Research Article

Organ-Tissue Level Model of Resting Energy Expenditure Across Mammals: New Insights into Kleiber's Law

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Background. Kleiber's law describes the quantitative association between whole-body resting energy expenditure (REE, in kcal/d) and body mass (M , in kg) across mature mammals as $REE = 70.0 \times M^{0.75}$. The basis of this empirical function is uncertain. **Objectives.** The study objective was to establish an organ-tissue level REE model across mammals and to explore the body composition and physiologic basis of Kleiber's law. **Design.** We evaluated the hypothesis that REE in mature mammals can be predicted by a combination of two variables: the mass of individual organs/tissues and their corresponding specific resting metabolic rates. Data on the mass of organs with high metabolic rate (i.e., liver, brain, heart, and kidneys) for 111 species ranging in body mass from 0.0075 (shrew) to 6650 kg (elephant) were obtained from a literature review. **Results.** REE_p predicted by the organ-tissue level model was correlated with body mass (correlation $r = 0.9975$) and resulted in the function $REE_p = 66.33 \times M^{0.754}$, with a coefficient and scaling exponent, respectively, close to 70.0 and 0.75 ($P > 0.05$) as observed by Kleiber. There were no differences between REE_p and REE_k calculated by Kleiber's law; REE_p was correlated ($r = 0.9994$) with REE_k . The mass-specific REE_p , that is, $(REE/M)_p$, was correlated with body mass ($r = 0.9779$) with a scaling exponent -0.246 , close to -0.25 as observed with Kleiber's law. **Conclusion.** Our findings provide new insights into the organ/tissue energetic components of Kleiber's law. The observed large rise in REE and lowering of REE/M from shrew to elephant can be explained by corresponding changes in organ/tissue mass and associated specific metabolic rate.

1. Introduction

Resting energy expenditure (REE), defined as the whole-body energy expenditure under standard conditions, is the largest fraction of total energy expenditure. Body mass was applied early in exploring the quantitative association between REE and body composition. The best empirical fit between REE (in kcal/d) and body mass (M , in kg) from mouse to elephant with a $\sim 330,000$ -fold difference in body size was derived by Kleiber [1, 2] and Brody [3],

$$REE = 70.0 \times M^{0.75}. \quad (1)$$

Equation (1) is the well-known Kleiber's law or 3/4 power law, one of the most widely discussed rules in bioenergetics

[2, 4]. Based on (1), Kleiber's law can also be expressed in terms of mass-specific REE,

$$\frac{REE}{M} = 70.0 \times M^{-0.25}. \quad (2)$$

According to Kleiber's law, small mammals (e.g., shrew) have lower REE but higher REE/M than do large mammals (e.g., elephant).

Although many investigators have attempted to clarify plausible mechanisms, a full understanding of Kleiber's law is still uncertain and represents a knowledge gap in the studies of bioenergetics [12]. Primary questions remain what is the biological mechanism of the quantitative association between REE and body mass across mammals? and why is

the REE/M ratio substantially smaller in animals with larger REE and body size?

The aim of the present study was to explore the potential physiologic and body composition basis of Kleiber's law. Our group derived and validated an organ-tissue level REE model for humans in 1998 [13]. According to the model, the magnitude of human REE is determined by two variables, mass of all organs/tissues and their respective metabolic rates at rest [14]. Our hypothesis is that the established organ-tissue level REE model for adult humans is applicable in mature mammals. Specifically, we evaluate the REE-body mass associations at the organ-tissue level across mammalian species.

2. Methods and Data Sources

2.1. Organ-Tissue Level REE Model for Mature Mammals. The principle of the organ-tissue level REE model is that whole-body energy expenditure at rest reflects the total resting energy consumption of all organs and tissues. A mechanistic equation of the organ-tissue level REE model for mammals can be expressed as

$$\text{REE} = \Sigma(K_i \times T_i). \quad (3)$$

Accordingly, a mass-specific REE (i.e., REE/M) model can be derived as

$$\frac{\text{REE}}{M} = \Sigma\left(K_i \times \frac{T_i}{M}\right), \quad (4)$$

where T is the mass of individual organs/tissues of mature mammals; T/M is the fraction of body mass as individual organs/tissues; K is the specific metabolic rate of organs/tissues; i is the organ/tissue number ($i = 1, 2, \dots, n$). Equations (3) and (4) demonstrate that the magnitude of REE (or REE/M) depends on both K_i and T_i (or T_i/M).

The K_i Values of Various Organs/Tissues across Mammalian Species. Previous studies reported that the resting metabolic rates of homologous organs have smaller K_i values in large animals compared to small animals [15]. The *in vitro* K_i values for liver and kidney vary allometrically with body mass across mature mammals [16].

Four organs (i.e., liver, brain, heart, and kidneys) are particularly active in mammalian energy metabolism during resting conditions [7, 8]. The *in vivo* K_i values of the four organs have been published for several mature mammals, including rat [5], rabbit, cat, dog [6], and human [7, 8]. For example, four human organs have high K_i values (all in kcal/kg per day): 200 for liver, 240 for brain, and 440 for heart and kidneys. In contrast, the average K_i values of the residuals are as low as 10.7 for humans [7].

Based on the information provided in Table 1, an exponential K_i - M function was derived for the four organs and residual mass [17],

$$K_i = a \times M^b, \quad (5)$$

where a and b are the organ/tissue-specific coefficient and scaling exponent, respectively. Although the exponent b

TABLE 1: Estimated K values of organ-tissue level components across mature mammals.

Species	M	KL	KB	KH	KK	KR
Rat	0.48	870	470	968	685	33.7
Rabbit	2.5	590	—	—	—	—
Cat	3.0	420	—	—	—	—
Dog	10	380	370	—	679	—
Human	65	251	230	668	482	20.7
Human	70	200	240	440	440	10.7
$K_i = a \times M^b$						
Coefficient a		683.9	446.6	890.3	689.7	29.96
Scaling exponent b		-0.2677	-0.1423	-0.1181	-0.0833	-0.1667
P value		0.975	0.961	0.855	0.848	0.827

Source of K data. Rat [5], rabbit, cat, dog [6], and human [7, 8]. Specific resting metabolic rates for liver, brain, heart, and kidneys of various mammals are consistent with results given by the above references. Specific resting metabolic rates for the residuals are calculated from the above references.

Abbreviations: M : body mass (in kg); KL, KB, KH, KK , and KR : specific resting metabolic rate of liver, brain, heart, kidney, and residuals, respectively (all in kcal/kg per day).

differs in various organs/tissues, all b values (all $r > 0.83$) are negative, indicating that the K_i values are smaller with greater body mass.

In the present study, the K_i values of the four organs and residual mass were predicted by (5) for different mammals (Table 2). Small mammals have higher K_i values than do large mammals. For example, liver's K value is 2533 kcal/kg per day for the shrew compared with 65 kcal/kg per day for the elephant. An important consideration is that the K_i values are much higher in immature mammals than that in adult mammals, including humans [18].

The T_i Values of Various Organs/Tissues across Mammalian Species. Because liver, brain, heart and kidneys are particularly active in resting mammalian energy metabolism, the following organ-tissue level model of body composition is applied,

$$M = \text{liver} + \text{brain} + \text{heart} + \text{kidneys} + \text{residual}, \quad (6)$$

where the residual is the sum of body components with lower metabolic rate at rest, including skeletal muscle, adipose tissue, skeleton, blood, skin, lung, connective tissue, gastrointestinal tract, and spleen. Residual mass is calculated as body mass minus the sum of liver, brain, heart, and kidneys mass.

A literature search was performed to collect data on body mass and mass of the four organs (Table 2). The database contains 111 species distributed in 11 mammalian orders: artiodactyla, carnivora, didelphimorphia, diprotodontia, eulipotyphla, lagomorpha, perissodactyla, primates, proboscidea, rodentia, and scandentia. Most of the data ($n = 99$) was obtained from a recent study of Navarrete et al. [11]. The mouse and dog (with body mass 20.42 kg) data were obtained from Martin and Fuhrman [9]; the rat,

TABLE 2: The organ-tissue level body composition, specific metabolic rates, and resting energy expenditure in 111 mammalian species.

Species	M	KL	KB	KH	KK	KR	TL	TB	TH	TK	TR	REE_p	REE_k	$(REE/M)_p$	$(REE/M)_k$
<i>Sorex araneus</i>	0.0075	2533	896	1586	1037	67.7	0.00038	0.00015	0.00011	0.00011	0.0068	1.8	1.8	245	238
<i>Crocidura russula</i>	0.010	2376	866	1542	1016	65.1	0.00055	0.00017	0.00008	0.00013	0.0086	2.3	2.1	237	224
<i>Lasiurus borealis</i>	0.014	2165	824	1480	987	61.4	0.00035	0.00017	0.00014	0.00011	0.013	2.0	2.8	148	205
<i>Lasionycteris noctivagans</i>	0.015	2115	814	1465	980	60.5	0.00033	0.00016	0.00016	0.00013	0.014	2.0	3.0	138	201
<i>Mus musculus</i>	0.015	2108	812	1463	979	60.4	0.00068	0.00036	0.00007	0.00028	0.014	2.9	3.0	196	200
<i>Myodes glareolus</i>	0.015	2087	808	1456	976	60.0	0.00067	0.00035	0.00010	0.00024	0.014	2.9	3.1	188	198
<i>Microtus agrestis</i>	0.015	2087	808	1456	976	60.0	0.00063	0.00039	0.00012	0.00017	0.014	2.8	3.1	183	198
<i>Neomys fodiens</i>	0.016	2080	807	1454	975	59.9	0.00055	0.00025	0.00014	0.00022	0.015	2.6	3.1	168	198
<i>Blarina brevicauda</i>	0.018	2011	792	1433	965	58.6	0.00093	0.00032	0.00018	0.00021	0.016	3.5	3.4	199	192
<i>Apodemus sylvaticus</i>	0.018	1997	789	1428	963	58.4	0.0011	0.00057	0.00014	0.00026	0.016	4.0	3.5	221	190
<i>Microtus pinetorum</i>	0.021	1925	774	1405	952	57.1	0.0011	0.00058	0.00015	0.00036	0.019	4.3	3.9	204	184
<i>Peromyscus leucopus</i>	0.022	1897	768	1396	947	56.6	0.0012	0.00074	0.00015	0.00030	0.020	4.5	4.0	204	182
<i>Apodemus flavicollis</i>	0.025	1835	755	1376	938	55.4	0.0010	0.00061	0.00018	0.00034	0.023	4.1	4.4	164	176
<i>Nyctalus noctula</i>	0.026	1824	752	1372	936	55.2	0.0005	0.00032	0.00037	0.00013	0.024	3.0	4.5	119	175
<i>Microtus arvalis</i>	0.027	1799	747	1364	932	54.7	0.0019	0.00039	0.00019	0.00055	0.024	5.7	4.7	213	173
<i>Mouse</i>	0.028	1781	743	1358	929	54.4	0.0018	0.00050	0.00016	0.00051	0.025	5.6	4.8	199	171
<i>Gerbillus perpallidus</i>	0.030	1748	735	1347	924	53.7	0.0010	0.00058	0.00013	0.00027	0.028	4.0	5.1	135	168
<i>Mustela nivalis</i>	0.032	1714	728	1335	918	53.1	0.0016	0.0018	0.00036	0.00043	0.028	6.3	5.3	196	165
<i>Acomys minous</i>	0.042	1593	700	1293	897	50.7	0.0009	0.0009	0.00018	0.00032	0.040	4.7	6.5	110	254
<i>Jaculus jaculus</i>	0.048	1543	688	1275	888	49.7	0.0011	0.0012	0.00045	0.00029	0.045	5.6	7.2	117	150
<i>Rhabdomys pumilio</i>	0.050	1523	683	1267	885	49.3	0.0018	0.0006	0.00021	0.00041	0.047	6.2	7.4	123	148
<i>Talpa europaea</i>	0.051	1514	681	1264	883	49.2	0.0015	0.0010	0.00031	0.00036	0.048	6.1	7.6	118	147
<i>Glaucomys volans</i>	0.055	1486	675	1254	878	48.6	0.0029	0.0019	0.00056	0.00059	0.049	9.2	8.0	167	144
<i>Arvicola terrestris</i>	0.062	1441	664	1237	870	47.7	0.0026	0.0011	0.00028	0.00070	0.057	8.1	8.7	131	140
<i>Glis glis</i>	0.083	1330	636	1194	848	45.3	0.0032	0.0015	0.00048	0.00068	0.078	9.9	10.9	118	130
<i>Tamias striatus</i>	0.104	1254	616	1163	833	43.7	0.0029	0.0024	0.00066	0.00081	0.097	10.8	12.8	104	123
<i>Octodon degus</i>	0.129	1182	597	1134	818	42.1	0.0048	0.0019	0.00041	0.0011	0.121	13.3	15.1	103	117
<i>Tupaia glis</i>	0.141	1156	590	1122	812	41.5	0.0034	0.0034	0.00117	0.0011	0.132	13.6	16.1	96.9	114
<i>Rat</i>	0.150	1137	585	1114	808	41.1	0.0092	0.0023	0.00070	0.0014	0.136	19.3	16.9	129	112
<i>Cebuella pygmaea</i>	0.163	1112	578	1103	802	40.5	0.0135	0.0044	0.00086	0.0019	0.142	25.8	18.0	158	110
<i>Rattus norvegicus</i>	0.210	1039	558	1071	786	38.9	0.0092	0.0023	0.00087	0.0015	0.196	20.6	21.7	98.0	103
<i>Cheirogaleus medius</i>	0.231	1012	550	1059	779	38.3	0.0063	0.0028	0.00093	0.0010	0.220	18.1	23.3	78.4	101
<i>Rat</i>	0.250	991	544	1049	774	37.8	0.0120	0.0020	0.00094	0.0021	0.233	24.4	24.7	97.6	99.0
<i>Mustela erminea</i>	0.259	982	541	1044	772	37.5	0.0100	0.0057	0.0025	0.0023	0.238	26.2	25.4	101	98.1
<i>Helogale parvula</i>	0.260	981	541	1044	772	37.5	0.0111	0.0052	0.0015	0.0025	0.240	26.1	25.5	100	98.0
<i>Sciurus vulgaris</i>	0.275	967	537	1037	768	37.2	0.0055	0.0063	0.0017	0.0017	0.259	21.4	26.6	77.9	96.7
<i>Callithrix jacchus</i>	0.312	935	527	1022	760	36.4	0.0178	0.0073	0.0028	0.0029	0.281	35.8	29.2	115	93.7
<i>Saguinus fuscicollis lagonotus</i>	0.330	920	523	1015	756	36.0	0.0144	0.0078	0.0033	0.0019	0.303	33.0	30.5	100	92.4
<i>Rat</i>	0.337	915	521	1012	755	35.9	0.0080	0.0019	0.0010	0.0023	0.324	22.7	31.0	67.3	91.9
<i>Rat (Wistar)</i>	0.390	880	511	995	746	35.1	0.0143	0.0019	0.0011	0.0028	0.370	29.8	34.6	76.3	88.6
<i>Sciurus niger</i>	0.412	867	507	989	743	34.7	0.0107	0.0075	0.0025	0.0030	0.389	31.3	36.0	75.8	87.4
<i>Sciurus carolinensis</i>	0.596	786	481	946	720	32.7	0.0164	0.0075	0.0028	0.0032	0.566	40.0	47.5	67.1	79.7
<i>Saguinus oedipus</i>	0.624	776	478	941	717	32.4	0.0209	0.0100	0.0037	0.0031	0.586	45.7	49.1	73.2	78.8

TABLE 2: Continued.

Species	M	KL	KB	KH	KK	KR	TL	TB	TH	TK	TR	REE_p	REE_k	$(REE/M)_p$	$(REE/M)_k$
<i>Mustela putorius</i>	0.640	771	476	939	716	32.3	0.0288	0.0104	0.0048	0.0040	0.592	53.6	50.1	83.8	78.3
<i>Leontopithecus chrysomelas</i>	0.642	770	476	938	716	32.3	0.0189	0.0132	0.0038	0.0041	0.602	46.8	50.2	73.0	78.2
<i>Guinea pig</i>	0.800	726	461	914	703	31.1	0.0270	0.0047	0.0023	0.0056	0.760	51.5	59.2	64.3	74.0
<i>Potorous tridactylus</i>	0.809	724	460	913	702	31.0	0.0237	0.0114	0.0048	0.0062	0.763	54.8	59.7	67.8	73.8
<i>Erinaceus europaeus</i>	0.950	693	450	896	693	30.2	0.0496	0.0043	0.0055	0.0089	0.881	74.1	67.3	78.0	70.9
<i>Sylvilagus floridanus</i>	0.972	689	448	893	691	30.1	0.0320	0.0079	0.0048	0.0063	0.921	61.9	68.5	63.7	70.5
<i>Ondatra zibethicus</i>	0.991	686	447	891	690	30.0	0.0260	0.0047	0.0030	0.0058	0.952	55.1	69.5	55.6	70.2
<i>Saimiri boliviensis</i>	1.00	683	446	890	690	29.9	0.0194	0.0290	0.0065	0.0067	0.941	64.8	70.2	64.6	69.9
<i>Martes foina</i>	1.41	624	425	855	670	28.3	0.0349	0.0190	0.0098	0.0073	1.335	81.0	90.4	57.6	64.3
<i>Mephitis mephitis</i>	1.45	619	424	852	669	28.2	0.0174	0.0098	0.0060	0.0066	1.409	64.2	92.5	44.3	63.8
<i>Trichosurus vulpecula</i>	1.55	608	420	845	665	27.9	0.0332	0.0127	0.0090	0.0135	1.482	83.3	97.2	53.7	62.7
<i>Martes martes</i>	1.60	603	418	842	663	27.7	0.0379	0.0205	0.0108	0.0088	1.525	88.6	99.7	55.3	62.2
<i>Cebus apella</i>	1.75	589	412	833	658	27.3	0.0493	0.0508	0.0134	0.0104	1.626	112	107	64.2	60.9
<i>Eulemur macaco macaco</i>	1.88	578	408	827	655	27.0	0.0778	0.0242	0.0091	0.0142	1.750	119	112	63.4	59.8
<i>Chrotagale owstoni</i>	1.96	571	406	822	652	26.8	0.0441	0.0233	0.0116	0.0128	1.868	103	116	52.3	59.2
<i>Vulpes corsac</i>	2.08	563	403	817	649	26.5	0.0356	0.0341	0.0217	0.0088	1.975	110	121	52.8	58.3
<i>Lemur catta</i>	2.08	563	403	817	649	26.5	0.0729	0.0228	0.0117	0.0112	1.956	119	121	57.3	58.3
<i>Eulemur fulvus fulvus</i>	2.50	535	392	799	639	25.7	0.0434	0.0225	0.0118	0.0095	2.413	110	139	43.8	55.7
<i>Felis silvestris</i>	2.57	531	390	796	638	25.6	0.0502	0.0381	0.0103	0.0154	2.459	122	142	47.6	55.3
<i>Didelphis virginiana</i>	2.63	528	389	794	636	25.5	0.1573	0.0083	0.0121	0.0229	2.433	172	145	65.5	54.9
<i>Aonyx cinerea</i>	2.68	526	388	793	635	25.4	0.1064	0.0359	0.0151	0.0306	2.487	165	146	61.5	54.7
<i>Leopardus geoffroyi</i>	3.10	505	380	779	628	24.8	0.0584	0.0321	0.0160	0.0307	2.963	147	164	47.4	52.8
<i>Lepus europaeus</i>	3.34	495	376	772	624	24.5	0.0904	0.0148	0.0289	0.0185	3.186	162	173	48.6	51.8
<i>Dasyprocta punctata</i>	3.40	493	375	771	623	24.4	0.1088	0.0228	0.0363	0.0213	3.211	182	175	53.5	51.5
<i>Potos flavus</i>	3.92	474	368	758	616	23.9	0.1657	0.0311	0.0211	0.0144	3.688	203	195	51.8	49.7
<i>Dasyprocta azarae</i>	4.10	469	365	754	613	23.7	0.0935	0.0238	0.0304	0.0227	3.930	182	202	44.5	49.2
<i>Varecia rubra</i>	4.20	466	364	752	612	23.6	0.0722	0.0357	0.0181	0.0224	4.052	170	205	40.4	48.9
<i>Alouatta sara</i>	4.40	460	362	747	610	23.4	0.0812	0.0565	0.0240	0.0099	4.228	181	213	41.1	48.3
<i>Monkey</i>	4.50	457	361	745	609	23.3	0.110	0.0420	0.0230	0.0210	4.304	196	216	43.5	48.1
<i>Martes pennanti</i>	4.79	450	357	740	605	23.1	0.113	0.0412	0.0274	0.0211	4.588	204	227	42.7	47.3
<i>Trachypithecus vetulus</i>	5.00	445	355	736	603	22.9	0.090	0.0720	0.0192	0.0154	4.803	199	234	39.8	46.8
<i>Lutrogale perspicillata</i>	5.10	442	354	734	602	22.8	0.152	0.0622	0.0485	0.0485	4.789	263	238	51.6	46.6
<i>Chlorocebus pygerythrus</i>	5.30	438	352	731	600	22.7	0.089	0.0808	0.0426	0.0121	5.076	221	245	41.7	46.1
<i>Lutra lutra</i>	5.33	437	352	731	600	22.7	0.255	0.0478	0.0514	0.0611	4.910	314	245	58.9	46.1
<i>Proteles cristata</i>	5.40	435	351	730	599	22.6	0.182	0.0399	0.0906	0.0243	5.063	288	248	53.4	45.9
<i>Agouti paca</i>	5.46	434	351	729	599	22.6	0.140	0.0321	0.0176	0.0222	5.248	217	250	39.7	45.8
<i>Macaca nigra</i>	5.60	431	350	726	598	22.5	0.095	0.1052	0.0239	0.0186	5.357	227	255	40.5	45.5
<i>Puma yagouaroundi</i>	5.90	425	347	722	595	22.3	0.116	0.0430	0.0296	0.0391	5.673	235	265	39.9	44.9

TABLE 2: Continued.

Species	M	KL	KB	KH	KK	KR	TL	TB	TH	TK	TR	REE_p	REE_k	$(REE/M)_p$	$(REE/M)_k$
<i>Hylobates concolor</i>	6.55	414	342	713	590	21.9	0.293	0.1378	0.0582	0.0352	6.026	363	287	55.3	43.8
<i>Prionailurus viverrinus</i>	7.30	402	337	704	584	21.5	0.160	0.0529	0.0335	0.0559	6.998	289	311	39.6	42.6
<i>Macropus agilis</i>	7.70	396	334	700	582	21.3	0.203	0.0308	0.0602	0.0463	7.360	317	324	41.1	42.0
<i>Lontra canadensis</i>	7.90	393	333	697	581	21.2	0.255	0.0425	0.0541	0.0747	7.474	354	330	44.8	41.8
<i>Dolichotis patagonum</i>	8.43	387	330	692	578	21.0	0.158	0.0365	0.0651	0.0360	8.134	310	346	36.8	41.1
<i>Symphalangus syndactylus</i>	8.50	386	329	691	577	21.0	0.294	0.1430	0.0515	0.0437	7.968	388	348	45.7	41.0
<i>Colobus guereza</i>	9.75	372	323	680	571	20.5	0.171	0.0865	0.0370	0.0233	9.432	323	386	33.2	39.6
<i>Felis chaus</i>	9.80	371	323	680	570	20.5	0.153	0.0497	0.0483	0.0819	9.467	346	388	35.3	39.6
<i>Lynx canadensis</i>	10.0	369	322	678	569	20.4	0.158	0.0826	0.0388	0.0549	9.666	340	394	34.0	39.4
Dog	10.0	369	322	678	569	20.4	0.420	0.0750	0.0850	0.0700	9.350	468	394	46.8	39.4
<i>Arctictis binturong</i>	10.3	366	320	676	568	20.3	0.915	0.0605	0.0752	0.0513	9.198	621	402	60.3	39.1
<i>Hystrix indica</i>	11.3	358	316	669	564	20.0	0.255	0.0407	0.0562	0.0524	10.85	388	430	34.5	38.2
<i>Theropithecus gelada</i>	11.4	357	316	668	563	20.0	0.236	0.1409	0.0772	0.0380	10.91	419	434	36.8	38.1
<i>Pudu puda</i>	13	345	310	658	557	19.6	0.206	0.0616	0.0505	0.0199	12.56	380	476	29.5	36.9
<i>Gazella gazella</i>	15	331	304	647	550	19.1	0.327	0.0793	0.120	0.0406	14.43	508	534	33.8	35.6
<i>Castor fiber</i>	15.6	328	302	644	549	19.0	0.345	0.0489	0.044	0.0783	15.05	485	548	31.1	35.2
<i>Macaca arctoides</i>	15.9	326	301	642	548	18.9	0.241	0.1180	0.061	0.0500	15.40	472	556	29.7	35.1
<i>Lynx lynx</i>	17.5	318	297	635	543	18.6	0.264	0.0943	0.093	0.0795	16.97	529	599	30.3	34.2
<i>Capreolus capreolus</i>	20	307	292	625	537	18.2	0.480	0.100	0.160	0.0800	19.18	668	662	33.4	33.1
<i>Cuon alpinus</i>	20.0	307	292	625	537	18.2	0.346	0.116	0.158	0.0764	19.30	631	662	31.5	33.1
Dog	20.4	305	291	624	537	18.1	0.447	0.096	0.153	0.0920	19.6	665	672	32.6	32.9
<i>Mandrillus sphinx</i>	23.0	295	286	615	531	17.8	0.331	0.168	0.076	0.0499	22.4	616	735	26.8	32.0
<i>Papio hamadryas</i>	23.3	295	285	614	531	17.7	0.392	0.174	0.103	0.0803	22.5	670	741	28.8	31.9
<i>Zalophus californianus</i>	34.0	266	270	587	514	16.6	1.274	0.310	0.168	0.2059	32.0	1161	986	34.1	29.0
<i>Hydrochaeris hydrochaeris</i>	34.0	266	270	587	514	16.6	0.696	0.084	0.104	0.1035	33.0	872	986	25.6	29.0
<i>Canis lupus chanco</i>	38.0	258	266	579	509	16.3	0.971	0.140	0.303	0.2069	36.4	1163	1071	30.6	28.2
Sheep	52	237	255	558	496	15.5	0.960	0.106	0.280	0.160	50.5	1274	1356	24.5	26.1
Reference women	58	200	240	440	440	10.4	1.40	1.20	0.240	0.275	54.9	1365	1471	23.5	25.4
Human	60	200	240	440	440	10.4	1.70	1.30	0.320	0.250	56.4	1490	1509	24.8	25.2
Reference man	70	200	240	440	440	10.4	1.80	1.40	0.330	0.310	66.2	1666	1694	23.8	24.2
<i>Panthera tigris altaica</i>	75	215	242	535	481	14.6	1.10	0.342	0.305	0.4246	72.8	1750	1784	23.3	23.8
Hog	125	188	225	503	461	13.4	1.60	0.12	0.350	0.260	123	2267	2617	18.1	20.9
Dairy cow	488	130	185	429	412	10.7	6.46	0.40	1.88	1.16	478	7304	7268	15.0	14.9
Horse	600	123	180	418	405	10.3	6.70	0.67	4.25	1.66	587	9449	8486	15.7	14.1
Steer	700	118	176	411	400	10.1	5.00	0.50	2.30	1.00	691	8973	9526	12.8	13.6
Elephant	6650	65	128	315	331	6.9	6.30	5.70	2.20	1.20	6635	48054	51548	7.2	7.8

Source of M and T_i data: mouse and dog ($M = 20.42$ kg) from Marting and Fuhrman, 1955 [9]; rat, guinea pig, dog ($M = 10$ kg), sheep, hog, dairy cow, horse, steers, and elephant from Elia, 1992 [7]; reference man and woman from Snyder et al., [10]; rest species from Navarrete et al., 2011 [11].

Abbreviations: M : body mass (in kg); KL , KB , KH , KK , and KR : Specific resting metabolic rate of liver, brain, heart, kidney, and residuals, respectively (all in kcal/kg per day); TL , TB , TH , TK , and TR : mass of liver, brain, heart, kidney, and residuals, respectively (all in kg); REE_p : resting energy expenditure predicted by the organ-tissue level REE model (in kcal/day); REE_k : resting energy expenditure calculated by Kleiber's Law (in kcal/day); $(REE/M)_p$: the ratio of resting energy expenditure by the organ-tissue level REE model to body mass (in kcal/kg per day); $(REE/M)_k$: the ratio of resting energy expenditure calculated by Kleiber's Law to body mass (in kcal/kg per day).

TABLE 3: The K - M and $(K \times T)$ - M functions for five organs/tissues across 111 mammals.

	$(K - M)$ function	$(K \times T)$ - M function
Liver	$KL = 683.9 \times M^{-0.2677}$ $r = 0.975$	$KL \times TL = 19.56 \times M^{0.6046}$ $r = 0.9694$
Brain	$KB = 446.6 \times M^{-0.1423}$ $r = 0.961$	$KB \times TB = 4.82 \times M^{0.6446}$ $r = 0.9538$
Heart	$KH = 890.3 \times M^{-0.1181}$ $r = 0.855$	$KH \times TH = 5.16 \times M^{0.8137}$ $r = 0.9830$
Kidneys	$KK = 689.7 \times M^{-0.0833}$ $r = 0.848$	$KK \times TK = 4.35 \times M^{0.7441}$ $r = 0.9825$
Residual	$KR = 29.96 \times M^{-0.1667}$ $r = 0.827$	$KR \times TR = 28.16 \times M^{0.8402}$ $r = 0.9996$

Abbreviations: M : body mass (in kg); KL, KB, KH, KK and KR : specific resting metabolic rate of liver, brain, heart, kidney and residual, respectively (all in kcal/kg per day).

guinea pig, dog (with body mass 10 kg), sheep, hog, dairy cow, horse, steer, and elephant data were obtained from Elia [7]; the reference man and woman data were obtained from Snyder et al. [10]. All collected published data were used as is and no judgment on data quality was made.

The Working REE Model across Mammalian Species. Based on models (3) and (5), a working REE prediction model can be derived at the organ-tissue level for mature mammals,

$$REE_p = \Sigma(a \times M^b \times T_i). \quad (7)$$

Accordingly, a working mass-specific REE (i.e., REE/M) model can be derived as

$$\left(\frac{REE}{M}\right)_p = \Sigma\left(a \times M^b \times \frac{T_i}{M}\right), \quad (8)$$

where M is body mass; T is the mass of individual organs/tissues; T/M is the fraction of body mass as individual organs/tissues; i is the organ/tissue number ($i = 1, 2, \dots, n$); a and b are the organ/tissue-specific coefficient and scaling exponent, respectively.

2.2. Statistical Analysis. Paired Student's t -tests were used to compare REE_p by (7) with REE_k calculated by Kleiber's law (i.e., (1)) and to compare the $(REE/M)_p$ by (8) with $(REE/M)_k$ from (2). Simple linear regression analysis was used to find the association between REE_p and REE_k as well as between $(REE/M)_p$ and $(REE/M)_k$. Scatter plots were applied to explore the association between REE_k (and $(REE/M)_k$) and REE_p (and $(REE/M)_p$). Data were analyzed by the Microsoft Excel version 5.0 (Microsoft Corporation, Redmond, WA). Statistical significance was set as 0.05.

3. Results

3.1. Organ-Tissue Level Body Composition of Mature Mammals. The data on body composition for 111 mammalian species are listed in Table 2. Body mass ranged from 0.0075 kg for the shrew (*Sorex araneus*) to 6650 kg for the elephant,

FIGURE 1: The $(K \times T)$ values (in kcal/d) of individual organs/tissues predicted by (9) on the ordinate versus body mass (M , in kg) on the abscissa across 111 mammalian species. The $(K \times T)$ values of liver, brain, heart, kidneys, and residuals are shown as the five thin lines. The resting energy expenditure (REE_p) predicted by (7) is represented as the thick line (upper). All REE_p ($K \times T$) and M values are on a logarithmic scale. The REE_p and M are significantly correlated: $REE_p = 66.33 \times M^{0.754}$; $r = 0.9975$.

with a $\sim 887,000$ -fold difference in body size. The variability in the mass of high metabolic rate organs is very large across mammalian species. The sum of the four organs (liver, brain, heart, and kidneys) varied from 0.00075 kg for the shrew to 15.4 kg for the elephant, with a $\sim 20,500$ -fold difference. However, the fraction of body mass as the four organs declined from 10.0% in the shrew to 0.23% in the elephant.

3.2. Model-Predicted REE across Mammalian Species. Based on (7), the model-predicted energy expenditure ($K \times T$) of individual organs/tissues was calculated as ranging from 0.0075 kg (shrew) to 6650 kg (elephant). The respective regression lines of $(K \times T)$ for liver, brain, heart, kidneys, and residual were derived and presented in Figure 1 and Table 3,

$$\begin{aligned} \text{for liver: } (K \times T) &= 19.56 \times M^{0.6046}; \quad r = 0.9694, \\ \text{for brain: } (K \times T) &= 4.82 \times M^{0.6446}; \quad r = 0.9538, \\ \text{for heart: } (K \times T) &= 5.16 \times M^{0.8137}; \quad r = 0.9830, \\ \text{for kidneys: } (K \times T) &= 4.35 \times M^{0.7441}; \quad r = 0.9825, \\ \text{for residual: } (K \times T) &= 28.16 \times M^{0.8402}; \quad r = 0.9996. \end{aligned} \quad (9)$$

Based on (7), the model-predicted REE (REE_p) was calculated (Table 2). The REE_p varies from 1.8 kcal/d in the shrew to 48000 kcal/d in the elephant. The REE_p is allometrically correlated with body mass across the 111 mammalian species (Figure 1),

$$REE_p = 66.33 \times M^{0.754}; \quad r = 0.9975. \quad (10)$$

The scaling exponent between REE_p and body mass was 0.754 with a 95% CI (0.744, 0.764), close to 0.75 ($P = 0.42$) for Kleiber's law at the whole-body level.

Model-predicted REE_p was correlated with REE_k by Kleiber's law (Figure 2),

$$REE_k = 1.0644 \times REE_p; \quad r = 0.9994. \quad (11)$$

There was no significant difference between REE_k and REE_p across the 111 species (paired Student's t -test, $P = 0.252$).

3.3. Model-Predicted REE/M across Mammalian Species. The model-predicted $(REE/M)_p$ was calculated by the working model (8), declining from 240 kcal/kg per day in shrew to 7.2 kcal/kg per day in elephant, that is, approximately 33 times greater in shrew than in elephant. The $(REE/M)_p$ was allometrically correlated with body mass across the 111 species (Figure 3),

$$\left(\frac{REE}{M}\right)_p = 66.33 \times M^{-0.246}; \quad r = 0.9774. \quad (12)$$

The scaling exponent between $(REE/M)_p$ and body mass was -0.246 with 95% CI $(-0.256, -0.236)$, close to -0.25 as for Kleiber's law at the whole-body level.

The model-predicted $(REE/M)_p$ by (8) was correlated with $(REE/M)_k$ calculated by (2) based on Kleiber's law (Figure 4),

$$\left(\frac{REE}{M}\right)_k = 1.0644 \times \left(\frac{REE}{M}\right)_p; \quad r = 0.9858. \quad (13)$$

There were differences between $(REE/M)_k$ and $(REE/M)_p$ in the 111 mammals (paired Student's t -test, $P = 0.020$). A Bland-Altman plot shows that there was no bias in REE/M differences, that is, $[(REE/M)_k - (REE/M)_p]$, in relation to the average of the two REE/M values,

$$\begin{aligned} \frac{REE}{M} \text{ difference} &= 0.001 \times \text{mean} \frac{REE}{M} - 3.33; \\ r &= 0.032, \quad P > 0.05. \end{aligned} \quad (14)$$

4. Discussion

In 1932 Kleiber first described what has become known as the "mouse-to-elephant" curve by plotting REE versus body mass across mammals and reporting that REE scales as the three fourths (0.75) power of body mass. A number of mechanisms and models have been proposed over the ensuing eighty years to explain Kleiber's law, including McMahon's model [19], four-dimensional model [20], Ecomonomos model [21], mass transfer model [22], supply-side fractal model [23], resource-flow model [24], and Darveau's model [25]. Up to now, however, there remains a lack of full agreement on the mechanistic basis of the 0.75 power of the REE-M relationship. The present study provides three new observations related to Kleiber's law.

4.1. New Insights into Kleiber's Law. Our previous study indicated that ~ 40 body components are distributed between distinct but connected levels: whole body, organ tissue, cellular, molecular, and atomic [26]. In principle, REE can be

FIGURE 2: The resting energy expenditure (REE_k , in kcal/d) calculated by Kleiber's law (1) on the ordinate versus the resting energy expenditure (REE_p , in kcal/d) predicted by the organ-tissue level model (7) on the abscissa across 111 mammalian species. Both REE_k and REE_p are shown on a logarithmic scale. The REE_p and REE_k are significantly correlated: $REE_k = 1.0644 \times REE_p$; $r = 0.9994$. The line of identity is shown.

FIGURE 3: The ratio of resting energy expenditure to body mass (i.e., $(REE/M)_p$ in kcal/kg per day) predicted by the organ-tissue level model (8) on the ordinate versus body mass (M , in kg) on the abscissa across 111 mammalian species. Both $(REE/M)_p$ and M are shown on a logarithmic scale. The $(REE/M)_p$ and M are significantly correlated: $(REE/M)_p = 66.33 \times M^{-0.246}$; $r = 0.9774$.

FIGURE 4: The ratio of resting energy expenditure to body mass (i.e., $(REE/M)_k$, in kcal/kg per day) calculated by Kleiber's law (2) on the ordinates versus the ratio of resting energy expenditure to body mass (i.e., $(REE/M)_p$, in kcal/kg per day) predicted by (8) on the abscissa across 111 mammalian species. Both $(REE/M)_k$ and $(REE/M)_p$ are shown on a logarithmic scale. The $(REE/M)_p$ and $(REE/M)_k$ are significantly correlated: $(REE/M)_k = 1.0644 \times (REE/M)_p$; $r = 0.9858$. The line of identity is shown.

expressed at whole body, organ tissue, cellular, and molecular levels, respectively [17, 27]. Kleiber's law was established at the whole-body level to explore the quantitative association between REE and body mass.

The first contribution of the present study and our previous investigation [17, 27] was to develop an organ-tissue level REE model across mature mammals. This physiological model is based on the concept that whole-body REE is equal to the sum of energy consumption by all organs and tissues in the postabsorptive state. By using the reported data of 111 mammals, we derived the allometric equations of REE for the five organs and tissues (9). We found that the sum of the energy consumption of the five organs and tissues is equal to REE_k as defined by Kleiber's law (Figure 1) with a scaling exponent of 0.754, similar to the value of 0.75 as observed by Kleiber.

4.2. The Body Composition Basis of Kleiber's Law. The second contribution of the present study was to provide the body composition basis of Kleiber's law, revealing in the process the large difference in organ/tissue mass across mammals. The comprehensive body composition database across mammals presented in Table 2 includes body mass and the mass of four high-metabolic rate active organs (i.e., T_i) in 111 mammalian species. The absolute T_i values of homologous organs increase with body mass. For instance, liver is only 0.00038 kg in the shrew compared with 6.30 kg in the elephant. The T_i is thus the major contributor of the large differences in REE between species (e.g., shrew, 1.8 kcal/d and elephant 48,000 kcal/d; Table 2). In contrast, the $(T/M)_i$ values of homologous organs decrease with body mass. For example, liver's $(T/M)_i$ value in the shrew of 0.0506 is much larger than that in the elephant 0.0009. The $(T/M)_i$ value is thus the major contributor to the large difference in REE/M between species, for example, shrew 245 kcal/kg per day versus elephant 7.2 kcal/kg per day (Table 2).

4.3. Physiological Basis of Kleiber's Law. The third contribution of the present study was to elucidate the physiological mechanism of Kleiber's law: the K_i values of homologous organs are not the same with larger K_i values in smaller mammals.

There are several available methods to estimate K_i values of individual organs and tissues. *In vitro* estimation of K_i values from organ slices has been applied to determine K_i values in mammals since the 1920s [16]. However, *in vitro* studies underestimate K_i values [8]. More recently *in vivo* estimation approaches have been applied to estimate the K_i values of organs [28, 29]. The oxygen consumption of an organ can be estimated by the arteriovenous differences in O_2 concentration across the organ, combined with the assessment of blood flow perfusion of the organ. Oxygen consumption of the brain has been assessed since 1990s by positron emission tomography (PET) with 2-deoxy $2^{[18F]}$ fluoro-D-glucose [30]. Other isotopes have also been applied such as ^{11}C -acetate. Recently, oxygen consumption can be assessed by PET combined with computerized tomography (PET-CT) or magnetic resonance imaging (PET-MRI). These

rapidly advancing methods provide new opportunities for estimating the K_i values of organs and tissues in mammals.

As *in vivo* determination of K_i values is still a technically demanding process, only a few studies have been reported for assessing the K_i value of organs and tissues in mammals (Table 1). In this paper most K_i values were predicted, rather than estimated. This is the major limitation of the present study. Further *in vivo* studies are needed to estimate the K_i values of individual organs and tissues in >100 mammalian species. This area is a major challenge for completely validating the organ-tissue level REE model and Kleiber's law.

Couture and Hulbert [16] estimated the K_i values of liver and kidney in five mammals (mouse, rat, rabbit, sheep, and cattle). Although these authors used *in vitro* methods, the estimated K_i values of homologous organs vary with body size, with allometric exponents -0.21 for liver and -0.12 for kidney, close to -0.2677 for liver and -0.0833 for kidney, observed in our *in vivo* study (Table 1).

Based on the observed K - M association [17, 27], we predicted the K values across mature mammals (Table 2). For example, liver's K value of 2533 kcal/kg per day in shrew is much larger than 65 kcal/kg per day in elephant. Therefore, the large difference in K_i values across mammals is the physiological basis for Kleiber's law.

In conclusion, although Kleiber's law is a simple mathematical function, this classic empirical expression does not reflect the underlying body composition and physiologic mechanism. We derived and evaluated a novel organ-tissue level REE model that provides a fundamental linkage between REE (REE/M) and body size. The high REE/M in small mammals can be explained by two variables operating jointly: the high fraction of body mass as liver, brain, heart, and kidneys and their high specific resting metabolic rates.

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