass anomalies occurring during pregnancy (Fig. 2).
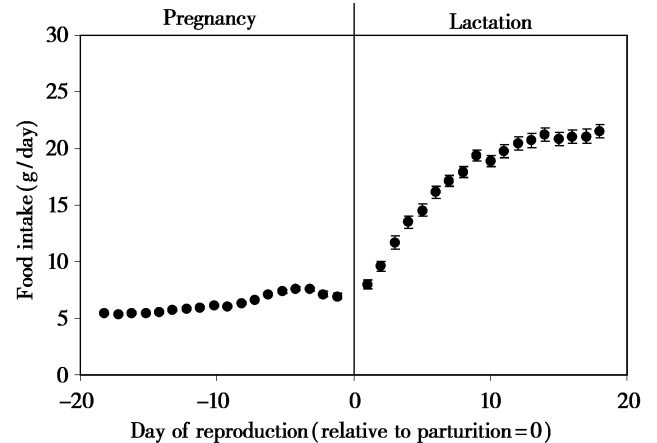

Fig. 1 Food intake each day throughout a baseline pre-breeding period, pregnancy and lactation for MF1 mice. Data averaged across 71 litters.
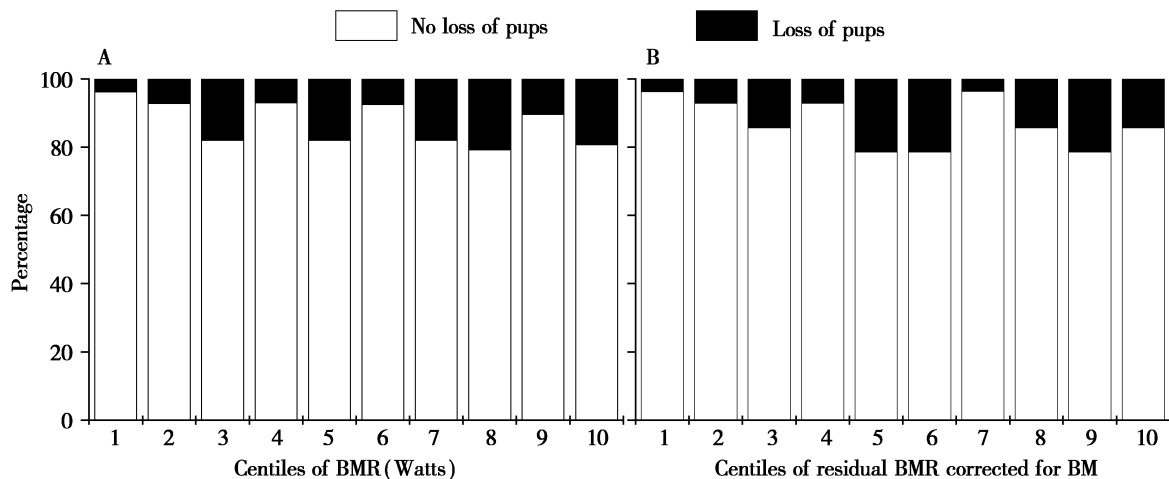

Fig. 2 The distribution of body mass anomalies during pregnancy in C57 BL/6 mice in relation to 10 percentile classes of Basal metabolic rate (BMR) and residual BMR with the effect of body mass removed. The mass anomalies are believed to be indicative of foetal resorption events (pup loss). Resorption was significantly more probable as BMR and residual BMR increased (from Johnston et al. 2006, submitted).

These mass anomalies probably reflect foetal resorption events. Because BMR is correlated with body mass this relationship might only be an artefact of both resorption rate and BMR being affected by mass, but the effect of BMR is also evident if the effect of mass is removed statistically (Johnston *et al.* 2006 submitted). This effect supports the hypothesis that resource intake in late pregnancy may be limited, perhaps by space competition in the abdomen between the alimentary tract and developing foetuses.

The most dramatic increase in food intake in MF1 mice occurred during lactation (Fig. 1). During the initial 10 days this increase was linear, but then it reached a plateau at about 23 g of food per day. Food intake at the plateau (between days 10 and 18) was related to litter size. Small litters reached plateau intakes of less than 23 g (Fig. 3A), but as litter size increased, food intake also increased to a plateau at around 23 g of food per day. The mice seemed to reach a limit in their food intake at this level. Although litter sizes increased, food intake did not increase in parallel.

A potentially trivial cause of this limit may be the dynamics of the cages in which we keep the animals. Perhaps 23 g is the maximal amount of food that a mouse can pull through the overhead hopper bars in 24 hours. By varying the method of food presentation we have shown that this limit in food intake is not mediated via the aspects of the cage the animals live in (Speakman and Król, 2005) and therefore appears to be a physiological feature intrinsic to the animals themselves. This apparent physiological limit in the capacity of the mouse to ingest food at peak lactation may underpin an important life history trait (maximum litter size) and an important life history trade-off. Because the maximum asymptotic food intake at peak lactation is fixed the energy that can be devoted to milk is also fixed. As litter size increases this milk must be divided between more and more offspring and consequently the pups wean at progressively smaller body masses (Fig. 3B：Johnson *et al.* 2001a). A physiological limit in the capacity to ingest food therefore appears to underpin the life history trade-off between the number and size of offspring. Presumably there is a minimum size of offspring at weaning that would stand any chance of survival. Where the declining relationship between pup size and litter size intersects this theoretical minimum viable pup size may define the maximum litter size. A distribution of natural litter sizes in this mouse strain is shown in fig. 4. It is noticeable that the asymptotic intakes for the mice that raised 14 and 15 pups were actually higher than the average 23 g limit (Fig. 3). Per-

haps these females were only able to raise such large litters because they were individuals that were capable of above average intakes and therefore still able to wean their pups at a pup mass of 7. 5 g. Natural litter sizes of 16 and above in this strain may not be feasible because of the interaction between the limit on maximal intake rate, and minimum viable pup size. However, it should also be borne in mind that the effects that occur in late pregnancy may also impose limits on litter size in this species.
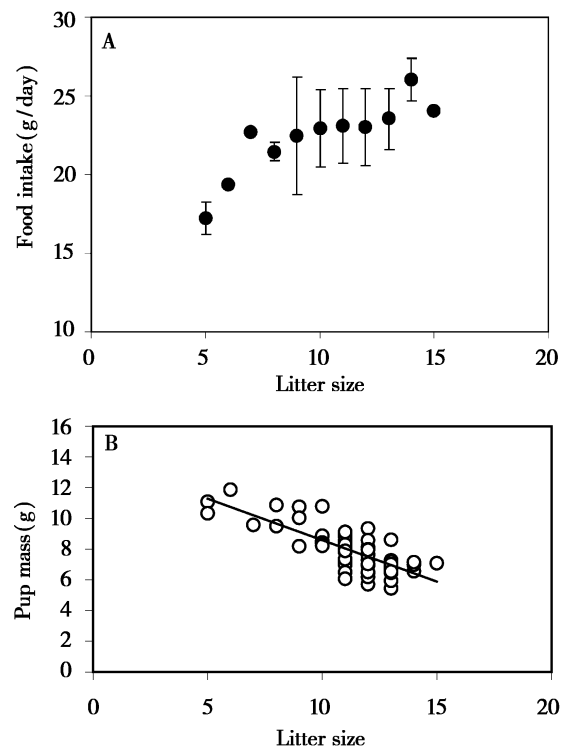

Fig. 3 A：Daily food intake averaged over the last days of lactation (10－18) plotted against litter size in MF1 mice. B：The trade-off between individual pup mass at weaning and litter size in MF1 mice. In both cases the data are summarised across 71 litters. (Data from Johnson *et al.* , 2001a)
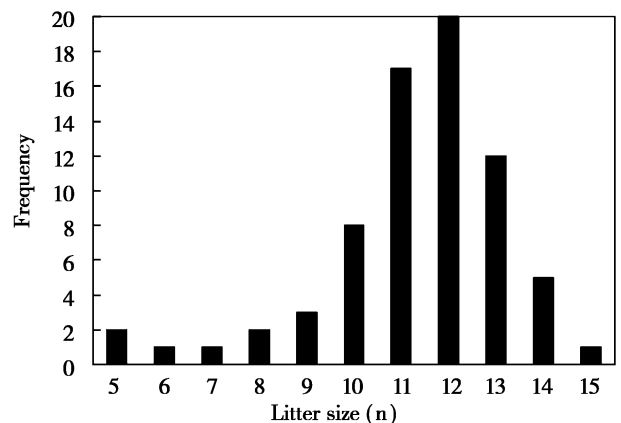

Fig. 4 Frequency of natural litter sizes at weaning in the MF1 mouse summarised across 71 litters.

3 How relevant are studies of domesticated rodents to wild animals?

The MF1 and C57BL/6 mice that we have studied are a product of domestication. While these mice are very amenable to study, an important question that could be asked is how relevant are the energy demands in such animals to the demands in wild rodents and other non-domesticated small mammals? Perhaps we are studying a system that is so divorced from the normal pattern that any insights we gain from these animals may be largely irrelevant. Studies of the energy demands of lactation in the wild are relatively rare largely because the technical demands of performing such work become almost impossible to apply in a field setting without adversely affecting the animals involved. Notable exceptions include the studies of ground squirrels by Kenagy 1989 and Hare and Murie, 1992, but even these exceptional studies do not allow day to day resolution of changes in energy demands or food intake.

In contrast many studies have examined the pattern of change in food intake across the reproductive cycle among other small non-domesticated rodents kept in captivity. These studies have the clear advantage that variation in environmental conditions and food supply can be minimised. Studies of the patterns of development in eutherian mammals have identified two very clear developmental strategies (reviewed in Martin and MacLarnon, 1985; Martin, 1989), with some species having prolonged periods of gestation followed by birth to a relatively well developed offspring that rapidly becomes independent of the mother and capable of feeding themselves relatively quickly after birth (precocial development). In contrast other species have a relatively short gestation that is followed by a more protracted period of lactation during which they are completely dependent on nutrient supply from the mother (altricial development). Utilisation of these strategies is not independent of body mass with mammals weighing more than 100 kg using only the precocial strategy, while species weighing less than 100 g utilise the altricial strategy almost exclusively, although some species follow what has been called an intermediate' strategy (defined in Martin and Maclarnon, 1985). As anticipated from their size mice follow the altricial strategy. Between 100 g and 100 kg species are found that follow either precocial or altricial strategies with a few 'intermediates' (Martin and MacLarnon, 1985; Martin 1989).

Clearly this dichotomy in developmental strategy may impact on the levels of energy investment by the mother during lactation (Oftedal, 1984; Hill, 1992;

Kam et al., 2006). Because it is the rarer strategy relatively few studies have addressed the levels of food intake of small rodents following the clearly precocial strategy (but see for example the studies of *Cavia porcellus*' Kunkele and Trillmich, 1997 and *Octodon degus*, Veloso and Bozinovic, 2000) with many more studies following the patterns of investment during lactation of species raising clearly altricial or 'intermediate' offspring. Some examples of these latter measurements are summarised in Table 1 (after Speakman, 2006 in press). This table is not intended to be a completely comprehensive summary. Converting estimated food intakes into energy intakes for those species where only food intakes are reported in the original papers, and converting energy expenditures into energy intakes using an assumed assimilation efficiency of 80% for those studies where average daily metabolic rate (AD-MR) was quoted, there was a significant effect of body mass ($F = 42.6$, $P < 0.001$) and a significant effect of reproductive status ($F = 30.6$, $P < 0.001$), but no significant interaction between these two variables ($F = 1.55$, $P = 0.225$) (Fig. 5). Using pairwise Tukey comparisons the non-breeding energy demands did not differ significantly from those in pregnancy, but the demands in lactation were significantly elevated above both the non-breeding and pregnancy demands. This analysis confirms the observation in our mice that increases in energy intake during pregnancy are relatively small. This does not mean that this period is unimportant since intake may still be limited at this low level. Nevertheless, the pattern observed in laboratory mice (and rats) that the costs of reproduction are substantially greater during lactation than in pregnancy appears to be very broadly applicable (Millar, 1977; Thompson 1992; Thompson and Nicoll, 1986).

There was a wide variation in the energy demands at peak lactation (Table 1, Fig. 5). The residual variation, once the effects of body mass had been removed, was significantly associated with litter size ($P = 0.0103$, Fig. 6) which explained 49.3% of the residual variance. Gestation period (days) reflecting position on the altricial-precocial continuum was not an additional significant factor ($P = 0.13$). The absence of an effect of this dichotomy might be expected given the selection of species that were either altricial or intermediate's trategists. Although litter size and body size explained much of the variation in energy intake at peak lactation there was still considerable variation in the energy intakes across species. These differences to an extent reflect different strategies for coping with the energy demands.

Table 1　Energy intakes of non-domesticated small (< 1 kg) rodents at different phases of the reproduction cycle. LS is litter size. Under P this is litter size at birth, under L this is litter size at weaning. Where original paper does not state which it is entered under both. Status is: NB non-breeding, P pregnant and L lactating. xNB is the intake expressed as a multiple of the non-breeding intake. In all cases (except ∗) the animals were studied in the laboratory at standard room temperatures (21 – 24 ℃) with ad libitum access to food. ∗∗ animals kept at 5 ℃ ∗ animals kept at 10 ℃ . In some cases the original data were quoted relative to body mass$^{0.75}$ and in these instances the actual intakes have been recalculated using the cited body mass. In other papers only mass of food ingested is cited and these have been converted assuming a dry mass energy content for the food of 20.9 kJ/g , unless a different value was cited in the paper. In yet other studies average daily metabolic rate (ADMR) is quoted. I have converted this to energy intake assuming a digestive efficiency of 80% .

Species	Mass	Status	LS	Food intake	Energy (kJ/d)	x NB	Reference
Peromyscus polionotus	13. 4	NB			54. 0		1
		L	3. 64		94. 0	1. 74	1
Clethrionomus gapperi	18. 8	NB		3. 80			2
	34. 0	P	5. 58	6. 39		1. 68	2
	27. 0	L		12. 0		3. 15	2
Peromyscus maniculatus	14. 5	NB			58. 4		1
		L	4. 30		144. 6	2. 47	1
Peromyscus maniculatus	20. 1	NB	5. 14	3. 5			3
	25. 8	L	–	9. 6		2. 70	3
Peromyscus leucopus	21. 0	NB			72. 45		1
		L	3. 91		143. 64	1. 98	1
Peromyscus eremicus	21. 5	NB			52. 0		1
		L	2. 42		104. 9	2. 02	1
Microtus pennsylvanicus	24. 0	NB		4. 82			2
	38. 2	P	5. 05	6. 57		1. 36	2
	31. 0	L		15. 5		3. 21	2
Clethrionomus glareolus	24. 5	NB			73. 2		4
	–	P	5. 0		99. 2	1. 35	4
	–	L	4. 0		162. 8	2. 22	4
Peromyscus leucopus	25. 0	NB	4. 0	3. 2			5
		L		6. 0		1. 875	5
	24. 5	NB ∗∗	4. 0	5. 5			5
		L ∗∗		8. 7		1. 58	5
Microtus arvalis	25. 3	NB	–		62. 3		6
	33. 9	P	4. 25		66. 5	1. 07	6
	–	L	4. 00		175. 7	2. 82	6
Peromyscus leucopus	25. 8	NB			62. 8		7
	25. 8	L	5. 0	8. 23	150. 1	2. 39	7
Phodopus sungorus	30. 0	NB			56. 0		8
	41. 0	P	5. 6		68. 0	1. 21	8
	35. 0	L			104. 3	1. 93	8
Peromyscus floridanus	42. 0	NB			94. 5		1
		L	2. 25		144. 0	1. 54	1
Onychomys leucogaster	45. 3	NB		4. 15	72. 8		9
	50. 7	L	4. 0	9. 49	166. 0	2. 28	9
Acomys caharinus	49. 4	NB			45. 8		10
	65. 8	P	2. 0		60. 9	1. 33	10
	46. 1	L	2. 0		63. 1	1. 38	10
Microtus brandtii	59. 3	NB			94. 54		11
	83. 6	P	8. 5		105. 22	1. 11	11
	51. 5	L	8. 5		334. 2	3. 53	11
Meriones crassus	93. 6	NB			113. 1		12
	90. 7	L	3. 75		120. 1	1. 05	12
	88. 8	NB			112. 5		12
	90. 6	L	4. 0		121. 5	1. 08	12
	92. 0	NB			147. 9		12
	92. 5	L	4. 18		153. 9	1. 04	12
Sigmodon hispidus	125. 8	NB			146. 8		13
	180. 2	P	5. 0		233. 9	1. 60	13
	125. 0	L	5. 0		193. 7	1. 30	13
Sigmodon hispidus	175	NB			158. 5		14
	241	P	7. 0		240	1. 51	14
	169	L	6. 9		450	2. 84	14
Sigmodon hispidus	145. 7	L ∗	5. 0		390. 4	2. 65ˆ	15
	127. 5	L	5. 0		269. 3	1. 83ˆ	15
Sciurus niger	880	NB			1516		16
		L	4. 0		3579	2. 36	16

References 1. Glazier, 1985; 2. Millar and Innes, 1985; 3. Millar, 1985; 4. Kaczmarski, 1966; 5. Hammond and Kristan, 2000; 6. Migula, 1969; 7. Millar, 1978; 8. Weiner, 1987; 9. Sikes, 1995; 10. Degen et al. , 2002; 11. Liu et al. , 2003; 12. Kam et al. , 2003; 13. Randolph et al. , 1977; 14. Mattingly and McClure, 1982; 15. Rogowiz, 1998; 16. Havera, 1979.
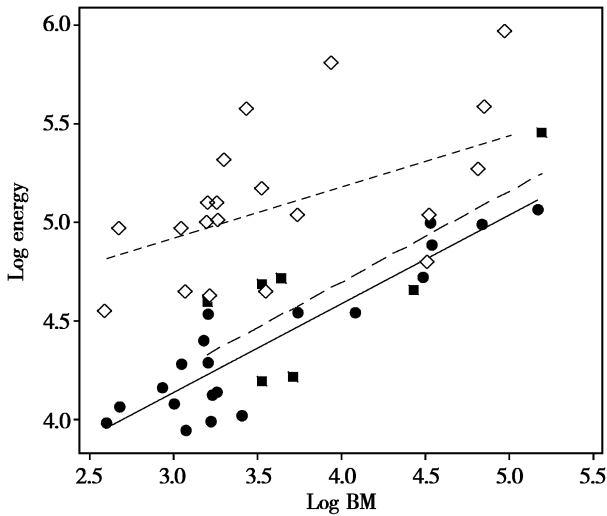
Fig. 5　Energy intake of female small non-domesticated rodents, when not breeding (●), pregnant (■) and lactating (□). There was no significant elevation in intake during pregnancy, but intake during lactation was significantly elevated compared to both non-breeders and pregnant individuals (complete data in table 1)
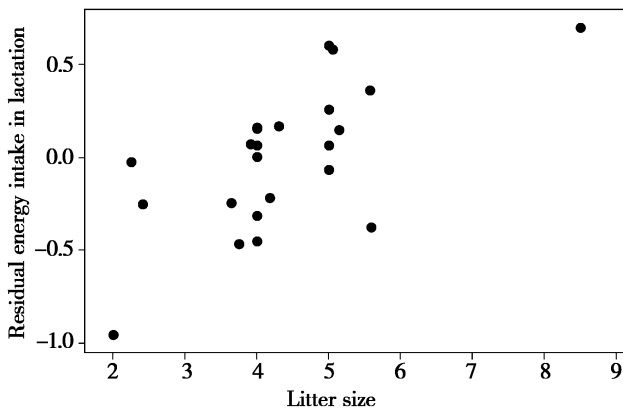

Fig. 6　Residual energy intake of small non-domesticated rodents during lactation with the effect of body mass (fig. 5) removed. Residual energy intake was significantly ($P = 0.0103$) associated with litter size (but not with gestation period – $P = 0.13$). Data in Table 1.

Hence the low values in the cotton rat (*Sigmodon hispidus*) and the hamster (*Phodopus sungorus*) reflect the fact that these animals deposit fat stores during the early phase of reproduction that are withdrawn in lactation which reduces the need to supply all the energy from food intake (Randolph *et al*. , 1977; Mattingly and McClure, 1985; Weiner, 1987, Rogowitz and McClure, 1995). Low demands in other species may reflect the use of compensatory mechanisms that reduce expenditure on other components like physical activity. However some of this residual variation will undoubtedly also reflect error variance due in part to errors in the conversion of data in the original sources into common units which required me to make assumptions about the energy content of the food and/or the digestive efficien-

cy of the animals.

Expressing the peak lactation energy intake as a multiple of the intake of non-breeding animals the average across all the rodents in Table 1 was 2. 1 ($sd = 0.72$, $n = 21$). This is considerably lower than the ratio in our studies of MF1 mice at 21℃ which equalled 4. 2. In part this is because the data for the other species in table 1 includes some values that are mean intakes across the whole of lactation, as well as 'peak' intakes. Even so, the intake of the MF1 mice at this temperature is within the 95% confidence limits of the prediction from the fitted regression equation from the non-domesticated rodents, given the body size and litter size for this animal. The importance of the differences in magnitude between the peak levels of intake in wild rodents and laboratory mice and rats remain uncertain. In most of the species studied in Table 1, peak intake of food during lactation is dependent on litter size. Generally however these patterns do not reach an asymptotic level as observed in the MF1 mice (Fig. 3). Two examples are shown in Fig. 7. Despite this absence of an asymptote in both species (and others) there is still an inverse relationship between the litter size and mean offspring size, indicating that increases in investment were insufficient to match elevated demand. These data suggest that the trade-off between litter size and pup mass is more complex than the simple model of the mother reaching an asymptotic intake at which point a fixed investment is divided between increasing numbers of offspring. Part of this trade-off, however, may be capacity limits in the offspring themselves and how these depend on litter size. Pup-pup competition may be a key element of the impact of litter size on their growth efficiency. In spite of these complexities, it is clear that understanding the nature of the sustained rate of intake will be an important aspect of our understanding of the energy demands of reproduction, and how this is associated with reproductive trade-offs.

4　The limit to sustained intake at peak lactation-central and peripheral limitation hypotheses

Two hypotheses concerning the nature of the sustained limit on intake were proposed in the early 1990s (Petersen *et al*. , 1990; Weiner, 1992; Hammond and Diamond, 1997). The first hypothesis was that the limit was imposed by the capacity of the alimentary tract to absorb food (energy) and process it into a form for mobilisation. This 'was called the central limitation hypothesis'. The second hypothesis was that the limit is imposed at the peripheral site where the centrally supplied energy is utilised: primarily the mammary
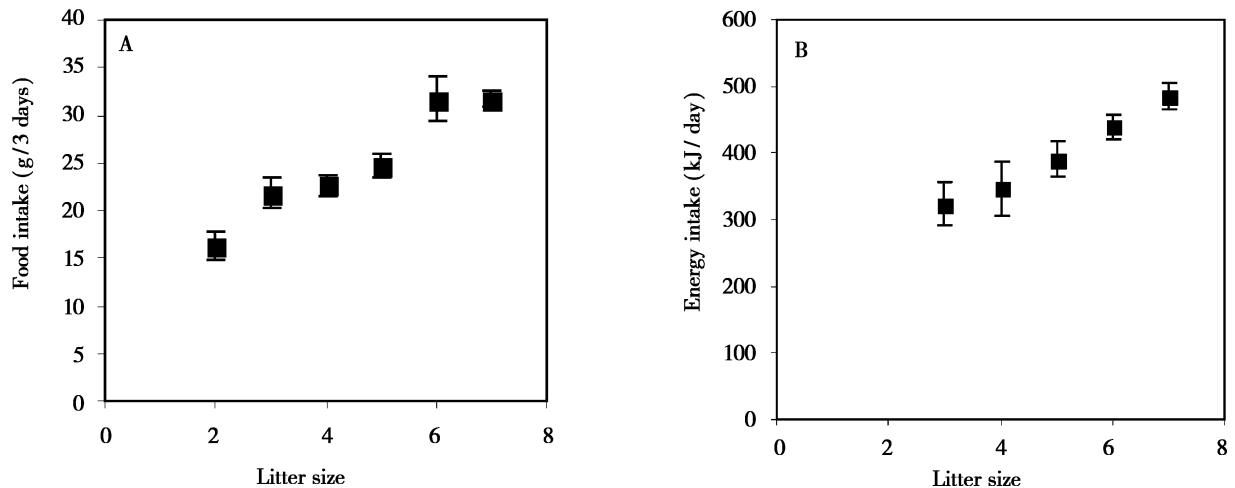
Fig. 7 A : Food intake at peak lactation (grams over 3 days) in relation to litter size in *Peromyscus leucopus* (drawn from tabulated data in Millar 1978) ; B : Energy intake during lactation (kJ/day) in relation to litter size in *Sigmodon hispidus* (drawn from tabulated data in Rogowitz 1998)

glands. This was called the 'peripheral limitation hypothesis'.

Hammond and Diamond (1992) manipulated litters of Swiss Webster mice and found that females did not elevate their food intake when given up to 23 pups. Similarly, we have also shown that MF1 mice given up to 19 pups also could not breach the 23 g limit that they reached during unmanipulated lactations with litters of greater than 10 offspring (Johnson *et al.* , 2001a). Faced with this problem of a litter size that is too large' females will often cull their offspring rather than eat more food. Johnson *et al.* , 2001a; Gandelman and Simon, 1978). In a separate experiment Hammond and Diamond (1994) prevented pups from weaning at their normal weaning age and hence their increasing growth demands all needed to be supplied by the mother until the pups were 24 days old. In these conditions the mothers also could not upregulate their food intake. The absence of an increase in intake when pup numbers are increased or lactation extended confirms there is a physiologically imposed limit, but does not separate between the peripheral and central limits hypotheses.

Giving female mice additional energy demanding tasks during late lactation can better separate the alternative hypotheses. The basis of these experiments is that, if the system is centrally limited, the total energy available will be fixed. Using some of this energy to perform another task will reduce the amount available to support milk production and the consequence will be a diminution of reproductive output. Alternatively if the system is peripherally limited the animals will increase their intakes to meet the combined demands, and reproductive output will remain unaffected. Three manipulations have been performed to test these ideas : lacta-

ting mice have been forced to exercise to obtain their food; they have been made simultaneously pregnant, combining the demands detailed in fig. 1 , and they have been exposed to cold.

Perrigo (1987) compared the reproductive strategies of house mice *Mus domesticus* and deer mice *Peromyscus maniculatus* by forcing females to run a pre-set number of revolutions (between 75 and 275) on a wheel to obtain each pellet of food. Despite the combined demands of lactation and locomotor activity, neither house nor deer mice exceeded the upper limit of food intake compared to unmanipulated mothers, given free access to food. As a result of the decreased amount of energy available for reproduction, the wheel-running house mice routinely killed some of the offspring throughout the first 12 days of lactation, whereas deer mice extended lactation well beyond normal weaning age.

Johnson *et al.* , (2001b) followed the intakes of mice that had been mated immediately post-partum and found that the mice concurrently lactating and pregnant did not respond to the increased energy burden by elevating their food intake. Instead, they delayed implantation at the start of the second pregnancy and the length of this delay was directly related to the numbers of pups. The animals therefore "avoided" overlapping their energy demands, perhaps because they could not elevate their total intake at peak lactation to accommodate both, or perhaps because it would be unfeasible to take in sufficient energy to support the current lactation if the abdomen was full of developing foetuses (the limited abdominal space idea). Similar observations were made in Rockland-Swiss mice (Biggerstaff and Mann, 1992), and in rats (*Rattus norvegicus* : Koiter *et al.* , 1999), when food intake in late lactation was

actually reduced in those rats that carried a simultaneous pregnancy, relative to rats just lactating, again perhaps reflecting a space constraint. Together, these activity and pregnancy studies indicate that the limits are centrally, rather than peripherally, mediated- although, in case of concurrent pregnancy, the evidence is less strong as the animals "avoided" the problem.

However, when Hammond et al. (1994) exposed lactating Swiss Webster mice to 8℃ (approximately 22℃ below the lower critical temperature), they found that food intake increased dramatically beyond the supposed centrally imposed limit. Similar observations have since been made in deer mice (Hammond and Kristan, 2000), MF1 mice (Johnson and Speakman, 2001) and cotton rats (Sigmodon hispidus) (Rogowitz, 1998). The capacity of the mice to elevate their food intake in the cold was completely at odds with the central limitation hypothesis. To test if the limit was imposed peripherally, Hammond et al. (1996) experimentally manipulated female mice by surgically removing some of their mammary glands during late lactation. The rationale behind this experiment was that if the capacity of the mammary glands was limited, then, if the mammary tissue was halved in size, the remaining tissue would be unable to compensate by elevating its milk production. However, if the capacity of the tissue was flexible and limited only by the centrally controlled supply of energy, then it would respond to the absence of half the tissue by expanding its capacity. They found that productivity in the halved glands did not increase, suggesting that the mammary gland was indeed the point at which the system was peripherally limited.

The above experiments suggested that there is a physiological limit in the capacity of the mammary tissue to secrete milk, which underlies the asymptotic food intake in late lactation and thus the trade-off between litter size and pup size and potentially defines the maximal litter size. When animals were manipulated at room temperature by giving them more pups to raise, food intake did not increase because milk production was limited by the capacity of the mammary glands. When exposed to cold conditions, food intake did increase (demonstrating a lack of central limitation) because of the combined demands for milk production (at maximal capacity) and increased thermogenesis.

Several other studies have been performed that also indicate that the limits to intake at peak lactation are not centrally mediated. These studies involve manipulation of the energy density of the food. If the energy density of food is decreased but animals have a central processing capacity limit, they should be unable to up-regulate their intake to compensate. Speakman et al. (2001) fed MF1 mice a diet that provided 25% less digestible energy than their normal food and then mated them. Food intake in the mice fed on the low energy density food increased at peak lactation by on average 3.8 g (from 23.1 to 26.9 g per day). In lagomorphs similar data are available for brown hares (Lepus europeaus) (Hacklander et al., 2002). When fed on a diet with lower energy content, asymptotic food intake in late lactation increased from 230 – 250 to 280 – 300 g per day. In consequence milk production was stable across the dietary treatments at around 35 g per day for females raising single offspring and 70 g per day for females raising twins. Conversely when energy density was manipulated in the opposite direction there was no indication that energy intake is elevated. For example, rats fed a high energy density diet during lactation, decreased their food intake to sustain energy intake constant (Denis et al., 2003).

An important aspect of the peripheral limitation idea is that milk production levels remain constant across the different manipulations reflecting the fact the mammary glands are working at capacity. Several studies have measured milk production and support this prediction. Rogowitz (1998) demonstrated in cotton rats that levels of milk production in rats at 21℃ and 8℃ were similar consistent with the mammary glands working at maximal capacity. Additional work has been performed in lagomorphs and mustelids. Drummond et al. (2000) studied milk production in rabbits (Oryctolagus cunniculus) and observed that, following natural deaths of some offspring, the flow of milk was unaltered. Fink et al. (2001) studied lactation in captive mink (Mustela vision) and showed that in mothers raising litters of 3, 6 and 9 offspring, milk production did not increase when litters increased from 6 to 9 offspring. However, other studies have failed to find this consistency (Johnson and Speakman, 2001; Król and Speakman, 2003a, 2003b; Król et al., 2003). We have now studied food intake and milk production in mice at peak lactation at three different temperatures: 30℃, 21℃ and 8℃. As predicted by the peripheral limitation hypothesis food intake increased across these measurements as temperature declined. However, unexpectedly, milk production and consequently pup growth were not constant across the different temperatures, but followed the pattern of food intake. Mice exported 88 kJ energy in milk per day at 30℃, 167 kJ at 21℃ and 288 kJ at 8℃. Moreover, the weaning masses of pups at 30℃, 21℃ and 8℃ averaged 6.1, 7.0 and 7.3 g, respectively. Consequently the colder it got the more food the mice ate, the more milk they pro-

duced and the heavier the pups were at weaning.

5 Sustained limits on energy intake some new ideas

These latter data are fundamentally inconsistent with both the suggestion that the limits are imposed by the capacity of the alimentary tract to process ingested energy (central limitation) and the suggestion that the limits reside in the milk production capacity of the mammary gland (peripheral limitation). There are a number of new ideas about the nature of the limit in food intake during lactation which have been recently summarised (Speakman and Król, 2005). For example, one of these novel ideas is that the limits are imposed by aspects of the 'neuroendocrinological system that regulates food intake rates the neural saturation hypothesis '. An alternative, suggested by Król and Speakman (2003a, 2003b), is that the capacity to expend energy during lactation at 21℃ might be limited by the ability of the female mouse to dissipate heat. Hence, manipulations at 21℃ that aim to stimulate both food intake and milk production notably increasing litter size (Hammond and Diamond, 1992), extending lactation (Hammond and Diamond, 1994), making them simultaneously pregnant (Johnson et al. , 2001b ; Koiter et al. , 1999 ; Biggerstaf and Mann 1992) and making them exercise (Perrigo, 1987) –all failed to increase either food intake or milk production, because the animals could not increase their heat production without risking fatal hyperthermia. In effect, this hypothesis is a central limitation idea, but is focussed around the ability to dissipate heat rather than assimilation from the gut. Under the heat dissipation limit hypothesis, when mice are exposed to the cold this is not an additional demand, but a relaxation of the heat dissipation limit, allowing the animals to elevate not only their food intake but also their milk production and thus the size of their offspring. Similarly, when mice were placed in the hot, this reduced their capacity to dissipate heat, restricted their food intake and milk production and led to smaller pups being weaned.

6 Heat as a constraint on reproductive energetics

For at least half a century it has been known that high ambient temperatures and humidity, or exposure to solar radiation, negatively affect milk production by dairy cows (Bos taurus) (Cobble and Herman, 1951 ; Brody et al. , 1958). Similar negative effects of high ambient temperatures have been reported in other large domestic animals such as wild pigs (Sus scrofa : Black et al. , 1993 ; Quiniou and Noblet, 1999 ; Renaudeau and Noblet, 2001) and sheep (Ovis aries : Abdalla et al. , 1993). Many of these larger animals also exhibit chronic hyperthermia during lactation (e. g. sows, Ul-

mershakibaei and Plonait, 1992). Although large domestic animals experinec difficulties with heat dissipation these effects may be far less significant in small mammals because they have much larger surface to volume ratios. Nevertheless, direct measurements of maternal body temperatures confirm that lactating rats (Croskerry et al. , 1978 ; Kittrell and Stainoff , 1988 ; Leon et al. , 1978, 1985) and Siberian hamsters Phodopus sungorus (Scribner and Wynne–Edwards, 1994a) are hotter than their non–reproducing equivalents. Studies of blood flow during lactation indicate that there is no major redirection of blood away from the mammary glands to facilitate heat loss (cattle, Lough et al. , 1990 ; Renaudeau et al. , 2003 ; goats Capra hircus, Sano et al. , 1985 ; rabbits, Lublin and Wolfenson, 1996), which would be a potential mechanism mediating the effect of heat on milk production.

There is a substantial body of behavioural literature following the pioneering work of Leon et al. (1978) which suggests that suckling behaviour of small rodents may be influenced by the risks of maternal hyperthermia. These studies included observations that rats terminated suckling bouts when their body temperatures rose. Similar effects have been reported in larger lactating animals that have contact with their offspring such as sows (Rebaudeau and Noblet, 2001), where elevated temperature led to reduced durations and greater frequencies of suckling bouts coupled with lowered milk production and piglet growth. Perhaps the best evidence comes from direct experimental manipulations of body temperature and examination of the subsequent effects on suckling behaviour. These experiments have only been performed on rats, but have involved two separate manipulations. Direct heating of the pre–optic area of the brain, which led to premature termination of suckling bouts, and injection of rats with morphine, which elevates body temperature and causes disruption of maternal suckling behaviour (Bridges and Grimm, 1982). However, rats are an order of magnitude larger than mice, so perhaps of greater relevance are the studies of Siberian hamsters, which show that during the daytime, the time spent with the litter in late lactation may be constrained by ambient temperature (Scribner and Wynne–Edwards, 1994b). Interestingly, the two sub–species of Siberian hamster (P. sungorus sungorus and P. sungorus campbelli) differ in the rates at which the offspring develop their own thermoregulatory capacities faster in P. s. campbelli (Newkirk et al. , 1998). This difference is reflected in greater and earlier problems in maintaining body temperature during suckling bouts by female P. s. campbelli (Scribner and Wynne–Edwards, 1994b) and consequent negative effects on pup growth in this

sub-species (Newkirk et al., 1998).

Despite a large literature indicating that there are direct effects of the litter on maternal hyperthermia, there are contradictory data. For example, experimental inductions of reduced body temperature using sodium salicylate did not extend suckling bouts (Bates et al., 1985). Although treatment of lactating rats with morphine simultaneously elevates body temperature and disrupts maternal suckling (above), the negative effect of morphine appears to be independent of its effects on body temperature. This is shown by experiments in which morphine was administered with naloxone, an opioid receptor antagonist. Blocking morphine with naloxone reversed the negative effects on maternal behaviour (Bridges and Grimm, 1982) but not maternal hyperthermia (Cox et al., 1976). Rats with experimentally induced increases in body temperature using morphine and naloxone combinations (Stern and Azzara, 2002) did not shorten their suckling bouts. However, this latter manipulation was performed only 7 days into lactation and it would be instructive to know if a similar absence of the effects of combined morphine/naloxone treatment were apparent later in lactation when pup heat stress is more profound. Body temperatures at which rats discontinue suckling are generally lower than the levels they tolerate while exercising outside the nest (Kittrell and Satinoff, 1988). Finally, rats fed low-quality protein in their diets did not show reduced performance when raised at 30℃ compared to 20℃ (Jansen and Binard, 1991), even though their litters probably generated similar heat dissipation problems. Overall, there is a definite negative effect of ambient temperature on lactation performance of large animals, but the significance of these effects in smaller animals like mice remains uncertain.

One indicator of the effects of heat on lactation in small mammals may perhaps be revealed in the changes in their thermoregulatory capacity in lactation. Many species of small rodent undergo large morphological and biochemical changes in their interscapular brown adipose tissue (BAT) when lactating. These modifications include reductions in the amount of BAT in mice, rats, ground squirrels and hamsters (Agius and Williamson, 1980; Wade et al., 1986; Johnston et al. 2001b) and reductions in BAT mitochondrial mass (Trayhurn et al., 1982; Trayhurn and Jennings, 1987). In late lactation, mitochondria-specific content of uncoupling protein 1 (UCP-1) is reduced to only 8% of the level found in non-breeding mice (Trayhurn and Jennings, 1987, 1988) and to 26% in ground squirrels (Nizielski et al., 1993). GDP-binding, which reflects non-shivering thermogenic capacity, is also reduced in lactating mice and rats (Trayhurn et

al., 1982) and ground squirrels (Nizielski et al., 1993), but not in hamsters (Wade et al., 1986). Brown adipose tissue is the main thermogenic organ in small rodents (Cannon and Nedergaard, 2004) and the changes observed in lactating rodents mediate a reduction in the noradrenaline-induced non-shivering thermogenesis (Trayhurn, 1983; Trayhurn et al., 1982), which is rapidly reversed upon weaning (Trayhurn and Jennings, 1987, 1988). In rats, the extent of decrease in thermogenic capacity is related to litter size (Isler et al., 1984), but this does not appear to be the case in mice (Trayhurn and Wusterman, 1987). Changes in other aspects of BAT physiology are also apparent during lactation, including reduction in activity of iodothyronine 5' – deiodinase, which catalyses conversion of thyroxine (T4) to triiodothyronine (Giralt et al., 1986). These physiological changes in BAT are consistent with small lactating animals attempting to reduce obligatory heat production. Trayhurn (1989) interpreted this reduction as an energy saving mechanism that increased the efficiency of milk production. However, in the light of our studies of limits to food intake in lactating mice described above, an alternative interpretation is that this down regulation not only saves energy that can be used for milk production, but also reduces the heat burden on the animal, allowing it to elevate milk production.

7   Conclusions

The energy costs of reproduction are probably a significant component underlying life history trade-offs. In this review I have summarised some of the work that has been performed to measure these costs in small mammals. Considerable progress in elucidating the limits on energy budgets during reproduction in small domesticated rodents have been made in the last 15 or so years. Patterns of energy intake during reproduction in domesticated mice are mirrored in the patterns of intake in wild rodents and other small mammals. This is encouraging because it suggests that studies in domesticated rodents may have broader relevance. The work performed in domestic mice has suggested that the limits on intake are mediated neither by a central processing constraint in the alimentary tract, or a milk secretion limit in the mammary glands. A recent novel hypothesis is that constraints may be imposed by the capacity of lactating rodents to dissipate heat. This is consistent with the down-regulation of the activity of the non-shivering thermogenesis system in small rodents. Despite the intensive research activity in this area we are still far short of being able to translate this knowledge into an understanding of a simple life history trade-off between the number and size of offspring.

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