Allometric scaling relationship between frequency of intestinal contraction and body size in rodents and rabbits

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This study aimed to establish an allometric scaling relationship between the frequency of intestinal contractions and body mass of different mammalian species. The frequency of intestinal contractions of rabbit, guinea pig, rat and mouse were measured using an isolated organ system. The isolated rings were prepared from proximal segments of jejunums and the frequency of contractions was recorded by an isometric force procedure. The coefficients of the obtained allometric equation were ascertained by computation of least squares after logarithmic transformation of both body mass and frequency. Significant differences ($p<0.001$) were shown in the frequency of contractions between different species. The highest frequency that corresponded to the mice was 57.7 min^{-1} and the 95% confidence interval (CI) ranged from 45.4 to 70, while rabbits showed the lowest frequency (12.71 min^{-1}, CI: 8.6–16.8). Logarithms of frequency were statistically proportional to logarithms of body mass (r=0.99; $p<0.001$). The data fitted an equation $F = 18.51B^{-0.31}$ and the 95% confidence interval of the exponent ranged from −0.30 to −0.32. The results of this study suggest that it is probably possible to extrapolate the intestinal contraction frequency of other mammalian species by the means of allometry scaling.

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1. Introduction

The membrane potential of smooth muscle cells in different regions of the gastrointestinal (GI) tract causes a spontaneous rhythmic motility known as the basic electrical rhythm (BER). This electrical potential with amplitude of −65 to −45 mV (Barrett *et al.* 2010) originates from the interstitial cells of Cajal (ICC). ICC form a complex network widely distributed within the submucosal, intramuscular and inter-muscular layers of the GI tract, where they function as a pacemaker for digestive system motility (Mostafa *et al.* 2010). There is evidence that this pacemaker system drives the BER and causes the spontaneous activities of smooth muscle cells in the gut. BER alone may not be able to induce contraction of smooth muscles cells, but the spike potentials, emerging during the depolarization phase of the electrical potential, force these contractions. The BER also synchronizes motor activity in gut, such that the peristaltic contractions, and other mechanical movements can only occur during depolarization phase of the electrical potential (Barrett *et al.* 2010). The frequency of BER-induced smooth muscle contractions were recorded in isolated organ systems by different studies (Berciket *et al.* 1994; Lammers *et al.* 2012). Studies show that the frequency of BER-induced contractions is not identical in different parts of the gut (Barrett *et al.* 2010). Additionally, differences between animal species have been reported (Gallego *et al.* 2008; Hu *et al.* 2010).

The question is, what kind of relationship can be established between a mammal's body size and the frequency of contractions induced by BER? In human medicine,

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allometric scaling has been used to predict human clinical pharmacokinetic parameters obtained from preclinical data (Obach *et al.* 1997). The allometric approach was primarily established by Cuvier at the end of the 19th century to describe the correlation between relative dimensions of brain and body mass changes (Gayon 2000). Five decades later, there was a lot of data illustrating the presence of interspecies allometric relationships between body mass and several physiologic functions as reviewed by Adolph (1949). Heart rate and respiratory rate in mammals, for example, appear to scale with a body mass exponent of approximately −0.25 (Adolph 1949; West and Brown 2005).

The body size of mammalians range from a 3 g bumblebee bat (*Craseonycteris thonglongyai*) to the elephant (*Elephas maximus*) with 3000 kg weight. Although there is a wide range of diversity in anatomy and physiology across mammal species, similarities in basic design of organ systems can be the basis of scaling relationships between different physiological characteristics, such as heart rate, blood flow, blood volume and organ capacities and longevity of animals (Mordenti 1986).

The aim of this study was to establish a likely allometric scaling relationship between the frequency of intestinal contractions and body sizes in different laboratory animal species. Establishing any relationship between these characteristics will facilitate a better understanding of basic allometric concepts including the biological clock. Also, the reduction of comparative parameters to a body-mass-independent form allows systematic comparison of GI function in different mammals.

2. Materials and methods

2.1 *Animals*

Adult males of four species of laboratory animals were used in this study. These different species of mammals included white New Zealander rabbits, Dunkin-Hartley guinea pigs, Wistar rats and Balb/c mice. A total of 40 animals, 10 of each species, were locally purchased and were group-housed at 20±3°C, relative humidity of 40–50% and 12 h light–dark cycle. The animals had access to standard commercial feed of each relevant species and drinking water *ad libitum*. All experiments received ethical approval from Institutional Animal Ethics Committee, and animals were treated in compliance with this committee's standard procedures.

2.2 *Preparation and contraction recording of isolated intestine*

The animals were first weighed and then sacrificed after being exposed to carbon dioxide gas. The abdomen was opened and the proximal section of jejunum was dissected and immediately placed in an oxygenated Krebs-Henseleit buffer solution with the following composition (in mM): NaCl, 118.0; KCl, 4.75; $CaCl_2$, 1.3; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; and glucose, 11. After washing the segments and detaching their connective tissue, rings of intestine (10–12 mm long) were carefully prepared and submerged in 20 mL tissue bath chambers containing Krebs solution maintained at 37°C and bubbled with 95% O_2 and 5% CO_2 gas mixture. The isolated rings were suspended into the chamber by two stainless steel holders passed through the lumen. One end of the rings was fixed to the bottom of the tissue chamber, while the other was connected to a force–displacement transducer to measure isometric contractile force recorded by a 4 Channeled Power lab. A resting tension of 1 g was applied to the suspended rings and then allowed to equilibrate for 45 min, while the bath buffer was replaced every 15 min. After equilibrium, the BER-induced contractions of each isolated ring were separately recorded for 10 min. Spontaneous rhythmic contractions of one ring per animal, or in other words, 10 rings per species, were recorded. The frequency mean of contractions per minute in each ring was calculated in 10 min time intervals.

2.3 *Allometric analysing*

In order to establish an empirical allometric relation, the data obtained from contraction frequencies and body mass were transformed to base 10 logarithms. Then they were fitted by a conventional least-square regression to obtain the allometric parameters with the formula of $F = aM^b$, in which F is the frequency and M is the body mass in kilograms. The factor a is the normalized constant and b is the scaling exponent (West and Brown 2005).

2.4 *Statistics*

Data was presented as the mean and 95% confidence intervals round the mean obtained from 10 experiments for each animal species. A one-way analysis of variance (ANOVA) was used to compare the average frequency and the ratio of BER-induced frequency of contractions to the body surface area in different animal species. The mean values of groups were compared using the Tukey *post hoc* test. A linear regression analysis was performed on the logarithmic transformed data of body mass and frequency of contractions. All statistical analyses were performed with BioStat 2008. A p-value less than 0.05 was considered significant.

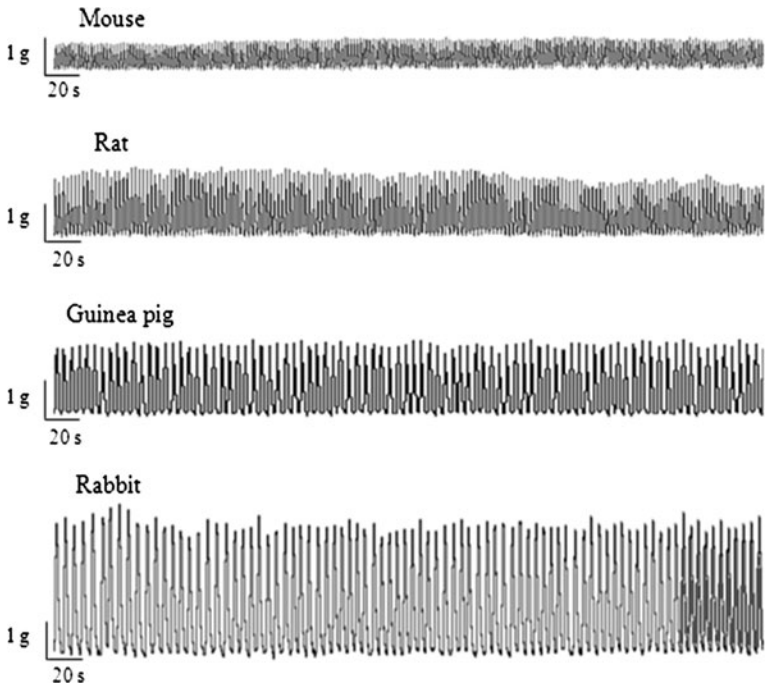

Figure 1. Representatives of BER-induced contractions recorded from the isolated rings taken from proximal part of the jejunum in four species of laboratory mammals.

3. Results

3.1 *BER-induced contractions*

Representatives of the contractions induced by BER in the isolated jejunum of four mammalian species tested in this study are illustrated in figure 1. As this figure clearly indicates, the frequency of intestinal contractions in the four species was not identical. The frequency of intestinal contractions induced by the BER in four animal species is summarized in table 1. This table shows that there was significant ($p<0.001$) differences in the mean frequency of intestinal contractions between tested animals, as determined by one-way ANOVA. The highest frequencies of contractions belong to the mouse, whereas the rabbit exhibited the lowest frequency. The average frequency of contraction recorded from the isolated jejunum of rat and guinea pig was between these two levels, while it was greater in rat than the guinea pig (table 1).

3.2 *Allometric relationship*

As shown in figure 2, logarithms of contraction frequency were statistically proportional to logarithms of body mass (r=0.99; $p<0.001$). The data fit an equation of: $F = 18.51B^{-0.31}$, where F stands for frequency and B is body mass. The 95% confidence interval around the scaling exponent ranged from −0.30 to −0.32.

4. Discussion

The present study sought to establish a likely allometric relationship between the frequencies of intestinal contractions

Table 1. Body mass and frequency of BER-induced contractions in four laboratory mammalian species

	Mouse	Rat	Guinea Pig	Rabbit
Body mass (g)	26.8 (CI:18.0–35.6)	273.6 (CI:189.7–357.5)	746.8 (CI; 682.9–810.7)	3287.3 (CI: 3095.0–3479.6)
Contraction frequencies (mm^{-1})	57.7 (CI: 45.4–70.1)	27.6* (CI: 19.2–36.0)	20.5* (CI: 13.8–27.6)	12.7* (CI: 8.6–16.8)

*p <0.05 (Tukey *post hoc* test, compared to mouse).

Data are represented as mean and 95% confidence intervals (CI) obtained from 10 animals in each species.

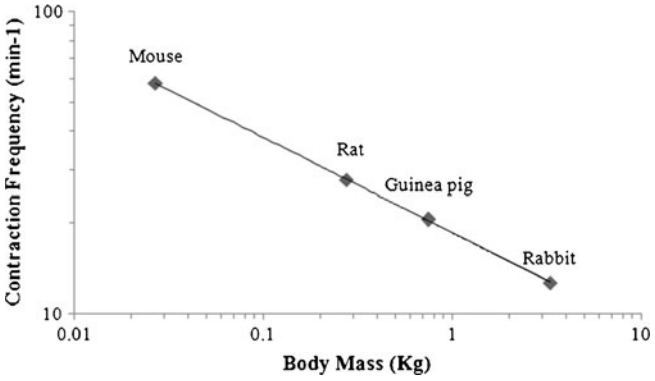

Figure 2. Frequency of BER-induced contractions in four laboratory mammalian species as a function of body mass (N=10 for each species). The data fit an equation: $F = 18.51B^{-0.31}$, where F stands for frequency and B is body mass.

induced by BER and body size of four mammalian species used as laboratory animals. The results of this study showed that the frequency of intestinal contractions in the laboratory mammal species is proportional to body mass to the power of −0.31.

Despite considerable diversity in the functions of different organisms, most of the fundamental physiological processes manifest an extraordinary plainness when viewed as a function of body mass. Body mass can be considered as the prime determinant of variation in biological functions when different animals are compared (West and Brown 2005). Allometry discusses degrees of disproportionalities among the biological processes and attempts to establish an equation of similitude by using a power function of body mass (Adolph 1949). Allometric scaling is now a generalized methodology used to predict and interpolate human clinical pharmacokinetic parameters obtained from preclinical data. The application of allometric scaling for BMR is the best known use of this methodology in biology and medicine, which was first shown by Kleiber (1932). BMR is a major factor for establishing allometrically scaled relationships between physiological or pharmacological characteristics (Riviere and Papich 2009). It is found that by increasing the size of the animal, BMR is also increased. The ratio estimated from BMR to body size in smaller animals is bigger in comparison to larger ones (Barrett *et al.* 2010). Mammalian BMR is proportional to the 0.67 exponent of body mass (White and Seymour 2003). While the results of our study show the scaling exponent of −0.31 for the frequency of intestinal contractions. Thus, we can include the possibility that this exponent is representing the inverse of the metabolic rate.

The scaling exponent of −0.31 for frequency of intestinal contractions, which has been established from data obtained in the present study, appear to be consistent with the exponent of gut beat duration reported by others (Adolph 1949). Even though the allometric power derived from the Adolph equation is the same as the allometric power expressed in the present study (−0.31), the slope is not the same in the two equations. This difference can be due to numerous reasons. In Adolph's allometric scaling, the frequencies of isolated gut contractions used to establish the equation have been collected from different references (Clark 1927). While in the present study, the frequencies of intestinal contractions have been obtained from various experimental species in the same experimental conditions prevailed in empirical studies. In Adolph's allometric scaling, if the allometric equation was derived between isolated gut frequency and body weight using the raw data (Clark 1927), the equation $F = 21.12B^{-0.3}$ will be obtained. This allometric equation is equal to $G=0.000093B^{-0.31}$ derived by Adolph by transforming the frequency of isolated gut in time by using frequency per hour as the unit of scaling (Adolph 1949). Furthermore, the data used by Adolph to derive the allometric equation was collected from rats, rabbits, cats and dogs, while in the present study, data was obtained from mice, rats, guinea pigs and rabbits.

It is found that there is an allometric scaling relationship between heart and respiratory rates, as other spontaneous rhythmic phenomena, and body mass with exponent of approximately −0.27 and −0.28, respectively (Adolph 1949; West and Brown 2005). These powers are relatively close to the exponent of −0.31 established in our study. From these findings, it can be hypothesized that the relation between frequency of spontaneous rhythmic activities and body mass may have a relatively close scaling exponent in different mammalian species, which represents an inverse relation when basal metabolic rate (BMR) is used. However, the limited number of mammalian species used in the present study warrants a more comprehensive allometric study to assess this claim.

In conclusion, the results of this study showed that although the frequency of intestinal contractions in different mammals is not identical, there is an allometric scaling relationship between frequency of intestinal contraction and body size. The frequency of intestinal contraction in rodent and rabbits tested in the present study was proportional to a −0.31 power function of body mass. Establishing a relationship between intestinal contraction and the rate of absorption can be important to predict drug and food absorption via intestine because of the major role of BER-induced contractions in regulating intestinal movements and the rate of food and drug absorption through the gut.

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References

Adolph EF 1949 Quantitative relations in the physiological constitutions of mammals. S*cience* **109** 579–585

Barrett KE, Barman SM, Boitano S and Brooks HL 2010 *Ganongs review of medical physiology* 23rd edition (New York: McGraw-Hill)

Bercik P, Armstrong D, Fraser R, Dutoit P, Emde C, Primi MP, Blum AL and Kucera P 1994 Origins of motility patterns in isolated arterially perfused rat intestine. *Gastroenterology* **106** 649–657

Clark AJ 1927 *Comparative physiology of the heart* (New York: Cambridge University Press)

Gayon J 2000 History of the concept of allometry. *Am. Zool.* **40** 748–758

Gallego D, Calve P, Donovan J, Rahmati R, Grundy D, Jimenez M and Beyak MJ 2008 The gaseous mediator, hydrogen sulphide, inhibits in vitro motor patterns in the human, rat and mouse colon and jejunum. *Neurogastroenterol. Motil*. **20** 1306–1316

Hu J, Gao WY, Gao Y, Ling NS, Huang LQ and Liu CX 2010 M3 muscarinic receptor- and Ca2+ influx-mediated muscle contractions induced by croton oil in isolated rabbit jejunum. *J. Ethnopharmacol.* **29** 377–380

Kleiber M 1932 Body size and metabolism. *Hilgardia* **6** 315–353

Lammers WJ, Stephen B and Karam SM 2012 Functional reentry and circus movement arrhythmias in the small intestine of normal and diabetic rats. *Am. J. Physiol. Gastrointest. Liver Physiol*. **302** 684–689

Mordenti J 1986 Man versus beast: pharmacokinetic scaling in mammals. *J. Pharm. Sci.* **75** 1028–1040

Mostafa RM, Moustafa YM and Hamdy H 2010 Interstitial cells of Cajal the master in health and disease. *World J. Gastroenterol.* **16** 3239–3248

Obach RS, Baxter GJ, Liston TE, Silber BM, Jones BC, Maclntyre F, Rance DJ and Wastall P 1997 The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. *J. Pharmacol. Exp. Ther*. **28** 36–58

Riviere JE and Papich MG 2009 *Veterinary pharmacology and therapeutics* 9th edition (New York: Wiley-Blackwell)

West GB and Brown JH 2005 The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization. *J. Exp. Biol.* **208** 1575–1592

White CR and Seymour RS 2003 Mammalian basal metabolic rate is proportional to body mass$^{2/3}$. *Proc. Natl. Acad. Sci. USA* **100** 4046–4049

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