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Phenotypic plasticity in laboratory mice and rats: a meta-analysis of current ideas on gut size flexibility

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ABSTRACT

Background: Animals' digestive tract represents the functional link between foraging and the energy available for survival, growth, and reproduction. In addition, gut tissue is one of the most expensive tissues to maintain in terms of energy and protein metabolism. Thus, gut size flexibility has been suggested to be one of the most important physiological adjustments to cope with changes in environmental conditions.

Hypotheses: (1) Animals adjust their digestive features to cope with changing environmental conditions, and increase gut size in parallel to increased food consumption. (2) Changes in different energy-demanding factors, such as lactation, pregnancy, and temperature, determine different magnitudes of gut size flexibility. (3) Changes in the amount of undigestible material in the diet mainly affect the size of the fermentative chambers, while changes in energy demands mainly affect the size of the small intestine. (4) The qualities of a demand, such as its relative intensity or duration, affect the amount of digestive flexibility.

Data incorporated: We focus on digestive organ length and dry mass of laboratory mice (*Mus musculus*) and white rats (*Rattus norvegicus*). We found and reviewed 25 studies that reported a total of 55 comparisons for small intestine length, 67 for small intestine dry mass, 25 for hindgut length, and 26 for hindgut dry mass.

Method of analysis: We conducted a meta-analysis in which we calculated the Hedges difference for each comparison, and using mixed-effects models plus heterogeneity tests to evaluate differences among factors.

Results: Although gut size flexibility was noted for all the experimental factors evaluated, there was variation in the amount of digestive flexibility determined by each factor. Changes in large intestine length were greater for changes in diet quality than for changes in energy-demanding factors, but this result was not observed for large intestine mass. A clear correlation between gut size flexibility and the number of pups reared during lactation was recorded.

Conclusions: The present analysis confirms previous hypotheses on gut size flexibility, providing strong quantitative support for them.

Keywords: digestive physiology, *Mus musculus*, phenotypic flexibility, *Rattus norvegicus*.

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INTRODUCTION

Phenotypic flexibility refers to reversible change in the traits of an organism due to changes in environmental conditions (Piersma and Drent, 2003). Different lines of evidence suggest that these reversible adjustments increase the fitness of an organism (Scheiner 2002; Pigliucci and Schmitt, 2004; Richter-Boix *et al.*, 2006; Teplitsky *et al.*, 2007), although this is not easily demonstrated by direct manipulation (see Schmitt *et al.*, 1999). The phenotypic flexibility of the digestive tract has received considerable attention (for reviews, see Karasov and Diamond, 1983; Starck, 1999; McWilliams and Karasov, 2001; Naya and Bozinovic, 2004) for several reasons. First, the gut represents the functional link between foraging (energy intake) and the energy available for survival, growth, and reproduction (Karasov, 1990; Secor, 2001). Hence, it could be expected that animals adjust their digestive attributes to changes in food availability or quality to maximize overall energy return and these components of fitness (Sibly, 1981). Second, gut tissue is one of the most expensive tissues to maintain in terms of energy and protein metabolism (Cant *et al.*, 1996). Thus, adjusting the amount of gut tissue to the functional demand could represent an important energy-saving mechanism.

Gut size flexibility in laboratory mice and rats has been studied for more than a century, mainly from three different perspectives. The first group of studies belongs to the classical physiological framework. The main purpose of these studies was the evaluation of digestive changes to variation in experimental factors, such as diet quality (e.g. Wierda, 1950; Dowling *et al.*, 1967), environmental temperature (e.g. Heroux and Gridgeman, 1958; Barnett and Widdowson, 1965), and reproductive status (e.g. Fell *et al.*, 1963; Campbell and Fell, 1964). The second group comprises studies conducted from 1990 within the context of a debate about central versus peripheral limitation (see Bacigalupe and Bozinovic, 2002; Speakman and Krol, 2005). These studies focused on the question of what imposes a limit on an organism's energy budget. From a digestive perspective, such studies yielded abundant data on the effect of lactation (e.g. Hammond and Diamond, 1992, 1994), environmental temperature (e.g. Konarzewski and Diamond, 1994), and the two combined (e.g. Hammond *et al.*, 1994; Krol *et al.*, 2003) on features of the gut. The third group of studies is still more recent, and refers to the analysis of combined energy demands on gut flexibility. The underlying idea of these studies was that combinations of factors are most representative of what really occurs in nature, as opposed to the operation of individual factors separately (Kristan and Hammond, 2000). In most cases, these studies combined parasitism with an additional energy-demanding factor, such as environmental temperature (e.g. Kristan and Hammond, 2000, 2003) or lactation (e.g. Kristan, 2002; Kristan and Hammond, 2004).

The aim of the present study was to combine the results of the above research and, by conducting a meta-analysis, quantitatively test current ideas on gut size flexibility in rodents. Meta-analysis is considered an excellent method of comparing and summarizing the results of multiple studies for several reasons (Arnqvist and Wooster, 1995). First, as a quantitative review, it can provide different information than that provided by a narrative review. Second, it establishes the effect size of a particular factor, which is very important when planning new studies because that permits one to estimate the required number of replicates. Third, it allows much better control of Type II statistical errors (i.e. failure to reject a false null hypothesis) by combining the results of many studies. Finally, it permits a statistical test of the effect of different factors, and also the assessment and correction of methodological problems. Here, we use meta-analysis to determine whether:

1. Animals adjust their digestive features to cope with changing environmental conditions, and increase gut size in parallel with increased food consumption.
2. Changes in different energy-demanding factors, such as lactation, pregnancy, and temperature, determine different magnitudes of digestive flexibility.
3. Changes in the amount of undigestible material in the diet mainly affect the size of the fermentative chambers, while changes in energy demands mainly affect the size of the small intestine.
4. The qualities of a demand, such as its relative intensity or duration, and not only its presence or absence, affect the amount of digestive flexibility.

METHODS

Database and specific hypotheses to be tested

We focus on laboratory mice (*Mus musculus*) and white rats (*Rattus norvegicus*) because these species provide enough information to allow a quantitative review, without introducing any taxonomic variation in the data set. Digestive organ length and dry mass were chosen as the response variables of our analysis because changes in digestive capacity in response to changing intakes is mainly achieved by reversible changes in these features (see Karasov and McWilliams, 2005). We found a total of 25 studies, published between 1934 and 2004, that contain useful data on these variables (Table 1). The numbers of comparisons on gut size retrieved from these papers were 55 for small intestine length, 67 for small intestine dry mass, 25 for hindgut length, and 26 for hindgut dry mass (Table 1). As can be observed, most of the studies analysed reported data only for the small intestine, and consequently much of our analysis is limited to changes in this organ.

From the database constructed, we quantitatively evaluate the following hypotheses:

1. Animals need to adjust the attributes of their digestive tract to cope with changing environmental conditions, and greater gut size is expected when the amount of undigestible material in the diet increases or when energy demands increase. This is because in both situations animals should increase their food consumption to balance digestible energy intake and output (Karasov and Diamond, 1983). To test this idea, we estimated the adjustments in small intestine length and dry mass for different experimental factors, and evaluated if the confidence interval around the cumulative effect size intersects zero.
2. Changes in different energy-demanding factors impose different energetic costs, and thus determine different magnitudes of digestive flexibility (Cripps and Williams, 1975; Hammond *et al.*, 1994). To test this hypothesis, we compared the adjustments in small intestine length and dry mass in relation to lactation, pregnancy, and changing environmental temperature.
3. Changes in the amount of undigestible material in the diet, which is inversely related to diet quality, mainly affect the size of the hindgut (i.e. the fermentative chambers), whereas changes in energy demands mainly affect the size of the small intestine (i.e. the absorptive chamber) (Gross *et al.*, 1985; Hammond and Wunder, 1991). To test this hypothesis, we compared changes in length and dry mass of the midgut (small intestine) and hindgut (large intestine plus cecum) between diet quality and energy-demanding factors.

Table 1. List of papers and number of comparisons used in the meta-analysis

Source		Small intestine length	Small intestine dry mass	Hindgut length	Hindgut dry mass
1	Abramson (1934)		2		
2	Barnett and Widdowson (1965)	6	5		2
3	Barnett and Widdowson (1971)	2	2		
4	Brown *et al.* (1979)	2			
5	Craft (1970)	2	2		
6	Cripps and Williams (1975)	3	3	3	2
7	El-Harith *et al.* (1976)		2		2
8	Hammond and Diamond (1992)	1	2	2	2
9	Hammond *et al.* (1994)	10	10		
10	Hammond *et al.* (1996a)	3	3		
11	Hammond *et al.* (1996b)	2	4	3	1
12	Hansen *et al.* (1992)	3		3	
13	Johnson and Speakman (2001)	1	1	1	1
14	Konarzewski and Diamond (1994)		3		
15	Kristan (2002)	2	2		2
16	Kristan and Hammond (2000)	2	4		4
17	Kristan and Hammond (2004)	3	3		4
18	Krol *et al.* (2003)		1		1
19	Peters *et al.* (1967)		1		1
20	Poksay and Schneeman (1983)		1		
21	Sigestad and Osborne (1972)		12		
22	Toloza *et al.* (1991)	4		4	
23	Wierda (1942)	2		2	
24	Younoszai *et al.* (1978)	4	4	4	4
25	Zhao *et al.* (1995)	3		3	

4. The relative intensity of a demand, not only its presence or absence, also affects the amount of digestive flexibility (Kristan and Hammond, 2004, 2006). To test this hypothesis, we analysed the relationship between flexibility in small intestine length and dry mass and the number of pups reared by lactating females.

Statistical analysis

To test the above hypotheses, we conducted a meta-analysis. For that purpose, we first calculated the effect size, as the Hedges difference (i.e. the difference between control and experimental means expressed in units of pooled standard deviation and corrected for small sample bias), and its associated variance for each comparison (see Rosenberg *et al.*, 2000; Gurevitch and Hedges, 2001). Next, we estimated the cumulative effect size for each experimental factor (E), its associated variance, and the confidence interval for an alpha value of 0.05, using a bootstrapping procedure with 1000 iterations (see Rosenberg *et al.*, 2000; Gurevitch and Hedges, 2001). A conventional interpretation of the magnitude of an effect size is: 0.2 represents a 'small' effect, 0.5 represents a 'medium' effect, 0.8 represents a 'large' effect, and values above 1.0

are considered a 'very large' effect (Cohen, 1969). In addition, we used Orwin's methods to estimate a fail-safe number – that is, a number of non-significant, unpublished or missing comparisons that would need to be added to the analysis to reduce the cumulative effect size to a 'minimum' value of 0.2 (see Rosenberg *et al.*, 2000). Finally, to evaluate differences in cumulative effect sizes (E) among experimental factors, we used mixed-effects meta-analytical models plus heterogeneity tests (see Rosenberg *et al.*, 2000; Gurevitch and Hedges, 2001). In these analyses, total heterogeneity (Q_T) was decomposed into the heterogeneity explained by the model (Q_M) and error heterogeneity (Q_E), in a similar fashion as in a one-way analysis of variance. Both Q_M and Q_E can be tested against a χ^2-distribution with $m-1$ degrees of freedom for Q_M and $n-m$ degrees of freedom for Q_E (where n is the number of comparisons and m is the number of factors). A significant Q_M means that at least one factor is significantly different in its cumulative effect size from the others factors. Pairwise comparisons between factors were assessed by heterogeneity tests, using the Bonferroni method to correct the critical alpha value. Analyses were conducted using Metawin® version 2.0, and Statistica® version 6.0, for the Windows® operating system.

RESULTS

We found that, except for the case of length under different environmental temperatures, adjustments in small intestine size to changes in experimental factors were always significant – that is, the confidence intervals around the cumulative effect size does not include zero (Table 2). In addition, the number of unpublished comparisons required to change the observed effect size to a minimum effect size is 258 for small intestine length and 509 for small intestine dry mass. For the case of small intestine length, lactation caused the greatest amount of change, followed by diet quality, pregnancy, and finally temperature. For the case of small intestine mass, lactation caused the greatest amount of change, followed by diet quality, pregnancy, and finally temperature (Table 2). In line with our third

Table 2. Cumulative effect size of small intestine flexibility (E), with the standard error (SE_E), 95% confidence interval (CI), and fail-safe number (FSN) for each experimental factor (n = total number of comparisons used in the analysis)

Factor	E	SE_E	CI	FSN	n
Small intestine length					
Lactation	2.02^{a}	0.20	1.54 to 2.51	202	22
Diet quality	$1.43^{a,b}$	0.42	0.67 to 2.40	90	12
Pregnancy	$0.47^{b,c}$	0.10	0.17 to 0.86	8	5
Temperature	0.16^{c}	0.04	−0.08 to 0.39	0	16
All factors	1.14	0.12	0.79 to 1.46	258	55
Small intestine mass					
Lactation	2.50^{a}	0.13	2.13 to 2.86	380	33
Diet quality	1.47^{b}	0.35	0.79 to 2.31	40	7
Pregnancy	1.46^{b}	0.21	0.93 to 1.97	69	11
Temperature	0.93^{b}	0.16	0.57 to 1.38	58	16
All factors	1.72	0.09	1.45 to 2.00	509	67

Note: Superscript letters denote significant differences between means.

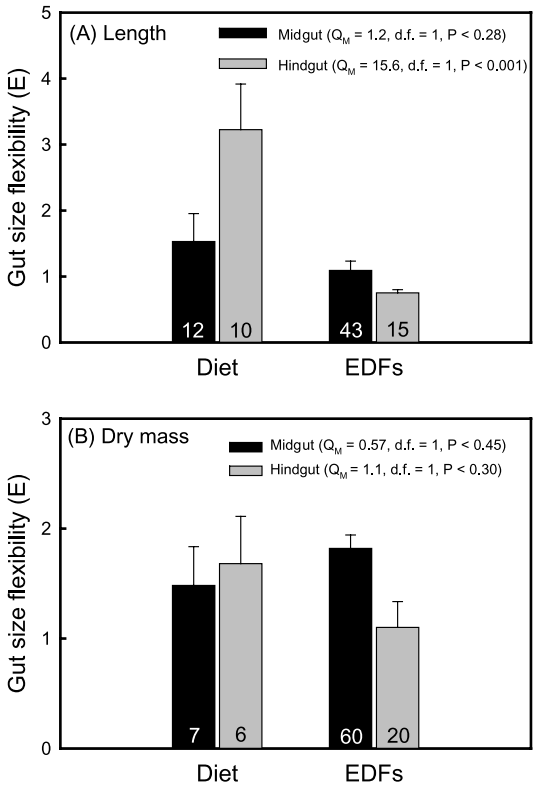

Fig. 1. Midgut (small intestine) and hindgut (large intestine plus cecum) flexibility due to changes in diet quality and energy-demanding factors (EDFs = lactation, pregnancy, and temperature). (A) Cumulative effect size for length. (B) Cumulative effect size for dry mass. Bars = 1 standard error. Total numbers of comparisons are given inside each bar.

hypothesis, we found that changes in large intestine length were greater for changes in diet quality than for changes in energy-demanding factors (Fig. 1A). However, this comparison did not reach statistical significance for the case of large intestine mass. Also, the inverse pattern predicted for the small intestine by the same hypothesis (i.e. greater values for energy-demanding factors) was not observed for length or mass (Fig. 1A,B). Finally, we found a highly significant correlation between the flexibility of small intestine length or dry mass and the number of pups reared during lactation (Fig. 2).

DISCUSSION

Gut flexibility has been suggested to be one of the most important physiological adjustments necessary to cope with changes in biotic and abiotic environmental conditions (Piersma and Lindstrom, 1997; Weber and Hedenstrom, 2001). Accordingly, we found that flexibility in small intestine length was highly significant for three of the four experimental factors evaluated, while flexibility in small intestine dry mass was significant for all four factors. In addition, the estimated fail-safe numbers were one order of magnitude greater than the number of studies analysed, which strongly suggests that our results are not due to publication biases.

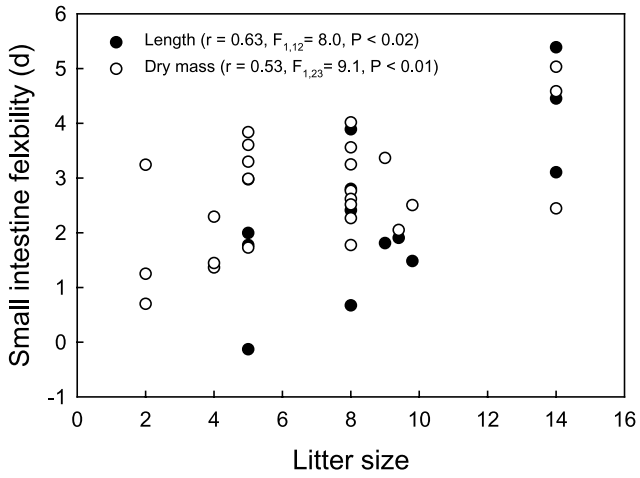

Fig. 2. Relationship between small intestine flexibility (effect size for length and dry mass) and litter size (number of pups reared during lactation).

Because animals usually compensate for the consumption of a low-quality diet or the increase in energy demands by increasing their food intake, an augmentation in gut dimensions at this time is expected from optimal digestion models (Sibly, 1981; Penry and Jumars, 1987; Martinez del Río *et al.*, 1994). According to these models, the performance of a reactor is directly related to its volume and the digestion and absorption rate, and inversely related to digesta flow rate. Thus, to avoid a decrease in digestive performance, animals should compensate for the increase in food consumption by increasing small intestine volume – which is related to an increase in gut mass and usually in gut length – and/or by increasing the summed digestion and absorption rate – which is usually achieved by an increase in small intestine mass (Karasov and Hume, 1997).

With regard to our second hypothesis, many studies on mammalian reproductive energetics have demonstrated that energy expenditure during lactation is higher than at any other period during the life of a female mammal (Millar, 1979; Thompson and Nicoll, 1986; Kenagy, 1987; Kenagy *et al.*, 1989). In addition, in small species the amount of nutrients and energy that can be supplied from body reserves obtained prior to lactation is restricted (Oftedal, 2000). Consequently, these organisms strongly depend on an increase in food ingestion at this time (Kenagy *et al.*, 1989; Speakman and Krol, 2005). Accordingly, we found that flexibility in small intestine mass and length during lactation is markedly greater than during other demanding circumstances, such as pregnancy or when animals are exposed to low environmental temperatures. This is in line with previous studies that compared changes in gut size during pregnancy and lactation (e.g. Poo *et al.*, 1939; Fell *et al.*, 1963; Cripps and Williams, 1975) or during lactation and cold temperatures (e.g. Hammond *et al.*, 1994; Hammond and Kristan, 2000). In addition, although there are limited data on the effect of lactation on wild species (and no data for pregnancy), observed values for laboratory species appear to be similar to those reported for wild species. For example, the lactation effect size for small intestine length in *Peromyscus maniculatus* that reared 5 pups at 23°C is 1.8 ± 0.3 [mean ± 1 standard error (data from Hammond and Kristan, 2000)], and that for *Microtus pinetorum* that reared 2–3 pups at 22°C is 1.4 ± 0.2 [mean ± 1 standard error (data from Derting and Austin, 1998)].

The notion that diet quality has a greater effect on hindgut flexibility than midgut flexibility can be traced to the first half of the twentieth century (e.g. Wetzel, 1928; Kestner, 1929; Addis, 1932). Wierda (1942) commented on these pioneers' works as follows: 'It was believed that the easily digestible diet had a stimulating effect upon the small intestine, and the high residue diet a stimulating effect upon the colon'. Wierda designed better controlled experiments, in terms of experimental animals and diets, and showed that, although the effect of a diet with a high content of undigestible material is noticeably at the level of the hindgut, the small intestine is also able to respond to changes in diet quality (Wierda, 1942, 1950). During the second half of the twentieth century, Wierda's results were supplemented by others (e.g. Younoszai *et al.*, 1978; Brown *et al.*, 1979; Poksay and Schneeman, 1983), which is reflected in our analysis of hindgut length flexibility. However, it is interesting that this pattern of hindgut flexibility was less clear for the case of dry mass. This suggests that the increased amount of food intake that usually occurs during the consumption of a bulky diet causes a greater mechanical distention of the fermentative chambers than an increase in the circumference or the organ's thickness. On the other hand, we did not find that changes in the amount of undigestible material in the diet result in smaller adjustments in small intestine length than do increasing energy demands. This contrasts with previous results from studies in wild rodent species, which demonstrated that lower temperatures produced greater increases in small intestine mass than did changes in diet quality (e.g. Gross *et al.*, 1985; Green and Millar, 1987; Loeb *et al.*, 1991). We suspect that this difference could be related to a methodological artifact. Specifically, studies on rats and mice comprise the evaluation of very heterogeneous substances (e.g. kaolina, agar, guar gum, pectin) and, in contrast with work in wild species, in many cases the concentrations of these substances are far from a natural range.

Finally, we found a positive and highly significant relationship between the number of pups reared during lactation and the magnitude of the small intestine response. In this sense, a linear increase in intestinal dry mass in parallel with litter size appears to be related to an increment in the intestinal mucosa layer – that is, the epithelium responsible for absorption and hydrolysis (Boyne *et al.*, 1966; Sigestad and Osborne, 1972; Hammond and Diamond, 1994; Hammond *et al.*, 1996a). Indeed, from a more general perspective, this result indicates that, as was recently proposed (Kristan and Hammond, 2004, 2006; Naya *et al.*, 2005), it is important to examine the qualities of a demand, such as its duration or intensity, not just its presence or absence.

In summary, by comparing the results of many studies, we have demonstrated that although adjustments in gut size in laboratory rodents occur under many circumstances, there is an important variation in the amount of digestive flexibility determined by different experimental factors. In general, our results confirm previous ideas on gut size flexibility (e.g. the comparison of gut flexibility among energy-demanding factors, and the relationship between litter size and mother gut flexibility), providing strong quantitative support for them. For others, they highlight some incongruity with previous results (e.g. the fact that changes in the amount of undigestible material in the diet did not provoke less adjustment in small intestine length than did increasing energy demands), which should be explored further.

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