Thermoregulation in mice exhibits genetic variability early in senescence

Patrick Gonzales · Brad A. Rikke

Received: 9 April 2009 / Accepted: 22 July 2009 / Published online: 11 August 2009
© American Aging Association 2009

Abstract Aging leads to a loss of thermoregulation that can be readily monitored in laboratory mice. However, it is unclear from previous studies—we provide a tabular summary of 15 articles—whether significant loss occurs by midlife (~15 months of age). In this study, we examined 34 females from 22 LSXSS strains starting at 4 and 8 months of age (17 mice per age group). We used transponders inserted just under the loose skin of the pelt and calibrated against rectal body temperature to measure temperatures quickly without restraint. We found that the mean body temperatures measured 5 months later (9 and 13 months of age) had dropped significantly below normal in both groups: 0.6°C lower in the younger cohort and 1.0°C lower in the older cohort. These drops were not associated with weight loss or signs of pathology. Notably, the loss of thermoregulation between 8 and 13 months of age also exhibited genetic variation that was highly significant ($P=0.004$). Such variation is potentially a powerful tool for determining the cause of thermoregulatory loss with age and whether this loss predicts senescence changes later in life, including the force of mortality.

Keywords Aging · Body temperature · Genetics · LSXSS · Mice · Thermoregulation

Introduction

Thermoregulation is an important component of homeostasis in mammals, responsible in humans and in mice for maintaining mean body temperature at 37°C. This regulation is achieved by the integration of neuronal processes to sense temperature change, hormonal processes to signal multiple organs, metabolic processes in muscle, fat, and liver to adjust heat production, and glandular, pulmonary, and vascular processes to adjust heat loss (Aniansson et al. 1986; Lauria et al. 1999; Van Someren et al. 2002; Passlick-Deetjen and Bedenbender-Stoll 2005). This intricate system is undoubtedly responsible for the great success of mammalian adaptability to various climates; however, such integration and complexity makes it challenging to identify the root cause of impaired thermoregulation.

Impaired thermoregulation is one of the hallmarks of senescence in mammals (Reynolds et al. 1985; Florez-Duquet and McDonald 1998; Moran and Mendal 2002; Degroot and Kenney 2006; Van Someren 2007), and the consequences can be serious: Human epidemiological studies indicate that most deaths due to hyperthermia and hypothermia occur in the elderly (Bai et al. 1995). The elderly also exhibit an attenuated ability to thermoregulate in the absence of extreme temperatures (Reynolds et al. 1985; Degroot and Kenney 2006). Besides the question of what causes this loss of thermoregulation, it is also of interest to know whether this loss is a biomarker of normal aging (Ingram et al. 1982).

P. Gonzales · B. A. Rikke (✉)
Institute for Behavioral Genetics, University of Colorado,
Campus Box 447, Boulder, CO 80309-0447, USA
e-mail: Rikke@Colorado.edu

To address these questions, it would be useful to determine the relative age at which loss of thermoregulation begins, and to this end, a number of studies have been conducted in mice and rats. As summarized in Table 1, the findings have been quite variable. Part of this variability could be genetic; but even studies of the same strain, such as C57BL/6, have not yielded a consistent result, suggesting that much of the variation is environmental. This environmental variation could be related to experimental design: Almost all of the experiments were cross-sectional rather than longitudinal, and T_b s were typically measured at only one time point under conditions of restraint.

In previous studies, we analyzed the T_b s of food-restricted mice from 22 LSXSS recombinant inbred strains and discovered a large amount of genetic variation (Rikke et al. 2003, 2004). Here, we have analyzed the longitudinal data from our ad libitum fed control mice to ask if there was a significant drop in mean T_b with age early in senescence and, if so, was there significant genetic variation in this drop. Our use of small, radiofrequency transponders allowed us to measure T_b s quickly without restraint at multiple time points around the clock for multiple, consecutive days. In this manner, we were able to mitigate the effects of temporal variation and obtain measurements that reflect 24-h means.

Materials and methods

All mice were female LSXSS recombinant inbreds (RIs), derived from long sleep (LS) and short sleep (SS) outbred strains (Markel et al. 1996). The LS and SS were created by selecting for differences in sedative-hypnotic sensitivity to ethanol starting from a heterogeneous stock of eight classical inbred strains. For traits not related to ethanol sensitivity, the strains are segregating randomly.

Females were used because this study was conducted as part of a larger study to measure genetic variation in the extension of female fertility by dietary restriction (results to be published). Previous studies have also suggested that females lose thermoregulatory ability with age just as males do (McLaren 1961; Estler 1971). Previous studies also suggest that the potential effects of estrous are negligible: Estrous in female mice occurs every 5 to 6 days, and the impact

on mean T_b averaged over seven or more contiguous days would be less than 0.1°C (Weinert et al. 2004).

Within each cohort, the mice were born within 1 week of each other (Rikke et al. 2004). Cohort 1, consisting of 17 mice from 11 strains, comprised all of the longitudinally studied, ad libitum fed mice from cohort 2a of Rikke et al. (2004). Cohort 2, also 17 mice from 11 different strains, comprised all of the longitudinally studied, ad libitum fed mice from cohort 2b. In each cohort, five strains were represented by one mouse, and six strains were represented by two mice. Cohort 2 was 4 months younger than cohort 1 but otherwise studied concurrently under the same conditions in the same colony room.

The husbandry conditions have previously been described (Rikke et al. 2003, 2004). In brief, the mice were singly housed in shoebox style cages in a specific pathogen-free facility. The mice were maintained under a 12-h light/dark cycle (lights on 7 A.M.) and given *ad libitum* access to food and water. Average room temperature was 23°C.

The T_b s were measured using commercially available, passive, radio-telemetry transponders (Biomedic Data Systems, Seaford, DE). Per the manufacturer's instructions, these rice grain size transponders, weighing ~0.1 g, were inserted without anesthesia under a loose fold of dorsal skin using a syringe (Rikke et al. 2004). All procedures were approved by the University of Colorado's Institutional Animal Care and Use Committee.

The T_b s were measured simultaneously in cohorts 1 and 2 during two temperature trials conducted 5 months apart. In the first trial, the T_b s were measured every 4 h for seven consecutive days. In the second trial, the T_b s were measured every 6 h for 10 days. A study of food-restricted mice, whose circadian pattern of T_b is much more variable than that of ad libitum fed mice (Rikke et al. 2003, 2004), indicated no appreciable difference in mean T_b s calculated on the basis of 4- versus 6-h intervals (Rikke et al. 2004). In both trials, T_b was measured within seconds after disturbing the cage, and a head-mounted red light was used at night to avoid turning on the room lights. Over the course of several days immediately after each trial, all transponders were calibrated (based on three to four readings) against rectal T_b (Thermalert TH-5, 1.7-cm probe) (Rikke et al. 2004). The statistical analyses were conducted using SPSS for Windows 16.0.

Table 1 Summary of studies that have assessed age-related changes in rodent body temperatures before 15 months of age under room-temperature conditions of 20–28°C

Reference	Strain(s) (sex)	Design	Ages (month)	Mice per age group	Time points per day	Number of days per age	Restraint ^b	Younger T_b , older T_b (°C)
McLaren 1961	C57BL/How (M)	C	2.5, 8	5–9	1	1	Yes (tail)	37.2, 37.3
	C57BL/How (F)	C	2.5, 8	5–9	1	1	Yes (tail)	37.6, 37.2
	C3H/Bi (M)	C	2, 8	5–9	1	1	Yes (tail)	39.2, 38.2*
	C3H/Bi (F)	C	2, 8	5–9	1	1	Yes (tail)	38.6, 37.8*
Estler 1971	NMRI (F)	C	1.25, 12	8–20	1	1	Yes	38.3, 37.8
Eleftheriou 1975	C57BL/6J (M)	C	2, 12	25	1	5	Yes	39.0, 36.9*
	DBA/2J (M)	C	2, 12	20	1	5	Yes	38.3, 37.9*
Leto et al. 1976	C57BL/6J (F)	C?	2, 14	8	12	1.33	Yes	38.1, 38.2
Habicht, 1981	C57BL/6 (M)	C	2, 12	15	1	3	Yes	37.4, 38.3*
	BALB/C (M)	C	2, 12	15	1	3	Yes	38.5, 39.5*
Balmagiya and Rozovski 1983	Sprague-Dawley (M)	L/C ^a	3, 13	24, 18	1	1	Yes	39.2, 38.5*
Hoffman-Goetz and Keir 1984	C57BL/6J (M)	C	6.5, 13.5	15–16	1 for 3 h	1	Partial (tether)	36.6, 35.8
Talan 1984	C57BL/6J (M)	C	3, 15	20	1	1	Yes (tube)	37.5, 37.4
Kiang-Ulrich and Horvath 1985	Fischer 344 (M)	C	3, 12	6	continuous for 3 h	1	No	37.1, 37.4
Talan et al. 1985	C57BL/6J (M)	C	8, 15	10, 30	1	1	Yes (tube)	38.2, 38.2
	C57BL/6J (M)	L	8, 11.5	9	1	1	Yes (tube)	38.2, 38.0
Talan and Engel 1986	C57BL/6J (M)	C	12, 14, 14.5	19–20	1	1	Yes (tube) ^c	36.2, 35.2*, 36.9*
	C57BL/6J (F)	C	12, 14, 14.5	19–20	1	1	Yes (tube) ^c	36.6, 36.0*, 37.1*
	C57BL/6 (M)	L	13, 14, 14.5	10	1	1	Yes (tube)	38.6, 37.2*, 38.5
	C57BL/6 (M)	L	12, 14, 14.5	19	1	1	Yes (tube)	38.3, 38.2, 36.5*
	C57BL/6 (M)	L	12, 14, 14.5	19	1	1	Yes (tube)	38.3, 38.2, 36.5*
McDonald et al. 1993	Fischer 344 (M)	C	6, 12	5–6	1	1	Yes	36.8, 37.0
	Fischer 344 (F)	C	6, 12	5–6	1	1	Yes	37.1, 37.3
McDonald et al. 1994	Fischer 344 (M)	C	6, 12	7–9	1	1	Yes	37.6, 37.5
	Fischer 344 (F)	C	6, 12	7–9	1	1	Yes	37.8, 38.1
Gabaldon et al. 1995	Fischer 344 (M)	C	6, 12	8, 8	1	1	Yes	36.8, 36.8
	Fischer 344 (F)	C	6, 12	6, 8	1	1	Yes	37.2, 37.2
Gordon 2008	Brown Norway (M)	C	4, 12	5, 6	Every 5 min	5	No	37.4, 37.4
	Brown Norway (M)	L	3, 14	8	Every 5 min	5	No	37.2, 37.2
this study	11 LXS RIs (F)	L	4, 9	17	6, 4	7, 10	No	36.9, 36.3*
	11 LXS RIs (F)	L	8, 13	17	6, 4	7, 10	No	36.7, 35.7*

C cross-sectional, L longitudinal

^a Mostly longitudinal but apparently 6 rats died between the two time points and the earlier measures were not excluded

^b Unless noted otherwise, restraint refers to holding the animal by the scruff of the neck while taking its rectal T_b

^c A notable contrast to the previous studies by Talan was that the rectal temperatures were measured immediately after restraint

* $p < 0.05$, statistically significant change with age (relative to youngest age for Talan and Engel)

Results

A longitudinal decrease in mean T_b over 5 months was tested for simultaneously in two cohorts of mice that differed in age by 4 months. All 17 mice in the

older cohort (cohort 1), assessed at 8 and then 13 months of age, exhibited a decrease in mean T_b . The grand mean (average across all mice) decreased from 36.7°C to 35.7°C, a drop of 1.0°C that was extremely significant ($P = 1.0 \times 10^{-6}$; SE = 0.13; paired

sample *t* test, two-tailed). The grand mean of 35.7°C was also clearly below normal, indicating loss of thermoregulation. Over this same time period, the grand mean for body weight (BW) did not change: 22.0 g at 8 months and 21.9 g at 13 months ($P=0.36$, $SE=0.24$, paired sample *t* test, one-tailed).

In the younger group of 17 mice (cohort 2), assessed at 4 and then 9 months of age, all but one mouse exhibited a decrease in mean T_b . The grand mean decreased from 36.9°C to 36.3°C, and this drop of 0.6°C was highly significant as well ($P=0.003$, $SE=0.14$, paired sample *t* test, two-tailed). The grand mean for BW increased slightly from 21.0 to 21.8 g ($P=0.06$; $SE=0.40$; paired sample *t* test, two-tailed).

The T_b drops in cohort 1 exhibited a large amount of strain variation, ranging from 0.1°C to 2.2°C (Fig. 1). This variation was much greater than the average variation within strain ($n=6$), and analysis of variance, which takes into account the small number of within-strain measures, indicated that the variation between strains was highly significant ($P=0.004$). This variation in T_b drop was not predicted by the strain variation in mean T_b that was present at 8 months of age ($R=-0.35$, $P=0.30$, two-tailed) nor was it strictly a function of the T_b means at 13 months: The correlation coefficient of 0.58, though significant ($P=0.03$, one-tailed), indicated that the T_b means explained only ~34% (0.58^2) of the variance.

We also asked whether this strain variation in T_b drop correlated with change in BW. It did appear that the mouse with the largest drop in mean T_b (2.2°C)

also lost an unusual amount of weight (nearly 3 g). However, there was no correlation between T_b drop and weight loss when this mouse was excluded ($R=0.19$, $P=0.24$, one-tailed), justified on the basis of its being a 3.7-SD Cook's distance outlier for leverage effects on the correlation (SPSS 16.0). The average drop in mean T_b with this mouse excluded decreased only slightly to 0.9°C, and this drop was still extremely significant ($P=7.6\times 10^{-7}$; $SE=0.11$; two-tailed, paired sample *t* test). The variance between strains relative to the variance within strains remained highly significant as well ($P=0.009$, ANOVA).

In cohort 2, the drop in mean T_b among the 11 strains ranged from 0°C to 1.5°C. Although there was greater variation between strains relative to the variation within strains ($n=6$), the difference was not statistically significant ($P=0.30$, ANOVA; one-tailed). The variation between strains was not predicted by the variation in mean T_b at 4 months of age ($R=-0.31$, $P=0.35$, two-tailed), and it was highly correlated with mean T_b at 9 months ($R=0.89$, $P=0.0001$, one-tailed).

Discussion

Our first important finding is that the mice in both cohorts exhibited a highly significant drop in mean T_b relatively early in senescence. This decline occurred in 33 out of 34 mice. The average decline in the younger cohort, assessed between 4 and 9 months of age, was 0.6°C ($P=0.003$), while the older cohort,

Fig. 1 Strain variation in the T_b drop between 8 and 13 months of age. Each bar represents the average decrease in mean T_b (°C) for that strain; the error bars are SE. ANOVA indicated that the variation between strains relative to the variation within strains was highly significant ($P=0.004$)

studied at the same time between 8 and 13 months of age, exhibited a larger drop of 1°C. The larger drop in the older cohort is consistent with an accelerated loss of thermoregulation due to aging.

Although several studies have previously suggested that rodents start losing their ability to thermoregulate early in senescence, many others have suggested that this is not the case (Table 1). One of the main differences between our study and earlier studies is that we used a longitudinal design. To our knowledge, longitudinal studies of T_b before 15 months of age in mice have only been conducted previously by Talan et al. (1985) and Talan and Engel (1986) and only on C57BL/6 males. In the Talan et al. (1985) study, consisting of nine mice, there was a non-significant but small decrease in the T_b average, from 38.2°C to 38.0°C between 8 and 11 1/2 months of age. In the 1986 study, a cohort of ten mice showed a sharp drop in T_b from about 38.6 to 37.2°C (~1.4°C) between 12 and 14 months that reverted back to 38.5°C just 2 weeks later. In a second cohort of 19 mice, T_b showed no decrease between 12 and 14 months and then a sharp drop from about 38.2°C to 36.5°C (~1.7°C) just 2 weeks later.

In addition to the longitudinal design, our study is the only one in mice to measure T_b s without restraint *and* do so at multiple time points around the clock *and* do so for multiple, consecutive days (at least seven). A similar design has also been used recently in a study of eight Brown Norway rats (Gordon 2008). This study indicated no significant decrease in mean T_b between 3 and 8 months of age and a surprising increase of 0.5°C between 8 and 24 months. The device used for monitoring T_b was a relatively large (7 g), battery-powered radiotransmitter that was surgically implanted in the abdomen; these implants are generally not used for long-term studies, and the implants increased the incidence of intestinal tumors and mortality such that only two rats survived to 24 months.

Our second important finding is that the loss of thermoregulation between 8 and 13 months of age exhibited significant genetic variation ($P=0.004$, ANOVA). A caveat is that our assessments were based on only one or two mice per strain. Nevertheless, the ANOVA was robust enough that when we excluded the strain showing the largest drop in mean T_b (2.2°C), the genetic variation remained highly significant ($P=0.009$). In addition, we obtained a total of 12 measures

of variance within strain, a reasonable sample size that indicated that the average standard deviation (square root of the variance) was only 0.3°C. This small variance within strain is likely attributable to our having determined the mean T_b of each mouse on the basis of more than 40 T_b measurements collected around the clock for at least 7 days.

Another potential but unlikely confound is that the LSXSS strains are sickly and subject to very early pathology. We recently measured the lifespans of ILS, ISS, and more than 40 LXS RIs, which are similarly derived and very closely related to the LSXSS (Williams et al. 2004). All of the mean lifespans were within the normal range for inbred strains of 20–33 months (B. Rikke et al., unpublished). We also measured whether the transponders shortened lifespan and found no effect (ANOVA, $P=0.22$, 598 mice with transponders, 275 cage mates with no transponder). Sickly mice also tend to exhibit weight loss, but the declines in mean T_b that we observed, with the exception of the largest drop, were not associated with loss of BW.

It is remarkable that mean T_b , being highly regulated, would exhibit a significant decline and significant genetic variation by just 13 months of age. Such changes, however, are consistent with the ultimate cause of senescence being a decline in the force of natural selection after the age of reproduction (reviewed by Finch 1990), and wild mice in particular have less than a 10% chance of living beyond 13 months (Austad and Kristan 2003). This declining force of natural selection and its effect on thermoregulation might be especially acute because of the inherent difficulty of maintaining a system whose functionality requires a high level of integration, perhaps similar to the decline in homeostatic complexity that characterizes old-age frailty in humans (Lipsitz, 2004). Mice may also be especially susceptible to thermoregulatory loss because of their small size, which causes them to lose heat rapidly and makes room temperature much more of a cold stress than it is for larger animals. Consequently, a decline in mean T_b prior to weight loss might be uniquely useful as a biomarker of aging in mice that is worth investigating further.

Several previous studies have found intriguing evidence that loss of thermoregulation in older mice (~24 months or older) might be a biomarker of aging. A study of C57BL/6J, A/J, and C57BL/6×A/J F₁s showed that the longer lived strains exhibited less decline in thermoregulatory ability by 25 months of

age (Talan and Ingram 1986). Loss of thermoregulation also predicted lifespan within strain in a study by Reynolds et al. (1985) and predicted lower resistance to cold stress in studies by Finch et al. (1969) and Talan et al. (1985).

On the other hand, the results of Conti et al. (2006) suggest that lower mean T_b per se has life-extension benefits, and several long-lived mutant mice have lower mean T_b s (Conti 2008). It is important, therefore, to distinguish between an age-associated decline in thermoregulation and the possible benefits of lower T_b per se (Rikke and Johnson 2004). Separating these two effects poses a difficult challenge, but genetic variation can be a powerful tool for uncoupling traits that are intimately related (Rikke and Johnson 2007). Our finding that the mean T_b s in our older cohort were only modestly correlated with the drop in mean T_b ($R=0.58$) suggests that it would be possible to identify variables that correlate more strongly with T_b drop versus T_b per se.

In conclusion, this study suggests that a large panel of RIs could be used to genetically dissect loss of thermoregulation due to aging in mice. Such studies could reveal whether this loss correlates temporarily with changes in temperature sensing, hormone signaling, heat production, or heat loss. In addition, it would be possible to map quantitative trait loci (QTLs) and test whether these loci affect one or more regulatory processes and whether they affect lifespan. QTLs of particular interest can be pursued using a combination of genetic, gene expression, and bioinformatic approaches to identify the underlying molecular pathways and genes (DiPetrillo et al. 2005; Drake et al. 2006; Li et al. 2006; Churchill 2007). This system genetics approach is developing rapidly and promises to be a powerful means of identifying the molecular mechanisms underlying many complex traits. Genetic variation provides an important starting point.

Acknowledgments Christine Martin and John Yerg provided excellent animal care and technical support. Funding was provided by the Ellison Medical Foundation and the National Institute on Aging (R01 AG024354).

References

- Aniansson A, Hedberg M, Henning G-B, Grimby G (1986) Muscle morphology, enzymatic activity, and muscle strength in elderly men: a follow-up study. *Muscle Nerve* 9:585–591
- Austad SN, Kristan DM (2003) Are mice calorically restricted in nature? *Aging Cell* 2:201–207
- Bai H, Islam MN, Kuroki H, Honda K, Wakasugi C (1995) Deaths due to heat waves during the summer of 1994 in Osaka Prefecture, Japan. *Nippon Hoigaku Zasshi* 49:265–274
- Balmagiy T, Rozovski SJ (1983) Age-related changes in thermoregulation in male albino rats. *Exp Gerontol* 18:199–210
- Churchill GA (2007) Recombinant inbred strain panels: a tool for systems genetics. *Physiol Genomics* 31:174–175
- Conti B (2008) Considerations on temperature, longevity and aging. *Cell Mol Life Sci* 65:1626–1630
- Conti B, Sanchez-Alavez M, Winsky-Sommerer R, Morale MC, Lucero J, Brownell S, Fabre V, Huitron-Resindez S, Henriksen S, Zorilla EP, de Lecea L, Bartfai T (2006) Transgenic mice with a reduced core body temperature have an increased life span. *Science* 314:825–828
- Degroot DW, Kenney LW (2006) Impaired defense of core temperature in aged humans during mild cold stress. *Am J Physiol Regul Integr Comp Physiol* 292:R103–R108
- DiPetrillo K, Wang X, Stylianou IM, Paigen B (2005) Bioinformatics toolbox for narrowing rodent quantitative trait loci. *Trends Genet* 21:683–692
- Drake TA, Schadt EE, Lusis AJ (2006) Integrating genetic and gene expression data: application to cardiovascular and metabolic traits in mice. *Mamm Genome* 17:466–479
- Eleftheriou BE (1975) Changes with age in protein-bound iodine (PBI) and body temperature in the mouse. *J Gerontol* 30:417–421
- Estler CJ (1971) Efficiency of thermoregulation in acutely cold-exposed young and old mice. *Life Sci* 10:1291–1298
- Finch CE (1990) Longevity, Senescence, and the Genome. The University of Chicago Press, Chicago
- Finch CE, Foster JR, Mirsky AE (1969) Ageing and the regulation of cell activities during exposure to cold. *J Gen Physiol* 54:690–712
- Florez-Duquet M, McDonald RB (1998) Cold induced thermoregulation and biological aging. *Physiol Rev* 78:339–358
- Gabaldon AM, Florez-Duquet ML, Hamilton JS, McDonald RB, Horwitz BA (1995) Effects of age and gender on brown fat and skeletal muscle metabolic responses to cold in F344 rats. *Am J Physiol* 37:R931–R941
- Gordon CJ (2008) Cardiac and thermal homeostasis in the aging brown Norway rat. *J Gerontol Ser A Biol Sci Med Sci* 12:1307–1313
- Habicht GS (1981) Body temperature in normal and endotoxin-treated mice of different ages. *Mech Ageing Dev* 16:97–104
- Hoffman-Goetz L, Keir R (1984) Body temperature responses of aged mice to ambient temperature and humidity stress. *J Gerontol* 39:547–551
- Ingram DK, Archer JA, Harrison DE, Reynolds MA (1982) Physiological and behavioral correlates of lifespan in aged C57BL/6J mice. *Exp Gerontol* 17:295–303
- Kiang-Ulrich M, Horvath SM (1985) Age-related differences in response to acute cold challenge (–10 degrees C) in male F344 rats. *Exp Gerontol* 20:201–209
- Lauria G, Holland N, Hauer P, Cornblath DR, Griffin JW, McArthur JC (1999) Epidermal innervation: changes with aging, topographic location, and in sensory neuropathy. *J Neurol Sci* 16:172–178

- Leto S, Kokkonen GC, Barrows CH (1976) Dietary protein life-span, and physiological variables in female mice. *J Gerontol* 31:149–154
- Li R, Tsaih SW, Shockley K, Stylianou IM, Wergedal J, Paigen B, Churchill GA (2006) Structural model analysis of multiple quantitative traits. *PLoS Genet* 2:e114
- Lipsitz LA (2004) Physiological complexity, aging, and the path to frailty. *Sci Aging Knowledge Environ* 2004(16):pe16
- Markel PD, Fulker DW, Bennett B, Corley RP, DeFries JC, Erwin VG, Johnson TE (1996) Quantitative trait loci for ethanol sensitivity in the LS x SS recombinant inbred strains: interval mapping. *Behav Genet* 26:447–458
- McDonald RB, Hamilton JS, Horwitz BA (1993) Influence of age and gender on brown adipose tissue norepinephrine turnover. *Proc Soc Exp Biol Med* 204:117–121
- McDonald RB, Murtagh CM, Horwitz BA (1994) Age and gender effects on glucose utilization in skeletal muscle and brown adipose tissue of cold-exposed rats. *Proc Soc Exp Biol Med* 207:102–109
- McLaren A (1961) Some causes of variation of body temperature in mice. *Q J Exp Physiol Cogn Med Sci* 46:38–45
- Moran DS, Mendal L (2002) Core temperature measurement: methods and current insights. *Sports Med* 32:879–885
- Passlick-Deetjen J, Bedenbender-Stoll E (2005) Why thermosensing? A primer. *Nephrol Dial Transplant* 20:1784–1789
- Reynolds MA, Ingram DK, Talan MI (1985) Relationship of body temperature stability to mortality in aging mice. *Mech Ageing Dev* 30:143–152
- Rikke BA, Johnson TE (2004) Lower body temperature as a potential mechanism of life extension in homeotherms. *Exp Gerontol* 39:927–930 Erratum in: *Exp Gerontol*
- Rikke BA, Johnson TE (2007) Physiological genetics of dietary restriction: uncoupling the body temperature and body weight responses. *Am J Physiol Regul Integr Comp Physiol* 293:R1522–R1527
- Rikke BA, Yerg JE 3rd, Battaglia ME, Nagy TR, Allison DB, Johnson TE (2003) Strain variation in the response of body temperature to dietary restriction. *Mech Ageing Dev* 124:663–678
- Rikke BA, Yerg JE 3rd, Battaglia ME, Nagy TR, Allison DB, Johnson TE (2004) Quantitative trait loci specifying the response of body temperature to dietary restriction. *J Gerontol Ser A Biol Sci Med Sci* 59:118–125
- Talan M (1984) Body temperature of C57BL/6J mice with age. *Exp Gerontol* 19:25–29
- Talan MI, Engel BT (1986) Temporal decrease of body temperature in middle-aged C57BL/6J mice. *J Gerontol* 41:8–12
- Talan MI, Ingram DK (1986) Age comparisons of body temperature and cold tolerance among different strains of *Mus musculus*. *Mech Ageing Dev* 33:247–256
- Talan MI, Engel BT, Whitaker JR (1985) A longitudinal study of tolerance to cold stress among C57BL/6J mice. *J Gerontol* 40:8–14
- Van Someren EJ (2007) Thermoregulation and aging. *Am J Physiol Regul Integr Comp Physiol* 292:R99–R102
- Van Someren EJ, Raymann RJ, Scherder EJ, Daanan HA, Swaab DF (2002) Circadian and age related modulation of thermoreception and temperature regulation: mechanisms and functional implications. *Ageing Res Rev* 1:721–728
- Weinert D, Waterhouse J, Nevill A (2004) Changes of body temperature and thermoregulation in the course of the ovarian cycle in laboratory mice. *Biol Rhythm Res* 35:171–185
- Williams RW, Bennett B, Lu L, Gu J, DeFries JC, Carosone-Link PJ, Rikke BA, Belknap JK, Johnson TE (2004) Genetic structure of the LXS panel of recombinant inbred mouse strains: a powerful resource for complex trait analysis. *Mamm Genome* 15:637–647