Metabolic consequences of pregnancy-associated plasma protein-A deficiency in mice: exploring possible relationship to the longevity phenotype

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Abstract
Mice born with the deletion of the gene for pregnancy-associated plasma protein-A (PAPP-A), a model of reduced local IGF activity, live ~30% longer than their wild-type (WT) littermates. In this study, we investigated metabolic consequences of PAPP-A gene deletion and possible relationship to lifespan extension. Specifically, we determined whether 18-month-old PAPP-A knockout (KO) mice when compared with their WT littermates have reduced energy expenditure and/or altered glucose–insulin sensitivity. Food intake, and total energy expenditure and resting energy expenditure as measured by calorimetry were not different between PAPP-A KO and WT mice when subjected to the analysis of covariance with body weight as the covariate. However, there was an increase in spontaneous physical activity in PAPP-A KO mice. Both WT and PAPP-A KO mice exhibited mild insulin resistance with age, as assessed by fasting glucose/insulin ratios. Oral glucose tolerance and insulin sensitivity were not significantly different between the two groups of mice, although there appeared to be a decrease in the average size of the pancreatic islets in PAPP-A KO mice. Thus, neither reduced ‘rate of living’ nor altered glucose–insulin homeostasis can be considered key determinants of the enhanced longevity of PAPP-A KO mice. These findings are discussed in the context of those from other long-lived mouse models.


Introduction
Pregnancy-associated plasma protein-A (PAPP-A) is a recently discovered metalloproteinase whose major physiological function, as so far identified, is to increase local insulin–like growth factor (IGF) bioavailability through the cleavage of inhibitory IGF binding proteins (reviewed in Boldt & Conover 2007). Reduced IGF signaling is associated with a prolonged lifespan in a variety of species (Kenyon 2001, Barbieri et al. 2003, Holzenberger et al. 2004, Richardson et al. 2004). Indeed, mice born with the deletion of the PAPP-A gene live ~30% longer than their wild-type (WT) littermates (Conover & Bale 2007). However, the mechanism(s) underlying this enhanced longevity have yet to be determined. With this study, we initiated investigation into key factors involved in lifespan extension in a mammalian model of reduced local IGF action.

Together, with insulin, IGFs are important regulators of cell metabolism and growth. The ‘rate of living’ theory of aging posits that a decrease in overall metabolic rate decreases the production of reactive oxygen species (ROS) during respiration, thereby slowing the aging process (reviewed in Masoro 2005). If so, then reduced IGF signaling might result in decreases in metabolism that could explain the increase in lifespan in PAPP-A knockout (KO) mice. Decreased body temperature and lowered metabolism in the Ames and Snell dwarf mice, long-lived growth hormone (GH)- deficient mouse models, would support this theory (Bartke et al. 2001). It is of note that these mice have low circulating IGF-I due to the loss of GH-dependent hepatic IGF-I expression. Studies of caloric restriction in rats provide evidence for an association between lifespan, circulating IGFs, and metabolic rate (Krystal & Yu 1994). Caloric restriction in rhesus monkeys also results in decreased core temperature and 24 h energy expenditure (Lane et al. 1996). On the other hand, there are several examples of reduced insulin and/or IGF-I signaling where the organism does not have to be metabolically compromised to age slowly (Barbieri et al. 2003, Holzenberger et al. 2003, Hulbert et al. 2004).

Furthermore, a progressive rise in insulin resistance is associated with aging (Ferrannini et al. 1996, Facchini et al. 2001), and a direct cause and effect relationship has been suggested. The ‘altered glucose–insulin system’ hypothesis suggests that the lifetime maintenance of low levels of glucose and insulin can explain life extension (Masoro 2005). Invertebrate models have been particularly informative (Broughton et al. 2005). However, animal models of extended lifespan are somewhat controversial in this regard. In support
of this hypothesis, GH-deficient and GH-resistant dwarf mice with reduced circulating IGF-I show decreased fasting levels of glucose and insulin and increased insulin sensitivity (Dominici et al. 2002, Coschigano et al. 2003, Bonkowski et al. 2006). There is a similarly reduced glucose–insulin profile with caloric restriction (Richardson et al. 2004). Seemingly against a direct relationship between aging and insulin resistance are the long-lived Klotho transgenic mice. These mice have an increase in lifespan and are insulin and IGF-I resistant (Kurosu et al. 2005).

In this study, we focused on the basic metabolic and activity profile of PAPP-A KO mice, a model of reduced local IGF-I action in the context of normal circulating IGF-I levels (Conover et al. 2003, Conover & Bale 2007). Specifically, we tested the hypothesis that aged PAPP-A KO mice have reduced energy expenditure and/or altered glucose–insulin sensitivity when compared with WT littermates.

Materials and Methods

PAPP-A KO mice

Mice with the targeted deletion of the PAPP-A gene were generated through homologous recombination in embryonic stem cells (Conover et al. 2003). These mice were on a mixed C57BL/6 and 129 background. WT and PAPP-A KO littermates from heterozygous breeding were used in studies. Genotyping was performed by PCR as described previously (Bale & Conover 2005). For all experimental animals, genotypes were reconfirmed on tail DNA at time of sacrifice. Data from mice with obvious tumors (one 18-month-old WT mouse) were eliminated from analyses. All mice were kept on a 12 h light:12 h darkness cycle with the light phase beginning at 0600 h.

Food intake, energy expenditure, and spontaneous activity

For food intake, mice were housed for 7 days in a controlled environment within individual plexiglas cages that matched the chamber used for energy expenditure and activity measurements. These cages have ceramic bowls designed not to tip allowing daily measurement of ad libitum food intake, which was performed for 5 consecutive days. Energy expenditure and physical activity were measured as previously reported (Novak et al. 2006, Barbosa et al. 2007). At least 24 h before the time of measurement, each mouse was allowed to acclimate to the testing conditions in a cylindrical chamber (7 l; 30 cm diameter×10 cm high) in the testing area. To measure energy expenditure, custom made small animal calorimeters with a 71 cylindrical chamber (Columbus Instruments; Columbus, OH, USA) were used. For calorimetry, the sample flow rate was set at 0-41 per min (lpm), and the chamber flow rate at which room air pumped through the chamber was set at 0-45–0-7 lpm, depending on the size of the mouse. Samples were collected once every 60 s for 25 h, except for the reference samples collected for 5 min after every 30 samples throughout the 24-h measurement period. Data for each calorimeter were monitored and compared with ensure that the data collected and reference values were comparable between sets of equipment. Data collected included VO₂ and VCO₂ (both in ml/kg per h), respiratory exchange ratio (RER, VCO₂/VO₂), and energy expenditure ([(3.815+1.232×RER)×VO₂] in kcal/h). Food and water were supplied ad libitum. The calorimetry and physical activity data were calculated every minute, and the energy expenditure data were 60 s behind the activity data, due to the time needed to move and process the air from the calorimetry chamber. To calculate resting energy expenditure (REE), we calculated the total daily energy expenditure (TDEE) for the minutes where there were no activity counts for the current and previous 5 min (see physical activity, below) and averaged them. When the REE is subtracted from the TDEE, this yields energy expenditure of activity (EEA).

Attached to the calorimeters were Opto-M Varimex Minor activity monitors. These devices contain 45 collimated infrared activity sensors that gather data regarding physical activity in three axes (horizontal x and y axes, plus vertical activity) as well as ambulatory activity (which excluded repetitive signals from a single beam). Data for physical activity and energy expenditure were collected simultaneously every minute, allowing correlation of the two variables in each animal tested.

Oral glucose tolerance and insulin sensitivity testing

For oral glucose tolerance testing, food was removed from cages at ~2100 h, and glucose (0-01 ml of a 10% glucose solution per g body weight) administered by gavage at ~0900 h the next morning. Blood was collected from the tail vein at 0, 5, 10, 15, 30, 45, 60, 90, and 120 min. Glucose was measured using a One Touch Ultra glucose meter (LifeScan, Milpitas, CA, USA). Insulin was measured at 0, 5, 10, 15, and 30 min using an Ultra Sensitive Rat Insulin ELISA Kit from Crystal Chem Inc. (Downers Grove, IL, USA). Area under the curve was measured using the trapezoid method. For insulin sensitivity testing, overnight-fasted mice were given food at 0830 h for 30 min. At 1200 h, mice then received an i.p. injection of regular insulin (75 mU/kg body weight) with blood collections at 0, 20, 40, and 60 min for glucose measurements. Insulin sensitivity was assessed by comparing rate-of-decay curves.

Pancreas immunohistochemistry

The pancreas was carefully dissected, fixed in formalin, embedded, and processed as described by Devedjian et al. (2000). Briefly, the entire pancreas was cut in 5 μm sections every 150 μm and every other section stained for insulin by the Tissue and Cell Molecular Analysis Core Lab using guinea pig anti-swine insulin antibody from Dako (Carpinteria, CA, USA). The Nikon Microphot-FXA and Nikon ACT-1 Version
2.6.2 (Melville, NY, USA) were used to photo-capture the slides. The number of islets and islet cell mass were measured using the polygonal lasso tool in Adobe Photoshop 6.0.1.

Results

Food, energy expenditure, and physical activity

Food intake, energy expenditure, and spontaneous physical activity were measured in 18-month-old WT and PAPP-A KO mice. Both male and female mice were studied, and the results are presented in Table 1. Food intake, expressed as g/day, and TDEE and REE, expressed as kcal/day, were significantly decreased in male and female PAPP-A KO when compared with WT mice. However, these calculations do not take into account the significantly smaller size of the PAPP-A KO mouse (Conover et al. 2003, Bale & Conover 2005). The normalization of the data for body weight indicated significantly increased food intake (males only), TDEE, and REE in PAPP-A KO mice when compared with WT littermates. However, in this case dividing by body weight may overcorrect energy expenditure values of the larger animals (Packard & Boardman 1999, Arch et al. 2006). Therefore, the data were subjected to the analysis of covariance which uses the group (genotype) comparison of regression lines to determine whether the groups differ when body weight is a covariate. The results of these analyses are presented in Table 2. Differences in TDEE and REE were accounted for by body weight and not by genotype. EEA was not significantly different in WT and PAPP-A KO mice and could not be accounted for by body weight. However, vertical activity was increased 30–110% in PAPP-A KO mice, reaching significance in males (Table 1). Thus, there was no decrease in energy expenditure in 18-month-old PAPP-A KO mice when compared with WT mice which would suggest that a compensatory slowing of metabolism was the direct link to longevity. On the contrary, there may be an increase in physical activity in the PAPP-A KO mice.

Glucose and insulin sensitivity

Fasting glucose and insulin levels were not significantly different between WT and PAPP-A KO mice at 4 months or 18 months of age (Table 3). In general, female mice had lower fasting insulin levels than male mice, which were independent of genotype. There was an increase in insulin levels in the older animals to maintain the same glucose levels, suggesting mild insulin resistance. This increase tended to be less in the PAPP-A KO mice but the data did not reach statistical significance. Oral glucose tolerance testing was performed on 12 h fasted WT and PAPP-A KO mice, both males and females at 18 months of age. There was no significant difference in the endogenous glucose or insulin response to the glucose challenge between PAPP-A KO and WT mice, either male (Fig. 1A) or female (Fig. 1B). Total pancreatic islet area and number were not significantly different in 18-month-old WT and PAPP-A KO mice (Table 4). However, there was a significantly smaller, by ~30%, average size of islets in PAPP-A KO when compared with WT mice. Sensitivity to exogenously administered insulin was not

Table 1 Food intake, energy expenditure, and physical activity. See Materials and Methods for descriptions and calculations. Results are mean ± s.e.m. of (n) mice

<table>
<thead>
<tr>
<th>Males</th>
<th>WT (7)</th>
<th>PAPP-A KO (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake</td>
<td>4.0±0.16</td>
<td>3.2±0.16a</td>
</tr>
<tr>
<td>TDEE</td>
<td>19.4±0.80</td>
<td>16.2±0.41a</td>
</tr>
<tr>
<td>REE</td>
<td>17.7±0.94</td>
<td>14.4±0.29a</td>
</tr>
<tr>
<td>BW</td>
<td>36.2±2.3</td>
<td>20.0±0.8a</td>
</tr>
<tr>
<td>Food intake/BW</td>
<td>0.11±0.005</td>
<td>0.15±0.004b</td>
</tr>
<tr>
<td>REE/BW</td>
<td>0.49±0.016</td>
<td>0.72±0.031b</td>
</tr>
<tr>
<td>TDEE/BW</td>
<td>0.54±0.019</td>
<td>0.82±0.032b</td>
</tr>
<tr>
<td>EEA</td>
<td>1.7±0.14</td>
<td>1.8±0.17</td>
</tr>
<tr>
<td>Horiz</td>
<td>24.6±3.30</td>
<td>26.0±3.19</td>
</tr>
<tr>
<td>Vert</td>
<td>4.6±0.92</td>
<td>10.0±1.31b</td>
</tr>
<tr>
<td>Ambul</td>
<td>5.8±0.93</td>
<td>5.3±0.77</td>
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</table>

<table>
<thead>
<tr>
<th>Females</th>
<th>WT (13)</th>
<th>PAPP-A KO (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake</td>
<td>3.3±0.17</td>
<td>2.6±0.24a</td>
</tr>
<tr>
<td>TDEE</td>
<td>12.7±0.53</td>
<td>10.5±0.24a</td>
</tr>
<tr>
<td>REE</td>
<td>11.4±0.55</td>
<td>9.3±0.29a</td>
</tr>
<tr>
<td>BW</td>
<td>30.1±1.7</td>
<td>21.0±0.8a</td>
</tr>
<tr>
<td>Food intake/BW</td>
<td>0.11±0.009</td>
<td>0.12±0.009</td>
</tr>
<tr>
<td>REE/BW</td>
<td>0.43±0.017</td>
<td>0.50±0.022a</td>
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<td>TDEE/BW</td>
<td>0.38±0.014</td>
<td>0.44±0.020a</td>
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<tr>
<td>EEA</td>
<td>1.1±0.12</td>
<td>1.2±0.07</td>
</tr>
<tr>
<td>Horiz</td>
<td>24.7±2.90</td>
<td>26.4±1.92</td>
</tr>
<tr>
<td>Vert</td>
<td>7.3±1.25</td>
<td>9.7±1.16</td>
</tr>
<tr>
<td>Ambul</td>
<td>6.3±0.94</td>
<td>7.2±0.79</td>
</tr>
</tbody>
</table>

Table 2 Analysis of covariance (ANCOVA) for energy expenditure measurements. The data in Table 1 were subjected to ANCOVA with body weight (BW) as the covariate. Group P value indicates whether groups are different in the dependent variable (food intake or EE) after BW is factored out. BW indicates whether the covariate had a significant effect on the measure. Group*BW interaction indicates whether the effect of BW on the food intake or EE of each group is the same. If this is significant, then the interpretation of a group effect would be hampered

<table>
<thead>
<tr>
<th>P value</th>
<th>Food intake</th>
<th>TDEE</th>
<th>REE</th>
<th>EEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>0.640</td>
<td>0.508</td>
<td>0.547</td>
<td>0.432</td>
</tr>
<tr>
<td>BW</td>
<td>0.069</td>
<td>0.016</td>
<td>0.006</td>
<td>0.781</td>
</tr>
<tr>
<td>Group*BW</td>
<td>0.546</td>
<td>0.104</td>
<td>0.104</td>
<td>0.444</td>
</tr>
</tbody>
</table>
significantly different in 18-month-old WT and PAPP-A KO mice, either male (Fig. 2A) or female (Fig. 2B).

Discussion

Mice lacking PAPP-A have relatively normal energy metabolism and glucose/insulin sensitivity compared with WT, age-matched littermates. Therefore, the findings of this study do not support reduced ‘rate of living’ or an ‘altered glucose–insulin system’ as key determinants of the enhanced longevity of PAPP-A KO mice. Although the underlying mechanism was not identified in this series of experiments designed to test specific hypotheses, the data are relevant in the context of current controversies in the biology of aging.

There was no decrease in total or REE in 18-month-old PAPP-A KO mice when compared with WT mice when the significantly smaller size of the PAPP-A KO mice was taken into account (Packard & Boardman 1999, Arch et al. 2006). Methods of normalization for body weight can lead to different conclusions and may explain some of the studies with caloric restriction and apparent decreases in metabolic rate. Furthermore, recent studies have suggested that, after an initial reduction, caloric restriction leads to equal or higher metabolic rates than ad libitum fed animals (Faulks et al. 2006). It has been assumed that a decrease in metabolic rate would prolong lifespan by decreasing exposure to ROS produced during respiration. Alternatively, under normal metabolic conditions, tissues from PAPP-A KO mice may be less vulnerable to oxidative damage by the virtue of increased ability to eliminate ROS or show increased mitochondrial efficiency thereby reducing ROS production. These have been suggested as contributors to longevity in other model systems (Balaban et al. 2005).

Furthermore, the PAPP-A KO mice had increased physical activity in the vertical axis. This reached statistical significance in males, although a similar trend for increased activity was seen in the females as well. What this behavior might mean can only be speculated upon at this time. Mice were monitored individually so it is not likely to be aggressive posturing, but rather spontaneous physical activity. There have been few studies monitoring physical activity in the various mouse

<table>
<thead>
<tr>
<th>4 months</th>
<th>WT</th>
<th>Glucose</th>
<th>Insulin</th>
<th>PAPP-A KO</th>
<th>Glucose</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>(9)</td>
<td>81±3</td>
<td>0.69±0.137</td>
<td>(9)</td>
<td>89±2</td>
<td>0.46±0.124</td>
</tr>
<tr>
<td>Females</td>
<td>(8)</td>
<td>88±8</td>
<td>0.38±0.080</td>
<td>(8)</td>
<td>91±8</td>
<td>0.36±0.088</td>
</tr>
<tr>
<td>18 months</td>
<td>Males</td>
<td>(11)</td>
<td>82±6</td>
<td>1.23±0.194a</td>
<td>(10)</td>
<td>79±6</td>
</tr>
<tr>
<td>Females</td>
<td>(7)</td>
<td>89±7</td>
<td>0.88±0.294a</td>
<td>(9)</td>
<td>78±6</td>
<td>0.59±0.100a</td>
</tr>
</tbody>
</table>

Glucose: mg/dl. Insulin: ng/ml. Results are mean±S.E.M. of n mice.

aSignificant difference between 4 months and 18 months.

Table 3 Fasting glucose and insulin levels

Table 4 Islet cell immunohistochemistry. Sections of pancreata were stained for insulin as described in Materials and Methods. Results are mean±S.E.M. of (n) mice.

Table 4 | WT (7) | PAPP-A KO (8) | P value |
| Islet | | | |
| Area (Pixels) | 49 786±25 531 | 39 492±8696 | 0.441 |
| Number | 147±36 | 136±25 | 0.802 |
| Average size (Pixels) | 390±50 | 278±20 | 0.048 |
models associated with aging research. In caloric-restricted mice and IGF-I receptor heterozygous mutant mice, there was no difference in total physical activity when compared to controls, although dimensional aspects were not recorded (Holzenberger et al. 2003, Faulks et al. 2006). Interestingly, spontaneously wiggling Caenorhabditis elegans were longer-lived than their counterparts that needed to be prodded to move (Herndon et al. 2002). Apfeld et al. (2004) suggest that in this model system there is a direct link between activity levels, insulin-like signals and lifespan. Thus, this aspect of the longevity profile warrants further study.

Fasting insulin/glucose ratios increased significantly with age in both WT and PAPP-A KO mice, suggesting mild insulin resistance. Notably, for the purpose of this study, it occurred in both groups and in both sexes. Thus, PAPP-A deficiency does not necessarily translate into a ‘youthful’ insulin–glucose profile, and there was no evidence for sexual dimorphism in insulin resistance as was seen in liver-specific IGF-I deficient mice with reduced circulating IGF-I levels (Tang et al. 2005). Eighteen-month-old WT and PAPP-A KO mice challenged with glucose had similar glucose tolerance curves. Insulin secretory capacity was assessed by immunohistochemistry of insulin-producing β-cells in pancreatic islets. Multiple sections of the total pancreas were stained for insulin to try to account for heterogeneity of islet distribution and size. Interestingly, the average size but not the number or total mass of pancreatic islets was significantly decreased in PAPP-A KO mice. β-Cell-specific IGF-I receptor KO mice exhibit normal development of β-cells but defective glucose-stimulated insulin secretion and impaired glucose tolerance (Kulkarni et al. 2002). Thus, local IGF signaling does not appear to be essential for normal growth of pancreatic islets, which may partially explain the normal islet mass and number in PAPP-A KO mice. However, secretion of insulin from pancreatic β-cells is dependent on IGF-I, and a diminished (but not complete) loss of local IGF-I action in PAPP-A KO mice may affect optimal secretory response without major impact on overall glucose homeostasis. Comparable studies in other mouse models of aging indicated decreased glucose tolerance in Ames and GH-resistant dwarf mice that was due to a decrease in total volume of the islets (Parsons et al. 1995, Liu et al. 2004), perhaps reflecting reduced GH and/or circulating IGF-I. Circulating IGF-I, which is not decreased in PAPP-A KO mice, is an important component of overall insulin action in peripheral tissues (Yakar et al. 2001). This may account for unaltered insulin sensitivity in PAPP-A KO mice. Caloric-restricted mice maintain glucose homeostasis with markedly less insulin, which may be associated with increased insulin sensitivity (Richardson et al. 2004). The co-existence of insulin resistance and enhanced longevity in Klotho male transgenic mice (Kurosu et al. 2005) makes sense, as discussed below, if insulin

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**Table 5** Metabolic parameters of long-lived mouse models. Data from the present study and other published studies were used to compile this table comparing PAPP-A KO, Ames dwarf, Snell dwarf, GH receptor KO, Klotho transgenic, calorically restricted (CR) and heterozygous IGF-I receptor mutant (IGFR+/-) mice. References can be found in the text.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAPP-A KO</th>
<th>Ames</th>
<th>Snell</th>
<th>GHRKO</th>
<th>Klotho</th>
<th>CR</th>
<th>IGFR+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifespan</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Metabolic rate</td>
<td>=</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Activity</td>
<td>↑</td>
<td>?</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Fasting insulin/glucose</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Glucose tolerance</td>
<td>=</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>=</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>GH</td>
<td>=</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Circulating IGF-I</td>
<td>=</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Local IGF-I action</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Gluc, Glucose; ↑, increased compared with control; ↓, decreased compared with control; =, no difference compared with control; ?, not known.

*Females only.

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and/or insulin sensitivity per se was not a key determinant of enhanced lifespan. Indeed, the extended lifespan of fat-specific insulin receptor KO mice may not be primarily due to reduced insulin signaling in adipose tissue, but rather a result of decreased fat mass (Bluher et al. 2003). The percentage fat is similar in WT and PAPP-A KO mice (data not shown). Thus, although we cannot completely rule out a role for reduced insulin signaling as a contributing factor to the longevity of PAPP-A KO mice, the similar fasting and fed levels of insulin ad libitum in WT and PAPP-A KO mice and the similar insulin sensitivity curves in the longer-lived PAPP-A KO mice indicate that this role would not be a decisive one.

Metabolic and activity data from different mouse models of longevity are summarized in Table 5. The many information gaps indicated in the table make it difficult to come to firm conclusions. However, there is no consistency across the seven models in metabolic rate, physical activity, fasting insulin/glucose, glucose tolerance, insulin sensitivity, GH, or circulating IGF-I levels. Of course this could be due to the specifics of the models and the testing methods. In addition, the age of the mice at the time of determination of metabolic parameters was not always apparent in the published articles in the different longevity models. This could be important for antagonist pleiotropic systems such as the IGF system, which can have beneficial effects early in life and detrimental effects late in life (Rincon et al. 2004). We chose 18 months as our ‘aged’ mouse group because after this time the WT mice tended to develop tumors, which could impact metabolic measurements. It is possible that alterations in metabolism occur in younger mice that could impact lifespan. However, this did not occur in those systems that were examined across ages (Coschigano et al. 2003). Uncertainties notwithstanding, one could propose decreased local IGF-I action as the common denominator in these long-lived mouse models. PAPP-A KO, Klotho transgenic, and IGF-I receptor heterozygous mutant mice have diminished local IGF-I signaling (Conover et al. 2003, Holzenberger 2004, Kurosu et al. 2005). It may be that Ames, Snell, and GH receptor-deficient mice have decreased local IGF-I action due to partial GH-dependence of IGF-I expression in peripheral tissues, although there is currently no evidence that these mice exhibit the loss of function of IGF-I signaling. Caloric restriction likewise has been shown to decrease IGF-I expression in hepatic and non-hepatic cells (Masternak et al. 2005, Papaconstantinou et al. 2005). Thus, a decrease in effective local IGF-I signaling, whether through decrease in IGF expression (GH deficiency/resistance, caloric restriction), decrease in IGF receptor signaling (IGF-I receptor mutation, Klotho overexpression), or diminished IGF bioavailability (PAPP-A deficiency), can increase lifespan in mice. Further studies are necessary to establish underlying mechanism(s) specific to the PAPP-A KO model that could enhance our overall understanding of lifespan determinants and suggest therapeutic targets to promote healthy aging.

Declaration of interest

There is no conflict of interest that would prejudice impartiality.

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References


Barbosa MT, Soares SM, Novak CM, Sinclair D, Levine JA, Aksy P & Chini EN. 2005. It may be that PAPP-A knockout mice and the similar insulin sensitivity curves in the longer-lived PAPP-A KO mice (data not shown). Thus, although we came to firm conclusions. However, there is no consistency across the seven models in metabolic rate, physical activity, fasting insulin/glucose, glucose tolerance, insulin sensitivity, GH, or circulating IGF-I levels. Of course this could be due to the specifics of the models and the testing methods. In addition, the age of the mice at the time of determination of metabolic parameters was not always apparent in the published articles in the different longevity models. This could be important for antagonist pleiotropic systems such as the IGF system, which can have beneficial effects early in life and detrimental effects late in life (Rincon et al. 2004). We chose 18 months as our ‘aged’ mouse group because after this time the WT mice tended to develop tumors, which could impact metabolic measurements. It is possible that alterations in metabolism occur in younger mice that could impact lifespan. However, this did not occur in those systems that were examined across ages (Coschigano et al. 2003). Uncertainties notwithstanding, one could propose decreased local IGF-I action as the common denominator in these long-lived mouse models. PAPP-A KO, Klotho transgenic, and IGF-I receptor heterozygous mutant mice have diminished local IGF-I signaling (Conover et al. 2003, Holzenberger 2004, Kurosu et al. 2005). It may be that Ames, Snell, and GH receptor-deficient mice have decreased local IGF-I action due to partial GH-dependence of IGF-I expression in peripheral tissues, although there is currently no evidence that these mice exhibit the loss of function of IGF-I signaling. Caloric restriction likewise has been shown to decrease IGF-I expression in hepatic and non-hepatic cells (Masternak et al. 2005, Papaconstantinou et al. 2005). Thus, a decrease in effective local IGF-I signaling, whether through decrease in IGF expression (GH deficiency/resistance, caloric restriction), decrease in IGF receptor signaling (IGF-I receptor mutation, Klotho overexpression), or diminished IGF bioavailability (PAPP-A deficiency), can increase lifespan in mice. Further studies are necessary to establish underlying mechanism(s) specific to the PAPP-A KO model that could enhance our overall understanding of lifespan determinants and suggest therapeutic targets to promote healthy aging.


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