REVIEW

Gut size flexibility in rodents: what we know, and don't know, after a century of research

Flexibilidad en el tamaño del tracto digestivo en roedores: qué sabemos, y qué no sabemos, después de un siglo de investigación

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ABSTRACT

Phenotypic plasticity comprises a central concept in the understanding of how organisms interact with their environment, and thus, is a central topic in ecology and evolution. A particular case of phenotypic plasticity is phenotypic flexibility, which refers to reversible change in organism traits due to changes in internal or external environmental conditions. Flexibility of digestive features has been analyzed for more than a century in a myriad of different species and contexts. Studies in rodents on gut size flexibility have been developed mainly from two different areas of the biological sciences, physiology and ecology. However, as for several other topics related with physiological ecology, both kinds of studies largely developed along separate paths. Herein, I evaluate altogether the information belonging to both areas. The major conclusions reached are: (1) there is a clear match between digestive morphology adjustments and change in environmental conditions, and gut size flexibility could be considered a widespread physiological mechanism occurring in laboratory and wild species, and under laboratory, semi-natural and natural conditions. (2) For laboratory species, the experimental factors that have been more investigated are diet quality, reproductive status, environmental temperature and fasting, while for wild species the more analyzed factors are diet quality and temperature. (3) For wild rodent species, no differences in small intestine length flexibility between methodological approaches nor species feeding categories has been identified. (4) It appears that high energetic demands are mainly coped with by changes at the small intestine level, while changes in the amount of undigestible material in the diet are mainly coped with by changes in the hindgut. (5) Change in gut length may be related to a decrease in food retention time (e.g., during diet dilution), while change in gut mass appears to be related to a need of higher specific absorption (e.g., during highly demanding periods). (6) The qualities of an energetic demand (e.g., its relative intensity) rather than simply its presence or absence can affect the amount of digestive flexibility. (7) Quantitative comparisons of the existing data are difficult due to several factors, such as the disparity of experimental treatments and differences in the types of data collected. At the end of this review, further directions for the study of digestive flexibility in rodents are presented.

Key words: digestive physiology, phenotypic plasticity, physiological flexibility, rodents.

RESUMEN

La plasticidad fenotípica constituye un concepto medular en el entendimiento de cómo los organismos interactúan con su ambiente y, por tanto, un tema central en ecología y evolución. Un caso particular de la plasticidad fenotípica es la flexibilidad fenotípica, la cual refiere a los cambios reversibles en un organismo producto de cambios en las condiciones ambientales. La flexibilidad en los rasgos digestivos ha sido estudiada por más de un siglo en diversas especies y contextos. Para el caso de los roedores, los estudios sobre la flexibilidad en el tamaño del tracto digestivo han sido desarrollados principalmente desde dos áreas de la biología, la fisiología y la ecología. Sin embargo, como ha ocurrido con muchos tópicos relacionados con la fisiología ecológica, ambos tipos de estudios se desarrollaron por vías separadas. En este trabajo se intenta evaluar de forma conjunta la información proveniente de ambas áreas. Las principales conclusiones alcanzadas son: (1) la flexibilidad en el tamaño del tracto digestivo puede ser considerada un mecanismo fisiológico ampliamente distribuido, existiendo un clara congruencia entre los ajustes en la morfología digestiva y los cambios en las condiciones ambientales. (2) Los factores experimentales más investigados han

sido la calidad de la dieta, el estatus reproductivo, la temperatura ambiental y el ayuno para las especies de laboratorio y la calidad de la dieta y la temperatura para las especies salvajes. (3) En especies salvajes no se han encontrado diferencias en la flexibilidad del largo intestinal entre estudios con distintas aproximaciones metodológicas ni entre especies con distintos hábitos tróficos. (4) Los cambios en la demanda energética parecen ser principalmente afrontados mediante ajustes en el intestino delgado, mientras que los cambios en la cantidad de material indigestible en la dieta parecen ser principalmente afrontados mediante ajustes en el ciego e intestino grueso. (5) Los cambios en el largo del tracto digestivo parecen estar relacionados con la necesidad de ajustar el tiempo de retención del alimento (e.g., durante la dilución de la dieta), mientras que cambios en la masa del tracto parecen estar relacionados con la necesidad de modificar la tasa de absorción específica (e.g., durante un periodo de alta demanda energética). (6) Las características de una demanda energética (e.g., su intensidad relativa), más que su simple presencia o ausencia, pueden afectar la magnitud de los ajustes en las dimensiones del tracto digestivo. (7) A pesar de la gran cantidad de trabajos publicados, comparaciones cuantitativas de los datos existentes son difíciles de realizar, debido a factores tales como la disparidad en los tratamientos experimentales y en el tipo de información reportada. Para finalizar esta revisión se presentan nuevas direcciones en cuanto al estudio de la flexibilidad digestiva en roedores.

Palabras clave: fisiología digestiva, plasticidad fenotípica, flexibilidad fisiológica, roedores.

INTRODUCTION

Phenotypic flexibility refers to reversible modifications in organism traits due to changes in environmental conditions (Piersma & Drent 2003). In the last two decades, different lines of evidence –e.g., the correlation between different phenotypes (products of flexibility) and fitness (Pigliucci & Schmitt 1999, Agrawal 2001), and the fact that flexibility is able to respond to both artificial and natural selection (Scheiner & Lyman 1991, Scheiner 1993, Scheiner 2002)– suggest that phenotypic flexibility is adaptive. Thus, although usually not easily demonstrable by direct manipulation (Dudly et al. 1996, Schmitt et al. 1999), reversible phenotypic adjustments to changing conditions are hypothesized to increase organism fitness.

The flexibility of the digestive system has been analyzed for more than a century in a myriad of different vertebrate species and contexts (for reviews see Karasov & Diamond 1983, Piersma & Lindstrom 1997, Starck 1999, McWilliams & Karasov 2001, Naya & Bozinovic 2004, Naya et al. 2007). There are two characteristics of this system that generate a high degree of interest in the study of flexibility. First, the gut represents the functional link between food intake and metabolizable energy, i.e., the energy available to meet all vital functions (Karasov 1990, Wunder 1992, Secor 2001). Second, the digestive tract comprises one of the more expensive tissues of the body (McBride & Kelly 1990, Cant et al. 1996), and thus, adjusting gut size to its functional demands

could represent an important energy saving mechanism.

Studies on gut size flexibility in rodents have been mainly developed from two different areas of the biological sciences, physiology and ecology. However, as for several other topics in physiological ecology, both kinds of studies largely developed along separate paths during the last century (Spicer & Gaston 1999). Studies coming from the physiological ground –here defined as those experimental studies conducted with laboratory species– started with the beginning of the 20th century, increased during the 1950's, and then the number of studies *per* year remained fairly constant until the present. In contrast, ecological studies on wild rodents were mainly conducted from the second half of 1980's to the present. This increased interest in digestive flexibility of wild species during the last twenty years is related to two facts. On one hand, optimal digestion models (Sibly 1981, Penry & Jumars 1987) provided a clear theoretical framework to interpret digestive adjustments as a response to changing environmental conditions. On the other hand, during the last two decades there also occurred a progressive recognition of some attributes of rodents that made them an attractive model to study digestive flexibility (Demment & Van Soest 1985, Hume 1989, Folley & Cork 1992, Justice & Smith 1992, Wunder 1992). First, in general terms, rodents have high mass-specific metabolic rates (due to their small body size), and thus, energy-saving mechanisms have a great value in these species. Second, the way by which food intake rate and gut volume scale with body mass

(approximately 0.75 and 1.0, respectively) determine that a potential buffer capacity of the gut, to cope with changes in food intake, decreases with body size; hence, gut size adjustments should be more relevant in small sized species. Third, many rodent species occur in highly variable environments, and consume poor quality diets and (or) diets which quality markedly change between seasons.

The main goal of the present review is to evaluate altogether the evidence on rodent gut size flexibility derived from both physiological and ecological grounds, in order to synthesize the major findings achieved in this research area during the last century. Also, I try to identify the principal gaps in the current knowledge and to propose further directions for the study of digestive flexibility in rodents. I focused on digestive flexibility at the level of gut gross morphology (i.e., digestive organs length and mass), because changes in digestive capacity in response to changing intake level is mainly achieved by reversible changes in these features (Karasov & McWilliams 2005).

THE PHYSIOLOGICAL LITERATURE

The effect of diet bulkiness

Roux (1906) probably was the first author that studied gut size flexibility in rodents. According to him, a concentrated diet, rich in easily digestible substances, was capable of stimulating the growth of the small intestine, thereby enabling a greater and more rapid digestion and absorption of the food (cited in Wierda 1950). During the first decades of the 20th century, other authors analyzed the effect of diet bulkiness on gut morphology (e.g., Kestner 1929, Addis 1932). These studies found that diets with high content of undigestible material caused an increase in stomach and cecum size, but did not affect the dimension of the small intestine. However, few years later, Wierda (1942, 1950) designed much more controlled experiments in terms of experimental animals and diets, and showed that, although the effect of a diet with high content of undigestible material (30 % agar) was noticeable at the level of the hindgut, the small intestine was also able to respond to changes in diet quality. Moreover, when a non-

fermentable substance (talc) was used as the bulky material, it was observed that the small intestine exhibited a proportionally greater increase in mass compared with the other digestive chambers (Friedman et al. 1953).

From these early works to the present, the study of diet bulkiness on gut size adjustments included the evaluation of several substances, such as cellulose and arabinose (Fischer 1957a), cellobiose (Fischer & Lee 1958), kaolin (Dowling et al. 1967), potato starch (Fischer 1957a, El-Harith et al. 1976), pectin (Brown et al. 1979, Ikegami et al. 1990), guar gum (Poksay & Schneeman 1983, Johnson & Gee 1986, Ikegami et al. 1990), gum xanthan (Ikegami et al. 1990), glucomannan (Tokunaga et al. 1986) and non-soluble polysaccharides from raw peas (Goodlad & Mathers 1990), soybean (Levrat et al. 1991), wheat bran and oat bran (Hansen et al. 1992). Because most of the latter studies used a fermentable substance as the bulky material, the observed increase in gut size was mainly due to an increment in the dimension of the cecum and colon (i.e., the fermentative chambers). In this sense, it is known that short chain fatty acids, generated during fermentation process, increased daily epithelial cell production three- (colon) to fourfold (jejunum) in the intestine of rats (Sakata 1987).

The effect of diet compounds

The analysis of specific dietary compound on gut size began with the work of Ershoff & Deuel (1944), who observed a marked dilatation of the cecum in a diet with high content of lactose. Subsequently, several papers were published on the effect of diet chemistry on gut morphology. Specifically, Jessie Fisher and co-workers conducted a series of experiments, during the late 1950, to evaluate the effect of diets with different contents of glucose, sucrose and lactose, (Lawrence et al. 1956, Fischer 1957a, 1957b, Fischer & Lee 1958, 1959). These papers clearly showed that adjustment in the mass of digestive organs occurs in parallel with changes in diet composition, and the authors suggested that gut size modifications may have an adaptive value. At the same time, Morgan & Yudkin (1957) studied the effect of saturated versus unsaturated fats in the diet on digestive

morphology. These authors pointed out that animals consuming a diet with saturated fatty acids increased the volume of food ingested, which in turn cause a rise in gut size (i.e., a bulkiness effect). However, they noted that a significant part of the differences is played by the composition of the diet, since changes in gut size also occurred in animals on the diet containing unsaturated fatty acids, where the amount of food ingested was practically equal to the controls. In a similar way, it was observed that the amount of protein in the diet can affect gut size, and a decrease in the size of the small intestine mass occurred in parallel to dietary protein content (Hill et al. 1968).

The effect of fasting

Jackson (1915) studied the effect of acute and chronic inanition on the weight of several internal organs in the rat. This work showed that a reduction in the weight of the digestive tract, from about 6.0 % of the body weight in normally feed rats to a 3.3 % (in the acute fasted trial) or 3.5 % (in the chronic fasted trial), occurs during inanition. Accordingly, Jackson concluded that the alimentary canal, together with the liver, lose weight much more heavily than the whole body, and therefore a decrease in absolute and relative weight it is observed. Several years later, these results were confirmed by other authors who demonstrated that the liver and the digestive tract comprise the organs that contribute the most to protein catabolism during fasting (e.g., Addis et al. 1936, Thaysen & Thaysen 1949, Ju & Nasset 1959). In addition, Ju & Nasset (1959) reported that a recovery of nitrogen content occurs 96 hours after feeding and that this recuperation was more rapid and complete in the small intestine than in other organs.

From the above mentioned works to the present, several studies investigated the mechanistic basis for the changes in gut size during fasting periods (e.g., Brown et al. 1963, Steiner et al. 1968, Levine et al. 1974, McNurlan et al. 1979, Goodman & Fleck 1980, Burrin et al. 1988, Dunel-Erb et al. 2001, see also Carey 1990, 1992, Carey & Cook 1991, Carey & Martin 1996 for data on *Spermophilus tridecemlineatus*). Although a detailed analysis of the evidence for these mechanisms is beyond the scope of the present review, it should be

noted that adjustments in both, cell size and cell number, are part of the overall response (for a recent review see Wang et al. 2006).

The effect of reproductive state

Abramson (1934) evaluated organ size changes that occur during pregnancy, and observed that the small intestine size began to increase from the first half of pregnancy, while the stomach increased only during the second half of this period. Five years latter, the changes in weight and protein concentration of different organs that occurs during pregnancy and lactation were analyzed again (Poo et al. 1939). Now, it was found that the organs where greater concentration of proteins occurs were the liver (mainly during the pregnancy) and the digestive tract (mainly during the lactation). After these two pioneering works, many other authors reported data on the effect of pregnancy and lactation on gut size (e.g., Souders & Morgan 1957, Fell et al. 1963, Campbell & Fell 1964, Peters et al. 1967, Craft 1970, Sigdestad & Osborne 1972, Cripps & Williams 1975, Mainoya 1978, Cañas et al. 1982). All these studies found a marked increase in the size of the small intestine during lactation (see Peters et al. 1967 for the only exception), but only a minor enlargement during pregnancy. In addition, these studies indicated that: (i) the adjustment in gut length occurs at a slower rate than that in gut mass, and digestive size changes are reversible (Cripps & Williams 1975), (ii) the increase in whole-animal metabolism observed during lactation is mainly due to an increase in weights of organs with high maintenance energy expenditures (i.e., intestine, liver and heart), although a rise in specific metabolic activity of different tissues also occurs (Cañas et al. 1982).

On the other hand, it should be noted that lactation in mice comprised a key model for the study of limitation to animal energetic budgets (Bacigalupe & Bozinovic 2002, Speakman & Krol 2005). Consequently, many studies conducted within this context during the last ten years provide data on gut adjustments during lactation. From the perspective of gut size flexibility, the reported data are very similar to those discussed in the previous paragraph: the size of the small intestine increased during pregnancy, and this increase is even greater

during lactation (Hammond & Diamond 1992, Speakman & McQueenie 1996). In addition, studies that evaluated lactation at different temperatures reported an additional increase in the mass of the small intestine in lactating females exposed to cold environments (Hammond et al. 1994, Krol et al. 2003).

The effect of environmental temperature

The first studies that evaluated the effect of environmental temperature on gut size were conducted in the context of the study of animal adaptations to the cold. At the end of the 1950's, Herox and co-workers acclimated rats to 6 and 30 °C and found an increase in the small intestine mass at lower temperatures (Heroux & Gridgeman 1958, Heroux & Campbell 1959). Indeed, it was observed that digestive tract changes occurred in both outdoor and indoor conditions, though it was less noticeable in the former situation. In the same vein, Barnett & Widdowson (1965) studied the adjustments that occur in mice exposed to cold for from days to many generations. It was found that an increase in small intestine size occurs in a cold environment, but this change did not augment beyond the first generation. After that, Musacchia & Barr (1969) reported an increase in the mass of the intestine at lower temperatures in the golden hamster (*Mesocricetus aureatus*). In the recent years, several authors have evaluated the effect of low environmental temperatures on the digestive tract, mainly in the context of energy budget limitation debate (Toloza et al. 1991, Konarzewski & Diamond 1994, McDevitt & Speakman 1994, Stalinski 1994). Again, the obtained results did not differ from those discussed above: higher energy demands due to low environmental temperatures determine an increase in gut size, mainly at the level of the small intestine.

The effect of combined energy demands

Barnett & Widdowson (1971) compared data on pregnancy and lactation at two temperatures, with previous data from virgin females also acclimated to warm and cold conditions (Barnett & Widdowson 1965). The main result of these works was that the small intestine mass was

shown to increase rather linearly from virgin females reared at 21 °C to lactating females reared at –3 °C, suggesting an additive effect of both demanding factors. More recently, two studies that analyzed the combined effect of temperature and diet quality indicated that although both factors are able to affect the small intestine mass and length, there was no interaction between them (Zhao et al. 1995, 1996). In the last years, Deborah Kristan and Kimberly Hammond evaluated the combined effect of parasitism and dietary caloric restriction (Kristan & Hammond 2001), parasitism and lactation (Kristan 2002, Kristan & Hammond 2004), parasitism and cold temperatures (Kristan & Hammond 2000, 2003), and parasitism, dietary caloric restriction and cold temperatures in mice (Kristan & Hammond 2006). The main result of these works is that depending on the type of demands that are combined, multiple demands will elicit responses that are either independent of each other (e.g., parasitism and lactation, or parasitism and temperature) or interact with each other (e.g., parasitism and caloric restriction).

Other physiological studies

There are other factors that determine change in the size of digestive organs, but data are too scarce to allow general conclusions. These included intermittent starvation (e.g., Holeckova & Fabry 1959, Fabry & Kujalova 1960, Holeckova 1964), hypothalamic lessons (e.g., Brobeck et al. 1943), acetylphenylydrazine administration (e.g., Conrad et al. 1965), germ-free rats (e.g., Goodlad et al. 1988), intestinal resection (e.g., Booth et al. 1959, Hammond et al. 1996b), diabetes (e.g., Jervis & Levin 1966), thyrotoxicosis (e.g., Levin & Smith 1963), growth hormone (Leblond & Carriere 1955), T4 hormone (e.g., Derting & Bogue 1993), sorbitol (Morgan & Yudkin 1957), polyethylene glycol (Loeschke et al. 1973), and chlortetracycline (Lee & Fisher 1958).

THE ECOLOGICAL LITERATURE

Evidences from the field

Interestingly, the first work that reported data on gut variation for animals collected in the

field was conducted in rats. Heroux (1961) observed that the enlargement of the digestive tract, recorded in indoor cold-acclimated white rats was lower than those observed in outdoor cold-acclimated animals. Then, he captured specimens from the field and compared their gut size flexibility against white rats reared in indoor and outdoor conditions. He found that, unlike cold-acclimated rats, field winter animals did not show an enlargement of the gut, and he explained the result by a combination of two factors. First, wild rats probably were more resistant to cold than white rats. Second, winter conditions may be less severe than cold conditions imposed on animals kept individually in a cold chamber.

After the just mentioned work, the changes in the gut size in relation to animal age, sex and reproductive state were evaluated in *Clethrionomys glareolus* (Myrcha 1964, 1965) and *Apodemus flavicollis* (Gebczynska & Gebczynski 1971). Taking them together, the main results of these studies were: (i) the digestive tract mass increases with body mass, but the ratio between both variables decreases with body mass; this result could be related with the decrease in relative metabolic demand with body size, (ii) seasonal change in gut size occurs, and is probably related more with the variation in food quality than with food availability, (iii) gut size increases during pup nursing, but not during pregnancy, (iv) reproductive adjustments of females in gut size are periodical and reversible. Between these early studies and the "bloom" of papers developed during the 90's (see below), there are a couple of works which tried to relate latitudinal patterns of body mass and population cycles of voles with nutritional variables, like food habitat and gut morphology (Hansson 1985, Hansson & Jaarola 1989). These works showed that animals of northern populations of *C. glareolus* and *Microtus agrestis*, that consumed food rich in cellulose and other undigestible materials, have greater gut size than southern populations. In addition, it was proposed that it would be advantageous for herbivorous animals living on high fiber diets (such as *M. agrestis*), to increase their digestive capacity in high density populations, whereas for mixed granivorous/folivorous animals (such as *C. glareolus*) it would be

advantageous to be able to rapidly change digestive physiology according to food supply.

As was previously mentioned, the development of optimal digestion theory (Sibly 1981), and the recognition of rodents as an attractive model to study digestive flexibility, motivated a myriad of field studies on gut size adjustments during the last twenty years. These studies demonstrated that: (i) seasonal variations in gut size are common and are mainly related with seasonal changes in diet quality and (or) environmental temperature (e.g., Bozinovic et al. 1990, Virgl & Messier 1992, Brokowska 1995, Derting & Noakes III 1995, Campbell & MacArthur 1998, del Valle & Busch 2003, Derting & Hornung 2003), (ii) however, in some species the change in gut mass is similar to that observed in body size (Zuercher et al. 1999), and in other species there is no clear pattern of seasonal variation (Hammond 1993, Voltura 1997), (iii) females exhibited greater gut size than males around the year, and this difference usually was more noticeable during the breeding season (Bozinovic et al. 1990, Norrie & Millar 1990, Brokowska 1995, Schwaibold & Pillay 2003), (iv) there are no clear trends in the relationship between food habitats and gut flexibility, where some results suggest that omnivorous are more flexible than herbivorous species (e.g., Brokowska 1995), but others not (e.g., Derting & Noakes III 1995), (v) when populations of the same species were compared, it was found that differences in gut size exist and that they are mainly related with differences in diet composition (e.g., Corp et al. 1997, Sassi et al. 2007), (vi) hibernation clearly affects the size of the gut (e.g., Galluser et al. 1988), and the increase in small intestine fresh mass during the activity season can reach 259 % in relation to the values observed during hibernation (Hume et al. 2002), (vii) studies in semi-enclosure conditions along an altitudinal gradient, demonstrate that digestive organs size can be affected by changes in both, ambient temperature and oxygen partial pressure (Hammond et al. 1999, 2001).

Experimental studies on wild rodents

Sibly's (1981) digestion model –and specifically his third prediction "animals consuming poorer diets should have larger

digestive chambers, other things being equals"– also stimulated the development of many experimental studies on gut flexibility, spreading the current knowledge from laboratory mice and rats to several wild species. For example, during the second half of the 80's, gut size flexibility was demonstrated in four wild species (*Microtus ochrogaster*, *Peromyscus maniculatus*, *Abrothrix andinus*, and *Arvicola terrestris*). The experimental factors tested in these studies were diet quality (Woodall 1989), and diet quality plus environmental temperature (Gross et al. 1985, Green & Millar 1987, Bozinovic et al. 1988). In general terms, it was concluded that both increased energy demands and lower diet quality determine a rise in gut mass and length, mainly at the level of the small intestine and the cecum.

From the beginning of the 1990's until the present, the number of studies on gut flexibility in wild rodent species showed an even more rapid growth. In a nutshell, the results of this research can be summarized as: (i) an increase in digestive organs size due to an increase in diet fiber content occurs in *Thomomys bottae* (Loeb et al. 1991), *Microtus ochrogaster* (Hammond & Wunder 1991, Castle & Wunder 1995, Young Owl & Baltzi 1998), *Clethrionomys glareolus* and *Microtus agrestis* (Lee & Houston 1993, 1995), *Microtus pennsylvanicus* (Young Owl & Baltzi 1998), *Microtus brandtii* (= *Lasiopodomys brandtii*, Pei et al. 2001a, Song & Wang 2006), *Meriones unguiculatus* (Pei et al. 2001b, Liu & Wang 2007), and *Akodon azarae* (del Valle et al. 2006), (ii) an increase in digestive organs size due to a decreasing environmental temperature occurs in *Microtus ochrogaster* (Hammond & Wunder 1991, Castle & Wunder 1995, Hammond & Wunder 1995), *Peromyscus maniculatus* (French & Porter 1994, Koteja 1996, Hammond & Kristan 2000), *Dicrostonyx groenlandicus* (Hammond & Wunder 1995), *Microtus pinetorum* (Derting & Austin 1998), *Microtus brandtii* (Song & Wang 2006), *Akodon azarae* (del Valle et al. 2004) and *Phyllotis darwini* (Bacigalupe et al. 2004, Naya et al. 2005), (iii) an increase in digestive organ's size due to lactation occurs in *Peromyscus maniculatus* (Hammond & Kristan 2000), *Microtus pinetorum* (Derting & Austin 1998), and *Octodon degus* (Naya et al. 2008a),

(iv) changes in gut size due to the interaction between temperature and parasitism were reported for *Microtus ochrogaster* (Raines 1989), between temperature and diet quality for *Dicrostonyx groenlandicus* (Nagy & Negus 1993), and between fiber and tannins content in the diet for *Octodon degus* (Bozinovic et al. 1997), (v) no change in gut morphology due to diet quality were recorded in *Arvicola terrestris* (Lee & Houston 1993) and *Phyllotis darwini* (Sabat & Bozinovic 2000), to photoperiod in *Microtus agrestis* (Krol et al. 2005), and to a toxic substance (albicard) in *Peromyscus maniculatus* (French & Porter 1994).

GENERAL CONCLUSIONS AND FURTHER DIRECTIONS

The major goal of this review was to evaluate altogether the evidence on gut size flexibility in rodents collected from the fields of physiology and ecology, in order to identify the major findings achieved in this area during the last century. In this sense, the analysis of published data allowed us to conclude that: (1) Gut size flexibility is a widespread physiological mechanism, occurring in laboratory and wild species, and under laboratory, semi-natural and natural conditions. Moreover, flexibility in rodents occurs in species with different food habits (e.g., from strictly herbivores to omnivores that mainly prey on invertebrates), body size (e.g., from 15-20 g to 6000 g), and life history traits (e.g., *Microtus pinetorum* versus *M. pennsylvanicus*). (2) Laboratory mice and rats appear to qualitatively demonstrate the digestive flexibility capacity of wild species, but a quantification of this has not been done yet. In this sense, some authors have claimed that changes in the field are lower than those found in indoor conditions (e.g., Heroux 1961), while others have expressed an opposite point of view (e.g., Hammond 1993). Obviously, at the core of this discrepancy is how much different indoor conditions are from natural conditions, which in turn, depends on species attributes (e.g., microhabitat use, territoriality, seasonal behavioral and physiological adjustment) and experimental design (how animals are reared or if nesting is allowed). (3) In laboratory species the experimental factors

that have been more investigated are diet quality, reproductive status, environmental temperature and fasting. There are many works on diet quality and temperature for wild species, but few studies evaluated reproductive status and no one evaluated changes during fasting. Related to this difference in the kind of factors evaluated, recent analyses showed that small intestine length flexibility differs between experimental factors in laboratory species but not in wild rodents (Naya et al. 2007, 2008b). (4) For wild rodent species, no differences in small intestine length flexibility between methodological approaches (experimental versus observational) nor between species feeding categories (omnivorous, herbivorous, insectivorous) has been identified (Naya et al. 2008b). (5) It appears that high energetic demands, such as those imposed by lower temperatures and reproduction are mainly coped with by change at the small intestine level (absorptive chamber), while changes in the amount of undigestible material in the diet are mainly coped with by change in the hindgut (fermentative chambers). However, for laboratory mice and rats it was shown that although changes in diet quality provoke greater adjustments in hindgut size than increased energy demands, there are no differences between both factors for the case of the small intestine (Naya et al. 2007). (6) Increments in gut length appear to be related with a need to augment food retention time (e.g., during diet dilution), while increases in gut mass appear to be related with the need of higher specific absorption (e.g., during increasing energy demands). This is in agreement with the fact that adjustments due to change in diet quality are similar for both small intestine mass and length, while adjustments due to change in energy demands are greater for small intestine mass than for length (Naya et al. 2007). (7) Some studies suggested that the qualities of an energetic demand rather than simply its presence or absence can affect the amount of digestive adjustments (Kristan & Hammond 2004). In this context, there was a positive relationship between gut size changes and both the number of pups reared (Sigdestad & Osborne 1972, Hammond & Diamond 1994, Hammond et al. 1994, 1996a) and the amounts of undigested material in the diet (El-Harith et al. 1976, Goodlad & Mathers 1990). (8) In spite of the impressive number of studies on changes in gut size in rodents, quantitative comparisons of the existing data are difficult (Derting & Austin 1998). This is because disparity among experimental treatments and how they are reported (e.g., diet quality experiments), differences in the types of data collected (e.g., length, wet mass, dry mass, masses of digestive organs with or without contents), variations in the kinds of statistical parameters reported (e.g., absolute means, least-squared corrected means, median), and differences in the amount of data reported (e.g., total gut versus each organ separately, all the dataset or only the significant changes).

To end this review, I want to point out some further directions for the study of rodents gut flexibility: (1) despite the likely evolutionary importance of physiological variability across populations inhabiting different habitats, relative few studies comparing gut flexibility among populations has been conducted. (2) Many rodent populations show first order dynamics (i.e., saw-toothed oscillations), and consequently, are excellent models to study the effects of contrasting densities on gut size flexibility under natural conditions. (3) A recent study found a clear correlation between small intestine length flexibility and latitude, reinforcing the adaptative value of digestive flexibility (Naya et al. 2008b). In order to advance our understanding on gut flexibility evolution, more global-scale comparative studies of this kind are desirable. (4) Information about the effect of different fixation techniques on gut tissue is scarce; this kind of data could be very relevant since it could allow the use of animals stored in zoological collections, and thus, to answer long term questions on digestive flexibility. (5) According to theoretical predictions from scaling, gut size flexibility should decrease with increasing body mass (see introduction). This result has not empirically tested yet. (6) Adjustments in the digestive organs are just one kind of potential phenotypic adjustments to changing environmental conditions. Information on the interplay between gut flexibility and other energy saving mechanism (e.g., torpor) is still scarce. (7) More experiments analyzing simultaneously short and long-term responses of gut size

adjustments are needed; this is especially relevant to reach a better understanding of the temporal dynamic of the digestive flexibility.

Gut size flexibility in rodents has been studied for more than a century, and consequently, many of the original questions have been already answered. However, as we can see, many others are awaiting to be explored.

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